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Postoperative Sedation Options in ICU

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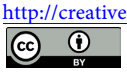

Abstract

This paper examines sedation options in ICU postoperative care. It highlights the necessity of sedation for patients' physical and mental comfort, safety, and reduction of delirium. The article advocates light sedation, primarily with non-benzodiazepines like propofol or dexmedetomidine, to improve outcomes. It introduces novel sedatives like ciprofol and remimazolam, suggesting they may be future alternatives in ICU sedation, although more research is needed.

Keywords

Light Sedation, Remimazolam, Ciprofol

1. The Necessity of Sedation

After surgery, patients may experience delayed recovery from anesthesia or require transfer to the intensive care unit (ICU) for continued monitoring and treatment based on their condition. Consequently, sedation treatment becomes necessary due to factors such as pain, restlessness, anxiety, intolerance for tracheal intubation, and human-machine confrontation with the ventilator [1]. Postoperative pain, a common occurrence, has been linked to adverse outcomes [2] [3] [4]. Furthermore, agitation following general anesthesia appears to be associated with the presence of postoperative indwelling catheters, endotracheal intubation, and patient characteristics indicative of preexisting mental health issues [5]. Critically ill patients often receive sedatives to alleviate anxiety, reduce the stress of mechanical ventilation, and prevent agitation-related injuries [6]. As a result, sedation treatment in the ICU has become a fundamental measure [7]. Moreover, sedation treatment not only affords physical and mental comfort (such as alleviating anxiety, promoting sleep, and mitigating negative memories to some extent) but also ensures safety and efficacy, particularly for mechanically

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ventilated patients, as well as organ protection by reducing the influx of noxious stimuli and alleviating sympathetic tension [7]. Additionally, sedation can lower the incidence of delirium and cognitive dysfunction, ultimately leading to improved patient prognosis to a significant extent [7]. Simultaneously, sedation has been found to reduce the production of inflammatory factors, thus contributing to improved patient outcomes [8]. A retrospective study examining the impact of deep sedation on the occurrence of early postoperative pneumonia and delirium following oral cancer reconstruction revealed that restless patients and those who were unable to receive sedatives were more likely to experience delirium and pneumonia [9].

2. Target Goal of Sedation

It has been shown in studies that early deep sedation is independently associated with delayed extubation and higher mortality [10]. Conversely, light sedation strategies have been found to reduce intensive care unit length of stay and ventilation time without negative impacts on patient mental health or safety [11]. The 2013 PAD guidelines recommend targeting light sedation or using daily wake-up trials, and minimizing benzodiazepines to improve short-term outcomes such as duration of mechanical ventilation and ICU length of stay [6]. Unless contraindicated, sedative drugs for adult ICU patients should be titrated to maintain light sedation [1] [7]. However, it is important to note that there is no universally accepted definition of light sedation [6]. The level of light sedation implies that the patient can wake up and follow simple actions, such as opening eyes, making eye contact, extending the tongue, making fists, and wiggling toes [1] [7]. Reliable and effective sedation scores such as the RASS score (−2 - 0 points) and SAS score (3 - 4 points) can be used for evaluation to determine the level of sedation [7] [12]. For most ICU patients, light sedation can effectively avoid over-sedation, ensuring patient comfort, safety, and wakefulness to enable easy weaning and extubation, aided by pain and delirium assessment, and facilitating early activities [13]. Although guidelines recommend light sedation, the quality of the evidence supporting this recommendation is not high. Studies comparing nosedation with light sedation and daily interruption of sedation have indicated no significant difference in patient prognosis between the two approaches [14] [15]. It is worth noting that sedation can suppress melatonin concentration [16], potentially affecting patient sleep quality and cell self-protective functions. Nosedation can influence the location of pressure ulcers in critically ill patients [17], mainly due to equipment use. Reducing unnecessary equipment usage may correspondingly reduce the risk of pressure ulcers in critically ill patients. A retrospective analysis of failed nosedation strategies in critically ill mechanically ventilated patients found that successful nosedation was associated with better hospital outcomes, while mortality and long-term outcomes were not affected by the success or failure of nosedation [18]. In conclusion, further randomized controlled trials are necessary to determine the most appropriate sedation strategy: deep seda-

tion, light sedation, or no sedation.

3. Sedative Drug Selection

Sedative drugs utilized in clinical practice are expected to possess certain characteristics, such as a rapid onset of action, a clear sedative effect, rapid metabolism, and an absence of apparent side effects on organ function [19] [20]. Presently, the most commonly employed sedative drugs include benzodiazepines (particularly midazolam), propofol, and dexmedetomidine [7]. According to PAD guidelines, non-benzodiazepines, such as propofol or dexmedetomidine, are recommended over benzodiazepines in sedation strategies to enhance clinical outcomes in mechanically ventilated patients [1]. This preference also extends to light sedation strategies. For instance, midazolam, one of the most commonly used benzodiazepines, is associated with a prolonged half-life and slow metabolism, which consequently delay patient awakening and extend mechanical ventilation time, resulting in prolonged extubation time, ICU stay, hospitalization time, and increased patient expenses [21]. Thus, reducing the utilization of benzodiazepines is crucial in preventing delirium and shortening its duration [7]. Nonetheless, the anxiolytic, amnestic, and anticonvulsant effects of benzodiazepines still hold significance in the sedation of ICU patients [7] [19] [22]. In a randomized controlled trial comparing midazolam, clonidine, and dexmedetomidine for preoperative anxiety in preschool children, midazolam was found to be more effective as an anxiolytic and less sedative [23]. Consequently, midazolam remains the primary choice sedative drug for certain critically ill patients necessitating prolonged sedation, despite its drawbacks.

In postoperative patient care, propofol is often preferred by clinicians due to its rapid onset of action, fast metabolism, and immediate recovery after drug withdrawal [19]. This choice aims to facilitate early awakening, extubation, and swift transfer out of the ICU. Studies have demonstrated propofol's superiority over midazolam in terms of safety and efficacy for endoscopic treatment of patients with liver cirrhosis and gastrointestinal bleeding [24]. However, a trial comparing the effects of midazolam and propofol sedation during endoscopic retrograde cholangiopancreatography in patients over 80 years old found no significant difference between the two [25]. Moreover, a randomized non-inferiority trial on medical thoracoscopy recommended against the use of propofol [26]. ICU patients, who often present with complex clinical conditions and rapid changes in health status, may experience propofol-related respiratory depression and decreased blood pressure, hindering the attainment of target sedation levels and impacting hemodynamics [19] [27]. Prolonged use of propofol can lead to propofol infusion syndrome, further restricting its utility [19] [28] [29]. Consequently, clinicians may only consider propofol for patients requiring blood pressure reduction or those with stable underlying hemodynamics.

Dexmedetomidine, a centrally acting α-2 agonist known for its sedative and analgesic properties, has been widely recognized for its role in the ICU [1] [7]. It

can effectively treat pain, agitation, and delirium in ICU patients, and studies have shown that it can reduce the occurrence of delayed cognitive impairment 1 week after cardiac surgery [30]. Additionally, in mechanically ventilated patients, dexmedetomidine has been found to improve patient prognosis, shorten mechanical ventilation time and hospital stay, and reduce total ICU costs when compared with sedative drugs such as benzodiazepines [31]-[36]. Moreover, a prospective randomized clinical trial published in 2018 revealed that patients sedated with dexmedetomidine had a lower incidence of postoperative delirium and postoperative cognitive impairment than those sedated with propofol; these patients were also found to be more likely to get out of bed and be discharged from the hospital earlier; however, there was no significant difference in complications [37]. In a study conducted by Winings NA *et al.*, it was found that dexmedetomidine is more suitable than propofol for long-term sedation treatment of critically ill trauma and surgical patients [38]. Furthermore, Rui Xu *et al.* found in a randomized controlled trial on the effects of dexmedetomidine and midazolam on cough and quality of recovery after partial and total laryngectomy that dexmedetomidine is an effective alternative drug in reducing cough and hemodynamic changes, and has a lower incidence of adverse events during the anesthesia recovery period after partial or total laryngectomy [39]. Similarly, an RCT study on the real-time evaluation of the independent analgesic efficacy of dexmedetomidine by XH Wang *et al.* found that dexmedetomidine has an independent analgesic effect, and systemic administration as an auxiliary drug is more effective than midazolam, providing a better analgesic effect without serious side effects [40]. In addition to its sedative and anti-delirium effects, dexmedetomidine has been discovered to reduce inflammatory response, stress, promote postoperative gastrointestinal function recovery, and reduce postoperative chills after cesarean section, among other benefits [41] [42] [43] [44]. However, its most common side effects are bradycardia and hypotension [1] [31]. For patients with underlying cardiac dysfunction or secondary cardiac insufficiency, the use of dexmedetomidine carries certain risks, and myocardial stunning can have serious consequences. Studies have demonstrated that dexmedetomidine sedation impairs cardiac systolic function [45]. Furthermore, a secondary cohort analysis of a randomized controlled trial (SPICE III) found that in patients aged 65 and younger who received a combination of dexmedetomidine and propofol sedation, prioritizing an increase in propofol dose was associated with a decrease in adjusted 90-day mortality rate, while an increase in dexmedetomidine may be associated with an increase in mortality rate [46]. In an RCT study on sedation of patients using dexmedetomidine for ICU mechanical ventilation, it was found that patients who received early dexmedetomidine sedation treatment had a similar mortality rate at 90 days compared to the conventional care group, and required additional sedatives to achieve the prescribed level of sedation; moreover, the dexmedetomidine group reported more adverse events than the conventional treatment group [47]. In mechanically ventilated adults in the ICU, a potentially important increase in body temperature has been associated with early

dexmedetomidine sedation, which may lead to misjudgment of treatment [48]. However, recent high-quality literature has confirmed that compared with propofol, dexmedetomidine for sedation in mechanically ventilated patients cannot reduce the patient's all-cause mortality, and the sedation effect is not as effective as propofol; furthermore, there were more adverse events related to slowed heart rate [49] [50].

Some studies have indicated that no drug is inherently superior to others in meeting clinical needs [7]. Other research [51]-[59] comparing the use of a single sedative drug with the combination of two sedative drugs has found that the combined application can yield similar efficacy with fewer adverse reactions and faster recovery, making it a potentially favorable option for ICU sedation. Additionally, studies [60] [61] [62] [63] [64] have explored the use of non-intravenous sedative drugs prior to surgery to enhance intraoperative satisfaction and postoperative recovery, potentially allowing for the achievement of target sedation while minimizing adverse effects associated with some sedative medications. In the context of ICU patients, it has been found that the use of sevoflurane for over 48 hours post-surgery can lead to faster return to spontaneous breathing, with sedation quality comparable to propofol-based regimens [65]. These findings suggest that exploring different sedation approaches may offer promising possibilities for improved patient outcomes.

4. Novel Sedatives

Ciprofol is a novel 2, 6-disubstituted phenol derivative which has demonstrated improved pharmacokinetics and pharmacological properties compared to propofol [66]. Studies have shown that the level of sedation or anesthesia induced by ciprofol is comparable to that induced by propofol in a non-operating room setting, and the safety profile of ciprofol is similar to that of propofol, with no reported pain during injection [67]. Moreover, research indicates that the sedative effect of 0.4 mg/kg of ciprofol is equivalent to 2 mg/kg of propofol; both ciprofol and propofol have demonstrated good tolerance and sedative effects and have been suggested for the sedation of mechanically ventilated patients in Chinese intensive care units [68]. Furthermore, a study on the application of propofol and ciprofol for postoperative ICU sedation among Chinese ICU patients receiving mechanical ventilation for 6 - 24 hours indicated that ciprofol was well tolerated and its sedation effect was not inferior to propofol [69]. Recent studies have also demonstrated that ciprofol can reduce epinephrine-induced oxidative damage, inflammatory response, and cardiomyocyte apoptosis [70]. This finding raises the potential for ciprofol to replace propofol. However, it is important to note that ciprofol has been associated with adverse reactions in experiments, including hypotension, bradycardia, and injection pain [68] [71] [72] [73].

Remimazolam is a short-acting benzodiazepine sedative drug [74] that induces sedation by binding to specific neurotransmitter (GABA) receptors in the brain [20]. It is mainly employed for anesthesia and sedation during endoscopic

procedures in China [19] [74], and has obtained approval for procedural sedation in the United States and Europe [75]. Compared with midazolam, remimazolam boasts advantages such as rapid onset of action, quick metabolism, and prompt recovery of patients upon discontinuation, thereby overcoming the drawbacks associated with the prolonged effects of midazolam [19]. Additionally, in comparison to non-benzodiazepine drugs like propofol and dexmedetomidine, remimazolam exerts a lesser inhibitory effect on respiration and circulation, thereby expanding its clinical utility [76]. During elective ERCP, patients administered with remimazolam experienced fewer instances of respiratory depression under deep sedation and also displayed hemodynamic advantages compared to those receiving propofol sedation [76]. Furthermore, remimazolam is well-suited for sedation of high-risk patients [19]. In a pilot study comparing remimazolam with propofol for long-term sedation in mechanically ventilated patients, remimazolam was demonstrated to be safe and effective [77]. However, its efficacy for postoperative sedation in the ICU has yet to be established [78]. Therefore, despite being an effective choice for short-term continuous sedation, particularly for ICU patients postoperatively, it is worth noting that some studies have demonstrated that remimazolam can impact circulation and breathing, which may serve as a limiting factor for its postoperative use [79] [80] [81].

5. Summary and Outlook

As medical treatment progresses and surgeries become more complex, patients experiencing critical conditions in the ICU following surgery require sedation that ensures safety and effectiveness, promotes faster recovery, and reduces the length of their ICU stay. In response to these demands, new sedative drugs such as remimazolam and ciprofol have emerged, exhibiting characteristics that are on par with traditional sedatives. Despite sharing some drawbacks with traditional sedatives, they are anticipated to serve as improved options for ICU sedation. However, there is a limited body of research on the use of these drugs for ICU sedation. Encouragingly, an increasing number of researchers are now undertaking relevant studies to address this gap in knowledge.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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