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EDITORIAL

CHALLENGES IN ANALGOSEDATION MANAGEMENT IN THE INTENSIVE CARE UNIT

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The primary goal of Intensive Care Unit (ICU) patients' pain and agitation management is to minimize patients' physical and psychological discomfort. As such, it is considered a vital ICU nursing challenge. Nonetheless, 79% of ICU patients report having experienced moderate to severe pain (1), and 71% have an agitation state at least once during hospitalization (2,3). Sedation practices in the critical care unit have been trending toward lighter sedation since the start of the new millennium, but patients continue to experience inadequate pain management and excessive sedation. While the analgosedation literature is relatively sparse, it offers a promising, patient-centered method for managing the triad of pain, agitation, and delirium, while reducing common complications associated with long-term ventilation (3).

Sedative and muscle-relaxant medications have been considered the best practice to promote ICU patients' comfort and tolerance to mechanical ventilation. However, the literature shows that this practice has increased adverse outcomes for ICU patients regarding health status, hospital stay length, infection development and mortality (4).

Pain is one of the most common symptoms among ICU patients. Undertreatment of pain at rest and during nursing and medical procedures causes increased patient's suffering; it induces pathophysiological and psychological adverse clinical responses (3,5,6). Notably, pain promotes catabolic hypermetabolism. The latter negatively affects wound healing, increases infection risk, alters hemodynamic function, and prolongs the need for mechanical ventilation (7). Patients also may experience pain either because of previously performed surgical interventions or painful diagnostic and therapeutic procedures. Furthermore, psychological reactions to pain undertreatment lead to psychomotor agitation and delirium (1,8). The latter conditions often impose treatment with sedative drugs. Sedation objectives in the ICU are to reduce agitation and ensure patient's safety, to minimize the risk of voluntary or involuntary patient self-removal of invasive devices (such as an endotracheal tube, drainages and catheters), to optimize mechanical ventilation compliance to reduce respiratory work and oxygen consumption, improving patient's comfort, and providing amnesia and ease to promote adherence to stressful diagnostic and therapeutic procedures (8).

Sedation in the ICU involves the targeted reduction of the patient's level of consciousness through intermittent or continuous administration of medication. There is no universal recipe for sedation that is suitable for all patients. It is important to consider the significant variability among patients, taking into account their age and disturbances in the function of organ systems. The condition of patients often changes during intensive treatment, and as the course of the illness evolves, so do the individual requirements for sedation. Because of this, an individualized approach to sedation is important, which involves regular re-evaluation and constant reassessment and adjustment of the choice of sedatives.

The type and dosage of drugs administered to critically ill patients should be adjusted to achieve optimal treatment outcomes. When considering sedation, it should always be combined with an analgesic strategy and recommended approaches in the ICU, such as the concept of "analgosedation" (analgesia-first sedation). This involves prioritizing pain control in critically ill patients to prevent discomfort and improve their overall treatment tolerance. By managing pain effectively, unnecessary risks from oversedation can be reduced.

The primary goal of analgesia and sedation in ICU care is to provide sufficient comfort and ensure pain-free treatment while minimizing patient's anxiety, agitation and other complications. Optimal sedation facilitates patient cooperation with medical procedures and reduces the likelihood of complications such as hemodynamic instability and pulmonary risks. Prolonged and excessive sedation can lead to long-term cognitive impairments and extended recovery periods.

The consequences of inadequate sedation are not negligible, regardless of whether it is undersedation or oversedation.

The consequences of undersedation include the following: anxiety and restlessness, inadequate mechanical ventilation due to poor synchrony with the ventilator, hypertension and tachycardia, hypermetabolism and increased oxygen demand, myocardial ischemia, accidental extubating and other adverse events, including the removal of catheters or drains and long-term consequences, such as post-traumatic stress disorder and chronic cognitive impairments.

The consequences of oversedation include hypotension, bradycardia and reduced perfusion, increased dependency on vasopressor drugs, prolonged delirium and recovery of cognitive function, prolonged mechanical ventilation and associated complications like ventilator-associated pneumonia (VAP), thromboembolic complications, gastrointestinal paralysis, muscular atrophy and weakness, extended ICU stays and hospitalizations and immunosuppression.

The implementation of standardized sedation protocols in ICUs ensures consistent and effective management. These protocols guide clinicians in selecting appropriate sedation levels, regularly evaluating patient's conditions, and adjusting interventions accordingly. Sedation levels should be assessed at defined intervals, typically every 1–2 hours, or more frequently as the patient's needs change.

Absolute contraindications to light sedation are the following: respiratory instability requiring high ventilatory support, severe hypoxemia requiring high fractions of inspired oxygen (FiO2),

severe hemodynamic instability and immediately post-cardiac surgery or similar critical procedures.
Relative contraindications to light sedation are high ventilatory demand and requirement for very high positive end-expiratory pressure (PEEP).

Deep sedation significantly increases the risk of delayed weaning from mechanical ventilation and the need for prolonged ICU care. Patients in deep sedation may not respond to physical stimuli or commands, leading to complications such as muscle atrophy, prolonged immobilization and increased mortality. Hence, it is emphasized that deep sedation should only be used in critically ill patients where absolutely necessary.

Sedative Drugs

Propofol

Propofol is a potent sedative and hypnotic agent with bronchodilator and anticonvulsant properties. It acts on GABA-A receptors, producing rapid effects within 1 to 2 minutes of administration. However, the drug must be administered cautiously, considering its potential for side effects, such as respiratory depression, hypotension, and, in rare cases, propofol infusion syndrome. Continuous sedation with propofol is typically used for durations of 24–48 hours at a dose of 4–6mg/kg/h. The side effects include hypertriglyceridemia, lactic acidosis, and bradycardia, which necessitate careful monitoring and dose adjustments to avoid complications (15).
Propofol is metabolized in the liver and excreted via the kidneys, with minimal accumulation even after prolonged use. It provides smooth, predictable sedation with a favorable recovery profile, which allows for rapid awakening once the infusion is stopped. However, in cases of prolonged use, care must be taken to monitor for potential drug accumulation, particularly in patients with impaired liver or kidney function.

Dexmedetomidine

Dexmedetomidine is a selective agonist of α2-adrenergic receptors with sedative, amnestic, sympatholytic, and mild analgesic properties. Its agonistic effect on α2 receptors reduces norepinephrine release in peripheral nerves and the brain (11). The sedative action of dexmedetomidine is mediated through inhibition of transmission in the **locus coeruleus**, a significant area in the brainstem responsible for maintaining and modulating wakefulness and attention. The analgesic effect of dexmedetomidine is not mediated through opioid pathways but rather through spinal α2 receptors.
Dexmedetomidine is administered as a continuous infusion, ensuring so-called cooperative sedation, characterized by the patient maintaining consciousness while achieving deep levels of sedation. Its onset of action is rapid, and sedation can be easily reversed by discontinuing the infusion. Patients can be awakened without agitation after stopping dexmedetomidine, remaining calm and communicative. When deeper sedation is unnecessary, they revert to a sleep-like state, with EEG patterns similar to natural non-REM sleep.

This drug has found a particular role during the weaning period of mechanically ventilated patients transitioning to spontaneous breathing. It is especially useful and recommended for sedating patients with delirium. The prevalence of delirium is lower in patients treated with dexmedetomidine compared to those receiving benzodiazepines. Clinical studies suggest that dexmedetomidine does not cause clinically significant depressive effects and does not result in respiratory depression. Measured respiratory rates and oxygen saturation levels remain stable during its use.

Benzodiazepines

For many years, benzodiazepines were the most commonly used drugs for sedation in intensive care units (ICUs). Current recommendations for sedation in mechanically ventilated patients prioritize the use of propofol and dexmedetomidine due to the adverse effects associated with prolonged benzodiazepine use. Prolonged administration of benzodiazepines leads to deep sedation and serious complications, primarily due to drug accumulation in critically ill patients, especially those with hepatic or renal insufficiency, as well as elderly patients (12). The use of benzodiazepines is associated with an increased prevalence of delirium among ICU patients. Benzodiazepines have sedative, anxiolytic, hypnotic and anticonvulsant properties. However, they lack analgesic effects. When administered in higher doses, especially in combination with opioids, they may induce profound sedation, muscle relaxation, respiratory depression, and cardiovascular instability. These effects are more pronounced in critically ill patients with respiratory insufficiency and organ dysfunction.

Midazolam

Midazolam is a short-acting, water-soluble drug from the benzodiazepine group. It is 2–3 times stronger than diazepam. It binds to specific receptor sites on the GABA-A receptor complex in the CNS, acting as a regulator of GABA-ergic agonist effects and resulting in sedative, anxiolytic, amnestic and muscle-relaxant effects. Due to its high lipid solubility and large volume of distribution, its effect starts quickly after administration. It causes minimal cardiovascular and respiratory depression (14).

The sedative effect appears within 1 to 2 minutes, making it particularly suitable for procedures requiring rapid sedation and short duration. It is metabolized in the liver via the cytochrome P450 system, producing an active metabolite (α-hydroxymidazolam), which is further metabolized in the kidneys. In cases of renal impairment, the active metabolite may accumulate, prolonging sedation and increasing the risk of respiratory depression. In clinical practice, the maximum dose of midazolam infusion is usually limited to 4.8mg/kg/day to prevent the development of tolerance or adverse effects. Prolonged use may result in withdrawal symptoms, which need to be managed carefully.

Lorazepam

Lorazepam has a slower onset of action than midazolam but lasts longer and is 5–10 times more potent than diazepam. It can be used in bolus doses or continuous infusion. It is less lipid-soluble than midazolam and has no active metabolites, making it suitable for use in critically ill patients, including those with renal or hepatic impairment.

The sedative effect of lorazepam develops within 5–20 minutes and lasts for several hours. The drug is metabolized in the liver through glucuronidation and is excreted primarily by the kidneys. In patients with renal or hepatic dysfunction, the drug may accumulate, leading to prolonged sedation (15).

Adverse effects: Prolonged administration or high doses of lorazepam may cause lactic acidosis, hyperosmolarity and toxicity, due to the accumulation of propylene glycol (used as a solvent). In cases of suspected toxicity, the drug should be discontinued, and supportive care should be initiated.

Excessive sedation caused by benzodiazepines

Excessive sedation caused by benzodiazepines can be quickly resolved with the administration of flumazenil. Flumazenil is administered via intravenous injection in an initial dose of 0.2mg, which can be repeated at intervals of 1 minute, up to a total dose of 1mg. The onset of action occurs within 60 seconds, and the maximum effect of flumazenil lasts about 6–10 minutes, depending on the administered dose.

Inhalational anesthetics for sedation in the ICU

Inhalational anesthetics are used in the ICU primarily for continuous sedation during procedural sedation. For prolonged sedation of critically ill patients in the ICU, their use is limited due to the lack of devices that allow safe dosing and elimination of active compounds, as well as the sedative effects persisting without metabolite formation. Modern devices, such as the Anesthetic Conserving Device (AnaConDa™) or MIRUS™, are compatible with modern ventilators, facilitating inhalation sedation delivery. These devices minimize environmental exposure by efficiently capturing expired vapors.

Studies suggest the effectiveness of inhalational anesthetics for both short-term and long-term sedation, with faster recovery times compared to intravenous agents. The dosage of inhalational anesthetics in ICU sedation is typically low (0.2–0.3 MAC, which corresponds to sub-anesthetic concentrations), ensuring a balance between sedation and physiological stability. Their use is associated with reduced intracranial pressure, making them suitable for neurocritical patients, especially those with traumatic brain injuries or elevated intracranial pressure.

Haloperidol

Haloperidol belongs to the first generation of antipsychotics. Its sedative and antipsychotic effects are due to its antagonism of dopamine receptors, particularly at the level of the central nervous system. This makes haloperidol effective in the treatment of critically ill patients in the ICU. It is used to manage acute agitation, with doses ranging from 0.2 to 5mg. Sedation typically occurs after intravenous administration in critically ill patients within 10–20 minutes.

Side effects of haloperidol include rigidity, spasms, extrapyramidal reactions (rigidity, tremors, spasms) and prolonged QT interval, which can rarely lead to ventricular arrhythmias. Intravenous administration is rarely associated with neuroleptic malignant syndrome (hyperreflexia, muscle stiffness and rhabdomyolysis).

Assessment of Analgesia Effectiveness

Considering that the condition of critically ill patients changes during intensive care, the need for and intensity of analgesia also changes. Continuous assessment of pain levels is crucial. Monitoring the effectiveness of analgesia involves repeated measurements at specific intervals as well as the systematic tracking of its efficacy.
To assess pain intensity, various strategies and scales can be used. While changes in vital parameters (heart rate, respiratory frequency, blood pressure, oxygen saturation) can be indicative of pain, they should only be supplementary to clinical observation and not considered as valid primary indicators of pain for critically ill patients. Instead, direct communication with patients who can self-report their pain is preferred.

Medications for Analgesia

The choice and combination of analgesics, as well as the careful titration of doses, significantly impact the treatment and outcomes of critically ill patients in intensive care units (ICU). The ideal analgesic should be one that acts quickly, has a short duration of action, does not produce active metabolites, and has a low risk of accumulation in the body. Significant progress in achieving optimal analgesia has been made using existing analgesics and the introduction of new drugs into clinical practice.

Opioid Analgesics

Opioid analgesics are the most commonly used analgesics in the ICU. They are administered intravenously, either as bolus doses or via continuous infusion. Their pharmacological effects are achieved by stimulating μ, δ, and κ opioid receptors. Among these, the μ-opioid receptors are the most important for analgesic effects. Some opioids, in addition to stimulating opioid receptors, also act on non-opioid receptors (e.g., tramadol) or other mechanisms (e.g., tapentadol). Depending on the dosage used, their effects vary. The most commonly used opioids in ICUs are morphine, hydromorphone, fentanyl, sufentanil and remifentanil (13).

Selection and Method of Analgesic Administration in the ICU

The central role in modern analgesia concepts in the ICU is played by opioids with a rapid onset of action and dose-dependent effects. Remifentanil is an excellent choice for analgesia in the ICU. It has a quick onset of action and is broken down by non-specific esterases in plasma, making its effects independent of infusion duration and organ function. This ensures a fast and predictable effect termination. The use of shorter-acting opioids reduces mechanical ventilation periods (MVP), improves differentiation of sedation levels, and reduces brain dysfunction, while minimizing side effects and their impact on mortality. Opioids can be administered continuously or intermittently via intravenous boluses at defined time intervals. The latter method has advantages but requires individual dose adjustments for each patient to achieve adequate speed and intensity of analgesia. Continuous opioid infusion is the most commonly initiated with a loading dose or by increasing the infusion rate until a therapeutic concentration is reached, followed by maintenance infusion. This approach avoids excessive drug concentration in tissues, which can prolong drug effects. Intermittent administration, while technically feasible, is not commonly used due to its short-lasting effect, which lacks sustained analgesia. Special caution is

needed for patients with liver or kidney failure, as drug accumulation in tissues can lead to unwanted effects. Intermittent administration can also ensure effective analgesia, avoiding drug accumulation in the body while maintaining a stable therapeutic effect. However, immediately after drug administration, concentrations may be too high, leading to side effects, and later drop below the required therapeutic level, making analgesia inadequate. The use of opioids as the sole analgesic in the ICU is not recommended. For critically ill patients, prolonged and excessive opioid use can lead to drug accumulation and numerous side effects, including prolonged sedation, respiratory depression, ileus and potentially increased intracranial pressure, and worsening thoracic mechanics. Other complications include hallucinations, delirium, hyperalgesia and others. Careful titration of opioids along with the concurrent use of non-opioid analgesics (paracetamol, nefopam, lidocaine, carbamazepine, clonidine, gabapentin, dexmedetomidine, ketamine) can reduce opioid consumption, the incidence of delirium and can improve analgesia (13). When using non-opioid analgesics within the multimodal analgesia concept in the ICU, their opioid-sparing effects must be carefully assessed to avoid excessive opioid use and minimize adverse effects.

Choosing Medications for Analgosedation

The choice and balance between sedation and analgesia depends on individual needs, chronic illnesses, indications for sedation, clinical conditions, existing organ dysfunctions, comorbidities, concurrent therapies and allergies. The pharmacokinetics and pharmacodynamics of medications in critically ill patients are often unpredictable due to complex drug interactions, increased drug sensitivity, organ dysfunctions, protein-binding changes, hemodynamic instability and drug accumulation. Incorrect medication selection and dosing can lead to adverse outcomes.

It is critical for physicians administering sedation in the ICU to be fully informed about the benefits, risks and potential side effects of each drug.

Research findings indicate that the choice of sedative and its administration can significantly impact short- and long-term treatment outcomes. Important parameters for selecting sedatives include the specific indication, the pharmacokinetics and pharmacodynamics of the drug, individual patient’s characteristics, cost-effectiveness, metabolism and the absence of active metabolites or adverse effects.

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