Introduction
Sedation is the reduction of irritability or agitation by the use of certain drugs mostly to facilitate therapeutic or diagnostic procedures. Scales for evaluation of the depth of sedation. Riker Sedation-Agitation Scale and Richmond Agitation-Sedation Scale are the most commonly used scales. Drugs. Sedation is generally produced by using medications from the group of opioids, benzodiazepines, intravenous and inhalation general anesthetic agents, neuroleptics, phenothiazines, α-agonists and barbiturates. Adverse effects of sedatives. Sedation is often associated with hypotension, prolonged mechanical ventilation and longer time on respiratory support, higher frequency of delirium, immunosuppression, deep vein thrombosis, increased risk for development of nosocomial pneumonia, all of which leads to the prolonged recovery time. Conclusion. Sedatives currently used in intensive care units are widely used, but they have limitations. The goal is to get the desired level of sedation with as few side effects as possible.

Key words: Intensive Care Units; Hypnotics and Sedatives; Monitoring, Physiologic; Risk Assessment; Clinical Protocols

nitrous oxide, “laughing gas”, was discovered in 1844 by Horace Wells, an American dentist. He first tried the effect of this gas himself, with a help of a colleague while the extraction of wisdom tooth. Afterwards, Wells applied nitrous oxide on his patients, using an animal bladder and a wooden tube, which he put into the patient’s mouth, while the nose was blocked. He performed successful operations during a period of one month. The first public demonstration was unfortunately unsuccessful, since the gas was not applied properly. Wells was declared a fraud and he gave up dentistry. In 1848, disappointed, he committed suicide using chloroform [2].
In the period between 1920s and mid-1950s, barbiturates were practically the only drugs used both as sedatives and hypnotics. Barbiturates were synthesized in 1864 by Adolf fon Bayern, although the synthetic process was developed and perfected by a French chemist Edouard Grimaux in 1879. He facilitated further development of barbiturate derivatives, which were widely applied [3].

As far as contemporary sedation is concerned, benzodiazepines (midazolam), dexmedetomidine opioids are most often used [4]. Morphine still occupies a significant place in the therapy, due to its analgesic and mildly euphoric effect and cost-effectiveness. Chloral hydrate is used for sedation in pediatrics, whereas in developed countries, nitrous oxide is the drug of choice, due to its practical use by a mask, leading to a mild euphoria and having an optimal analgesic effect. In dental practice, nitrous oxide is most often used in combination with oxygen [5, 6].

The development of intensive care units dates back to the times when artificial ventilation was established using rudimentary machines which did not have the ability to synchronize with patient’s respiratory efforts. The consequence was deep sedation, up until the point when the patient was able to breathe without the help of a respirator. Apart from the use of microprocessor controlled ventilators in last decades, which are synchronized with patient’s respiratory effort, new, short-acting sedatives and analgesics have significantly changed this approach. Today, intensive care is part of a multidisciplinary approach including a large team which participates in treating critically ill patients. As far as the sedation of patients is concerned, the choice of analgesics and sedatives is important, taking into consideration the potential allergy to drugs, organ dysfunction (especially liver and kidneys), the need for rapid start of action and/or cessation of the drug induced effect, the extended duration of therapy, as well as the primary response to the therapy. Analgesics and sedatives are used according to patients’ needs, using the smallest effective dosage. The accumulation of drugs and their metabolites is being taken into consideration, as well as the adverse effects to which the application of these drugs may lead, particularly in critically ill patients. The manner of drugs administration is being planned, in the sense of continuous or intermittent administration [7].

### Scales for evaluation of the depth of sedation

The assessment of the depth of sedation implies the use of various scales. Riker Sedation-Agitation Scale (SAS) (Table 1) and Richmond Agitation-Sedation Scale (RASS) (Table 2) are the most commonly used. These scales are also a part of the protocol for the assessment of the state of delirium in the intensive care unit (ICU), Confusion Assessment Method (CAM) for the ICU, as a part of Intensive Care Delirium Screening Check-list (ICDSC).

Scales for assessment of the sedation depth are used in order to achieve the optimal level of sedation. However, if that is not achieved, the patient is agitated, which leads to a poor synchronization between the patient and the ventilator and consequently to insufficient ventilation. A possibility of delirium must be considered, involuntary removal of

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**Table 1. Riker Sedation-Agitation Scale (SAS)**

| Level | Term and Description | Description |
|-------|----------------------|-------------|
| 7     | Dangerous Agitation  | Pulling at endotracheal tube (ETT), trying to remove catheters, striking at staff, thrashing side-to-side./Povlačenje endotrahealnog tubusa (ETT), pomeranje katetera, agresivnost prema osoblju, bacakane iz strane u stranu. |
| 6     | Very Agitated        | Frequent and strict verbal reminding of limits is necessary, patient is biting ETT. Potrebno strogo i stalno verbalno podsećanje na limite, pacijent grize ETT. |
| 5     | Agitated             | Anxious and agitated, calms down to verbal instructions and commands. Ankiozan i agitiran, miran na verbalne instrukcije i naredenja. |
| 4     | Calm and Cooperative | Calm, awakens easily and follows commands. Miran, lako se budi, sledi komande. |
| 3     | Sedated              | Difficult to arouse, awakens to verbal command and gentle shaking, follows simple commands, but drifts off again./Teško se budi, ali na verbalne komande i blago drmanje, sledi jednostavne komande, ali ponovo „se isključi”. |
| 2     | Very Sedated         | Aroused to physical stimuli but does not communicate or follow commands, spontaneous movements are present./Budi se na fizičke stimuluse, nije komunikativan i ne sledi komande, spontani pokreti prisutni. |
| 1     | Unarousable/Ne mogu da se probude | Minimal or no response to stimuli, does not communicate or follow commands. Minimalan odgovor, ili ga nema, na stimulus. Nije komunikativan niti sledi komande. |

Legend/Legenda: ETT – endotracheal tube/endoratraheal tubus
electrodes and catheters, as well as the development of the post-traumatic stress. On the other hand, the elevated level of sedation leads up to unnecessarily prolonged mechanical ventilation, which can be accompanied by complications such as ventilator associated pneumonia or other lung damage, neuromuscular dysfunction, diaphragm dysfunction and numerous other damages. Due to these reasons, it is very important to find the right balance and to establish the appropriate level of sedation in ICU [8].

**Drugs**

Numerous types of drugs are used for sedation. They include opioids, benzodiazepines, intravenous and inhalation general anesthetic agents, neuroleptics, phenothiazines, α-agonists and barbiturates. On one side these drugs are used in order to help the patient, while on the other they have potentially harmful and adverse effects. Therefore, doctors in the ICU have to be well acquainted with all characteristics of these medications, in order to provide the patient with the most adequate care [9].

Sedatives are drugs most often used in the ICU. However, there are no ideal sedatives. The properties of an ideal sedative include: sedative, analgesic and anxiolytic effects, minimal cardio-vascular and respiratory side-effects, rapid onset and offset of its effects, no adverse effects on kidney and liver functions, having inactive metabolites, no interactions with other drugs and being cost-effective. This is exactly why there is no ideal sedative agent, and a large number of drugs and their combinations are in use. There are no defined sedation regimes, so the choice of suitable drugs is being made according to individual needs of the patient, his characteristics and clinical symptoms [10].

**Intravenous anesthetic agents**

*Propofol.* Propofol is an intravenous anesthetic agent which has a sedative, hypnotic, anxiolytic and retrograde effect in subanesthetic doses, but has no analgesic effects. It has a wide range of advantages including anticonvulsant and antiemetic effects, and it decreases the intracranial pressure [11, 12]. The most important side-effect of propofol is that it leads to hypotension due to peripheral vasodilation and negative inotropic and chronotropic effects. It is a lipid emulsion; therefore its intravenous administration is painful. Out of other side effects, a dose dependent respiratory depression and hyperlipidemia may occur. Propofol infusion syndrome is rare, but a very serious drug reaction. It is characterized by a progressive heart dysfunction, a severe metabolic acidosis, hyperkalemia, hyperlipidemia, acute renal insufficiency, and rhabdomyolysis. Hemodialysis or hemofiltration is recommended for elimination of propofol and its toxic metabolites [13].

*Benzodiazepines*

Benzodiazepines are most frequently used drugs for sedation of patients with severe illnesses or injuries. They lead to sedation, anxiolysis or hypnosis, depending on the number of receptors which are activated. Anxiolytic effect is manifested by binding to so called benzodiazepine receptors, which represent locations in the limbic system, after which occurs the activation of the inhibitory transmitter gamma-aminobutyric acid (GABA) affecting the nearby neurons (serotonin, dopamine, acetylcholine, noradrenaline and others) via GABA receptors. There are GABAa, GABAb and GABAc receptors. Benzodiazepines manifest their effect via GABAa receptors [14]. Generally, they lead to enhanced affinity of GABAa towards receptors, which consequentially makes easier for chloride channels to open up and lead to fast hyperpolarization. This is how their sedative and hypnotic effect is explained [15]. They do not lead to general anesthesia, but can induce respiratory and cardiovascular depression. They are bound with plasma proteins and are not eliminated by dialysis.

*Midazolam.* Midazolam is the most commonly administered short-lasting, water soluble benzodiazepine which becomes liposoluble in the blood and rapidly crosses the hematocerebral barrier and enters the central nervous system. Midazolam is suitable for sedation in ICU due to titration to a desired level of sedation, anterograde amnesia which does not change previously learned information, respiratory and cardiovascular stability and existence of a specific antagonist [16]. Anterograde amnesia is developing almost momentarily after the intravenous administration and it usually persists for 20 – 40 minutes after a single dose. It significantly influences the patients’ stay in ICU, since they do not remember unpleasant experiences. The time of half elimination varies greatly, and neutralization is unpredictable due to prolonged distribution. This is exactly why unpredicted awakening and extended extubation time can appear if it is administered for more than 72 hours. In comparison to propofol, midazolam induces a lower frequency of hypotension, but a greater time variation in the recovery after the cessation of drug administration [17]. The antagonist is Flumazenil (Anexate), which can neutralize the effect of benzodiazepine.

*Lorazepam.* Lorazepam is a long-acting benzodiazepine, relatively low as far as liposolubility is concerned and relatively slow acting. Due to these features, it is not a good choice for rapid agitation control. If administered through continuous intravenous infusion, it has a long time of half elimination (10 - 30 hours). Because of that, it is cumulating and the sedation is prolonged. That is why it is more appropriate for bolus administration. Solutions which are used for preparation of lorazepam may lead to hyperosmolarity, lactic acidosis and renal tubular acidosis, if administered alongside the drug in extended or higher dose. If higher dose is taken orally, it may cause diarrhea [18, 19].
Other benzodiazepines. Diazepam is not commonly used for sedation of patients in ICU and it can be administered intravenously; however, continuous administration should be avoided due to a long half-time of elimination, from 30 - 60 hours. It may lead to renal dysfunction [20]. Diazepam is also used in pediatrics, especially when administered rectally.

Barbiturates

Thiopentone. Barbiturates are still occasionally used in ICU. Deep sedation with thiopentone can be used for burst suppression of status epilepticus, although today propofol is more often used. Also, by administering continuous infusion one can induce so called “barbiturate coma” with severe trauma of the central nervous system (CNS), with the aim of decreasing cerebral metabolism. Thiopentone has immunosuppressive effect in certain doses. Literature data indicate the influence on serum potassium level during thiopentone induced coma. It is necessary to monitor serum potassium level in these cases, in order to avoid additional complications [21].

Alpha2 agonists

Dexmedetomidine. Dexmedetomidine is an alpha2 agonist of newer generation, with sedative, sympatholytic and anxiolytic properties. It shows greater affinity towards alpha2 receptors compared to Clonidine, due to which it has more expressed sedative effects. Sedation by alpha2 agonists differs from sedation with other sedatives. Patients can be awaken readily and their cognitive performance on psychometric tests is usually preserved. This is exactly why patients are more communicative and they cooperate better compared to other types of sedation. Dexmedetomidine reduces the postoperative vomiting reflex and enables better tolerance of endotracheal tube, in comparison to other sedatives [22]. Bolus administration has an important influence on cardiovascular system. Initially it leads to peripheral vasoconstriction, which consequently induces hypertension and reflex bradycardia, and later leads to central effects which are shown in vasodilation, hypotension and bradycardia. Cases of arrhythmia and sinus arrest have also been recorded. Due to these reasons, bolus administration of dexmedetomidine is not recommended, that is caution and monitoring is necessary during administration. Dexmedetomidine provides the anesthesiologist to rapidly awake the patient, who tolerates the endotracheal tube well, without respiratory depression, which makes it an ideal sedative [23].

Clonidine. Clonidine is also from the group of alpha2 agonists which reduces blood pressure and lowers heart rate by reducing sympathetic stimulation. Although it was initially used as an antihypertensive drug, it has not found its adequate and expected application in the field of cardiology. Clonidine provides sedation with minimal respiratory depression and has analgesic properties in larger doses, with scarce opioid effects. It also decreases cerebral blood flow and cerebral oxygen consumption [24]. There are some data showing that sedative doses of Clonidine lead to reduced rapid eye movement sleep phase in healthy volun-

Table 2. Richmond Agitation-Sedation Scale

| Level/Vrednost | Term/Termin               | Description/Opis                                      |
|---------------|--------------------------|-------------------------------------------------------|
| +4            | Combative Borben         | Overtly combative, violent, dangerous to staff.       |
| +3            | Very agitated Veoma agitiran | Aggressive, removes endotracheal tube, catheters.    |
| +2            | Agitated Agitiran        | Frequent non-purposeful movements, “fights against ventilator”. |
| +1            | Restless Uznemiren       | Anxious, but not aggressive.                          |
| 0             | Alert and calm Oprezan i miran | Not fully awake, but is opening eyes to voice (longer than 10 seconds). |
| -1            | Drowsy Pospan            | Nije potpuno budan, ali otvara oči na dozivanje (duže od 10 s) |
| -2            | Light sedation Blaga sedacija | Briefly awakens, eye contact to voice (less than 10 seconds). |
| -3            | Moderate sedation Umerena sedacija | Movement or eye opening to voice, without eye contact. |
| -4            | Deep sedation Duboka sedacija | No response to voice, eye opening to physical (pain) stimulation. |
| -5            | Unarousable Ne mogu da se probude | No response to voice or pain stimulus. |

Tatić M, et al. Sedation in the Intensive Care Unit
Morphine. Morphine is still considered a significantly strong and very frequently used opioid analgesic. It causes depression of the respiratory, vasomotor, and cough center, but on the other side, it stimulates the vomiting center. It causes a decrease of basal metabolism and circumstantially the decrease of the body temperature. It also causes bradycardia, miosis, and increased intracranial and intraocular pressure [27]. Morphine is metabolized in the liver into morphine-6-glucuronide, which is being eliminated a lot slower than the morphine itself and it crosses the brain barrier a lot slower, which, as an aftereffect, causes the prolongation of its impact. The analgesic effect is the most important characteristic of morphine. In a dosage-dependent manner it causes the increase of the pain barrier, and it also changes the emotional reaction to the pain and causes general sedation [15]. Euphoria occurs with approximately half of the patients, whereas with some of the patients dysphoria is possible as well [15]. Due to its positive characteristics, as well as its efficiency, morphine still represents "the gold standard" in postoperative period.

Fentanyl. Fentanyl is a synthetic opioid, which is 100 times more potent than morphine. It has, above all, a wide application in the treatment of intraoperative pain. In case of prolonged infusion, its accumulation occurs, and this is the matter one should take care of [28].

Sufentanil. Sufentanil is an opioid with the most powerful analgesic effect. It is 500 – 1000 more potent than morphine. It is suitable for sedation, since if it is used in mild dosage, it does not compromise hemodynamic stability. It is metabolized in the liver, metabolites are inactive and they are being eliminated through the kidneys.

Alfentanil. Alfentanil is an analogue to fentanyl with approximately 1/10 of the fentanyl potency, but it is a short-acting opioid used in a single dosage. It is frequently metabolized in the liver. It has a small volume of distribution. A smaller bit is being egested with no alterations, whereas the greater part is eliminated in the form of metabolites, through urine [7].

Remifentanil. Remifentanil is a popular opioid analgesic of newer generation and its metabolism does not depend on the liver function. Studies show a higher quality of sedation, good hypnotic effects and a shorter time for extubation. When using this medicine, it is very important to know its characteristics. Special bolus application is unnecessary and it is potentially hazardous due to bradycardia and hypotension [29].

Ketamine

Ketamine is an antagonist of N-methyl-D-aspartate receptors. It can be used for the introduction and maintenance of anesthesia, as well as a medication for sedation in the ICU. It causes a condition which is, due to its symptoms, known as “dissociative anesthesia”. In some aspects, it might be an ideal sedative, since it has both sedative and analgesic impact. It is also significant that it causes cardiovascular stability and bronchodilation. However, due to its connection with hallucinations, its independent usage in the ICU is not recommended. Ketamine is useful for patient comfort in painful procedures within the scope of intensive care, especially in pediatrics (punctures, drainages) and with bending of burns. It is also useful with patients who endured trauma, for maintenance of the respiratory musculature tonus and reflexes and for preservation of hemodynamic stability. It is frequently used in prehospital conditions, as well as a supplement to the opioids in the check-up of the post-operative pain. Ketamine was traditionally contraindicated for the check-up of increased intracranial pressure. However, contemporary attitudes have changed, since if there is a risk of hemodynamic instability, ketamine might be a very useful medication. It is also used with very severe bronchospasm, although its bronchodilator effect is very small. Inhalation anesthetics and propofol are more efficient in this respect [30, 31].

Inhalation anesthetics

In sedation, of inhalation anesthetics, the following are most frequently used: isoflurane, sevoflurane and desflurane. According to some studies, isoflurane has presented efficient, safe sedation up to 96 hours, with quicker awakening in relation to midazolam, and similar awakening in relation to propofol, however with increased number of patients with delirium. Isoflurane is also a powerful bronchodilator and it has a significant role in therapy of status asthmaticus [32]. Desflurane has also shown faster awakening after a short-term postoperative sedation (<12h), as well as quicker mental recovery in relation to propofol. There are special systems for application of inhalation anesthesics (sevoflurane) in the ICU.
Antipsychotics (tranquilizers)

Neuroleptics are used in the treatment of agitation caused by hyperactive delirium, with the option to include haloperidol and oral antipsychotics, such as chlorpromazine, olanzapine, risperodine. Haloperidol is most frequently used since it can be applied intravenously, frequently as a preventive measure, taking care of adverse effects for the cardiovascular system. Patients should be followed for arrhythmia, such as torsade de pointes, and it should be applied with precaution in the patients whose QT interval is prolonged. Dosing of medicine is performed according to the individual needs of the patient. Contemporary manuals for the control of delirium recommend a short-time application of haloperidol or olanzapine, with the recommendation of dexmedetomidine for prevention [33].

Non-opioid analgesics

Nonsteroidal anti-inflammatory drugs (NSAID) are used as a supplement to opioids in the therapy of pain in certain patients in the ICU. They must be used with precaution since they might cause damage to kidneys and erosion of gizzard mucosa due to their impact on renal production of prostacycline. They also have a characteristic of higher risk of myocardial heart failure and a stroke [34].

Adverse effects of sedatives

Prolonged sedation is an intervention whose side effects are often underestimated. They cause hypotension and decrease in perfusion, prolong mechanical ventilation, and in the worst case, the need for tracheostomy. Apart from this, prolonged sedation causes postponed respiratory support, higher frequency of delirium, immunosuppression, deep vein thrombosis, increased risk for development of nosocomial pneumonia, all of it leading to prolonged recovery time [35]. On the other side, decreased sedation causes the condition of general discomfort, as well as hypertension, tachycardia, hypercatabolism, increased usage of oxygen, atelectasis, infection and psychological trauma [36]. Consequently, due to this very reason, doctors in ICU must be very familiar with the medicines applied in the therapy, in order to achieve desired effects. As it was stated beforehand, ideal sedative does not exist. Every medicine has certain side-effects, and it is the task of every doctor to estimate whether the application of medicine causes more benefit than harm to the patient.

Sedation and functions of the Central Nervous System

A great number of clinical studies have analyzed the relationship between the usage of benzodiazepines and deterioration of the CNS functions, especially in severely sick patients (critically ill, surgical patients, with trauma, burns) treated in ICU for a long period of time.

Data on the effects of opioids differ a great deal. Sedation with dexmedetomidine, in comparison with benzodiazepine, decreases the possibility of damage or duration of dysfunctions of the CNS. The ABCDE strategy, that stands for AB (Awakening and Breathing trials), C (Choice of sedation), D (Delirium monitoring and management), as well as E (Early Exercise), may decrease the incidence of acute and prolonged dysfunction of the CNS [37]. In the same manner, using bispectral index (BIS) for monitoring the depth of sedation makes it possible to establish the level of sedation. Monitoring the impact of sedatives on the CNS expressed numerically (above 60 - 80) may, correctly represent the level of consciousness i.e. the level of being awake [38].

Early mobilization

Contemporary studies show that early mobilization has a significant impact on the patients’ functional outcomes, safety, and the length of stay in the ICU. Early physical therapy significantly reduces the incidence of delirium in the ICU. In the same manner, the protocol of early mobilization decreases the usage of sedatives and analgesics, and supports enhanced recovery after surgery. In patients on mechanical ventilation, every day without sedation, alongside the physical therapy, significantly improves the functional status and shortens the time in the ICU [39, 40].

Conclusion

Sedation is a very significant issue in the management of the critically ill patients. Consultations with doctors and the manner of sedation according to specific and individual characteristics of patients provide safe and adequate treatment. Currently accessible sedatives that are used in Intensive Care Units are acceptable and are widely used, but they also have limitations. Instead of searching for ideal sedatives for critically ill patients, their application should be based on the principles of pharmacology and pharmacokinetics of medicines. By establishing the aims of sedation, according to individual characteristics and current conditions of the patient, it is possible to provide a rational treatment strategy for each patient in the intensive care unit. In the same way, early mobilization of patients who are still in the intensive care unit, reduces the occurrence of intensive care unit delirium and consequently reduces the usage of sedatives and analgesics, thus contributing to enhanced recovery and shorter stay in the intensive care unit.
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