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PROPER SEDATION AND PAIN MANAGEMENT IN VENTILATED PATIENT - REVIEW

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Abstract:
The administration of sedation and analgesia is a crucial aspect of the comprehensive care provided to numerous patients using mechanical ventilation in the critical care unit (ICU). In order to select an appropriate medicine usage strategy, it is imperative to possess a comprehensive understanding of the existing body of research that serves as the foundation for evidence-based recommendations. In addition, it is crucial to take into account the ongoing scholarly exploration that takes place throughout the period between the establishment of consensus guidelines, while we anticipate the forthcoming release of updated clinical practice guidelines. The administration of sedation and analgesia plays a crucial role in the care of patients necessitating mechanical breathing. In order to maximize both short-term and long-term outcomes in mechanically ventilated patients, it is imperative to use an evidence-based methodology when providing sedatives and analgesics.

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INTRODUCTION:

One of the most difficult tasks in critical care nursing today is managing pain, agitation, and delirium in mechanically ventilated patients. Priorities in nursing care include measures to reduce the physical and psychological discomfort, as well as the unpleasant memory, connected with endotracheal intubation and mechanical ventilation. For decades, substantial dosages of sedation and/or neuromuscular paralysis were considered best practice to enhance patient comfort and ventilator tolerance [1].

MOST ICU patients who are in for mechanical ventilation are given sedative and analgesic drugs. They are essential components of the complex treatment of these patients, helping to reduce patient discomfort and the risk of agitation and inadvertent self-extubation. However, these drugs can have negative side effects, such as longer mechanical breathing and ICU length of stay [2,3]. Several review papers and guidelines have been published to help optimize the usage of these drugs in ICU patients. The implementation of procedures for ICU sedation and analgesia resulted in advantages such as fewer ventilator days. Although pain and sedative research in the ICU has developed, little is known about contemporary procedures. Questionnaires revealed physicians' or nurses' preferences for pain and sedation rating systems, as well as sedative and analgesic medicines [4,5,6]. As recently pointed out, such an approach may fail to reflect what is actually done at the patient's bedside. Furthermore, the stated use of devices for measuring sedation might range from 8% to 49% in Germany and from 16% to 61% in Denmark [5,6].

Because there may be a significant gap between the conceptualization of guidelines, physicians' remarks, and actual practice, there is a need to document what happens on a daily basis in ICUs so that those findings can be included in future national guidelines [7]. Current pain and sedative techniques in the ICU are confined to the use of drugs. Despite the fact that ICU patients must undergo numerous procedures, only one big study [8] has addressed the issue of analgesic administration during procedural pain.

Many mechanically ventilated patients in the intensive care unit (ICU) require sedation and analgesia as part of their care. To select an effective medication-use approach, it is vital to grasp the body of literature that serves as the foundation for evidence-based recommendations [9].

During mechanical ventilation, most mechanically ventilated patients experience some level of pain. As a result, it is vital for clinicians to prioritize analgesia while evaluating "sedation" in the mechanically ventilated patient. Otherwise, mechanically ventilated patients' pain may be mistaken as agitation, which cannot be properly controlled with sedative medicines alone [10]. Pain from surgical incisions or trauma is usually visible, but other signs of pain management may be more subtle. Endotracheal suctioning, for example, or the insertion of invasive catheters is frequently uncomfortable. Other probable causes of pain include preexisting conditions such as skeletal fractures from metastatic disease and prolonged immobility during bed rest. Many people experience discomfort simply from having an endotracheal tube in their trachea. As a result, consensus perspectives on sedation of mechanically ventilated patients strongly suggest an intensive approach to pain management [11]. Pain is typically difficult to detect since many mechanically ventilated patients are unable to communicate its presence, and clinical factors such as changes in vital signs are not always accurate markers. As a result, in mechanically ventilated patients, monitoring toward analgesia is critical [12].

DISCUSSION:

As stated in a recent Rapid Practice Guidelines publication in Intensive Care Medicine [13], patients with ARDS or other life-threatening illnesses may require neuromuscular blocking agents (NMBAs) to optimize mechanical ventilation (MV). Case studies of people who were chemically paralyzed but awake reveal the terror they felt. As a result, the best clinical practice guidelines advocate for deep sedation and amnesia, as well as good analgesia, prior to neuromuscular blockade [14]. Although a 2010 trial found that NMBAs increased survival in severe ARDS patients [5,] a bigger trial failed to duplicate these findings [15]. As a result, the indications for NMBAs in ARDS are currently being contested [13]. NMBAs should only be used as a last resort for patients with the most severe ARDS.

The primary purpose of analgesia/sedation for lung protective ventilation strategy patients is to give comfort and safety, permit lifesaving measures, and preserve patient connection with staff and family to promote early physical and cognitive recovery [13]. A multimodal patient-centered approach, comprising effective early analgesia, appropriate sedation, and delirium/agitation-free emergence, is required for all people in the ICU [14] and should be considered for ARDS patients as well. However, no prospective analgesia/sedation studies in ARDS patients have been

done. We believe a three-tiered sedation depth method (i.e., light (RASS + 1/ 1), moderate (RASS 2/ 3), and deep (RASS 4/ 5) [15]) may be beneficial. The rigid application of a one-size-fits-all technique is discouraged. Instead, the following rules should be followed to ensure appropriate sedation in the majority of patients:

In most patients, aim for minimal or no sedation, and prioritize appropriate analgesia and short-acting sedative medications if needed [16]. Accept short intervals of mild sedation (RASS 2/ 3) to overcome ventilator asynchrony or discomfort when pain control and ventilator settings have been optimized [17]. Regularly monitor the sedation level with a validated method and reassess the goal sedation level at least twice daily. Validated tools should be used to measure pain and delirium on a regular basis. Titrate all drugs to achieve a specific level of sedation. Deep sedation (RASS 4/ 5) is occasionally required. Sedatives should be chosen in this circumstance based on the patient's age, organ function, and comorbidities. To avoid the unnecessary use of sedatives and the risk of producing severe drowsiness, consider regulating the mechanical ventilator and the patient's respiratory drive first in all circumstances. It should be noted that this proposed three-tier sedation depth technique should not be used solely based on ARDS severity (i.e., mild, moderate, and severe) because some severe ARDS patients tolerate light sedation without considerable patient/ventilator asynchrony [17]. Based on the aforementioned considerations, [**Figure 1**] depicts a possible methodology for guiding sedation management under protective breathing without NMBAs.

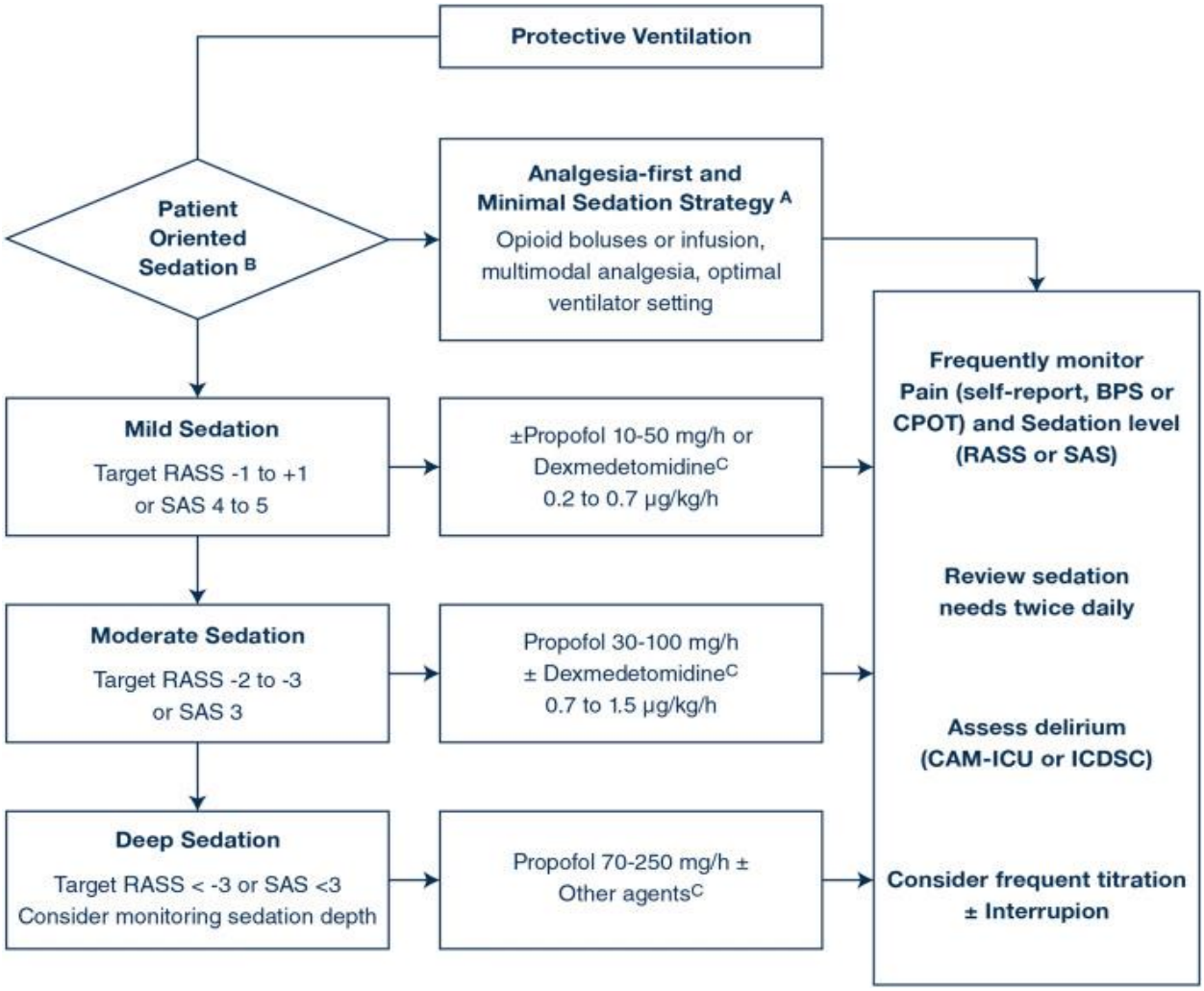

Figure 1: Analgesia and sedation without NMBA for protective lung ventilation strategy.

The challenges associated with supplying sedatives to critically sick patients have been further exacerbated by disruptions in the supply chain caused by the COVID-19 pandemic. These disruptions are primarily due to the heightened demand for sedatives, stockpiling practices, temporary factory shutdowns, and limitations on exporting. This information is supported by reference number 18. There are internationally accessible websites that provide regular updates to aid in the identification and management of drug shortages. Notable instances of such shortages include fentanyl, propofol, midazolam, and cisatracurium. As the shortages progress, it may become necessary to explore the use of less frequently utilized medications for the purposes of inducing analgesia, sedation, or therapeutic paralysis. This is despite the limited availability of data on the efficacy of these specific medicines or the customary guidelines advising against their use.

The use of nurse-directed analgesia/sedation policies, which empower bedside nurses to modify opioid and sedative dosages (often based on pain and sedation scales), has been shown to decrease drug administration and facilitate liberation from mechanical ventilation (MV) and discharge from the intensive care unit (ICU) [19,20]. While it may not be essential or provide additional advantages to implement a formal methodology when patients are already being treated with a minimum sedation approach by highly competent nurses [21], excessive sedation continues to be prevalent in numerous intensive care units (ICUs). Therefore, the implementation of an analgesia/sedation protocol often proves advantageous. The extent to which nurses are able to modify analgesia-sedation levels based on a protocol is contingent upon the organizational structure, cultural norms, and legal framework of the intensive care unit (ICU) [22,23]. The involvement of physicians is crucial in all instances, as they play a pivotal role in modifying drug dosages and engaging in discussions with the ICU team regarding specific concerns, irrespective of the implementation of a protocol. Additionally, physicians are responsible for addressing the overall objective of analgesia-sedation on an individual basis. This is particularly necessary in the context of acute respiratory distress syndrome (ARDS), which presents a complex scenario for managing analgesia and sedation. The implementation of daily interruption of infusions in patients receiving opioids and/or sedatives has been linked to a decrease in mechanical ventilation (MV) duration and other advantageous outcomes. This is likely due to several factors: firstly, it encourages healthcare providers to reassess the necessity of sedatives; secondly, it mitigates the accumulation of medication; and thirdly, it facilitates a shift towards intermittent or "as needed" administration strategies [24]. The inclusion of a daily interruption approach in a sedation program that aims to achieve mild sedation does not result in any additional reduction in mechanical ventilation (MV) days, as indicated by a study [25]. Although there is a lack of randomized controlled trials (RCT) comparing intermittent and continuous administration in adults with acute respiratory distress syndrome (ARDS), existing research provides some insights. For instance, a randomized controlled trial conducted on children who underwent cardiothoracic surgery [25] and an observational study conducted on adults [26] indicate that the intermittent administration strategy may result in reduced drug administration and shorter duration of mechanical ventilation (MV). However, additional research is required prior to endorsing an intermittent administration technique as opposed to continuous treatment for all individuals. It is imperative for these studies to consider the conflicting hazards associated with both procedures, such as the potential for heightened agitation and self-extubation with the intermittent strategy, and the possibility of delayed alertness and cognitive recovery with the continuous strategy [26].

Analgesic-based sedation:

The appropriate utilization of analgesics and sedatives has the potential to enhance the well-being of mechanically ventilated patients, facilitate the process of liberating them from ventilator support [27], and potentially decrease the occurrence of chronic pain [28]. The concept of "analgosedation" involves the administration of an analgesic prior to a sedative for the purpose of pain management, sometimes referred to as "analgesia first." Alternatively, analgosedation can also involve the use of an analgesic that possesses sedative qualities, known as "analgesic-based sedation." Various strategies have been devised to mitigate the reliance on sedatives and enhance the process of ventilator weaning [27]. The implementation of a multimodal analgesia strategy involves the utilization of many analgesic agents, each with distinct mechanisms of action. The utilization of many analgesics can yield advantageous outcomes by mitigating the negative effects associated with each specific medication [29]. The concurrent administration of non-opioid drugs, such as low-dose ketamine, paracetamol, and/or nefopam, may offer potential protection for patients against the adverse effects associated with opioids, including drowsiness, hallucinations, and opioid hyperalgesia, dependency,

and withdrawal [28]. Prudent administration of analgesics by meticulous titration (employing an algorithm, daily interruption, and intermittent dosing) alongside the use of comforting non-pharmacological therapies (such as music or relaxation techniques) can potentially mitigate the occurrence of cognitive recovery setbacks, which is a crucial factor in the successful liberation of patients from ventilators.

Opioids, which exhibit rapid onset and dose-dependent effects, as well as the capacity to alleviate excessive respiratory drive, continue to serve as the primary analgesic treatment for Acute Respiratory Distress Syndrome (ARDS) [27]. Nevertheless, it is important to acknowledge that these interventions are not devoid of negative consequences. These include: (1) the suppression of the immune system, (2) the potential for drug accumulation leading to prolonged sedation and respiratory depression, which can impede the liberation from ventilator support, (3) the development of tolerance within a 48-hour timeframe, (4) the manifestation of withdrawal symptoms upon discontinuation [28], (5) the occurrence of hyperalgesia and chronic pain syndromes with prolonged utilization, and (6) the possibility of ileus, which can result in increased abdominal pressure and subsequently exacerbate respiratory mechanics. While the effectiveness of non-opioid analgesics (such as paracetamol, ketamine, and nefopam) in reducing opioid use and associated adverse effects, as well as improving pain management in critically sick individuals, has not been extensively studied in the context of acute respiratory distress syndrome (ARDS) [29]. Ketamine, a pharmacological agent that acts as an antagonist of the N-methyl-D-aspartate (NMDA) receptor, has the ability to produce strong analgesic effects while not interfering with respiratory function. This characteristic makes it a promising candidate for adjunctive treatment with opioids in patients with acute respiratory distress syndrome (ARDS) who are nearing readiness for liberation from mechanical ventilation [30]. Nevertheless, a randomized controlled trial conducted at a single site, which had 40% of patients with acute respiratory failure, conducted a comparison between the administration of remifentanil and low-dose ketamine vs remifentanil and a placebo. This trial did not demonstrate any significant reduction in opiate usage [31]. Additional research is required prior to endorsing the utilization of ketamine for its potential to reduce opioid consumption. Infusions at a dosage of 1 mg/kg/h or more have the capacity to elicit profound drowsiness as a result of the dissociative anesthetic properties of ketamine. This sedative impact is accompanied by an elevated likelihood of emerging hallucinations and hypertension. The analgesic efficacy of nefopam is similar to that of low-dose opioids, while without exerting any impact on respiratory drive or consciousness. The administration of paracetamol, whether orally or intravenously, according to a predetermined schedule, has been shown to result in a reduction in opioid intake. However, it is important to note that intravenous usage of paracetamol may lead to adverse effects such as tachycardia and hypotension.

Sedatives:

Sedatives are pharmacological substances that are commonly used to induce a state of calmness

Both propofol and midazolam, which are GABA agonists, have the ability to decrease respiratory drive, promote immunosuppression, and induce severe sedation [27]. Propofol is considered a more favorable choice in comparison to midazolam due to its reduced likelihood of causing prolonged drowsiness and/or delirium. Additionally, propofol offers greater titratability, allowing for more precise dosage adjustments. Furthermore, propofol's clearance is not reliant on the functioning of the liver and kidneys. Nevertheless, it is important to note that propofol has the potential to induce hypertriglyceridemia and a condition known as propofol-related infusion syndrome (PRIS), particularly when administered at doses equal to or greater than 60 mcg/kg/min. Dexmedetomidine, an alpha-2 agonist, does not exhibit immunosuppressive effects or diminish respiratory drive. It possesses analgesic-sparing qualities and, in contrast to propofol or midazolam, has the potential to enhance sleep quality and potentially prevent the occurrence of delirium. It is not feasible to achieve a profound level of drowsiness using dexmedetomidine as the sole agent [30]. In a major randomized controlled trial (RCT) including a diverse population of mechanically ventilated patients in the intensive care unit (ICU), dexmedetomidine was employed as the primary sedative agent. It is noteworthy that two-thirds of the patients assigned to the dexmedetomidine group also received propofol. The study findings indicated that there were no significant differences in outcomes between the dexmedetomidine group and the propofol group [12]. In patients with acute respiratory distress syndrome (ARDS) who are in need of profound sedation, the use of intravenous midazolam or supplementary antipsychotic drugs may be necessary for those who do not achieve sufficient sedative levels with continuous opioids, propofol, and dexmedetomidine. Nevertheless, it has been observed that

benzodiazepines exhibit an elevated propensity for inducing delirium [28]. Volatile anesthetics, such as isoflurane and sevoflurane, have the ability to induce drowsiness ranging from mild to deep levels, even in patients who are challenging to sedate using benzodiazepines and opioids [31]. A randomized controlled trial conducted at a single site shown that the use of sevoflurane was linked to reduced awakening and extubation durations in comparison to intravenous administration of propofol or midazolam [32]. In a comparative study including ARDS patients, the administration of sevoflurane was found to result in enhanced oxygenation, as well as reduced levels of alveolar/systemic inflammation and lung epithelial injury [33]. The administration of sedation in the intensive care unit (ICU) via inhalation necessitates the use of specialist equipment, such as inline tiny vaporizers that provide humidification and antibacterial properties. Additionally, monitoring procedures are essential, including the measurement of tidal volumes, end-tidal gas concentrations to assess volatile agents, and monitoring of carbon dioxide levels and temperature to detect potential cases of malignant hyperthermia. Furthermore, adequate gas scavenging techniques should be employed to ensure the safe removal of waste gases. When employing a specialized ICU equipment for inhaled sedation, the utilization of heated humidifiers is precluded due to the inherent presence of heat and moisture exchange capabilities inside the device. It is imperative for the ICU staff to possess a comprehensive understanding of the technical considerations associated with the utilization of inhaled sedation in clinical settings [33].

Remifentanil is a pharmaceutical compound that belongs to the class of 4-anilidopiperidine derivatives of fentanyl. It is characterized by the presence of an ester connection to propanoic acid, which contributes to its pharmacological properties. The substance exhibits a brief duration of action and demonstrates analgesic properties, which align with its role as an agonist at the μ-receptor. In comparison to remifentanil, the major metabolite known as remifentanil acid exhibits minimal action. According to a study by reference [34], Remifentanil exhibits a quick onset of action, typically occurring within approximately one minute. Similarly, the drug demonstrates a prompt offset of activity after withdrawal, typically ranging from around three to ten minutes.

Several meticulously conducted trials have examined the comparative effectiveness of sedation using analgesia-based Therapeutic Efficacy with remifentanil, morphine, fentanyl, or sufentanil in patients ($n \geq 20$) undergoing post-surgical, trauma, and/or medical interventions, while receiving mechanical ventilation in an intensive care unit (ICU) environment. The administration of remifentanil demonstrated efficacy in providing analgesia-based sedation for mechanically ventilated patients inside the intensive care unit (ICU) environment. Remifentanil demonstrated a high rate of achieving optimal sedation, with a minimum of 78% of the time being dedicated to this state. Furthermore, the use of remifentanil demonstrated comparable durations of optimal sedation and similar percentages of hours in which patients experienced no or minor pain, when compared to the administration of fentanyl or morphine. Furthermore, when comparing remifentanil with other opioids such as fentanyl and morphine, it was often observed that there was a higher requirement for further sedation. However, this trend was not observed with sufentanil regimens. The efficacy of remifentanil was shown to be comparable to that of fentanyl, morphine, and sufentanil in relation to recovery parameters. Several studies, including one that investigated prolonged mechanical breathing, have found that remifentanil is linked to a considerably reduced duration of mechanical ventilation compared to fentanyl or morphine. Moreover, it has been shown in certain studies that remifentanil is linked to a notably reduced extubation time compared to fentanyl, morphine, or sufentanil. Additionally, remifentanil has been found to result in a shorter duration of time until discharge from the intensive care unit (ICU) when compared to fentanyl or morphine. Two studies have reported the lack of tolerance to remifentanil, whereas another study found that 29% of individuals receiving remifentanil developed tolerance. The findings of a prospective cost-consequence analysis indicate that the use of a regimen based on remifentanil may result in cost reductions related to staff expenses [33,35].

The implementation of a pain and sedation champion to strengthen evidence-based solutions is crucial. Since the 1970s, critical care pharmacists have been an integral part of multidisciplinary ICU teams, significantly influencing several aspects of patient care such as pain management and sedation [36]. According to the guidelines of the task force established by the American College of Clinical Pharmacy (ACCP) and the Society of Critical Care Medicine (SCCM), critical care pharmacists are responsible for assessing medication therapy, detecting side effects, and performing pharmacokinetic monitoring as part of their core services [37]. These services comprise the essential activities that the chosen champion must undertake to effectively manage the drug regimen for each

individual patient. The practice of sedation hygiene is of utmost importance and necessitates ongoing attention, as it entails the use of advanced pharmacological knowledge and expertise. Pharmacists have demonstrated their effectiveness in advocating for sedation hygiene and can assume a crucial role in customizing pain and sedative protocols to enhance patient outcomes [38].

Similar to previous investigations (39,40), the Ramsay scale was frequently employed to evaluate sedation levels. It is important to acknowledge that the Ramsay scale was not originally intended for assessing sedation in the intensive care unit (ICU) setting. Furthermore, its reliability and validity have been found to be only moderately satisfactory. Regardless of the specific sedation assessment tool employed (such as the Ramsay scale, Sedation-Agitation Scale, or Richmond Agitation-Sedation Scale), a significant portion of our patient cohort exhibited a profound level of sedation. Although the administration of sedatives decreased over time, there were no substantial alterations in the dosage of sedative agents during the initial week of their intensive care unit (ICU) admission. This finding aligns with the results of a recent survey conducted in Germany, which revealed a discrepancy between the intended amount of sedation and the actual level achieved [41].

Previous research has indicated that alert patients undergoing procedures have evaluated pain intensity levels ranging from 30 to 100 mm. Additionally, certain procedures have been identified as the most stressful experiences for patients in the intensive care unit [33,39]. Nevertheless, there was only one study that comprehensively documented the analgesic practices linked to typical procedures performed in the intensive care unit (ICU). In the aforementioned multisite study, which encompassed a total of 5,957 adult patients, it was observed that a minority of patients, namely less than 20%, were administered opioids either prior to or during six specific procedures. Furthermore, a significant majority of patients, amounting to 63%, did not get any form of analgesic medication. It is recommended to employ the Behavioral Pain Scale (BPS) when administering painful operations to patients who are unable to communicate, as a means of evaluating the effectiveness of analgesic measures. A higher incidence of pain behaviors was seen in patients who underwent procedures compared to those who did not have any procedures [41].

CONCLUSION:

Numerous sedation strategies have been investigated, encompassing interventions such as daily cessation of sedation and the implementation of goal-directed sedation algorithms. Medications may be administered through continuous intravenous infusion. However, it is crucial to note that active pharmaceuticals and their metabolites might build due to several factors mentioned earlier. Therefore, it is imperative to exercise caution and ensure that the medication dosage remains at a minimum level while still achieving sufficient analgesic and sedative effects. It is evident that there is a need to focus on developing suitable protocols and guidelines within the intensive care unit (ICU) setting. These protocols and guidelines should aim to promote the consistent utilization of sedation and pain scales, improve the management of procedural pain, and ensure the appropriate administration of sedatives and analgesics. These endeavors have the potential to yield significant enhancements in both patient comfort and therapeutic outcomes.

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