
Montenegrin Society
of Anesthesiology
and Intensive Care
E S A IC
European Society of
Anaesthesiology and
Intensive Care
1st INTERNATIONAL
CONGRESS OF
ANESTHESIOLOGY &
INTENSIVE CARE
13 - 15. October 2023.
BUDVA, MONTENEGRO
Montenegro

European Society of Anesthesiology and Intensive Care

ESAIC endorsed the 1st International Congress of Anesthesiology and Intensive Care

Accredited International Congress of the Health Council of the Republic of Montenegro on the Continuing Education Accreditation Program.

1ST International Congress of Anesthesiology and Intensive Care

13 – 15. October 2023.

Budva

Montenegro

- Proceeding -

Montenegrin Society of Anesthesiology and Intensive Care

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PAPERS

The Role of Ultrasound in The Airway Management *

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Introduction

Ultrasound (US) offers an extensive number of attractive advantages when compared to the competitive imaging techniques or endoscopy for critically ill patients. Some of the most important advantages of using bedside US are its broad availability, repeatability, portability, relatively affordable price, safety, and painless applicability. In this lecture, I will highlight the crucial potential applications of ultrasonography in the airway management.

US anatomy of the upper airway

An US probe with a frequency of more than 7.5 MHz is appropriate for the upper airway US examination, due to the higher frequency, which gives a better resolution of the superficial organs and tissues. In spite of the high impedance of air-filled spaces, analysis of the soft tissue and cartilages of the upper airway is possible, including: the floor of the mouth, posterior part of the tongue, supra- and infra-hyoid bone region, larynx and trachea. The US examination of the floor of the mouth usually includes the posterior part of the tongue and its base, which presents the tongue as an iso- to hypoechoic organ. Moving the US transducer from the mouth floor caudally in the transverse view, the hyoid bone with characteristically inverted U-shaped hyperechoic line (reflection of the US wave) and the acoustic shadow underneath can be assessed. By further sliding of the US probe caudally, the main laryngeal cartilages can be visualized. Thyroid and cricoid cartilages are visible as homogeneous, hypoechoic well-defined structures, connected with iso-echoic crico-thyroid ligament. Caudally from the cricoid cartilage, tracheal cartilage rings can be assessed by longitudinal and transversal view. Cartilage rings are clearly visible as hypoechoic, well-defined, lens-shaped structures.

Verification of endotracheal tube position

US provides dynamic anatomic evidence of the correct physiologic function of the ETT in paralyzed or apneic patients during and after resuscitation; it effectively and quickly shows the movement of the diaphragm and pleura, both of which are indirect quantitative and qualitative indicators of lung expansion. If the ETT is in the correct position, bilateral and equal motions of the diaphragm toward the abdomen are likely to be visible on ultrasound, which represents the equal bilateral expansion of the lungs. When using the intercostal (2nd or 3rd intercostal space) ultrasonographic view, it is also easy to identify the so-called "lung sliding" sign, a sort of "to-and-fro" movements of the pleura synchronized with ventilation. If the aforementioned sign is imaged on the left or on both sides of the chest, it should correspond to regular bilateral lung ventilation, thus verifying correct ETT position. In contrast, if the ETT is in the esophagus, expansion of the lungs will not occur as a result of mechanically-delivered breath, indeed, when the patient is paralyzed or apneic, the esophageal intubation will result in an immobile diaphragm or paradoxical movement of the diaphragm (due to the instillation of positive pressure into the abdomen) and intercostal view will result in the absence of motions of pleura on both sides of the chest (i. e. absence of "lung sliding"). Finally, if it is not possible to see the movements of the left diaphragm - or the image is significantly minimized - then the tube is in the right main bronchus; pleural movements ("lung sliding"), will only occur on the right side of the chest, while the "lung pulse" should be visible on the left side.

Preintubation assessment

Unsuccessful intubation of a pharmacologically paralyzed patient leads to devastating consequences, and since it can be challenging to predict a difficult airway with surety, other methods have to be considered. Hyo-mental distance, measured by US, in the neutral- and head-extended positions (low hyo-mental distance ratio) is considered as an excellent predictor of a difficult intubation in obese and morbidly obese patients with a large neck circumference.

Proper ETT size selection

Within the framework of pediatric and neonatologic anesthesia and critical care management, the selection of a proper dimension of ETT is crucial and multiple studies suggest US as a useful tool for this. Subglottic upper airway diameter measured by ultrasonography is an excellent predictor of correct cuffed and uncuffed ETT sizes for pediatric patients.

Ultrasound-guided upper airway anesthesia

Airway management during laryngoscopy or endotracheal intubation in awake patients is often associated with laryngospasm, coughing and undesirable cardiovascular reflexes, which can be either abolished or blunted by anesthetizing the upper airway, in the first place the superior laryngeal nerve. The precise position of superior laryngeal nerve block, located between the hyoid bone and thyroid cartilage, can be seen with ultrasonography, and a guided block is therefore possible to perform.

* Parts of this text were published in: Šustić A, Protić A. Ultrasound and airway management. In: Jankowich M, Gartman E, edts. Ultrasound in the intensive care unit. Springer SBM, New York (USA) 2015:175-190.

Ultrasound-guided percutaneous tracheostomy *

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Introduction

Percutaneous dilatational tracheostomy (PDT) is a well-founded and safe tool for gaining tracheal access in intensive care, but it sometimes can lead to serious complications and bronchoscopic or ultrasound (US) guidance is recommended. Even bronchoscopic guidance provides the excellent visualization and is used frequently, there are certain disadvantages when compared to US. Firstly, potential complications of bronchoscopy are compromised ventilation and significant hypercarbia with resultant elevated intracranial pressure - which is not tolerated well by patients with severe head or spinal cord injury. Secondly, bronchoscopy potentially can induce pulmonary hyperinflation and pneumothorax, since airway resistance is significantly increased. Third, bronchoscopy does not give us any information about vascular structures located pretracheal. And finally, with bronchoscopy it is not possible to determine an exact space between tracheal rings with absolute certainty. Therefore, US has been suggested to guide the puncture of the trachea, and this has proven to be a very successful method applicable even in difficult cases.

The technique

The trachea and paratracheal soft tissues of the neck, due to their superficial position, are easily examined at the highest resolution with high-frequency US probes. The anterior tracheal wall, thyroid and cricoid cartilages, tracheal rings and pretracheal tissue are well imaged, enabling the clinician to choose the optimal intercartilagineous space for tracheostomy tube placement. Furthermore, the US clearly shows the relationship between the thyroid gland and the vascular structures of the neck to the trachea.

The trachea is visualized in vertical medial section using a linear transducer, prepared in a sterile sheath. The endotracheal tube is then withdrawn until the cuff is just underneath the vocal cords. After the tip of the tube passes the second tracheal ring, the intensity of the Doppler signal is heavily increased due to an enhanced signal

from unencumbered, turbulent air, which at the same time implies the confirmation of a proper position of endotracheal tube. The site of the puncture is normally selected between 2nd and 3rd tracheal ring, following a clear US verification of anatomy of the thyroid and cricoid cartilage and tracheal rings. The US transducer is then pulled cranially until the lower edge of the transducer is placed above the 2nd tracheal ring, below which the tracheal puncture will be performed. It is not mandatory to avoid the thyroid isthmus, if situated alongside the planned puncture canal, since isthmus penetration is frequent but generally harmless in PTD.

After procedure, the correct position of tracheostomy tube can be confirmed using US, at the same time excluding a potential pneumothorax.

* Parts of this text were published in: Šustić A, Protić A. Ultrasound and airway management. In: Jankowich M, Gartman E, edts. Ultrasound in the intensive care unit. Springer SBM, New York (USA) 2015:175-190.

How To Reduce the Environmental Impact of Volatile Anesthetics?

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Introduction

This paper will review the state of knowledge of the environmental impact and the estimation of the potential climate forcing of common inhaled anesthetic drugs: desflurane, sevoflurane, isoflurane, methoxyflurane and nitrous oxide. There is increasing concern within the health care community about the role care delivery plays in environmental degradation, sparking research into how to reduce pollution from clinical practice. Inhaled anesthetics are a particular research area of interest for mainly two reasons: Firstly, several of the gases are potent greenhouse gases, and are emitted directly to the environment. Secondly, there are options to both reduce waste gas emissions and to substitute medications and procedures while still delivering high quality care. Proper understanding of the emission estimates and the climate metrics used, are necessary to ensure their consistent application in guiding mitigation strategies and accounting at various scales.

Emissions to the atmosphere give rise to four general concerns: stratospheric ozone depletion, photochemical air pollution (tropospheric ozone and particle formation), formation of hazardous degradation products and climate change. This paper deals mainly with climate change. None of the volatile anesthetics gives rise to photochemical air pollution. The chlorine-containing isoflurane and methoxyflurane are, together with N_2O, all ozone depleting substances. The ozone depletion potential (ODP) is the commonly used index that conveniently compares the effectiveness of one mass unit of a substance in destroying ozone to that of CFC-11 (CCl_3F). Due to the relatively short atmospheric lifetimes of both isoflurane, and especially methoxyflurane, their resulting impact on ozone depletion is small (see Table 1). The ODP value for N_2O is dependent on the level of other GHGs and the degree of halogen loading in the stratosphere, and is 0.015 for the year 2000[1]. Finally, the degradation products and atmospheric fate of the halogenated anesthetics have been studied using chamber studies and detailed knowledge of oxidation products and mechanisms exist. In general, atmospheric oxidation of the halogenated anesthetics produce carbonyl

and ester type products whose dominant fate in the environment is reaction with OH radicals or uptake into rain, cloud and ocean water, followed by hydrolysis. Lately, there has been a substantial research interest in the sources and environmental impacts of trifluoroacetic acid (TFA). [2,3,4,5]TFA is a ubiquitous component of the world's oceans[6,7] and its presence in ancient ocean water suggests a significant natural oceanic source. TFA is neither bioaccumulative nor especially toxic, but it is persistent.[8] Of the four halogenated anesthetics listed in Table 1, iso-, des- and sevoflurane can lead to formation of TFA through atmospheric gas and heterogenous processes.

Like all sectors of society, the health care community is required to act, to reduce and abate the impact on climate change.[9] Recent estimates of the contribution of global health care to the forcing of climate change range from 4.4-5.2% of total global greenhouse gas emissions.[10] Establishing realistic greenhouse gas inventories for all operations are key to these efforts. That includes a full accounting for impact on climate from anesthetic gases, which, in turn, relies on dependable parameters and understandable matrices for the calculation of carbon emission equivalents. Inconsistent application of methods and reporting, incomplete understanding of the matrices involved, and continuously changing climate impact parameters can be confusing to the non-specialist. This paper reports the state of knowledge regarding the key parameters needed to access the impact of anesthetic gases on the environment, with particular focus on the compounds' potential contribution to climate change.

The global warming potential (GWP)

The global warming potential (GWP) is the metric commonly adopted in national and international agreements to assess the potential contribution of a greenhouse gas to climate change. The effect on climate from atmospheric gas can be compared by considering the change in the net atmospheric irradiance (W m^{-2}) at the tropopause (about 10 km altitude) caused by a change in the gas concentration. The change normally considered is based on a 1 ppb (parts per billion, 10^{-12}) increase in the concentration of the gas in the troposphere and is termed *radiative efficiency* with units of W m^{-2} ppb^{-1}. Different gases will act over different timescales. The GWP was introduced in the first assessment report of the Intergovernmental Panel on Climate Change[11] and is the most widely used climate metric. It reflects the time-integrated radiative forcing due to a pulse emission of a unit mass of gas, normalized by the reference gas CO_2. For a time-horizon t' it can be defined as:

$$GWP(x(t)) = \frac{\int_0^{t'} F_x \exp(-t/\tau_x) dt}{\int_0^{t'} F_{CO_2} R(t) dt} \quad \text{(I)}$$

where F_x is the radiative forcing per unit mass of species x, F_{CO2} is the radiative forcing of CO_2, R(t) is the response function that describes the decay of an instantaneous pulse of CO_2, and with the decay of the pulse of compound x assuming it obeys a simple exponential decay curve determined by a response time of τ_x. The denominator in expression (I) is the absolute global warming potential (AGWP) for CO_2. Knowing the GWP for a particular anesthetic gas, one can obtain the CO_2 equivalency for an emission of the gas by simply multiplying the mass of the gas emitted (in kg) and the GWP of the gas. The GWP value will depend on the choice of time horizon in the calculation above. Typically three time-horizons, 20, 100, or 500 years, are used as standard time frames of reference. This choice of timeframe is directed by one's choice of focus on either the short-, medium-, or long-term impacts, respectively. Halogenated anesthetics decay relative quickly in the atmosphere in comparison to the reference compound, CO_2. This is reflected in that their GWPs become smaller with increasing time horizon. It can be argued[12] that given the importance of CO_2 in climate change, and with its atmospheric lifetime of approximately a century, climate impact estimates, at least from a policymaking standpoint, should be derived using time horizons that capture a significant portion of the total impact of CO_2. Organizations such as the United States Environmental Protection Agency and European Environmental Agency use the 100-year time horizon for comparing the impacts of both short and long-lived greenhouse gases and suggests that health care greenhouse gas accounting follows this precedence with consistency.

To estimate the GWP for a particular anesthetic agent the following physical/chemical data is needed: The infrared (IR) absorption spectrum of the compound and the lifetime of the compound in the atmosphere. The radiative efficiency of a compound depends directly on the infrared spectrum and indirectly on the atmospheric lifetime of the compound. One must realize that the GWP is a function of both the radiative efficiency and the atmospheric lifetime of the forcing agent, and small changes and refinements in estimation methodologies for both these terms, as well as changes in the radiative efficiency of CO_2 "itself", will result in slight changes to the GWP values. Further considerations in accessing the environmental impact of an anesthetic agent may include the environmental fate of the degradation

products from the anesthetic compound. However, these products are not expected impact the climate impact from the waste gas emissions to any significant degree.

The absorbance of IR radiation

The IR absorption spectra of the anesthetic gases is measured in the laboratory with a high degree of accuracy. Figure 1 shows the spectrum of outgoing IR radiation from Earth together with the absorption bands of N_2O and the commonly used halogenated anesthetic gases, isoflurane ($CF_3CHClOCHF_2$), desflurane ($CF_3CHFOCHF_2$), sevoflurane ($(CF_3)_2CHOCH_2F$) and methoxyflurane ($CH_3OCF_2CHCl_2$). The intensities of absorbance (absorption cross sections) for these molecules are determined with a very high degree of confidence, with estimated uncertainties of less than 5% (95% confidence) [13]Gases that absorb strongly in the "atmospheric window" (see figure 1) in the Earth's IR emission spectrum, can be particularly effective at affecting the Earth's radiative balance. This region of 8-14 microns (700-1300 cm^{-1}) in the spectrum of the outgoing terrestrial infrared radiation is otherwise largely void of strong absorbance bands, allowing for efficient escape of IR radiation to higher altitude in the atmosphere and cooling of the planet. The volatile anesthetic gases are greenhouse gases partly because they possess strong IR absorption bands in the "atmospheric window".

The atmospheric lifetime

The atmospheric lifetimes of the compounds listed in Table 1 are mainly governed by their rates of reaction of hydroxyl (OH) radicals in the atmosphere. The OH radical is the "garbage man" of the atmosphere, formed by sunlight driven photolysis of ozone in the atmosphere, a process that leads to the formation of $O(^1D)$ oxygen radicals that then reacts with water vapor to give OH radicals. Except for N_2O, the anesthetic compounds are lost from the atmosphere only through reaction with OH radicals. Rate coefficients for the OH radical reactions have typically been measured experimentally using a range of different techniques and associated error ranges, and published in a variety of scientific journals over nearly four decades. Published rate coefficients are compiled in a comprehensive online database by the National Institute of Standards and Technology (NIST)[14] and critical reviews of reported rate coefficients are performed periodically in a series of evaluated sets of rate constants and other photochemical parameters by the National Aeronautics and Space Administration Panel for Data Evaluation.[15] As a result, the reaction kinetics are well determined with an estimated uncertainty range of (±10-20%) (95% confidence [16]

Calculation of atmospheric lifetimes, τ, (defined as the time it takes for the reactant concentration to fall to a factor of 1/e = 0.368 of the initial value) can be complicated. Due to temporal and spatial variations in reactant concentrations, it is often necessary to use complex atmospheric chemical and transport models to accurately determine lifetimes.[17] For short-lived molecules with lifetimes of less than a few months, e.g. methoxyflurane, the spatial and temporal distribution of OH radicals will strongly determine the distribution of the compound in the environment and the local atmospheric lifetime of the species. Still, for well-mixed compounds, with lifetimes greater than a few months, the average atmospheric lifetime with respect to reaction with OH radicals can be estimated based on two simple methods, which give very similar results: Either a simple calculation for a chemical decay through reaction with OH radicals in the atmosphere (a 24-h average tropospheric of 1.0×10^6 molecules cm^{-3})[18], or, alternatively, a relative scaling to the atmospheric lifetime of methyl chloroform due to reaction with the OH (6.1 years) using rate coefficients at a temperature of 272 K. The atmospheric lifetimes for iso-, des- and sevoflurane listed in Table 1 are determined in this fashion. For a short-lived gas like methoxyflurane (τ ~4 days), its local lifetime will depend strongly on the location of the emission and the chemical conditions of the atmosphere.

The GWP, the calculation and overall uncertainties

A combination of updates in the estimated lifetimes, the RE calculation-methods for the compounds and the value of the AGWP(CO_2) have led to higher GWPs for the anesthetic compounds over the last decade. Table 1 includes the most recently reported values for iso-, des-, sevo- and methoxyflurane. Uncertainties associated with GWP values are governed by uncertainties in the compound's lifetime, RE and the AGWP(CO_2). The uncertainties vary from compound to compound, but higher uncertainty will be associated with shorter-lived compounds principally due to challenges in estimating the non-uniform horizontal and vertical mixing in the atmosphere.

The GWP is the metric that scientific and regulatory communities rely upon when conducting environmental life cycle assessments and carbon footprint estimates. It is recognizably less than optimal, and the changing input parameters leads to the consternation and bewilderment of the health care community and others working with sustainability assessments. As discussed above it is an inherent aspect of the metric that the input parameters must necessarily change due to changes in the atmospheric environment. Part of the changes in GWPs, as can be observed from Table

1, can be attributed to progressive improvements in the scientific understanding of the compound's atmospheric chemistry and physics. It is both gratifying and worth some consideration that the range of GWP values reported for iso-, des-, and sevoflurane (when one disregards the atmospheric lifetime error)[20] over the past decade have varied less (10-13%) than the estimated uncertainty ranges for the GWP estimates. There is high confidence that the most recently published values (Table 1) reflect our best estimate of the GWP values and recommend their adoption by the global health care greenhouse gas accounting community. At the same token, it should be stressed that use of the previously recommended GWP values in past inhaled anesthetic greenhouse gas analyses do not impart any un-reckoned error, beyond the inherent uncertainties associated with such calculations and use of the GWP metrics. Study comparisons and time series, however, should account for differences in GWP values.

Conclusion

This paper presented an easily accessible assessment of the state of knowledge regarding the climate impact of volatile anesthetics. The atmospheric chemistry of these compounds is well understood, and the GWP values can be used to limit the environmental impact. If possible, the use of desflurane and N_2O should be avoided or limited. There are other ways of limiting the environmental impact, but beyond the scope of this paper. One way is to reduce the fresh gas flow. Another option is the development of technology to capture and destroy the anesthetics in use. There are companies already providing this service. In addition, research is ongoing in this area.

Table 1: Recently published atmospheric parameters for N_2O and halogenated anesthetic gases.

Compound	Atmospheric Lifetime in years	Global Warming Potential, GWP_{100}	(Stratospheric) Ozone Depletion Potential, ODP	References	Estimated Trifluoroacetic Acid (TFA) yield	Global atmospheric mean mole fraction (ppt)
Nitrous Oxide **N_2O**	109	273*	0.015	WMO 2018[1]	0%	332 (2019)[19]
Isoflurane **$CF_3CHClOCHF_2$**	3.2 3.5 3.5	510 490 539*	0.03	Sulbaek Andersen *et al.* 2012[20] WMO 2018[1] *IPCC AR6* 2021[19]	95±5%	.097 (2014)[21]
Desflurane **$CF_3CHFOCHF_2$**	14 14.1 14.1	2540 2300 2590*	0	Sulbaek Andersen *et al.* 2012[20] WMO 2018[1]	< 20%	0.30 (2014)[21]

				IPCC AR6 2021[19]		
Sevoflurane **$(CF_3)_2HCOCFH_2$**	1.1 1.9 1.9 1.4	130 185 195 144*	0	Sulbaek Andersen *et al.* 2012[20] WMO 2018[1] *IPCC AR6* 2021[19] Sulbaek Andersen *et al.* 2021[22]	< 100%	0.13 (2014)[21]
Methoxyflurane **$CH_3OCF_2CHCl_2$**	0.15	4*	n/a	Hass *et al.* 2019[23]	0%	n/a

* *Recommended GWP values*

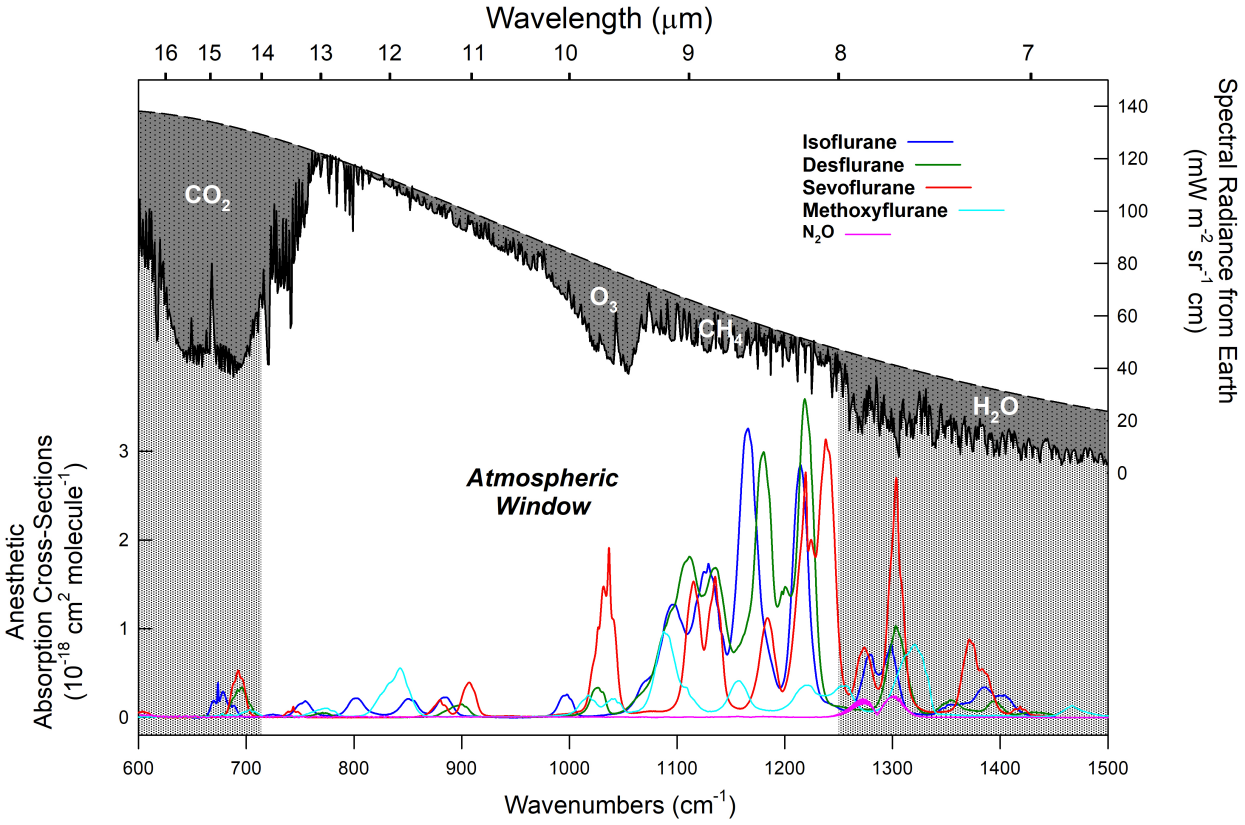

Figure 1. Naturally occurring major greenhouse gases in the atmosphere (CO_2, H_2O, O_3 and CH_4) attenuates the outgoing radiation resulting in a non-ideal Plank curve. IR spectra are shown for isoflurane (blue trace), desflurane (green trace), sevoflurane (red trace), methoxyflurane (cyan trace) and N_2O (pink trace).

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New aspects of the old drug: Intraoperative and postoperative analgesia with systemic Lidocaine

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Summary

Postoperative pain still remains untreated. The common pain treatment with opioids is accompanied with adverse effects like nausea and obstipation. On the other hand, epidural catheter placement is an invasive and expensive procedure.

In recent years, the attention is given to systemic lidocaine in treatment of postoperative pain. The benefits of perioperative and postoperative lidocaine infusion include reductions in pain, nausea, ileus duration, opioid requirement, and length of hospital stay. The non-opioid lidocaine is safe, easy to use and less expensive. The analgesic action of intravenous lidocaine is multifactorial, but still unclear. This mechanism is likely not primarily a sodium channel blockade, but also other effects is described.

More controlled clinical studies with the use of systemic lidocaine in different surgical intervention may bring more relevant information about this analgesic approach.

Keywords: *systemic lidocaine, postoperative pain, efficacy, safety*

Introduction

Postoperative pain still remains untreated and presents the challenge for anesthesiologists and surgeons. Poorly treated postoperative pain has reflection in organ and systems dysfunction, like cardiovascular, pulmonary, gastrointestinal and renal system. The postoperative recovery and discharge are enhancing. The untreated postoperative pain may result in the developing of chronic pain. The time is a key factor in developing a chronic pain after untreated acute pain.

Each year, more than 230 million people undergo surgery worldwide; more than half of them suffer from severe pain after surgery. In 2011, United States Institute of Medicine, reports 80% of patients suffered from postoperative pain, and 88% of them have moderate, severe or extreme pain (1). International Association for the Study of Pain (IASP) is trying to bring together the scientists and clinicians, to share their knowledge and improve global pain management. Each year, they announced global initiatives against the pain. Year 2019 is "Global Year against Pain in the Most Vulnerable", which means pain treatment in elderly, infants and young children, in individuals with cognitive impairments and pain survivors of torture. Year 2017 was global year against pain after surgery (iasp-pain.org).

The first choice is pharmacological treatment of postoperative pain with opioids. Opioid use is accompanied with adverse effects like nausea and obstipation, and respiratory depression, but also the opioid overdose and opioid-related deaths are rising (2). On the other hand, the opioid free analgesia and anesthesia (OFA) has become popular in recent years (3). There are data supporting the multimodal approach of non-opioids: nonsteroidal anti-inflammatory drugs (NSAD), ketamine, magnesium, anti-inflammatory corticosteroids, alpha-2-adrenergic agonists and delta ligands, and intravenous local anesthetics-lidocaine; and the reduced incidence of postsurgical pain.

In this article, we are focused on intravenous use of lidocaine for treatment of acute postoperative pain.

Pharmacologic characteristics of lidocaine

Lidocaine [2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide] is the first modern local anesthetic, prototype of amino amide derivatives. Lidocaine is discovered in 1946 by Löfgren and Lundqvist, and approved for use in humans by the US Food and Drug Administration in 1948 by the trade name Xylocaine (4).

Intravenous lidocaine for postoperative analgesia was applied for the first time in the 1958 (5).

Intravenously administered lidocaine is initially distributed to highly vascularized organs (heart, brain, lungs, and kidneys) than to less vascularized organs (adipose tissue, skin, muscle). Lidocaine has the high volume of distribution and around 60-80% of its molecules are bound to plasma proteins (α 1-acid glycoprotein) (6).

About 90% of lidocaine is metabolized in the liver by the microsomal enzyme system (cytochrome P450). His active metabolites are monoethylglycinexylidide (MEGX) and glycinexylidide (GX). Lidocaine and its metabolites are mainly excreted through the kidneys, while less than 10% is excreted unchanged in the urine. The elimination half-life of lidocaine is between 90 and 120 min in most patients, but may be prolonged in patients with hepatic insufficiency or congestive heart failure (7).

The well-known pharmacological action of lidocaine is the blockade of sodium gated channels in neural tissues, which result with interruption of neuronal transmission (8).

The mechanism of analgesic effect of intravenous lidocaine is still unknown, however multiple mechanisms regarding the site of action have been proposed, such as Na^+ channel blockade, modulation of K^+ and Ca^{2+} channels, blockade of presynaptic dopamine and muscarinic receptors, inhibition of N-methyl-D-aspartate (NMDA) receptors, direct action on the spinal dorsal horn neurons and reduced conduction and excitability of unmyelinated C fibers. It is likely that there is not just one mechanism responsible for lidocaine-mediated antinociception, but a complex synergy of multiple pathways (9).

Despite the anti-nociceptive and anti-hyperalgesic action lidocaine has also antiinflammatory, antimicrobial and anticancer effect. Lidocaine is cardioprotective, neuroprotective and anticonvulsant.

Dosage of intravenous lidocaine

International consensus statement (10) recommended a loading dose of lidocaine no more than 1.5 mg/kg given as an infusion over 10 minute, and continue with infusion of lidocaine, no more than 1.5 mg/kg/h for no longer than 24 hours. All the patients must be closely monitored. If the infusion is extended after 24h, the rate of lidocaine infusion must be reduced to approximately 50%.

Lidocaine is considered to have a greater margin of safety than other local anesthetics. Central nervous system toxicity occurs when plasma levels rich 5μg/ml. When continues infusion of intravenous lidocaine is administered at clinically relevant doses (1–2 mg/kg/h), it usually results in plasma concentrations that remain below 5 μg/ml.

However, many other conditions must be considered to prevent toxicity systemic local anesthetics, such as: the use of other local anesthetics at the same time

or within the period of action. The use of intravenous lidocaine is contraindicated in patients with heart failure, hepatic and renal impairment, and in combination with some antiarrhythmics (e.g. amiodarone, disopyramide, quinidine, sotalol) and beta blockers (11).

Clinicians should be aware of the symptoms of the toxic effect of lidocaine and interlipids should be present in places where intravenous lidocaine is applied (12).

Clinical use of intravenous lidocaine and discution

Nowadays, intravenous lidocaine is used in treatment of postoperative surgical pain, in almost all types of surgeries.

The use of intravenous lidocaine in abdominal surgery is mostly studied and the analgesic effect of lidocaine during perioperative and postoperative pain treatment at these patients are clinically improved. Administrations of systemic lidocaine decrease the incidence of postoperative nausea and vomiting and early recovery of bowel function. The meta-analysis from Marret and colleagues (13) concluded that intravenous lidocaine administration decreased the duration of ileus, length of hospital stay; decrease the postoperative pain intensity and the incidence of nausea and vomiting.

Barral et al. (14) in randomized control study (RCT) analyzed 60 patients underwent major abdominal surgery. Thirty of them received systemic lidocaine during the surgery. The results suggest that perioperative infusion of lidocaine decreases the intensity of postoperative pain, reduces the postoperative analgesic consumption, without significant adverse effects.

The same results were shown after laparoscopic surgery (15).

In orthopedic patients, the effect of intravenous lidocaine has been studied during surgery in patients with bone fractures and total joint arthroplasty.

Forouzaan et al. (16) concluded that the application of intravenous lidocaine, compared to intravenous morphine, was a significantly more effective for pain treatment in patients with bone fractures.

A randomized, double-blind, placebo-controlled study by Sun and colleagues (17) analyzed intravenous administration of lidocaine in patients after total knee arthroplasty, and the conclusion of this research showed that patients in the lidocaine group had lower postoperative pain rates, assessed by the numeric pain scale at rest and during movement, and, also, had a shorter duration of hospitalization.

The latest study by Nallbani et al. (18) analysed 90 patients underwent elective total joint arthroplasty and limb fracture repair. Less postoperative pain during rest and movement and lower rate of additional analgesics were significant in lidocaine group.

There are few studies with intravenous lidocaine in urogenital surgery and cardiothoracic surgery. Perioperative lidocaine infusion was shown to be of benefit in these patients (19, 20).

Intravenous lidocaine as an element of multimodal analgesic therapy is analyzed in major spinal surgery in children. In double blind RCT study 41 children who received lidocaine had improvement of analgesic measures in first 24 hours, and decrease in opioid consumption (21).

In our practice, we started using intravenous lidocaine for pain treatment in perioperative and postoperative period in different surgical interventions. The target groups are neurosurgery and spinal surgery, pediatric surgery and chronic cancer pain patients.

Conclusion

The introduction of intravenous lidocaine presents the revolution in postoperative pain treatment. Systemic lidocaine should be seen as an additional option of analgesia for anesthesiologists. Its administration is lower in cost compared to other medications, also more achievable and clinically safe. Lidocaine is a good alternative to promote efficient analgesia in patients that have any contraindication to neuraxial anesthesia. The effort of elaborating more controlled clinical studies with the use of systemic lidocaine in different surgical intervention may bring more relevant information about this analgesic approach.

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A Possible New Path for Bariatric Surgery Airway Management

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The bariatric surgery airway management has always been a challenge because of the numerous concerns related to limited neck mobility, difficult mask ventilation and potentially difficult intubation.

However, the more experience has been acquired it appears that, with proper preparation and the advent of modern video airway devices the endo tracheal intubation does not seem to be as difficult as previously thought.

The same concern has been kept in mind about the risk of aspiration during the airway management. Yet, the endotracheal intubation is still performed with NDMR and manual ventilation without Sellick maneuver, a basic contradiction.

In fact, more and more literature describe the use of the supraglottic devices (SGD) in bariatric patients without any problems.

The main drawback in using an SGD in this type of surgery was the impossibility of threading a bougie through a dedicated channel to calibrate the gastric cut and/or help with the drainage.

In 2017 a novel SGD appeared: the LMA Gastro. Consisting of a traditional LMA combined with a large bore channel, this device was conceived for gastroscopies and duodenoscopies. At an attentive examination and bench testing it became evident that any device used in the bariatric surgery can be threaded along this channel.

So why not use the device in bariatric surgeries as well?

On the 30th of July 2019 and with the permission of my chief of department and with all the possible and thinkable precautions and back up solutions ready, I used, seemingly for the first time in the world, this device for 5 (FIVE) consecutive bariatric surgeries. Later on I found out that another colleague from Australia (Dr. Adrian Sultana) used the same device, sometimes even in an emergency for about 40 cases, but at the time I did my cases I was not aware of it.

All the surgeries went totally smooth, absolutely no accident, aspiration or need to intubate. The experience was a total surprise for me. The surgeons didn't feel any difference in their operative conditions.

But only 5 cases may seem too little to convince the traditionally risk averse clinicians to start using it. The difficult process of getting the IRB permission to do a larger study is ongoing. It seems that nailed concepts in our brains and fear of medico-legal concerns are stronger deterrent factors than exact pressure measurements.

The airway management with this device, in fact brings another safety layer for the patient as no muscle relaxant is given until there is safe control on the ventilation.

The presentation I'm giving describes the technique used, the screenshots and videos done during these procedures.

As in any medical procedure there may be problems down the road, but with proper preparation the bariatric surgeries can be safely performed with this new device.

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Laparoscopy and Obese Patient – Challenges and Solutions

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According to the WHO obesity is defined as Body Mass Index above 30 kg/m^2. Obesity is further classified as Group 1 (30-34.99 kg/m^2), Group 2 (35-39.99 kg/m^2) and Group 3 (above 40 kg/m^2), also known as morbid obesity.

Obesity is a multisystem, chronic, pro-inflammatory, metabolic disorder. Obesity affects respiratory system and cardio cicylatory system, I following manner: the dysfunction of the respiratory system might be of obstructive or restrictive type. Furthermore, there might be dysfunction of breathing during sleep in a form of obstructive sleep apnea, or obese hypoventilation syndrome.

Dysfunction of the cardio circulatory system in obese patients can be high blood pressure, pulmonary hypertension, arrhythmia and myocardiopathia.

Obesity is associated with metabolic diseases such as diabetes.

Obese patients often suffer from gastro esophageal reflux and are with higher risk of vein thrombembolism.

Obesity has already been proven a risk factor which increases overall perioperative morbidity and mortality due to possible respiratory complications, cardio circulatory complications, thromboembolism and metabolic disturbances. Obesity is associated with excessive metabolically active fat tissue which leads to increased consumption of O_2 and increased production of CO_2.

All of the abovementioned facts pose danger for patient undergoing surgery and anesthesia, and especially so when the surgery is laparoscopic.

Laparoscopic surgery means creating pneumoperitoneum using carbon dioxide under pressure. This type of surgery increases the risk of carbon dioxide absorption and a risk of hypercapnia. When performing anesthesia in obese patients undergoing laparoscopic surgery, there are many considerations: securing airway, avoid reflux and aspiration, maintain mechanical ventilation considering the lung and volume capacities of obese patient; maintain stable haemodynamics, prevent thrombosis and closely monitor the patient for postoperative complications.

The respiratory system is perhaps the most affected system during laparoscopic surgery in obese patients. First step is to secure airway, as these patients might have difficult airway. Preoperative assessment of the airway with standard tests: Mallampati, Upper lip bite test, Thyromental distance.

Then, the anesthesiologist must take into consideration the changes in pulmonary compliance, volumes and capacities. Reduced compliance of the thoracic wall due to deposition of fat tissue in the chest and abdomen.

Reduced pulmonary compliance due to increased pulmonary blood flow and viscosity.

The reduced total pulmonary compliance leads to reduced functional residual capacity (FRC). FRC can drop up to 50 % of the original value before the anesthesia. FRC is responsible for the continuous oxygenation of the pulmonary capillary blood during expirium. Low ERV (Expiratory Reserve Volume) and Low values of the FRC lead to rapid desaturation.

Reduced compliance of the lungs and chest, together with barotraumas during mechanical ventilation, lead to hypoventilation. Increased intra-abdominal pressure and reduced compliance of the chest wall means that there is reduction of the static and dynamic lung volumes. Pneumoperitoneum transfers the pressure to the chest cavity, diaphragm is lifted, lungs are compressed, excursion of the lungs and chest is made more difficult. Thoracic and pulmonary compliances are further reduced Compression of the lungs leads to further reduction of the FRC, and controlled mechanical ventilation is made more difficult during reduced thoracic pulmonary compliance.

Common respiratory complications after laparoscopy are:

- Obstruction of the upper airway
- Moderate hypoxemia (SpO_2 90-93% while recieving O_2 via nasal cannula)
- Severe hypoxemia ($SpO_2$90% while receiving O_2)
- Aspiration following the extubation
- Bronchospasm
- Bronchopneumonia
- Pulmonary thromboembolism
- Atelectasis

Strategies for lung protection during laparoscopic surgery are:

- Preoperative evaluation

Following features may indicate presence of significant underlying respiratory disease and increased anesthetic risk:

- Arterial saturation < 95%
- Forced vital capacity < 3 l or Forced expiratory volume in 1 s < 1.5 l
- Respiratory wheeze at rest
- Serum bicarbonate concentration > 27 mmol
- Arterial PCO_2 > 6 kPa

During the induction and maintenance of anesthesia:

Consider pre oxygenation with trans nasal rapid oxygen insufflation to diminish the risk of micro aspirations and gastric distension.

HELP-head elevated laryngoscopy position

Protective ventilation with low breathing

tidal volumes (6-8 ml/kg PBW)

Plateau pressure ideally bellow 16 cm H_2O

Keep the lungs “open”

Applying PEEP of 5-15 cm H_2O

Noninvasive ventilation in early postoperative period.

Cardio- vascular system and laparoscopy:

Hemodynamic changes due to autonomic response: (general anesthesia, head down position, pneumoperitoneum).

Induction of GA: ↓ heart rate ↓ arterial pressure.

Pneumoperitoneum : ↓ CO

↑ Vasopressin

↑ SVR

Vagal modulation, and sympathetic modulation.

Prevention of venous thromboembolism:

Pharmacological DVT prevention with LMWH (Enoxaparin 0.5 mg BW)

Intermittent pneumatic leg compression. Intermittent pneumatic leg compression improves cerebral oxygenation during laparoscopy.

Conclusion:

Obese patients are at higher risk of developing perioperative and postoperative complications.

In order to avoid, recognize and treat these complications in timely manner, adequate preoperative evaluation, applying protective ventilation strategies, DVT profilaxis and close monitoring of the patient's respiratory status and hemodynamics is recommended.

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Cochlear Implantation – Anesthesia Challenges

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Cochlear implants are an acceptable therapeutic options for the patients with irreversible hearing loss. Congenital hearing loss affects 1 to 3 per 1000 newborns.

The reason for deaf children is deaf-mutizm, and deaf-mutizm could be an isolated non-syndromic sesorineural hearing loss (N-SNHL), if the patient has problem associated only with the vestibulocochlear nerve, or syndromic sensor neural hearing loss, that appears with other medical symptoms, that make a syndrome.

The term syndromic sesorineural hearing loss (SNHL) is used if a patient has hearing loss in addition to other medical abnormalities, like pigments in retina (retinitis pigments' form), abnormal iodine metabolism associated with thyroid goiter (euthyreotic form) or cardiac arrhythmias (cardiac form).

Approximately 80 percent of children with genetic hearing loss have isolated non-syndromic sensor neural hearing loss and 20 percent of children with genetic hearing loss have other associated findings (syndromic sesorineural hearing loss).[1]

Speaking about technical aspects, cochlear implants are extremely expensive computerized electric prostheses that partially replace the functions of the cochlea. The surgery is time consuming and complicated, and the anesthesia technique plays a crucial role in success of cochlear implant surgery.

Preoperative anesthetic evaluation of the patients, no matter if they are pediatric or adult patients, is very important. But, pediatric patients could have various types of unrecognized symptoms, before surgery, that are very important from anesthetic point of view.

University clinic for ear, nose and throat surgery in Skopje, start with cochlear implantation in 2007. Macedonian academy of sciences and arts, medical department, in coordination with our clinic, made a project about inherited deafness, and nowadays we have a map of inherited deafness in Republic of North Macedonia.

Pre-implant preparation of deaf patients requires objective assessment of hearing, magnetic resonance imaging of temporal bone (MRI) or computer tomography (CT) scan of the temporal bones and internal auditory canal. Some of these preparation, like magnetic resonance imaging of temporal bone (MRI), CT scan of the temporal bone and brain evoked response audiometry (BERA) testing requires general anesthesia. Finally, the cochlear implantation surgery technique requires general anesthesia in induced hypotension technique.

Anesthetic considerations include preoperative familiarization with the patient and his/her family. The most common problems that have specific anesthetic significance are: the presence of difficult airway (thyroid goiter or thymus persistence) or cardiac arrhythmias (prolonged QT interval).

The other major problem is hemostasis disturbances (beta thalassemia) that can affect pediatric patients, and adult patients, too.

The implantation surgery is time consuming, approximately 3 or 4 hours, and is performed via a trans-mastoid approach. The operative technique is complicated and necessitates preservation of functional integrity of the facial and cochlear nerve. Electro-surgical instruments like monopolar ones, should not be used once the cochlear implant is in place. Cochlear implants can be damaged by electrical discharge from electrical cautery; hence, cautery was not used once cochlear implant was inserted

Preoperative anesthetic preparation of the patients is very important. In coordination with the pediatricians and audiologist, we have to make a good evaluation of children's medical history to find out the form of hearing loss (syndromic or nonsyndromic sesorineural hearing loss). If the children has syndromic sensor neural hearing loss, additional investigation should be performed for preparation for general anesthesia.

Speaking about the challenges, the first challenge for the anesthesiologist that has to fall asleep the patient in general anesthesia is induced hypotension technique. This technique is required for all the patients scheduled in general anesthesia, no matter they are pediatric or adult patients. The anesthesiologist has to produce condition of bloodless surgical filed, for that purpose. [2, 3]

We are using induced hypotensive general anesthesia technique for pediatric patients. Our goal is to reach 20% lower values of preoperative values of mean arterial pressure – MAP, and maintained the values of MAP during the whole operation. The

goal of induced hypotensive general anesthesia technique for adult patients is to reach 30% lower values of preoperative values of mean arterial pressure – MAP, and maintained the values of MAP during the whole operation.

Second challenge for the anesthesiologist is to facilitate the use of nerve stimulators, that technical support engineer is doing after surgical placement of the electrode of cochlear implant, that has 24 small canal electrodes, and every single one has to be tested before the closure of the operative field. For that purpose we are giving nondepolarizant muscle relaxant only at the beginning of the operation, just for tracheal intubation. Maintenance of general anesthesia is possible with remifentani – sevoflurane or remifentanil, propofol – sevoflurane balanced anesthesia technique.

General anesthesia protocol start with premedication. Pediatric patients were premedicated with solution of midazolam orally, 0.5mg/kg body weight, 20 minutes before departing at the operating theatre. Adult patients were given 7.5mg tablets midazolam, or 5mg diazepam tablet, for the same purpose.

Intravenous premedication at the operating theatre include atropine 0.5 $\mu g.kg^{-1}$ and fentanyl, 0.5 $\mu g.kg^{-1}$.

Anesthetic induction always starts with preoxygenation with 100% oxygen for 3 min. Anesthesia induction was done with propofol 2–3 $mg.kg^{-1}$ intravenous and maintained with end-tidal 1.5 MAC sevoflurane in 2:1 ratio mixture of nitrous oxide and oxygen. Neuromuscular blockade was done with injection rocuronium 0.5 $mg.kg^{-1}$i.v.single dose.

Intubation was done with an appropriate-sized endotracheal tube and checked for bilateral air entry and the tube was secured firmly in place. Attenuation of pressor response of tracheal intubation was done with dexmedetomidine 1 $\mu gm.kg^{-1}$ 10 minutes infusion, just before anesthesia induction, at adult patients, ASA 1 or 2. [4, 5]

All patients were placed in mastoidectomy position, for external, subcutaneous electrode placement. Insertion of internal electrode into a cochleostoma, that has 24 electrodes inside, and everyone has to be tested after the placement, requires the same position of the patient.

Intraoperative blood loss was controlled with technique of mild hypotension. The mean arterial pressure (MAP) was kept around 60 mmHg throughout the surgery. As all patients were below 2.5 up to 5 years of age, warming blankets were used to prevent hypothermia. Facial nerve preservation is important during surgery;

therefore, before the identification via electrical stimulation of facial nerve, the effect of muscle relaxant has to be weaned. Stapedius reflex is very important sign for the surgeon, too.

The third challenge of cochlear implantation surgery and general anesthesia, is to treat troublesome post-operative complications such as nausea, vomiting and vertigo. We manage postoperative nausea and vomiting with ondansetron (0.1 mg/kg intravenously, before the surgery, at adult patients) and dexamethasone (0.15 mg/kg, intravenously, before the surgery, for the pediatric patients).

Postoperative analgesia was treated with paracetamol. Intravenous dose of paracetamol is 7mg/kg for the children up to 35kg weight and 15mg/kg for the children that are more than 35kgs weight, and 1g intraoperative solution of paracetamol, respectively, for the adult patients.

The fourth challenge for this operation is the duration of the surgery.[6] the duration of surgery for cochlear implantation usually is 4 hours, so, adverse events could be seen mostly at younger patients, patients younger than 1 year of age. Our patients were no younger than 2,5 years of age, and we have no complications related with general anesthesia.

There is a study about duration of the surgery that investigate surgical, anesthetic, and device-related complications associated with cochlear implantation (CI) in children younger than 1 year of age.[7] There is a multicenter, retrospective chart review of children with severe-to-profound sensor neural hearing loss, who underwent cochlear implantation with a Cochlear Nucleus Implant System before 1 year of age.

There were no major anesthetic or device-related complications. Adverse events were reported in 34 of implanted ears (14%; 7 major, 27 minor). Sixteen adverse events occurred ≤30 days of surgery, and 18 occurred >30 days of surgery. The 30-day readmission rate was 1.5%. The rate of adverse events did not correlate with preexisting medical comorbidities or duration under anesthesia. There was no significant difference detected in complication rate for patients younger than 9 months of age versus those 9 to 11 months of age. This study demonstrates the safety of cochlear implantation surgery in infants and supports reducing the indication for cochlear implantation to younger than 1 year of age for children with bilateral, profound sensor neural hearing loss obtaining a Cochlear Nucleus Implant System.

Postoperative hemorrhage and cerebrospinal fluid leak or flap necrosis are the most common complications after the cochlear implant surgery.

Where are we now in the story of cochlear implantation?

Cochlear implants are the revolutionary technology that enables deaf children to develop spoken language on par with their normally-hearing peers.[8]

By the end of the year 2021 about 80,000 cochlear implants had been shipped worldwide. In India (1.4 billion population in 2021), 500 cochlear implants are placed in a year.

In Republic of North Macedonia, (2 million population in 2021) 10 - 15 cochlear implants are placed in a year. Patients chosen for these procedure are children under 2.5 years and they have prelingual deafness. They often pose challenges like anxiety, because of the hearing loss.

University clinic for ear, nose and throat surgery in Skopje started with cochlear implantation in 2007. In 25 years, 250 cochlear implantations were performed under general anesthesia. 190 of the patients (76%) were pediatric patients (2-5 years old), and 60 (24%) were adult patients (21-60 years old).

Conclusion

Cochlear implants are extremely complex and costly electronic devices. The anesthesiologist is an integral member of the cochlear implant team whose anesthetic as well as communication skills are put to test. The role of anesthesiologists is crucial for such expensive operations for better outcome. Preoperative preparation and anesthesia technique used for implantation (intraoperative anesthesia management), plays a big role in success of cochlear implant surgery.

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Implementation Of the First Eras Protocol for Caesarean Section and Its Influence On Our Practice

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The idea of a better and faster recovery process after surgery is not new, but its implementation in everyday practice began in the late 1990s in Scandinavian countries by Prof. Kehlet and Wilmore (1). The first data came from colorectal surgeons whose main aim was to return patients to normal life as soon as possible. Before this concept was created, the whole process of preoperative examinations and postoperative fasting had been lengthy, resulting in very slow and exhausting recoveries for the patients.

The whole idea was to prepare the patient for surgery in a shorter period of time, ensuring the best possible physical and mental conditions for the procedure with a short fasting period. This is an excellent example of great teamwork between an anesthesiologist and a surgeon, involving active patient participation for the first time."

The idea of enhanced recovery after surgery (ERAS) has spread to other surgical branches after successful implementation in colorectal surgery. It has been implemented in urology, orthopedic surgery, laparoscopic surgery, pancreatectomy, breast surgery, gynecological oncology, bariatric surgery, esophagectomy, spine surgery, cardiac surgery, thoracic surgery, and head and neck surgery (2-6). The ERAS protocol for Caesarean Section (CS) was one of the last to be implemented in clinical practice.

Influenced by the rapid spread of ERAS programs and protocols and their fantastic results, the ERAS® Study Group was established in European countries (UK and Scandinavian) based on evidence in 2009."

The ERAS® Society was officially registered as a non-profit medical society in Stockholm, Sweden, in 2010. The founding fathers of the ERAS® Society are Ken

Fearon (UK), Olle Ljungqvist, Arthur Revhaug, Maartin von Meyenfeldt, and Cornelius de Jong.

Since then, this society has organized many meetings worldwide, encouraging surgeons in various branches to adopt the ERAS program. At this moment, the ERAS Society has 22 protocols for different types of surgery, each with a multidisciplinary approach.

The first published articles about ERAS in obstetrics were in 2013 (7).

In 2020, the Society for Obstetric Anesthesia and Perinatology (SOAP) published an official statement about the ERAS (ERAC - Enhanced Recovery After Caesarean) protocol, which was the result of the hard work of an entire group of experts (8).

Initially, ERAS was developed in Western countries (UK, Germany, USA), but in the last few years, it has also spread to developing countries such as China, Bhutan, India, and Serbia.

Developing a new protocol is very challenging, and the first step is to form a group of enthusiasts from different fields (anesthesiologists, surgeons/obstetricians, nurses, hospital managers). The most important thing is to find a coordinator. This unique program and protocol vary in every hospital and every country and are tailored for each specific setting. It takes a few months from planning to implementation.

Before creating the protocol, it is very helpful to conduct a pilot survey, then find the team members and start with tailoring (9).

After the creation, the next big step is to present it to the hospital manager and integrate it into the healthcare system.

One of the most important parts is providing written patient information and education. The patient's strong desire to return to normal daily activities and work as soon as possible is a cornerstone of the entire process. The second important aspect is providing written information to other team members involved in the process (surgeons/obstetricians, midwives, post-operative care nurses, pediatricians).

The whole concept is divided into 3 parts: preoperative, intraoperative, and postoperative.

The preoperative task is to prepare the patient for surgery, ensuring the best health, nutritional, and mental conditions. ERAS is not suitable for every patient, and surgeons/obstetricians carefully select these patients. Typically, patients with mild

comorbidities, where serious complications and longer hospital stays are not expected, are chosen. They are the first in line to receive information about the protocol, and randomization is performed

The role of the anesthesiologist is to prepare the patient, explaining what to expect during surgery (CS) and after surgery (pain management), performing surgery under spinal anesthesia, and providing effective postoperative pain relief.

The surgeon/obstetrician employs minimally invasive surgical techniques, avoiding the use of drains and tubes.

Patients are highly motivated to recover quickly and avoid returning to the hospital with complications.

In Serbia, there is only one real ERAS protocol for CS, at UCCV in Gynecology and Obstetrics Hospital in Novi Sad, which was recently published (10).

ERAS influence on everyday practice:

At UCCV in Gynecology and Obstetrics Hospital in Novi Sad, this protocol has improved our practice in many ways. Patients now have a shorter preoperative in-hospital stay (they come to the hospital on the day of CS), a better intraoperative experience, fantastic postoperative pain control, and they start earlier with liquid and solid food intake. On postoperative day 3, they are discharged home. Patient satisfaction is at the highest level. Nurse satisfaction is also high, as they have patients who do not complain and use oral medication instead of intravenous. Hospital management is satisfied because all hospital costs are significantly reduced.

Conclusion: Implementing a new protocol in a developing country is a challenging process, requiring multidisciplinary teamwork. In the ERAS concept, the patient plays a crucial and active role. The implications for everyday work are manifold, with a high level of patient satisfaction being one of the most significant outcomes.

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Enteral Nutrition-Food for Health and Strength

Danijela Jovanović Božinović sc. ph.

Energy and nutrients are important if we want to maintain health and growth. Different medical conditions sometimes require special diets and nutritional support. Impairment of nutrient intake or uptake leads to malnutrition. Malnutrition leads to an abnormal body composition, diminished physical and mental function and impaired clinical outcome of diseases. It increases morbidity, complication and rehospitalization rate, leads to loss of independence, reduced quality of life, higher mortality and higher treatment costs.

Thus, it is important to find patients at risk or malnourished who are in need of nutritional support. First step is screening and then, if necessary, detailed assessment of nutritional status is needed. If the patient is malnourished or at risk, the next step is adequate nutritional intervention. There are different options depending on the patient status. If the professional dietary counseling and diet fortification with natural products are not enough, oral nutritional support (ONS)/sip feeding should normally be recommended to all patients who are malnourished or at risk of malnutrition and who cannot cover their nutritional needs with a normal, balanced diet. Functional GI and swallowing are a must.

When the patient is unable to cover nutrient demands with an oral diet, enteral tube feeding should be applied. If nutritional support is required, but needs cannot be met by enteral route, the option is parenteral nutrition (TPN or SPN).

Adequate nutritional intervention decreases complications and mortality. If we want to achieve positive effects, an appropriate site of feeding within the GI tract and the type of diet is essential. Knowledge of available enteral substrates is important if we want to choose the most appropriate nutritional treatment.

General Characteristics of Enteral Diets

Commercially available formulae for EN include those for tube feeding and the oral nutritional supplements (ONS) which can also be administered by tube if necessary. They are regulated by the **European Commission Directive** 1999/21/EC as "dietary foods for special medical purposes" used for the dietary management of patients under medical supervision.

Their main purpose is to improve patient's total food intake in order to improve clinical outcomes.

Standard enteral formulae have a composition which reflects the ideal values of macro and micronutrients for a healthy population. They are sufficient for the majority of patients, but sometimes, patients have specific requirements.

There are several types of products that can be used for oral and/or tube feeding - adult and pediatric; polymeric, oligomeric and monomeric; standard and disease-specific.

Basic Content of Enteral Nutrition

Enteral nutrition products contain **carbohydrates**, **lipids** and **proteins** from high quality natural products (cows' milk, soy, fish, olives and others) and **vitamins, minerals and trace elements** in sufficient amounts (complete enteral formulas that contain 1500 kcal cover 100% of RDA – with standard ONS usually 1000 ml enough to cover daily requirements).

Whole protein formulae contain milk proteins – casein and soy proteins as **nitrogen source**, while peptide-based formulae contain hydrolysates of soy, lactalbumin, gelatine and/or whey. Elemental formulae contain free amino acids without glutamine.

In standard polymeric formulae, **fat sources** are from sunflower, soy, safflower and corn oils with high amounts of polyunsaturated ω-6 fatty acids. Canola, rapeseed and/or fish oils (source of ω-3 fatty acids) and olive oil (ω-9 monounsaturated) are also included. Can contain coconut oil (MTC). Formulae is nutritionally complete when polyunsaturated fatty acids are added (at least 5% of lipid calories).

Partial enzymatic hydrolysates of corn starch (generally maltodextrins with at least 10 glucose molecules) are most common **carbohydrate** sources in traditional low fibre feeds. Fibre formulas contain fructose oligosaccharides, guar gum and a mixture of cereal fibres. Sucrose in small amounts increases palatability. May contain starch. In elemental formulas, around half of total carbohydrate content are simple sugars.

Enteral diets are safe for patients with lactose intolerance, coeliac disease, hypercholesterolaemia and gout, because they generally do not contain lactose (trace amounts <1g/100 are present in some) cholesterol, purines or gluten in biologically relevant amounts.

Special ingredients like antioxidants, omega-3 fatty acids and PUFAs, α-linoleic acid, nucleotides (in immune-enhancing formulae), glutamine, arginine, vitamins and trace elements like A, D, B6, B12, folic acid, zinc, copper, iron, and manganese can be added. They may potentially improve immune function, inhibit inflammatory processes and reduce oxidative stress.

Types of Nutritional Supplements

There are many commercially available supplements. They have different composition, purpose and the form (liquid, semi-liquid or solid) and can be divided in various ways (nutritionally complete/incomplete, pediatric/adult, ONS/tube feeding, polymeric/oligomeric/ monomeric, etc.)

Nutritionally incomplete oral supplements contain only protein or only carbohydrates, carbohydrates and minerals, only fats or are fat-free formulations, may contain other macro-and micronutrient supplements, only vitamins and/or minerals in the form of pills, powders, drinks, etc. They can't be the only source of nutrition, but addition to the normal, oral diet.

Nutritionally complete formulae can safely be used as the only source of nourishment for prolonged periods. These formulas are balanced in macro and micronutrients content and can be standard and special (for specific diseases). Standard formulas reflect the proportions of the ingredients of a normal oral diet (macro and micronutrients) and under EU law, 1500 kcal of the product must provide 100% of the RDA for vitamins and minerals. They are sufficient for most of the patients. In general, formulae for tube feeding are nutritionally complete and some ONS are not.

There are different types of formulae.

Whole protein, polymeric formulae contain intact proteins, lipids in the form of long chain triglycerides (LCTs) and carbohydrates, commonly as a mixture including maltodextrins and different fibres. Polymeric formulas are usually nutritionally complete diets. Their composition reflects the reference values of macro- and micronutrients in the population. Osmolality is close to physiological (200-350 mosmol/kg). They are indicated in about 90% of patients. According to ESPEN guidelines, standard diets are recommended when patient can't eat or if only enteral nutrition is possible and the tolerance of enteral feeding is good. If there are no contraindications, those diets can be the first choice diets for the in patients in ICU, surgery, oncology, Crohn's disease, acute pancreatitis, liver cirrhosis and alcoholic

steatohepatitis, acute and chronic renal failure renal failure and haemodialysis, HIV, chronic heart failure, and neurological diseases (mainly stroke and motor neurone diseases).

There are different variations of polymeric formulas (normal/high energy, normal/high protein, fibre containing).

"Normal" or "standard" energy formulae contain 0.9-1.2 kcal/ml; high energy formulae are above this, low energy formulae are below.

Standard adult formulae adult contain 15-20% of energy from whole protein, ~30% of energy from lipid (dominantly long-chain triglycerides), 50-55% of energy from carbohydrates (dominantly low glycemic index), 10-20mg/ml fibre (fibre-free options are also available), full amounts of vitamins and trace elements, 85% water, ~1 kcal/ml. They are gluten-free and with minimal lactose.

Children formulas usually contain 10-15% of energy from proteins, 30-50% from lipids 50-60% from carbohydrates (proportion depends on the age of the child), ˜80-90% water and 0,65-1 kcal/ml.

High energy formulae (energy dense diets and high lipid formulae) are modifications of standard formulae (>1.2 kcal/ml). This is achieved by removing water from a standard formula (70-75% vs. 85%), and by a small increase in the lipid fraction (> 30). They are useful when there is a need for fluid restriction (cardiac and renal disease), or in those with electrolyte imbalances and may be suitable for patients with pulmonary disorders and in Cystic Fibrosis because of higher lipid concentration.

High protein diets contain more than 4g/100 ml (20-25% whole protein molecules). They are mainly used for patients in catabolic states in severe malnutrition with coexisting inflammation, increased catabolism and/or loss of protein and problems with wound healing, Crohn's disease, patients on hemodialysis or HIV infection. Patient's renal function needs to be satisfactory.

Fibre-containing formulas contain fibres. Fibres are carbohydrates (components of plant cell walls and plant cells) that reach the colon undigested and are metabolically and energetically available there. The main components of dietary fibre are (according to chemical structure): non–starch polysaccharides, inulin and oligosaccharides, resistant starch and lignin. Fibres can be soluble and insoluble. They have many benefits and some of them include: slow gastric emptying and decrease of appetite (helpful in body weight control). Lowering of the plasma LDL and cholesterol

levels and reducing postprandial blood glucose and insulin responses is helpful in cardiovascular diseases and diabetes. Non-fermentable fibres are effective in prevention of constipation, diverticulosis, even colorectal cancer.

In cases of food allergy, intolerance or absorption disorders, oligomeric or monomeric diets might be necessary.

Oligomeric diets contain oligopeptides (mainly di- and tripeptides, instead of whole proteins), carbohydrates (smaller molecules), and a higher percentage of MCTs as lipid source, which improves digestion and absorption. They are partially "pre-digested" and, theoretically, more easily absorbed than whole protein formulae. They are indicated when whole protein formulae are not tolerated and when capacity for absorption is severely impaired. They can also be useful in the initial phase after prolonged starvation, in selected patients with short bowel syndrome and enterocutaneous fistulae. Jejunal feeding (critical care patients, severe acute pancreatitis) is also indicated. Patients with Crohn's disease related fistulae or radiation enteritis, wasting in HIV patients with diarrhea will use these formulas. Their osmolality is higher (300-600mOsmol/L), so they can sometimes cause osmotic diarrhea.

Free amino acid formulae –elemental, monomeric, low molecular weight and chemically defined formulae – provide nitrogen in the form of single amino acids. Their osmolality is the highest (500-900).

Main indications are: severe malabsorption, congenital metabolic disease and severe allergy to dietary protein and multiple food allergies.

To avoid intolerance of oligomeric, monomeric and high protein diets caused by their higher osmolality, these formulas can be temporarily diluted at the beginning of their administration, with e.g. 0.9% NaCl or 5% glucose.

Disease – Specific Formulas

Disease-specific formulas are modified so they can fulfill the needs of specific groups of patients with special nutritional requirements because of the disease, digestive or metabolic disorder.

They create optimal conditions for treatment, improve nutritional status and decrease complications of the disease. There are different types of formulas, most commonly used are for diabetes, renal failure, cancer, liver failure, disease of the pancreas and biliary tract, respiratory diseases and to prepare the patient for surgery.

Renal formulas

Renal impairment is nutritionally very complex, and when preventing and treating malnutrition it is important to maintain fluid and electrolyte balance, reduce the accumulation of toxic products and minimize blood urea nitrogen. There are several types of formulae used in patients with renal failure.

Standard formulas are suitable for many patients with mild to moderate renal impairment. They are suitable in Acute renal failure, but in case of electrolyte derangements, renal formula is recommended.

If chronic renal failure is conservatively treated in order to preserve renal function**,** standard formulae are used for short term feeding, but for EN > 5 days we use special renal formula, essential amino acids and ketoanalogues in with very low protein formulas.

Different types of formulas are used in patients in the pre- dialysis period and for patients on dialysis.

Formulae for pre-dialysis period are high energy (1.3-2 kcal/ml) with reduced protein content (6-10% of energy sources, 2-5g/100ml). Energy is from fats and carbohydrates, both at about 45%. Proteins are of high biological value, with all the essential amino acids. Part of the fat is provided as MCT. The mineral content, (eg Na, K, Cl, Ca, P, Mg) is limited. Additionally, it contains carotenoids, L-carnitine, and taurine.

In CRF during hemodialysis we use Dialytic formulae. These patients have increased energy and protein demand (>1.7g/kg/d) because of the huge protein losses during hemodialysis and peritoneal dialysis. "Dialytic formulas" are high in energy (1,5-2 kcal/ml) and have high protein content (oligopeptides and free amino acids) - 7.5-8.1 g/100ml. 15-18% energy is from protein and the remaining energy is from carbohydrate and fat, relatively equally distributed (40-45% each). They can contain histidine, taurine, tyrosine and carnitine, and the amount of potassium and phosphate is reduced.

Pulmonary formulas are usually low carbohydrate, high fat formulae. Standard feeds can be used in acute or chronic respiratory disease. For type 2 respiratory failure special formulas that contain a higher proportion of energy from fat are better options. In acute respiratory distress and critical care according to ESPEN guidance on Critical Care Nutrition there is no need for a special formula. If acute respiratory distress is

associated with carbon dioxide retention, immune modifying formulae can have an advantage. In stable chronic obstructive pulmonary disease, according to current ESPEN guidelines, pulmonary formulae don't have additional advantages, compared to standard, high protein or high energy feeds.

Ketogenic formulas are used for ketogenic diets. Their function is to create conditions which simulate the body's response to starvation, where fat is the primary source of energy, so they contain minimal amounts of carbohydrate and protein and increased amounts of fat.

Diabetes formulas are used for patients with diabetes. "**Classical"** diabetes formulae are similar to standard diet with fibers and they are used in uncomplicated diabetes mellitus. The content of polysaccharides (carbohydrate around 35% of the energy provision) and soluble and insoluble dietary fibre (soya, tapioca) is higher. They can be isocaloric and hypercaloric. Sucrose is replaced by sweeteners: acesulfame K, sodium saccharins, fructose. Fibres (average content 6 types) have many beneficial effects in diabetic patients. Some fibres can reduce insulin sensitivity. Also, they can delay gastric emptying and bowel transit, reduce glucose diffusion through unstirred water layer and accessibility of α-amylase –all these actions modulate response to glucose.

In high MUFA diabetes formulae, polymeric formulae are adapted to contain a higher total amount of fat (up to 35% of energy in the form of mono-unsaturated fatty acids -MUFA) and less carbohydrate. Fibre is also added. They are standard for tube feeding in the sick and hyperglycemic patient.

Formulae for Patients with liver disease contain higher (2-3 times more) proportions of branched-chain amino acids valine, leucine, isoleucine and lower levels of aromatic amino acids and methionine than standard formulae. They are usually whole protein diets with a high lipid content, low in sodium but high in energy (typically 1.3 kcal/ml), because patients are often catabolic and in need of fluid restriction. The overall content of protein is normal (average of 12% of energy from protein), normally without fibre. These formulas also contain 6-10-times more MCT, which helps to reduce the absorption of LCT and perhaps also cholestasis. According to the ESPEN guidelines for liver disease nutrition, these formulas are indicated in patients with encephalopathy, in alcoholic steatohepatitis, decompensated cirrhosis and in some postoperative patients. In patients with **acute hepatic failure** according to ESPEN, it is recommended to use standard polymeric feed.

Most patients with **Neurological Disease** can use **standard formulas**, but in some conditions (acute head injury) energy demand is sometimes higher than 40 kcal/kg per day. In motor neurone disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease and multiple sclerosis the focus is on safe and effective administration, not on specific nutrients. When artificial nutrition is needed after a stroke, the use of high energy, high protein preparations is recommended.

Immune-modulating formulae contain glutamine, arginine, ω3-fatty acids, nucleotides and antioxidants, individually or in combination, in supraphysiological amounts, with the intention of improving the immune response to metabolic stresses such as: trauma, infections, mild sepsis, burns, surgery, radio- or chemotherapy, surgery for abdominal and oesophageal cancer, head, neck, ARDS, pressure sores. They are contraindicated in severe sepsis (increased mortality).

Formulae for oncological patients have high energy and protein content in low volumes (125-150ml) and can affect anorexia and tumor-related catabolism. They contain additional components, such as antioxidants (carotenoids and selenium), omega-3 fatty acids, EPA, DHA or MCT, prebiotics and fibre.

ONS for pancreatic and biliary tract diseases are generally incomplete ONS, that contain whole or pre-digested protein source (whey protein or hydrolysate or short peptides from peas) and carbohydrate source is mainly maltodextrin. They are fibre and fat-free, with an energy content of 0.6-1.5 kcal/ml. Indications are chronic pancreatitis and cholelithiasis, some types of malabsorption in short bowel, Crohn's disease, chemotherapy and/or radiotherapy.

Preparing the patient for surgery

Fasting before surgery is unnecessary and it is now recommended that patients are nourished actively. As a part of ERAS procedures, it is recommended to use low caloric (0.5 kcal/ml), low osmolality carbohydrate drinks with additional electrolytes. This procedure is safe, it reduces insulin resistance and catabolic reaction after surgery and length of stay in the hospital is shortened. The patient is less hungry, thirsty, and doesn't feel nausea and anxiety. Suitable formulas are most effectively used 800ml in the evening before surgery and 400ml in the morning of the surgery.

Conclusion

Malnutrition is a major health problem, so it is crucial to assess nutritional status and identify patients who are at risk or malnourished. If the patient can swallow and

when oral feeding is possible, use of ONS is recommended until the patient starts with adequate oral food intake. When nutritional needs cannot be met with oral diet (including oral supplements) enteral tube feeding is indicated. It is important to know the patient's state and characteristics of the available products in order to choose the best option for the patient.

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Management of Brain-Dead Donor for Organ Transplantation

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Introduction

Organ and tissue transplantation is one of the most advanced medical treatment methods. For patients with end stage chronic organ failure, transplantation is the only option for survival. Only in the case of kidney failure there is an alternative treatment (dialysis). Demand for organ transplantation is increasing all over the world, but there are not enough organs available to meet the need. This shortage of organs is now the limiting factor in treating many patients with end-stage chronic organ failure and has led to high numbers of patients on waiting lists. In Europe, in the year 2021, 36,000 patients received transplants, and 41,000 new patients were registered on waiting lists, which means nearly 5 patients were added to a transplant waiting list every hour. In Slovenia, about 120 organs are transplanted every year, and about 200 patients are registered on waiting lists[1]. In order to improve healthcare services and provide a better quality of life, the use of donor grafts (DG) seems to be the best possible alternative option nowadays. For this cause, many donor-transplantation centers have established a legal network for sharing their results, experiences, and protocols. The early identification of a potential donors plays a crucial role. A potential organ donor is defined by the presence of either brain death or a irreversible brain injury that leads to fulfilling the brain death criteria[2]. Brain death is defined as the irreversible loss of all brain functions, including the brain stem[2]. Brain death must be confirmed with a clinical examination and with instrumental methods such as an electroencephalogram (EEG), somatosensory (SEP) and motor (MEP) evoked potentials, transcranial Doppler ultrasonography (TCD) and cerebral scintigraphy. However, cerebral angiography is considered the most sensitive confirmatory test in the determination of brain death.

When determining brain death, additional causes that could affect the clinical picture of the non-responsive apneic coma in the patient must be excluded. These causes include alcohol intoxication, toxic effects of drugs (hypnotics, sedatives, neuroleptics, and relaxants), endocrine and metabolic coma, circulatory shock, severe

primary hypothermia, and other causes of deafferentation (encephalitis or vascular defects of the brain stem)[1].

After brain death has been proven, a conversation is held with the relatives of the deceased to discuss organ donation[1].

Since confirming the diagnosis until organ explantation, all forms of aggressive and intensive care treatment are mandatory. Strict organ-protective intensive care of the potential organ donor is therefore the first step towards a successful transplant and in the treatment of the future organ recipient. Several pathophysiological changes in brain-dead subjects are shown to have a huge impact on transplantation outcomes. The central sympatho-adrenergic regulation of circulation and the pituitary temperature regulation are disrupted during development of irreversible loss of brain function. There is an interruption in hypothalamic-pituitary-adrenocortical regulation. The rising ICP results in a massive release of proinflammatory and anti-inflammatory cytokines as well as catecholamines. Brain death results in the loss of central regulatory mechanisms, which leads to several pathophysiological changes in hemodynamics, hormone balance, body temperature, and lung function[2].

Cardiovasculare changes: Hemodynamic instability in brain-dead donors is a very frequent condition mainly caused by increasing intracranial pressure (ICP) and developing Cushing reflex as response due to progressive brainstem ischemia. With increasing ICP, there is compensatory arterial hypertension, perhaps associated with bradycardia. As brain damage progresses and ICP rises to the point where cerebral perfusion is impaired, progressive ischemic damage through the entire brain and brain stem will cause hypothalamic activation of the autonomic system (so-called catecholamine storm), leading to further central redistribution of blood volume, increased afterload and visceral ischemia. This is characterized by a systemic stress response with increase in circulating catecholamines. Hemodynamic repercussions is activation of alpha-1-adrenergic receptors that causes vasoconstriction and increased arterial blood pressure (first phase of the Cushing reflex). The circulating high levels of catecholamines can lead to increased oxygen consumption, myocardial ischemia arrhythmias and cardiac injury (Takutsubo) The severity of changes depends in part on the speed of onset of brain death. Slower increases in ICP resulted in lesser increases in catecholamine concentrations and a lower incidence of myocardial ischaemic damage. However, evidence showed that myocardial ischemia is detected in 20-25%, and echocardiographic evidence of myocardial dysfunction is seen in 40% of brain-dead donors being considered for heart donation. After the catecholamine

storm, there is a loss of sympathetic tone. As a result of activation of baroreceptors in the aortic arch and damage to brain stem vasomotor nuclei with loss of peripheral vascular tone, parasympathetic activation leads to hypotension, reduced cardiac contractility, and bradycardia (second phase of the Cushing reflex). The resulting hypotension, if untreated, leads to hypoperfusion of all organs, including the heart, and may contribute to rapid donor loss[2].

Respiratory changes: As irreversible brain ischemia causes changes in the cardiovascular system, similar changes are seen in the lungs of a brain-dead person. Neurogenic pulmonary edema (NPE) and inflammatory acute lung injury are the two main factors related to brain-death-induced lung injury and dysfunction. The NPE is related to a catecholamine storm caused by hemodynamic and sympathetic mechanisms. The catecholamine storm leads to systemic vasoconstriction and an increase in cardiac afterload, thus increasing left ventricle and left atrial pressures. The blood is shifted from the periphery to the central compartment, causing an increase in both pulmonary blood volume and pulmonary artery pressure. Increased left atrial and pulmonary artery pressures may lead to a massive increase in pulmonary capillary pressure and pulmonary edema. This elevated hydrostatic pressure would ultimately lead to structural damage to the capillary endothelium. Proinflammatory mediators that are released following brain death may further contribute toward lung injury by promoting infiltration of activated neutrophils into the lungs. Other contributing factors for lung dysfunction include chest trauma, aspiration, and atelectasis. Long-term dependency on mechanical ventilation also creates a predisposition toward nosocomial chest infections[2].

Endocrine changes: Brain death may cause significant endocrine changes that vary in timing and severity, resulting in anterior and posterior pituitary failure. Posterior pituitary function is very commonly lost, leading to diabetes insipidus(DI) followed by electrolyte loss, hypovolemia, and hemodynamic instability due to polyuria. This is usually followed by decreased thyroid-stimulating hormone secretion resulting in a rapid decline in the level of free triiodothyronine. Thyroid failure causes depletion of high-energy phosphates and impairs cardiac contractility, favours anaerobic metabolism, and results in an increase in lactate. Hyperglycemia is a very frequent endocrine disorder due to reduced insulin concentration and insulin resistance, which is further exacerbated by the release of epinephrine, exogenous steroid administration, or infusion of dextrose-containing solutions. Finally, donor stress responses are blunted due to the adrenal insufficiency that is often seen in brain

death, and decreased levels of cortisol and adrenocorticotropic hormone contribute to hypotension and cardiovascular instability in these patients. Anterior pituitary function may be preserved or only partially affected perhaps because of preserved pituitary blood flow[2].

Hematologic changes: In brain-dead patients, anemia is a common finding, especially if traumatic injury appears to be the cause of death. Moreover, fluid administration and coagulopathy are more likely to worsen the condition due to the presence of tissue thromboplastin and plasminogen activators released from the necrotic brain, leading to disseminated intravascular coagulopathy(DIC)[2].

Thermoregulation: Hypothermia is commonly present in organ donors due to the dysfunction of the thermoregulatory control. Once it develops, it may directly affect cardiac function, induce arrhythmias, and trigger coagulation cascades[2].

Management of organ donors:

General principles: Managing a brain-dead donor requires supportive nursing and medical care and therapy until organ retrieval. However, maintaining optimal hemodynamics and organ perfusion is necessary for long-term graft survival. Monitoring required to optimize the number and function of transplanted organs consists of the usual hemodynamic and respiratory monitoring for critically ill patients. This includes continuous monitoring of temperature, blood pressure (BP), heart rate (HR) and rhythm, oxygen saturation, and urine output. Invasive monitors such as arterial lines and central venous catheters are often utilized for continuous invasive blood pressure (IBP), monitoring and assessment of pulse pressure variation (PPV) and/or systolic pressure variation (SPV) and central venous pressure (CVP) to optimize volume status. The echocardiogram provides information about ventricular contractility, interventricular septum thickness, inferior vena cava compressibility, the presence of an intracardiac shunt, valve disease, and, with the use of Doppler, the flow velocity of the anterior descending coronary artery. They can be particularly important for donors with coronary disease risk factors.

Cardiovascular principles and fluid menagment: Goals for the management of hemodynamic status in donors are as follows: **1.** to maintain normovolemia; **2.** to control blood pressure (BP); **3.** to optimize cardiac output (CO) to maintain perfusion pressure of all organs; **4.** to minimize use of vasoactive agents. Cardiovascular goals for potential organ donors are: HR 60–120 beats/min, Arterial systolic pressure ≥100 mm Hg, Mean arterial pressure(MAP) ≥70 mm Hg, CVP 6–10 mm Hg, Urine output

1-3 ml/kg/hr. **Hypertension**: Anti-hypertensive drugs are typically not required after brain death due to the transient nature of the autonomic storm. If necessary, short-acting antihypertensive drugs, such as esmolol, sodium nitroprusside, hydralazine, labetalol, or nitroglycerine, are preferred as long- term use of anti-hypertensive drugs are usually not required. **Hypotension**: Systemic hypotension is very common in brain-dead donors and may occur in up to 97% of cases. Signs of continuing hemorrhage (external, gastrointestinal, urinary, abdominal etc.) should be checked. Three management strategies are commonly adopted. These strategies include volume expansion, vasopressors and inotropes, and hormonal replacement. **Flud:** the decision for fluid selection should be considered based on serum electrolytes, sugar levels, hemodynamics of the patient estimated volume deficiency, and polyuria from diabetes insipidus (DI). The recommendations are as follows **1.** Crystalloids with balanced salt content should be used to avoid hypernatremia (concurrent DI). Lactated Ringer's solution, Hartmann's solution, Plasmalyte, and halfnormal saline (0.45%) are frequently used ; **2.** Colloids, such as hydroxyethyl starches, need to be avoided in organ donors as they can damage renal epithelial cells and cause early graft dysfunction in the transplanted kidneys; **3.** Albumin solutions (4% and 20%) can be used to reduce the amount of fluid volume administered. **Vasoactive agents**: Patients require additional vasoactive agents when adequate fluid resuscitation is not sufficient to restore BP and CO. It has been estimated that approximately 80%–90% of donors require inotropic and/or vasopressor support. Depending on local practices and protocols, noradrenaline, adrenaline, vasopressin, dopamine, and/or dobutamine are commonly used solely or in combination. High doses of catecholamines (e.g. norepinephrine >0,05mcg/kg/min) should be avoided if possible. Vasopressin in doses of 0.5-4 IU/h is highly effective in managing DI and reduces the hemodynamic need for using different catecholamines. **Combined hormonal therapy**: Although "triple-therapy", the combination methylprednisolone, vasopressin, and triiodothyronine (T3) remains controversial, some studies have reported that it may improve both hemodynamic stability in brain-dead patients, as well as the quality of the procured organs. Combined hormonal therapy is particularly indicated in patients in which volume loading and vasoactive medications have not produced hemodynamic stability. **Treatment of tachyarrhythmia:** Standard therapies, such as amiodarone or cardioversion, can be used to treat arrhythmias While atropine is not useful in the management of bradycardia, adrenaline, isoprenaline, or pacing, may be effective in such cases[2,3].

Ventilation The goals of mechanical ventilation are to maintain tissue oxygenation and protect the lungs for transplantation. Lung protective ventilation includes low tidal volumes of 6 to 8 mL/kg of predicted body weight, **1.** peak airway pressure: <40 cmH2O; **2.** plateau airway pressure: < 35 cmH2O; **3.** fraction of inspired oxygen (FiO2): lowest possible to maintain peripheral arterial oxygen saturation (SpO2) > 92% and PaO2>80 mmHg; **4.** PEEP: 5-10 cmH2O, adjust to maintain PaO2>80 mmHg; Optimizing fluid therapy. The goal is a negative fluid balance if the donor is hemodynamically stable and CVP < 8mmHg for lung transplantation. Re-recruitment is particularly important after tracheal suction or after apnoea testing[2,3].

Renal function: Management of the donor includes optimized hemodynamics, fluid resuscitation, normalized electrolytes, and adequate urine output of 1–3 ml/kg. Renal management should be achieved by appropriate fluid management and judicial use of vasopressor drugs. Dopamine has no significant renal protective effect on renal function in the critically ill and can be deleterious in donors if fluid management is inadequate but might have beneficial effects in renal transplantation. The mechanism here could be related to moderation of preservation injury and inflammation, donor cardiovascular effects ,or recipient treatment[2].

Endocrine Management: Positive effects on the routine administration of thyroid hormones as a part of the brain-dead organ donor management protocol have not been reported in many studies. Although T3 levels decrease in roughly 75% of patients, very few brain-dead donor patients actually reach significantly lowT3 levels, while free T4, conversely, seems to be less affected with only one-third presenting subnormal values. Actually, abnormal thyroid function values seen after brain death are more consistent with “sick euthyroid syndrome” rather than true hypothyroidism.Routine replacement of thyroid hormones is not recommended for all organ donors. Some guidelines suggest thyroid hormone supplementation only if impaired cardiac performance is documented despite overall good general management. Only patients with true hypothyroidism will actually benefit from thyroid hormone replacement[2,3].

Corticosteroids : High doses of corticosteroids may reduce brain death-induced inflammation and help to modulate immune function, thus improving donor organ quality and post-transplant graft-function. Therefore, treating brain-dead donors with corticosteroids is often recommended. The main purpose of using corticosteroids is not to treat adrenocortical failure, but rather to attenuate the immune responses and reduce the catecholamine requirement for maintaining BP[2,3].

Insulin: Major hormonal alterations caused by brain death may result in insulin resistance and gluconeogenesis. Moreover, the practice of administering solutions containing dextrose and the use of corticosteroids may further worsen glucose homeostasis . Hyperglycemia is closely associated with reduced host immune responses that result in an increased risk of infection, worsening of renal function in renal transplant recipients, as well as osmotic diuresis. It is generally accepted that uncontrolled hyperglycemia should be treated and deceased hyperglycemic organ donors should be treated as other critically ill patients[2]. Blood glucose should be maintained < 150mg/dL (8,3mmol/L)[2,3].

Anti-diuretic hormone: If the patient develops DI, electrolytes should be monitored frequently and corrected accordingly. If left untreated this may result in hypovolemia, hyperosmolality, hypernatremia, hypermagnesemia, hypokalemia, hypophosphatemia, and hypocalcemia.Intravenous (IV) fluids should be given to replace fluid loss through urine and a balanced salt solution or fluids with low-sodium content (5% dextrose or 0.45% saline) should be used to maintain sodium levels between 135 and 145 mEq/L. DI can be treated by replacement of fluid with adequate crystalloid solutions and by administration of desmopressin. Vasopressin can also be used as an alternative to desmopressin[2,3].

Hematological Management: Anemia: The most likely causes of anemia during donor care manage- ment are continued blood loss or excessive blood draws per formed for laboratory testing, with hemolysis very unlikely to occur. The target is to maintain the hematocrit (Hct) above 30% and hemoglobin(Hb)>90-100g/L. If the Hct drops below 30%, red blood cells (RBC) should be transfused rapidly. Hct levels should be reassessed 1 hour after every RBC infusion, with repeated transfusion necessary if Hct levels remain below 30%[2,3].

Coagulopathy: Coagulopathy should be treated promptly with management including the administration of red blood cells, clotting factors, and platelets. However, the transfusion of blood or blood products should be given only when necessary The goals are as follows: thrombocytes >50x109/L, fibrinogen>1g/L, prothrombin time (PT) <1,5, activated Partial Thromboplastin Clotting Time(aPTT)<36[2,3].

Infectious Disease Protection: The diagnosis of sepsis may be difficult in brain death as elevated leukocyte count and tachycardia are non-specific for infectious processes. Additionally, fever may not be clinically evident in some patients due to

hypothalamic dysfunction. Antimicrobial therapy should be given based on the results of gram staining or cultures; empirical therapy can be started if recommended by the transplant team to treat suspected pathogens causing infection[2].

Hypothermia: Maintaining core temperature >35°C with active warming/reduce heat loss. Hypothermia is aimed to be prevented rather than treated. Active warming can be achieved using warm blankets, fluid warmers, and heated humidifiers in ventilator circuits administration of warm IV fluids and by adjusting the ambient temperature[2,3].

Conclusion

1. Early identification and accurate management of a potential organ donor are the foundations of good practice in transplantation medicine;
2. Adequate support immediately before and after the onset of brain death can increase the number of actual donors as well as the rate of transplanted organs per donor and improve the quality of the transplanted organs;
3. Discussion with families and reducing refusal of relatives;
4. Implementation of donor management protocols.

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Neuromonitoring in Carotid Surgery - Is the Awake Patient Still the Gold Standard?

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Introduction

A key moment in the development of carotid surgery involved the violation of one dogma - that brain perfusion should not be interrupted for more than three minutes, because after that period irreversible damage to neurons occurs. In order to perform the reconstruction of the carotid artery, the blood flow through it must be temporarily stopped. This fact raises several important questions: Can the brain withstand temporary ischemia without functional and structural lesions? Can this ischemia be reduced, abolished, or mitigate its consequences?

Today, various methods and techniques for identifying brain hypoperfusion and neurological status during carotid endarterectomy are in use, but testing the awake patient seems to be the simplest and most reliable, and it represents the "gold standard" in carotid surgery. Cerebral ischemia leads to varying degrees of disturbances of consciousness and motor function failures. It is important to carry out neurological testing even after the clamping period, because neurological complications can occur an hour after the clamp is released from the common carotid artery. It is important to note that there are conditions and situations when clear communication with the patient is impossible, such as a previous stroke with consequent dysarthria, dysphasia, deafness, and the use of a "foreign language" by the patient or doctor, i.e. not all patients are suitable for this type of treatment. neurological monitoring.

Assessment of neurological status and cerebral perfusion

With the development of vascular surgery, various techniques have been applied throughout history to make the operation safer: systemic hypothermia, arterial

hypertension, hypercarbia, hypocarbia, but mostly without significant results. More significant progress was achieved with the application of extraluminal protective shunt (*Cooley*, 1956)[1] and intraluminal protective shunt (*Javid, Thompson*, 1961). Today, according to the use of the shunt, surgeons can be divided into those who never use it, those who use it selectively, and those who always use it. Even the installation of a temporary shunt is not completely safe for the patient, because it can lead to air embolism, microthrombosis of parts of the plaque, dissection of the internal carotid artery.

There are numerous methods and ways to assess cerebral flow, as well as brain functions, during procedures on the carotid blood vessels. The most basic are: intraoperative neurological status of the patient, retrograde bleeding and pressure, electroencephalogram (EEG), somatosensory evoked potentials (SSEP), transcranial Doppler, cerebral oximetry.

Neurological status can be assessed intraoperatively, only if the patient is under regional anesthesia. Regional anesthesia certainly represents the best intraoperative monitoring of cerebral flow, however, during such an operation there is a special stress in the awake patient. Excessive secretion of catecholamines, and their repercussions on the cardiovascular system, can do more harm than good.

Electroencephalography (EEG)

Through continuous intraoperative electroencephalogram monitoring, we indirectly obtain information about the impact of ischemia on cerebral circulation, especially during the period of carotid blood vessel clamping. If significant changes in electrical activity are registered, placement of a shunt is indicated, especially if the registered changes do not resolve with drug therapy (pressure raising, anti-edematous therapy).

Electroencephalography (EEG) is an indirect method of measuring cerebral blood flow. As a method, it is quite frequent, easy to use, although with limited sensitivity and specificity (69%: 89% *Evans*, 73%: 92% *Stoughton)*. [2,3] . EEG interpretation requires the presence of a neurologist, the detection of ischemia can be "delayed" by up to three minutes, and it is subject to the effects of diathermy, hypotension, general anesthetics, previous strokes. The detection of ischemia by EEG is related to the most superficial layers of the cortex, while it does not provide information about the subcortical layers.

Somatosensory evoked potentials (SSEP)

SSEP give us information about the functional integrity of the brain stem, that is, they represent the reaction of the brain stem to peripheral stimuli. Most often, the median nerve is stimulated in the area of the wrist, and the reaction of the brain stem is assessed based on changes in electrical activity. A decrease in cerebral flow after clamping the carotid arteries can cause changes in the electrical activity of the brainstem. The somatosensory evoked potential changes when the regional flow is less than 18 ml/100g. of brain tissue per minute. Therefore, SSEP may be a good indicator for the use of a shunt during carotid endarterectomy.

Somatosensory evoked potentials (SSEP) in Horst's study had a sensitivity of 60% and a specificity of 100% [4]. In *Lam's* study (comparison of EEG and SSEP), the sensitivity and specificity of EEG were 50% and 92%, respectively, 100% and 94% for SSEP [5]. A recent study by *Rowed* indicates the absence of false positive and false negative results when using SSEP. Evoked potentials have the ability to detect ischemia in subcortical zones, but this ability is weaker for the cortex compared to EEG. Ischemic episodes occurring outside the "zone" of the middle cerebral artery are difficult to detect with SSEP [6].

Transcranial Doppler ultrasound (TCD)

Intraoperative monitoring of cerebral perfusion with transcranial Doppler enables the detection of intraoperative (micro) embolism during dissection, clamping and de-clamping, changes in the degree of flow during clamping, and the degree of brain reperfusion compared to initial values. By using doppler, we have the possibility of measuring the flow before and after clamping the carotid arteries, as well as detecting embolic episodes. Morphological and hemodynamic flow parameters through the anterior, middle and posterior cerebral arteries [7] are usually monitored.

Transcranial Doppler ultrasound (TCD) has been introduced into clinical practice as a modality for monitoring ipsilateral flow through the middle cerebral artery (VMCAi) during carotid endarterectomy. Its use enables continuous monitoring of blood flow, as well as embolic complications, and the identification of patients at risk of hyperperfusion syndrome after endarterectomy. An analysis of the literature leads to contradictory results about the possibilities of TCD in the detection of ischemia, often due to differently designed studies that are difficult to compare. McCarthy in a prospective study from 2001 found that VMCi < 30 cm/s, clamp/preclamp ratio < 0.6, and VMCi reduction > 50% have sensitivity, specificity, positive predictive value and negative predictive value of 92%, 49%, 19% and 98% for

the first parameter, 92%, 75%, 33% and 99% for the second parameter, and 8 3%, 77%, 32% and 97% for the third parameter, and concluded that TCD is not a reliable method for determining the need for an intraoperative shunt [8]. *Horn* in his multicenter retrospective study on the detection of microembolic signals (MES) postoperatively by means of TCD (> 8 MES /h) supports the reliability of this method [9].

Retrograde "stump" pressure

Measurement of retrograde "stump" pressure can give us useful information, but even today there is no clear consensus on the values below which the use of a shunt is indicated. It is performed by puncturing the common carotid artery after clamping part of the common and external carotid arteries. In addition to the value of retrograde pressure, other parameters are also used that are calculated from it, namely cerebral perfusion pressure and collateral hemispheric vascular resistance. The value of cerebral perfusion pressure above which intraluminal shunt should not be used is 18 mm Hg. There is no clear common position for retrograde pressure values (20, 50, 70 mmHg), so this parameter cannot be considered reliable for the use of a shunt. The use of the BIS index (bispectral index monitoring system) is indicated in cases performed under general anesthesia, because the BIS monitor is primarily designed to monitor the depth of general anesthesia, and how much useful information it can provide us about cerebral flow deserves further research [10] .

Carotid "stump" pressure (SP) in the *Whittly* study values below 50 mmHg is generally accepted as the limit for selective use of shunt in operations under general anesthesia [11]. *Calligaro* finds the lower limit to be 40 mmHg with a false negative rate of 1% [12] . These results must be viewed critically, because blood pressure depends on flow and resistance, so it can be high with poor cerebral flow (high resistance) or low with good cerebral flow (false positive) in loss of vascular resistance.

Cerebral oximetry (rSO2)

rSO2 in a clinical study by Rigamonti et al. on 50 patients undergoing carotid endarterectomy under block anesthesia had a sensitivity and specificity of 44% and 82% with a 15% reduction in oximetry. The author concludes that the method is simple, non-invasive, with clinical correlations with EEG findings, but low sensitivity and specificity 13. The data correlates with the Samar study, which found high negative but low positive predictive values 14 .

Medical protection of the brain intraoperatively is reduced to the intravenous administration of fluids (crystalloids/colloids), in order to maintain optimal blood

pressure, i.e. good perfusion pressure through the cerebral circulation, with the use of vasopressors (ephedrine, phenylephrine), or vasodilators (Na nitroprusside, Urapidil), with the same goal, and the use of hyperosmolar solutions (mannitol 20%), in order to prevent brain edema.

Conjunctival oxygen pressure (pcjO2)

pcjO2 has resulted in poor correlation with cerebral oxygenation in animal studies. Michell's study confirmed the low sensitivity and specificity of this method [15]. Jugular venous saturation (SjO2) does not have high sensitivity or specificity due to the fact that venous blood from different areas of the brain returns to the jugular venous vessels. The use of xenon has two important limiting factors, namely the complicated routine use and the discontinuity in the measured values.

Anesthesiological techniques in carotid endarterectomy

Anesthesiological goals in carotid endarterectomy include protection of the brain and heart from ischemic damage, control of heart rate and blood pressure, safe airway, and absence of patient pain. These goals should be met while keeping in mind one goal from the "second plan", no less important, which is to have an alert and cooperative patient (at least at the end of the operation), for the much-needed neurological evaluation. The importance of a preoperative visit should be emphasized, with a detailed understanding of the patient's complete health condition, with special emphasis on the cardiovascular system, which includes a series of repeated measurements of blood pressure and frequency, with the aim of determining the acceptable range of these parameters intra and postoperatively. It is recommended not to allow discontinuity of current cardiac and antiplatelet therapy perioperatively. On the day of surgery, the patient should be relaxed, cooperative and calm, because anxiety and fear are closely related to the uncontrolled reaction of the cardiovascular system (increase in blood pressure and pulse), i.e. increase in oxygen consumption in the myocardium, which directly correlates with the frequency of intraoperative incidents. Carotid endarterectomy is traditionally performed under general endotracheal anesthesia. In the last decade of the last century, increased interest in carotid endarterectomies under regional anesthesia developed. The choice of anesthetic technique is still debatable.

General endotracheal anesthesia in carotid surgery has some advantages: reduced metabolic activity of the brain with better protection in case of short-term

ischemia, greater comfort with less stress for both the surgeon and the patient, and a secured "airway" [16].

The main disadvantage of general endotracheal anesthesia is the mandatory additional monitoring of cerebral perfusion, which is usually expensive, along with all the other complications that general endotracheal anesthesia entails.

Regional anesthesia has its advantages, namely: awake and cooperative patient (monitoring of consciousness and motor response - monitoring of cerebral perfusion) [17,18,19] , better preserved brain autoregulatory brain mechanisms, low cost, and simplicity of execution.

However, regional anesthesia also has its drawbacks, greater stress for both the surgeon and the patient, the possible appearance of hemodynamic instability, the presence of patient movements (swallowing), and a less secured "airway". Many prospective studies have emphasized the advantages of regional anesthesia in carotid endarterectomy [20] . Regional anesthesia certainly represents the "best intraoperative monitoring" of cerebral flow, however, when choosing an anesthetic technique, one should take into account many different factors, not only the possibility of monitoring brain functions.

Patients and methods

The research was designed as a prospective randomized study with two groups of subjects: N1 (superficial cervical plexus block) and N2 general endotracheal anesthesia of 35 subjects each.

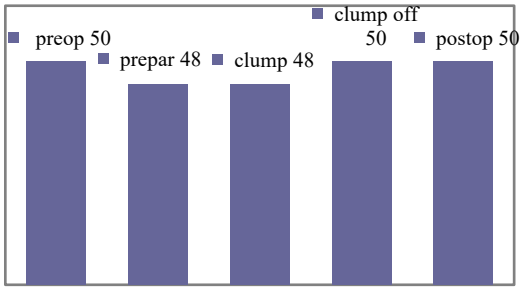
In our study, a modification of the Scandinavian Stroke Scale was used as a pattern of neurological monitoring in subjects of group N1 (block). The modification referred to the removal of parameters used to evaluate the quality of life, the presence of permanent or temporary disability, while the parameters useful for rapid assessment of the neurological status intraoperatively, and the eventual occurrence of cerebral ischemia, were retained. The maximum number of points is fifty, and the lower limit of satisfactory neurological status was 40 points. In the N2(OET) group, neuromonitoring was performed by monitoring cerebral oximetry (rSO2) values.

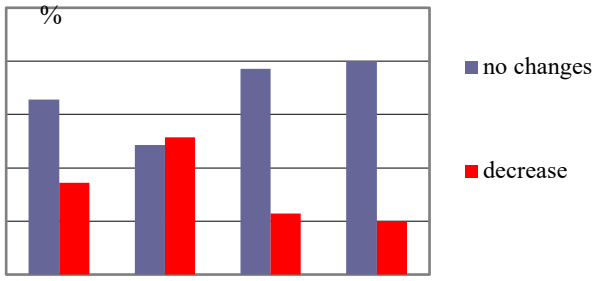
Table 1. Modified "Scandinavian stroke score"

consciousness	**full 12**	**somnolent 6**		**no consciousness 0**
Motor response	**normal 12**	**slightly weak 8**	**severely weak 4**	**no response 0**

Orientation	**full**	**12**	**2 criteria**	**8**	**1 criteria**	**4**	**desoriented 0**
Speech	**normal**	**12**	**unintelligible**	**8**	**answer yes/no**	**4**	**aphatic 0**
Maximal							**50**

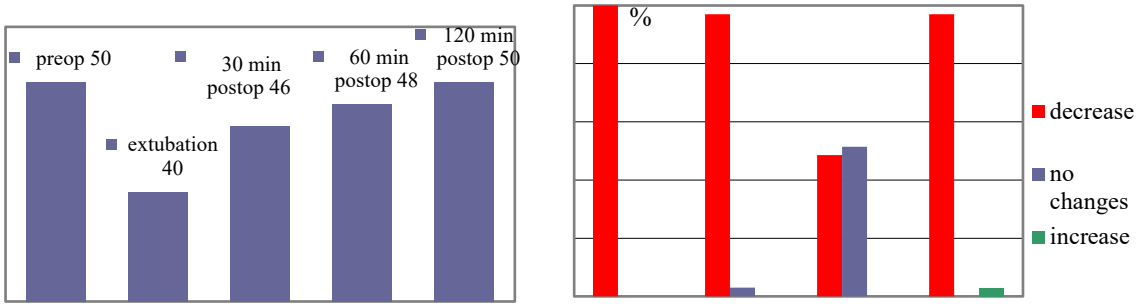
In all phases of the operative procedure, the SSS score in most patients of the N1 (block) group was unchanged compared to preoperative (94,2%), except in the clamping phase, where a drop in the SSS score was recorded in more than half of the patients (51.4%) - the influence of analgosedation. In all patients of this group, the change in the SSS score compared to the preoperative score ranged up to -10. Regardless of the change, it is important to note that all patients had a total score above the lower limit of forty points, except for one patient who developed a transient ischemic attack (TIA) intraoperatively, near the end of the common carotid artery clamping phase. Compared to the preoperative SSS score (50 points), this patient had 36.0% (18 points) lower SSS in the clamping phase and 20.0% (10 points) lower SSS in the release phase, and 8% (6 points) lower postoperatively.





Graph 1. and 2. Values of SSS by stages of the operation and the percentage of patients according to the movement of the SSS score by stages of the operative procedure in relation to the preoperative values - Block group – awake patients

In group N2 (OET), the neurological examination was performed preoperatively, upon awakening, and 30, 60 and 120 minutes postoperatively. In the phase of awakening from general anesthesia, no patient received the maximum number of points - 50. The highest score in this phase was 44 points for 1 patient (2.9%), 30 patients were evaluated with 42 or 40 points each. (85,7%), and 4 patients (11.4%) received the lowest number of points - 38. In the phase 120 minutes postoperatively, 26 patients (74.3%) were assessed with the highest number of points, which is the same percentage of patients with the maximum almost as well as in the preoperative phase. Eight patients (22.9%) had an SSS score of 48 points, and 1 patient (2.9%) had a score of 46 points.



Graph 3. and 4. Values of SSS by stages of the operation and the percentage of patients according to the movement of the SSS score by stages of the operative procedure in relation to the preoperative values - GA group

Quality neurological monitoring significantly reduces neurological complications during endarterectomy. Clinical evaluation of an awake patient is currently the "gold standard" of neurological monitoring. The most frequently used alternative techniques have limited sensitivities and specificities, are expensive, and often require the presence of trained personnel. About ¼ of strokes related to carotid endarterectomy occur intraoperatively, and about 1/3 of them are of hemodynamic origin, while 2/3 are of embolic nature. Transcranial Doppler ultrasonography (TCD) is a relevant technique in the early detection of embolic complications, and its use is justified in awake patients as well as in general anesthesia.

Conclusions

Adequate and reliable monitoring of cerebral perfusion is the "conditio sine qua non" of every carotid endarterectomy. In this regard, the cervical block allows us superior monitoring of general endotracheal anesthesia - an awake patient. However, cerebral perfusion monitoring is certainly not the only thing of crucial importance for a successful endarterectomy. Hemodynamic stability, respiratory stability, adequate analgesia, patient (and surgeon) comfort are aspects of equal importance for the successful performance of endarterectomy, and low perioperative and postoperative mortality and morbidity. Monitoring cerebral perfusion in general endotracheal anesthesia requires additional, as a rule, expensive equipment and trained personnel. Despite this, none of the techniques can be compared to the rough neurological assessment of an awake patient in terms of efficiency, promptness, and simplicity of execution.

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Nutrition Support for Critical Ill Child in PICU- Anesthesiologist Point of View

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Nutrition of critical child admitted in PICU for reasons of trauma, operation, sepsis or other reasons is actually integral part of therapy. For all patient after admission we should do initial assessment of nutritional status, and, as long as they stay in ICU. In case when normal food intake is not enough to satisfy energy expenditure we start with nutritional support. The preferred route is enteral, combination of enteral and parenteral, and, in case that there is no other way parenteral support. When done on appropriate way, on time, as a result we will prevent malnutrition, achieve faster recovery, better healing of wound, easier weaning from mechanical ventilation, lower incidence of infection and shorter stay in ICU.

Introduction

Trauma, severe infection, operation, activates the complex mechanism of metabolic, neuroendocrine, and immune reactions. As result of activation we have glycogenolysis, glyconeogenesis, lipolysis and proteinolysis to obtain energy, first from glycosis and then from free fat acids, and ketones. After admission and resolving main problems like hemodynamic instability, respiratory support , infection we do nutritional assesment of child in first 24-48 h, calculate REE (resting energy expenditure), and start with nutritional support. Nutritional assesment include: detailed anamnesis and medical hystory,weight/height, lenght, mid uper arm circumference, head circumference , complete lab tests , BMI and Schoefield equation for REE. Some conditions or medications can have influence on REE , for example: sedation, muscle relaxans-decrese REE, fever >38 increse energy needs. Energy intake in EN, in acute phase and stable phase , start from 25% of REE and increase to full REE, in recovery phase 2xREE and higher. In PN energy intake in acute phase should be less than REE, in stable phase 1.3-1,5xREE, in recovery phase it depends of age: 0-1y 75-85kcal/kg/d; 1-7y 55-65 kcal/kg/d; 12-18y 30-35kcal/kg/d.

Table 1. Schoefield equation for REE (resting energy expenditure)

Age	Male	Female
0-3y	60.9x W(kg)-54	61.0xW(kg)-51
3-10y	22.7xW(kg)+495	22.5xW(kg)+499
10-18y	17,5xW(kg)+651	12.2xW(kg)+746

Enteral nutrition

The most preferred route of nutritional support. Benefits of EN are: preservation of gut function, activation of normal GIT neuroendocrine function, secretion of digestive juices, preservation of gut mucosis, prevention of bacterial recolonisation, safety, and cost (commercially available formulas are cheaper 2-4 times than parenteral one).

Indication: When ever normal oral route is not enough to support energy needs; disorders of digestion and absorption; disorders of GIT motility (chronic intestinal obstruction, Hirschprung disease); increased energy needs , growt failure, chronic malnutrition. Depending on duration of EN <4 w or > 4 w, and risk of aspiration gastric route, or post pyloric route is used . Most used formulas for EN: Standard-polymeric formula: commercially available, complete in content of macro and micronutritiens, 1kcal/ml energy, and isoosomolar. Post pyloric feeding polimeric formulas contain nutritients which are extensivelly hidrolised and predigested so they can be absorbed in jejunum.

Contraindication for EN: absolute (NEC, intestinal perforation, GIT obstruction - mechanical/paralitic ileus), hemodinamic instability; relative (intestinal dysmotility, toxic megacolon, GI bleeding, high output fistula, nausea, vomiting, diarrhea, difficult intake of food (face trauma, burns of face and oral cavity). Enteral feeding can be given by bolus or by continuous infusion using pumps for enteral feeding.

Table 2. Practical example of EN

ENTERAL FEEDING						
Bolus				Continuous		
Age	**Start**	**Advance**	**Tolerated volume**	**Start**	**Advance**	**Tolerated volume**
0-12 mo	10-15 ml/kg every 2-3h	10-30 ml per feed	20-30ml/kg every 4-5 h	1-2ml/kg/h	1-2ml/kg every2-8 h	6ml/kg/h
1-6 y	5-10ml/kg every 2-3 h	30-45 ml per feed	15-20ml/kg every 4-5 h	1ml/kg/h	1ml/kg every 2-8 h	1-5ml/kg/h
>7 y	90-120 ml Every 3-4h	60-90 ml per feed	330-480ml every 4-5 h	25ml/h	25ml every 2-8 h	100-150ml/h

Parenteral nutrition

Is used to treat children who cant receive suffitient oral or EN due to impaired or immature GIT function. Indication for use : when EN is contraindicated, EN not enough to satisfy energy demands, when it is not possible to use EN. PN should follow fluid needs, energy needs, stage of illnes, age of child, risks. Energy intake in PN is 10-20 % less than in EN. 1 g of lipids will give 9 kcal, 1 g of carbohyidrates 4 kcal, and proteins 4 kcal. 20% iv lipid emulsions are better than 10%. In acute phase it is contraindicated to give aminoacids due to suppression of autophagy. Preferred route of giving PN is use of CVC. PN should be given using iv pumps. Recommended requirements of amonoacids for stable child are between a 1,5-3 g/kg/d ; Na(1-3mmol/l/d),K(1-3mmol/l/d),Cl(2-4mmol/l/d). All children on PN should receive vitamins, Mg, Phosphate, Thiamine,and other micronutrients.

Table 3. Holliday Segar formula for fluid maintenance in child

<10 kg	**100ml/kg/24**	**4ml/kg/h**
10-20kg	1000ml+50ml/kg>10kg	40ml/h+2ml/kg/h>10kg
>20kg	1500ml+20ml/kg >20kg	60ml/h+1ml/kg/h>20kg

Table 4. Lipid requirements

Weight	Starting dose	Advacement dose	Maximal dose
<10 kg	1g/kg/d	1g/kg/d	3,5-4g/kg/d
11-45kg	1g/kg/d	1g/kg/d	2-3g/kg/d
>45 kg	0,5-1g/kg/d	0.5-1g/kg/d	1,5-2g/kg/d

Table 5. Glucosis requirements

Weight	Acute phase mg/kg/min	Stable phase mg/kg/min	Recovery mg/kg/min
<10kg	2-4	4-6	4-6
11-30kg	1,5-2.5	2-4	2-4
31-45kg	1-1,5	1,5-3	1,5-3
<45kg	0.5-1	0,5-1	1-2

Levels of triglcerides should be between 3mmol/l (neonate and infant) and 4,5mmol/l for older children, in case of elevated values iv volume of lipid emulsions is corected.

Complications of PN are: CVC related complications (infection, occlusion, central venous thrombosis, pulmonary embolism), instability of parenteral solutions, interaction with medication, metabolic and nutritional complications, hepatobiliary complication.

Monitoring during nutritional support include: antropometry , lab tests (complete blood count, crp, albumins, gas analysis, glucosis , electrolytes, phospates, calcium, Mg, liver tests, albumines, cholesterol/trigliceride, urea, creatinin, urin , EKG ,pulse, BP. Glycosis check each 4h first day, other lab tests daily.

One of complication of nutritional suport in PICU patient that can occcur is refeeding syndrom. It is severe fluid, electrolyte imbalance and metabolic abnormality . It occures after, prolonged period of suboptimal nutrition intake over days and weeks, weight loss, malnutrition, diarrhea, vomitus, prolonged period of nil per mouth >7 days, hyperglycemic patients, insulin supplementation , chronic

therapy(diuretics, antacids), chemotherapy, anorexia. It occurs sometimes to any critically ill child in first 48 h. Pathophisiology of reefeding sy: during starvation level of insulin is decresed, glucagon elevated. Catabolic process include conversion of glucagon to glycosis as main energy source , and then glyconeogenesis from lipids and proteins, main energy source becomes free fat acids and ketones. After nutrition support starts we have oposite: conversion to glycosis as main energy source instead fat and proteins, insuline release, causing uptake of glycosis, P, K, Mg , water, into cells for synthesis of proteins. Main disturbances are electrolytic: hipokalaemia, hipomagnaesiemia, hipophosphataemia, oedema. If not recognised it can lead to severe life thretening complication: cardiac failure, respiratory failure, encephalopathy, cardiac arythmias, muscle weakness, renal, hematological complication.

Prevention include: less energy intake at start of PN /EN (50% of REE), in high risk patients-supplementation of Mg, P, Ca, K, Thiamine 1-2 mg/kg/d, vitamins, and micronutrients. Glucosis intake not to exceed 11-12 g/kg/d for infants, max dose 18 g/kg/d. For todlers 10 mg/kg/d. Monitoring includes: temperature, EKG, BP, respiratory function, diuresis, weight, glucosis every 4 h on first day, lab test daily, liver test 2-3 times per week, levels of trigliceride, treatment of hipo and hyperglicemia, as well as electrolyte deficit.

Conclusion

Nutritional support in PICU is part of therapy, if well planned, with monitoring, prevention and treatment of possible complication it will provide faster recovery and better outcome for patient.

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New Rules in Pediatric Transfusion

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Bleeding:

It has been proven that 10%– 15% of children admitted to a PICU have at least one episode of clinically relevant bleeding. [1] As a result of blood loss, the development of hypoxemia occurs both due to the reduced number of erythrocytes, which reduces blood oxygen saturation, and due to the loss of fluid itself - hypovolemia, which leads to a decrease in cardiac output. [2]

Anemia was observed in 74% of patients who stayed in the ICU for more than 2 days (due to hemoragy, hemolysis, phlebotomy). It has been proven that preoperative anemia in infants and older children is associated with worse postoperative recovery and outcome. Therefore, it is recommended to do anemia screening 3-4 weeks before surgery.

Transfusion in the pediatric population can be life saving, but also can lead to complications. Inadequate use of transfusion is associated with 4x higher morbidity and 5x higher mortality. A worsening of the condition is possible in premature children with increased intracranial pressure, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, iron overload, inadequate neurological development. [3] Therefore, it is very important to form and implement standard transfusion guidelines even though that is very challenging. The problems are primarily due to difficulties in the existence of verified data, limited amount of evidence-based literature, lack of data from studies due to the very small number of studies performed in the population of pediatric patients with impaired general condition. A significant amount of transfusion data in the pediatric population is still based on historical, outdated data or refers to the adult population. Such data are not adequate due to:

- physiological differences compared to the adult population: delivery and consumption of oxygen, hemoglobin level (differences in relation to age)

- different co-morbidities (coronary disease is less common, congenital malformations are more common).

The decision to transfuse is multifactorial and includes:

- laboratory parameters: hemoglobin, hematocrit, lactate levels and $ScvO_2$, parameters of anemia,
- bleeding and coagulation disorders
- clinical presentation (e.g. signs and symptoms of anemia)
- age, underlying medical status (e.g. prolonged bleeding time)

TAXI RBC guidelines [4] – a guide for the application of erythrocyte transfusion

The guide is necessary because it has been proven that children often receive more transfusions than they really need due to difficulties in determining the adequate amount. Over 2/3 of RBC transfusions are given prophylactically in children who are not bleeding. Therefore, it is necessary to follow the criteria from the guide:

1. General population of critically ill children, tranfusin of RBC should be given:- if Hb is 5g/dl in hemodynamically stable patients- consider if Hb is between 5-7g/dl based on clinical assessment (due to insufficient data)- not required in critically ill children with non-life threatening bleeding for Hb >7g/dl.
2. If the hemoglobin concentration is below:- 7-10 g/dl for acute brain trauma- 7-8 g/dl for stem cell transplantation and oncology patients- 9 g/dl as the maximum threshold for uncorrected cardiac defect
3. Limit the post-transfusion increase in Hb to a maximum of 2 g/dl above the recommended concentrations for the age, because it is more important that the hemoglobin concentration is 7-9.5 g/dl than attempting to correct it to normal range for age.

When it comes to acute hemorrhage, transfusion is recommended when the blood loss is greater than 15-20% of the total amount of blood. Hb values are less useful because significant losses can occur before detection via laboratory values, although Hb concentration ≤ 5g/dl is the absolute lower limit for a critically ill patient.

For life-threatening bleeding, it is recommended: RBC: plasma : platelets = 1:1:1 or 2:1:1 [5]

Future studies are recommended to determine if low titer group O whole blood is more efficacious and safe compared to reconstituted whole blood in children with hemorrhagic shock [6]

Emergency situations: First therapy line is to correct anemia if it exists, ensure adequate delivery and avoid factors increasing O_2 consumption. It is necessary to maintain high PaO_2, adequate cardiac output and intravascular volume and to avoid leftward shift of ODC. [7] Regarding the therapeutic benefit of erythropoetin administration (it increases erythrocyte synthesis) it has not been proven to improve cognitive and neurodevelopmental outcomes. [8]

Specifics of neonates:

This population differs from the rest of the pediatric population by numerous physiological characteristics. In the first 3-4 minutes of life, they can't produce alloantibodies to red cell ABO Ag, so hemolytic reactions are rarer. In newborns, fetal Hb is present in a concentration of 70-80% in term newborns and 97% in preterm newborns. Their compensatory mechanisms are immature (response to hypoxemia, reaction to trauma or stress, immune system, metabolism. Therefore, it is very difficult to determine the criteria for the transfusion of newborns (NICU study). Their total blood volume is smaller, but high according to their body weight. The possibility of side effects is significantly higher. According to the ETTNO and TOP studies in ELBW infants, increasing the hemoglobin concentration did not improve the outcome of survival without neurodevelopmental impairment. [9,10]

It has been proven that in the absence of impaired tissue oxygenation, hemodynamically stable newborn does not need RBC transfusion even when Hb concentrations are lower than recommended. (ref)

Intracranial hemorrhage does not seem to depend on platelet count, so it is not useful to transfuse Tr, because even more ICH occurred in infants with a higher platelet count.

Possible reasons include the interaction between adult platelets with the neonatal coagulation system, which differs in a lower concentration of coagulation factors, but a higher VWF factor and decreased levels of coagulation inhibitors. [11]

Recent studies provide guidance about transfusion thresholds and indications. [12]

In future research, we should focus on finding new markers that can help us decide on the application of transfusion in newborns, such as the latest IPC marker - the number of immature Tr - for the diagnosis of neonatal Tr-penia. [13]

Platelet transfusion

Threshold values for platelet transfusion in adults can't be applied to the pediatric population primarily because children have a higher chance of clinically significant bleeding that does not depend on the platelet count. [12]

Based on the PlaNeT2/MATISSE study:

- In premature babies, it is safer and there is lower risk of severe bleeding if no. Tr t 25 × 10^9/L than 50×10^9/L, because a higher number of Tr in a transfusion is associated with a 7% higher chance of death and/or massive bleeding. A higher incidence of bronchopulmonary dysplasia was also noted, but there were no differences for other complications such as retinopathy of prematurity and necrotizing enterocolitis.[14]

Guidelines from the United Kingdom

BCSH-update British committee for standards in hematology:

- Recommended number of Tr: > 25×10^9 /L - if no bleeding is present, including fetal and neonatal alloimmune thrombocytopenia (NAIT) without bleeding or family history of intracranial hemorrhage > 50×10^9 /L – if present bleeding, current coagulopathy, for surgical prophylaxis or NAIT with positive family history of intracranial hemorrhage > 100×10^9 /L - massive bleeding or major surgery (e.g. neurosurgery)

Platelets are indicated for the treatment of hemorrhage associated with a congenital qualitative defect of platelets (e.g. Glanzmann thrombasthenia, BernardSoulier syndrome) and in the presence of cardiopulmonary bypass, uremia, EKK, even if the platelet count is normal. [12]

TAXI-CAB

Good Practice Statements Applicable to All Critically Ill Children

- When deciding on the transfusion of plasma and/or platelets to a critically ill pediatric patients, the following can help us:

    1. hemostasis parameters, application of VEM, TEG and ROTEM monitoring, conventional coagulation tests (CCT) - PT, INR, PTT

and platelet count, as well as other laboratory tests (e.g. for the diagnosis of qualitative disorders of platelets)

2. clinical presentation - symptoms and signs of bleeding, signs of increased intracranial pressure
3. comparison of desired and unwanted effects as well as alternatives for plasma and platelet transfusion. [6]

- If an ICP monitoring device must be inserted in neurologically deteriorating critically ill pediactric patient with TBI and/or ICH, platelets should be considered if $< 100\times10^9$ /L
- Oncology patients: prophylactically if Tr $< 10\times10^9$ /L, and for therapeutic purposes if there is moderate to severe bleeding
- In case of sepsis: in the absence of bleeding, we can consider giving Tr if they are $< 10\times10^9$ /L
- In case of moderate bleeding if they are below 50×10^9 /L
- For non-cardiac surgery platelets might be considered:

If there is no bleeding when $\leq 20\times10^9$ /L

If there is severe bleeding when ≤ 50×10^9/l

Plasma transfusion may be considered to correct PT, INR aPTT if values are ≥ 2x compared to reference values. [15]

For interventions outside the operating room:

- plasma transfusion if the INR is > 2.5
- transfusion of platelets if the number of Tr $\leq 20\times10^9$ /L
- prophylactic use in case of elective lumbar puncture when Tr $< 20\times10^9$ /L
- it has not been proven whether there is any benefit from platelet transfusion if their number is 20-40×10⁹ /L

Prophylactic administration of Tr has no benefit in minor procedures (e.g peripheral cannula insertion, CVC removal, bone marrow aspiration and biopsy) [16]

Plasma:

Prophylactic administration of plasma in children has not been proven effective for the correction of mild coagulopathy because it only unnecessarily increases the risk. It is not recommended to use:

- for the correction of coagulopathy in newborns if the bleeding is not clinically significant
- for volume expansion, improvement of wound healing or as the first line of therapy for coagulation factor deficiency if inactivated plasma with concentrated coagulation factors or recombinant factor are available.
- in children who do not bleed but have a slight disturbance of coagulation (INR <2.5)

It can be used in infants who have significant bleeding, including those who require massive transfusions or are at high risk of bleeding.[12]

Cryoprecipitate:

It is primarily used for fibrinogen replenishment. Previously it was used as a source of factors VIII, XII and VFW before the advent of their concentrates. Cryoprecipitate has a significantly smaller volume (10-15 ml) in contrast to plasma (200-250 ml), which is important in the transfusion of pediatric and volume-sensitive patients. Determining the therapeutic threshold for the use of fibrinogen is still controversial - although the recommended values go up to 100 mg/dl (for congenital hypofibrinogenemia) and 150-200 mg/dl for secondary deficit due to trauma or cardiovascular surgery. [12] A fibrinogen concentration of 30-50 mg/kg or cryoprecipitate (5-10ml/kg) can be used to raise plasma fibrinogen concentrations above standard values. [12]

PCC – prothrombin complex concentrate:

The use of PCC with 4 coagulation factors can be significant in children in whom fresh frozen plasma cannot be administered and when we want to avoid the negative effects of fresh frozen plasma. Further research should justify the indication for their use, effectiveness, optimal doses as well as side effects in critically ill patients. [17]

Antifibrinolytics:

- In children with an increased risk of bleeding (cardiac patients, scoliosis, craniosynostosis), the use of tranexamic acid significantly reduces preoperative blood loss and ER transfusion. [18]

- 10mg/kg followed by 5mg/kg is not less effective than a single dose of 50mg/kg [19]

Adequate administration of transfusion can save life, but the disadvantages are that it can also be dangerous and expensive. As far as the pediatric population is concerned, whenever possible, unnecessary administration of blood and blood products from other persons should be reduced. It is very important to determine the criteria in the therapeutic application of transfusion depending on the age but also in relation to the morbidity and mortality of children and to find an approach to maximite benefit and minimize harm effects.

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Management of Pediatric Neurotrauma

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Introduction

Pediatric neurotrauma is the leading cause of death and disability in children more then 1 year of age despite increases in prevention programs [1] .Neurotrauma includes traumatic brain injury (TBI) and spinal cord injury (SCI). Knowledge about the age-specific types of injury and how to manage children with neurotrauma is essential to understanding and recognizing the extent and degree of injury and to optimize outcomes.

Sustaining a brain injury in early childhood can delay or interrupt foundational neurodevelopment [2]. Despite extensive gains in our understanding of the molecular basis of TBI , there remains no specific "magic bullet " therapy to improve outcomes.

In this article, we rewiew the epidemiology, pathophysiology and clinical management of pediatric severe TBI.

Epidemiology

Most children with multiple trauma have TBI and most trauma deaths are associated with TBI. Following TBI, 10-15 % children are classified as severe with an associated mortality rate of 50 % [3]. However , overall mortality is lower in children as compared to adults **(2.5 % vs.10,4 %)** but certain factors predict worse outcomes [Table 1].

Each year in the USA , more than 450,000 children present to emergency department (ED) because of TBI with a male to female ratio of 3:2. The majority of children (90 %) suffers from minor injuries .Nevertheless, 10 % children with TBI require hospitalization and up to 2.5 % children with TBI per year do not survive their sustained injuries [4].

Boys have a four times risk of fatal TBI compered to girls. In the age group 1 -4 years, children require hospitalization because of fall-related TBI. In school age injuries are frequently due to the increasing mobility- bicycle crashes mostly . In adolescence, injuries resulting from automobile craches increase dramatically.

Table 1. Predictors of poor outcomes after pediatric TBI

Age < 4 years
Cardiopulmonary resuscitation
Multiple trauma
Hypoxia (PaO2 <60 mmHg), Hyperventilation (PaCO2 <35 mmHg)
Hyperglycemia (glucose > 13 mmol/l), Hyperthermia (temperature >38 C)
Hypothension (SBP < 5th percentile for age)
Intracranial hypertension (ICP > 20 mmHg) , Poor rehabilitation

Pathophysiology

The primary damage in TBI is mechanical contusion after direct impact. The consequent inflammatory responses and apoptotic cascade activation result in secondary brain damage. This contributes to the development of cerebral edema (CE) which peaks 24-72 h after TBI and exacerbates neuronal damage by limiting cerebral blood flow (CBF).

It's essential to anticipate worsening of CE in patients with severe TBI, which, if not prevented, can ultimately lead to refractory increased ICP, brain herniation and death [5].

Patterns of Injury and Diagnosis

Children are more susceptible to TBI because they have a larger head to body size ratio, thinner cranial bones providing less protection to the intracranial contents, less myelinated neural tissue which makes them more vulnerable, and a greater incidence of diffuse injury and CE compered to adults (80 % vs. 50 %).

Pediatric TBI can be categorized as : **primary injury** which is consequence of initial trauma or impact of force (e.g. epidural/ subdural hemathoma , subarachnoid/interventricular hemorrhage, diffuse axonal injury (DAI), abusive head trauma(AHT), vascular injuries) **secondary injuries** which occurs as a complication of primary injury (e.g. acute : diffuse cerebral swelling, brain herniation, infarction, infection and chronic injuries: hydrocephalus, encephalomalacia , leptomeningeal cyst).[6]

The Pediatric Glasgow Coma Scale (PGCS) is commonly used to asses consciousness and define the severity of TBI (Table 2).

Table 2. Pediatric Glasgow Coma Scale

		>1 year	<1 year	
Eye opening	4	Spontaneously	Spontaneously	
	3	To verbal command	To shout	
	2	To pain	To pain	
	1	No response	No response	
Best motor response	6	Obeys	Spontaneous movements	
	5	Localizes pain	Localizes pain	
	4	Flexion-withdrawal	Flexion-withdrawal	
	3	Abnormal flexion	Abnormal flexion	
	2	Abnormal extension	Abnormal extension	
	1	No response	No response	
		>5 years	**2–5 years**	**0–23 months**
Best verbal response	5	Oriented and converses	Appropriate words and phrases	Coos and smiles appropriately
	4	Disoriented and converses	Inappropriate words	Cries
	3	Inappropriate words	Cries and/or screams	Inappropriate crying and/or screaming
	2	Incomprehensible sounds	Grunts	Grunts
	1	No response	No response	No response

Classification of the severity of TBI depends on GCS, with mild TBI having a GCS 13-15, moderate TBI having a GCS 9-12 and severe TBI having a GCS < 9.

Rapid imaging is important for indentifying the extent of the primary damage and triaging those patients who might require urgent surgical intervention. Computed tomography (CT) is the primary modality used for this purpose [7]. Magnetic resonance imaging (MRI) is more sensitive than CT in evaluating DAI. However, there is no evidence to support the efficacy of routine MRI in immediate management.

Management Of Severe TBI

In 2019, the third edition of the Guidelines for the Management of Pediatric Severe TBI was updated (Table 3).

Baseline care should be administrated at the stage of initial management to achive better outcomes and IPC control. It consists : proper sedation/analgesia ,intubation and mechanical ventilation,euvolemic status achievement,fever treatment,coagulopathy correction, minimum hemoglobin maintenance age-adjusted,neutral head positioning with 30 ® head-of-bed elevation and antiepileptic drug therapy [7].

IPC monitoring is recomanded to improve clinical outcomes of all patients with severe TBI. **Therapeutic target threshold for IPC is suggested to be less than 20 mmHg** [7]**.** Cerebral perfusion pressure,CPP , defined as the diference between MAP and ICP; is a pressure that drives blood flow to the brain.A constantly low CPP is associated with poor outcomes**. Guidelines for the Management of Pediatric Severe TBI only recommend keeping the minimum CPP>40 mmHg**[7]**.** Intravenosus osmotic therapy is widely used to control ICP.Usually, 20 % mannitol is administrated at a dose ranging between 0,5 – 1.0 g/kg. However, mannitol increases the risk of hypovolemia and hypothension, which must be avoided in severe TBI. **Therefore,hypertonic sline is associated with the more favorable cerebral hemodynamics and fastest resolution of increased ICP and was the only medication that improve CPP.The suggested dosage of 3% saline ranges between 0.1-1 ml/kg/h.**[7]**.**

High-dose barbiturate therapy is recommended for hemodinamically stable patients with refractory increased ICP. Phenobarbital is the drug of choice. If IPC remains stable below 20 mmHg for 24 h, phenobarbital can be gradually discontinued over 24-96 h [7].

Maintaining normothermia is essential for pediatric patients with severe TBI, as fever exacerbates secondary brain injury [8].**Therapeutic hypothermia** reduces CE,prevents the progression of secondary brain injury and reduces ICP[7].

Decompressive craniotomy (DC) is recommended in pediatric severe TBI for treating herniation or refractory increased ICP, achieving level III of recomandation due to significant early and late complications (expansion of contusion volume,hemorrhagic infarction, infection, seizures,hygroma and hydrocephalus)[7].

Table 3.Summary of the update 2019 Brain Trauma Foundation recommendations

Topic	Level	Recommendation	Updated content
Neuroimaging	III	To improve overall outcome	CT examinations should not be used to rule out the possibility of elevated ICP
Hyperosmolar therapy	II	For ICP control	Hypertonic saline (3%) is recommended at doses of 2–5 ml/kg over 10–20 min
	III	For ICP control	Hypertonic saline (23.4%) is suggested for refractory ICP at doses of 0.5 ml/kg
		Safety	To avoid sustained (>72 h) serum sodium >170 mEq/l is suggested to obviate anemia and thrombocytopenia; avoiding >160 mEq/l to circumvent DVT
Sedation, analgesia and neuromuscular blockade	III	For ICP control	Avoid bolus of midazolam and/or fentanyl to control ICP because of risk of cerebral hypoperfusion
Seizure prophylaxis	III	Seizure prevention	Insufficient evidence to recommend levetiracetam over phenytoin based on efficacy either toxicity
Temperature control	II	To improve overall outcome	Prophylactic moderate hypothermia (32–33°C) is not recommended over normo-thermia
	III	For ICP control	Moderate hypothermia is suggested for ICP control
		Safety 1	Rewarming should be carried out at a rate of 0.5–1°C every 12–24 h
		Safety 2	If phenytoin is used during hypothermia monitoring level is suggested to minimize toxicity
Nutrition	III	To improve overall outcome	Early (within 72 h from injury) enteral nutrition is suggested
Corticosteroids	III	To improve overall outcome/for ICP control	The use of corticosteroids is not suggested Note: Previous recommendation is not intended to circumvent the use of replacement corticosteroids (chronic therapy, adrenal suppression, injury of the hypothalamic pituitary axis)

CT, computed tomography; DVT, deep vein thrombosis; ICP, intracranial pressure.

Conclusion

The Guidelines for the Management of Pediatric SevereTBI have been updated to include better treatment options even if the evidence remains insuffitient. The treatment algorithm should be adjusted to individual needs and circumstances.

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Thoracic Spinal Anesthesia, Should It Be Endorsed

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"Thoracic spinal anesthesia" would suggest the administration of spinal anesthesia specifically targeting the thoracic region of the body. This might involve injecting anesthetic medication into the subarachnoid space in the thoracic area to achieve regional anesthesia for surgical procedures in that region. It's worth noting that the use of spinal anesthesia in the thoracic region would likely be performed by a trained anesthesiologist and tailored to the specific needs of the patient and the surgical procedure. The primary goal would be to provide effective anesthesia and pain relief while considering the patient's safety and well-being.

Thoracic spinal anesthesia can be used for a variety of surgical procedures that involve the thoracic region of the body, which includes the chest, upper abdomen, and upper back. Here are some examples of surgical procedures that can potentially be performed under thoracic spinal anesthesia:

1. Breast Surgery: Procedures such as breast augmentation, breast reduction, and mastectomy can often be performed using thoracic spinal anesthesia.
2. Thoracic Surgery: Some surgeries involving the lungs, pleura, or chest wall can be done with thoracic spinal anesthesia, depending on the specific situation.
3. Upper Abdominal Surgery: Certain abdominal surgeries involving the upper abdomen, such as gallbladder removal (cholecystectomy) or surgeries on the liver or spleen, might be suitable for thoracic spinal anesthesia.
4. Upper Back Procedures: Surgeries on the upper back, such as spine procedures or surgeries related to the upper thoracic vertebrae, could potentially use thoracic spinal anesthesia.
5. Rib Fracture Repair: Surgical repair of fractured ribs in the upper thoracic area might be performed under thoracic spinal anesthesia.

6. Implantation Procedures: Procedures involving the placement of devices or implants in the thoracic area, such as pacemakers or defibrillators, might be candidates for thoracic spinal anesthesia.
7. Certain Gynecological Procedures: Some gynecological surgeries, such as procedures involving the upper reproductive organs, could potentially be performed using thoracic spinal anesthesia.
8. Plastic and Cosmetic Surgery: Various plastic and cosmetic procedures involving the chest or upper back could be done with thoracic spinal anesthesia
9. Laparoscopic cholecystectomies, and
10. Abdominal cancer surgery

General anesthesia is the standard for most surgeries; however, some drawbacks can include negative drug side effects, prolong recovery, and inadequate pain control. There is currently renewed attention to thoracic segmental spinal anesthesia for several common surgeries. Injection of anesthetics intrathecally into the preferred body height and above where the spinal cord terminates has been revealed to be valuable in these certain circumstances.

Anesthesiologists are hesitant to perform spinal anesthesia above the termination of the conus medullaris due to fear of injuring the spinal cord. However, thoracic spinal anesthesia has been demonstrated as a safe and effective method for various surgeries, including laparoscopic cholecystectomies, breast cancer lumpectomies, and abdominal cancer surgery

For spinal anesthesia, a typical dose might include a local anesthetic medication injected into the subarachnoid space. The dosage can be influenced by the choice of the anesthetic agent and whether any adjuvants are used to enhance the effects or prolong the duration of anesthesia. Adjuvants are medications added to the local anesthetic to improve pain relief or to reduce potential side effects.

Dexamethasone, a corticosteroid medication, is often used as an adjuvant in spinal anesthesia, including thoracic spinal anesthesia. The use of dexamethasone as an adjuvant in regional anesthesia techniques has gained attention due to its potential benefits in enhancing the quality of anesthesia and improving postoperative outcomes. The reasons why dexamethasone might be used as an adjuvant in thoracic

spinal anesthesia include: anti-inflammatory effects (by reducing inflammation at the site of injection, it may help improve the quality and duration of anesthesia by preventing or reducing nerve irritation or inflammation, prolonged pain relief, reduced nausea and vomiting, decreased pain sensitization, lowered requirement for analgesics.

Case series: In Kosovo, we present a series of case reports performed in thoracic surgery, and abdominal laparoscopic surgery, from different group of anesthesiologist. We have conducted the technique in more than 14 patients, eight undergoing radical mastectomy, and six undergoing laparoscopic cholecystectomy. All patients have positive results and no major side effect or complications have been reported. Further studies are needed to confirm its safety and benefits.

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Airway Management in Head and Neck Pathology

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Airway management in head and neck pathology has its own specificities and requires good coordination between the anaesthesiologist and otolaryngologist or head and neck surgeon (1). The anatomical area of airway management intervention directly overlaps with the present head and neck pathology. If the present pathology is physically large or significantly changes the anatomical relations, then it can represent an obstacle to the intervention itself. On the other hand, an inappropriate intervention, either too rough or too long, can lead to a worsening of the pathology itself in an anatomical or physiological sense.

Generally, head and neck pathology is considered a risk factor for airway management. Anatomical predictors of a difficult airway are primarily related to unfavourable anthropometric proportions of the mouth, face, and neck (small mouth, short thyromental distance, complete dentition with protruding incisors, reduced mandibular protrusion, short neck, large neck circumference, reduced neck extension, Mallampati 3 or 4), but also on existing tumours and conditions after surgical or radiotherapy interventions in the head and neck area. The presence of a moustache and beard, lack of teeth and a history of snoring are cited as predictors of difficult or failed manual ventilation with a face mask (2). Predictors of difficult or impossible videolaryngoscopy related to head and neck pathology are limited mouth opening, presence of blood, secretions and vomiting in the oropharynx and high Cormack-Lehane by directoscopy (2). Predictors of difficult or failed placement of a supraglottic device are a small mouth, upper airway pathology and limited neck mobility (2). Predictors of difficult or failed emergency front of neck access (eFONA) are thickened skin changes after surgery or radiation, neck flexion deformities and displaced trachea (2).

Despite some studies say that in head and neck surgery the incidence of difficult laryngoscopy is 19%, and difficult intubation is 8% (3), there is, fortunately, a whole series of technical possibilities for successful airway management in head and neck surgery. The experience of anaesthesiologists, especially those specializing in head and neck surgery, significantly contributes to successful intubations (4). The last decade has been marked by the greater availability and application of various equipment and devices for the airway management that can help in the management of difficult airway in clinical practice (5). In case of difficult intubation, the current guidelines recommend the use of alternative devices as early as possible (6,7,8). A series of individual techniques for managing the airway in head and neck surgery (direct and video laryngoscopy, surgical endotracheal intubation with a surgical laryngoscope or rigid bronchoscope, flexible bronchoscopes, optical and video stylets, supraglottic aids) can be combined into a series of combined (so-called hybrid) techniques, which increase the overall success of airway management (9). The numerous advantages of videolaryngoscopy contribute to the trend of increasing use of videolaryngoscopy as the basic technique of airway management in routine clinical practice instead of classic direct laryngoscopy (10). In head and neck surgery, awake videolaryngoscopy also has certain advantages over awake flexible bronchoscopy (11).

Although anaesthesiologists primarily deal with airway management in the narrow sense i.e. intubation, the role of otorhinolaryngologists or head and neck surgeons, who primarily treat head and neck pathology itself, should not be neglected. The airway is a common anatomical site for both the anaesthesiologist and the otolaryngologist or head and neck surgeon, although the approaches and techniques of airway management differ. An anaesthesiologist takes care of the airway that collapses iatrogenically during induction of general anaesthesia because of anaesthetics and neuromuscular blockers, while an otolaryngologist or head and neck surgeon performs surgical intervention on the airway itself or in its immediate vicinity. The anaesthesiologist is excellent at handling various types of direct laryngoscopes and video laryngoscopes, supraglottic and subglottic devices, flexible bronchoscopes. An otolaryngologist or head and neck surgeon is excellent at handling rigid bronchoscopes, flexible laryngoscopes, and surgical instruments. In critical situations where intubation is impossible, joint interventions of an anaesthesiologist and otorhinolaryngologist or head and neck surgeon are possible, where good

communication and well-coordinated teamwork come to the fore in which specialist skills complement and take over each other.

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Target Controlled Infusion (TCI) Anaesthesia in Thyroid Surgery

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Target controlled infusion (TCI) is a clinically available computer-controlled method of intravenous drug administration, in which the initial bolus dose and maintenance drug infusion rate are adjusted according to pharmacokinetic/pharmacodynamic (PK/FD) models (1). TCI is a registered method of drug administration in most countries of the world except the United States of America (USA), where total intravenous anaesthesia (TIVA) is used exclusively. Nowadays TCI is a technology of proven safe and reliable administration of certain anaesthetics and opioids in population-adjusted FK/FD models (2,3). There are commercially available FK/FD anaesthetic models for propofol (modified Marsh, Schnider, Paedfusor for children, Kataria for children, Cortinez for children, Cortinez for obese) and dexmedetomidine (Dyck). Opioid PK/FD models are commercially available for remifentanil (Minto), fentanyl (Shafer), sufentanil (Gept), alfentanil (Maitre, Scott&Stanski), and hydromorphone (PCA). The existing commercial models, with imperfection related to the appropriate selection of certain groups of patients, can be used in all types of surgery. However, given that much of the publication comes from the US area where TIVA is used exclusively, published evidence supporting the use of TCI in specific surgeries is often lacking. However, based on the knowledge of the principle of action of TCI, certain evidence for TIVA of a specific drug can be extrapolated to TCI as well.

TIVA has several clinical comparative advantages over balanced anaesthesia with inhalational anaesthesia that are significant and applicable in head and neck surgery in general and in thyroid surgery specifically. TIVA has been proven to significantly reduce the stress response during head and neck surgery (4). During endoscopic sinus surgery, TIVA ensures a bloodless operating field (5). Compared to inhaled anaesthetics, infusion of propofol, which is an antiemetic, reduces

postoperative nausea and vomiting (6). TIVA ensures good preservation of cognitive functions (7). It is applicable in all age groups.

TIVA is the recommended technique if intraoperative neuromonitoring of the recurrent laryngeal nerve is used in thyroid and parathyroid surgery. An important prerequisite for successful intraoperative neuromonitoring of the recurrent laryngeal nerve is an anaesthesiology protocol in which it is necessary to reduce the influence of neuromuscular blockers and inhalation anaesthetics on the evoked signals, but at the same time maintain sufficiently deep anaesthesia to avoid spontaneous activity of the vocal cords that interferes with the correct interpretation of neuromonitoring results (8).

In our institution, for many years, we routinely use the TCI method for intravenous infusions of propofol in thyroid or parathyroid surgery when using intraoperative neuromonitoring of the recurrent laryngeal nerve. As a rule, we use the Schnider model, except for obese patients for whom the Schnider model is not adapted, in which case we choose the Marsh model. According to our clinical experience, there is no significant difference between these two TCI models in thyroid or parathyroid surgery.

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Heart Transplantation

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Heart transplantation (HT) became a reality in the late 1960s after nearly half a century of research in surgical techniques, pathophysiology, and immunology related to HT. Norman Shumway performed the first adult HT in the United States on January 6, 1968, at the Stanford University hospital. A team led by Donald Ross performed the first HT in the United Kingdom on May 3, 1968. Adrian Kantrowitz performed the world's first pediatric HT on December 6, 1967 in New York. Worldwide, more than 100 transplants were performed by various doctors during 1968. Only a third of these patients lived longer than three months. Major advances in survival should be credited to Dr. Margaret Billingham, the founder of cardiac transplantation pathology, for her early recognition and grading of transplant rejection following cardiac transplantation. She also described chronic rejection and techniques in heart endomyocardial biopsy. The next big breakthrough came in 1983 when cyclosporine entered widespread usage. In October 1994, left ventricular assist devices (LVADs) were approved for supporting patients as a bridge to HT. In 2021, there were a total of 8232 HTs at the global level, while 2026 HTs were performed in Europe[1]. In selected patients, HT is the definitive treatment for acute or end-stage heart failure, with a median survival of approximately 10 years.

Cardiac Transplantation Indications[2]: 1. Cardiogenic shock requiring either continuous intravenous (iv) inotropic support or circulatory support with a device such an intra-aortic balloon pump (IABP), LVAD, or total artificial heart (TAH), **2.** Persistent NYHA Class IV heart failure(HF) symptoms refractory to maximal medical therapy (LVEF<20%; peak VO2<10-12ml/kg/min), **3.** Intractable or severe anginal symptoms in patients with coronary artery disease(CAD) not amenable to percutaneus or surgical revascularization, **4.** Intractable life-threatening arrthythmias unresponsive to medical therapy, catheter ablation, and/or implantation of intracardiac defibrillator (ICD), **5.** Retransplantation, **6.** Congenital heart diseases unsuitable for surgical treatment, **7.** Progressive pulmonary hypertension (PH) , which could become a contraindication for heart transplantation in the future, **8.** Unacceptable quality of life, inability to perform daily activities

Absolute Contraindications[2]: Systemic illness with a life expectancy <2 yrs despite transplant, including the following: **1.** Malignancy within 5yrs, **2.** Active systemic infection, including HIV/AIDS (CDC definition of CD4 count <200 cells/mm3), **3.** Systemic lupus erythematosus or sarcoidosis that has multi-system involvement and currently active, **4.** Severe, nonreversible PH (PA systolic pressure >60mmHg, Mean transpulmonary gradient > 15mmHg, Pulmonary vascular resistance > 6 Wood units) -consider combined heart-lung transplant, **5.** Significant obstructive pulmonary disease (forced expiratory volume in 1 second FEV1 <1L/min), **6.** Irreversible renal or hepatic dysfunction (consider concurrent kidney or liver transplantation)

Relative Contraindications[2]: 1. Advanced age (rarely ≥70 years old), **2.** Severe symptomatic peripheral vascular and cerebrovascular diseases (symptomatic carotid stenosis, abdominal aortic aneurysm >6cm, severe diabetes melitus with end-organ damage, peripheral vascular disease not amenable to percutaneous or surgical therapy), **3.** Psychosocial issues: psychosocial instability, ongoing history of substance abuse, or inability to comply with complex medical regimen and follow up care, **4.** Obesity (BMI > 35 kg/m2) , **5.** Recent pulmonary infarction (6-8wks), **6.** Active infection expecting device–related infection in patients with VAD, **7.** Drug, tobacco, or alcohol abuse within 6mos, **8.** Difficult to control hypertension, **9.** Acive peptic ulcer disease, **10.** Heparin induced thrombocytopenia within 100days, **11.** Creatinine > 2,5 mg/dL, or creatinine clearance < 25ml/min, **12.** bilirubin >2,5mg/dL, serum transaminases >3, INR>1,5 off coumadin, **13**. irreversible neurological or neuromuscular disorder.

Donor Selection: Normal LV function is predictive of suitability for heart transplantation. Coronary angiography may be perfomed on patients >40yrs. Multiple large retrospective registry studies have demonstrated that donor hearts with initial low ejection fraction (EF) may have reversible dysfunction particularly in the setting of younger age or brain death/ severe brain injury causing neurogenic stress cardiomyopathy. Systolic function of these donor hearts may continue to improve post transplantation. Donor-recipient factors such as size, blood component ABO compatibility, gender, HLA –antibody compatibility are also be assessed. Finally, the surgeon will directly inspect the donor heart[4].

Hemodynamic Optimization Recipients: The presence of pre-transplant PH in heart organ recipients increases the risk of post-transplant PH and deterioration in right ventricular function in the donor heart. Right heart catheterization should be performed on all adult candidates in preparation for listing, and periodically when

patients are listed. Medical therapies include diuretics, inotropes, and vasoactive agents, both inhaled (i.e., nitric oxide and prostacyclins), and iv (i.e., nitroglycerin and nitroprusside). PDE-5 inhibitors (i.e., sildenafil) has demonstrated some beneficial effects[3].

Timing And Coordination: To minimise the ischaemia time of the donor organ and the preimplantation anaesthesia time in the recipient, induction of anaesthesia should be carefully coordinated with the arrival of the donor heart. Ischemia time should be kept well to 240 minutes[3].

Monitoring And Induction of General Anesthesia:

Immunosuppression therapy is initiated 1 hour before going to the operating room, using either basiliximab (Simulect) 20mg or thymoglobulin 1.5 mg/kg (maximum 125mg). The therapy continues in the ICU in accordance with the protocols. A high dose of methylprednisolone (500mg-1gr) is usually administered prior to the aortic clamp unclamping. Once admitted in the ICU, the patient will receive 125 mg bolus of solumedrol every 8 hours, with a specific descending dose scheme.

If the patient is receiving anticoagulation therapy with heparin, it is discontinued prior to going to the operating room. For patients being treated with warfarin, the target INR is <1.5. If the INR is higher, reversal is required using low doses of iv vitamin K (2.5-5mg). Fresh frozen plasma or prothrombin complex concentrate can also be considered as alternative options. Antimicrobial drugs are administered after induction of anaesthesia according to institutional protocol.

Monitoring: Peri-operative monitoring of heart transplant recipients should include routine monitoring, invasive measurement of arterial blood pressure(IBP) by inserting an arterial catheter, central venous pressure (CVP) by inserting central venous catheter, pulmonary artery sistolic pressure (PAPs,), pulmonary artery mean pressure (PAPm), pulmonary capillary wedge pressure (PCWP) by inserting PAC (pulmonary artery catheter- Swan Ganz), mixed venous oxygen saturation (SvO_2) cardiac output CO, cardiac index(CI), transesophageal echocardiography (TEE), near-infrared spectroscopy (NIRS), bispectral index (BIS), core and peripheral temperature measurement, continuous assessment of urinary output[2,3].

Anesthetic Induction: Patients may be stable at home or critically ill in the ICU. Patients may receive either iv or inhaled pulmonary vasodilator therapy. Recipient have had previous cardiac surgery or could be receiving some form of temporary

mechanical circulatory support, such as extracorporeal membrane oxygenation (ECMO) or LVAD, biventricular assist device (BIVAD), pacemaker (PM) or implanted ICD or medicamentous IV inotropic agents. Recipient acuity and complexity very greatly. General considerations for a candidate for cardiac transplantation include the underlying etiology of heart failure, documented waitlist priority status as an organ recipient, and assessment of comorbidities. All heart transplant recipients should be considered extremely fragile and prone to excessive hypotension in response to standard doses of sedative and opioid drugs. Drugs for inducing anaesthesia should be given slowly, allowing adequate time to determine their peak haemodynamic and hypnotic effects, which may be prolonged because of low CO. Midazolam or etomidate in combination with fentanyl or sufentanil are commonly used for anesthetic induction. Midazolam and etomidate are preferred to propofol for hypnosis, due to the less impact on hemodynamics. Sevoflurane or propofol infusion (4 mg/kg/h) in combination with fentanyl or sufentanil are the options for maintenance of general anesthesia. Continuous infusion with remifentanil is preferable for the less impact on renal function since it is metabolized by plasmatic esterase. This is particularly important in patients with CO and preexisting renal failure. Muscle relaxants with minimal cardiovascular effects (vecuronium or rocuronium) are usually used[2,3,5].

Cardiopulmonary Bypass (Cpb): Before cannulation for CPB, i.v. heparin is given at a standard dose (350–500 U kg^{-1}), targeting an activated clotting time above(ACT) 400–500 s. Repeat heparin dosing or antithrombin III concentrate (500 U) may be required in patients who have heparin resistance (antithrombin III deficiency) as a consequence of preoperative heparin therapy. From 0.5 to 5% of patients with end-stage heart disease can develop HIT (heparin-induced thrombocytopenia), due to repeated heparin exposures. Alternative anticoagulation, with direct thrombin inhibitors (bivalirudin and argatroban) is recommended in such patients. During CBP keep mean arterial pressure (MAP) about 60–80 mmHg and hemoglobin (Hb) levels at least about 8–9 mg/dL, which means to guarantee an adequate oxygen delivery (DO_2). We must ensure adequate glycemia control, urine output. Moderate hypothermia (28-30 ^{0}C) is commonly used to improve myocardial protection[2].

Postcardiopulmonary Bypass[2,3,5]: A heart rate(HR) of 90-110 beats /min, MAP> 65mmHg, CVP of approximately 12-16 mmHg and 14-18mmHg PCWP are often required in the immediate post CBP period. The transplanted heart is denervated, with loss of direct sympathetic input via the stellate ganglion and parasympathetic

input via the vagus nerve. Surface alpha and beta receptors are present, but the graft responds in an attenuated and delayed manner to circulating catecholamines. Transplanted heart unresponsive on pharmacological stimulation may require temporary epicardial PM. Inotropes/vasoactive support is usually required for CPB weaning. A combination of DOO pacing (90–110 beats min^{-1}) and low-dose dopamine (3–5 μg kg^{-1} min^{-1}) or dobutamine (3–5 μg kg^{-1} min^{-1}) is a reasonable strategy because they provides inotropic support to the new heart, especially to the right ventricle, which is the one more at risk of failure. Isoprenaline at low-moderate dose (0.02–0.04 mcg/kg/min) due to the positive chronotropic effect helps to maintain a heart rate of 100–110 bpm. Adrenaline (0.02–0.2 mcg/kg/min) provides inotropic support to the new heart, especially to the right ventricle. Milrinone (0.25–0.5 μg kg^{-1} min^{-1}) or other phosphodiesterase inhibitors (enoximone at 5–8 mcg/kg/min) as an inotrope and pulmonary vasodilator. Levosimendan (0.1–0.2 mcg/kg/min) has also been reported to reverse low cardiac output after heart transplantation. Noradrenaline (0.05–0.2 μg kg^{-1} min^{-1}) or/and vasopressin (2,5-5 U/h) is/are used as a vasopressor. Inhaled nitric oxide (iNO) at 10–20 ppm can be used as a pulmonary vasodilator and to attenuate primary graft dysfunction (PGD). In a scenario of severe vasoplegia resistant to previously mentioned vasopressors, methylene blue (0,5-2mg/kg) can be used. The choice of vasoactive drugs tends to be based on institutional preference.

The most common cause of failure to separate from CPB is right ventricle (RV) failure caused by impaired systolic function and increased PVR. RV failure is identified with TOE as RV dilatation and reduced free-wall contractility, tricuspid regurgitation and leftward bowing of the atrial and ventricular septum increasing the CVP above 15 mmHg .Treatment of RV failure involves optimising preload, augmenting RV contractility and reducing pulmonary vascular resistance (PVR). Patients who fail to wean from CPB or who do so with marginal haemodynamics (MAP<65 mmHg, CI<2 L min^{-1} m^{-2} and CVP>15 mmHg) despite modest-to high-dose inotropic and vasopressors support should be placed on mechanical circulatory support. Options include venoarterial (VA) ECMO or a temporary RV assist device. Evidence suggests that early institution of VA ECMO is the best option[4]. Before weaning from CPB, the patient must be rewarmed to a temperature of 36 ^{0}C.

Basic ventilation strategies to reduce pulmonary artery resistances such as hyperoxia and moderate hyperventilation are mandatory. Ventilation should be set at 60–100% FiO_2, 6–8 ml/kg TV (tidal volume), and low-moderate positive end-

expiratory pressure (PEEP 5–6 cmH_2O, after recruitment maneuver, with the intention to prevent lung atelectasis.

Anticoagulation and hemostasis: when the aortic and right atrium cannulas are removed, we need to guarantee an appropriate heparin reversal with protamine. We also give the patient 2 g of tranexamic acid at the induction of general anesthesia and 2 g (25–50 mg/kg) with protamine in association with 1 g of gluconate calcium, to avoid hyperfibrinolysis and replace calcium deficiency. If hemostasis is insufficient and the patient is still bleeding, we need to check for coagulation disorders via ROTEM(rotational thromboelastometry). Severe bleeding is not a rare condition especially in patients with previous heart surgery. RBC and platels which are administered should be leucodepleted.

Fluid Managment[2]: Fluid management should be "goal directed" that is, guided by the above-mentioned hemodynamic and echocardiographic parameters, and with the aim to avoid a fluid overload, which is very harmful for the lungs and the right ventricle, while providing adequate intravascular space filling. This should be done via balanced colloids and crystalloids in order to avoid electrolyte disorders and hyperchloremic hyperkalemic metabolic acidosis. Adequate oxygen delivery is ensured by maintaining the Hg level around 10–11 g/dL and an adequate plasma oncotic power is ensured by giving the right amount of albumin.

ICU Management[5]: The first 72 hours following heart transplantation is critical for both the short- and long-term prognosis of the patient. **Immediate postoperative complications**: **1. Arrhythmias** may be triggered by postoperative inflammation originating from suture lines or from high-dose inotropic support in the immediate postoperative period. **2. Vasoplegia syndrome** (VS) is rare but can be lethal following HT. It consists of severe refractory hypotension, metabolic acidosis, and low systemic vascular resistance. **3. Hyperacute rejection occurs** when circulating preformed antibodies to the donor heart are present, resulting in graft failure within minutes to hours of transplantation. Plasmapheresis, aggressive immunosuppression and corticosteroids therapy, with a focus on eliminating or removing the preformed antibodies provides the best chance of survival for these individuals. For patients in cardiogenic shock, ECMO support may be indicated while antirejection therapy is being administered. **4. RV failure** is another common complication in the immediate postoperative period. Several factors contribute to the likelihood of RV failure. In most younger donor hearts, the RV is naïve to elevated PA pressures and is, therefore, susceptible to acute RV failure at time of implantation into a recipient with pulmonary

hypertension. Treatment of RV failure includes volume optimization, inotropic support, afterload reduction, and mechanical circulatory support. iNO is commonly used postoperatively for heart transplant patients with elevated pulmonary pressures and RV dysfunction. Therefore, other modalities to unload the right ventricle (such as milrinone, levosimendan,ventavis, nesiritide, and sildenafil) are also utilized. **5. Primary graft dysfunction (PGD)** compared to secondary graft dysfunction, occurs when there is no discernible cause (such as hyperacute rejection or PH) leading to RV failure. **6. Acute kidney injury** (AKI) is commonly encountered in the CICU following heart transplantation. **7. Infections** are early postoperative complication. With the routine use of bacterial and viral prophylaxis, there has been a significant reduction in pneumocystis pneumonia infection and herpes viridae (including citomegalovirus(CMV))[5].

Long term complications of heart transplantation[4]: 1. Infections are a common complication following heart transplantation, predominantly within the first year after transplantation when it causes 30% of deaths. The high incidence of infection-related deaths within the first year might be explained by the higher dosage of immunosuppression which is required to control the more intense immune reponse early after transplantation. **2. Acute rejection**: Allograft rejection may occur at any time during the post-transplant period especially with discontinuation of immunosuppressants. The episodes of acute rejection necessitate emergency management with increased immunosupression, for example, iv immunoglobulin and plasmapheresis . At times, the patient may need mechanical circulatory support. Up to 30% of recipients may expirience rejection within the first year. **3. Graft failure and cardiac allograft vasculopathy:** Cardiac allograft vasculopathy is the atherosclerotic obstructive disease of coronary vessels. It may result from a variety of causes, for example, immune-mediated vascular injury, ischaemic endocardial injury before transplant, immunosuppressive agents, CMV infection, hyperlipidaemia, smoking and hypertension. **4. Renal insuffiency (RI):** RI is a strong predictor of survival after transplant. Risks for early RI, developing within 1yr of transplant, are increased donor and recipent age, increased serum creatinine at the time of transplant, presence of a VAD, female, rapamycin use at discharge and IL2R-antagonist. **5. Malignancy:** Cadiac transplant recipients require life long immunosuppression. Chronic immunosppression increases the risk of malignancies.

The Results In Transplanted Patients In Slovenia: From 1990 to the end of 2021, the Ljubljana UMC performed 384 heart transplants, 17 out of those in 2021. Sixteen

(94%) patients had an urgent and 1 (6%) an elective transplant. The multi-year average (2009–2021) waiting period for an elective heart transplant was approximately 240 days and for an urgent heart transplant about 55 days. Of all patients with a heart transplant in 2021, 47% needed the procedure due to ischemic heart disease and 35% due to dilated cardio- myopathy. Additional reasons for the transplant include valvular heart disease (6%), hypertrophic cardiomyopathy (6%) and congenital heart defects (6%). Survival of adult heart transplant ricipiens in% (1990-2021, n=384) was 93%, 89%, 77% at 30 days, one-year, five years, respecively. The patient survival rates are comparable with those from the international reference register kept by the International Society for Heart and Lung Transplantation (ISHLT)[6].

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Basic Principles of TCI

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During surgery, the intens of painful surgical stimulation the body experiences can change rapidly. This requires adjusting the drug effects quickly and precisely. Anesthesia is essentially titration of drugs according to need. During Total Intravenous Anesthesia (TIVA), conventional infusions can't quickly increase drug levels for sudden stimulation increases or decrease them fast enough for low stimulation periods. They also can not keep drug levels steady in the plasma or brain during constant stimulation.

The pharmacodynamic (PD) approach which is addressing this, adjusts drugs based on clinical findings, hemodynamic effects, EEG parameters, or other techniques for measuring anesthesia depth. The pharmacokinetic (PK) approach involves understanding concentration-effect relationships, minimal alveolar concentrations, therapeutic window concentration, dosing schedules to achieve these levels, and Target-Controlled Infusion (TCI).

TCI systems use PK models to control drug distribution and elimination mathematically. Different TCI systems might use variations of the Bolus, Elimination, Transfer (BET) scheme. The way a drug behaves after a bolus dose or continuous infusion is different. Bolus dose behavior is represented by a single-compartment model, while repeated administrations or infusion use two or three-compartment models.

After an IV bolus, the concentration over time shows a curve. The curve displays three phases: rapid distribution, slow distribution, and elimination. Drugs return to the plasma through rapid and slow distribution volumes and get metabolized and eliminated.

For continuous infusion methods, understanding a drug's pharmacokinetics is crucial. A three-compartment PK model is often used to predict drug behavior. The pharmacokinetics of most anesthetic agents are considered to best fit the three compartment models. These compartment volumes have no real anatomical correlation. They are theoretical volumes that can be remotely thought as the blood

volume (V1), a "vessel rich" compartment (V2) and a "vessel poor" compartment (V3). The volumes represent solubility, with higher solubility meaning a larger volume.

Elimination half-life is useless in a multi-compartment model. Therefore, a term called context-sensitive half-life was created. This concept is defined as "the time required for the plasma concentration of the drug to decrease by 50% after stopping the drug infusion". As the peripheral compartments fill (saturate), the cessation of drug action will depend more on metabolism and excretion from the central compartment. Agents with high clearance and short context-sensitive half-lives should be used for rapid onset of action and rapid recovery.

Pharmacokinetic models predict plasma concentration after a bolus dose or infusion within a specific time frame. These are typically obtained from measured plasma levels in a group of patients, considering variables like dose, patient characteristics, and measured plasma concentrations. Numerous algorithms suitable for a three-compartment model have been published to target plasma concentrations and site concentrations.

In TCI, the system calculates the required bolus dose and subsequent infusion rate to maintain the desired plasma drug concentration. The effect of the drug (brain concentration) will depend on the concentration in the central compartment (V1) and this is also the compartment where the drug is excreted from the body because it is also balanced by the kidneys, liver and lungs.

When the anesthetist wants deeper anesthesia for patient and increases the target concentration, the system gives a quick injection of the drug into the central compartment. This makes the level of the anesthetic drug in the blood rise quickly. The amount of drug put in is figured out based on how much plasma the central area can hold and how much drug is needed to reach the desired level. Once the system calculates that the drug level is where it should be, it stops the quick injection and starts a slower one. Because of practical reasons, the system does these calculations and changes the injection rate every 10 seconds. This means that even though the drug going out of the central area changes all the time, the injection rate changes like steps on stairs. If a three-part model is being used, then three sets of these injections are needed. Even though the targeted drug level stays the same, a steady injection is needed to replace the drug that the body gets rid of. Two sets of injections, which get slower and slower over time, are needed to balance out the movement of drug from

the central area to the other two parts. Because of all this, the injection rate slows down gradually until it stays the same (this takes more than 24 hours).

The effect of a drug depends on its concentration at the site of action. There is an hysteresis in clinical effect when the target plasma concentration of the agent is increased or decreased, since the clinical effect of a drug is determined by the effect site concentration not the plasma concentration. For pharmacokinetic/pharmacodynamic modeling, an effect-site compartment can be added. Due to its negligible volume, the rate constants for movement in and out of this compartment are the same (K1e = Keo). Keo should be used to describe the rate at which the drug is excreted from the site of action, but the site of action is generally considered to be an additional volumeless compartment, so there is no need for separate rate constants describing the movement into and out of the action compartment.

The drug concentration in the central compartment (V1) will be balanced with the effect site (i.e., the brain) depending on how rapidly the drug can cross the blood-brain barrier. The speed depends on the drug's physicochemical properties, how high its concentration is (higher concentration typically leads to a faster onset), factors like membrane transport proteins, and even the patient's genetics (among other reasons for titration).

Futhermore, a connection should be established between the drug concentration in the effect site and the actual clinical effect. For most intravenous anesthetics, it's assumed that the effect is directly related to the number of occupied receptors. From this, it can be deduced that there's a spectrum from no effect when no receptors are occupied to maximum effect when all receptors are occupied, and any additional increase in concentration won't lead to an increase in effect. A common approach to describe this relationship between drug concentration in the effect site and observed effect is the sigmoid Emax model. This model is a four-parameter empirical model: E0 represents the effect when no receptors (zero) are occupied (i.e., full consciousness, like a BIS of 97); Emax is the effect when all receptors are occupied (maximum effect, like BIS 0, seen in EEG burst suppression); EC50 is the concentration of effect site where 50% of the effect is achieved (e.g., a BIS of 50), and an exponential constant (gamma, γ) influences the slope of the concentration-response curve. Receptor occupancy isn't directly measured, and it should be understood that the drug's effect isn't as simple a physical entity as something like temperature. Signal translation, processing, smoothing, and interpretation will influence the final number seen on a

monitoring device. Additionally, the effects of IV drugs are often multifaceted: some are desirable, some are not (side effects). Although all these effects share the same PK driver (e.g., blood concentration), the PD model, including ke0, can be entirely different.

Different clinical effects arise from drug actions on various systems and may involve different lag times and rate constants. Propofol will not only render the patient unconscious but also induce vasodilation and, at higher concentrations, reduce heart contractility.[21] These effects necessitate different PD models and different ke0 values. If the cardiac ke0 is faster than the brain's ke0, it becomes evident how challenging it is for the administering anesthetist to avoid a well-known phenomenon – cardiac effects. This complexity is why anesthesia is perceived as intricate and even considered more of an art than a science by some.

Pharmacokinetic interactions happen when one drug affects the way another drug is processed in the body. Although these interactions should be considered, it's rarely needed to change the intended levels of drugs due to pharmacokinetic interactions. On the other hand, the more important concern is the synergistic effects resulting from pharmacodynamic interactions between anesthesia drugs. These interactions often lead to the need to decrease the target concentration of drugs.

The TCI systems offer options for pharmacokinetic (PK) algorithms. The Marsh and Schnider models are the most commonly employed for propofol administration, each carrying its own set of advantages and disadvantages. Existing models were developed using data from select populations, the use of which is, strictly speaking, limited to these populations.

A novel pharmacokinetic-pharmacodynamic (PK-PD) model for propofol has been created, employing the bispectral index (BIS) as the specific parameter of interest. This model has been constructed using data gathered from 30 previously published studies. Through this PK-PD model, it becomes possible to project propofol levels and BIS values across a broad spectrum of individuals, encompassing neonates, the elderly, and those with higher body mass indices (BMIs). Anesthetists utilized the Eleveld model in TCI to attain meaningful intraoperative Bispectral Index (BIS) values for various groups including children, adults, elderly individuals, and obese adults.

Remifentanil can be administered through Target-Controlled Infusion (TCI) using the Minto model. However, due to its relatively simple pharmacokinetics, it can also be administered as a standard infusion (μg.kg-1.min-1).

In what are known as open-loop TCI systems, the infusion regimen remains constant, while closed-loop TCI systems incorporate input from continuously measured variables (such as somatosensory evoked potentials for assessing anesthetic depth, blood pressure, measured blood concentrations, and exhaled drug concentrations). The primary algorithm of the concurrent closed-loop anesthesia control system. The flow chart illustrates the multi-input-multi-output system designed for managing neuromuscular blockade and the depth of anesthesia.

The advent of versatile, user-friendly and commercially avaliable target-controlled drug delivery systems has simplified Total Intravenous Anesthesia (TIVA) and made it as simple as using a vaporizer. It is of utmost importance to subject TCI infusion systems to as through a check as the anesthesia machine.

Infusion pumps are widely utilized in anesthesia and intensive care settings. Unfortunately, there has historically been a high occurrence of critical events linked to their use. Nevertheless, a majority of these incidents stem from human error. As a result, substantial efforts have been invested in developing more advanced and user-friendly pumps, constructing drug libraries, establishing standard techniques for drug dilution, and monitoring infusion sites and pressures. One of the distinctive features of TIVA is its capability to achieve precise drug titration, affording separate control over sedation and analgesia.

It is important to note that the adoption of TIVA should not overshadow inhalation anesthesia, provided there is appropriate training and rational utilization, especially when utilizing "smart" pumps designed to enhance safety. Inhalation anesthesia holds an evident advantage in the ability to monitor vapor concentrations in the respiratory tract. However, technology for measuring propofol in inspired air is also available and may potentially be introduced in future clinical applications.

Awareness should not be more prevalent than inhalation anesthesia, especially with the introduction of "smart" pumps that enhance safety, alongside proper training and rational utilization. Inhalation anesthesia holds an obvious advantage in the ability to monitor vapor concentrations in the respiratory system, but technology is also available to measure propofol in inspired air and might become commercially viable in future clinical applications.

To minimize incidents during TCI, careful consideration must be given to the preparation of drug infusions, programming TCI pumps, and selecting the appropriate pump.

An anesthetist using a TCI system for administering anesthetic agents can establish a desired concentration (often termed as the target concentration) and modify it based on observed responses to the set target concentration. This approach allows for separate provision of unconsciousness and analgesia. The process involves titration during induction, determining a propofol concentration for achieving unconsciousness, and then maintaining a consistent dose. Additionally, the concentration of opioids can be adjusted based on the extent of surgical stimulation (pain).

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Anaesthesia Tips in Paediatric Liver Transplantation

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The attempt of the first liver transplantation was led by Thomas E Starzl in 1963. at University of Colorado Health Sciences Centre where he has done the first successful one, lately in 1967. A 2 -year survival rate in pre-cyclosporine era (1963 - 1979) was 30% related to 84 paediatric cases, while in cyclosporine era (1980-1986) was 70%. Today in experienced centres long-term patient survival rate is over 90% (including infants)[1]. The first paediatric liver transplantation in Croatia was performed from living donor in University Hospital Centre Zagreb in 2001. Despite challenges related to low frequency of paediatric cases with end-stage liver disease, especially in limited pool of less than 4 million overall population of Croatia, programme is continued. Paediatric transplantation team in terms of surgeons was presented as Croatian model that includes paediatric hepatic surgeon, and vascular, microvascular/plastic, transplantation adult surgeons resulted with 3.3% of post transplantation thrombosis of hepatic artery. The biliary atresia among other causes as hepatitis, alpha-1 antitrypsin deficiency, Allagile syndrome and other metabolic diseases was the most frequent indication for transplantation. Children were age from 4 months to 16 years and were performed 33% liver transplantations with segmental grafts from living donors, 49% segmental and 18% whole grafts from deceased donors. Survival rates are 64.5% (5-year) and 61.1% (10-year) and suggests multifactorial aspects for improvement[2,3].

Preanesthetic assessment (detailed medical history report, examination – clinical, laboratory, and diagnostics of each organ system) is extremely important in transplantation process as well as the plan related to the equipment and monitoring in operating room, choice of anaesthetics, other drugs, and blood products. Liver transplantation has 3 main surgical phases: preanhepatic (recipient hepatectomy), anhepatic (implantation of the donor liver), and neohepatic (revascularization). There is a relatively high risk for development of complications in all phases of liver transplantation procedure so the crucial role to diminished them is to be familiar with all steps and to react properly and on time. Challenges are related to vast fluid shifts, electrolyte variations, metabolic disorders, sudden haemodynamic changes, and

coagulation impairment during the surgery merged with previously underlying causes and all organs affected by primary liver disease[4,5].

There are more than few anaesthesia tips related to paediatric liver transplantation, from the need to have experienced paediatric anaesthesiologists, sufficient vascular accesses and arterial lines, constant monitoring of coagulation abnormalities to balance between the possible scenarios of haemorrhage to the possible thrombotic complications, good haemodynamic management to preserve perfusion of liver graft that is at the end the primary goal, and the importance of recording intraabdominal pressure and metabolic changes to optimize the stability of the graft and the patient . Last two tips will be more discussed in this paper.

Intraabdominal pressure can be measured directly (peritoneal dialysis catheter) and indirectly (intravesical manometry, intragastric manometry) [6,7].

Proposed paediatric specific definitions related to intrabdominal pressure (IAP), intraabdominal hypertension (IAH), and abdominal compartment syndrome (ACS) [8]:

1. ACS in children is defined as a sustained elevation in IAP of greater than 10 mmHg associated with new or worsening organ dysfunction that can be attributed to elevated IAP
2. The reference standard for intermittent IAP measurement in children is via the bladder using 1 mL/kg as an instillation volume, with a minimal instillation volume of 3 mL and a maximum installation volume of 25 mL of sterile saline
3. IAP in critically ill children is approximately 4–10 mmHg
4. IAH in children is defined by a sustained or repeated pathological elevation in IAP >10 mmHg

Intraabdominal pressure should be measured already in preoperative phase since increased values have immense influence on respiratory function, cardiovascular system, kidney and gastrointestinal function, and neurological changes. Intraabdominal pathology related to elevated IAP (portal hypertension, enlarged liver and spleen, ascites) and optimization before transplantation will reduce the complications and mortality9,10.

The dynamic of IAP values is extremely important during transplantation and in postoperative period. Surgical closure of the abdominal wall could increase IAP

and lead to significant haemodynamic swings and difficulties in further mechanical ventilation. Anaesthesiologist should immediately alarm the surgeon to postpone final abdominal closure and use some of temporary closure methods 11. Another reason for IAH after transplantation is early formation of ascites probably related to hyperdynamic circulation, sodium levels, malnutrition, port-pulmonary hypertension, heart decompensation but also complications as thrombosis or stenosis of graft or infection. Preoperative diagnosis of biliary atresia was most commonly associated with postoperative ascites generation, and also is more frequently seen in paediatrics than in adults which is explained by reduced liver graft 12. Unrecognized IAH will lead to difficulties with the weaning, haemodynamic instability, impaired renal function, changes in consciousness, threaten graft viability, and at the end to multiple organ failure and liver rejection. IAP monitoring could clearly clarify the optimal timing to patch reduction or definitive abdominal closure and the time to PICU discharge13.

Frequent blood sampling is crucial to follow up and correct metabolic changes that occur during the entire transplantation process mostly expressed at anhepatic phase and in post-reperfusion period. Anhepatic stage is characterized with hypoglycemia (stopped process of gluconeogenesis merged with depleted stores of glycogen), hypocalcemia (mostly due to calcium binding to citrate from blood products), metabolic acidosis (related to the loss of liver function to metabolize lactate), and less usually in hyperkalemia. Supplementation with calcium, glucose infusion, sodium bicarbonate, etc is necessary to avoid detrimental effects of severe postreperfusion syndrome. This syndrome is accompanied with depletion of ATP, mitochondrial damage, activation of Kupffer cells, oxidative stress, and upregulation of cytokine response. Metabolic homeostasis will contribute to stabilization of cardiac membrane, optimization of blood pressure, heart rate and vascular resistance together with adequate volume resuscitation and vasopressors support, and coagulation derangements as well14,15,16,17.

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Comparison Of the Efficacy of Thoracic Epidural Analgesia And Peripheral Nerve Block In Thoracic Surgery

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Perioperative analgesia has a significant role in thoracic surgery and we are paying attention not only at patient satisfaction, but also at prevention of postoperative complications.

Effective pain management has a big influence on ventilatory capacity and mobility, decreasing the rates of complications, the recovery time of patients and reduce the hospital stay and costs.

Epidural anesthesia and thoracic paravertebral blocks were main streams for many years. By introducing of ultrasound into everyday practice, new blocks called interfascial plane blocks were included.

Ultrasound-guided thoracic wall blocks have an important role in multimodal pain therapie and make a good combination between opiate based and neuraxial pain management.

Interfascial plane blocks cannot provide surgical anesthesia, but their contribution to offer analgesia is clinically very important.

Knowledge of anatomy is of key importance to perform good blocks and to choose the appropriate one for the planned surgical procedure. The sensory innervation of deep tissues is a big source of pain (e.g. muscles, ligaments and bone) but it is often underestimatet.

Anterolateral blocks can be used as additional blocks in an opiate based pain management, whereas the dorsal procedures are an alternative to neuraxial anaesthesia.

In regional anesthesia there are many different ultrasound-guided approaches to the thoracic wall, from ventral (PECS I/II), followed by the lateral (serratus anterior), up to the dorsal blocks (paravertebral and erector spinae plane).

Thoracic epidural analgesia was the gold standard for pain relief in thoracic surgery. This neuraxial technique based on injecting a local anesthetic in the epidural space near the spinal cord to block spinal nerve roots. But epidural anaesthesia is lately for minimally invasive thoracic surgery, due to risk-benefit considerations, left out. Thoracic epidural anesthesia can have potential complications, such as epidural hematoma, spinal cord injury, and phrenic nerve palsy caused by high anesthetic level.

Nevertheless, awake videothoracoscopic lung resection can be safely performed under thoracic epidural anesthesia. Despite possible complications, it remains the method of choice. The same applies for a thoracotomy.

PROSPECT guidelines recommend erector spinae plane block or paravertebral block for postoperative analgesia after video-assisted thoracoscopic surgery, but we do not have studys about evaluating chronic postsurgical pain.

Minimally invasive thoracic surgery (MITS) reduce postoperative pain but it still causes significant pain. Ultrasound-guided fascial plane blocks of the chest wall are became alternatives to thoracic epidural or paravertebral block because they are simpler and safer to perform.

The mechanism of these blocks is a blockade of sensory afferent neurons in the targeted fascial planes and peripheral nociceptors in the surrounding tissues. They rely on the spread of local anaesthetic medication between muscle layers of the chest wall.

The erector spinae plane block is nowadays alternative to the thoracic epidural. First time was ESP described in 2016 as a regional block for thoracic neuropathic pain. This interfascial technique interrupts pain sensation by injecting a local anesthetic agent between the muscular layers of the thoracic wall and has the ability to block the dorsal and ventral branches of the spinal nerves through the craniocaudal spread of up to four dermatomes above and below the injection site.

ESP block occurred with the patient in a sitting or lateral decubitus position, with a high-frequency linear transducer placed in cephalocaudal or longitudinal orientation over the paramedian line. The aim is to visualize the ribs and pleura at the level of the 5th thoracic vertebra and transverse process.

At this point is possible to identify the trapezius, rhomboid major, and erector spinal muscles. A needle should be inserted up to the interfascial plane to the erector

spinae muscles group, facing the transverse process. The ESPB can be performed at all levels of the spine and provides analgesia to most regions of the body.

Taking into account the fact that the post-thoracotomy pain is one of the most severe types of postoperative pain and it can last up to 2 months after the operation, it is clear that can become chronic in more than 40% of patients. Pain therapy after thoracic surgery is important for reduction of postoperative pulmonary and cardiac complications.

Because of the challenge in pain therapy, many approaches were suggested, but a multimodal therapeutic strategy that provides a central or peripheral block associated with nonsteroidal anti-inflammatory is still the main vector. Thoracic epidural analgesia is regarded as the gold standard treatment for post-thoracotomy pain management because it results in early extubation, better ventilatory mechanisms and gas exchange, decreased incidence of atelectasis, pneumonia and chronic postoperative pain.

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Four Horsemen of Apocalypse: Lactate, CRP, Albumin, PCT

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The Four Horsemen of the Apocalypse are a group of mythical riders representing the forces of man's destruction described in the Bible in chapter six of the Book of Revelation. They are traditionally named after the powers they represent: War, Famine, Pestilence, and Death.

There are many interpretations and comments about these horsemen, but the main point is they are good symbols to warn humanity about the men-made disasters. According to these symbols, C-reactive protein (CRP) (war), albumin (famine), procalcitonin (PRC) (pestilence) and lactate (death) may be accepted as The Four Horsemen of the Apocalypse for the anaesthesiologists who struggle with the diseases and operations resembling disasters occasionally.

<u>*CRP (War):*</u> CRP is an evolutionarily conserved protein which is a pentamer of five identical subunits binding to phosphocholine (PCh) in a calcium dependent manner. As an acute phase plasma protein and key factor of innate immunity, it is released from hepatocytes after acute infections, injury and trauma. Interleukin (IL)-6 signalling regulates the synthesis of CRP in the liver. CRP levels also increase in disorders like autoimmune diseases, malignancy, chronic wounds after injury, inflammatory conditions, and metabolic disorders. The high sensitivity CRP (Hs-CRP) is a biochemical test which measures very low levels of CRP in plasma as a predictive marker of cardiac disease risk and stroke. CRP increases six hours after the beginning of proinflamatory process and reaches to peak level between 24-48 hours with a half life of 19 hours. CRP levels remain stable as they have no diurnal variations and no relation with food intake.The isomer nCRP activates the classical complement pathway, promotes apopitosis,induction of phagocytosis, supresses adherence of platelets to neutrophils and have more anti-inflammatory properties compared to mCRP. In addition, mCRP delays apopitosis by promoting chemotaxis and recruitment of circulating leucytes to area of inflammation. Risk of cardiovascular disease may be high if Hs-CRP level is > 2 mg/ L.

Albumin (Famine): Human serum albumin (HSA) is a non-glycosylated, negatively charged, single-chain polypeptide composed of 585 amino acid residues with a relative molecular mass of 66.438 kD. It is synthesized by the liver at a rate of approximately 200 mg/kg/day, with a half-life of 21 days, and subjected to catabolism in the muscles, liver, and kidneys at a rate of 4% per day. Albumin, accounting for 60% of the total plasma protein, has various physiological functions, such as maintaining 70% to 80% of effective plasma colloid osmotic pressure, coordinating vascular endothelial integrity, anti-oxidant and anti-inflammatory activities, maintaining the acid-base balance, and participating in the transport, distribution, and metabolism of a variety of endogenous and exogenous substances. The normal concentration of plasma albumin is 35 to 50 g/L. In clinical practice, hypoalbuminemia often occurs because of reduced albumin synthesis due to liver dysfunction, redistribution of serum albumin due to capillary leakage, or increased loss via the intestinal and renal routes. Hypoalbuminemia (defined as a serum albumin concentration less than 35 g/L) reportedly has an incidence of 24% to 87% in critically ill patients, while severe hypoalbuminmia (a serum albumin concentration less than 25 g/L) has an incidence of 5.0–9.6%. Hypoalbuminemia is an independent risk factor for increased short- and long-term mortality and an increased incidence of acute kidney injury (AKI) in patients with acute conditions such as trauma, cardiogenic shock, and sepsis. HSA is mainly used for fluid resuscitation and the treatment of hypoproteinemia in critically ill patients although there are controversial results regarding whether the use of albumin in critically ill patients improves their clinical prognosis. Albumin therapy is currently recommended in spontaneous bacterial peritonitis with ascites, refractory ascites not responsive to diuretics, large-volume paracentesis, post-paracentesis syndrome, and the treatment of hepatorenal syndrome as an adjunct to vasoconstrictors. New indications for albumin therapy are linked to the antioxidant activity of albumin and its effects on capillary integrity. Large-pore hemofiltration and albumin exchange are promising liver support therapies for liver failure and other toxic syndromes. Worldwide shortage and high cost of human albumin (native and recombinant) arouse the need for new usage criteria, protocols, and guidelines for appropriate utilization of albümin.

Procalcitonin (Pestilence): This is a serum prohormone released from various tissues after induction by proinflammatory mediators and endotoxins. As an indicator of severe bacterial infection such as sepsis, bacterial meningitis and pneumonia, PRC seems to be superior for diagnosis of bacterial infection compared to the common

biomarker CRP. PCT has been used in situations where differential diagnostics is needed. According to recent research, PCT is valuable when monitoring antibiotic treatment, and that PCT can be useful to reduce antibiotic use in several severe bacterial infections when used as a serial (delta-PCT) than a single measurement. In 2018, due to an international expert workshop PCT algorithm for patients with sepsis, a low PCT, <0.25 ng/mL in non-ICU patients and <0.5 ng/mL in ICU patients are indicators for not using antibiotics. In patients with moderate or high severity of infection, empiric therapy may be used, but antibiotics can be discontinued if PCT declines from the peak by >80% and/or below the proposed cut-off values. In addition, PCT should be tested every 24–48 hours to monitor antibiotic treatment.

Lactate (Death): In normal states of oxygenation during aerobic metabolism, mitochondria efficiently generate adenosine triphosphate (ATP). Glucose is converted by glycolysis to pyruvate that enters the Krebs (citric acid) cycle with acetyl-coenzyme A serving as the intermediary to unleash the chemical energy of molecular oxygen to generate the majority of cellular ATP during oxidative phosphorylation. When there is an anaerobic situation, the pyruvate produced by glycolysis is instead shunted toward the production of lactate by the enzyme lactate dehydrogenase. Lactate is produced in all cells to varying degrees: muscles (25%), skin (25%), brain (20%), intestines (10%), and erythrocytes (20%). In addition, lactate is a signal molecule in the brain to link neuronal activity, metabolism, substrate availability, and blood flow and may be involved with short-term memory and panic disorders. Lactate is released from the tissues into circulation and metabolized in the liver (60%) and kidneys (30%). It is directly filtered and reabsorbed by the kidney with only a small percentage lost to urine to generate ATP in times of stress at the tissue level via glycolysis (Cori cycle). Lactate and lactic acid are different biochemical concepts. Lactate as anion [lactate]– is a weak base formed directly by the conversion from pyruvate behaving as a buffer that accepts some of the protons generated during the hydrolysis of ATP to adenosine diphosphate. In times of demand, excessive hydrogen may be produced due to glycolysis quicker than the Krebs cycle and oxidative phosphorylation. When aerobic metabolism is unable to utilize the excess hydrogen ions or neutralization by the other buffer systems is inadequate, the result is acidosis. Hyperlactatemia is therefore mostly a consequence of cellular acidosis and not a direct cause of acidosis. When arterial pH falls below normal range and is concurrent with hyperlactatemia, it is commonly termed lactic acidosis. Using a term such as sepsis -or drug-associated lactic acidosis is more appropriate for this reason. Lactic acidosis is categorized as type

A when it is due to tissue hypoxia or systemic hypoperfusion and type B caused by other factors. In septic shock patients treated with catecholamines, hyperlactatemia with an elevated lactate/pyruvate ratio is more correlated with a prognosis of multisystem organ failure and death. Another point is that lactate may increase in the presence of oxygen when cellular mitochondria are unable to process all the pyruvate presented to them. In these situations, increasing the fraction of oxygen will not be an effective therapy.

In conclusion, the anesthesiologists are inevitable partners of the defence teams in disasters as exemplified recently by their glorious practice in COVID- 19. Hereby, the knowledge about the biomarkers like lactate, C-Reactive protein (CRP), albumin and procalcitonin (PCT) has proven to be very useful for decision making in operation rooms and ICU.

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ERAS Protocol in Liver Surgery

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The ERAS (Enhanced Recovery After Surgery) protocol for liver surgery has 25 items. Most of these items have a high level of evidence and a strong grade of recommendation. These items are: preoperative counseling, prehabilitation, preoperative biliary drainage, preoperative smoking and alcohol cessation, preoperative nutrition, perioperative oral immunonutrition, preoperative fasting and preoperative carbohydrate load, pre-anesthetic medication, anti-thrombotic prophylaxis, preoperative steroids administration, antimicrobial prophylaxis and skin preparation, minimally invasive surgery, epidural, postoperative intravenous, and postoperative per oral analgesia, wound catheter and transversus abdominis plane (TAP) block, prophylactic nasogastric intubation, prophylactic abdominal drainage, preventing intraoperative hypothermia, postoperative artificial nutrition and early oral intake, postoperative glycemic control, prevention of delayed gastric emptying, stimulation of bowel movement, early and scheduled mobilization, postoperative nausea and vomiting (PONV) prophylaxis, fluid management and monitoring/audit.[1]

Optimal postoperative pain therapy is an imperative for good postoperative care and treatment of all surgical patients. Also, this refers to surgical interventions during which resection of liver parenchyma is performed. Adequate postoperative pain therapy reduces surgical response to stress, improves bowel motility, promotes earlier mobilization, improves breathing, reduces the number of postoperative complications, and therefore increases patient satisfaction. Postoperative analgesia, one of the main components of perioperative patient treatment, is given special consideration for the accomplishment of all these aims.[2,3]

Adequate pain therapy begins with the patient arrival at the surgical facility, by talking to him, wishing to clarify the actual postoperative course and potential postoperative pain management. In intraoperative period, pain therapy is continued by placement an epidural catheter or peripheral blocks, opioids administration, using special anesthetic techniques and procedures... Postoperatively, multimodal analgesia is the standard of care in pain management.[2,3]

The application of thoracic epidural catheter (TEC) in liver surgery has numerous controversies. In addition to the intraoperative application of vasopressors, and problems with coagulation during TEC removal, further problems arise such as prolonged hospital stay and that there are no advantages to using PDK. But it is evident that the use of TEC has beneficial effects and is safe in liver surgery. Certainly further research is needed.[4,5]

We use the ERAS protocol for liver resection in order to help our patients recover as quickly as possible following such significant surgical procedures (open liver surgery) with the fewest possible postoperative consequences. One of the dilemmas in this protocol is the application of thoracic epidural anesthesia (TEA). In the protocol is written: "Intrathecal opioids and peri-incisional catheters are recommended, but TEA is not recommended". The main reason for this statement is “risk of bleeding due to the postoperative prolongation of prothrombin time can make timing of removal of the epidural catheter problematic, the sympathectomy from TEA can induce hypotension due to vasodilation, which can complicate fluid therapy, necessitate the need for low-dose vasopressors, and compound the risk of acute kidney injury” [1,6].

The greatest anesthesiologists fear is bleeding after TEA placement following liver surgery. We wanted to investigate whether coagulation disorders in patients who undergo open liver surgery lead to complications related to TEA and increased bleeding, during placement and after removal of TEA. This prospective cohort study was concluded in The Department of anesthesiology of Clinic for digestive surgery, University Clinical Center of Serbia where we followed 36 patients from May 2021 to March 2023. Our study shows that 58.3% of patients had major resection of liver tissue. Most of postoperative complications related to TEA (accidental removal of epidural catheter) 19.4% occurred on the first postoperative day. The removal of the epidural catheter was scheduled on the postoperative day 3. There were no complications related to TEA placement in terms of increased bleeding caused by coagulation disorders which was confirmed by other authors. TEA was very effective in the postoperative pain therapy.[7] There were no complications related to the intraoperative use of TEA in open liver surgery. Intraoperative use of vasopressors was more common in operation where TEA was used.

Removal of TEA on the third postoperative day was not associated with bleeding risks. Based on literature data and our results, we believe that the use of TEA in open liver surgery is a safe method for reducing postoperative pain. Further research is

needed to confirm the positive effects and safety of the application of the epidural catheter in liver surgery.

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Procedural Sedation and Analgosedation in Pediatric Intensive Care Unit

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Abstract

An essential part of care in the pediatric intensive care unit (PICU) is providing critically ill children with appropriate sedation and analgesia. Finding the perfect combination of adequate analgesia and sufficient sedation in a patient group with a wide range of ages, sizes, and developmental stages can be challenging. Administration of sedatives and analgesics to critically ill patients may be challenging and complicated by unpredictable pharmacokinetics (PK) and pharmacodynamics (PD). It is important to keep in mind that optimal agents for procedural sedation and analgesia (PSA) differ from those used for long-term sedation in the PICU. In addition to pharmacological measures, different non-pharmacological methods can be applied and have been shown to be effective for pain relief in children.

Introduction

Procedural sedation and analgesia (PSA) are defined as the administration of amnestic, anxiolytic, or analgesic agents, which facilitates the completion of painful procedures, ensures the immobility and safety of the patient, and prevents the child from remembering or feeling the interventions.[1,2]

As opposed to adults, most children are unable to comprehend the necessity of medical intervention and often refuse to comply with medical professionals. Furthermore, children require invasive testing, monitoring, and challenging, frightful medical procedures in the PICU, requiring the administration of analgesics and sedatives.[3] Even in the PICU, pediatric patients have historically, for a long time, been restrained physically during procedures.[4]

It is already common knowledge that infants hospitalized to critical care units (ICU) endure a number of painful treatments during their stay. A newborn may require up to 14 attempts to successfully insert an intravenous cannula, according to the EPIPPAIN 1 study, which collected data in 2005-2006.[5] A secondary analysis of the EPIPPAIN 1 study found that the use of specific analgesics for painful procedures in ICUs was more frequent during the daytime than at night. Moreover, a sharp decrease in the use of analgesics from morning to afternoon, followed by a gentle decline thereafter, was described, which can be considered an indicator of poor quality care that needs to be overcome.[6]

It is important to keep in mind the numerous challenges associated with applying procedural sedation and analgesia, even in the PICU. Apnea, hypotension, laryngospasm, bradycardia, clinically evident pulmonary aspiration, total airway obstruction, lifelong neurological impairment, or even death, are examples of significant adverse events.[7] Children treated with midazolam, propofol, and morphine were more likely to experience high levels of post-traumatic stress syndrome (PTSS) within one month of being released from the PICU.[8]

Due to the fact that many sedatives given to children are used off-label or unlicensed and have not completed the strict testing requirements to be approved for pediatric usage, children represent an at-risk population.[9,10]

Pharmacokinetics/pharmacodynamics

The pharmacokinetics (PK) of drugs in infants and children is strongly influenced by developmental changes in absorption, distribution, metabolism, and elimination. Children undergo many PK alterations as they grow and mature; drug distribution changes, hepatic enzymatic capacity matures, and renal function develops. For example, CYP3A4 is responsible for primarily metabolizing midazolam. Because of the immature CYP3A4 enzyme activity in an infant, a decreased clearance of midazolam would be expected. As a result, the dosing regimen for adults cannot be simply or linearly extrapolated to children, especially in neonates and infants.[11] In comparison to adults and children, neonates and infants have higher fentanyl clearance and volume of distribution (Vd), which is likely due to increased hepatic blood flow and/or different protein binding.[12]

In everyday clinical practice it is noticed that the severity of the critical illness itself may have a significant impact on analgesia and sedation. For example, the

underlying illness of a critically ill child (e.g., sepsis) will influence the response to the administered drug to be different compared to a healthy child.[13]

Pharmacological agents

The choice of drug and the route of administration used during PSA in the PICU should consider the criteria related to the type of procedure that the patient will undergo, as well as the criteria related to the baseline state and comorbidities. Benzodiazepines and opioids are traditionally used for PSA in the PICU, α-2 agonists and intravenous anesthetics are used as adjuncts in the therapeutic arsenal. The key to success and safety is to titrate drugs based on the patient's response and the onset time of the drug(s) administered.[14] Combinations of different drugs can also be used to provide procedural sedation in the PICU. A combination of ketamine and propofol ("ketofol") allows a smaller dose of each one, thus potentially improving the quality, safety, and duration of recovery time.[15] With few side effects, procedural sedation in the PICU using ketamine and midazolam is considered generally safe.[16]

Most sedatives and analgesics in the PICU are administered intravenously. Enteral administration may lead to sub-optimal analgesia and sedation due to a slower onset or a prolonged and unpredictable duration.[17] In addition, in many children, especially in surgical intensive care units, enteral intake is stopped. Intranasal (IN) drug administration has become an alternative way to less invasive and quick delivery of drugs, mainly in pediatric emergency departments when intravenous access is not yet established.

Non-pharmacological measures

The main advantages of non-pharmacological therapies include simplicity of use, apparent safety, viability, and simplicity of learning, all of which would permit the universal application of any of these interventions.18 Non-pharmacological measures could be divided into five main groups (environmental control, feeding methods, cognitive techniques, complementary techniques, physical methods). The use of non-pharmacologic pain therapy varies among PICUs and may be underreported or underutilized.19

Conclusion

Pain relief is a basic human right at any age. Children have historically received inadequate care for discomfort and invasive treatments. A rational choice for a particular agent should be based on the desired effects of the drug, its

pharmacokinetic properties, and its side-effects. It would be wise to take steps to cut down on the number of painful and stressful procedures in the PICU. Different non-pharmacological methods can be applied and have been shown to be effective for pain relief in children.

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Neuromuscular Blocking Agents in Pediatric Anesthesia - Cons

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Abstract

To date, there is little consensus on the use of neuromuscular blocking agents (NMBA) during paediatric surgery. It is known that children have markedly variable sensitivities to non-depolarizing NMBA at different ages. Other reasons for omitting muscle relaxants are numerous. Among these are: pharmacogenomics differences, challenging objective neuromuscular monitoring, surgical procedures in which paralysis is undesirable, possible allergy to muscle relaxants, the presence of neuromuscular disorders, brief procedures, risk of perioperative respiratory adverse events, and numerous existing relaxant-free techniques for intubation and maintenance of anaesthesia in children.

Pharmacogenomics - significant individual differences

Butyrylcholinesterase enzyme (BChE) is a hydrolase of succinylcholine. More than sixty BChE gene variations are considered to be responsible for the hydrolysis enzyme dysfunction or instability, which leads to approximately 65% of succinylcholine related apnoea. The most frequent mutation in the BChE gene is the Kalow (K) variant. The mean duration of succinylcholine induced muscle relaxation was up to 4 minutes longer in K-variant patients than in wild-type patients. Variations in the genetic sequence of BChE, especially BChE * I3E4-14C, BChE * FS126 and BChE * 328D, were closely related to prolonged duration of succinylcholine action. Seven new mutation sites of BChE gene (I373T, G467S, W518R, L184S, V421A, M462I and R577H) were further identified as essential biomarkers for prolonged action of succinylcholine.

Variations of several key genes, including but not limited to organic anion-transporting polypeptide 1B1 (SLCO1B1), organic anion-transporting polypeptide

1A2 (SLCO1A2), ABCB1 and genetic variants of pregnane X-receptor (NR1I2), have considerable consequences for individual pharmacokenetic differences of rocuronium.[1,2]

Anaphylaxis - all neuromuscular-blocking drugs are not the same

Although anaphylaxis during anaesthesia is a rare event, neuromuscular blocking drugs are responsible for 62% of anaesthesia-related anaphylaxis. The incidence of intraoperative anaphylaxis is 1:2499 for rocuronium and 1:2080 for succinylcholine whereas for atracurium it is 1:22,451.[3]

Children are not small adults

Infants and young children are sprinters and not marathoners. The limitations of subjective assessment and under recognition of residual paralysis may be a particular concern with use of NMBA among infants. Skeletal muscle and the diaphragm undergo extensive functional maturation during the first year of life. The neonatal diaphragm lacks fatigue resistant type 1 fibers, and neonates have multiple physiologic factors that increase vulnerability to respiratory failure. Infants and young children have compliant, easy collapsible airway structures, proportionally large tongues, and short necks, which make them more prone to obstruction. If their normal anatomy is combined with the weakness and hypotonia that can result from residual neuromuscular blockade, they are set up for the development of respiratory insufficiency or failure and upper airway obstruction. These problems can lead to weakness, hypotonia, and airway obstruction, which leads to hypoxemia, which results in bradycardia, cardiac arrhythmias, and cardiac arrest. Neuromuscular transmission is immature in neonates and small infants until 2-months of age. Therefore, it is entirely plausible that some infants may have a reduced TOF ratio without muscle relaxation.

The primary factors leading to slow and incomplete NMB recovery following NMBA administration among NICU infants could include: hepatic and renal immaturity, acid-base or electrolyte derangement and accumulation in an expanded extracellular fluid volume.[4]

Objective neuromuscular monitoring may be challenging

Objective neuromuscular monitoring may be challenging, especially in smaller children due to the limited space and the small arms which will often not be accessed because of the sterile draping and surgical equipment. Anaesthesia care providers

frequently experience problems with neuromuscular monitoring. These may be the most important reasons why objective neuromuscular monitoring is not routine. Without quantitative monitoring residual neuromuscular block (RNMB) cannot be excluded in paediatric patients (Klucka). The most important finding of Klucka et al. trial was a low rate of neuromuscular blockade monitoring (2.5%) It can be considered very low when compared to data from the adult population, where the reported rate is up to 24.4%. In the study od Ledowski et al. the incidence of RNMB was 28.1%. Severe RNMB (TOF ratio < 0.7) was found in 6.5% after both no reversal and neostigmine, respectively. Complications in the postoperative acute care unit were infrequent, with no differences between reversal and no reversal groups.[5-7]

Beware of the extravasation of muscle relaxant in children

The use of small cannulas in children necessitates the use of relatively greater force, increasing the risk of extravasation. The extravasated muscle relaxant serves as a "depot" preparation. Minor extravasation may delay the recovery of full muscle power.[8]

Risk of perioperative respiratory adverse events

Scheffenbichler FT et al.[9] hypothesized that a high intraoperative NMBA dose would be associated with an increased risk of perioperative respiratory complications, including respiratory failure, pulmonary oedema, reintubation, and pneumonia, in paediatric patients undergoing surgery with general anaesthesia. Subcohorts of paediatric patients particularly vulnerable to the respiratory side-effects of NMBA are: infants, paediatric patients undergoing surgeries of short duration and high ASA risk score.

Twelve US Multicenter Perioperative Outcomes Group hospitals were included in a multicenter observational matched-cohort study of adult surgical cases between January 2014 and August 2018. In multivariable analysis, sugammadex administration was associated with:

30% reduced risk of pulmonary complications, 47% reduced risk of pneumonia, 55% reduced risk of respiratory failure, compared to neostigmine.[10]

On the other hand, in the case of an unexpected difficult pediatric airway sugammadex should not be administered if the child is rapidly deteriorating with decreasing oxygen saturation and hemodynamic compromise. In such a circumstance, a surgical airway is the priority, and the administration of sugammadex may delay

rescue techniques and oxygenation! The reversal of neuromuscular blockade may take up time, as well as not guaranteeing a return to spontaneous ventilation, particularly when an anatomical cause of upper airway obstruction exists.[11]

Current evidence for the use of sugammadex in children

Adverse effect profile with sugammadex has generally included minor and self-limited issues including nausea, vomiting, pain, hypotension, and headache. A mild prolongation of the PT and aPTT, lasting for 60 min, has been reported in patients receiving large doses of sugammadex (16 mg/kg).[12]

The adverse effects of sugammadex in pediatric patients are described in the literature. In most cases, severe bradycardia occurred in patients presenting cardiac comorbidities. Conversely, Carvalho et al. described two case reports of healthy pediatric patients in which, despite complying with drug administration recommendations, severe bradycardia was diagnosed and reversed only after treatment with atropine.[13]

Sugammadex is a cyclodextrin compound. Gamma-cyclodextrins are common food additives. Little is currently known about the mechanism of sugammadex-induced anaphylaxis due to the lack of sugammadex-specific IgE antibodies available for testing, and skin prick tests for the drug are still in development. Emerging case reports in the literature lacked previous exposure to sugammadex, suggesting cross-reactivity between sugammadex and another substance including a suspected case of anaphylaxis to the rocuronium- sugammadex complex.[14]

Reversal of neuromuscular blockade with sugammadex has been suggested in clinical scenarios and patient populations where reversal of neuromuscular blockade with acetylcholinesterase inhibitors may be relatively contraindicated including myotonic dystrophy, myasthenia gravis and Angelman syndrome.[12]

Tracheal intubation without neuromuscular blocking drugs in children

With increased use of the laryngeal mask airway in children, the number of children requiring tracheal intubation has reduced significantly but for many operations where a tracheal tube is required, muscle relaxation is not necessary and some authors strongly supports relaxant-free techniques in children for elective surgery. Relaxant-free techniques of tracheal intubation do work well in the majority of paediatric cases and should be in the repertoire of every paediatric anaesthesiologist! The most useful techniques are propofol or remifentanil

supplementation after a sevoflurane induction or either a propofol / alfentanil, a propofol / remifentanil or a propofol / remifentanil/ dexmedetomidine induction sequence.[15-18]

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Chronic Postsurgical Pain

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Introduction

Acute pain following surgery is a predictable, physiological response to tissue damage. Patients are prepared for some degree of pain or discomfort but expect that it will pass. However, up to one third of patients undergoing common surgical procedures report persistent or intermittent pain of varying severity at one year postoperatively [1].

Chronic post-surgical pain (CPSP) is one of the most frequent complications after surgery, with an important negative impact on patients' quality of life that constitutes significant economic and healthcare burdens.

Definition

CPSP was first defined in 1999 by Macrae and Davies [2], and later expanded by Macrae [3] in 2001, as "pain that develops after surgical intervention and lasts at least 2 months; other causes of pain have to be excluded, in particular, pain from a condition preceding the surgery". An updated definition of CPSP, or persistent postsurgical pain (PPSP), was later proposed by Werner and Kongsgaard in 2014 [4]. The proposed definition was "pain persisting at least three months after surgery, that was not present before surgery, or that had different characteristics or increased intensity from preoperative pain, localized to the surgical site or a referred area, and other possible causes of the pain were excluded (e.g., cancer recurrence, infection)".

The definition of CPSP (i.e. chronic postsurgical or post-traumatic pain) was standardised in 2019 after the inclusion in the new International Classification of Diseases, Eleventh Revision (ICD-11):

- Pain develops or increases in intensity after a surgical procedure or a tissue injury.
- Pain persists beyond the healing process, that is ≥3 months after the triggering event.

- Localisation: either at the surgical/area of injury, or projected onto the innervation area of a nerve in this area, or related to a dermatome or Head's zone (after surgery or injury to deep somatic and visceral tissue).
- Other causes of pain (e.g. pre-existing pain conditions, infection, malignancy) are excluded.
- Chronic post-surgical pain can often show characteristics of neuropathic pain.
- It is distinguished between tissue trauma arising from a controlled procedure in the delivery of healthcare (surgery) and forms of uncontrolled accidental damage (other traumas).

The inclusion in the ICD-11 raises awareness of the condition as a disease rather than merely a symptom, and the need for specific treatment and management [5].

Incidence

A study by Fletcher et al. of surgical patients in Europe demonstrated that 11.8% of patients have moderate to severe pain, while 2.2% have severe pain (NRS ≥ 6), at 12 months after surgery. Persistent pain can occur following various operations, ranging from simple and common ones (to illustrate, herniorrhaphy, caesarean section or dental extraction) to complicated surgeries (such as thoracotomy, radical mastectomy or hysterectomy).

The reported incidence of CPSP varies for different surgical procedures and in different studies, ranging from a low of 5% to a high of 85%. For example, studies have reported incidences ranging from 50%–85% following limb amputation, 11%–57% following mastectomy, 30%–55% after cardiac surgery, 5%–65% after thoracotomy, and 5%–63% following hernia repair [6].

Risk factors

The early identification of risk factors can allow risk stratification and the implementation of preventative treatment strategies. Several factors from the periods before, during and after surgery have been identified across different studies, but the evidence is not conclusive. Besides the type and approach of surgery, various other risk factors have been attributed to CPSP. Some of them are patient factors (including female gender, being a young adult, genetic predisposition, and psychosocial factors), preexisting patient conditions (for example, pain present preoperatively, and any preexisting painful conditions in other parts of the body), and perioperative factors

(for instance, duration and type of surgery, extent of nerve damage intraoperatively, and severity and duration of acute postoperative pain) [1].

Mechanisms And Characteristics

Chronification of pain is complex and the underlying patho-physiology includes peripheral (at the site of injury) as well as central (spinal and supraspinal) sensitisation. The inflammatory and immune response to axonal and tissue damage, including the release of neurotransmitters peripherally as well as in the spinal cord, leads to (micro)glial activation, ectopic neural activity and altered activity in the dorsal horn. There are also changes in the supraspinal processing including brain network connectivity and changes in endogenous, descending pain modulation. The molecular mechanisms of CPSP have been described in several reviews. [7,8,9,10].

As a consequence of the central sensitisation processes, patients developing CPSP often report typical clinical symptoms such as hyperalgesia (increased painful sensation caused by a noxious stimulus), allodynia (painful sensation caused by a usually non-painful stimulus), dysaesthesia (unpleasant touch perception or tingling) indicating nerve damage and central sensitisation very early after surgery [11].Some of these changes can be assessed and tested, for example by using quantitative sensory testing (QST) early after surgery. Hyperalgesia detected early after surgery might predict prolonged, chronic neuropathic pain after surgery [12]. Although 35–57% of patients with CPSP show signs of neuropathic pain, the incidence for different surgeries varies widely and is highest after thoracotomy, mastectomy and amputation. This indicates procedure-specific aspects such as injury to the subcostal nerves during thoracic surgery and injury to the brachial nerve/axillary plexus during mastectomy. Patients with neuropathic CPSP report more intense pain, greater limitations in activities of daily life and reduced quality of life. Other mechanisms such as visceral, inflammatory and neuroplastic pain might play a role in procedures such as knee surgery, hip surgery and abdominal surgery that are less likely to be associated with neuropathic CPSP [13,14].

Prevention

Currently, there is no definitive way to prevent the occurrence of CPSP. Various techniques have been tried, by anesthesiologists and surgeons alike, to reduce the risks, but with variable success. Identifying the risk factors in each patient and applying a timely preventive strategy may help patients to avoid the distress of chronic pain. Anesthesiologists are requested to identify risk factors, analyze the

already available evidence on use of prophylactic drugs, individualize the therapy, and effectively treat acute and subacute pain. There is also the crucial role of the surgeon in the prevention of CPSP.

Regional anesthesia techniques can favorably impact the outcome of the surgical patient, particularly concerning pain. Anesthesia blockades can prevent central sensitization by decreasing nociceptive afferent stimuli to the dorsal horn of the spinal cord. Epidural anesthesia and paravertebral block were shown to be valuable in reducing the incidence of CPSP in thoracic and breast surgeries, respectively.Evidence shows that spinal anesthesia plays a preventive role for CPSP in patients submitted to C-section. Also, continuous intravenous infusion of lidocaine was shown to be useful for preventing CPSP after breast cancer surgery [15].

Treatment of CPSP

As any type of chronic pain, the treatment of CPSP is challenging. Evidence is still lacking and controlled randomized studies are required to establish the benefits of the several currently proposed treatments. Similarly, to non-cancer pain conditions, treatment based on pathophysiology may be useful for CPSP.

Numerous attempts to treat CPSP have been carried out with drugs and procedures, such as anticonvulsants, antidepressants, local anesthetics, opioids, capsaicin, NMDA antagonists, epidural block, neurotoxins, acupuncture, physical exercises, spinal and magnetic neurostimulation, revision surgery, laser, mirror therapy, and interventionist techniques. Thus far, however, the beneficial impact of each technique cannot be safely stated [15].

Conclusion

Acknowledging the existence of CPSP and its well-established risk factors is crucial for the anesthesiologist's daily practice. By using this knowledge, we can impact the outcome of many patients submitted to routine procedures and who, depending on how they are managed, can evolve to CPSP, a disease that is poorly understood now. Among the surgical patients, 5% to 75% may develop CPSP. This is a major challenge requiring greater awareness and commitment from everyone, including surgeons and anesthesiologists.

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10 N Rules (Principles) In Pediatric Anesthesia

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The aim of the Safe Anesthesia For Every Tot initiative is to address the well known risk factors and causes for anesthetic morbidity, to focus on the safe conduct of anesthesia in young children and to provide guidance on markers [1]. This initiative addresses the well known perioperative risks in young children, perioperative causes for cerebral morbidity as well as gaps in regulations, working, teaching and research [1-4]. Clinical history and physical examination findings are crucial for the early recognition of the critically ill child [1-7].

"State of the art" in pediatric anethesia is frequently defined and propagated at scientific meetings, congress and in the literature in the form of expert lectures, opinions and reviews [1]. However, economic pressures and sometimes lack of even basic staffing and logistic resources may lead to situations in which low-risk anesthesia is conducted by insufficiently trained and inexperienced personel, insufficiently equipment and thus rapidly turns into high-risk anesthesia [1]. The skill and dedication of the anesthesiologist is much more important than what drugs are being used [1,2,5].

Up to 75% of children may experience fear/anxiety during anesthesia, mostly during induction [1-7]. Preoperative anxiety in children may result from the fear of pain, unfamiliar surroundings, the presence of strangers and parental anxiety[1-7]. Some children will openly say they are frightened, others cry and become agitated [1-7]. Anxiety may reduce cooperation, contribute to emergence delirium and increase pain and behavioral disturbances (sleep disturbances or nightmares, enuresis, separation anxiety and increased fear of doctors) after surgery[1-7]. Age-appropriate psychological preparation, parental presence and pharmacological premedication can be used to reduce anxiety in children [1-7]. Awareness - postoperative recall of sensory perception during general anesthesia is a significant, underreported anesthetic complication.

Risk factor for awareness include drugs (neuromuscular blockade, thiopental, TIVA) to minimise this complication it is necessary to use complete monitoring perioperatively [1-7].

Maintenance of physiological body fluid homeostasis is important for normal organ function [1] . Reduced preoperative fasting times with 6-4-2 hours rule [1,6]. Hypovolemia results in hypoperfusion and tissue hypoxia and leading cause of perioperative cardiac arrests (POCA) in children [1,6]. Hypervolemia results in dilutional coagulopathy and tissue edema [1,6]. Prevention and treatment include preoperative clinical assessment (capillary refill time, urinary output), correct preoperative disturbances if required and consider using invasive pressure monitoring, repeted arterial blood gas analysis and non-invasive cardiac output monitors perioperatively [1,6]. Lactate is one a cluster of markers of cellular perfusion and oxygen delivery [6].

Cardiac output and organ perfusion is primarily dependent on the heart rate and blood pressure in young children [1-7]. Suitable pediatric equipment for precise measuring of blood pressure and heart rate, treating relevant hypotension and bradicardia, monitor volume status and tissue perfusion are using to keep normotension and normal heart rate perioperatively in pediatric patients[1].

The primary goal consensus approach to the pediatric airway is the prevention of periopartive hypoxia in children [1,8]. Prevent hypoxia through regular parctice, teaching and training staff, using established airway algorithms, protocols, equipment and devices, recognize and treat all kind of airway obstructions are the crucial steps [1,8].

Changes in arterial carbon dioxide tensions signifficantly affect body homeostasis including the acid-base status, the sympathomimetic tone and organ blood flow[1-5]. Prevention requires regular teaching and training of ventilation strategies with considering limitations of monitoring, airway equipment and adequate ventilation management [1-5, 7,8].

Monitor plasma sodium concentrations during major surgery and/or in children with comorbidities is necessery to achieve normonatremia perioperatively [1,6,7]. Plasma sodium is a major determinat of neuronal excitability, serum osmolality and therefore extracellular fluid volume [1,6,7]. Acute perioperative changes in plasma sodium concentrations are a leading cause of avoidable morbidity and mortality in children [1,6,7]. Prevention and treatment include prolonged parenteral fluid administration and usage balanced isotonic solutions [1,6,7].

Blood glucose homeostasis is important for ensuring a continuing energy supply and stable plasma osmolality [1,6]. Small infants have reduced glycogen storage capacity and hence have a limited ability to maintain blood glucose concentrations during periods of fasting[1,6].

Monitor body temperature continuosly is necessary to prevent hypothermia (problem in children exposed to anethetic drugs, caused increasing metabolic rate and oxygen consumption, prolonged bleeding time and increased risk for postopertaive infection) or hypertermia (iatrogenic overheating, malignant hyperthermia, thyrotoxicosis and sepsis) [1-5,7].

Establish standards for prevention, recognition and tretament of pain (use a multi-modal approach to pain therapy), emergency delirium and PONV (use a combination of psichological and pharmacological treatments) provide a simple matrix of clinical goals [1-5].

The 10 N rules (principles) should be applied to all pediatric anesthetic procedures from all anesthesia providers.

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Pediatric Airway Management: How Far Have We Come?

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Airway management plan for anesthesia in pediatric patients should includ all possible complications and their management before administering any anesthtetic drugs. The incidence of perioperative critical events in children is 5,2%, respiratory complications related to the airway management are one of the main causes, with the incidence of 3,1% and remain a significant cause of morbidity and mortality [1,2,3]. The major risk factor for these critical events is actually age of children. Neonates and infants are at particularly high risk due signicicant comorbidities and those undergoing emergency inteventions.

Airway obstruction and delayed management lead rapidly to hypoxemia, respiratory acidosis, bradycardia and cardiac arrest due to children have a decreased oxygen reserve and increased oxygen consumption as well as higher carbon dioxide production when compared with adults [4].

Transient perioperative hypoxemia usually does not result in immediate postoperative morbidity but prolonged hypoxemia and bradycardia increases the risk of cognitive and motor impairment in later life in pre-term neonates [4].

APRICOT study revealed evidence supporting the beneficial effect of years of experience of the most senior anaesthesia team member for respiratory and cardiac critical events, rather than the type of health institution or providers [1]. NECTARINE study showed that perioperative complications in infants associated with increased risk of morbidity and mortality are mainly hypotension (□30% decrease in blood pressure), reduced oxygenation (SpO2□85%), and anemia [2]. Risk of those critical events increases by congenital anomalies, prior neonatal medical conditions, patients requiring intensive care, and neonatal gestation. Timeline of developments in pediatric airway management starting with 1950's with definition of pediatic airway anatomy, 1990's with supraglotic airway devices in pediatric airway management but

the real progress started in the first decade of the 21st century with EXIT (ex uteri intrapartum treatment) intubation, and fiberoptic bronchoscopy and videolaryngoscopy as golden standards in daily practice for management of difficult pediatric airway [1,5-8]. Then, over the following years, the guidelines were, at first, a modification of adult based approaches, and only later were the guidelines made specially for pediatric patients [1,4]. Over the following years, the neuromuscular blocker was added to the guidelines, and the ultrasound started being used in airway management [1,8]. The next step was ECMO (Extracorporeal membrane oxygenation) incorporation in protocols of resuscitation and Later on, the Vortex protocol was implemented, and the latest addition was apneic oxygenation [1]. During COVID-19 pandemic, there are special airway management protocols which define the standard of care. Nowadays we have American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Pediatric Airway, the newest one, with purpose to guide the management of children with difficult airways, optimize first attempt successes, improve patient safety during procedures, and minimize/avoid adverse effects [1].

Careful pre-anesthetic evaluation, a history of a difficult management, which is highly sensitive and specific for the diagnosis of a difficult airway, physiological changes such as active flue or flu episode within the past three weeks, a history of epiglottitis, bronchospasm, rhinitis, obstructive sleep apnea syndrome, adenoid or tonsillar hypertrophy and clinical assessment with recognition of possible signs and symptoms of airway obstruction including stridor, wheeze, cyanosis, dyspnea, suprasternal retractions will reduce airway management related complications [1-13]. Anatomical abnormalities of the lower third of the face, low-set ears, limited neck mobility, inability to open the mouth at least 3 of the child's finger breadths and inability to bite the upper lip with the lower teeth is a finding associated with difficult pediatric airway [1-13].

Regarding previosly pediatric airway is classified into normal airway, impared difficult airway (suspected, altered, acquired, unanticipated or unexpected) and expected difficult airway (anticipated, known abnormal [1-8]. Normal pediatric airway is a healthy airway without past history of physical and anatomical disorders and routine airway management is normally easy [1-8]. But even the normal, heathy pediatric airway could become difficult during the anesthesia.

The anatomy of the pediatric airway is reassessed in vivo and new findings is that the pediatric larynx has the same cylindrical shape of the adult larynx, even

elliptical, with the anteroposterior diameter longer than the lateral diameter and having two narrowness, at the level of the cricoid ring, as described in old studies, and at the level of the vocal cords as a new finding [1,5].

Ultrasound (US) in pediatric airway mangement is used to make measurements that help predict a difficult approach to the airway also superficial neck scan allows to identify the location of the cricothyroid membrane and tracheal rings for guidance should the need for FONA and correct endotracheal intubation as well as selective ventilation due to endobronchial intubation can be detected by US through comparison of bilateral pleural movement [1,5].

A large number of devices for approaching pediatric airway are available in the market but mandatory is that all equipment as well as resuscitation drugs should be prepared in appropriate sizes or dosages in working condition. All tools to establish a safe pediatric airway and to manage possible complications must be ready for immediate use and anesthesilogists should be trained for the usage the most accesible and adequate devices for every circumstance [1-13]. There is rarely a need for FONA in the otherwise healthy child without history and findings for a difficult airway. It may occur following airway trauma, swelling or anaphylaxis in the otherwise healthy child or rapid respiratory deterioriation in a child with a known difficult airway. Preventing the need for emergency FONA by identifying high risk patients (pre-existing concerns about the ability to oxygenate/ ventilate) is essential for optimal pediatric airway management [1,12].

The different algorithms give priority to facial mask ventilation over endotracheal intubation because it is usually easier to ventilate children with the adequate facial seal technique, highlighted that multiple tracheal intubation attempts lead to preventable harm and must be avoided and call for help is essential that help and suitable assistance is sought at an early stage. Techniques such as apneic oxygenation, ECMO and fetal EXIT may save lives in many cases [1,5].

Do not forget that bag-mask ventilation is the cornerstone for successful oxygenation and ventilation [1-13]. But good bag-mask ventilation tecnique requires daily practice. Difficult face mask ventilation in healthy children is very rare (incidence is 0.02%) [1]. There are two techniques of beg-mask ventilation: one-person bag-mask ventilation technique, performed with the left hand gripping E-C (third, fourth and fifth fingers lift the jaw up, thumb and index fingers hold mask tight against the face) and with the right hand bagging, and two-persons face mask

ventilation technique which means E-C is gripped with both hands of one provider and the other provider does bagging [1].

The best framework to guide us through safe and secure airway management is a combination of: good knowledge, good airway assessment, planning, minimum standard of equipment, and implementation of difficult airway algorithms along with personnel dedicated to teaching, training and practice without losing sight of the fact that the cornerstone of pediatric airway management continues to be facial mask ventilation and oxygenation.

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Epidemiology And Outcomes of Nosocomial Infections in Pediatric Intensive Care Units

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Nosocomial infections (NI) directly impact the mortality rates of children in pediatric intensive care units (PICUs). NI occurs within 48 hours after a patient is admitted to the intensive care unit (ICU) or within 48 hours after the patient is discharged (1). The prevailing types of NI in this setting include central line-associated bloodstream infection (CLABSI), which accounts for approximately 25–30%, followed by ventilator-associated pneumonia (VAP) at 20–25%. Other notable NI include catheter-associated urinary tract infection (CAUTI) at a rate of 15% and surgical site infection (SSI) at 11% (1,2).

Nosocomial infection significantly impacts the disease's progression, particularly in severe cases, resulting in elevated death rates, morbidity, prolonged hospitalization, and increased hospital stay costs. In Europe, the mortality rate varies from 36 to 42% (3).

Identifying microorganisms and promptly administering antibiotics are essential components of treating NI. Nevertheless, the improper use of broad-spectrum antibiotics can develop antimicrobial resistance, leading to an elevated death rate (4,5). Implementing antibiotic de-escalation can potentially prevent adverse outcomes in a significant proportion of patients with culture-negative sepsis, ranging from 30.6% to 56.4%. Additionally, even in patients with positive cultures, there is a possibility of reducing the duration of therapy (6-8).

Significant improvements in healthcare practices have recently decreased nosocomial infections in pediatric intensive care units (PICUs). This achievement may attributed to the implementation of stringent asepsis measures, meticulous hand hygiene procedures, diligent infection surveillance, responsible antibiotic usage, and

adherence to comprehensive care protocols (1). The rising prevalence of drug resistance and the emergence of infectious diseases provide a significant and concerning challenge, mainly due to the limited availability of effective antibiotics (1).

Bloodstream infection

Bloodstream infection is a life-threatening complication in critically ill patients.

Multi-drug-resistant bacteria and fungi increase the risk of invasive infections in hospitalized patients and are difficult to treat in critical care units (9). Clinical symptoms, such as leukocytes and neutrophils in patients with acute high fever and microbiological test findings, are used to diagnose bloodstream infections (10).

Central Line-Associated Bloodstream Infection (CLABSI)

Nontunneled catheters are the most commonly used catheters, which are inserted percutaneously and account for most CLABSIs. There are three main routes of contamination of the central line: skin migration of organisms along the external surface of the catheter into the bloodstream; hematogenous route from pre-existing infection or other sources such as VAP, CAUTI, etc.; and contaminated infusate (1). Identifying microorganisms in blood culture or non-culture-based microbiologic testing establishes a central bloodstream infection. This infection occurs when a central venous catheter (CVC) has been present for a duration exceeding two calendar days, and the infection cannot be attributed to any other source. Approximately 40-80% of central line-associated bloodstream infections (CLABSIs) are attributed to gram-positive organisms, including coagulase-negative staphylococci and staphylococcus aureus (1). The remaining cases are caused by gram-negative pathogens and candida (11,12). Pseudomonas is frequently observed in severe diseases, neutropenia, or previous colonization, such as in individuals with cystic fibrosis. Candida is commonly linked to femoral catheterization, total parenteral nutrition (TPN), extended use of broad-spectrum antibiotics, hematological malignancies, and solid organ or hematopoietic stem cell transplantation (11).

Ventilator-associated pneumonia VAP

Intubation and mechanical ventilation significantly elevate the likelihood of developing ventilator-associated pneumonia (VAP) by 6–21-fold (12). To establish a diagnosis of VAP, the patient must have undergone mechanical ventilation for 48 hours or more. A novel or deteriorating infiltrate, consolidation, cavitation, or pleural effusion, as seen by a chest radiograph, is also required (13). Furthermore, a patient

needs to possess one or more of the subsequent criteria: the presence of purulent sputum or a modification like sputum, together with identifying an organism in a blood culture not associated with any other source of infection (1,12). The process of isolating microorganisms from a material acquired by transtracheal aspiration (1,12). The causative agents of ventilator-associated pneumonia (VAP) commonly include aerobic gram-negative bacilli, with a prevalence of 45% to 100% (12). Examples of these bacilli include Acinetobacter species and Escherichia coli.

Catheter-associated urinary tract infection (CAUTI)

The dissemination of CAUTI can occur through extraluminal and intraluminal mechanisms (14). The catheter bypasses the flushing mechanism of the urinary system, allowing the migration of perineal and urethral flora into the bladder by extraluminal means. An intraluminal infection is an ascending condition due to the retrograde movement of germs from contaminated urine within the drainage bag. Closed drainage systems are effective in reducing the occurrence of infection by restricting bacterial access to urine. According to previous research, individuals who underwent catheterization for a short duration, namely seven days or less, exhibited a risk ranging from 10% to 50% for biofilm development. Conversely, it was shown that nearly all patients who underwent catheterization for an extended period exceeding 28 days exhibited biofilm formation (15). Colonization is the term used to describe the presence of a microorganism in a urine culture. In this context, colonization does not lead to clinical symptoms and is often resolved after catheter removal (14,15). Organisms responsible for catheter-associated urinary tract infections (CAUTI) exhibit heightened antibiotic resistance, posing a significant challenge in treatment. Additionally, a notable proportion of CAUTI patients, specifically 3%, have an elevated risk of acquiring bacteremia. Patients who experience complicated catheter-associated urinary tract infections (CAUTIs) are at heightened risk for developing hypertension and end-stage renal disease (ESRD) later in life. According to research conducted by the National Healthcare Safety Network (NHSN), it was shown that uropathogenic E. coli (UPEC) is responsible for 23.9% of instances of catheter-associated urinary tract infection (CAUTI) (14,15). Candida sp. follows this at 17.8%, Enterococcus sp. at 13.8%, and Pseudomonas aeruginosa at 10.3% (1,14).

Surgical site infection

The incidence of surgical site infection (SSI) is responsible for around 11% of mortality cases in the intensive care unit (ICU) (16). SSI refers to an infection at the

location where a surgical procedure has been performed. The condition may manifest as a superficial restriction on the epidermis or progress to a deeper level, affecting organs and impairing functionality. SSI can arise from surgical site contamination by indigenous or exogenous bacteria (16). The incidence of surgical site infections (SSI) varies according to the specific surgical procedure, with rates of 2.1, 3.3, 6.4, and 7.1 per 1000 procedures observed for clean, clean-contaminated, contaminated, and unclean surgeries, respectively. The prevalence of Methicillin-resistant Staphylococcus aureus (MRSA) in SSI has exhibited an upward trend, rising from 12% in the year 2000 to 43.7% in 2020 (1,16).

Multidrug-resistant organisms

The presence of multi-drug-resistant bacteria or fungi in hospitalized children can heighten the susceptibility to invasive infections, particularly inside intensive care units (ICUs), posing significant treatment challenges (17). There has been a growing global incidence of bloodstream infections (BSI) caused by multidrug-resistant pathogens, particularly in pediatric intensive care units (PICUs). According to the World Health Organization (WHO), the issue of antibiotic resistance has been recognized as a significant worldwide public health concern (18). This determination is mainly based on the observed increase in the prevalence of bacteria that are resistant to antibiotics, coupled with a decline in the discovery of new antibiotics (18). In the context of individuals displaying symptoms indicative of bloodstream infections, it is imperative to provide broad-spectrum antibiotics as an initial course of treatment promptly. This empirical approach is crucial, as it has been seen that initiating timely and appropriate practical treatment is correlated with enhanced survival rates.

Antimicrobial resistance is linked to the prolongation of appropriate antimicrobial treatment, heightened death rates, higher utilization of resources, and elevated expenditures (19).

Conclusion

Concerning the prevailing nosocomial diseases, septicemia, pneumonia, and urinary tract infection were identified as the most prevalent occurrences. Nosocomial infection (NI) is well acknowledged as a significant financial burden for healthcare institutions. The primary expense directly connected with nosocomial infections (NI) is from the elevated length of stay (LOS) beyond what is medically necessary. The prevention of nosocomial infections is an essential process in ensuring the quality of healthcare. Obtaining precise data about nosocomial infection rates is crucial to

assessing the effectiveness of existing infection prevention measures and strategizing future local and national initiatives. To effectively address the issue of sepsis, hospitals must implement comprehensive strategies encompassing integrated pathways, protocols, and instructional programs. These initiatives should focus on enhancing sepsis detection, diagnosis, and treatment while incorporating measures to forecast antimicrobial resistance, optimize antibiotic prescribing practices, and improve source control.

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Recent Controversies in Therapeutic Approach in Intensive Care Medicine

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Although there is no consensus on the definition of critical illness it is common to describe intensive care medicine as a multidisciplinary specialty that is dedicated to the comprehensive medical treatment of patients who have already developed or who might develop acute, life-threatening organ dysfunction. Those patients who present with acute acute, life threatening physiologic derangements require timely resuscitation, in many cases even before a definitive diagnosis. In the light of rapid technological developments in medicine and enormous publishing of scientific papers on the topic of intensive care medicine, there becomes evident that many protocols and procedures in intensive care medicine might rapidly change with consequent changes in the philosophy and practice of this field of clinical medicine.

Despite numerous areas of intensive care medicine when large amount of data might be controversial, there have been many changes in safety, quality and provision of treatment and care enabling chances for recovery of critically injured or critically ill patients.

Close monitoring of vital functions of critically ill patients is a cornerstone of intensive care therapy necessary for titration of treatment. At present invasive monitoring is considered as the most accurate but non-invasive monitoring is associated with less complications and there is a trend of developing more precise and accurate devices that could be of great importance in continuous process of monitoring.The most explored methods including electrical bioimpedance and bioreactance, measuring of cardiac output by respiratory parameters, monitoring of cardiac output by ultrasound, inductance thoracocardiography, have been improved but further developments are necessary for provision of accurate non-invasive devices for use in everyday practice.

Respiratory failure is one of serious conditions that necessitates treatment in intensive care medicine unit. There have been debates and controversies in regard to

invasive and noninvasive respiratory support for various populations of patients with various comorbid states. Pandemic of COVID-19 has been the greatest challenge to healthcare systems and especially intensive care medicine since the invention of ventilators from the thirties of the last century. Enormous numbers of patients with COVID-19 and severe respiratory failure made a pressure for finding better and more effective strategies of respiratory support. Noninvasive monitoring and nonivasive methods of respiratory support were used, while non-invasive ventilation (NIV) has been shown as a method of adequate respiratory support for great number of patients that could reduce the incidence of endotracheal intubation and mortality. Due to limited availability of invasive mechanical ventilator support in the situation of huge numbers of patients with acute respiratory failure it turned out that noninvasive ventilator support could provide adequate respiratory support in the critical period.

Among the questions that are important for treatment of patients with respiratory failure clinicians address the possibility and usefulness of continuous capnography during mechanical ventilator support, airway-pressure release ventilation, adaptive pressure control modes, unique tidal volume for all patients, noninvasive ventilation for all types of respiratory failure.

Fluid resuscitation is very important issue in circulatory failure, defined as a life-threatening, generalized form of acute circulatory failure with inadequate oxygen and substrate utilization resulting in cellular dysfunction and consequent organ dysfunction, regardless the pathophysiological processes that have led to this serious condition. Resuscitation with fluids may increase stroke volume and cardiac output depending of the responsiveness status of the patient. The fluid challenge approach with administration of small quantities of fluids through a short period of time is quite important for determination of preload reserve of the patient. Despite the most recent technological developments, reliability of the measurement of the response variable changes exerted by fluid challenge is relatively insufficient.Dynamic methods of assessing circulatory status rely on heart-lung interactions, but they are useful in a selected population of patients. Pulse pressure variation and stroke volume variations are most commonly used dynamic methods.

Fluid administration, vasopressors and inotropes are the first line of therapy for the different types of shock taking in regard the pathophysiology and the mechanism of action. Along with constant publishing of the findings of experimental research and clinical trials, new recommendations and suggestions are released which are of great importance for the management of circulatory failure.

Besides the traumatic brain injury, or spinal medulla injury and cerebral infarction due to haemorrhage or thrombosis, neurological problems are common in intensive care unit. The pathophysiology of septic encephalopathy is poorly understood, but patients usually recover their cognitive function after resolution of sepsis. Seizures and cerebrovascular disorders are also common conditions in patients who are critically ill. While patients with neuromuscular diseases that might cause respiratory failure are commonly on mechanical respiratory support, neuromuscular alterations developed during hospitalization in intensive care unit are important causes of failure to wean from mechanical ventilation with subsequent long-term morbidity.

Sepsis as a life-threatening condition that might progress from dysregulation to severe multiple organ dysfunction is recognised as a global health problem. At the end of last century and the beginning of new millennium the Surviving Sepsis Campaign was launched, with publishing of recommendations regarding therapeutic approach to septic patient and with aim of global decrease of sepsis burden and decrease of mortality of this severe condition. Several revisions to the sepsis recommendations have been released. The latest sepsis guidelines focus also on viral along with bacterial infections, with recommendations that initiating resuscitation and management should start in the frame of one hour from the moment of suspicion of the clinician. Numerous studies and guidelines regarding the sepsis and septic shock management have been published during last decades. Besides the administration and timing of antibiotics, administration of glucocorticoids, choice of fluids and vasopressor and inotrope therapy, novel therapies and additional therapies are under research, but quite a large problem of adherence to recommendations of treatment and management of critically ill patients with sepsis is a great diversity of the level and resources of the intensive care units worldwide.

Developing of acute kidney injury in critically ill patients is associated with increased morbidity, longer stay in ICU and increased mortality. Over the past years, experimental and clinical research revealed that the development of acute kidney injury might be the consequence of complex interactions between the primary derangement and subsequent activation of inflammation and coagulation. In contrast to previous understanding, recent experimental and clinical data have shown that alteration of renal function might occur without histological signs of the damage of tubular cells. According to that findings, it is postulated that patients in the intensive care unit might have increased mortality due to acute kidney injury. Experimental and

small clinical observational studies have shown that acute kidney injury might affect innate immunity and the susceptibility to infection.

Patient with critical condition may develop acute liver failure as a sudden deterioration of liver function due to infection or intoxication in the absence of underlying liver disease. This condition should be recognized as soon as possible so that prompt diagnosis and appropriate treatment could be initiated. On the other hand, patients with cirrhosis and chronic liver insufficiency might be hospitalized due to complications or other medical conditions. Among the questions that should be addressed, the questions of specific treatments and symptomatic treatments that should be initiated for decrease of morbidity and mortality are of great importance.

Nutritional support in the critically ill patient is very important and complex. Several recent studies have shown changes in the understanding of the pathways of metabolic response to critical condition. It is very important to emphasize the various aspects of nutritional management and monitoring of the metabolic response along with assessment of requirements in calories, protein, lipids and micronutrients.

Hyperglycaemia is a common finding in critically ill patients and it is associated with unfavourable clinical outcome. Initial clinical trials of intensive insulin therapy with targeting blood glucose levels in tight frame of physiologic levels showed improved outcomes, but later trials did not show benefits, on the contrary there was evidence on increased adverse events with this approach. Numerous papers on the topic have evaluated other glycaemic indices (time-in-target blood glucose range, stress hyperglycaemia ratio, glycaemic variability). In addition, the patient's preexisting glycaemia and preadmission possible diabetic control may have strong influence on the glycaemia variations in the critically ill patients. There is a kind of consensus that majority of medical societies support glucose control in the range of slight hyperglycaemia in the patients in intensive care unit.

Very important topics like pain, circadian biology, sleep and delirium in patients in critical condition, have been in focus of research in last years. Few years ago new recommendations on these important issues were released as clinical guidelines PADIS (pain, agitation/sedation, delirium, immobility and sleep disruption). These guidelines have shown lack of evidence-based data with consequent difficulties in evidence-based decision making. Research in the field of circadian biology is very important as they give possibility to learn on the interventions that might realign circadian rhythm in critically ill patients.

Early mobilization and rehabilitation with maintenance of cognitive and functional status of critically ill patients may have positive effects on functional, cognitive, and emotional outcomes with significant influence on their families and health care professionals.

Many authors have addressed family-centred care in intensive care unit, that imply frequent talks to family members, including families on daily rounds and explaining the most important issues of treatment in detail to members of the family.

Addressing the post-intensive care unit syndrome enables the interventions that might prevent this entity like environment modifications, early mobilization, improvement of sleep and circadian rhythm in critically ill patents.

Ethical challenges are very strong and important in the daily work in intensive care medicine unit, and they include severe conditions of the patients while unrealistic expectations of the therapeutic measures, what may be quite difficult due to the difficult situations regarding the expectations of the family members.

The concept of intensive care that emerged after polio epidemic seven decades ago, has been developing through all these years along with scientific research and technological development that enable and dictate everyday clinical practice. Recognition of the clinical conditions that might progress to critical condition is of paramount importance for institution of effective and timely treatment that might give chance for resolving the underlying disease or state, with shorter hospital stay, better clinical outcomes and satisfaction of the patients and families.

When critical condition is diagnosed, critically ill patients necessitate multidisciplinary diagnostic and therapeutic approach with special emphasis on continuous monitoring of parameters and general state and tailoring treatment accordingly to ensure stability, resolving of the disease and recovery.

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Use of Thrive Oxygenation in Anesthesia for ENT Procedures

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The meaning of the of THRIVE acronym is:

T - transnasal, H – humidified, R – rapid, I – insufflation, V – ventilation, E – exchange.

The definition of high-flow oxygenation is: the application of nasal high-flow when the patient receives moistened, heated oxygen at a flow rate of more than 30 l/min and breathes spontaneously. With THRIVE, everything is the same, but the patient does not breathe, i.e., is apneic. It is a physiological method for oxygenation and ventilation of patients in general anesthesia who hypoventilate or do not breathe.

History of THRIVE

The term THRIVE , describing the technique of prolonged apneic oxygenation in patients for ENT surgery is introduced in 2015, by Patel and Nourael , who introduced the application of high-flow moistened and heated oxygen through a nasal cannula for optimal preoxygenation of patients with expected difficult airway(1).

Principles of THRIVE:

1. The apneic oxygenation that has been applied for over 100 years. Administering 100% oxygen in the pharynx without respirations prolongs the time to desaturation, but does not eliminate CO2 completely, leading to respiratory acidosis[2]. Ventilation occurs without ventilatory movements – oxygenation and removal of CO2 without lung ventilation, as a result of the interaction primarily of the supraglottic vortex from above and cardiogenic oscillations from below. Cardiogenic oscillation is a phenomenon of compression and expansion of the small airways caused by the inflow and outflow of blood into the chest with each heart beat. Cardiogenic inhalation accounts for 7-15 ml/heart beat, which means approximately 840 ml/min CO2 is removed and replaced with 100% oxygen, leading to significantly lower CO2 accumulation. The degree of increase in EtCO2 with THRIVE is 0.15 kPa/min, which is one-third of the expected increase in apneic oxygenation. There is an aventilatory flow of gases – the difference in alveolar uptake of O2 and

excretion of CO2 generates a negative pressure gradient of up to 20 cm H2O, driving oxygen into the lungs.

2. Primary supraglottic vortex is produced by high oxygen flow, used at 70-90 l/min entering through the nose and swirling around the soft palate, exiting through the mouth. It creates a highly turbulent supraglottic vortex that constantly replenishes the pharynx with oxygen and prevents room air to entry. The vortex efficiently passes through the upper airway, which usually constitutes 50% of the resistance of the entire respiratory system. With efficient breathing "directly from the glottis," the work of breathing is reduced by about 50%. The vortex is not transmited deep into the trachea and itself can not cause the observed gas exchange, i.e., CO2 excretion.
3. CPAP : the high flow generates positive pressure in the airways while the patient's mouth is opened, reducing the possibility of the upper airway collapse and atelectasis in the lower airways. CPAP is linearly dependent on flow rate, and it is approximately 7 cm H2O with a flow of 60 l/min and closed mouth. It causes alveolar recruitment, improves the ventilation-perfusion ratio, and reduces shunt.ž
4. Apneic ventilation is flow-dependent gas exchange wich causes the flushing of the anatomical dead space , and there is no rebreeding of the dead space. Therefore, less minute ventilation is required to maintain equally effective alveolar ventilation.
5. Functional residual capacity of lungs is increased by the pulmonary mechanisms,
6. Esophageal pressure at this time remains low, about 3 cm H2O, meaning there is no increased risk of gastric insufflation.

Advantages of THRIVE are: flushing of the dead space of the pharynx, reduction of the airway resistance, increased end-expiratory lung volume (FRC), it causes positive pressure in the airways-PEEP in the orolaryngeal space (the upper airway) .

THRIVE technique is widely used in a clinical practice today:

- In the ENT surgery is best documented for adult and pediatric microlaryngoscopy, awake tracheostomy, trismus, pharyngeal and laryngeal stenosis , ...

- During procedures such as fiberbronchoscopy or intubation with a fiberbronchoscope, gastroscopy, ERCP, electroconvulsive therapy,...
- For optimal preoxygenation – the nasal cannula remains during the intubation process.
- In the management of a difficult airway – extends apnea time during laryngoscopy, reduces work of breathing during awake fiberoptic intubation.
- At the extubation, it is very successfull as a backup in the case of the need for reintubation, reduces the frequency of respiratory complications and the need for reintubation[3].

Other applications include postoperative treatment, especially of the cardiac and thoracic patients, treatment of acute respiratory and cardiac failure, and has been significant in the treatment of Covid 19 infections. Patients with decreased oxygen reserve as pregnant women, sepsis, obesity, intestinal obstruction has a significant beneficiton from the use of THRIVE.

Application of THRIVE in anesthesia for ENT procedures:

THRIVE is currently used in anesthesia for rigid and flexible bronchoscopy, for microsurgical operations of the larynx, for emergency and elective tracheotomies[4,5], in anesthesia for patients with special needs and children, in cases of insufficient mask ventilation due to large facial tumors (e.g., Rhinophyma), in the management of difficult airway and in tracheal procedures (resection, reconstruction, stenosis)[6].

Anesthetic techniques used with THRIVE are TIVA, TCI, muscle relaxants can and/or may not be applied, the method is used with apnea or witht the patient's spontaneous breathing.

Monitoring during the procedure includes ECG, non-invasive blood pressure measurement, saturation, respiration. Because the EtCO2 capnography can't be reliably used, transcutaneous CO2 measurement, ABS for monitoring hypercapnia and acidosis, and BIS are incorporated.

Procedure for rigid bronchoscopy:

Preoxygenation is performed with THRIVE, anesthesia includes TIVA and muscle relaxants. A rigid bronchoscope is introduced in to the trachea, and manual balloon ventilation is connected to confirm gas loss along the bronchoscope. Afterwards, THRIVE is connected to the rigid bronchoscope with all vents open to prevent barotrauma or volutrauma due to high oxygen flow. After the procedure, the

rigid bronchoscope is removed, THRIVE is placed on the nasal cannula and the patient is awakened[7].

Procedures in laryngeal microsurgery:

For this type of procedure, it is crucial to select the type of procedure based on the expected duration and amount of bleeding. Most commonly, procedures are performed on the vocal cords (e.g., augmentation, thyroplasty, cyst surgery, biopsies), resections of glottic, subglottic, and supraglottic lesions (e.g., stenoses, papillomatosis). Increasingly, it is also used in laser surgery with FiO2 0.3 or oxygen turned off for 1 minute before using the laser[8,9].

Emergency and elective tracheotomy:

When performing a tracheotomy, the patient should be positioned with an elevated thorax by 25-30 degrees. In addition to the significant improvement in oxygenation, the general condition of the patient also improves, with reduced restlessness, agitation, hyperventilation, and hypertension caused by hypoxia. THRIVE, with its constant positive airway pressure, keeps the collapsible parts open. This allows sedation without a negative effect on oxygenation; with spontaneous ventilation, it maintains saturation even with significant airway obstruction[5].

Patients with special needs and children:

The method is also used for patients with psychomotor limitations and extremely uncooperative patients. In children, it should be noted that with apnea, the rise in EtCO2 is faster than in adult patients because THRIVE apparently does not allow sufficient removal of CO2 in children , limiting apnea duration to 10-12 minutes for children. This is explained by a higher metabolic demand for oxygen, smaller FRC, and higher minute ventilation per kilogram in children. Therefore, its use is safer with present ventilation or hypoventilation. Gas flow for THRIVE in children is calculated at 2-4 l/kg/min.

Procedures in otosurgery:

THRIVE provides ideal conditions for otosurgery procedures lasting up to approximately 45 minutes (myringotomy, insertion of ventilation tubes, ..).

Management of a difficult airway:

Using THRIVE significantly extends the apnea time while maintaining oxygenation until the definitive management of the airway.

Limitations of using THRIVE:

Duration of use - 30-40 (60?) minutes[10], after which respiratory acidosis develops with its complications, arrhythmia, and death.

Complete airway obstruction (especially upper), collapsibile tracheal diseases , but it should be noted that there was no observed flow disturbance due to secretions in the airway or significant upper airway obstruction.

Body structure (upper airway, obesity) – in patients with a BMI over 30, desaturation occurs more quickly.

Use of lasers and diathermy: Ahmad and colleagues described the possibility of inflammation during intraoral use of monopolar diathermy with THRIVE. Therefore, in the UK, there is a recommendation NOT to use THRIVE with lasers and diathermy, although it's described that a lower oxygen concentration (Fi O2 0.3 - 0.5?) is safe for use.

Application of THRIVE should be avoided in patients with maxillofacial trauma due to airway swelling; in a skull base fractures, there is a risk of pneumocephalus; it is also not recommended in existing pneumothorax.

Keep in mind that THRIVE does not provide a definitive secure airway as there is a possibility of reflux and aspiration of a gastric contents.

Questions for further research are: the place of THRIVE in unexpected difficult intubation; use of THRIVE with laser and diathermy; use of THRIVE in patients with BMI more than 30; duration of use of THRIVE with apnea; place of THRIVE in "can not ventilate, can not intubate" situation.

Conclusion:

THRIVE is an essential tool for anesthesiologists in situations with difficult airway, awake or anesthetized fiberoptic intubation, awake tracheostomy, or emergency tracheostomy.

The application of THRIVE is increasing, in all patient categories and for a large number and varieties of procedures. For patient safety, one should always be aware of the method's limitations and have a backup plan and method for definitive airway management and safe completion of the surgical procedure. In this lecture, we will present anesthesia procedures with THRIVE performed in our hospital, KBC Sestre Milosrdnice at the Clinic for Otorhinolaryngology and Head and Neck Surgery.

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Frailty And Peri-Operative Risk Assessment in Emergency Surgery

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Frailty is a clinical syndrome with several criteria present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. It may be associated with lower education and income, poorer health, and higher rates of comorbid chronic diseases and disability. [1]. It is a result of decreased homeostatic reserve, with poorly regulated multiple physiologic and subcellular paths. It is of great importance throughout perioperative period, while patients are subject to high levels of stress and inflammation. [2]

Frailty is associated with ageing and is characterized by a vulnerability to stressor: internal (e.g., infections) and external (e.g., turbulences in person's immediate environment, or a breakdown in social care). Frailty represents a considerable global healthcare burden. Analysis of 21 cohorts of 61,500 community dwelling older adults, across mainly developed countries, estimating global frailty prevalence in those aged 80–84 years to be 15.7%, increasing to 26% in those aged > 85 years. [3] NHS England, from UK, estimate that 1.8 million people aged > 60 years are living with frailty, with diagnoses concentrated in those aged > 85. [4]

Frailty inclines an individual to amplified healthcare dependency. Multiple use of prescribed drugs, frequent emergency hospital admissions and prolonged hospital stays, faster transition to residential care, and ultimately, higher rates of mortality

Frailty significance during the perioperative period

Medical professionals are using term "frailty" to describe a multiple weakness, vulnerability and decreased physiologic reserve. Distinct from medical comorbidity and functional disability, evidence suggests that frailty more accurately predicts hospitalization, institutionalization, and mortality among elderly outpatients. Frailty is especially important in the perioperative period, during which patients are subject to high levels of physiologic stress and inflammation.

Perioperative medicine is being established to provide optimal preoperative, intraoperative and postoperative care for all patients, with a focus on those at high risk of adverse postoperative outcomes. The high-risk group is defined as surgical patients with an aggregate 90-day mortality rate greater than 1/20. These high-risk patients are predominantly those with age related physiological changes, accumulation of multimorbidity and geriatric syndromes including frailty. With the advent of this new speciality, perioperative medicine, it is no surprise that there has been a focus on identifying patients with frailty in order to modify the perioperative pathway and achieve improved outcomes for individual patients. Projections for the future by 2030, assumes that 1/5 of all surgical procedures will be conducted in patients over 75 years old. [5]

What to expect?

By the surgical pathology nature, it is often degenerative, neoplastic, or metabolic. It is predictable that the surgical population is ageing. While frailty is associated with ageing, it not exclusively observed in older people, nor all elder people are frail. Number of studies have analised the prevalence of frailty with variation in rates reported across surgical specialties. In those undergoing elective orthopaedic surgery, 23% were frail in comparison to emergency hip fracture surgery where 53% of patients were defined as frail. [6] Considering cancer surgery, studies report a prevalence of 25% of patients undergoing elective cystectomy and high prevalence of frailty in emergency general surgical patients of 39%. [7] In vascular surgery, aortic aneurysms and peripheral arterial disease increase with age, with an estimated 52% of elective vascular patients being frail. [8]

How to evaluate?

Analysing already existing literature, POSE-Study group synchronised and conducted an observational study, Peri-interventional Outcome Study in the Elderly (POSE). [9] Together with all other variables and followed patients' characteristics, all-inclusive geriatric evaluation incorporated signs of anaemia, nutritional status, history of falls, functional dependency [10], the Mini-Cog [11], the timed 'Up & Go' (TUG) test [12] and frailty. The POSE frailty evaluation was based on the accumulation of deficits model.[9,13] Frailty was scored as present if at least four of the following six markers were present: Mini-Cog score 3 or less; albumin level 33 g^{-1} or less; one fall in the last 6 months; haematocrit level less than 35%; partially or totally functionally dependent; and at least three comorbidities. [9,11,12]

Lowering the risks

Frequently reported complications for patients above 80 years old associated with in-hospital mortalities were bleeding, respiratory and mental deterioration with unplanned intubation and septic shock. Nevertheless, 30-day mortality rate of 4.2%, in patients above 80 years, represents well tolerated anaesthesia in quite vulnerable population. Several mortality-related risk factors have been identified. Importance of peri-interventional organization and services for elderly, patient-centred and flexible treatment approaches. Prehabilitation programmes, peri-interventional geriatric expertise and post-discharge surveillance are needed. [9]

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Abdominal Compartment Syndrome: Management And Treatment in ICU

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Introduction:

In 2006, the World Society of the Abdominal Compartment Syndrome gave the first definitions for abddominal compartment syndrome (ACS). According to this intraabdominal hypertension (IAH) was defined as a peak intra-abdominal pressure (IAP) value of ≥ 12 mmHg at a minimum, as two standardized measurements obtained 1-6 hours apart should be reserved for the scenario of an increase IAP before overt signs appear. Furthermore, in the prodromal phase splanchnic hypoperfusion may occur long before the classic manifestations of ACS become evident. ACS was defined as severe IAH (≥ 20 mmHg) associated with the new onset of single or multiple organ failure (as assessed by the daily SOFA score or an equivalent scoring system, with organ failure defined as SOFA organ system score of ≥ 3). The more severe the degree of IAH the more urgent is the need for decompression of the abdomen (by either medical or surgical methods) with resolution of the damaging pressure.

New definitions were accepted in 2013: a polycompartment syndrome is a condition where two or more anatomical compartments have elevated compartmental pressures; abdominal compliance is a measure of the ease of abdominal expansion, which is determined by the elasticity of the abdominal wall and diaphragm. It should be expressed as the change in intra-abdominal volume per change in IAP; the open abdomen is one that requires a temporary abdominal closure due to the skin and fascia not being closed after laparotomy; and lateralization of the abdominal wall is the phenomenon where the musculature and fascia of the abdominal wall, most exemplified by the rectus abdominals muscles and their enveloping fascia, move laterally away from the midline with time.

Intra-abdominal pressure higher than 15mmHg can cause significant end-organ dysfunction, failure and patient death. Normal adult has IAP between 0-5. In the Intensive Care (ICU), typical ICU patient has IAP between 5 and 7mmHg, post-

laparotomy patient betwwen 10 and 15 mm Hg, patient with septic shock between 15 and 25 mmHg, while patient with acute abdomen between 25 and 40 mm Hg.

According to the classification ACS iscatagorized in three categories: primary, secondary and recurrent ACS. Primary (surgical) ACS is condition associated with injury or disease in the abdomino-pelvic region that requires early surgical or

angioradiologigal intervention, or that develops following abdominal surgery (abdominal organ injuries that require surgical repair or damage control surgery – DCS, secondary peritonitis, bleeding pelvic fractures or other causes of massive retroperitoneal hematomas). Secondary (medical) ACS refers to conditions that do not require early or angioradiological intervention such as: sepsis and capillary leak, severe acute pancreatitis, major burns and other conditions requiring massive fluid resuscitation). Finally, recurrent ACS refers to the condition in which ACS redevelops following previous surgical or medical treatment of primary or secondary ACS.

Understanding Abdominal Compartment Syndrome

A critical IAP that leads to organ failure is variable by patient and a single threshold cannot be applied globally to all patients. Abdominal perfusion pressure (APP) is superior to IAP, arterial pH, base deficit and lactate in predicting organ failure and patient outcomes.

There is a general lack of clinical awareness of IAH and IAP and there is great variations in opinions among surgeons, intensivists values, regarding their values. Many ICUs never measure IAP, so detection and management of IAH and ACS are inconsistent, and no consensus exists on the optimal timing of measurement or when decompressive laparotomy should be performed (1, 2).

Indications for measuring IAP are: 1. Postoperatively in patients with abdominal surgery if the abdomen is distended; 2. Patients with open or blunt trauma; 3. Mechanically ventilated patients with other organic dysfunctions; 4. Patients with distended abdomen or signs or symptoms caused by ACS (oliguria, hypoxia, hypotension, unexplained acidosis, mesenteric ischemia andincreased intracranial pressure); 5. Patients with polytrauma in which abdomen is temporary closed; and 6. Patients who were resuscitated with a large volume of fluids in the context of increased capillary permeability (peritonitis, septic shock, polytrauma).

From the proposed techniques, bladder pressure measurement is validated, standardized technique with less discomfort and infection risk.

Pathophysiological implications

Pulmonary dysfunction in ACS is a result of interactions between the abdominal and the thoracic compartment. An increase in intra-abdominal pressure causes a graded disturbance in pulmonary physiology ranging from mechanical and cardiovascular to systemic derangeme. Mechanical problems include: decreased FRC, alveolar dead space ventilation, ventilation/perfusion mismatch, increased intrathoracic pressures and decreased oxygen delivery. Mechanical ventilation is performed with protective lung strategies which may prevent the transfer of inflammatory mediators and the transfer of bacteria and bacterial endotoxins from the blood stream into the lungs and vice versa. Racional concept to keep the lung open during the whole ventilatory cycle is the main goal.

Elevated IAP and its effect on renal function is often the first sign of impending ACS. Acute elevation of IAP above 30 mmHg causes oliguria. Large clinical studies have identified that IAH ≥ 15 mmHg is independently associated with renal impairment and increased mortality. The etiology is not well established, it may be multifactorial:

reduced renal perfusion, increased systemic vascular resistance and alterations in

humoral and neurogenic factors. The risk of renal impairment with IAH might be further exacerbated by hypovolemia.

IAH pressures > 10 mmHg might increased arterial resistance, increase venous pressures and this plus increased mesenteric vascular resistance with tissue oedema and sepsis m give alteration in the inflammatory cascades and result in hypoxia.

The concept of perfusion is crucial as ACS has local effect on kidney and liver and the entire abdominal cavity. Current dilemma is how much fluids to give – enough to maintain perfusion yet not too much to cause ACS?

IAH can reduce the flow in the lumbar venous plexus, and subsequent increases the pressure in the cerebral spinal fluid of the spinal canal with a secondary increase in the ICP. According to this, recent head injury should be considered an absolute contraindication for laparoscopic procedures. The abdomen and brain are commonly considered to be two distant and unrelated organ systems. These potentially dangerous changes, especially in the presence of brain injury and decreaed cerebral compliance, can have significant dentrimental effects on patient morbidity and

mortality. Finally, ACS has detrimental effect to whole body, involving all body system and might provoke multiorgan failure.

Medical conditions that cause ACS in ICU

It is anticipated that 30-50+% of all ICU patients have some IAH and are at risk for ACS (3). Abdominal compartment syndrome after damage control surgery for major abdominal trauma might occur as a result of massive intestinal edema, intra-abdominal packing and retroperitoneal haematoma. If the abdomen is closed, intra-abdominal pressure may rise to a level (>25 cmH2O) where it leads to significant cardiovascular, respiratory, renal and cerebral dysfunction (4). To tackle the problem, it is advisible to let the abdominal wound open (the need for temporary closure and staged re-operation) and perform temporary abdominal closure with absorbable mesh closure, plastic IV bag closure, vacuum pack dressing or wittmann patch. In this condition the role of the intensivist is to detect early risk factors and signs of ACS/IAH with serial moniroting of IAP and to Consult surgeon for consideration of abdominal decompression if persistent IAP with impending organ failure.

Secondary ACS may occur in severely burned patients who usually develop IAH/ACS within 48 hours after injury. The generalized increase in capillary permeability that occurs in severe burn patients contributes to extensive edema formation and intraperitoneal accumulation of “third-space” fluid. Bowel edema and fluid translocation is further worsened by venous hypertension caused by elevated IAP. The risk of ACS is higher in burned patients with a higher percentage of total body surface area (TBSA) burned. ACS typically occurs when resuscitation volumes are greater than 275 mL kg-1during the first 24 hours or TBSA burned is larger than 60% (5). ACS may develop after excessive fluid resuscitation in burn patients. Ischemic insult / SIRS requiring fluid resuscitation with a positive fluid balance of 5 or more liters within 24 hours casuses IAP elevation. Prevention and diagnosis of IAH and ACS in burned patients include: IAH/ACS should be suspected in all patients with severe burns, IAP measurement should be performed every 2 to 4 h throughout the resuscitation period in burn patients with more than 20% TBSA, IAH/ACS might occur in patients without circumferential 3rd degree burns of their trunk, burn patients with smoke inhalation may also be at risk of fluid sequetration, judicious use of fluids and avoidance of fluid over-resuscitation is the key element in the prevention of secondary ACS, hypertonic lactated saline or plasma-based resuscitation requires less fluid and is associated with a lower risk of IAH and ACS. However, no benefit in preventing IAH has been proven (6). To take care of burn patients, how to do this

remains an art rather than a science. The fact is that over recent decades more fluids are being given to burn patients has led to the introduction of the concept of "fluid creep". Management of IAH and ACS in burn patients include: non-operative and percutaneous interventions may be applied before surgical decompression is considered, nasogastric decompression, the removal of excess fluid by ultrasound-guided percutaneous drainage or by a combination of continuous veno-venous hemofiltration (CVVH) with ultrafiltration and/or diuretics, are simple and possibly effective tools to reduce IAP. Finally, an escharotomy of the trunk to improve abdominal wall compliance should be performed early, especially in the presence of 3rd degree burns. Concern exists regarding surgical decompression in burn patients. The open abdomen after a laparotomy requires a temporary abdominal closure technique. Although decompressive laparotomy is a definitive therapy, wound maintenance and infection control may then become difficult. Strong emphasis needs to be placed on the tremendous morbidity and high mortality of an open abdomen in patients with burns. Also the presence of significant protein loss via an open abdomen needs to be considered. Early enteral and/or parenteral nutrition is of the utmost importance in these hypercatabolic patients.

Severe pancreatitis acuta is one of the conditions that may lead to ACS. ACS as a complication of AP can be predicted or anticipated using commonly utilized scoring systems, like SIRS and Apache II. ACS dreaded complication of acute pancreatitis (11% with SAP) and is associated with increase in mortality (30-60%) (7). The etiology of Acs in pancreatic patients includes fluid sequestration / inflammation and increased fluid administration. The sequele is shock with renal and pulmonary failure as well as mesenteric hypoperfuson and ischemia. Contributors to IAH and ACS in acute pancreatitis are pancreatic and peripancreatic edema (often fuleled by fluid resuscitation), ascites and illeus. Abdominal waal compliance decrease which contribute to IAH and ACS is due to the abdominal wall edema and abopminal pain. Key poinst are fluid therapy and pain management. An infusion rate of 5-10 ml/kg /h with response monitoring is appropriate for most patients. There is no clear superior type of fluid, so more studies are required (8, 9). Agressive fluid strategy (10-15 ml/kg/h is associated with higher APACHE II, higher rate of MV, higher incidence of ACS, higher rate of sepsis and higher mortality. However inadequate fluid (as measured by rise in HCt at 24h results in necrotizing acute pancreatitis in all patients (10). The key factor is prevention through judicious use of fluid resuscitation. Nonsurgical interventions, such as nasogastric decompression, or percutaneous

drainage of ascites should be instituted early when IAP increases. Surgical decompression remains debated, but may be beneficial when timed appropriately. Open abdomen management with negative pressure therapy results in acceptable morbidity when managed appropriately. Management considerations include: Early detection via frequent monitoring of at risk patients screen for IAH/ACS in new ICU admissions with new or progressive organ failure, look for trends of increasing abdominal pressures, preserve organ perfusion and treat clinical conditions with grades I and II. Anticipate emergent surgical interventions to prevent tissue damage/death and anticipate patient to return with an alternative surgical closure or "open" abdomen is crucial.

Conclusion

It is recomended to not wait for signs of ACS to check IAP. By then the patient has one foot in the grave and the opportunity for medical therapy is lost, to monitor all high risk patients early and often and to trend IAP like a vital sign.

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Severe Polytrauma Management in the ICU, Multidisciplinary Approach

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Polytrauma is the leading cause of mortality and disability in young people, especially in those younger than 35. It is also the third most common cause of death amongst the young. These patients are mostly with no comorbidities, so this presents social and economic problem too. Polytrauma patients are very complex and challenging. Complexity of clinical picture with massive hemorrhage, traumatic brain injury, pulmonary contusion, pelvic fracture and other requires close cooperation of medical specialist disciplines involved. Polytrauma presents involvement of more than one system like associated head, chest, spinal and pelvic injury. Rapid assessment, diagnosis and stabilization of this patients is needed and requires a multidisciplinary team with experience. Many of these patients have dramatic clinical picture upon admittance in hospital. ISS is used to evaluate severity of patient's trauma. ISS > 25 is considered severe polytrauma. After initial resuscitation and stabilization and damage control surgery (DCS) there are many complications that can occur such as infection and thromboembolic complications. Respiratory, cardiovascular, metabolic and immunological consequences of trauma resuscitation and massive transfusion are very frequent. Duration of polytraumatised patients' stay in the intensive care unit can be very long but multiple treatment modalities and adequate and dedicated work with these patients will bring final resuscitation. In this work we present a 27 years old male, who had a car accident. He was severely injured, and had several deadly injuries. The car accident happened not far away from our hospital, so he arrived within a golden hour of initial resuscitation. Upon arrival he was in deep hypovolemic and hemorrhagic shock, and after an urgent all body scan, he was immediately transferred to the operation room. He had several interventions after he was admitted in the intensive care. He spent 6 months in ICU and during that time he had many complications, and operative interventions, such as SIRS, brain empyema, several bladder operations, and stabilization of pelvis. Team work of many specialists and multimodal approach to treatment resulted that after long stay in

intensive care with many operations and complications he was transferred to another ward, and soon after that he went home.

Pathophysiology of polytrauma is very complex. Massive soft tissue and bone injury, hypoxia, hypotension, and subsequently ischemia, reperfusion injuries, compartment syndrome, infection, operative interventions, induce a host response. Local and systemic release of inflammatory cytokines, complement, arachidonic acid derivates, reactive oxygen metabolites are leading to systemic inflammatory response syndrome (SIRS). Endothelial cell damage, accumulation of leucocytes, disseminated intravascular coagulopathy (DIC), disturbances of microcirculation are leading to apoptosis and necrosis of parenchymal cells and development of MOF or MODS. Sepsis develops occasionally in trauma patients with 10% of trauma deaths due to sepsis. Once sepsis is diagnosed treatment must be immediately initiated with appropriate empiric antimicrobial, followed by the specific antibiotic therapy based on blood culture. Several biomarkers have been identified to be involved in the acute phase of the systemic inflammation cascade caused by trauma and directly related to the severity of injury such as procalcitonin (PCT), C-reactive protein (CRP), High density lipoprotein (HDL), interleukin 6(IL6). Respiratory support is needed to provide adequate oxygenation and ventilation. Inadequate oxygen delivery only worsens tissue hipoperfusion. Circulatory stabilization is performed with volume load, and vasopresor use can improve microvascular perfusion. Hypothermia should be corrected promptly. In ICU we are dealing with all respiratory, cardiovascular, metabolic and immunological consequences of trauma resuscitation and massive transfusion. Trauma is usually followed by uncontrolled massive bleeding. oagulopathy develops early afther trauma and is present in 25 to 36% of trauma patients, it correlates with severity of trauma and is associated with high mortality. Combined mechanisms contribute to complex coagulopathy. Excessive consumption of coagulation factors and platelets, dilution coagulopathy due to administration of large volumes of fluids, use of multiple red blood cells without fresh frozen plasma and platelets, acidosis that attenuates thrombin generation and platelet function , hypothermia that slows down enzyme reaction and platelet function. Triad of hypothermia, acidosis and coagulopathy is recognized as a significant cause of death in patients with trauma injuries. Patients with pulmonary trauma can suffer from contusion, aspiration, atelectasis, infection. Pulmonary contusion after blunt or penetrating trauma is caused by disruption of capillaries of the alveolar walls and septa and leakage of blood into alveolar spaces and interstitium. This is leading to

poor blood gas exchange, and hypoxia. This includes ventilation/perfusion mismatching, increased intrapulmonary shunting, increased lung water and loss of compliance. Pulmonary contusion occurs in 25 - 30 % of all chest blunt trauma. All this represents risk factor for developing ARDS. So ventilatory techniques are needed for providing adequate ventilation and oxygenation. Lung protective ventilation is usually used, and in some cases there is need for veno-venos extra corporal membrane oxygenation (ECMO). Computing tomography is very sensitive in diagnosing pulmonary contusion and differentiating it from areas of atelectasis and aspiration. Pelvic injuries occur in 25% of polytraumatised patients. Damage of visceral and vascular structures is common in pelvic fracture, causing rapid exsanguination and have high mortality rate. Mortality rate in isolated pelvic fracture is 8%, and can be as high as 50% in polytrauma. Different protocols and guidelines were established for management of pelvic trauma. Usually, in the initial phase of resuscitation external fixation for pelvic fracture is performed and definitive internal fixation is performed later, after hemodynamic stabilization of patients. Management of pelvic fracture is followed with use of lot of blood and blood products, and massive blood protocol is used, with the same amount of red blood cells (RBC) and fresh frozen plasma (FFP), given to the patient to achieve hemodynamic stability. Urological injuries in pelvic fracture are noticed in 6-15% of cases. The bladder due to its anatomic position is prone to rupture in pelvic fracture. Frank haematuria is associated with bladder rupture in 16-27% of patients who sustain pelvic fracture. Traumatic disruption of urethra appears in pelvic fracture too. These complications are usually solved by performing suprapubic cystectomy and inserting catheter. The Injury Severity Score (ISS), a scoring system which is commonly used in traumatology has values ranging from 0 to 75,and increases with severity (the higher the score, the higher the injury severity, and therefore, the higher the mortality). An ISS of 16 and higher tends to be considered as polytrauma, and ISS>25 is considered to be a severe polytrauma. Traumaa patients are the largest consumers of blood and blood products, and since they are urgent patients they often receive oldest blood. Duration of transfused red cell storage has been associated with increased mortality and risk of multiple organ failure , even with leucoreduction. Red cell hemolysis may lead to accumulation of free radicals and to regional and systemic vasoconstriction and oxidative injury. Some of the polytrauma patients with prolonged stay in ICU develop persistent inflammation immunosuppression and catabolism syndrome (PICS).They experience recurrent infectious complications that lead to prolonged hospitalization, many surgical procedures and frequent readmissions. PICS is characterized by chronic low grade

inflammation, suppressed host immunity and loss of lean body mass, despite nutritional interventions. They often develop infections with multi-drug resistant organisms.

We present 25 years old male with no prior comorbidities who had a car accident. This car accident happened not far away of the hospital, so he came within golden hour of resuscitation. He was admitted in hospital in a deep hemorrhagic and hypovolemic shock, his blood pressure was 85/55 and pulse was 130 bites/min. He was tahipnoic, unconscious, and he was intubated as soon as he came. Upon his arrival he got an urgent all body scan, and after that he was admitted in the intensive care unit (ICU). He was monitored and put on mechanical ventilation, and an initial resuscitation with crystalloids started and vasopressor support was induced. CT scan revealed that he had transection of thoracic aorta pars descendeentis, acute subdural hematoma of the right side, multiple rib fracture of the right side I-VI and XII, haematothorax of the right side, pulmonary contusion on both sides, retroperitoneal haematoma, renal contusion of the right side, fracture of pelvis, fracture of transversal procesuss of lumbar vertebra I-III, and traumatical lesion of urethra and bladder. After initial resuscitation in ICU, he was transferred to the room for interventional radiology where thoracic endovascular aortic repair (TEVAR) procedure was done by interventional radiologist. After that, an initial stabilization of pelvis with C-clamp was done, as well as tamponade of abdomen, and cistofix was inserted. After this urgent operative interventions, and damage control surgery (DCS), he was admitted in the ICU where further resuscitation continued. During this interventions he got massive transfusion of blood and blood products, tranexamic acid infusion was administered. In the next few days he was hemodynamically unstable, and vasopressor and inotropic support was administered too. He was sedated and ventilated mechanically. After nine days when he was more stable, he got surgical tracheostomy, and two days after that an opened reposition of fracture of pelvis with internal fixation was done. Twelve days after that control brain CT scan revealed development of subdural brain empyema, so he was urgently operated by the team of neurosurgeons. An aggressive empiric antimicrobial therapy was administered, and in spite of that biomarkers of sepsis continued to rise, and he remained febrile. Blood cultures were taken regulary, and antimicrobial therapy was administered according to the result of blood cultures. Several days later on the control CT diagnostics an diaphragm rupture was found, but since he was hemodynamically unstable again he could not be operated in that moment. Twenty days later, when his hemodynamic

status got better and biomarkers of sepsis lowered a thoracotomy was done and he got suture of diaphragm. Since he had rupture of bladder and urethra, he had several urological interventions and operations in the second month of his stay in ICU. Reparation of bladder was done and also endoscopical insertion of urethral stent and debridement and suttura of bladder. He was observed by urologist all the time, and later uretrocystoscopy was done and double J sonde was inserted. Despite of all this, owing to the suprapubic catheter he had, his urine output was regular. After fifty-seven days a percutaneous endoscopic gastrotomy (PEG) was done. Since he was laying for so long time with osteosynthetic material in his pelvis sacral decubitus occurred and inflammation of lumbosacral region. After that debridmen of vulneris and necrectomia as well as extraction of fixators from pelvis was done. Neurological examination revealed that he was paraplegic with dumb soles. But as his general condition was better later, he started to move his legs. We also discovered that he was suffering of hypothireosis, so he was receiveing levotiroxin 75 mg every morning. He was also anemic all the time, and hyponatremic. After four months, since he was hemodynamically stabile, he had no temperature, and markers of sepsis lowered, he was conscious and communicative and breathing spontaneously, he was transferred to orthopedic ward. Three days later he had a cardiac arrest and was reanimated, after which he was admitted to ICU again. Next two months he spent in ICU. He was receiving both parenteral and enteral nutrition. Since he had good motility of gut he was fed by nasogastric tube at first, and later by PEG. A nutritionist was engaged in his nutrition therapy too. In spite of all this efforts to keep him well nourished, he lost his body mass, and was extremely cahectic. During all the time of his long stay in intensive care he was receiving gastro protection and deep vein thrombosis prophylaxis. A control ultrasound of lower extremity was done regulary, to check if there is thrombosis. Physiotherapy was introduced too, as soon as he became hemodynamically stable. During almost all time of his long stay in the intensive care we were dealing with hemodynamic instability, anaemia, infection, imunosupression, metabolic disturbances, malnutrition. But in spite of severity of his trauma and many complications that occurred during his treatment, team work of many specialists, multiple treatment modalities and dedicated care resulted in his definite resuscitation and after 6 months of stay in ICU, he was transferred to another ward. Soon, he went home. Now he drives a car in his village again.

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Opioids Pain Treatment in Oncology Patients

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Pain is one of the significant symptoms of cancer. Even with a large number of different drugs, moderate and severe pain occurs in more than 50% of cancer patients[1]. Cancer pain is a complex, time-varying symptom and is the result of various mixed mechanisms that lead to pain, and they include inflammatory, neuropathic, ischemic and compression mechanisms in different places[2]. Cancer pain shares the same neurophysiologic pathway as pain in patients without cancer, and that process includes activation of afferent sensory pathways by constant painful stimulation, transduction, transmission, modulation and perception[3]. Etiologically cancer pain can be divided into nociceptive, neuropathic, mixed and of unknown origin. According to Bennett et al. (2012), cancer pain is nociceptive pain in about 59% of patients, 19% is pure neuropathic pain, mixed pain (nociceptive and neuropathic) is in about 20% of cases, and in 2% of cases cancer pain is of unknown origin. Considering that neuropathic pain is more difficult to treat compared to other types of pain, we can expect a good therapeutic effect in at least 81% of patients[4]. In his work from 2007, Van den Beuken showed through a meta-analysis of 52 studies that moderately severe or severe pain occurs in more than 1/3 of cancer patients and that the prevalence of pain is 33% after curative treatment, 53% on average in all stages of the disease, 59% after anticancer treatment and 64% in an advanced stage of the disease[5]. The existence of pain depends on the location and type of tumor as well as the stage of the disease[6].

Pain assessment

A good assessment of the nature of the pain and the possible cause of the pain is essential for a good approach in pain therapy. Each type of pain requires a detailed examination because the mechanism can be different and this directly affects the choice of pain therapy. Also, chronic pain, which we are already treating, should be evaluated from time to time because the existing pain may have worsened or a new one may have appeared and the old one has remained at the same level. Pain is a combination of a sensory sensation and an emotional reaction to certain stimuli and

has a strong subjective component, so we get the largest amount of information about pain through a good patient history. A specific examination of the history of pain includes three main things: intensity, location and pathophysiology of pain. The following questions can help us a lot: when does the pain occur, where does it hurt, what is the intensity of the pain, what affects the onset and what affects the weakening of the pain, what do you think is the possible source and trigger of the pain.

An initial evaluation of pain can begin with the PQRST characteristics:

P (Palliative factors): What affects pain reduction?

Q (Quality): Describe what the pain is like.

R (Radiation): Is it spreading?'

S (Severity): How bad is the pain?

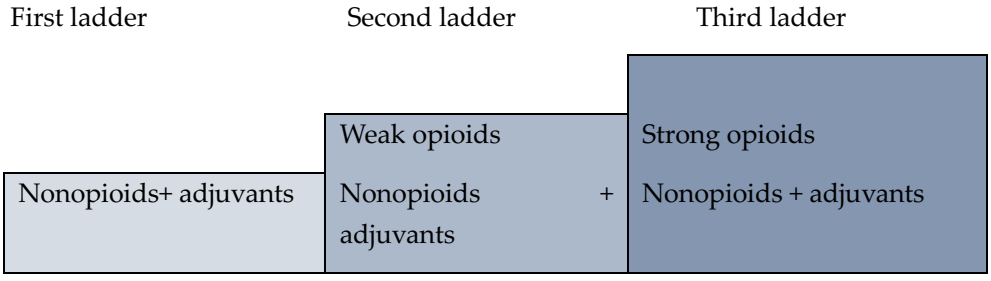
T (Temporal): Is it constantly present or intermittent?

The two most important things we get from a conversation with a patient are the description of the pain and the intensity of the pain.

Analgesic ladders

In 1996, the World Health Organization (WHO) published the so-called "analgesic ladders" (picture number 1) to which the WHO said that all patients have the right to pain therapy and that those with moderate or severe pain should also use drugs that have stronger effect than NSAIDs, which are weak and/or strong opioids7.

Picture number 1: Analgesic ladders of the WHO



The choice and dose of pain treatment depends on the nature and severity of the patient's pain. The World Health Organization has developed a three-step approach to pain management that provides a stepwise approach to the treatment of malignant pain (WHO, 1996), but the stepwise approach is also applied to the management of non-malignant pain. We start the therapy with the weakest analgesic, and then

progressively stronger analgesics are prescribed until pain relief is achieved. WHO recommends the following stepwise approach to pain therapy[9]:

1. Step 1 (mild pain) – acetylsalicylic acid, paracetamol and other NSAIDs and adjuvant drugs
2. Step 2 (moderate pain) - a weak opioid, such as tramadol, codeine, or dihydrocodeine plus Step 1 medications.
3. Step 3 (severe pain) - strong opioids such as morphine, methadone, oxycodone, tapentadol, buprenorphine, hydromorphone, or fentanyl plus Step 1 medications.

Today, there is more and more talk about the fourth step (ladder), which are interventional procedures that should help reduce the intensity of pain and reduce the use of drugs. A ten-year prospective validation study of the application of analgesic ladders published by the WHO showed that around 70% of patients with cancer pain are cured or have a significant reduction in pain by applying these recommendations8.

The WHO also presented the basic principles of the application of drug therapy, and they imply the use of drugs9:

1. By mouth - preference is given to the administration of drugs per os as long as it is possible and effective. Wherever possible, analgesics should be administered non-invasively to provide the patient with the greatest degree of independence and comfort.
2. According to the hourly rate - do not skip doses. In order to achieve continuous relief from the pain of cancer patients, analgesics should be taken at fixed time intervals, depending on the duration of the effect of the selected drugs.
3. According to the steps - application of therapy depending on the intensity of the pain.
4. According to each patient - consider the associated diseases, the individual condition of the patient and his general condition. It is exceptional that the doses we prescribe are determined according to the intensity of the pain and not according to the patient's weight or age.
5. Pay attention to details - side effects, tolerance, prophylactic treatment of side effects.

6. In the treatment of patients with cancer pain, the most important thing is a multidisciplinary approach. This implies that it is necessary to treat the patient who has pain and not the pain in the patient.

The therapy of moderate pain involves the inclusion of weak opioids in the therapy in addition to the first-line drugs (NSAIDs and coanalgesics) recommended by the WHO.

The most commonly used weak opioids are tramadol and codeine. They have an upper efficiency limit, i.e. the maximum predicted dose to be prescribed in one day.

Tramadol is a synthetic analgesic that works in two ways:

a. inhibits nociception through opioid receptors and acts as an opioid analgesic

b. blocks the uptake of serotonin and noradrenaline, i.e. causes antinociception by stimulating descending inhibitory pathways and thus acts as a non-opioid analgesic

Tramadol shows dose dependence in relation to analgesia, has no clinically significant effect on respiratory and cardiovascular parameters, is useful in patients with poor cardiopulmonary function, including the elderly, obese and smokers. It is useful in patients who cannot take NSAIDs. The maximum daily dose of tramadol is 400 mg divided into 4 doses. Tramadol is metabolized in the liver by the cytochrome P450 enzyme system into five major metabolites (from M1 to M5). Biotransformation in the liver via: O- (CYP2D6) and N- (CYP3A4 and CYP2B6) demethylation, glucuronidation and sulfation. Only one metabolite is pharmacologically active and that is O-desmethyl tramadol, designated as M1. M1 has a higher affinity for Mi receptors than tramadol. The metabolism of Tramadol to M1 in humans is slow and the serum concentration of M1 never exceeds 25% of Tramadol. Tramadol is eliminated via hepatic metabolism and its metabolites are eliminated primarily via the kidneys. 90% is excreted through the kidneys, about 30% unchanged and about 60% of the administered dose in the form of metabolites. The remaining 10% is excreted through feces.

Codeine is a natural alkaloid derived from opium (methylmorphine). It is transformed in the liver into an active metabolite (only 10%) that has a stronger analgesic effect than codeine itself. If the demethylation of codeine is blocked with some drugs (ranitidine, cimetidine, paroxetine, fluoxetine), the analgesic effect may be

absent. Usual doses are 30-60mg every 4 hours. The maximum daily dose is 240-360mg. Equianalgesic codeine is 1/10 the action of morphine (Codeine:morphine=10:1).

In case of sudden deterioration and increase in pain intensity, the second stage of the WHO can be skipped and strong opioids can be administered directly (the so-called analgesic lift).

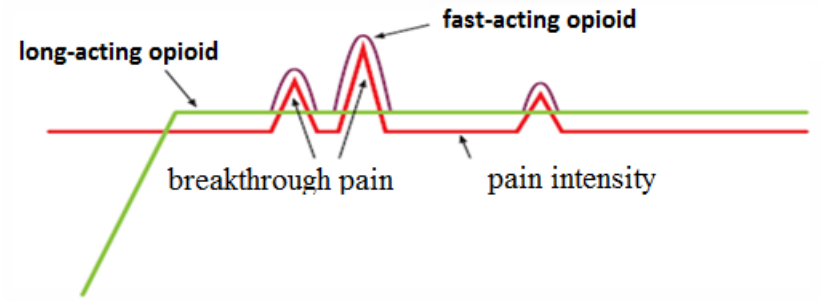
Severe pain therapy - Strong opioids are used in the third stage of chronic cancer pain therapy when pain intensity reaches ≥ 7 on the VAS scale. Strong opioids are the basis of the treatment of severe chronic pain and their use depends on the estimated severity of the pain and not on the stage of the disease or the estimated length of survival of the patient. The main drug used is morphine, but there are also alternatives such as hydromorphone, oxycodone, oxycodone+nalosone, fentanyl, buprenorphine, tapentadol and methadone. Morphine is the gold standard in the treatment of cancer pain, and the strength of other opioids is usually compared to its effect. It has a strong analgesic effect, and there are numerous drug formulations and ways of administration. It is well resorbed from the GIT and has first-pass metabolism through the liver, which affects the bioavailability of 25-30%. The main metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). It is eliminated through the kidneys. It is extremely important to know that opioids can be fast-acting and long-acting depending on the length of their action. Almost all strong opioids can be found in these two forms. Fast-acting opioids are used for titration of pain, i.e. to establish the optimal daily dose of opioid that is needed to cover the pain with an opioid, and they are also used in case of breakthrough pain as an additional analgesic to the already prescribed long-acting analgesic therapy. We prescribe long-acting opioids in a situation where the pain is constant, lasts throughout the day and night, and when it cannot be neutralized or significantly reduced by other means. The majority of cancer patients have pain that is constant throughout the day.

Considering that the pain is constant, we should start basic therapy with a long-acting opioid. There are formulations of long-acting opioids that are administered orally (hydromorphone, oxycodone, tapendatol) or transdermally (fentanyl, buprenorphine). Our goal is to prescribe a daily dose of a long-acting opioid that will cover the intensity of the pain for most of the day, but in a dose that is just as calculated, because we can also administer very large doses of the drug, and then we will surely anesthetize the patient, but he will not be physically fit due to the excessive

dose and functionally capable because the side effects of the drug will manifest themselves. This means that our goal is to find the optimal daily dose of a long-acting opioid that reduces the intensity of pain to a VAS value of 1-2, and that in case of breakthrough pain during the day, the patient uses a fast-acting opioid in those situations. Each patient reacts differently to painful stimuli and therefore to the applied dose of opioids, which tells us that the introduction of therapy should be done gradually and the dose of a long-acting opioid should be increased slowly until the desired effect is achieved. If the patient does not have problems with the digestive tract and the act of swallowing, we can administer hydromorphon tablets as a long-acting opioid. It is metabolized in the liver by glucuronidation (not via CYP450) and excreted in the urine. The main site of absorption is the large intestine, it is applied only once a day and the main advantage of using hydromorphone is the simplicity of dosing and the possibility to adjust the dose every day because one tablet works for 24 hours and the effect of the drug is seen already after 6-8 hours of taking the tablet.

Transdermal fentanyl is also a long-acting strong opioid, but in order to achieve its effect and a stable plasma concentration value, it needs to pass from 12-24 hours, and it works for a total of 72 hours, so the transdermal patch needs to be changed every 72 hours. Dose titration is difficult because the dose can be changed every third day (72h) when the patch itself is changed.

Picture number 2: schematic representation of the action of opioids in chronic cancer pain



The intensity of the pain is shown in red, and in green our wish that the dose of the long-acting opioid be slightly higher than the intensity of the pain. The application of a fast-acting opioid in the case of breakthrough pain is shown in bright color. Chronic cancer pain therapy is well prescribed if, after administration of a long-acting opioid, the patient does not have pain greater than VAS 1 to 2 and there is no need to take a fast-acting strong opioid more than 2 times a day. This combination of drugs allows the pain to be kept under control and the patient to be able to function normally physically and mentally.

Pain breakthrough is a transient exacerbation of pain that occurs spontaneously and may be associated with expected or unexpected causes despite relatively stable and well-controlled underlying pain[10]. The characteristics of pain breakthrough are: fast onset (Average time to maximum intensity is about 3 min; lasts for a short time (on average about 30 min); can be frequent during the day; intensity is strong pain[11].

Breakthrough of pain can be incident (predictable or unpredictable) and spontaneous. When the pain is predictable (expected during some action, movement, defecation) then a strong fast-acting opioid can be administered in advance. When it is unpredictable or spontaneous, it is of great importance to us that the opioid acts quickly but also for a short time, because in 64% of cases the pain passes spontaneously within the first 30 minutes of onset and even 87% within the first 60 minutes[11].

The fast-acting strong opioid fentanyl can be administered in several ways: oral transmucosal, buccal tablets, sublingual, intranasal spray, pectin nasal spray, mucoadhesive buccal disc. Intranasally applied fentanyl is the most useful because its bioavailability is about 89%.

The nasal epithelium is highly permeable to lipophilic drugs such as fentanyl, there is a large surface area of the nasal mucosa (150-180 cm2) that is well supplied with blood. The nasal mucosa has a pH of 5.5–6.5, which is a necessary pH for the optimal function of the glycoproteins to which drugs are bound and direct connection with the CNS via the olfactory pathway. It is also effective in patients with dry mouth and mucositis, and the application is quick and easy, and the metabolism of the first pass through the liver is avoided[13].

Sometimes absorption enhancers of nasally administered fentanyl are used to overcome the problem of small volume, so additives such as polymers, gel or polysaccharides (PECTIN, chitosan) are added to prolong the contact time of the drug with the nasal mucosa and increase the absorption of the drug.

Dosing is done at intervals of ≥ 4 hours in doses of 100, 200, 400 or 800 μg and the maximum number of doses per day is four[14].

Conclusion:

- Pain significantly affects the quality of life of patients with its physical but also emotional component (fear).

- Chronic cancer pain is successfully treated in 70-90% of patients if we follow WHO recommendations
- There is no maximum, but optimal dose of opioids that should be prescribed to the patient
- A patient with pain should be treated multidisciplinary, not the patient's pain.

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New Approach to Pain Therapy in the Acute Postoperative Period

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Great developments have been made in surgical and anaesthesia techniques in last decades in terms of safety and reducing invasiveness of the procedures with common aim of striving for better clinical outcome, shortening the length of hospitalization, decreasing the number of complications and achieving good quality of life after surgical procedure. Despite all advances in the techniques and health care process the number of patients who may suffer from acute uncontrolled postoperative pain may rise to twenty percent or more, depending on the surgical procedure and the clinical setting.

According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Acute pain that occurs after surgical procedure should be controlled and resolved during the healing period.

Pathophysiology of acute postoperative pain is complex. Surgical trauma initiates numerous changes at the site of injury with consequent responses that include inflammation, peripheral sensitization and transmission and modulation at different levels of nociceptive input from the peripheral sites to central pain pathways and sites of pain perception. That complexity of the processes and nociceptive pathways along with activation of inhibitory pathways has been even more intricate by influences of different biological response, different psychological and cultural features and different sociological context.

Inappropriate treatment and control of acute postoperative pain may lead to numerous complications and adverse effects that in general lead to increased morbidity, prolonged hospital stay, decreased quality of life and may contribute to increased mortality in most severe cases.

There is also evidence that moderate and severe postoperative pain may continue in the postoperative period with great possibility of developing the

conditions of chronic pain states with numerous physical, psychological, social and economic adverse effects for the individuals and the whole society.

In the light of attempting to give optimal healthcare in the field of surgery and anaesthesia optimization of prevention and relief of acute postoperative pain are essential for good clinical practice.

Persistent postsurgical pain that may last quite longer than the typical healing process, has been recognized as a very important problem after surgical procedures and may increase up to one third of the operated patients after some specific operations like amputations, mastectomy, thoracotomy and repairs of hernia.

Despite many scientific advances and developments in practical solutions of pain control, acute uncontrolled pain after surgery remains a serious problem and a cause of suffering of the patients in everyday clinical practice.

In the attempt to manage this problem in some health care systems acute pain teams have been introduced with special focus on pharmacological and nonpharmacological ways of pain alleviation. There have been rather high percentages of moderate to severe pain in a review of published data of pooled scores of pain experience from about twenty thousand patients treated by three different protocols of pain control (intramuscular analgesics, patient controlled analgesia and epidural analgesia.

Side effects of analgesics as well the comorbidities that patients may suffer from, are the most important limiting factors in provision of effective and safe postoperative pain control.

Side effects that might associate the use of pharmacologic agents in the early postoperative period are well defined and the clinician have to bear in mind all the adverse effects and the individual features of the patients and the specific characteristics of the surgery performed.

Acute pain that may last and be persistent even after healing process may initiate pathophysiological processes in the peripheral and central nervous systems with a consequent chronic pain state. The importance of preventing the development of chronic pain states has been well described in numerous papers.

Therefore, every effort should be done to make advances in formulating new agents and techniques that may improve pain control for acute postoperative pain with greater possibility of reducing the incidence of chronic pain states.

For years alleviating of postoperative pain was a part of general humanitarian attitude in clinical practice. In the last decade of the last century evidence of the importance of the rapid functional recovery and diminishing the stress response to surgery have come in the focus of research and clinical practice. Adequate pain control after surgery is a very important part of overall health care process that enable adequate postsurgical recovery, optimal length of hospitalization, good recovery, good quality of life and satisfaction of the patient, in other words good clinical practice.

On the other hand, there should be found a balance between the well-known benefits of good postoperative analgesia and the risks of adverse effects of opioid treatment which may evolve to disorder of prolonged inappropriate opioid use.

Pain assessment is very important in everyday practice what should be of importance in reducing subjective pain. In the attempt to assess the pain in a relatively simplified way the American Pain Society launched the campaign of the pain as the fifth vital sign, in which unimodal pain score -numerical pain score was the main indicator of pain intensity. Nowdays , it is recognized that that campaign contributed to the increased prescription of opioids with possible many adverse effects, and the term of pain as the fifth sign is abandoned.

Simultaneous provision of relief of suffering, rapid functional recovery and minimising of persistent postoperative pain and inappropriate prolonged opioid treatment should give the best clinical results in acute pain control. According to this multifactorial aspect pain scores that take into account functional ability/disability associated to acute pain have been developed and used in clinical practice.

Instead of using the WHO analgesic ladder to guide use of analgesics, procedure-specific analgesic techniques are recommended by some authors. These protocols involve the use of analgesics and regional analgesia techniques that could be most suitable for that surgical procedure. It is recommended to perform regional analgesia techniques in the vicinity of the site of surgery what could be associated with minimal changes of motor function and reduction of the systemic side effects.

Among the non-pharmacological strategies to improve pain control quite important are psychological preparation and some physical techniques. In previous period routine use of epidural analgesia and patient controlled analgesia for major surgical procedures have been shown to be associated with restriction of mobility and consequent morbidity, so that approach should be abandoned in the light of other

analgesic techniques. The minimisation of opioid use may reduce the morbidity associated with opioid treatment, but when necessary oral formulations in appropriate doses could be administered with the aim of faster rehabilitation.

Multimodal analgesia that comprises treatment with different pharmacologic and nonpharmacologic measures that might act on different levels on the site of the injury and nociceptive pathways and structures of neuromatrix may be very important in achieving appropriate pain control with good functional recovery.

Individualized pain management could be of great importance in preventing persistent postoperative pain. This protocol could involve adequate psychological preparation, use of opioids and nonopioid pharmacological agents (like ketamine, local anaesthetics, the gabapentinoids), performing regional anaesthesia, local infiltration of adjacent structures to the site of injury.

Daily assessment of pain scores could be very important in identifying patients who could develop persistent postoperative pain and planning the follow up and treatment procedures in order to prevent or alleviate that condition.

The primary aim of adequate clinical practice should include optimal pain relief and functional recovery after surgical procedure along with decrease of complications, decrease of morbidity and achieving of good quality of life and satisfaction of the individual patients and the whole community.

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Dysphagia in ICU

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World Gastroenterology Organisation defined dysphagia as ''The perception that there is an impediment to the normal passage of swallowed material''. If the difficulty is with the initial phases of a swallow, it is called "oropharyngeal dysphagia". The obstruction sensation during the passage of foods/liquids from the mouth to the stomach is called "esophageal dysphagia".

The incidence is reported as 11% in the general community. One in 17 people will develop some form of dysphagia in their lifetime. In patients with stroke, 40–70%, and with neurodegenerative diseases, 60–80% dysphagia is developed. The incidence is reported as 60-75 % in patients underwent radiotherapy for head and neck cancer. More than 50 % of elderly patients suffer dysphagia in nurse houses.

Swallow is a complex procedure. It involves cranial nerves V, VII, IX, X, XII and over 50 muscles and cortical structures. Swallowing consists of oral, pharyngeal, and oesophageal phases. Oral phases are managed by the motor cortex, the others are reflexive. Oesophageal sphincters prevent air from entering the oesophagus and stomach during breathing; protect the reflux of gastric juice into the oesophagus and throat.

Upper dysphagia (oropharyngeal) usually develops due to neorological diseases. Dental defects, dry mouth, muscle weakness, and impaired laryngeal protective functions are some of the other reasons. Lower dysphagia (oesophageal) is due to 85% functional or structural gastrointestinal diseases.

Dysphagia has life threatening consequences. The serious one is aspiration pneumonia as a result of aspiration of food, colonized secretion and gastric content. Malnutrition, dehydration and worsened life quality are other consequences.

The European Society of Geriatric Medicine accepts dysphagia as a geriatric symptom. The physiological regression at the mouth and throat sensory receptors, muscle efficiency, saliva production, impaired elasticity of the connective tissue, impairment of hyoid cartilage and laryngeal mobility are old age-dependent factors. According to Umay et al's. review, all persons older than 85 years old and more than 65 years old with any sign or risk factor should be accepted having dysphagia.

Polipharmacy, cognitive dysfunction, sarcopenia, and fragility are important risk factors for these age groups.

Weakened or absent voluntary cough reflex, coughing/choking during and/or after feeding, change of voice during/after feeding, head and posture changes during feeding, food residue in the mouth, repetitive and multiple swallowing, presence of signs of lower respiratory tract infection, decreased oxygen saturation by pulse oximetry during/after feeding, pneumonia history more than 3 times a year, speech disorders (Breathing, swallowing and phonation are with the same muscles) are the associated signs and symptoms of the swallowing.

In ICU units, dysphagia should be in mind. Acute neurological disease, previous neurological conditions, neuropathy/fragility, and prolonged mechanical ventilation with ETT are major risk factors in ICU. High APACHE II or SOFA, gender, and comorbidities such as hypertension, kidney disease, diabetes, COPD, heart failure, smoking, and transesophageal ecocardiography are less frequent risk factors. It is reported that after 48 hours of ventilation, the risk of dysphagia increases by 14% per day of ventilation. Interestingly cumulative doses of propofol and midazolam used and ICU and hospital length of stay are not risk factors.

Six potential mechanisms are suggested for ICU acquired swallowing disorders including post extubation dysphagia (PED). They are orophageal and laryngeal trauma, neuromuscular weakness, altered sensorium, gastroesophageal reflux, reduced laryngeal sensation and breathing and swallowing dyssynchrony.

Althouhg accurate identification of swallowing disorders in ICU patients is crucial to determine the safe type of oral alimentation, screening for dysphagia is not yet considered standard of care in most ICUs. It is likely because of restraints in resources and limited awareness. PED is underrecognized health-care problem with considerable impact on clinical outcomes.

Nurse screening plays a vital role and bedside swallowing tests are the simplest tests. Gugging swallowing screen test (GUSS), and volume- viscosity swallowing test (V-VST)are preferable bedside swallowing tests. They minimize aspiration and similar to daily consuming foods. These tests assess symptoms of dysphagia at various volumes and densities. GUSS test consists of 2 parts, which are divided into 4 subtests and these 4 subtests must be performed sequentially. Totally 4 levels of severity can be determined, and for each level of severity, different diets are recommended. V-VST

can be combined with pulse oximetry. A 3% decrease in SpO2 with the absence of coughing shows silent aspiration.

The flexible endoscopic evaluation of swallowing (FEES), or the videofluoroscopic swallow study (VFSS), may be regarded as the gold standard of dysphagia assessment in the critically ill. FEES can be performed at the ICU bed using a small flexible endoscope passing through a nostril into the epipharynx so that the oro-/ hypopharynx and the glottic area can be visualized.

How can we manage the dysphagia in ICU? Dysphagia management's aim is to prevent aspiration and its complications. The management is based on adaptive, compensatory and rehabilitation procedures. Adaptation procedures consist of changing the structure of food, often in cooperation with a dietician. The diet should be concentrated on liquid foods dysphagia. Solid food should be ground for solid food dysphagia. The diet can stimulate the receptors of the mouth and support the swallowing reflex. If there is xerostomia, the oral mucosa is moustrized. Compensation management generally requires cooperation with a physiotherapist. The swallowing reflex can be supported by changing the body posture and proper positioning of the head in relation to the body during a meal. Rehabilitation is carried out by an experienced therapist and requires the patient's cooperation, which may be difficult or impossible in the case of neurological dysphagia ICU. In some cases, only surgical procedures can prevent the patient from choking on saliva or food. A radical procedure involves separating the airway from the digestive tract by selecting a tracheal fistula or nutritional gastrostomy oftenly.

Pharmacological treatment of dysphagia is used in the treatment of gastroesophageal reflux, but also disorders of oesophageal motility and tension. In selected cases, pharyngeal electrical stimulation, transcranial current stimulation have been used to treat dysphagia.

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Multidrug Resistant Gram-Negative Infections in ICU – Where Are We Now?

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Multidrug resistant organism (MDRO) infections cause prolonged hospitalization, excess morbidities and mortalities, and subsequently contribute to huge economic burdens [1]. Multidrug resistance is one of the top threats to global health. The "ESKAPE" pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) were first described in 2008, and remain to be leading causes of MDRO infections throughout the world. While infection rates due to MDRO are continuously increasing, antimicrobial agents which are active against MDRO, especially carbapenem-resistant Gram-negative bacteria (CR-GNB), remain limited. In 2017, the World Health Organization (WHO) also urged prioritization of drug discovery and research for MDRO. The WHO listed A. baumannii, P. aeruginosa, and Enterobacterales as critical priority, and E. faecium as high priority in urgency for the need of new antimicrobial agents [2]. A new terminology has been proposed for the categorization of resistance in Gram-negative pathogens. Multi-drug resistant (MDR) is defined as the acquired nonsusceptibility to at least one agent in three or more categories of antimicrobial agents, and extensively-drug resistant (XDR) is the nonsusceptibility to at least one agent in all but two or fewer categories of antimicrobial agents. Finally, pan drug resistant (PDR) is the nonsusceptibility to all agents in all categories of antimicrobial agents [6]. This statement was proposed by Magiorakos et al. in 2012, when new β-lactam-β-lactamase inhibitors (BLBLI) and novel antimicrobial agents were not launched in the market for the treatment of MDR, XDR, and PDR Gram-negative pathogens [3]. However, a new definition of resistance for Gram-negative infections defined as difficult-to-treat resistance (DTR) has recently been proposed as treatment-limiting resistance to all first-line agents, including all β-lactams (carbapenems and β-lactamase inhibitor combinations) and fluoroquinolones [4]. On the other hand, there is a considerable knowledge gap for the treatment of PDR

Gram-negative strains, which are linked to extremely high all-cause mortality, ranging from 20 to 71% [4,5]. Therapeutic options for DTR and PDR K. pneumoniae, A. baumannii, and P. aeruginosa are scarce, initiating salvage treatments counting upon synergistic combinations (in vitro or animal model), increased exposure regimen adapted to the MIC of the pathogen, as well as the introduction of novel antibacterial agents [6]. Furthermore, increased antimicrobial use worldwide occured due to increased hospital admissions during the COVID-19 period, which in turn resulted in worsening of health-care-associated and multidrug-resistant infections [7,8].

In this paradoxical scenario prescribing antibiotics for multidrug-resistant gram-negative bacteria (MDR-GNB) infections has become a significant challenge for clinicians worldwide, stretched between the well-known limitations of the old drugs, fear of promoting resistance by using the new antibiotics, the paucity of data on the effects of newly developed antibiotics against MDR-GNB and the costs of the new antibiotics. In this current setting, in 2022, European Society of Clinical Microbiology and Infectious Diseases (ESCMID) provided guidelines for the treatment of infections caused by MDR-GNB (endorsed by European Society of Intensive Care Medicine) [9]. A systematic review was performed including randomized controlled trials and observational studies, examining different antibiotic treatment regimens for the targeted treatment of infections caused by the third-generation cephalosporin-resistant Enterobacterales (3GCephRE), carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant Pseudomonas aeruginosa (CRPA) and carbapenem-resistant Acinetobacter baumannii (CRAB).

In very short review for purpose of this article, strong recommendation for treatment of infections caused by MDR-GNB were given as following: 1.) in patients with bloodstream infection (BSI) and severe infection due to 3GCephRE for treatment with carbapenem (imipenem or meropenem) as targeted therapy, 2.) in patients with CRE infections susceptible to and treated with ceftazidime-avibactam, meropenem-vaborbactam or cefiderocol, no recommendation were given for combination therapy, 3.) in all patients with CRAB infections, no recommendation for polymyxin-meropenem combination therapy or polymyxin-rifampin combination therapy.

Conditional strenght of recommendation were given to: 1.) in patients with BSI due to 3GCephRE without septic shock, ertapenem instead of imipenem or meropenem may be used, 2.) in patients with severe infections due to CRE, treatment with meropenem-vaborbactam or ceftazidime-avibactam if active in vitro, 3.) in patients with severe infections due to CRE carrying metallo-β-lactamases and/or

resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam, treatment with cefiderocol could be applied, 4.) in patients with severe infections due to difficult to treat CRPA, treatment with ceftolozane-tazobactam. Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam at this time, 5.) in patients with CRAB susceptible to sulbactam and HAP/VAP, first line treatment is ampicillin-sulbactam, and 6.) in patients with severe and high-risk CRAB infections, combination therapy including two in vitro active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations) is recommended.

Since the issuing of the priority list in 2017, new antibiotics with activity against MDR-GNB were approved by the European Medicines Agency (EMA) and and the US Food and Drug Administration (FDA), none of which has a new mode of action and all followed a fast-track development pathway that is granted to drugs potentially addressing unmet medical needs [4]. Ceftolozane-tazobactam FDA and EMA approved for cIAI and cUTI, HAP and VAP, and (in EMA only) for the treatment Gram-negative infections in patients with limited treatment options; Meropenem-vaborbactam EMA approved for cUTI, HAP and VAP, and for the treatment Gram-negative infections in patients with limited treatment options; Imipenem-cilastatin/ relebactam FDA approved for cUTI and cIAI; EMA approved for HAP and VAP and for BSI with a suspected respiratory source, and for the treatment Gram-negative infections in patients with limited treatment options; Cefiderocol EMA approved for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

General practice recommendations and antibiotic stewardship (ASP) considerations plays very important role in good practice for managing ICU infections (Figure 1). Optimal antibiotic dosing schemes should be used, with attention to adverse effects, especially with the old antibiotics-polymyxins and aminoglycosides. Dosing and mode of administration should be optimized by pathogen and indication, with use of therapeutic drug monitoring whenever available. Source control should always be a priority, to optimize outcomes and shorten antibiotic treatment durations. Testing against the new BLBLI and polymyxins is recommended for CR-GNB that are resistant to all β-lactams. Follow-up cultures are recommended in case of treatment failure, especially for CR-GNB, to detect resistance development. For pan-resistant CR-GNB, the panel recommends selection of antibiotic treatment with the least

resistant antibiotic/s based on MICs relative to the breakpoints, but mainly optimal source control (good practice statement).

Principles and practice of ASP should include: the right antibiotic, for the right indication (right diagnosis), the right patient, at the right time, with the right dose, route and duration of therapy, causing the least harm to the patient and future patients. Formulary policies, such as monotherapy used instead of combination therapy, which covers the likeliest etiological agent or pathogenic organism relevant to the site of infection, should be employed whenever possible.

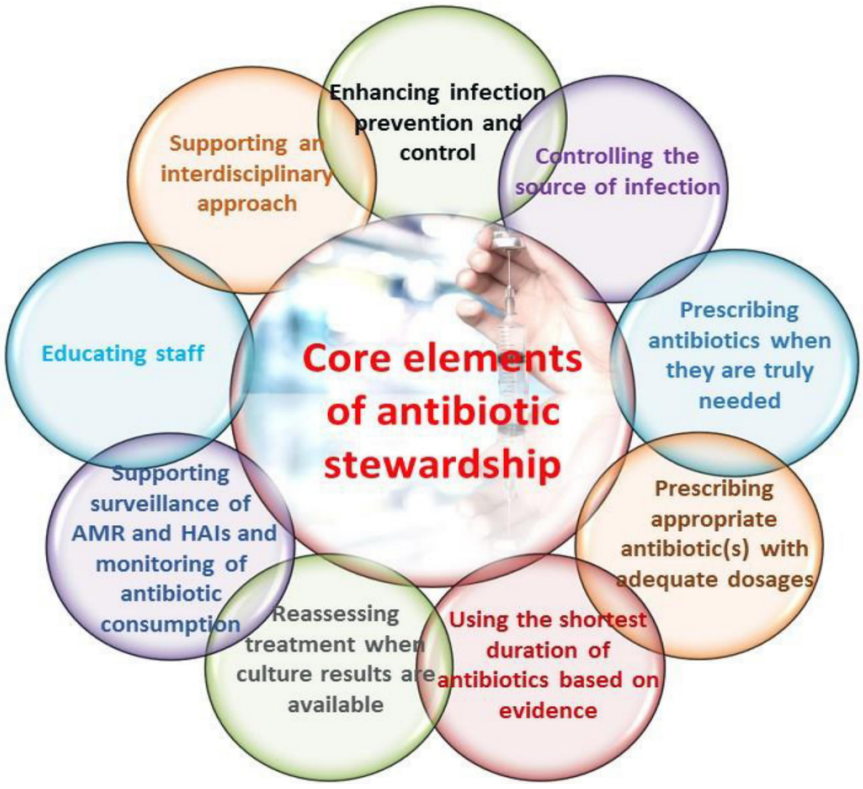

Figure 1. Core elements of ASP to optimize the treatment of infections and reduce adverse events associated with antibiotic use. Available from: https://infectionsinsurgery.org/core-elements-of-antibiotic-stewardship/

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The permissive strategies in Intensive Care Units (ICU): actual trend?

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Introduction

The enemy of "better" is often "the best" during treatment of the patients in intensive care units (ICU). Often junior physicians in ICU may face difficulties treating the patients due to lack of expertise and experience. So junior colleagues (but not only them) tend to overreact in front of difficult situation in intensive care unit. Those reactions may be helpful for the patients being right decisions, but in several moments can cause new complications due to drug side effects or performed procedures. The actual literature offers a variety of articles of so-called permissive strategies (hypotension, hypoxemia, hypertension, hypercapnia, and oliguria) in ICU.

Permissive hypotension

Thomas Latta performed an attempt of intravenous fluid resuscitation for the first time. 1879–1881 Kroneecker and Landerer stated that in cases of blood loss the most valuable thing is to rapidly restore the vascular bed volume. The development of fluid therapy was in the 1920s, by Alfred Blalock (1). Permissive hypotensive resuscitation (PHR) is an advancing concept aiming towards deliberative balanced resuscitation whilst treating severely injured patients. Permissive hypotensive resuscitation (PHR) is the intentional lowering of blood pressure during fluid resuscitation by restricting the volume of crystalloid fluid administered until definitive surgical control of bleeding occurs. Systolic blood pressure is generally maintained at 90 mmHg to consider permissive hypotension (2). Advantages of permissive hypotension include minimizing fluid administration amounts, minimizing excessive fluid administration side effects (interstitial edema formation in several target organs, electrolytes disturbances, and hyperchloremic acidosis), and minimizing the dose and the duration of vasopressors. Minimizing vasopressors can also reduces their side effects as ischemia of peripheral tissues, excluding regions of the body from perfusion, cerebral ischemia, tachyarrthymias, and coronary spasms (3). Owattanapanich et al, published a meta-analysis including 2114 studies but only

30 studies were selected for this meta-analysis. This meta-analysis founded that hypotensive resuscitation had significant better results compared to aggressive resuscitation during trauma patients' treatment. The authors founded a reduced incidence of Adult Respiratory Distress Syndrome, multiple organ dysfunction, and a non-significant increased risk for Acute Kidney Injury (3). The National Heart, Lung, and Blood institute prevention and early treatment of Acute Lung Injury Clinical trial published an interesting paper in The New England Journal of Medicine. They included 1563 patients form 60 centers in USA and divided them in 2 groups: liberal and conservative fluid strategies. They founded that restrictive fluid therapy and permissive hypotension were not associated with an increased mortality by day 90 (4). Perner et al, were of idea that the hypotension must be aggressively treated if there is hypoperfusion verified (5). Lamontagne et al, published a paper based on their study enrolling 118 patients. They concluded that non-significant differences of cardiac arrythmias in lower and higher blood pressure, and a decreased hospital mortality in patients over 75 years old with lower mean arterial pressure (6). The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is effective than a higher target is unknown. The results of Lavillegrand et al, suggested that aggressive treatment of sepsis induced hypotension can be reserved in case of hypoperfusion signs (7).

Permissive hypercarbia

Permissive hypercapnia is a derivate of very difficult mechanical ventilation in such specific situation as bronchial asthma, COPD, Covid-19, and ARDS. During lung protective mechanical ventilation strategies, hypercarbia is a well-known consequence of this ventilatory strategy. ARDS Clinical Practice Guidelines of 2021, published in Journal of Intensive Care, recommends the lung protective ventilation strategies based on low Tidal volume (4-6 ml/kg/IBW) and limiting plateau pressure as well (8). Several authors emphasized that for maintaining PaCO2 up to 80 and pH up to 7.20, may have some contraindications. The contraindications of permissive hypercapnia are pulmonary hypertension and increased intracranial pressure (9). Luca Bigatello et al had explained in detail the physiological effects of hypercapnia. The physiological effect of hypercapnia includes tachycardia, increased pulmonary resistance, increased intracranial pressure, increased endogenous catecholamines, and reduced catecholamines efficacy. Beitler had published an interesting paper recommending limiting plateau pressure under 30 cmH_2O and driving pressure under 15 cmH_2O (10).

Permissive hypoxemia

Permissive hypoxemia concept is especially spread during Covid-19 pandemic. The aim of oxygenation has been changed due to being unable to reach the desired value. During this period, the physicians of intensive care unit verified low PaO2 and O2 saturation, but mildly low values were not life threating scenarios. A group of authors had recently published a paper in The New England of Medicine. They arrived in conclusion that lower oxygenation group did not have an increased mortality compared to higher oxygenation target group in patients with acute hypoxemic respiratory failure admitted in ICU (11). So, increasing PaO2 must be accurate and taking in consideration all the preexisting problems of the patient. Individualizing the patient is of great importance and can increase the possibilities of better prognosis.

Permissive hypertension

To minimize ischemia size during stroke events, American Heart Association guidelines of 2022 recommend maintaining a permissive hypertension state i.e., to have blood pressure target less than 220/120 mmHg and if thrombolysis is performed the blood pressure target must be less than 185/110 mmHg. The same guidelines for hemorrhagic stroke recommend having systolic blood pressure target between 130-150 mmHg, suggesting that lowering systolic blood pressure below 130 mmHg may be harmful to the patient (12). Several authors concluded that achieving a target systolic blood pressure of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg (13). Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACHE 2) did not support efficacy of intensive SBP reduction below 140 mmHg, and individualizing the patients who can benefit is crucial (14).

Permissive oliguria

It is from many years ago reported that urine output less than 0.5 ml/kg/h is considered oliguria. If oliguria occurs the physicians in intensive care units tend in the first step to fill the vascular bed through fluid administration or increasing the blood pressure by fluid or vasopressor administration. Using fluids seems to be successful in some cases but not in other situation. So, prior of fluid administration the physicians must be ensured that the patient may be fluid responsive. Fluids are drugs and have their own side effects. The aim must be to correctly restore vascular bed without side effects as hypervolemia, edema, electrolyte disturbances, and acid base disorders.

Ostermann et al have published an interesting paper emphasizing that oliguria may be nowadays as 0.3 ml/kg/h urine for less than 4 hours. According to Ostermann this must be the cutoff for fluid administration to increase urine output (15). Another interesting paper published by Myles et al, concluded that 0.3 ml/kg/h of urine output is not correlated with an increased incidence of acute kidney injury (16). Mizota et al are of idea that urine output 0.3 ml/kg/h are associated with an increased risk for acute kidney injury but not the values 0.3-0.5 ml/kg/h (17). Another group of authors concluded that urine output of 0.2 ml/kg/h can be tolerated not giving fluid boluses if there is no additional risk factor for acute kidney injury (18).

Taking home messages

Critical care thinking is a normal daily practice for every physician working in ICU. Individualizing the patients ("one size does not fit to all"), thinking before overacting, and not considering guidelines as tabu, are hallmarks of permissive treatment.

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Place For Pediatric Tracheostomy, Anesthesiology Point of View- Our Experience Pediatric Tracheostomy

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Introduction

There is a wide range of basic and advanced techniques and ways of securing pediatric airways nowadays: from invasive to noninvasive, intubating and non intubation techniques. Growing number of airway devices on the market is a sign that no device is perfect nor one size fits all. Surgical tracheostomy is a life-saving procedure performed for emergent or expectant airway compromise due to upper airway obstruction or to support the need for prolonged ventilation. Although it is generally thought of as safe, morbidity in the pediatric population is higher than in adults due to smaller operating field, immaturity of tissues, anatomical specificities of the child's neck, or presence of craniofacial dysmorphism. In some cases, tracheostomy is also a permanent solution for airway management. According to the literature, indications for tracheostomy in pediatric patients have changed a bit. Since the introduction of the procedure it was primarily used for emergency airway management because of the upper airway obstruction primarily by infections origin (eg. diphtheria or croup, polio). Because of effective vaccination protocols and the widespread use of antibiotics, infectious diseases have become less and less of a concern. Instead, tracheotomy is now performed at a young age because of congenital anomalies of the respiratory tract, prolonged mechanical ventilation and intubation, and airway toilette.

Methods

Retrospective chart review was performed on pediatric patients who had a tracheostomy during the 5-year study period (between 2018 and July 2023) at University Hospital Centre Zagreb (UHC), Croatia. Patients were excluded if they were older than 18 years of age at the time of tracheostomy. Patient charts were reviewed for the following variables: gestational age, birth weight, gender, age at the

time of tracheostomy, primary indication for tracheostomy, procedure type (emergency vs. elective) and mortality.

Table 1. Indications for tracheostomy

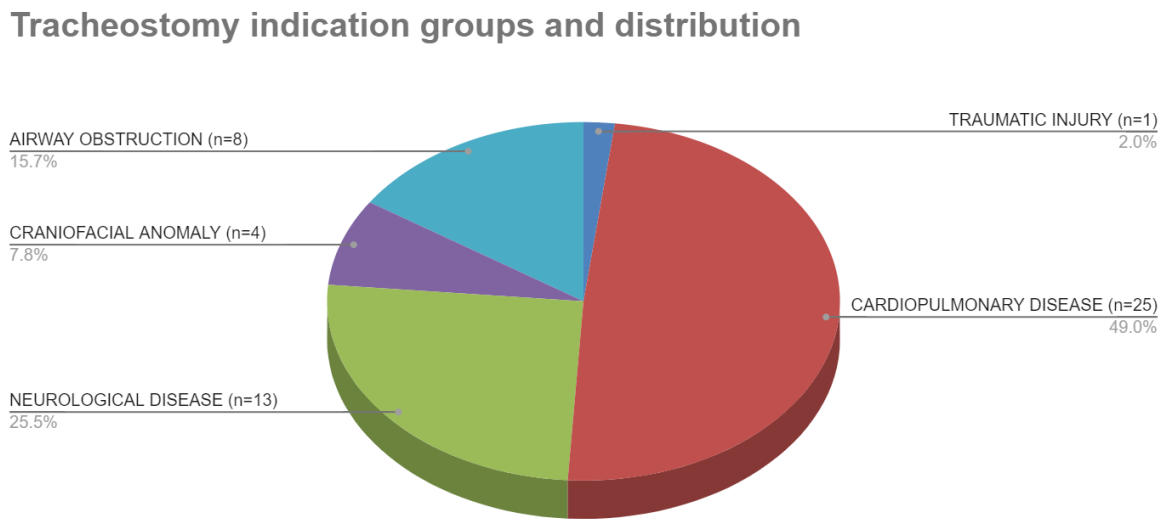
Airway obstruction	Cardiopulmonary disease	Craniofacial anomalies	Neurologic impairment	Traumatic injury
Bilateral vocal cord paralysis	Prematurity, Bronchopulmonary dysplasia	Micrognathia, Retrognathia	Arnold-Chiari malformation	Drowning
Subglottic stenosis	Congenital heart disease	Choanal atresia	Central respiratory dysfunction	Ingestion of corrosive material
Tracheobronchomalacia	Congenital lung disease	Pyriform aperture stenosis	Brain Tumor	Fall
Vascular malformation	Pneumonia	CHARGE	Seizure	Laryngotracheal trauma
Laryngeal cleft	Pulmonary hypertension	Apert's	Cerebral Palsy	Motor vehicle accident
Complete tracheal ring	Chronic lung disease	CHAOS	Neuromuscular diseases	Smoke inhalation injury
Laryngeal stenosis	Restrictive lung disease	Crouzon	Encephalopathy	Maxillofacial fractures
Subglottic hemangioma		Di George sy	Guillain- Barre	
NF teratoma		Pierre-Robin	Spinal muscular atrophy	
Rhabdomyosarcoma		Pfeiffer	Others	
		Treacher Collins		
		Velocardiofacial sy		

Source: Gergin O, Adil EA, Kawai K, Watters K, Moritz E, Rahbar R. Indications of pediatric tracheostomy over the last 30 years: Has anything changed?. Int J Pediatr Otorhinolaryngol. 2016;87:144-147. doi:10.1016/j.ijporl.2016.06.018

Results

According to the surgical protocols, a total of 50 surgical tracheostomies have been done during that period, in pediatric patients (<18 years old). Main indications for the procedures have been divided into 5 groups: airway obstruction, cardiopulmonary disease, craniofacial anomalies, neurological disease and traumatic injury, as per table 1. Majority of indications for tracheostomy were for cardiopulmonary (n= 25; 49%) and neurological disease (n= 13, 25,5%), followed by congenital or acquired airway obstruction (n=8; 15,7%), craniofacial anomalies (n=4, 7,8%) and only 1 case of traumatic injury (2%) as shown in Figure 1. All the patients were ASA 3 or more, with more than 2 comorbidities. Some patients had

simultaneously more congenital defects: eg. cardiopulmonary and airway obstruction or craniofacial and neurological disease. Two thirds of the pediatric tracheostomies were performed for children under one year of age, and one-fifth for children under one month of age. 14 (28%) were premature and 10 (20%) had a low birth weight.



Picture 1. Tracheostomy indication groups and distribution

The age at tracheostomy was younger in patients who had a tracheostomy for airway obstruction, cardiopulmonary or craniofacial anomalies when compared to patients with neurologic impairment or traumatic injury. Ten (20%) out of 50 patients had an emergency tracheotomy. Main reasons for that were impeding upper airway obstruction: 3 of 10 patients cannot be intubated, and they were ventilated with 2 hands face mask technique, one was managed by the use of supraglottic airway during the tracheostomy. The rest were intubated in the operating room, using a videolaryngoscope. Over the last 5 years, there were no tracheostomy-related deaths.

Discussion

Our results are consistent with those published in recent papers. The rising number of tracheostomies in the smallest ones, eg, infants, opens a new chapter in properly selecting the size of the tracheostomy tube, since not only internal diameter (ID) matters, but the length of the tube also. The smallest pediatric tracheal tube can be too long for some infants, if the neonatal tracheal tubes with the same ID but shorter are not available. Draping and padding cushions can overcome some situations, but fiberoptic check of the correct position of the cannula in the unextended neck after the procedure, before transport in the ICU is then recommended. Multiple anatomical,

physiological and contextual issues have to be taken into account while managing those patients. Pediatric candidates for tracheotomy are few and often burdened by their primary diseases, requiring interdisciplinary planning, timing and preparing for the procedure. Many candidates are on anticoagulants, vasopressors and with very limited physiological reserves. Careful positioning and tube handling during the procedure is demanding and very important, so as the stay sutures, especially in infants. Because of this, the decision to perform a tracheotomy in infants and children must be carefully weighed and made on a case-by-case basis, the same is applied to the decannulation process after resolution of the primary indication for the procedure, unless this is a permanent solution.

Conclusion

Although seldom performed, tracheostomy is the procedure of choice in the select group of pediatric patients. The risks and benefits of the procedure must be weighted for each patient. Pediatric airway management doesn't end in the operating room, especially as far as the tracheotomy is concerned. Dedicated stoma nurses are crucial for patient and caregivers education and safety. In proper indications and with adequate preparations, the procedure is safe and effective in managing the airway of pediatric patients.

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Disorders of the Lower Respiratory Tract in the ICU, Bronchoscopic View

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Introduction

Diseases of the lower respiratory tract are a common cause of admission of patients to the intensive care unit. These diseases can be inflammatory in nature, such as pneumonia, the result of mechanical obstruction outside the airways, obstruction by tumors or other masses inside the airway, and the result of diseases of the circulatory system. Bronchoscopy can provide important information according to which further treatment can be adjusted, such as mechanical ventilation, surgical intervention, or microbiological diagnostics. As an interventional method, bronchoscopy is extremely useful in acute airway obstruction by a foreign body, whether it is of exogenous origin, such as an aspirated foreign body, or it is related to the clots or secretions that were formed inside the airway. In addition to patients in the intensive care unit, bronchoscopy should also be used in emergency patients, such as trauma victims, who have ventilation asymmetry that cannot be explained by the injury itself.

Aspiration

Aspiration is a complication of foreign body/material entering the airway. It is common in polytraumatized patients and in patients with a disorder of consciousness, such as neurotrauma (1). It can occur during intubation in patients with acute abdomen. The result of aspiration can be aspiration pneumonitis, as well as obstruction of the airway by food. Early bronchoscopic removal of foreign material is necessary in these patients (1, 2). Along with the lavage of the respiratory tract with saline, bronchoscopic visualization can help to remove any residual foreign bodies, thus reducing the possibility of airway obstruction.

Inflammatory diseases

Inflammatory diseases of the lower respiratory tract that cause admission to the ICU are multifaceted (3). Pneumonia is the most common and can lead to life-threatening hypoxia and inability to ventilate. Depending on the etiology of

pneumonia, bronchoscopy may not show changes in the morphology of the tracheobronchial tree, except for narrowing and hyperemia of the airways (Figure 1A). Narrowing of the airway by secretions is common in patients with bacterial pneumonia. They are caused by edema and hyperemia or the mucous trapping of the respiratory tract.

In the exudative phase of pneumonia, especially in patients with a morphologically altered tracheobronchial tree, such as bronchiectasis, copious expectoration and inability to eliminate secretions can lead to airway obstruction with secretions (Figure 1B). The desaturations that are often observed in these patients require bronchoscopic lavage of the respiratory tract along with the use of appropriate antibiotics. In a situation where the secretion is abundant positional drainage may be helpful (Figure 1C).

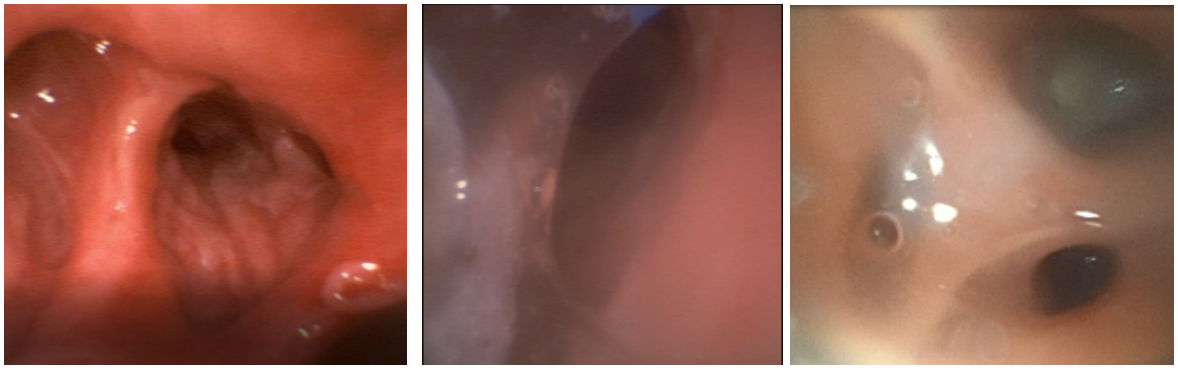

Figure 1A. Bronchoscopic appearance of the carina in bacterial pneumonia. The mucous membrane is hyperemic, with visible areas of inflammation that bleed when touched. 1B. Abundance of grain secretion in the respiratory tract, which causes desaturation and interferes with mechanical ventilation of the lungs. 1C. Appearance of right bronchus with purulent secretions.

In addition to localized changes in pneumonia and tracheobronchitis, narrowing of the airway was observed in septic patients. Taking samples for microbiological analysis is certainly recommended even in situations where there are no convincing and visible localized changes in certain lung segments.

Atelectasis

Atelectasis of the lungs is a common reason for hypoxia and admission to the ICU, and can be observed both with or without bronchopneumonia (3). If the cause of atelectasis is compression from outside the thecheobronchial tree, narrowing of the trachea may be apparent. With tumor infiltration, deformations of the trachea and main bronchi can be seen bronchoscopically, and samples can be taken for cytological analysis. In the case of obstruction by coagulum, a foreign body or a tumor eroding the tracheobronchial wall, bronchoscopy can help in the diagnosis and therapy of the

obstruction (Figure 2). In patients with atelectasis (Figure 3), early bronchoscopy can significantly shorten the length of the mechanical ventilation and ICU stay (4, 5).

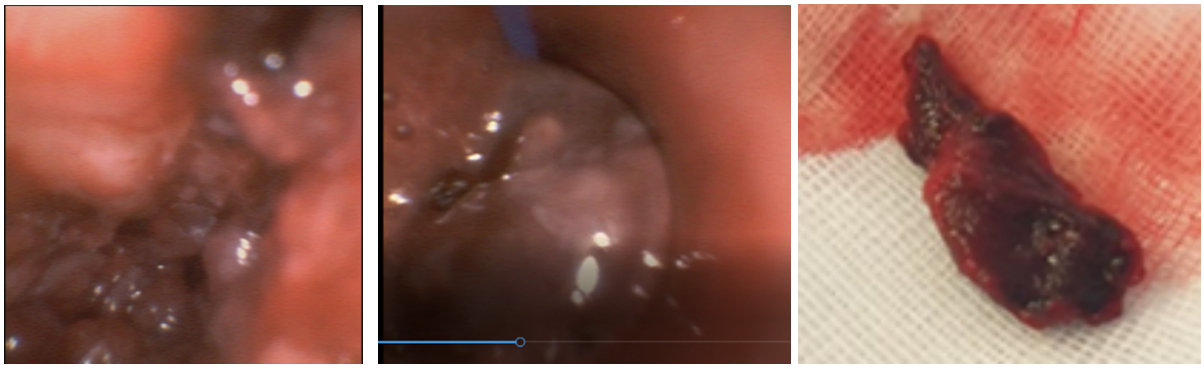

Figure 2a Obstruction of the right bronchus in a 23-year-old patient leading to lung atelectasis. 2B. Bronchoscopic view of the clot after mobilization before entrance into endotracheal tube. 2C. A solid organized clot that was removed bronchoscopically from the right bronchus.

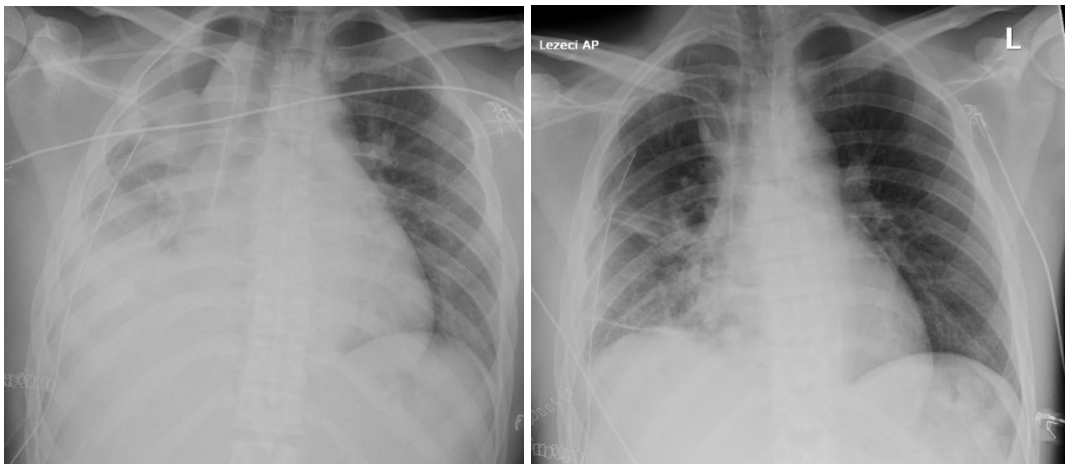

Figure 3A. Right sided atelectasis caused by clot in the right main bronchus. 3B. After the clot formed after the chest contusion (Figure3) was removed from the bronchus, the were lungs re-expanded.

Cardiac decompensation

Cardiac decompensation in conservatively treated patients o rafter cardiac interventuions can lead to accumulation of extravascular lung water. In this situation, the airways will be pressed from the outside, narrowed, and secretions trapping the airways may be present in them (6). The tracheal and bronchial wals will be edematous and pars membranacea of the trachea may protrude into the lumen and trachea in these patients (Figure 4).

Figure 4. A cross section from thoracic CT scan of the lungs in a patient with pneumonia and cardiac decompensation. With the narrowed lumen of the trachea and bronchus, it is obvious that the membranous part was pushed into the airway lumen. Atelectatic areas of the lungs caused by the collapse of the small airways and the inability to expectorate are also visible nearby.

Injuries

Injuries of the large airways can represent a serious problem during the treatment of patients in the ICU. These include mechanical chest trauma, such as rupture of large or small airways that will result in the formation of fistulas with surrounding organs or tissues. A complication of this injury is the release of air into the surrounding tissue, i.e. the formation of subcutaneous emphysema or pneumothorax (7). If the injury is on the distal parts of the airway, it will be necessary to place a thoracic drain (Figure 5).

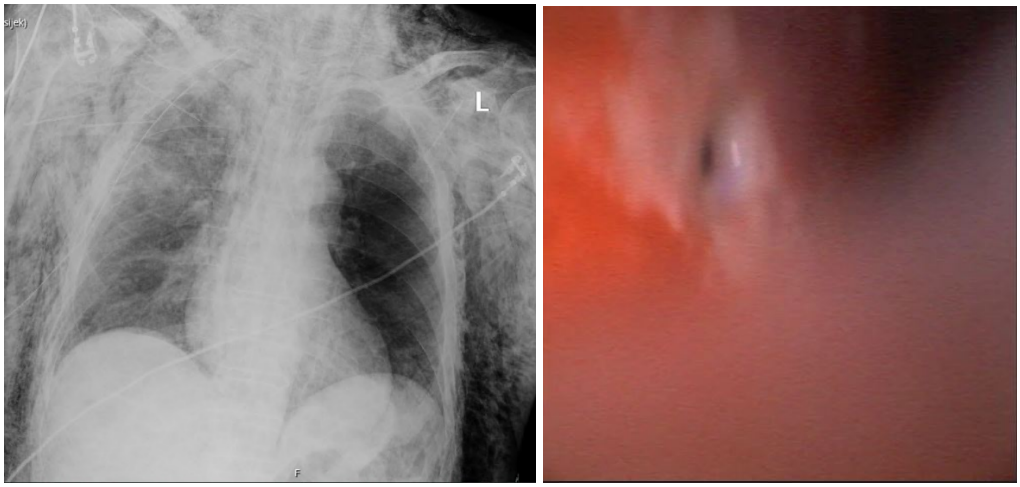

Figure 5A. Subcutaneous emphysema after fracture of the sternum and tracheal rupture was treated by displacement of tracheal cuff, thoracic drainage and subcutaneous needles placement. 6B. Bronchial fistula in the patient with recurrent pneumonias, just below tracheal bifurcation observed by bronchoscopy. It was treated by thoracic drain, antibiotics, and adjustment of ventilation pressures.

Injuries of the large airways include fistulas that occur after long-term intubation, due to the mechanical trauma with suction catheters, bronchoscopes, or

those that occur due to compression of the cuff on the tracheal wall. If the injury is in large proximal parts of the tracheobronchial tree, it may require a change of cuff location, reduction of pressure in the cuff, reduction of ventilation pressures and sometimes surgical intervention at the site of the airway injury. In these cases, microbiological surveillance and treatment of infection should be associated interventions.

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) is one of the most common airway-related interventions performed by anesthesiologists in the ICU. The goal of BAL is to wash out the contents inside the tracheobronchial tree with a stream of fluids, usually saline, take the samples for microbiological analysis and remove the obstruction of the airway with secretions. BAL is performed with the help of an assistant, so that the tip of the bronchoscope with the working channel is placed near by the contents to be flushed out (Figure 6).

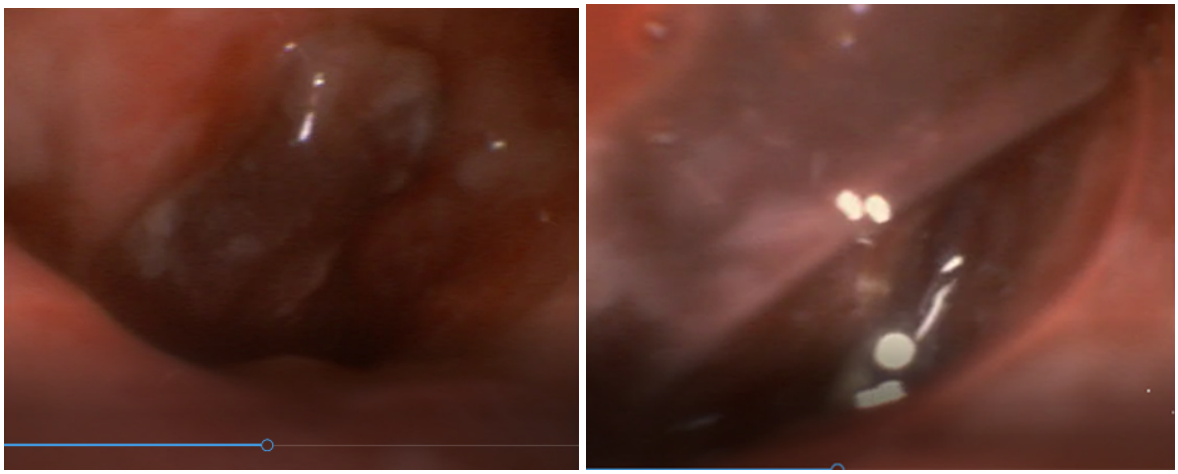

Figure 6. Bronchoscopic wiev of bronchial obstruction during bronchoalveolar lavage. After several washouts, the organized secretions were removed. A *Pseudomonas aeruginosa* infection was conformed In the BAL.

After aspiration, the procedure can be repeated several times, if secretions adhere to the airway walls. If the content is solid and cannot be easily aspirated, tools such as forceps can be used that are introduced through the working channel. When removing adherent secretions, especially if the patient has a respiratory tract infection, bleeding can sometimes occur. It can be stopped by local application of tranexamic acid or adrenaline (8).

In conclusion, it should be emphasized that the application of bronchoscopy facilitates diagnosis and contributes to solving of several problems related to the lower

respiratory tract. This valuable technique should be a routine method and part of the skills that every anesthesiologist acquires during residency.

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Fetal And Maternal Outcomes for Caesarean Delivery; Comparing the Effect of General Vs Regional Anesthesia

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A Caesarean delivery, also called C-section or Caesarean birth, is the surgical delivery of a baby through a surgical cut or incision in a woman's abdomen and uterus. It can be performed as elective or emergency operation. According to the World Health Organization (WHO), C-sections are medically necessary in about 10-15% of all births in Western countries, but this rate is much higher. In the USA and the UK, one in three babies are born this way. In Germany the rate goes 30% and higher. Although the operation has become very safe over the years, it is still associated with greater maternal mortality and morbidity. Therefore, the type of anesthesia which will be performed has important role of the outcome of C-section. Anesthesia for C-section can be achieved through general anesthesia (GA) or regional anesthesia (RA) which can further be spinal anesthesia (SA), epidural anesthesia (EA) or combined spinal – epidural (CSE). Anesthesia guidelines recommend regional anesthesia as a first choice. In the USA the use of neuraxial techniques has been increasing since 1980s, particularly with SA (80% of C-sections are done under RA). There is increased use of neuraxial techniques, particularly for parturient with coexisting morbidities. RA is even used in situation that is usually considered as indication for GA such as cord prolapse, preeclampsia and placenta previa. But both GA and RA have their advantages and disadvantages. With general anesthesia there is a risk of failed intubation, failed ventilation, pulmonary aspiration, awareness, pain, and fetal depression. However, GA remains a necessary choice when there is a lack of time, contraindication, refusal or when the RA fails. Regional anesthesia can cause significant hypotension, which may affect both mother and fetus, local anesthetic toxicity, post Dural punction headache, nerve damage. RA is contraindicated in woman with coagulation (clothing disorders). The advantages of RA include reduction of the incidence of GA complications, early bonding between a mother and a baby. Spinal anesthesia has a faster onset of action and requires less drug but causes more hypotensive episode than epidural.

Several studies tried to evaluate which type of anesthesia is better and safer for both mother and baby, looking through results of maternal and fetal outcomes. A

recent study, (Iddrisu, M., Khan, Z.H. 2021) presents a systematic review of 14 studies (1924 women), randomized clinical trials and observational studies between 2010 and 2019. Conclusion of this study is that RA benefits for maternal and fetal outcome are superior to GA.

But there are studies with different conclusion, like Cochrane meta-analysis study (Bosede B. Afolabi et al. 2012). This Cochrane data base of systematic review includes randomized and quasi randomized control trials, evaluating the use of RA and GA in women who had C-section for any indication. Twenty-two studies (1973 women) contributed data to this review. And conclusion is that there is no evidence to show that RA is superior to GA.

Maternal outcomes

Mortality – Even though the GA is associated with higher morbidity and mortality, randomized clinical trials and meta-analysis have been unable to prove that any of the techniques is associated with the mortality. Probably, these findings reflect an improvement in the GA techniques; implementation of algorithms for managing the difficult airway and prevention of pulmonary aspiration; and increase use of RA for high-risk C-section patients.

Morbidity

Blood loss – Compared with the GA women having either EA or SA, had lower estimated blood loss. But this blood loss did not have any significant effect on the rate of blood transfusion.

Intraoperative hypotension – There were no significant changes in the blood pressure and the heart rate during the perioperative period but intraoperative hypotension was more in RA. Therefore, more intravenous fluids and vasopressors were used than in the GA.

Hearth rate – Higher heart rates were recorded in the GA than in the RA.

Pre and post operative hematocrit – One study reported significant difference which favored EA and SA.

Surgical wound infection – In Cochrane's meta-analysis no study is reporting surgical wound infection were found.

Nausea and vomiting – Nausea is more frequent in RA while vomiting is more frequent only in the SA group.

Pain – The perception of pain during the C-section was less when the GA was used than the RA, but time to request for analgesia was longer with the RA (320 min in RA vs 175 min in GA). In the GA there was higher intraoperative analgesia requirement.

Satisfaction – The studies are divided regarding this aspect. One shows that patients were more satisfied with the RA, but contrary to this other show that postoperative patients' satisfaction was higher in the GA.

Neonatal outcomes

Fetal umbilical arterial blood PH – It was lover in the RA than in the GA. But this did not have any significant effect on the baby because there was no cyanosis, body color change or respiratory distress. Some think that fetal umbilical arterial blood PH was adversely affected by the use of ephedrine.

Fetal umbilical vein blood PH – no differences found.

Neonatal neurological adaptive score – no differences were found.

APGAR score – the 1st minute and the 5th minute the APGAR score of fetuses born to mothers exposed to the SA were higher than those exposed to the GA. 1st minute fetal APGAR scores between CSE and GA showed no significant difference. The number of babies with 1st minute APGAR score <7 was higher in GA followed by SA which was converted to GA and SA at the least. No differences were found in the 5th minute APGAR score comparing between RA and GA. Fetal distress, depression and resuscitation were recorded less in the RA as the babies were born very active.

Supplementary oxygen requirement of ventilation during adaption – one study found no difference in the need for supplementary oxygen and another trial did find the difference. The percentage of neonates requiring oxygen or positive pressure ventilation during neonatal adaption was 14% for the GA group vs 5% for the SA group.

Conclusion

Although national guidelines of developed countries recommend the RA as a first choice, especially with elective C-sections, the GA still has a widespread use and is considered safe for mother and fetus. Decreased morbidity and mortality percentages which have earlier been referred to the GA has to thank the advancement of anesthesiologic skills regarding difficult airway and introduction of algorithms. The GA has its own purpose, especially in situations characterized with the lack of time,

when contraindications for the RA are present and when a patient refuses the RA. In the Clinical Center of Monetenegro, there is still a negligible percentage of C-sections undertaken in the RA. Even though all the information about types of anesthesia is being provided during the preoperative preparation, patients are choosing type of anesthesia regarding if they prefer to sleep or not.

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Invasive Candidiasa, Causes, Symptoms, Treatment

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Abstract:

Fungal infections are a growing problem in the ICU, and as they are associated with high morbidity and mortality, especially in critically ill patients, this significantly prolongs hospitalization and contributes to the high cost of treatment. The incidence of fungal infections is constantly increasing (since 1980, the incidence has increased by more than 350%). Most yeast infections are caused by Candida spp., especially Candida albicans. In addition to invasive candidiasis, there are also other causes of infections such as Aspergillus, Fusarum, Zygomycetes. There are many different sources of fungal infections, and timely diagnosis and adequate therapy greatly reduces complications in the treatment of such patients.

Guidelines in treatment are based on an assessment of the severity of the disease, local epidemiological data, the type of strain causing the infection, which is identified microbiologically, and the application of appropriate antifungal therapy. In the last fifteen years, the spectrum of antifungal therapy has been expanded, so polyenes, azoles, echinocandins are used for therapeutic purposes... When applying the drug, we consider the effectiveness of the drug itself, as well as the risk of its application, as well as the price. Echinocandins, if given on time, as the drug of first choice, due to their fungicidal effect, are more effective and contribute to shortening the duration of the fungal infection, and therefore to the prevention of complications.

Keywords: *invasive fungal infection, candidiasis, echinocandins, prophylaxis, therapy*

Introduction

Invasive fungal infections are 70-90% caused by various species of fungi from the genus Candida, and of all hematogenous infections, Candida spp. in the USA it is represented in 8-10% of cases, while in Europe it is represented in a smaller percentage compared to the other causes (2-3%), most likely due to the insufficient specificity of the diagnostic tests.

The most frequently isolated of all Candida species is C. albicans (65-70% of all candidiasis), followed by C. parapsilosis, C. glabrata, and C. tropicalis. Other species that are less pathogenic and less common are C. krusei, C. dublinensis, C. kefir, C. lusitaniae and C. rugosa are diagnosed thanks to additional microbiological techniques for differentiation, and they are present as a consequence of the increase of vulnerable populations (C .kefir, for example, occurs in patients who were previously treated with Caspofungin).

Invasive Candidiasis (IC) is, by definition, infections of deeply located tissues (under the skin and mucous membranes) or other normally sterile sites, documented by histopathological and/or microbiological cultures.

Risk factors

The sources of IC are many and varied. They are classified into endogenous, such as mucocutaneous colonization or gastrointestinal flora, or overgrowth of fungi due to the use of antibiotics, and exogenous, contaminated material, staff hands, infusomata...

Individual risk factors for the development of invasive fungal infections

1. Extended stay in ICU
2. Corticosteroids and immunosuppressants therapy
3. Diabetes mellitus
4. Central venous catheter
5. Total parenteral nutrition
6. Gastrointestinal surgery
7. Prolonged use of antibiotics
8. Age
9. Hemodialysis
10. Neutropenia
11. APACHE II>20
12. burns>50%
13. polytraumatized patients

There are several rules for predicting the development of candidiasis in which risk factors are grouped and proceeded into the corresponding score - these are the so-called prediction rules. In this way, we identify the patients that have the at high risk of contracting invasive candidiasis. One of the most famous is Ostrosky-Zeichner: it refers to the systemic administration of antibiotics for 1-3 days or the presence of CVK for 1-3 days and at least 2 of the following factors: TPN (1-3 days), dialysis (1-3 days). , mayor surgery (the up to 7 days), pancreatitis (up to 7 days), use of corticosteroids (3-7 days) and other immunosuppressive therapy (up to 7 days)

CANDIDA SCOR CS

Major surgery in ICU (1 point)

TPI (1 point)

Severe sepsis (2 points)

Candida colonization (1 point)

CS<3 low risk for IC

Diagnostics

Diagnosis in critically ill patients is not simple at all because the clinical picture is not associated with specific symptoms, and it is difficult to distinguish it from bacterial infections, and on the other hand, laboratory tests have many shortcomings, so we raise doubts in patients who are febrile for more than three days, despite application of broad-spectrum antibiotics.

We use laboratory diagnostic methods.

Direct detection of fungi (tissue culture) would be the gold standard because a positive culture means a present infection (specificity 100%), but suboptimal sensitivity (30-70%) as well as a long incubation time significantly reduce the effectiveness of this diagnosis.

Candida mannan and galactomannan, i.e. detection of surrogate markers (parts of the fungal wall) - shows different sensitivity depending on the Candida species and is the most sensitive for C.albicans (about 94%), while for other strains the sensitivity is significantly lower, only 40-50 %. The sensitivity is increased by the detection of Antibodies for fungi.

Newer diagnostic methods: PCR (fungal DNA), Maldi TOF are not clinically widely used, and despite their price, high hopes are placed on them.

Therapeutic guidelines

The therapy of invasive candidiasis is carried out depending on whether it is a suspected or documented fungal infection. In patients with suspected candidiasis, present risk factors, without signs of infection, and without culture confirmation, prophylactic therapy is applied. The goal is to prevent infection in patients at increased risk. Prophylactic treatment is usually carried out using Fluconazole 800 mg (12 mg/kg) as a loading dose, followed by 400 mg (6 mg/kg) per day. In this way, the incidence of invasive candidiasis is significantly reduced. Therapy is carried out until the resolution of the disease, more percisely. as long as the patient is at high risk or until candidiasis is confirmed, when therapy becomes therapy for infection.

Preemptive therapy is based on the presence of several risk factors in patients with increased candida colonization without current infection, serological tests can also be positive. The choice of drug is based on clinical picture, I.e. the general condition of the patient, and in the presence of hemodynamic instability, echinocandins are the drugs of first choice.

Empirical therapy is carried out in patients with clinical signs of infection, such as persistent fever despite antibiotic therapy, and these are usually patients with multiple risk factors. Start of the therapy is necessary as soon as possible, and the first-line drugs are Echinocandins.

Documented candidiasis, therapy should be administered when microbiologically is confirmed. A more recent ESCMID(2012) recommendation is to use echinocandins as first-line therapy, especially in unstable patients.

Treatment of documented invasive candidiasis

ESCMID (2012) first line Caspofungin 70 mg as loading dose, then 50 mg/day, or Micafungin 100n mg, Anidulafungin 200 mg/day as loading dose then 100 mg daily. In every other case: Liposomal Amphotericin B 3mg/kg, Voriconazole 3-6mg/kg, Fluconazole 400mg, is considered an alternative to this kind of therapy.

Conclusion:

Patients in the ICU have many risk factors for candidemia. Invasive fungal infections are still significantly associated with morbidity and mortality. The diagnosis is difficult to establish and the therapy usually starts late. In this moment, the key

thing is the awareness of the clinician in recognizing the patients. Echinocandins, as drugs of first choice, if administered on time, can significantly prevent the occurrence of invasive candidiasis.

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Acute Pain Treatment in Children

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Pain is, by the definition of the International Association for the Study of Pain (IASP), "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". This definition was revised in 2020: Pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

Pain is a symptom that warns children and parents that they should seek medical help. Acute pain is caused by injury or inflammation, has a biological protective role, and is essential for survival because it warns of damage to body tissues and helps establish a proper diagnosis.

Chronic pain lacks the warning function of physiological nociception, and it is maintained by factors pathogenetically and physically remote from the initial cause, such as peripheral and central sensitization, altered pain modulation, glial activation, and neuroimmune signalling.

Recognition of pain and its measurement and quantification is especially important in children, which is a challenging task, especially in the child's pre-verbal phase.

There is a misconception that children, especially newborns and infants, do not feel pain the same way as adults due to the immaturity of the central nervous system, i.e. incomplete myelination of nerves and receptors, mediators and pathways of pain transmission that are still developing. This does not correspond to the actual development of the neuroanatomical substrate of pain conduction in children.

Analgesics are often not administered adequately due to a lack of knowledge of the pharmacokinetics and pharmacodynamics of drugs in children and for fear of opioid side effects and wariness of the potential for a child's addiction to opioid analgesics.

Acute Pain Assessment

Recognition of pain and its measurement and quantification to apply the appropriate analgesic and evaluate the effect is especially important in children.

The experience of pain includes sensory, emotional and cognitive aspects. How the child will deal with pain and how it will be interpreted depends on the child's age, level of cognitive development, gender, upbringing, temperament, previous painful experiences, and family and cultural heritage.

Depending on the child's age, the expression of pain varies, so it is necessary to apply pain measurement scales in accordance with the child's cognitive development. Only indirect methods can assess pain in the pre-verbal phase of the child's development. Physiological changes associated with acute pain are an increased rate of breathing, increased heart rate and blood pressure, sweating and a drop in peripheral oxygen saturation. These are acute, short, and sharp pain indicators, which cannot be used for long-term, chronic pain. Changes in the child's behaviour related to pain are crying, restlessness, facial grimaces, touching the injury, and pulling the legs to the stomach, which are used in many behavioural scales only or combined with physiological indicators. The most common scale used to assess children's pain in the pre-verbal phase of development is the **FLACC** (Face, Legs, Activity, Crying, Consolability), a scale that tracks five indicators scored from 0 to 2 points, a total of 10 points.

The best is self-assessment of pain because pain is a subjective experience. It is usually used in children aged five and above when cognitive development enables the child to understand the principles of the visual analogue scale. The FACES, OUCHER, and numerical scales (for school-aged children) are most often used.

Older children use a numerical scale (0 to 10 or 0 to 100), from no pain to the worst pain they can imagine. School children can also fill out more complicated questionnaires about pain, in which the intensity, quality, localization, and spread of pain and the child's mood are determined, such as the Gill-Melzack or *Pediatric Pain Questionnaire*.

Medical staff should be educated on the importance of pain assessment and evaluation of therapy's success. Pain intensity should be quantified to determine the analgesic's necessary strength and measure the analgesia's success. Pain assessment is the fifth vital sign and should be entered on the therapy list of a hospitalized child.

Pain Chronification

If applied analgesia is inadequate or lacking, the worst scenario could happen - the chronification of pain. The mechanisms involved in the development of chronic pain are varied and complex. Pain processes are plastic and unrelieved pain may lead

to changes in the neural structure involved in pain generation. Mechanisms associated with the transition from acute to chronic pain are thought to involve peripheral and central sensitization, gliopathy, genetic priming, and alterations in the corticolimbic circuitry.

The primarily investigated are two processes: peripheral sensitization of nociceptors, where events around the damaged site combine to allow a lower intensity stimulus to evoke an action potential in the fibre, and central sensitization, where changes occur in the spinal processing of primary afferent inputs, continuing hyperalgesia and enlarging the area of hyperalgesia and allodynia. Peripheral and central sensitization of sensory nerve fibres are the primary reasons for hypersensitivity to pain after injury, mainly in inflammatory and neuropathic pain.

Some authors point out that according to recent human neuroimaging studies, there is some evidence that supports the contribution of the corticolimbic circuitry, or the "emotional brain," in persistent pain states and contrasts this to the concept that central sensitization secondary to peripheral injury plays the biggest role in determining chronic pain. Corticolimbic learning mechanisms could lead to cortical reorganization.

Where Do Children Encounter Acute Pain?

Acute pain is often the reason for visiting the emergency department, especially surgical emergencies, the possible leading causes being trauma or inflammation.

Children have the greatest fear of procedural pain. Many invasive procedures, like venepunctions, spinal taps, swabs, and aspirates, are needed to establish a diagnosis. To minimize stress, EMLA cream (eutectic mixture of lidocaine and prilocaine) should be applied to intact skin 30 to 45 minutes before the procedure. Analgosedation may be used for more invasive diagnostic or therapeutic procedures, combining short-acting analgesics and hypnotics. Popular combinations are propofol or midazolam with opioids fentanyl, alfentanil, or ketamine intravenously.

The choice of sedatives and analgesics must be adjusted to the intensity of pain, extensiveness and duration of the procedure (surgeon's skill included) and if the child stays in the hospital after the procedure or is going home.

The combination of ultrasound-guided peripheral nerve blocks with light sedation could be used in the emergency department. For establishing the block, the child's cooperation is needed; the advantage is that the child should not be fasting.

Non-pharmacological methods could be used for procedural pain, including e psychological methods of preparing the child. The doctor should familiarize the child and parents with the procedure that will be carried out in simple and comprehensible terms. This reduces the child's anxiety, but the child's fear and pain must not be minimized, and the painlessness of procedures that we know are painful should not be promised. The presence of parents during painful procedures can reduce the distress of both parent and child and increase the satisfaction of the parents, enabling a calmer approach to the child.

There are many methods of diverting the child's attention, and lately, virtual reality is increasingly used for analgesia during painful diagnostic or therapeutic procedures.

Often general anaesthesia is needed for procedures like cystoscopy, gastro- or colonoscopy, and bronchoscopy. For perioperative pain treatment, several terms are used - preemptive analgesia (applying analgesics before painful stimuli), preventive analgesia (applying analgesics in the whole perioperative period - before, during and after the operation) and multimodal analgesia - a combination of analgesics working on different parts of pain path. Combination of NSAIDs, whose mode of action is peripheral cyclooxygenase inhibition, with local anaesthetics with presynaptic inhibition of primary afferent fibres or with opioids with postsynaptic inhibition of secondary nociceptive neurons or NMDA receptors blocking drugs or α- adrenergic agonists is used.

The multimodal principle is often used in ICUs for postoperative or posttraumatic analgesia. When there is a need for mechanical ventilation, long-term analgosedation is applied. Postoperative regional anaesthesia with sedation could be used, like epidural analgesia continuously or PCA with local anaesthetics with adjuvants or peripheral nerve blocks with catheters. Short-term analgesia should be provided for many invasive procedures (procedural pain). The problem in paediatric ICU is that children are of various ages, with many concomitant diseases, various diagnoses, organ dysfunctions, and possible drug interactions. The analgesia should be tailored to each and every child specifically.

Analgesics

Due to a lack of knowledge of the pharmacokinetics and pharmacodynamics of drugs in childhood, there are frequent mistakes in using analgesics, like them being administered in too small doses and at too long intervals, and by an inappropriate

route. Peripherally and centrally acting analgesics, local anaesthetics and supportive therapy are used to treat pain in children. Balanced multimodal analgesia is used by applying smaller doses of drugs that act on various receptors and parts of the pain pathway, reducing the side effects of analgesics and enhancing their combined action.

After assessing the pain intensity, an analgesic of appropriate strength and duration of action must be applied by the appropriate route.

The easiest and the most straightforward route is oral, but there are situations when the oral route is impossible. Due to the possibility of precise dosing and titration of analgesics, an intravenous route is recommended. The rectal route is uncomfortable for older children, and resorption is unreliable. Subcutaneous and intramuscular administration is painful and should be avoided.

New ways of administering analgesics are intranasal and buccal. Many analgesics and sedatives could be administered intranasally, such as ketamine, fentanyl, midazolam, and dexmedetomidine, while midazolam can be administered buccally too.

Intranasal administration has proven to be very useful when rapid drug action is required because the action occurs as quickly as during intravenous administration, avoiding the need for venipuncture.

After assessing the pain intensity, pain estimated as mild is treated with paracetamol and non-steroidal anti-inflammatory drugs.

Paracetamol (acetaminophen) is an analgesic and antipyretic widely used in paediatric patients. Its action inhibits cyclooxygenase in the central nervous system (CNS) but not in other tissues; it does not inhibit platelet aggregation and has no anti-inflammatory effect. In newborns and infants, there is a risk of toxicity due to the immature P-450 system in the liver, and the dose is limited by potential hepatotoxicity. Intravenous paracetamol enables efficient multimodal analgesia because it ensures a predictable plasma concentration.

Non-steroidal anti-inflammatory drugs (NSAIDs) have a triple action - analgesic, antipyretic and anti-inflammatory. Ibuprofen and diclofenac in the form of syrup, tablets and suppositories are primarily used in children, but irritation of the gastric mucosa and bronchospasm is possible in asthmatics. They act by peripherally inhibiting cyclooxygenase enzymes and inhibit the synthesis of prostaglandins, mediators of inflammation and pain. They can be used for pre-emptive analgesia as

part of premedication, as part of a multimodal regimen treatment and continuing after surgery.

Metamizole, propyphenazone and acetylsalicylic acid, often used for mild pain treatment, should be avoided in children due to serious side effects (aplastic anaemia, agranulocytosis, Reye's syndrome).

For medium-intensity pain, tramadol could be used, a centrally-acting analgesic with weak binding to μ-receptors and an inhibitor of noradrenaline and serotonin reuptake. It could be combined with paracetamol or NSAIDs for multimodal analgesia.

For severe pain, opioids should be used. Opioids achieve their analgesic effect by binding to opioid receptors in the brain, brainstem and spinal cord. They also have side effects, such as constipation, itchy skin, urinary retention, nausea and vomiting. Difficulty in breathing, hypotension and bradycardia are the most dangerous side effects. Respiratory failure is possible to reverse with opioid antagonists, naloxone and naltrexone.

Morphine should be titrated in acute pain paying attention to the circulating volume, while due to peripheral vasodilatation and histamine release, morphine can cause hypotension.

Fentanyl is a synthetic opioid, it works quickly, and the action lasts 30-40 minutes. It is less likely to cause hypotension but can cause respiratory arrest if administered rapidly, especially in combination with sedatives. A possible side effect of fentanyl administration is chest rigidity. For shorter painful procedures, it is safer to use alfentanil since it has a faster onset of action and shorter duration of action. Remifentanil is used for intense pain of a short duration due to its rapid onset and rapid recovery time. It could be used in children for short, day case procedures, while its pharmacokinetics allow a faster postoperative recovery. Remifentanil metabolism undergoes rapid hydrolysis by non-specific tissue and plasma esterases with an ultra-short and predictable duration that would not have accumulation issues.

Sufentanyl is approximately 5 to 10 times as potent as its parent drug, fentanyl and 500 times as potent as morphine. After a single bolus, sufentanil has kinetics similar to fentanyl with a short-duration of clinical effect of approximately 30 minutes.

Ketamine is a phencyclidine derivative that causes "dissociative anaesthesia" with amnesia, analgesia, and preserved brainstem reflexes. It is widely used in

emergencies because it maintains the patient's hemodynamic stability with spontaneous breathing. It is suitable for asthmatics because it is a bronchodilator. However, it increases secretion in the airways, which can be prevented with antisialagogues, e.g. atropine. Its primary mechanism of action is non-competitive antagonism at N-methyl D-aspartate (NMDA) receptors.

Ketamine could cause unpleasant phenomena when waking up, such as hallucinations, which the simultaneous use of midazolam can prevent. S(+) ketamine has twice the analgesic effect of the R(−) isomer, so it is administered in half the dose of racemic ketamine and causes fewer side effects.

Dexmedetomidine is a newer drug for use in the analgosedation of children, a central alpha-2-adrenergic agonist. It acts on receptors primarily located in the locus coeruleus, resulting in sedation and anxiolysis, and by acting on alpha-2 receptors in the posterior horns of the spinal cord, it causes analgesia. It acts as a sedative, analgesic and anxiolytic without respiratory depression, but bradycardia and hypotension are possible. Intranasal administration is perfect for emergency situations and short diagnostic or therapeutic procedures.

Local Anaesthetics and Regional Analgesia

Local anaesthetics are applied topically for infiltration, peripheral nerve, and central neuraxial blocks.

Local anaesthetics that act topically are applied on the skin and mucosa, such as EMLA cream and lidocaine gel, for procedures on the skin and mucous membranes to control procedural pain.

Bupivacaine, in 0.25% or 0.5% solution, is used when longer-term analgesia is needed because the effect lasts up to 6 hours. Levobupivacaine is the S-enantiomer of bupivacaine racemic form. Its action is similar to that of bupivacaine, but it is less toxic. Due to its long-lasting effect, it is most often used in paediatric anaesthesia because it provides long-term postoperative analgesia for up to 8 hours.

Ropivacaine is a newer local anaesthetic that takes effect in 8-10 minutes. It is less cardiotoxic than bupivacaine, so its use is increasingly important in children.

Overdose or inadvertent intravenous application of local anaesthetics can lead to cardiac arrhythmias and convulsions, so there must be resuscitation equipment in places where local anaesthesia is used.

The technique of blocking the conduction of peripheral nerves is increasingly used in paediatric emergency rooms. The advantage of the mentioned technique is that the child does not have to be fasting, so painful procedures or surgical interventions are not postponed. Restlessness, fear or the child's non-cooperation reduce the advantage of the regional technique, so drugs with a general effect should be used instead.

Peripheral continuous blocks via a catheter (femoral block, brachial plexus block, fascia iliaca nerve block, sciatic nerve block) are increasingly used in children for injuries, postoperative analgesia, early physical therapy and treatment of chronic pain.

New local anaesthetics such as ropivacaine and levobupivacaine promise less toxic effects on the heart and central nervous system and less motor blockade. The anatomy of the nerves in children (small diameter of the nerves, short distance between the nodes of Ranvier) allows the use of low concentrations of local anaesthetics.

Possible complications of regional anaesthesia are nerve injury, failure to establish a block, inadvertent intravascular drug administration, and local anaesthetic toxicity. Performing the block using ultrasound improves the safety of regional anaesthesia. Visualization of the space ensures greater success and quality of the block, the exact location of the nerve is shown regardless of anatomical variations, and the spread of the local anaesthetic is visible in real-time. Therefore, smaller amounts of local anaesthetic are needed for a faster start of the block and a more prolonged effect. With the help of ultrasound, a peripheral nerve block is performed faster, safer, and more efficiently, with less anaesthetic and fewer complications.

Analgesia in Special Conditions

In special conditions like craniocerebral trauma or pain in acute appendicitis, there is always a fear of analgesic administration that might interfere with an accurate diagnosis.

For decades, it was considered that analgesics should not be used for acute pain in the abdomen because they can mask the clinical picture and make it impossible to diagnose. Many studies have questioned this strategy. Today, other diagnostic methods are known and used, such as monitoring inflammatory parameters and radiological methods like ultrasound and computed tomography of the abdomen. Debunking that myth is a breakthrough in pain management in the emergency room.

In the case of a head injury, there is always a fear of using analgesics and sedatives, which can obscure the clinical assessment of the severity of the injury. An analgesic should be administered after the initial assessment of the child's condition using point systems (Glasgow coma score, Trauma score, Paediatric trauma score) because the physiological response to pain and the child's restlessness increase intracranial pressure. Adequate analgesia is critical for all major trauma patients, so analgesics should be used and titrated to the effect.

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Peripheral Nerve Blocks with USG In Children

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Considerable progress has been made in the field of regional anesthesia over the last decade. Data demonstrating improved outcomes and increased patient satisfaction with regional anesthesia have generated more interest in its utilization. Advancements in ultrasound technology have allowed regional anesthesia to use new techniques. This dynamic landscape also applies to pediatric regional anesthesia. Adaptability is a central tenet of the specialty, and as such, the development of new blocks requires not only proof of efficacy and safety, but also an ongoing evaluation of the advantages that novel blocks provide over more standard the postoperative analgesia therapies.

Paediatric regional anaesthesia (RA) has become an integral part of the current paediatric anaesthetic care. Although Dalens had established the first paediatric RA teaching programme in France by the early 1980s, its scope in the paediatric anaesthetic practice has significantly expanded as a result of the recent enhancement in the ultrasound (US) image quality.1

Despite the paucity of randomised controlled studies in paediatric compared with adults, evidence of the benefits of RA in children has started to emerge. In infants, RA improves haemodynamic stability, reduces the incidence of post- operative respiratory complications, decreases catecholamine production and the metabolic stress response to surgery and promotes a fast return of gut function and feeding. Studies in older children have also shown that RA reduces postoperative opioid consumption.

Updates from the latest North America Pediatric Regional Anesthesia Network (PRAN) registry of more than 100,000 nerve blocks showed that RA in children has an acceptable level of safety comparable with adult practice, with US technology progressively replacing nerve stimulator techniques and with the majority of nerve blocks being performed under general anaesthesia. Neuraxial blocks are gradually abandoned in favour of single-shot or continuous peripheral nerve blocks (PNBs).

Anatomical Differences

Central Nervous System

During normal development, the rate of growth of the vertebral column exceeds that of the spinal cord. This has clinically significant implications for the relationship between surface landmarks and anatomy when performing central neuraxial blocks in paediatric patients. The changes in the central nervous system with increasing age are outlined in Table 1.

Peripheral Nervous System

The differences between children and adults are outlined in Table 2

Local Anaesthetic Choice

Amide local anaesthetics (LAs) are frequently used in PRA. Ropivacaine and levobupivacaine are considered less cardiotoxic than bupivacaine. Ester LAs, such as chloroprocaine, are metabolized efficiently by plasma cholinesterases and are considered safer than amide LAs.6,7

Weight-based calculation of the maximum LA dose is essential in avoiding life-threatening local anaesthetic systemic toxicity (LAST). Recommended doses are outlined in Table 3.

Peripheral Nerve Catheters

Peripheral nerve catheters (PNCs) allow continuous analgesia and should be considered for any child who has (or is anticipated to have) significant acute pain, such as postoperative pain, ischemic pain or amputation pain. PNCs reduce opioid requirements and subsequently minimize the risk of opioid-related adverse effects, such as nausea, vomiting, constipation and respiratory depression.

Compared with a single injection regional block, continuous catheter techniques allow the following:

- Prolonged duration of analgesia
- Reduced opioid requirement and opioid-associated adverse effects
- Earlier ambulation, Shorter hospital stay

A PNC can be left in situ for up to 7 days; however, each additional day beyond the fourth day increases the risk of catheter- related infection. When deciding upon

the duration of catheter use, the analgesic benefits should be weighed against the risk of infection.

Complications specifically related to PNC include the following:

Catheter equipment failure, including dislodgement, migration, blockage, leakage, disconnection Skin reactions resulting from dressings Risks associated with single injection techniques (eg, nerve injury, failed block, LAST)

Controversies In Regional Anesthesia

Awake Versus General Anaesthesia

In adult patients, regional anaesthesia performed awake or under light sedation allows early detection of LAST and reduced risk of intraneural injection. However, in children, performing a regional block awake or with minimal sedation may result in child distress and movement during block placement. Furthermore, a frightened child is unlikely to report symptoms of LAST. The American and European Societies of Regional Anaesthesia Joint Committee Statement recommends that PRA perform under general anaesthesia or deep sedation has an acceptable safety profile and is considered to be the standard of care.

Compartment Syndrome

Compartment syndrome (CS) is caused by increased pressure inside a fascia compartment resulting in impaired blood flow and, if unrecognized, may result in muscle ischaemia and myonecrosis. One of the early symptoms of CS is pain, and there is concern that PRA could mask this pain. While there is no current evidence that the use of regional analgesia increases the risk of CS or delays its diagnosis, caution should be exercised, and we recommend the following for patients at risk of CS:

- Maintain a high index of suspicion and careful monitoring. If CS is suspected, compartment pressures should be urgently assessed.
- Use dilute LA solutions (eg, 0.1%ropivacaine) because they are less likely to mask ischaemic pain and less likely to produce a motor block.
- Avoid the use of additives because they will increase the density of the sensory and motor block.

Table 1: Differences with adults

Characteristics		Clinical implications
Anatomical	Nerves, vessels, and tendons are smaller; very superficial; with less adipose tissues; and lie close together	Potential risk of injury to nerve and structures around nerves; US imaging improves accuracy of needle placement
	The endoneurium has less connective tissue	Early onset of both sensory and motor blocks with a risk of prolonged motor block, even with lower concentrations of LA
	Nerves have shorter diameter with incomplete myelin sheath. Complete myelination may take several years	Caution must be taken whilst advancing needle during caudal anaesthesia to avoid dural puncture
	Neonates:	
	The dural sac ends at S3–S4 (S2 in adults)	Spinal anaesthesia should be performed below L4
	The intercristal line is at L5-S1 (L4–L5 in older children and adults)	
	Spinal cord terminates at L3 (L1 in adults)	
Physiological	Results of high cardiac output: (i) Increased systemic absorption of LA	Increased risk of cardiac toxicity
	(ii) Relatively high proportion of cardiac sodium gated channels are in an open state, with a high affinity to LA	
	Hepatic metabolism of LA is not fully functional until 9 months of age.	Risk of drug accumulation after repeated doses of LA or during continuous infusion
	There is reduced concentration of α_1-acid glycoprotein until 1 yr of age	
	Lumbar ortho-sympathetic component is poorly represented in children	Children are less prone to hypotension after neuraxial block

Table 2: Differences in Peripheral nerves at children

Structure	Neonate	Child	Adult	Clinical Implication in Children
Myelination	Very immature	Myelination completed by 12 y of age	Complete myelination	• LA rapidly penetrates the nerves, producing fast-onset block. • A low concentration of LA can achieve a high-quality dense block.*
Endoneurium	Loose endoneurium	Loose endoneurium	Relatively firm	• Greater spread of LA produces a fast onset and high-quality block. • LA is absorbed quickly away from the nerves, producing a shorter-duration block.*
Vasculature surrounding nerves	Rich vasculature	Rich vasculature	Less vascular	• LA is absorbed quickly away from the nerves, resulting in a shorter duration of block.*

Table 3: LA doses

		Maximum Hourly Infusion Rate, by Age, mg/kg/h		
	Maximum Bolus Dose, mg/kg	4 mo to 1 y	1 to 4 y	>4 y
Ropivacaine	3	0.25	0.35	0.4
Bupivacaine	2	0.25	0.35	0.4
Levobupivacaine	3	0.25	0.35	0.4
Lidocaine	5 (10 with adrenaline)	Not recommended		
2-Chloroprocaine	7 (10 with adrenaline)	10 (without adrenaline)		
Procaine	7 (10 with adrenaline)	Not recommended		

Paediatric regional anaesthesia helps to ensure optimal analgesia. It is opioid sparing and has beneficial effects on the autonomic, metabolic and immunological systems. Regional anaesthesia is a useful adjunct that can reduce the dose of general anaesthetic agents required, and in some cases may be used as a sole anaesthetic technique or with minimal sedation. An appreciation of the differences in the anatomy, physiology, pharmacology and controversies associated with regional anaesthesia in children compared with adults is required prior to performing peripheral nerve blocks to ensure it is performed safely and effectively.

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Peripheral Nerve Blocks With USG in Adults

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Ultrasound guidance has greatly influenced the practice of regional anaesthesia in the last 15 yr. Between 1884, the year when Carl Koller performed the first regional block for eye surgery in Vienna, and the late 1970s, the main developments were in new local anesthetic drugs and the introduction of mainly anatomical methods for nerve identification.

The introduction of ultrasound into clinical practice brought a solution to this problem closer. The first paper in this field was published in 1978, a Doppler ultrasound blood flow detector was used to facilitate supraclavicular brachial plexus block. At this time, detailed knowledge of the ultrasonographic appearance of neural structures was poor, and the ultrasound technology was not suitable for visualization of nerves. The first direct use of ultrasound for a regional block was in 1994, again for supraclavicular brachial plexus block.

In the ensuing 10 yrs., ultrasound technology advanced in parallel with the understanding of its use and the development of block techniques, which suited the use of ultra- sound. The increased interest and investment in ultrasound led manufacturers to design machines specifically for regional anesthesia, and software to facilitate peripheral nerve blocks. Better quality images should produce better quality blocks. Recent studies have demonstrated the cost- effectiveness of ultrasound-guided regional anesthesia in daily clinical practice.

We use USG in these main peripheral nerve blocks in clinical practice.

Interscalene Brachial Plexus Block:

Indications: Anesthesia and analgesia for shoulder, upper arm, and clavicle sugeries

Goal: Local anesthetic spread around superior and middle trunks of the brachial plexus, between the anterior and middle scalene muscles

Transducer: Linear, high frequency

Needle: 23-22 gauge, 5 cm short bevel

Local anesthetic volume: 7-15 mL

The Brachial Plexus is formed by the ventral rami of the roots C5 to T1. These roots join to form the superior (C5, C6), middle (C7), and inferior trunks (C8, T1) above the clavicle.

The trunks then branch into anterior and posterior divisions.

Supraclavicular Brachial Plexus Block:

Indications: Anesthesia and analgesia for humerus, elbow, forearm and hand

Transducer: Linear

Needle: 22-23G, 5 cm short bevel

Local anesthetic volume: 20-25 mL

- Place the transducer in a transverse orientation, just above the clavicle.
- Identify the first rib, pleura, subclavian artery, and a collection of hypoechoic oval structures (brachial plexus) located posterior and superficial to the artery.

Infraclavicular Brachial Plexus Block:

The cords assume a circumferential disposition around the axillary artery on their course deep to the pectoralis major and minor muscles

The three cords of the brachial plexus surround the axillary artery. Their names are derived from their relationship to it: lateral, posterior, and medial cord.

Axillar Brachial Plexus Block:

Indications: Anesthesia and analgesia for elbow, forearm and hand surgeries

Transducer: Linear

Needle: 22-23G, 5 cm short bevel

Local Anesthetic: 20 mL (8 mL above the artery, 8 mL below artery, 4 mL for the musculocutaneous nerve)

Femoral Nerve Block:

The femoral nerve is the largest branch of the lumbar plexus. It originates from the dorsal divisions of the ventral rami of the L2 to L4 lumbar nerves.

Indications: Anesthesia and analgesia for hip, femur, anterior thigh, knee and patella procedures; analgesia for hip fracture

Transducer: Linear

Needle: 22-23G, 5 cm short bevel

Local anesthetic volume: 10-15 mL

Saphenous Nerve Block at the Adductor Canal:

Analgesia for knee surgery, skin anesthesia of the medial aspect of the leg below the knee.

Indications: Analgesia for knee surgery, skin of the medial aspect of the leg below the knee (e.g., ankle or foot surgery). Can be combined with sciatic nerve block for surgery below the knee (e.g., foot amputation, ankle fracture).

Transducer: Linear or curved (larger patients)

Needle: 22 G, 5-8 cm.

Local anesthetic volume: 10 mL

In the proximal thigh, the saphenous nerve travels together with the femoral vessels in the femoral triangle and into the adductor canal under the sartorius muscle.

Obturator Nerve Block:

Indications: Supplemental analgesia for hip and knee surgeries (considered as rescue block for knee surgery), prevention of thigh adduction response during transurethral bladder surgery, relief of painful or permanent hip adductor spasticity

Goal: Local anesthetic spread in the fascial planes containing the branches of the obturator nerve

Transducer: Linear or curved (larger patients)

Needle: 21-22 gauge, 5 or 10 cm short bevel

Local anesthetic volume: 5-10 mL in each interfascial plane or around each branch of the obturator nerve; 10-15 mL for the proximal approach

Sciatic Nerve Block:

Indications: Anesthesia and analgesia for foot and ankle surgery, procedures on and below the knee involving the posterior aspect of the knee, and above-knee amputation

Goal: Local anesthetic spread within the sheath containing the sciatic nerve

Transducer: Low-frequency curvilinear transducer (or high-frequency linear transducer for subgluteal approach)

Needle: 22 gauge, 8-10 cm insulated stimulating needle

Local anesthetic volume: 10-20 mL

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ABSTRACTS

Diagnostic And Prognostic Significance of Angiopoietin-2 Biomarker in Adult Acute Respiratory Distress Syndrome

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The Best Oral Presentation – I Prize

Abstract

Introduction:

Acute respiratory distress syndrome (ARDS) is defined as the sudden onset of respiratory problems with the development of progressive hypoxia with bilateral changes in the lungs, which are verified by chest X-ray or computed tomography. ARDS is the most common clinical syndrome of acute lung inflammation. The basis of the pathophysiological events of ARDS is damage to the alveolar-capillary membrane of the lungs, with the consequent accumulation of protein-rich fluid in the alveoli. Destruction of the alveolar epithelium and endothelium occurs with infiltration of inflammatory cells. Angiopoietin-2 (Ang-2) is one of four members of the growth angiopoietin family. It exerts its effect by binding to the Tie-2 tyrosine kinase receptor, which is present in lung endothelial cells. The binding of Ang-2 to this receptor activates several processes: damage to the endothelial barrier, increasing vacular permeability, adhesion and migration of inflammatory cells. The main goal of the research is to determine the diagnostic significance of serum concentrations of Angiopoietin-2 in the adult form of ARDS. Also, is there a statistically significant difference in the serum concentration of angiopoietin-2 in patients with ARDS with a favorable and unfavorable outcome of the disease.

Methods:

The research included critically ill patients (n=96). Two thirds of the subjects had a diagnosis of ARDS (n=69), while the rest (n=27) constituted the control group. Within the first 24 hours after the diagnosis of ARDS, serum Ang-2 concentration was determined. The outcome of the treatment was monitored for 28 days. Ang-2 concentrations were measured using a commercial ELISA-USCN Life Science, USA,

R&D Systems, Inc. In the applied tests, the limit values of the probability of risk are at the significance level of 95% ($p<0.05$) (difference in statistical parameters significant) and 99% ($p<0.01$) (difference in statistical parameters highly significant).

Results:

Examining the difference in Ang-2 concentration between ARDS and the control group, showed a high statistically significant difference ($p=0.000$) ($p<0.01$). The mean values of Ang-2 in the ARDS group and the control group were 3180 pg/ml and 19.5 pg/ml, respectively. The total mortality of ARDS patients was 52.5%. Deceased patients have statistically significantly higher Ang2 biomarker values. Mean values of Ang-2 in surviving and deceased ARDS patients were 3673.22 pg/ml and 6019.22 pg/ml, respectively.

Conclusion:

The role of biomarkers in the diagnosis and prognosis of ARDS is multiple. Timely establishment of an accurate diagnosis is paramount. The identification of biomarkers would contribute to a better understanding of the pathophysiology of the disease due to the heterogeneous and complex nature of ARDS. By analyzing biomarkers, we would try to differentiate ARDS of different etiology, as well as which biomarkers are important in establishing a diagnosis and which in predicting ARDS.

Keywords: *ARDS, biomarkers, Ang-2;*

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Effect Of Preoperative Administered Magnesium Sulfate on Postoperative Pain Intensity in Patients After Laparoscopic Cholecystectomy

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The Best Oral Presentation – II Prize

Introduction:

Postoperative pain is one of the biggest problems in surgical practice and it negatively affects patients' treatment. Magnesium-sulfate is analgesics adjuvant agent that is used in multimodal analgesia. Its blockade of N-methyl-D-aspartate (NMDA) receptor and calcium channel has an important meaning to anesthesia. Laparoscopic cholecystectomy is surgery in which gall bladder is removed, and it is one of the most common laparoscopic interventions.

Aim:

Aim of this study was to analyze the effect of preoperative given magnesium-sulfate on postoperative pain intensity as well as usage of analgesics in perioperative period that can reduce cost of treatment.

Method:

This is a randomized, prospective, cohort study which included 60 patients. Protocol of premedication, anesthesia and perioperative monitoring was standardized for all the patients. All the patients were given ketoprofen and metamizol-Na intravenously (i.v.) in standard doses 10 minutes before the end of the surgery and then metamizole-Na on every 8 hours in postoperative period. Patients were divided in two groups: first in which patients were given only ketoprofen and metamizol-Na as mentioned, and second group in which patients were treated before the operation with 2g of magnesium-sulfate in i.v. infusion of 100ml NaCl solution. Pain intensity was measured using numerical rating scale (NRS) after the surgery and then on every six hours during the first 72 postoperative hours. Every patient was given Tramadol if the pain score was 5 or higher. Also, we measured usage of Fentanyl during the operation.

Results:

60% of our patients were women. The average age was 58. The Magnesium-treated patients had significantly lower pain intensity in first and second measurement ($p<0.05$), also patients in this group had a lower demand for Tramadol. The average dose of Fentanyl in the Non-magnesium group was higher, and it was 6.3 ml ($p<0.05$)

Conclusion:

Our and results of other studies on this topic suggest that magnesium-sulfate is associated with lower early postoperative pain intensity, usage of perioperative analgesics and intraoperative fentanyl consumption. Understanding of postoperative pain and its treatment significantly contributes to improved patient care, the prevention of postoperative complications and a faster recovery.

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Management of Difficult Airway in Advanced Bechterew's Disease - CASE REPORT

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The Best Oral Presentation – III Prize

Abstract:

Introduction: Ankylosing spondylitis (Bechterew's disease) is a chronic, seronegative, progressive inflammatory disease of the locomotor system. It most often starts in the sacro-femoral joint, and then spreads to other joints, ligaments and other connective formations of the spinal column. In the later stages, the disease also affects peripheral joints, and manifestations also occur on the eyes and structures of the cardiovascular, respiratory and gastrointestinal systems.After a few years, the disease ends with ossification of all connective structures and ankylosis of the joints, so that the spinal column becomes a single ossified block (a condition known as "bamboo stick").

The disease is 5 to 7 times more common in men than in women. It most often occurs between the ages of 15 and 30. The general incidence of ankylosing spondylitis is about 0.25%.

Advanced Bechterew's disease presents with increasing ossification of spinal column, from lower lumbar segments upwards, first causing impossibility to place spinal block in lumbar region, and later, due to stiffness of cervical spine, difficult intubation because of inability to extend and/or flex the neck during direct laryngoscopy and intubation. Mask ventilation, on the other hand, usually is possible.

Case report:

Here we present a 59-year-old patient who was scheduled for elective gallbladder and ventral hernia surgery in the same act, and whose ankylosing spondylitis was very advanced. After a thorough anesthesiological evaluation of the airway and determination of the degree of limitation of the extension of the cervical spine, intubation was first attempted on spontaneous breathing, with deep sedation of the patient. After several unsuccessful attempts by experienced anesthesiologists,

intubation was attempted with a fiberoptic bronchoscope, with the assistance of a thoracic surgeon. Finally, the airway was secured with a surgical tracheostomy by the ENT medical team.

The following day, an elective surgical procedure was performed, which was planned.

Conclusion: During the evaluation of this case, it is determined that, first of all, it is necessary to make the best possible assessment and prepare an adequate plan in the form of an algorithm for the care of the respiratory tract, for the safety and security of these patients during the surgical intervention under general endotracheal anesthesia.

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Spontaneous Uterine Rupture in Pregnancy as Cause of Hemorrhagic Shock: Resuscitation and Bleeding Management – CASE REPORT

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Introduction:

Hemorrhagic shock is a form of hypovolemic shock in which severe blood loss leads to inadequate oxygen delivery at the cellular level (1). If the bleeding continues unrecognized, death quickly follows. Rupture of the uterus, as a rare complication in the second trimester of pregnancy, can lead to hemorrhagic shock. According to data from the World Health Organization, the average incidence of uterine rupture (UR) is 5.3/l0 000. Maternal mortality ranges between 1 and 13%, and neonatal mortality between 74 and 92% as a result of UR (2). Multiparity and previous cesarean sections are known risk factors for uterine rupture during pregnancy (3,4). With early recognition of bleeding, along with surgical hemostasis, goal directed fluid therapy and blood derivative replacement and aggressive resuscitation, an irreversible phase of shock and death can be prevented.

Case report:

A 32-year-old female patient, in the 20th week of pregnancy, was brought to the Emergency Center of the Clinical Center of Montenegro due to sudden abdominal pain and exhaustion. Previously she had 3 pregnancies and all three were ended by caesarean section. On admission, she was anemic, hypotensive with normal heart rate, no visible vaginal bleeding, distended abdomen, diffusely painful during palpation. An ultrasound examination with a vaginal probe indicated the existence of one fetus in the uterus, who biometrically corresponds to 20 weeks of gestation, a normal amniotic fluid and a properly inserted placenta. Ultrasound of the abdomen and small pelvis diagnosed an abundant amount of free fluid in the abdominal cavity. She was taken urgently to the operating room, where, under general anesthesia, an exploratory laparotomy revealed a uterine rupture and a hysterectomy with left adnexectomy was performed. During the operation, massive bleeding occured, where the measured

blood loss was 4000ml, and the estimated blood loss was around 5000ml. Accordingly, an extensive replacement of blood derivatives with antifibrinolytics was administered intraoperatively and a resuscitation procedure was carried out with crystalloids and continuous infusion of noradrenaline, all with the aim of achieving adequate perfusion pressure and maintaining diuresis of more than 0.5 ml/kg/h. Postoperative replacement of fluids and blood derivatives is prescribed in relation to point-of-care (POC) tests and mesured values of central venous pressure (CVP). Aggressive measures applied to stop the bleeding and replace the lost intravascular volume as soon as possible led to the rapid recovery of this patient and her discharge from the intensive care unit on the second postoperative day.

Conclusion:

Rupture of the uterus is a well-known emergency in obstetrics and must be recognized in time in order to implement adequate measures to control and manage bleeding, to prevent the onset of hemorrhagic shock or at least its irreversible phase. Early recognition and early resuscitation in the event of hemorrhagic shock are the basis for reducing mortality and morbidity in patients with uterine rupture.

Keywords: *hemorrhagic shock, uterine rupture, pregnancy, bleeding management, resuscitation*

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Awake caudal anesthesia for inguinal hernia repair in premature infants - CASE REPORT

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Introduction:

Inguinal hernia reparation is one of the most common operations in the neonatal period. It is more common in male children, especially in babies with a birth weight less than 1500 grams. In these patients in the postoperative period, after general anesthesia, there is an increased risk for the development of respiratory complications. The caudal block represents a type of epidural anesthesia that is achieved by applying a solution of local anesthetic through the sacral opening. It is especially suitable for premature infants of low birth weight that are at higher risk for developing respiratory complications in the postoperative period. Studies have shown that patients were without major complications during and after anesthesia. This type of anesthesia is used in the world for a long period of time. In our hospital, awake caudal anesthesia for surgical reparation of inguinal hernias in premature infants and neonates was started with this patient.

Case report:

Our patient was premature male infant at 29th week of gestation (body weight at birth 1170 grams) with severe form of respiratory distress syndrome at birth and complications accompanied by extreme immaturity of the lungs and other organs. After birth, 40 days was intubated and on mechanical ventilation. After completing the treatment, which lasted 18 weeks in the neonatology center, the child is planned for surgical reparation of inguinoscrotal hernia. The body weight of the child was 3560 grams in the moment of operation and anesthesia. Preoperative laboratory analysis was well-maintained. After conducting preoperative milling in accordance with age to the operating room was brought with already provided venous route. Standard monitoring included ECG, non-invasive arterial pressure, peripheral oxygen saturation (SpO2). For sedation was given ketamine 1mg/kg iv, propofol 1mg iv in a bolus dose, then propofol continuously 5 mg/kg/h iv which gradually decreased until the end of the operation. Through the nasal catheter, he breathed in oxygen 2L/min. After positioning the patient in the left side the caudal space is punctured between the

sacral horns which build the sacral hiatus, where the sacro-coccygeal membrane is palpated. Aspiration to exclude the presence of cerebrospinal fluid or blood, and by getting negative pressure on the clip, confirms that we are in the epidural space. A caudal block was performed and 1 ml/kg/BW bupivacaine 0.25% was injected using a 22 GA - needle. Vital parameters after drugs administration where in the reference range (HR 127/min, SpO2 97-100%, TA 70:41 mmHg). Ten minutes after the single dose of local anesthetic is accessed to prepare the operating area. During the intervention child breathed spontaneously, hemodynamic was stable, normoglycemic, vital parameters were within reference limits. Operation ended without impaired spontaneous breathing and no postoperative apnea or respiratory complications were encountered.

Conclusion:

Caudal block in sedation is a simple method that should be considered more as a form of anesthesia in the neonates and premature infants in which there is an increased risk of developing respiratory complications in the postoperative period.

Keywords: *anesthesia, caudal block, neonates, premature infants.*

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Ganglioneurinoma of the Mediastinum of a Six-Year-Old Child - CASE REPORT

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Ganglioneuroma is a rare and benign tumor of autonomic nerve fibers arising from the sympathogonia of the neural crest, which are completely undifferentiated cells of the system. However, ganglioneuromas themselves are fully differentiated neuronal tumors that do not contain immature elements. Ganglioneuromas most often occur in the abdomen, but these tumors can grow anywhere where there is sympathetic nervous tissue. Other common sites include the adrenal gland, paraspinal retroperitoneum, posterior mediastinum, head, and neck. A ganglioneuroma is usually asymptomatic and is usually discovered only when being examined or treated for another condition. For example, a tumor in the chest area can cause breathing difficulties, chest pain, and compression of the trachea. They can be diagnosed visually with a CT scan, MRI scan, or ultrasound of the head, abdomen, or pelvis. Blood and urine tests may be done to determine if the tumor is secreting hormones or other chemicals. A biopsy of the tumor may be required to confirm the diagnosis. If there are symptoms or major physical deformities, treatment usually consists of surgery to remove the tumor. Most ganglioneuromas are noncancerous, so the expected outcome is usually good. However, a ganglioneuroma can become cancerous and spread to other areas or it can grow back after removal. This case report is about a six-year-old boy, who had complaints about twenty days before hospitalization in the form of coughing. Based on the clinical picture, physical findings, X-ray, CT, MRI of the chest, and pathohistological findings of the puncture biopsy, diagnosis ganglioneurinoma mediastinal lateris dex. There, the mass of the right hemithorax, which almost fills the trachea, causes compression of the trachea in the segment immediately before the bifurcation and the heart moves to the left and forward, compressing the descending thoracic aorta. After complete preoperative preparation, the child is scheduled for surgery. Preoperative preparations were made

in terms of complete blood count, minerals, ABS, heart ultrasound, and a multidisciplinary approach to surgery. The introduction and course of anesthesia went smoothly. The child was hemodynamically stable the whole time. Fluids, antibiotics, and blood products of the appropriate blood group were prescribed. It is placed by C.V.K. v.jug.lat.dex. and thoracic drain. The operation lasted four hours. After extubation, the child was transferred to the Intensive Care Unit of the Pediatric Clinic, accompanied by an anesthesiologist. He stayed in intensive care for two days, and in good general condition was transferred to the Children's Surgery Clinic. On the fifth postoperative day, the thoracic drain was removed and on the eighth day of hospitalization, he was discharged home in good general condition with a recommendation to continue therapy and regular checks are sent home. The control X-ray of the lungs is normal.

Keywords: *ganglioneuroma of the mediastinum, anesthesia, team.*

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The axillary block in treatment of radial and brachial artery spasm during percutaneous coronary intervention: A case report

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Abstract

Introduction:

Transradial approach for percutaneous coronary intervention (PCI) is increasingly being performed worldwide as a first choice for arterial access. One of the most common complication encountered during transradial procedure is radial artery spasm (RAS). RAS has been defined as one of the major disadvantages of transradial approach. We described a case of severe arterial spasm during the procedure PCI, refractory to conventional methods, and spasm resolution using a regional axillary nerve block.

Case presentation:

A 43-year-old man presented for coronary angiography with diagnosed myocardial infarction the day before. The cardiologist introduced a 6 F sheath into right radial artery. At the start of procedure severe radial and brachial artery spasm has occurred and the sheath was entrapped. The patient was treated with different treatment modalities (vasoactive medications, sedation, forearm heating, induction of local acidosis) but arterial spasm sustained for more than one hour. Finally, the anesthesiologist was involved and after deep sedation with Propofol, Fentanyl and Midazolam, which also was been ineffective, he performed the axillary block of plexus brachialis, to block sympathetic vascular tone. A nerve stimulation guided block was performed. The nerve stimulator is set to deliver 0.5-1.0mA (2 Hz, 0.1 msec), electrical connections with the 22G, 50 mm insulated needle and neutral electrode were checked and the multiple-injection (stimulation) technique was used. The local anesthetic of choice was 1.2 % Lidocaine and a total volume of 40 ml was given. The artery spasm was relived after 10 min and the motor block lasted almost two hours. The cardiologist decided to complete the PCI with a transfemoral approach.

Conclusion:

When sedation and vasoactive therapy failed, we recommended using axillary block for radial artery sheath removal. The axillary brachial plexus block is the most widely performed upper limb block. It is relatively simple to perform and one of the safest approaches to brachial plexus block.

Keywords: *radial artery spasm, axillary block*

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Total Anesthesia for Surgical Treatement of Neck Phlegmona in Thyreotoxic Patient

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A 37-year old female presented with swelling and redness of the anterior side of the neck, painful swallowing and elevated body temperature (38.5^0C).

After diagnostic workup: ENT examination (lateral and posterior pharyngeal wall swelling); lab. findings (WBC 25.7 (neu 88.3%, mono 7.53%), CRP 149.1 (0-8.2 mg/L), fibrinogen 9.0 (1.8-4.0 g/L), Eritrocyte sedimentation rate 60/hour); Chest x-ray and lung auscultation – normal; neck ultrasound and CT: signs of inflammation and infection with free gas collections; neck phlegmona was suspected and urgent surgery was indicated.

Preanesthetic visit: Based on clinical findings and vital parameters (tremor of upper extremities, BP 180/90, ECG - sinus tachycardia 120 bpm); acute thyreoiditis was suspected. Previous history revealed afterwards hyperthyreosis treated with Propylthiouracil (PTU), no regular checkups or drugs used for 2.5 years.

Due to the increased risk of thyreoid storm, surgery was postponed and thyreoid hormons checked. An endocrinologist was consulted, therapy (PTU, propranolol, and KI) prescribed.

Clinical signs of phlegmona deteriorated (neck swelling and redness); control neck CT-scan showed progression of neck phlegmona. Further delay of surgery was assessed as lifethreatening, and the patient informed and consented.

Anesthetic management –monitoring (EKG, invasive BP, body temperature, $EtCO_2$, SpO_2, TOF), induction (oxygen/air, remifentanyl (1 mcg/kg -1min), tiopenton sodium (6mg/kg), rocuronium (0.6mg/kg)), pulse and blood pressure regulation (esmolol and metoprolol, NTGL), anesthesia maintenance (sevoflurane (2-4 Vol%), remifentanyl 2 mcg/kg/min), postoperative analgesia (ketorolac and tramadol), and care adjusted according to the current equipment and supplies of the Anesthesia Clinic.

Neuromuscular block was not pharmacologically reversed. When spontaneous ventilation established sevoflurane was turned of, patient extubated while still asleep to minimise rise in BP and hearth rate. When regained consciousness transferred to ICU where BP and hearth rate were controlled (propranolol). Continued thyreostatic and triple antibiotic therapy (ceftriaxone, metronidazole, amikacin). Fluid balance and continuous analgesia with tramadol were maintained.

Discharged from the ICU 5th postop day, 15th postoperative day secondary sutures done, 21st day discharged home.

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Percutaneous Dilatational Tracheostomy at A Patient with A Neck Trauma – CASE REPORT

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Introduction:

Percutaneous dilatational tracheostomy (PDT) has become one of the indispensable surgical procedures in the Intensive care unit (ICU). Tracheostomy is a common surgical technique in seriously-ill patients, especially percutaneous dilatational tracheostomy, because of its multiple advantages over surgical. tracheostomy.

Case description:

A 63-year-old man patient was admitted to the ICU, after primary diagnostical observation at the Emergency room. Initially, he came to the Emergency room with a history of alleged assault on the neck from a high of 5m, immediately before his arrival. All data were obtained heteroanamnestically, because the patient was unconscious. After primary diagnostical observation, including computer tomography (CT) for polytrauma protocol, he was diagnosed with "Laesio traumatica region corporis multiplicum alia, specificata". CT showed emphysema in soft tissues at the neck; the right thyroid cartilage bent posteriorly and dislocated along its entire length to the back and left; suspected fracture of right thyroid cartilage; consequently left thyroid cartilage was dislocated forward and anteriorly; the remaining part of the larynx was normal. At ICU, he has been intubated for 6 days and on mechanical ventilation, without any possibilities for extubations. So, on the 7th day of stay in ICU, the bronchoscopy-guided PDT was performed, in order to enable spontaneous breathing as soon as possible. The procedure, that was performed is Grigg's technique. Anti-coagulative medications were discontinued 12 hours before the procedure. The complication in our case was that hyperextension of neck was impossible to be made. Also, the thyroid cartilage was dislocated, and anesthesiologist had to make insertion between second and third cricoid rings. The patient was positioned in a not standard hyperextended position for tracheostomy. Using the single dilatator, the procedure is performed using a standard preparation and drape. The patient was ventilated on

100% oxygen and vital signs are continuously monitored. Local anesthesia augmented by intravenous sedation is required. A 1.5 cm incision is placed one to two fingerbreadths above the cricoid cartilage, and the subcutaneous fat is separated using a curved hemostat. At this point, a flexible bronchoscope is inserted and aligned with the tip of the endotracheal tube (ETT). The bronchoscope and ETT are slowly withdrawn until the incision is maximally trans-illuminated, allowing continuous visualization of the entire procedure. In this case, 14-gauge catheter introducer needle is inserted between second and third tracheal rings, even it is more common to make insertion between first and second tracheal rings. A J-wire threaded through the intricate allows the placement of an introducer dilator. The final step involves inserting a preloaded tracheostomy tube over the J-wire/guiding catheter unit. The procedure passed without complications, such as bleeding, one of the most frequent complications. In a cross-sectional study, Karimpour et al. investigated the complications of PDT in 184 patients using the Griggs method. The overall frequency of complications was 16.7%, the frequency of bleeding was 9.3%, puncture of the tracheal tube cuff1.6%, subcutaneous emphysema 1.1%, and loss of airways 1.7%. After 20 days in ICU, the patient was breathing spontaneously through the tracheostomy cannula. At ICU, decanilman wasn't made, because there was an edema of the vocal cord. On the 23rd day of stay, the patient, who was awake and conscious, hemodynamically and respiratory stable, was transferred to the Clinic for Otorhinolaryngology.

Discussion:

Our anesthesiologist decided to do a PDT on the 7th day of stay in the ICU, to prevent further complications. This procedure was done successfully despite complicating factors of the patients, such as the tracheolaringeal injury and short neck. A chest X-ray was taken to assess possible complications of the PDT procedure and correct placement of the tracheostomy tube. It showed that the tracheostomy tube was in the correct position, and the procedure was performed without complications. Even though we did the early tracheostomy,and didn't follow established recommendation, which is 2 to 3 weeks after endotracheal intubation

Conclusion:

Our experience confirms the use of PDT in the ICU as a useful method in providing conditions for prolonged ventilation in patients after neck trauma. In our case, PDT is more recommended because it causes less infection with smaller

incisions, resulting in faster spontaneous closure of the stoma after removing the tube. Also, this was a faster procedure with less post-operative complications than the open surgical method.

Keywords: *percutaneous dilatational tracheostomy, neck trauma, laryngotracheal injury, mechanical ventilation, intensive care unit.*

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Treatment Of a Patient with Leptospirosis in Central Intensive Care Unit: CASE REPORT

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Abstract

Introduction:

Leptospirosis is a zoonosis, transmitted mostly by rodents. It occurs mainly in developing countries, in tropical regions, but it is also present in other countries. It is seasonal in nature, and humans are usually infected indirectly, through water contaminated with animal excrement. The entry point of the infection is most often a cut on the skin, and lacerations of the mucous membranes. The clinical picture can be diverse, and thus the differential diagnosis is difficult, because leptospirosis can imitate autoimmune diseases as well as other infectious diseases. The clinical picture varies from mild forms with fever, headache and myalgia, to severe clinical conditions, such as Weil's disease with the development of jaundice, renal insufficiency and bleeding. The severe form of this disease is diffuse alveolar hemorrhage (DAH), which occurs in 3.7% of cases and is the main cause of mortality (70%).

Case presentation:

A 56-year-old man, without previous comorbidities, was admitted to the central intensive care unit as an emergency. On admission he is disoriented, tachycardic, anuric, and markedly icteric. From the anamnestic data, we find out that for the previous 10 days he was febrile, with pronounced malaise, myalgia and nausea, vomiting and loose stools. In the laboratory data, we find high parameters of inflammation, anemia, thrombocytopenia and marked azotemia (creatinine 1155) and hyperbilirubinemia. After diagnostic procedures and complete invasive monitoring, we decide on early hemodialysis, on the first day of admission. The empiric antibiotic therapy (Meronem and Dovicin) and other supportive therapy were included. In the first 10 days of hospitalization, he was hemodialyzed 3 times, after which the renal

function recovered. On the sixth day after admission, serological tests showed that it was Leptospirosis. On the ninth day after admission, he became hemodynamically unstable, his blood count dropped and he was taken to the operating room, where peritoneal bleeding and a retroperitoneal hematoma were found. The source of bleeding is not identified, and the retroperitoneal space is tamponed. After two days, due to severe hemorrhagic shock, he was again taken to the operating room, where the branches of the right hypogastric artery were ligated and retamponade was performed. For the third time, the patient was taken to the operating room for detamponade and hemostasis revision. Later on, the patient's hemodynamic condition stabilized, the laboratory findings were corrected, and on the 17th day after admission, he was transferred to the vascular surgery department.

Conclusion:

Leptospirosis, although not a common disease in our region, can lead to very serious life-threatening conditions, which require a multidisciplinary approach and treatment in an intensive care unit. Although our patient had a severe form of leptospirosis, which was complicated by hemorrhage, owing to the quick diagnosis and early multidisciplinary treatment, the outcome of the disease was favorable.

Keywords: *leptospirosis, multiorgan failure, renal failure*

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Subarachnoid Hemorrhage During Pregnancy- CASE REPORT

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Abstract:

Pregnancy-related subarachnoid hemorrhage is rare, but it causes maternal and neonate high mortality and morbidity.

The most common cause of subarachnoid hemorrhage during the period of pregnancy and during puerperium is rupture of an intracranial aneurysm. During pregnancy rupture of an intracranial aneurysm still remains the commonest cause of SAH. The reported prevalence of subarachnoid hemorrhage during pregnancy is 10/100.000 patients.

Based on literature reports 90% of SAH occurs during pregnancy, 2% during labour and 8% during postpartum period.

We present a case of a woman in the third trimester of pregnancy admitted to our Clinic for Gynecology and Obstetrics with neurological signs and symptoms - sudden-onset headache, vomit with nausea. CT scan showed saccular aneurysm of the anterior communicating artery (ACA) and subarachnoid hemorrhage (SAH). SAH due to aneurysmal ruputure was menaged by multidisciplinary team. After caesarean section, the woman underwent craniotomy clipping surgery. The patient delivered healthy, male infant. A favorable postoperative course and a recovery of neurological and general conditions followed.

Keywords: *pregnancy, aneurismal subarachnoid hemorrhage.*

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How effective is noninvasive ventilation in Covid-19 patient hospitalized in ICU, lying in prone position? A review of the literature

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Introduction:

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019**.** Approximately 5% of the patients who contract COVID-19 require admission to ICUs. Non-invasive ventilation (NIV) has been used to manage early acute hypoxemic respiratory failure (AHRF) caused by COVID-19. Prone positioning is a conventional method to enhance oxygenation in Acute Respiratory Distress Syndrome (ARDS) patients who need mechanical ventilator. It is proven that oxygenation is significantly more beneficial in prone position compared to the supine position.

Methods and results:

During our experience in our hospital, we have encountered many severe cases hospitalized with acute worsening of respiratory status with acute respiratory failure, in ICU who have been lying in prone position. Some hospitals strongly discourage the use of noninvasive approaches, favoring early intubation, and others use noninvasive approaches quite commonly. The contention is that failure rates of noninvasive approaches in patients with COVID are high, and these are aerosol-generating procedures (AGPs) that place caregivers at increased risk of contracting COVID-19.In this paper we discuss the pros and cons of using NIV in patients in the prone position, taking into consideration our experience too.

Conclusion:

Noninvasive respiratory therapies may be of particular benefit in reducing the risks to healthcare workers by obviating the need for intubation, a potentially highly infectious procedure. It is expected to improve oxygenation and decrease the work of breathing. It can reduce the need for mechanical ventilation and complications

associated with it. Close monitoring and early identification of NIV failure are key to avoid delayed intubation-associated mortality.

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First Hybrid Repair Technique of Thoracic Aortic Aneurysm in Montenegro

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Thoracic aortic aneurysm (TAA) is an enlargement of the thoracic part of the aorta. This condition is occurring in approximately 6-10 per every 100,000 people and its occurrence is predisposed by various comorbidities (hypertension, Marfan's syndrome, atherosclerosis, older age, etc.)[1]. For the first time in Montenegro in March 2022, a hybrid technique of thoracic aortic aneurysm repair was performed. Here we will present the anesthesiological approach and technique used on this patient, as well as the postoperative treatment. A 63-old-man presented with pain in his left arm and left half of the chest and immediately below the origin of the left subclavian artery, a saccular pseudoaneurysm of the thoracic aorta measuring 8 cm with thrombotic masses on the anterior lateral wall. He was treated with Hybrid repair method for TAA. The patient remained in good condition after the procedure. Even though most cases of TAA are asymptomatic, when present with symptoms, they vary in intensity. In this case, TAA presented with chest pain (one of the most common symptoms)[2]. This case was managed using the hybrid method which resulted in the resolution of symptoms without any complications.

Keywords: *thoracic aortic aneurysm, hybrid technique, anesthesia*

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Commercial Flights and Medical Emergencies – Is There a Doctor On Board?

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In 2022, 9.3 million commercial flights were recorded in Europe alone. It is believed that 70% of commercial flights are attended by someone from of medical personnel and that the need to provide professional medical assistance was requested on one of 600 flights1. The aim of this literate overview is about medical emergencies that can occur on commercial flights and how to react in given situations. We conducted a research through PubMed databases in January 2023 for studies that have accessed in-flight emergencies and topic summaries published between 2000 and 20221-10. We were using search terms relevant to medical emergencies that occur on flights. The most common health emergencies that occur among both the adult and pediatric population on commercial flights are syncope, gastrointestinal, respiratory and cardiovascular problems. Cardiovascular and neurological problems are the most common reason associated with the change of flight direction and or forced landing11. The presence of doctors on commercial flights, as well as other medical personnel with the assistance of cabin crew and adequate use of equipment and medicines from medical aid kits, enables adequate care of passengers until landing at the nearest airport for transport to the place of further treatment if it is necessary. Despite numerous works and research, unfortunately, there is still no official protocol for dealing with medical emergencies on commercial flights.

Keywords: *CPR, emergencies, commercial flights*

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Epidural Anesthesia for Caesarean Section in A Patient With Basilar Artery Aneurysm – CASE REPORT

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Introduction

The incidence of unruptured intracranial aneurysm is 2% of the general population with a significant prevalence in the generative period, when the risk of rupture is more pronounced. The main feature is accidental detection due to non – specific resistant headaches. In this case report we discuss the anesthetic management for cesarean delivery of a parturient with an unruptured aneurysm

Case Report

36-year-old pregnant woman was prepared for a caesarean section under neuraxial anesthesia based on neurosurgical recommendations according to an accidentally discovered unruptured aneurysm of the basilar artery. One year ago, she was regularly monitored neurologically and radiologically, perioperatively without neurological symptoms. She denied allergies, and stated regular antiarrhythmic therapy (Verapamil 40mg). Pre-anesthetic examination revealed unremarkable vital signs. The anesthetic technique of choice was epidural anesthesia, L3-L4 level and administration of local anesthetic - levobupivacaine 0.5% with opioid adjuvant - fentanyl . Concomitantly, a ephedrine infusion was started (25mg/500ml sol.Ringer) and continuously titrated to maintain systolic and mean arterial pressure. Intraoperative and postoperative anesthesia evaluation was unremarkable at 1 hour and 24 hours postpartum. The patient did not exhibit any neurological deficits during the peripartum period. Pain control was provided regularly for 6 hours with Levobupivacain 0.25% with opioid adjuvant.

Discussion

The relationship between the mode of delivery and risk for aneurysm rupture is not well defined. Hemodynamic stability is crucial for safe and secure anesthesia and controlling the risk of aneurysm rupture. The decision on anesthetic management is significantly influenced by the physiological changes of pregnancy because they

increase the risk of aneurysm rupture as a result of sudden changes in intracranial pressure.

Keywords: *Unruptured basilar artery aneurysm, parturient, epidural anesthesia, caesarean section*

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Foreign Body in Airway – 15 Years of Experience

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Introduction:

Accidental inhalation of foreign body (FB) is cause of morbidity and mortality in childhood.

Aim and method:

In this research, our aim was to present 15 years of experience related to aspiration of FB in the airway and rigid bronchoscopy (RB). And to evaluate factors that can help us in adequate diagnosis of presence of FB. From January 2008 til February 2023, 67 patients, with suspected FB aspiration, were admitted into our tertiary level institution. 62 of them were included in this study. We analized age, gender, comorbidities, clinical status, physical exam, lung X-ray, acide-base status, type of FB, complications, duration of intervention, time past of possible aspiration and ASA score. Medical records were analized retrospectively. Statistical analysis we used was SPSS 22.

Results:

Children with suspicion on presence of FB were often mail then female (54.8% vs 45.2%). RB were performed most often between first and second birthday. FB in airway were found in right bronchus in 22 patients (56.4%), in left bronchus in 13 patients (33.3%), in both brochi (right and left) in 2 patients (5.1%), one on carina (2.5%) and one in trachea (2.5%). Younger children aspirated more often organic FB, and older children aspirated more often unorganic FB. Average duration of intervention was 43.2 minutes. Children with suspected FB were in the most cases ASA score I. The most often findings in acide-base status were compensated metabolic acidosis and mild respiratory alcalosis. FB was founded in 39 of 62 children (62.9% vs 37.1%). In our institution there is high level of negative bronchoscopy. Making exactly diagnosis is very demanding. There is need to avoid unnecessary bronchoscopies, so as to avoid oversight of FB in the airway. In this study we tried to evaluate which factors correlate

with presence of FB. In number of studies patological X-ray had the most positive predictive value. The percentage of positive X-ray was from 48% to 62% from study to study. In our research positive X-ray was found in 28 children (73.7%). The most often findings on X-ray were hyperinflation and atelectasis. Presence, at the same time, of positive hetero(anamnesis), clinical exam and patological X-ray had a high level of suspicion of presence of FB (71.7% vs 28.9%). The most often signs and symptoms were clasical trias: cough, wheezing and diminished sound on aspiration side. Two major compications were noted, in one case bleeding in tracheobronchial tree and in one case death. FB in trachea and bronchi was removed with RB in general anaesthesia. After removing of FB, bronchoscope was introduced again because of inspection, removing mucus secretion and remaining parts of FB.

Conclusion:

RB is safe method for extracting FB with rare but possibly fatal complications. Prevention of inhaled FB is extremely important. Parents should not give their children nuts, seeds, unpeeled fruit and vegetable because only child age not less then five has good coordination between swallowing and breathing. While eating child should be in proper position and toys should be adjusted according to age.

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Optimal Head Position for Right Internal Jugular Vein Cannulation?

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Abstract

Introduction:

The right internal jugular vein (IJV) is more direct to the superior vena cava (SVC) and right IJV cannulation is associated with a less incidence of complications 1. The safe puncture of the IJV is achieved by using anatomical landmarks on the skin's surface and thus passing the needle along the anticipated line of the vein. The unexpected puncture of the common carotid artery (CCA) during right IJV cannulation is reported at a frequency as 10.6% with external landmark method and 1% with real-time ultrasound2. To mitigate these problems, several methods have been utilized, such as head rotation, the valsalva maneuver, and positive intrathoracic pressure during artificial respiration, which increases the jugular filling3. The aim of the study was to determine the optimal position of IJV and CCA for the purpose of safe and successful placement of CVC in relation to head rotation angle using external landmarks.

Methods:

After approval of EC and signed ICFs, the prospective cohort pilot-study included 60 volunteers bouth gender. Socio-demographic and antropometric data were collected: age, body mass and body mass index, body height, neck lenght and neck circumference. Each volunteer was placed in a neutral supine position. At carotid triangle, using a 7.5 MHz linear probe of an ultrasound system [SonoEye IPX7 (CHISON)], the right IJV depth, the IJV and CCA diameters were measured at three positions 0°, 15°, and 30° depending of the head rotation angle to the contralateral side using protractor system. The overlap length of IJV and CCA which was defined as the longest distance between the tangent of the most outer point of the CCA and the most inner point of the IJV, was measured. When the tangent did not cross the IJV, the

overlap was considered to be zero so the distance was measured. The percentage of overlap between IJV and CCA were calculated according formula. All data were collected and analized using SPSS 21 Statistic Softver.

Results:

In relation to gender, difference was found in body weight, body height, neck circumference and neck lenght ($p < 0,01$). Neck circumference corelate with body weight and body height compare to neck lenght which corelate to body height ($p < 0,01$). No found corelation between demografic and antropometric characteristics of volunteers with IJV-CCA overlape precent or distance in all three positions ($p > 0,05$). IJV depth was significantly different between 0° and 15°,0° and 30°, 15°and 30° ($p < 0,05$). No found differnce in overlape precent between three positions (p 0,116) No found difference between overlap in milimeters ($p > 0,05$). IJV-CCA distance was significantly different in 30° position compare to 0° and 15° ($p < 0,05$).

Conclusion:

Socio-demografic and antropometric characteristics had no influence to IJV-CCA relation. Head tilt for 30° in opposite side provided the most frequent overlape and the smallest IJV-CCA distance followed with the most depth position of the IJV.

Keywords: *Internal jugular vein, cannulation, ultrasound, external landmarks, common carotid artery*

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Spinal And Epidural Procedure as Methods Of Analgesia For Childbirth In General Hospital Kotor

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Introduction:

Childbirth pain is one of the most painful and joyful experiences in a woman's life. Neuraxial analgesia techniques are consider the most effective methods pain relief during childbirth, of which are used in General Hospital Kotor epidural and spinal analgesia. The lack of epidural catheters and difficulty of personnel organization are the main reasons why the percentage of analgesia during childbirth is lower than in certain institution of the same rank in the region.

Methods:

In the course of 2022, in General Hospital Kotor, occasionaly, some women in labor requested pain relief of natural childbirth, which, in agreement with the anesthesiologist and gynecologist, is in most cases were enabled. Depending on the availability of epidural catheters and the affinity of the anesthesiologist which was available at that time, the women in labor received epidural or spinal analgesia. During 2022. year, 39 women in labor requested a painless delivery. In one case, due to busyness duty and standby anesthesiologist, that was not possible, the other 38 had the privilege to give birth to a healthy child, and the act was not accompanied by pain.

Results:

Out of a total of 303 natural births in 2022. year, 21 women in labor received spinal analgesia and 17 epidurals, that is, 12.5% of women in labor had a pain-free delivery. Both performance techniques analgesia was performed according to all principles of asepsis and antisepsis. Spinal analgesia is carried out with a pencil point spinal needle 26G diameter , at the L4-L5 level, with a combination of fentanyl in a dose of 20-25mcg, and 0.5% bupivacaine in a dose of 2.5-3.5mg, and epidural, after placement of the epidural catheter,with a combination of 0.125% bupivacaine and 50-75mcg fentanyl in a bolus dose of 15ml, with adequate monitoring and availability of resuscitation equipment. After 5 minutes of spinal, and 20-25 minutes after the

epidural anesthesia, all women in labor rated the pain intensity as less than 4 on a numerical scale of pain up to 10. Two births ended with caesarean section - one after spinal analgesia where the woman in labor received spinal anesthesia, level above the prior administration site; the second after the epidural, where an adequate dose of anesthetic was given through the catheter, without reinjection exposing the mother to even the slightest pain. Therefore, the success rate of labor pain relief was 94.26%. There were no cases of anesthesiology complications neither in mothers nor their babies.

Conclusion:

Considering that both spinal and epidural analgesia are safe, fast and effective pain relief techniques childbirth, today, in the 21st century, would have to be part of common medical practice and not available to a smaller number of privileged patients. With adequate cooperation with the gynecologist and obstetrician nurse, and due to the fact that epidural catheters are very often unavailable to us, we give priority to spinal analgesia because it is faster,simpler and cheaper as a method of analgesia during childbirth

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Successful Treatment of Severely Injured Patient with Bmi>50 In ICU During 52 Days – CASE REPORT

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Abstract

Introduction:

Polytrauma is the leading cause of death in young patients under the age of 40. These patients are usually without any comorbidity and this represent a big socio-economic problem. Initial resuscitation of this severely injured patients is very important, but even if there is lack of adequate initial resuscitation within golden hour, urgent diagnostic and further management of this patients in ICU with team work can result in definitive resuscitation.

Methods, results:

36 years old male with body mass index (BMI >50 had a motorcycle accident. He had severe pelvic and both lower extremity trauma. He has been referred from other hospital to ICU approximately 3 hours after sustaining injuries without being adequately reanimated. During that time he lost a lot of blood, so he came in severe traumatic and haemorrhagic shock, barely, breathing, unconscious. He had no peripheral pulse, his systolic blood pressure was under 60 mm Hg. Upon admittance in ICU he has been put on mechanical ventilation and inotropic and vasopressor support was induced. He was extremely anemic so he has been treated with cristaloids, transfusion, fresh frozen plasma, albumin, platelets, krioprecipitat, tranexemic acid. He was also anuric, with high values of urea, creatinin and potassium. After stabilization of cardiovascular system, we were able to put him on a continuous venovenous hemodiafiltration (CVVHDF) which lasted for 10 days. Despite the initial treatment the parameters of inflammatory response grew higher and he developed systemic inflammatory response syndrome (SIRS). Empiric antibiotic therapy was administered at first, and later according to the results of blood cultures. With adequate and aggressive antibiotic and other support therapy and care, his general condition improved and inflammatory parameters lowered. We were able to wean him from mechanical ventilation, and soon he was extubated and breathing

spontaneously. All the manipulations and care of this patient were additionaly complicated because of his BMI. After hemodynamic stabilization, he had external fixation of both lower extremities and anterior external fixation was placed for initial stabilization of the pelvic fracture. He also underwent left orchiectomy because of the injury of left testicle. After improving of patients general condition and blood count he underwent definitive pelvic stabilization. With the help of the multidisciplinary and multimodal approach in treatment of this patient and fight with infection, we were able after 52 days to significantly improve his condition and to transfer him to orthopedic ward for further treatment.

Conclusion:

Even if there is no adequate initial resuscitation, team work and multimodal approach in treatment of severely injured patients can bring good outcome.

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COVID-19 in ICU of General Hospital Kotor

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Abstract

Introduction:

Outbreak of COVID-19 pandemic has created high demands for Intensive care units (ICU) worldwide, and surpassed their capacities. In the last few years, a lot of papers have been published about the mortality of patients with COVID-19 pneumonia in intensive care units, around the world. This paper aims to show the outcome of treatment of patients with COVID-19 pneumonia in the intensive care unit of OB Kotor. Also to contribute to a more comprehensive analysis.

Methods:

Data on the outcome of treatment, method of treatment and some demographic data were processed from the computer system of the FZOCG, as well as the medical histories of patients that werw treated of COVID-19 infection in OB Kotor.

Results:

Out of a total of 742 patients treated for COCID-19 infection, 136 patients (18.3%) were managed in ICU. Men made up 62.5%, and women 37.5%. Of the 136 patients, 99 (73%) were on NIV and 37 (27%) were on invasive ventilation. The mortality of patients on NIV was 82.83%, while the mortality of patients on IV was 100%. The largest number of patients, 72.03%, were older than 60 years. All patients were treated with antibiotics.

Conclusion:

This paper demonstrates the need for a detailed analysis of the treatment of patients in the COVID system of Montenegro, in order to identify weak points and lead to the organisation improvement of the health system in a pandemic situation.

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Bronchopulmonary Aspergillosis – CASE REPORT

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Introduction:

Pulmonary aspergillosis is an infection or allergic reaction caused by several types of fungal organisms (most commonly Aspergillus fumigatus). The individuals most at risk of developing this pathology are those with chronic pulmonary pathology (pre-existing cavity lesions) and immunocompromised individuals. The annual incidence of bronchopulmonary aspergillosis is 1-2 cases per 100,000 inhabitants. The forms of pathology presentation are: simple bronchial colonization, allergic broncho-pulmonary aspergillosis, aspergilloma, bronchocentric granulomatosis, extrinsic allergic alveolitis or invasive pulmonary aspergillosis.

Clinical case:

Patient T.K., 61 years old presented to the "Shefqet Ndroqi" University Hospital with a history of several years of dry cough, chest discomfort and body weakness. These signs have increased in recent times for which she was presented to the hospital.

The patient refers that since 2012 she has been investigated as Suspect Pulmonary aspergilloma for which she has performed several imaging and laboratory examinations carried out over the years, but despite them she has not received treatment for Aspergilloma. The patient reports that she has no chronic pulmonary pathology. She is hospitalized at SUSN for further examinations.

Thoracic CT: Centrally located mediastinum, without obvious lymphadenopathy. Two posterior pulmonary opacities are evident in the superior lobe of the sinister lung in nodular form with pleural thickening and minimal pleural fluid at this level.

Examination of sputum for eosinophils: Aspergillus spp are evident. as well as quite neutrophils. Bronchial lavage examination is recommended.

Serum IgE: 118.1 IU/mL (<100IU/ml) (**POSITIVE)**

Fibrobronchoscopy: Transnasal passage. Normal larynx, vocal cords with normal structure and mobility. Trachea with hyperemic mucosa. Sharp mobile tracheal carina. Both hemisystems: Their primary, lobar and segmental bronchi with

hyperemic mucosa fragile to the touch, with mucotic secretions, free to depth after aspiration. BK and fungal lavage was obtained in the sinister hemisystem.

Fungal culture of bronchial lavage: **POSITIVE** for Aspergillus flavus and Candida Glabrata.

Based on the above examinations, the diagnosis is made: **Pulmonary Aspergilloma.**

In general consultation with the service chiefs and thoracic surgeons, it was decided that the patient is suitable for surgical intervention and thoracotomy is planned for the removal of Pulmonary Aspergilloma.

The intervention was performed, which was successful and without post-operative complications.

Discussion and Conclusion:

Bronchopulmonary Aspergillosis is not a common diagnosis seen in routine. The most risked patients are those with chronic lung diseases as Bronchial Asthma, Cystic Fibrosis, pre cavity lesions and those immunocompromised. Thus, the physician must always be aware that in patients not having improvement by treatment, should make the differential diagnosis of bronchopulmonary aspergillosis.

In this case, patient was suspected for many years as Aspergilloma, but the diagnosis was not concluded. Diagnosis of the pathology is made by means of serial IgE measurement, skin tests against Aspergillus Spp., culture of bronchial secretions and imaging examinations. The treatment varies according to the forms of manifestation and is represented by treatment with antifungals, corticosteroids or surgical intervention.

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Difficult Airway Management Caused by Undiagnosed Hypopharyngeal Tumor In Elective Surgery - CASE REPORT

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Introduction

A good assessment of the airway is one of the main parts of the preoperative preparation, especially with the increasing use of the long-acting relaxant in the introduction, with the aim of providing adequate conditions for ventilation and intubation. Potential causes are congenital or acquired malformation, burn, trauma, or tumor change.[1,2]For the anesthesiologist, the biggest challenge is securing the airway and preventing the scenario of impossible ventilation and / or intubation. In hypopharyngeal tumors, this scenario increases to 16.9% with a 1% prevalence.[3]

Case report

A 38-year-old man was admitted for elective calculous gallbladder surgery after standard preoperative treatment. History of tonsillectomy, diclofenac allergy, and antihypertensive therapy. Routine airway assessment and Mallampati score did not indicate possible airway obstruction. Monitoring of vital functions is provided in the operating room. Propofol 1.5 mg / kg bw was administered for induction of anesthesia and as a relaxant Cisatracurium 0.15 mg / kg bw. After two minutes of ventilation, laryngoscopy showed a tumor mass in the right hypopharynx, which prevents visualization of the vocal cords and intubation. After 30 min mask ventilation patient was awakened and transferred to the intensive care unit. Examined by an otorhinolaryngologist who confirms the finding and after CT diagnosis, the existence of a tumor mass in the hypopharynx is determined. The patient was sent to a higher-ranking institution for further examination and treatment planning, while the operative treatment of gall bladder calculus was postponed until further notice.

Discussion

Hypopharyngeal tumors are rare in the general population with only 2-3% newly diagnosed annually in the male population over 55 years of age.[4,5,6] An unexpected scenario of difficult airway and potentially difficult ventilation is the

biggest stress for the anesthesiologist. In everyday work, this requires adherence to algorithms and protocols for difficult airway management with constant education of anesthesiologists. In that case significant assistance to the anesthesiologist for establishing the airway provide - video laryngoscope, fiberoptic bronchoscope and cricothyrotomy set. In our case, intubation was attempted three times, but after failure it was decided to wake the patient respecting the algorithms for difficult airway management.

Keywords: *difficult airway, hypopharyngeal tumors, general anesthesia, intubation*

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Perioperative Anaesthetic Management for Patient with Mediastinal Masses

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Abstract

Introduction:

Patients with mediastinal masses, which are preparing to undergo mediastinoscopy or VATS biopsy of the tumour, in order to get pathohistological diagnosis, are in high perioperative risk to develop respiratory and cardiovascular life-threatening complications. Mediastinal tumours include malignant and benign forms with different rates of disease progression and tissue invasion. Mediastinal masses can compress the major airways and surround structures (vena cava sup, pericardia, pleura). Clinical presentations can be dyspnoea, orthopnoea, stridor, syncope, right heart and pulmonary vascular compression, syndrome vena cava superior, etc. However, some patients can be asymptomatic despite they have large mediastinal mass. Apparently, normal airway perioperatively may develop an obstructive airway under general anaesthesia (new publications do not support this assertion). Cardiorespiratory collapse can occur with the use of sedative premedication, induction of anaesthesia with the use of muscle relaxants, change of posture, supine position, use of IPPV, tumour resection, tracheobronchomalacia due to prolonged compression by the mediastinal mass. The obstruction of airway can be distal to the tube. Therefore, this situation requires high professional skills and experience and institutions should have algorithms to decrease perioperative morbidity and mortality.

Methods:

Based on a search through electronic data base and literature for guidelines for preoperative investigations, predictors of perioperative risks and strategies for management of patients with TU mediastina. In addition is case report which shows author's experience on the topic.

Conclusion:

Anaesthetic management of patients with mediastinal masses can be very challenging and stressful for an anaesthesiologist. This article suggests perioperative management modalities to minimize perioperative risks. First, **preoperative assessment** must be done in detail: signs and symptoms, pre-treatment of mediastinal mass, CT scan evaluation, pulmonary function testing, thoracic echocardiography. **Intraoperatively** we can consider avoiding general anaesthesia, use of flexible and rigid bronchoscope, and depending on status of a patient; canulation of femoral artery, ECMO, stenting of trachea. Above all, multidisciplinary approach and good communication between surgeon and anaesthesiologist are essential.

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Anesthesia For the Ambulatory Gastrointestinal Endoscopic Procedure, Our Experience

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Ambulatory anesthesia shows exponential growth, especially in the last decade. Patients are aware of the benefits of anesthesia, they want safety and comfort, and leave themselves in the hands of the anesthesia team with confidence. In any case, due to various difficulties and risks that may occur during ambulatory anesthesia, such units should be formed within the hospital. The choice of patient is up to the gastroenterologist. All our patients are adults, most with various comorbidities, so the anesthesiologist has a large number of possible, serious problems as a burden. The positive side of this anesthesia is the psychological moment, because the patient's condition is actually the most important for accepting the intervention and the type of anesthesia, then minimal staying, quick and easy recovery, very little possibility of nosocomial infections and economic calculations that are important for the institution and the Health Fund. In everything, the most important thing is that the team is experienced, reliable and professional. Also, the unit must be equipped with appropriate equipment with a central oxygen supply. The team must have a good selection of drugs for anesthesia and other contingencies. Our team administers intravenous anesthesia. In 100% of cases it is a triad, namely: Propofol (hypnotic, sedative and antiemetic in subanesthetic doses), Fentanyl (synthetic opioid analgesic) and Midazolam (benzodiazepine with strong anxiolytic, amnesic, hypnotic, antiepileptic and sedative properties). Our goal is to show our results in work in the gastroenterology cabinet using the optimal ambulatory anesthesia technique with the use of Propofol, Fentanyl and Midazolam, as an optimal and safe triad.

Methodology and Results:

Patients come on the day of the intervention with an appointment, they are prepared for the intervention with an empty stomach and intestines, which is suitable for anesthesia, they also have fresh laboratory tests. Our sample represents 80 patients, all adults, ASA groups I-IV. Colonoscopy was performed in 64 patients, colonoscopy and gastroscopy in 7 (where the patients were under anesthesia for the longest time) and only gastroscopy in 9. After the anesthesiologist looks at the findings, takes a good anamnesis and registers all significant elements that may have an impact on the

occurrence of complications (allergies, recent colds, medications, other significant diseases), the patient signs the consent for the intervention to be performed under short-term intravenous anesthesia. The anesthetist pulses the intravenous cannula with a diameter of 16-18 G and connects the patient to the monitor. We connect the patient to the ECG only if there is a significant cardiac history. Before the start of the procedure, the patients were connected to a non-invasive monitoring, ECG, blood pressure, pulse and saturation were measured. All were administered with 2 ml of Fentanyl, 2-3 mg of Midazolam and 1 mg/kg of Propofol, with repeated addition of Propofol as needed. During the induction, the time of loss of consciousness and loss of the palpebral reflex was measured and recorded. The induction score was considered "excellent" if the patient fell asleep within one minute and sleep was maintained for three minutes or longer (70 patients had an "excellent" score), "good" if he fell asleep within one minute and required an additional dose (7 patients iamlo "good" score) and "poor" if he does not fall asleep within one minute and more doses are needed for induction (3 patients had a "poor" score). Of the 80 patients, 76 had no hemodynamically significant changes. Awakening from anesthesia a few minutes after the last repeated dose of Propofol took place with a verbal command in all 80 patients. Fifty patients walked (with the help of a nurse) to the observation room (at a distance of 10 m), the other 30 were transported on wheelchairs. In 18 patients, a drop in saturation below 80% O2 was recorded, which was corrected by O2 therapy, via an oxygen mask. Only two patients had SpO2 fall below 50% (obstructive patients with anamnestic history), which was also corrected with O2 doses of 6l and more.

Discussion and Conclusion:

Some of the problems with this type of anesthesia are that the gastroenterologist sets the indication for intervention, so the anesthesiologist meets the patient for the first time. Also, these patients have a lot of comorbidities, ASA score of I-IV, so we can expect complications. The good thing is that patients are received prepared with a scheduled intervention hour. After the anesthesiologist looks at the findings, takes a good anamnesis and registers all significant elements that may have an impact on the occurrence of complications (allergies, recent colds, medications, other significant diseases), the patient signs the consent for the intervention to be performed under short-term intravenous anesthesia. The anesthetist pulses the intravenous cannula with a diameter of 16-18 G and connects the patient to the monitor. We connect the patient to the ECG only if there is a significant cardiac history. The biggest problems are with chronic patients, who take a large number of medications, and it is clear that

the anesthesia team can be faced with many serious problems (which was not observed in any patient out of 80 monitored). We noticed that the triad of medicines used is safe and comfortable, so that the awakening is quick and pleasant. The majority of patients comment that they have the feeling that they slept for a long time, that they woke up rested and that they would repeat the same anesthesia without any problems. Also, the gastroenterologist's comment was that his work is extremely pleasant, because he thinks that the patients are managed ideally by the anesthesiology team. All patients left the observation room half an hour to an hour after the intervention, accompanied by a relative or friend, with advice not to drive motor vehicles by themselves.

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