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ANALGESIA AND SEDATION IN THE INTENSIVE CARE UNIT

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Abstract: Sedation and analgesia are essential components in the management of all critically ill patients. The main indications for use include relieving patient discomfort, anxiety and agitation, promoting mechanical ventilation, preventing displacement of endotracheal tubes and decreasing cellular metabolism. Based on the above, the main objective of this work was to review and compare sedation and analgesia medications in patients admitted to the ICU. To this end, a qualitative/descriptive narrative literature review was carried out, using online databases such as SciELO; PubMed and Lilacs. Scientific articles, monographs and theses in Portuguese, English and Spanish were selected. Currently, there is a wide variety of pharmacological agents available to meet the diverse needs of this heterogeneous group of patients. Targeting treatment toward specific, individualized goals will ensure that the patient's needs are met. All sedatives currently available for use in the ICU have limitations. Rather than searching for an ideal medication, medication delivery strategies that focus attention on the principles of sedative pharmacology in critical illness must be utilized. Choosing the appropriate drug for analgesia and sedation will maximize therapeutic success and minimize complications.
Keywords: Analgesia; sedation; intensive care unit.

INTRODUCTION

Sedation and analgesia are essential components in the management of all critically ill patients. The main indications for use include relieving patient discomfort, anxiety and agitation, promoting mechanical ventilation, preventing displacement of endotracheal tubes and decreasing cellular metabolism (BARRA; NASCIMENTO; BERNARDES, 2006).

Pain is a common experience for most intensive care unit (ICU) patients and they do not recognize that pain also contributes to agitation. It is the most common memory that patients have of their stay in the ICU. In this regard, inadequate analgesia and anxiety may precipitate the accidental removal of endotracheal tubes or intravascular catheters used to track or administer life-sustaining medications.

As a result, sedatives and analgesics are becoming one of the most widely used and used medications in the ICU, as equally important ideas were mentioned that early detection of pain, sedation, sedation and delirium are problems that, if not detected and treated, are distressing for patients and associated with increased morbidity and mortality in the ICU (SAKATA, 2010).

Intravenous benzodiazepines and propofol are sedatives commonly used in ICUs. However, these agents are associated with excessive sedation in 40 to 60% of patients, which can lead to prolonged intubation, delirium, and drug-induced hypotension. Evidence shows that newer volatile anesthetic agents are associated with faster extubation times, greater cardiovascular safety without end-organ toxicity relative to our normal intravenous agents for short-term sedation in critical care. The use of this volatile agent in the ICU is a new technique that utilizes a specialized distribution and elimination procedure that involves staff training, cultural acceptance, and sedation protocols and daily interruption of sedation does not appear to vary compared to the majority of findings analyzed (SANTOS; MARTINS; GONÇALVES, 2016).

Adequate sedation is an important component in the care of critically ill patients. Deep levels of sedation are associated with many negative effects, such as increased time on mechanical ventilation, longer ICU stay, delirium, memory disruptions, and increased

short- and long-term mortality. In ICU patients, especially those with mechanical ventilation, the delirium rate reaches 80%, in addition to increased mortality, longer hospital stays, higher hospital costs and poor long-term outcomes are normal. These and other harmful effects of deep sedation can be minimized by employing a strategy of sedation protocols that aim for lighter levels of sedation and daily interruption of the sedative infusion (SANTOS; MARTINS; GONÇALVES, 2016).

Analgesia, which as a basis for sedation can reduce the amount of sedatives used, is a key and fundamental component of treatment in the management of ICU patients, and we can, therefore, point out that an analgesic sedation protocol can reduce the incidence of delirium due to reducing the amount of sedatives used. Specific physiological changes that critically ill patients experience can have a direct impact on the pharmacology of medications, possibly contributing to discrepancies in response between patients.

Objective measures of pain, sedation, and anxiety have been validated for use in the ICU for assessment and medication titration. An evidence-based approach to administering these medications will lead to changes in patients' short- and long-term outcomes (SHINOTSUKA; SALLUH, 2013).

Therefore, based on the above, this work's main objective was to review and analyze the main sedation and analgesia medications in patients admitted to the ICU. To this end, a qualitative/descriptive narrative literature review was carried out, which aims to provide greater familiarity with the proposed subject through what the authors have confirmed in studies. The bibliography referenced here was located in online databases such as SciELO; PubMed and Lilacs. Scientific articles, monographs and theses in Portuguese, English and Spanish were selected.

THEORETICAL REFERENCE

Pain is a common experience for most ICU patients. Failure to recognize that pain often leads to agitation and may result in excessive administration of sedatives. Pain can result in many adverse events, including increased endogenous catecholamine activity, myocardial ischemia, hypermetabolic states, and anxiety. Furthermore, it is noteworthy that opioid requirements are reduced in patients sedated with benzodiazepines instead of propofol (SHINOTSUKA; SALLUH, 2013).

However, sedatives must never be administered as a substitute for adequate analgesia. A strategy that strives to focus initially on ensuring adequate analgesia often reduces the need for other sedatives in many critically ill patients. Therefore, patients must be reassessed frequently to ensure that the pain is being treated appropriately (BATTAGLIN; OLIVEIRA FILHO, 2013).

Although pain is certainly a cause of anxiety in most ICU patients, many patients suffer from anxiety even after analgesia is treated. It is clear that being seriously ill and dependent on others for care can invoke anxiety. Therefore, sedation strategies must recognize and respond to this problem. Dyspnea is common in ICU patients and can be a source of distress. Coughing is common in intubated patients, especially during suctioning. Excessive coughing can contribute to patient-ventilator dyssynchrony. Opioids can relieve coughing in intubated patients (MARTINS; OLIVEIRA; FERREIRA, 2013).

Excessive oxygen consumption (V O2) can be harmful in patients with respiratory failure or shock. A shift in the delicate balance between oxygen supply and consumption may be an important component of the management of these patients. Previous work has shown that oxygen consumption can be reduced early on by an average of 15% after administration of sedatives and opioids. For

some patients, such as those with shock or severe hypoxemic respiratory failure, this reduction in oxygen consumption may be important for cardiopulmonary stability (HANCđ et al., 2013).

Although it may seem intuitive that amnesia for the period of critical illness is desirable, data to support this notion are lacking. On the contrary, we have experience that the absence of memory of a period in a person's life can be unsettling for some, even if that period is the experience of a critical illness. The notion that complete amnesia may be harmful has been supported by some studies. Therefore, we believe that the only circumstance in which complete amnesia is mandatory is during the administration of neuromuscular blockers. Certainly, more data are needed to improve our understanding of the impact of sedation and amnesia on long-term psychological outcomes in critically ill patients (SHINOTSUKA; SALLUH, 2013).

Some patients may demonstrate periods of disorientation during which psychotic behavior occurs. Sometimes an aggressive type of behavior may occur. Reasons for such behavior include medications, sepsis, fever, encephalopathy (hepatic or renal), paranoia, or withdrawal syndromes (alcohol, tobacco, or other illicit drugs). Treatment of agitated behavior is another indication for ICU sedation. This behavior generally responds well to neuroleptic medications, such as haloperidol (SANTOS; MARTINS; GONÇALVES, 2016).

STRATEGIES FOR ADMINISTRATION OF SEDATIVES IN THE ICU

Because no single medication can achieve all indications for sedation and analgesia in the ICU, a combination of medications, each titrated to specific end points, is typically a more effective strategy. A combination strategy may allow for lower doses of individual drugs and reduce drug accumulation problems. Sedatives and analgesics can be administered by intermittent bolus or continuous infusion. The first can result in periods of oversedation and undersedation and increased demand for nursing time (SANTOS; MARTINS; GONÇALVES, 2016).

In fact, for many critically ill patients who require aggressive levels of sedation, this approach can be extremely taxing on ICU professionals and potentially distract attention from other patient care issues. The purported benefits of continuous sedative infusions include a more consistent level of sedation with increased levels of patient comfort. The perceived convenience that this strategy provides for both patients and caregivers is probably the biggest reason for its popularity (HANCđ et al., 2013).

Ideally, sedation of critically ill patients would be optimized if strategies that address the pharmacokinetic and pharmacodynamic profiles commonly observed in these patients were well understood and described and, in turn, provided specific guidance for medication administration. Unfortunately, critically ill patients often present unpredictable changes in these profiles (BATTAGLIN; OLIVEIRA FILHO, 2013).

Critically ill patients may have altered liver and/or kidney function that impairs drug clearance. Drug interactions, altered protein binding and circulatory instability are common. In the ICU, sedatives generally have multicompartmental pharmacokinetics with

a tendency to accumulate in the peripheral compartment and consequently prolong the clinical effect. Titration of drugs against clinical outcomes can be extremely inaccurate. This is particularly true given that the two extremes of sedation (extreme agitation versus drug-induced coma) are so dramatically different (MARTINS; OLIVEIRA; FERREIRA, 2013).

Despite efforts to minimize the amount of sedatives administered, many patients with respiratory failure require sedative doses much higher than those cited in the literature and recommended by drug manufacturers. Occasionally, these patients may even require pharmacological paralysis (SHINOTSUKA; SALLUH, 2013).

The inability to monitor a patient's mental state during the course of critical illness is a major disadvantage of deep sedation. Acute organ failure is a common complication of critical illness. Ideally, a daily head-to-toe assessment for the presence of organ failure must be routine for every critically ill patient. However, many patients kept under the veil of sedation may not be neurologically evaluated. A non-communicative, critically ill patient may develop unrecognized intracranial disorders, intrathoracic or intra-abdominal catastrophes. Communication and a complete physical examination can detect these problems early and avoid urgent diagnostic studies and therapeutic interventions after the problem has progressed (HILDRETH et al., 2008).

A daily sedative interruption strategy may enable focused downward titration of sedative infusion rates over time, streamlining the administration of these medications and minimizing the tendency for them to accumulate. Exceptions to this recommendation include patients requiring muscle paralysis, who must never be awakened from sedation until the effect of the paralytic agent has worn off. In this group, it is advisable to interrupt neuromuscular blockade daily or even twice a day to assess the adequacy of sedation and analgesia and the continued need for neuromuscular blockade. Additionally, patients at high risk for myocardial ischemia may have ischemia precipitated by sedation interruption. More data are needed to improve our understanding of the risks of routinely discontinuing sedatives in these patients. Patients in surgical ICUs were not included in our study and, therefore, the risks and benefits of daily interruption of sedatives in this population are not known (MORO; MÓDOLO, 2004).

MAIN AGENTS ANALGESIA AND SEDATION IN ICU

Premedications are administered to mitigate anxiety and potentially negative physiological responses that may occur during ICU admission, due to pain, anxiety or for intubation. The optimal timing of premedication depends on the concerning abnormal physiological response. Typical premedications include the following: midazolam, fentanyl, atropine and lidocaine (HILDRETH et al., 2008).

The selection of induction agents is based not only on patient-specific factors, but also on the specific characteristics of the medication (MARTINS; OLIVEIRA; FERREIRA, 2013).

Fentanyl is a centrally acting synthetic opioid agonist used to attenuate the sympathetic surge in pain receptor stimulation that occurs with intubation. Examples of some patients at risk of additional injury from a sympathetic surge include those who have lost the capacity for cerebral autoregulation and those with acute ischemic heart disease and acute aortic aneurysms or dissections. These patients would benefit from narcotics, with fentanyl being the opioid of choice due to its high degree of lipophilicity, lack of histamine release, rapid onset of action and

short duration of action (MORO; MÓDOLO, 2004).

A dose of 1 to 3 μg/kg is recommended 3 minutes before induction. It is hepatically metabolized by oxidation and has no active metabolite. The most common adverse side effect associated with fentanyl is respiratory depression (MORO; MÓDOLO, 2004). Administration of fentanyl for more than 30 to 60 s must minimize respiratory depression. Chest wall stiffness that can make ventilation nearly impossible can occur with fentanyl. However, this is mainly observed after large doses (e.g. 100 μg/kg) and must not be a concern with a single dose as premedication (MARTINS; OLIVEIRA; FERREIRA, 2013).

Fentanyl can cause respiratory depression and lower blood pressure. In the setting of sepsis or other conditions that may reduce blood pressure, other agents must be considered. Sinus tachycardia, hypertension, palpitations, and bradycardia have also been reported. Chest wall rigidity is an uncommon but serious adverse effect of fentanyl that can make it extremely difficult for patients to ventilate.

Paralytic medications may be necessary to allow effective ventilation in the setting of fentanyl-induced muscle rigidity. Fentanyl exposes patients to the risk of opioid addiction. The risk of CNS depression increases with concomitant use of other CNS depressant agents, such as benzodiazepines or ethanol. As with other medications, allergic reactions may occur (BATTAGLIN; OLIVEIRA FILHO, 2013).

Fentanyl must not be used if there is a known allergy to opioids. Concomitant use of fentanyl with a cytochrome P450 3A4 inhibitor may result in increased plasma concentrations of fentanyl. Patients who have recently had a P450 3A4 inducer discontinued may have increased plasma fentanyl concentrations (ALMEIDA et al., 2004).

Historically, lidocaine has been used to blunt the sympathetic response to intubation in patients with suspected elevated intracranial pressure (ICP). The sympathetic surge associated with intubation may cause additional increases in ICP. The mechanism of lidocaine blunting this response is not completely understood, but it is believed to work through a combination of reflex suppression, inducing peripheral GABA receptor anesthesia, brain stem depression, slowed brain metabolism, and membrane stabilization, decreasing the rate of depolarization and repolarization (HANCđ et al., 2013). Vaillancourt and Kapur (2007) refuted this claim and suggested that the practice does more harm than good.

A reduction in mean arterial pressure by 30 mm Hg after administration of lidocaine was reported in a study of patients who received lidocaine before ISR (HANCđ et al., 2013). Furthermore, Samaha et al. (1996) showed that ICP still increases when patients receive lidocaine, it is just a more modest increase. Despite its lack of reported efficacy, lidocaine is still widely used. The typical dose is 1.5 mg/kg (common 100 mg) and has a relatively quick onset of action, 45 to 60 seconds (MARTINS; OLIVEIRA; FERREIRA, 2013).

Lidocaine undergoes hepatic metabolism. Other side effects associated with lidocaine include hypotension, which may further decrease cerebral perfusion pressure in a patient with traumatic brain injury and arrhythmia. However, none of the studies mentioned above evaluated adverse effects. Furthermore, lidocaine interacts with several medications, including dronedarone (pro-arrhythmic), amiodarone (increases the risk of hypotension) and monoamine oxidase inhibitors (causes hypotension) (MORO; MÓDOLO, 2004).

Propofol is a highly lipid-soluble phenolic derivative, which is a GABA agonist and is

used as an induction agent for ISR. The dosage of propofol used for induction in healthy patients is 1.5 mg/kg (common, 100-200 mg).

As obese patients have an increased volume of distribution but a decreased elimination rate compared to lean patients, actual body weight must be used for propofol dosing (HILDRETH et al., 2008).

Propofol's high degree of lipophilicity allows it to cross the blood-brain barrier very quickly, resulting in a rapid onset of action. This medication redistributes very quickly in peripheral tissues and is metabolically eliminated quickly, resulting in a short-lived action. The elimination rate and central volume of distribution decrease in elderly patients and, therefore, lower doses of propofol must be considered (50-100 mg) (MARTINS; OLIVEIRA; FERREIRA, 2013).

Due to its hepatic metabolism to water-soluble sulfate and glucuronide conjugates, it is suitable in patients with hepatic or renal insufficiency. Propofol decreases ICP and is therefore an appropriate agent for use in induction in patients with increased ICP. A study of 6 patients with head trauma who received a bolus of propofol for induction showed a mean decrease in ICP of 14 mm Hg2 (HILDRETH et al., 2008).

In patients with bronchospasm, propofol is an appropriate induction agent due to its mild bronchodilatory effects. Another point to highlight is that this drug does not have analgesic properties and is the drug of choice for induction in pregnant women as it is a category B drug (WILBUR; ZED, 2001).

A disadvantage of propofol is that it has calcium channel and β-adrenergic receptor antagonist properties, which can induce hypotension and bradycardia. Caution must be exercised in patients with volume depletion, hypotension, or reduced ejection fraction. Concomitant opioid use, abdominal surgery, poor physical status, female sex, and older age have all been associated with an exaggerated hypotensive response. With prolonged infusion (> 72 hours) and high concentration (> 75 μg / kg / min), there is a risk of propofol infusion syndrome (FRANCO et al., 2020).

Pain with peripheral administration of propofol is common, which can be alleviated by the use of lidocaine, use of a larger peripheral vein or central venous administration. Traditionally, propofol is thought to be contraindicated in patients with egg allergies. However, the top 5 allergens associated with an egg allergy are isolated from egg whites. Propofol is an oil-water emulsion that uses soybean oil and egg lecithin.

Egg lecithin is a highly purified phosphatidyl from egg yolk, therefore, theoretically, propofol must not induce an allergic response in patients with an egg allergy. The isopropyl or phenyl groups and not the lipid vehicle were considered responsible for the few reported IgE-mediated anaphylactic reactions associated with propofol (FRANCO et al., 2020).

Etomidate is a sedative-hypnotic derivative of imidazole, which stimulates GABA receptors to block neuroexcitation and induce unconsciousness. The dosage range is 0.2 to 0.6 mg/kg (common, 20-50 mg), with the most common dose used being 0.3 mg/kg. In hemodynamically unstable patients, dose reduction to 0.2 mg/kg may be considered. An adjusted body weight is recommended in morbidly obese patients. The main advantages of etomidate are that it has minimal cardiovascular effects, reduces ICP and does not cause histamine release (MARTINS; OLIVEIRA; FERREIRA, 2013).

Etomidate also has a rapid onset of action, short duration of action and is eliminated by the liver. Etomidate has no analgesic effects. Following administration of etomidate, myoclonus, which may be confused with seizure activity, may occur

with an incidence rate of 22% to 63%. It is clinically inconsequential and ends when the NMB comes into force. Pain on injection is a common side effect and is secondary to propylene glycol diluent. Etomidate was also associated with increased postoperative nausea and vomiting when compared to thiopental. Etomidate causes a moderate reduction in intraocular pressure (IOP). Additionally, etomidate causes a 20% to 30% decrease in cerebral blood flow, resulting in a moderate reduction in ICP that can last for several minutes (AGGARWAL et al., 2016).

Recently, several small studies have shown that a single dose of etomidate is associated with adrenal insufficiency in critically ill patients. However, most of these studies were small and insufficient to assess mortality (AGGARWAL et al., 2016). More studies need to be carried out to further clarify the association of etomidate with mortality (MARTINS; OLIVEIRA; FERREIRA, 2013).

Etomidate can cause elevation or decrease in blood pressure, apnea, laryngospasm, tachycardia, bradycardia, hypoventilation, myoclonus, adrenocortical insufficiency and hypoaldosteronism. It can also cause injection site reactions, nausea, vomiting and hiccups. As with other medications, allergic reactions may occur (AGGARWAL et al., 2016).

Etomidate must not be used in case of sepsis or adrenal insufficiency. It is extensively metabolized in the liver; therefore, caution must be exercised when administering etomidate to patients with liver disease. It must not be used if there is a known allergy to the medication (AGGARWAL et al., 2016).

Ketamine is highly lipophilic and easily crosses the blood-brain barrier and causes functional and electrophysiological brain dissociation. Intense amnesia occurs secondary to the dissociative effects of ketamine, inducing a trance-like cataleptic state by non-competitive glutamine inhibition of N-methyl-d-aspartic acid (NMDA) receptors in the thalamocortical and limbic central nervous system (CNS). In addition to its amnesic effects, and unlike any other induction agent, ketamine provides analgesia. It does this through antagonism of the NMDA receptor, which potentiates the activity of the opioid receptor. The induction dose of ketamine is 1 to 2 mg/kg (common, 100 mg) (OLIVEIRA et al., 2004).

Ketamine is metabolized hepatically to an inactive metabolite, norketamine, which is excreted renally. Ketamine exerts sympathomimetic effects, such as increasing heart rate, blood pressure and cardiac output, stimulating CNS flow and decreasing catecholamine reuptake. Because of these sympathomimetic effects, ketamine is an excellent induction agent for patients with hypotension. However, ketamine may worsen hypotension and exacerbate myocardial depression in patients who are catecholamine depleted (NUNES; CAVALCANTE; FRANCO, 2011).

This includes patients with prolonged hypotension; a maximum dose of 1.5 mg/kg is recommended in these patients. Historically, it was thought that ketamine must be avoided in patients with increased ICP, initial studies demonstrating increased cerebral oxygen consumption, increased cerebral blood flow, and increased ICP. More recent studies have demonstrated that in sedated and mechanically ventilated patients, ketamine does not increase ICP (OLIVEIRA et al., 2004).

Ketamine increases myocardial oxygen consumption, raising concerns about its use in patients with coronary artery disease. There are concerns that ketamine may increase intracranial or intraocular pressure, therefore, in the context of possible increased intracranial or intraocular pressure, other agents may be preferred.

Common adverse effects of ketamine include rash, diplopia, vomiting, involuntary movements of the head and extremities, increased secretions and emergency reactions, hypertension, and allergic reactions. One of the most concerning potential adverse effects of ketamine is laryngospasm, which can be serious. Ketamine is generally administered within 60 seconds to reduce the risk of respiratory depression, apnea, and increased pressor response. As with other medicines, allergic reactions may occur. Ketamine must not be used if there is a known allergy to the drug or in patients with a history of psychosis (OLIVEIRA et al., 2004)

Its use as an inducing agent is most commonly seen in the pediatric population. The induction dose of midazolam is 0.2 to 0.3 mg/kg. When used alone, it has a slow onset of action (up to 5 minutes) and causes incomplete loss of consciousness. If opioids are administered concomitantly, the onset of action improves to 90s. Both moments are unacceptable in the configuration of an ISR (NUNES; CAVALCANTE; FRANCO, 2011).

Patients receiving midazolam as an induction agent may experience a dose-related decrease in systemic vascular resistance and myocardial depressant effects, and a dose reduction must be considered in volume-depleted or hemodynamically unstable patients. After the large dose required for midazolam induction, elderly patients and those with heart failure or liver disease are expected to experience a prolonged sedative effect with midazolam (NUNES; CAVALCANTE; FRANCO, 2011).

Midazolam must not be used if there is a known allergy to benzodiazepines. May reduce blood pressure, so it is not recommended in case of shock (NUNES; CAVALCANTE; FRANCO, 2011).

FINAL CONSIDERATIONS

Analgesia and sedation are important components in the treatment of ICU patients in order to facilitate the management of pain, anxiety and agitation, avoid equipment failures, involuntary extubation and improve patient coordination on mechanical ventilation. However, excess of these drugs contributes to increased morbidity and mortality. The ideal treatment would be based on the implementation of clinical and pharmacological interventions, guided by scales and guidelines.

Sedation is an important component of the treatment of critically ill patients in the ICU, especially for those requiring mechanical ventilation. Currently, there is a wide variety of pharmacological agents available to meet the diverse needs of this heterogeneous group of patients. Targeting treatment toward specific, individualized goals will ensure that the patient's needs are met.

All sedatives currently available for use in the ICU have limitations. Rather than searching for an ideal medication, medication delivery strategies that focus attention on the principles of sedative pharmacology in critical illness must be utilized. To choose the appropriate drug for analgesia and sedation will maximize therapeutic success and minimize complications.

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