

Sedative Agents for Clinically Ill Patients

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Abstract

Introduction: Patients' agitation is a usual indicator of distress. In critically ill patients, distress is caused by various reasons: pain, fear/anxiety, dyspnea, or delirium are common among these patients.

Aim of Work: In this review, we will discuss Sedative agents use in critically ill patients, sedative medication properties and regimens.

Methodology: We did a systematic search for most recent available evidence regarding common sedative agents, their properties and use in critically ill patients.

Conclusion: In critically ill patients, distress is caused by various reasons: pain, fear/anxiety, dyspnea, or delirium are common among these patients; this is especially obvious if these patients are intubated or having difficulty communicating with their caregivers. Agitation due to distress may manifest clinically with ventilator asynchrony and vital sign abnormalities. Physicians' goal is to comfort patients with distress and attenuate increases in sympathetic tone. There is no single best sedative agent that is always superior in all clinical situations.

Keywords: *Sedative Agents; Ill Patients; Analgesic Medications*

Introduction

Sedative and analgesic medications are commonly discussed together due to the facts that pain is a usual cause of distress and patients' comfort is essential aim of management. Patients' agitation is a usual indicator of distress. In critically ill patients, distress is caused by various reasons: pain, fear/anxiety, dyspnea, or delirium are common among these patients; this is especially obvious if patients these are

intubated or having difficulty communicating with their caregivers [1]. Agitation due to distress may manifest clinically with ventilator asynchrony and vital sign abnormalities. Nevertheless, increased sympathetic tone due to distress has a negative physiological effects [2]. Physicians' goal is to comfort patients with distress and attenuate increases in sympathetic tone. Sedative-analgesic medications should be based on observed rather than anticipated distress to avoid the increased risk of over sedation which has been correlated to untoward clinical outcomes. There is no single best sedative agent that is always superior in all clinical situations. Sedative medication selection must be individualized according to patient characteristics, desired outcomes, contraindication, and clinical diagnosis. In this review we will discuss most common sedative agents with their properties and characteristics that influence their consideration. Selecting the right sedative, initiation, maintenance and withdrawal could be dedicated another review.

Methodology

As systematic search was conducted regarding most available evidence discussing the sedative agents and their properties. We have used PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant available and accessible articles were reviewed and included. The terms used in the search were: Sedative agents, Intensive care unit, critically ill patients, agitation in ICU, and relieving distress.

Causes of distress: identifying the causes and how to approach in non-pharmacological methods

Before considering any management plan, efforts should be directed toward possible causes of distress and agitation. Possible causes of agitation in critically-ill patients include anxiety, delirium, pain, dyspnea, and neuromuscular paralysis. These conditions may occur separately or concomitantly.

Anxiety is a sustained state of apprehension and autonomic arousal in response to real or perceived threats [1]. In critically ill patients, agitation commonly results from fear and frustration such as fear of death, suffering or inability to move or communicate. This may manifest clinically by nausea, headache, dyspnea and palpitations and diaphoresis among other symptoms of restlessness. Addressing adequately for the possible cause of anxiety is always ideal and may improve concomitant problems. For example, if inadequate ventilation causes dyspnea for the critically ill patient consequently leading to distress, sedating these patients appropriately, we can adjust the ventilator settings. Thus, strategies to correct hypoxia or dyspnea should be explored prior to the use of medications.

Delirium is defined as an acute and potentially reversible impairment of consciousness and cognitive function that fluctuates in severity [1]. The condition is associated with prolonged hospitalization and higher mortality rate in critically ill patients [3-5]. It is highly prevalent among ICU patients, however, delirium cases are frequently unrecognized in elder and in case of hypoactive delirium [6,7]. Experts have suggested to change the name of "hypoactive delirium" to "acute apathy syndrome" due to its different group of causes than "hyperactive delirium" [8]. Drug or alcohol withdrawal usually causes a hyperactive delirium [9]. Iatrogenic (as medications), environmental causes, and infections may be the underlying cause of delirium. Hence, it is essential to search for these factors before considering treatment plan. The initial presentation of acute delirium includes abnormal perception, and disorientation that is worsen at night. Investigations show diffuse slowing of brain activity by electroencephalography (EEG).

Pharmacological sedation is required in all patients undergoing neuromuscular blockade because neuromuscular paralysis without sedation is an extremely frightening and unpleasant sensation. It is worth mentioning that keeping critically ill patient paralyzed without adequate sedation does not mask the physiological response to stress. For example, Blood pressure and heart rate can correlate with patient discomfort in these cases.

Many evidence suggest early initiation of non-pharmacological strategies to alleviate patients' agitation. These strategies should be initiated simultaneously with methods directed toward distress causes. Reassurance, family involvement with regular visit, adequate and frequent communication with patients, preserving a normal sleep cycles, and cognitive-behavioral therapies (such as music therapy)

are suggested methods [10]. In one randomized trial with 140 mechanically ventilated patients, two strategies were examined. The first strategy involved no sedation with continuous verbal comfort and reassurance, while the second group underwent continuous sedation with daily interruption [11]. The trial concluded that patients in the first group with no sedation had more ventilator-free days, shorter ICU stay, decreased length of hospital stay, and fewer incidence of delirium. However, quality of life assessment, post-traumatic stress disorder and depression were similar between the two groups during 2 years follow up [12].

Common Sedative agents: Properties and regimens

Benzodiazepines: Benzodiazepines as midazolam and lorazepam are among the best sedative agents used in the intensive care unit (ICU). They can be infused intermittently or continuously with a relatively short duration of effect. Diazepam infusion is less commonly used to sedate patients in the ICU as is not suitable for continuous infusion. Benzodiazepines act on specific receptors in the gamma aminobutyric acid (GABA) receptor complex and promote the binding of this inhibitory neurotransmitter [13]. Low doses of benzodiazepine are used as anxiolytic whereas a higher doses have sedative, anticonvulsant, muscle relaxation effects. These agents cause respiratory and cardiovascular depression. The benzodiazepines differ in potency, rapidity, and duration of action however, they are no difference in effectivity in equipotent doses. Binding affinity for the GABA receptor determines the potency of benzodiazepine while the speed of crossing the blood-brain barrier determine the rapidity of action. Lorazepam has the highest binding affinity and the greatest potency while midazolam and diazepam are of lower affinities and potencies [14]. Contrarily, midazolam and diazepam are more lipophilic, hence, readily cross the blood-brain barrier and have a quicker onset of action. Repeated dosing leads to longer duration of action than initial intermittent infusion. This could be explained by lipophilic property that leads to rapid redistribution from the central nervous system to peripheral tissue sites. However, accumulation in fatty tissue occurs with repeated administration. Thus, more benzodiazepine is stored in obese patients rendering these patients to a greater risk for prolonged effects.

Propofol: Propofol is a common intravenous anesthetic that used as a sedative in agitated critically ill adults. The drug is applied as a continuous infusion in the ICU rather than an intermittent due to its association with dose- and rate-dependent hypotension. This was evidenced by a large observational study including a 25,981 patients receiving propofol, 15.7 percent developed hypotension; the majority of hypotensive episodes occurred within 10 minutes of induction via a bolus infusion [15]. Due its short duration of action, propofol is especially practical when rapid sedation and rapid awakening is desirable as in case of the need for frequent neurological examination or imaging. In comparison with midazolam and lorazepam, propofol infusions were associated with a lower mortality rate, shorter hospital stay, and weaning from mechanical ventilation (MV) as demonstrated by a multi-center analysis of more than 3000 ICU patients [16]. However, more data are needed to confirm this result. Another large trial concluded that propofol infusions with daily interruption resulted in significantly lower number of mechanical ventilation days in comparison with intermittent bolus of lorazepam [17]. Activation of the central GABA receptors with modulation of hypothalamic sleep pathways appear to be propofol mechanism of effect [18-21]. Propofol is a highly lipophilic agent that is insoluble in water. Therefore, it is formulated as an emulsion for intravenous administration. The emulsion is usually prepared by soybean oil or egg lecithin thus, the drug is considered contraindicated in patients with hypersensitivity to eggs, egg products, soy, or soy products. However, some reviews suggest a need for further evaluation of this issue [22,23]. Propofol has anxiolytic, anticonvulsant, and muscle relaxant effects with no direct analgesic effects. Due its high lipophilic character that aids a rapid cross of blood-brain barrier, the onset of action is usually of less than one minute. Propofol has a relatively very short duration of action that ranges from 3 to 10 minutes during short-term use (< 48 hours). This short duration reflects a rapid metabolism of propofol by the liver and elsewhere, however, hepatic or renal dysfunction does not affect its elimination. Propofol's accumulation in adipose tissue and duration of effect following long-term administration is poorly understood, however it has been suggested that repeated dosing lead to prolonged action in a similar mechanism to benzodiazepine [24]. Fospropofol is a water-soluble propofol prodrug that is metabolized to propofol, formaldehyde, and phosphate by alkaline phosphatase enzyme. The US food and drug administration (FDA) has approved Fospropofol for sedation in adults undergoing diagnostic or therapeutic procedures [25]. One study compared variable methods of fospropofol administration in addition to propofol, fospropofol was well-tolerated and effective for short-term sedation [26].

Dexmedetomidine is alpha-2-agonist agents that is highly selective and centrally acting. The central blockade leads to anxiolytic and sedative effects; some degree of analgesia may also occurs. Dexmedetomidine is safe sedative on respiration with no inhibitory effects. The US Food and Drug Administration (FDA) approved the usage of dexmedetomidine for initial sedation of mechanically ventilated patients for up to 24 hours. Beyond that 24 hour limit, there is a concerns of increasing the risk of withdrawal effects as hypertension. Although, such withdrawal effects have not been consistently found in studies [27,28]. Many studies have illustrated the role of Dexmedetomidine in reducing the duration of MV and ICU time when compared with traditional sedatives in the ICU [29-37]. A meta-analysis of 7 studies and 1624 patients found that the usage of dexmedetomidine is associated with 22 percent reduction in MV days and 14% in the length of stay [29]. However, the reliability of evidence regarded as low to very low. Studies compared it with midazolam have suggest that dexmedetomidine decreased the duration of mechanical ventilation by 1.7 to 1.9 [30-32]. One large randomized study aimed to compare dexmedetomidine with propofol. There was difference on the duration of mechanical ventilation [30]. However, multiple small studies have demonstrated a mixed effects [33,36,38]. Different types of studies have reported the effect of dexmedetomidine on risk reduction and duration shorting of delirium. Although, many studies showed no benefits when compared with other sedative agents in the ICU [29,30,32,39-45]. In one randomized trial on critically ill adults in the ICU comparing it with placebo, low-dose nocturnal dexmedetomidine prevent the development of delirium in these patient by 26 percent without altering sleep quality or any other adverse effects [46]. Dexmedetomidine does not appear to have benefits on mortality rate. An open-label randomized trial including 4000 patients who were mechanically ventilated for less than 12 hours, dexmedetomidine was compared to usual care [47]. Mortality rate after 3 months of follow up was exactly the same between the two groups. Moreover, patients receiving dexmedetomidine required supplemental sedative agent to achieve the target of sedation. However, a small decrease in mortality was found in postoperative patients undergoing cardiac surgery [29,40]. Dexmedetomidine carries the benefits of being more cost-effective than other sedative agents [35]. Transitioning from dexmedetomidine to oral clonidine may be a safe and cost-effective way to continue sedation with a centrally acting alpha-2-agonist in patients who are hemodynamically stable and have a functional gastrointestinal tract [48].

Antipsychotics: Antipsychotics, as haloperidol, is widely used to treat delirium in critically ill patients in the ICU. Intravenous haloperidol has a mild sedative effect in dose-dependent manner with minimal depressive effects on respiration and circulation. Haloperidol and the other neuroleptics antagonize dopamine and other neurotransmitters. However, their precise mechanism of action is poorly understood. Its rapidity of actions ranges between 5 to 20 minutes with a variable duration of effect that depends upon the cumulative dose. Evidence is lack about its role in reduction of mechanical ventilation duration or delirium duration. Some studies concluded that haloperidol does not appear to prevent or decrease the duration of delirium in these patients. Hence, guidelines make no recommendation favoring its use over other anti-psychotics for delirium [9,49]. One randomized trial on critically ill patients at risk of delirium reported that compared with placebo, 2 mg of intravenous haloperidol three times a day did not affect the incidence of delirium, survival, duration of MV, or length of ICU stay [50]. Another randomized trial aimed to compare haloperidol with placebo in ICU patients with hyperactive or hypoactive delirium, there was no difference in survival without delirium or coma [51]. There was also no difference in 30 or 90 day mortality, duration of mechanical ventilation, or time to ICU or hospital discharge.

Atypical antipsychotics: Atypical antipsychotics as quetiapine and olanzapine, risperidone and ziprasidone have also been used in adult ICU patients to treat delirium. Despite some evidence suggests delirium improvement in critically ill patients by oral antipsychotic [52,53], there is a paucity of data about outcomes, efficacy, or safety of oral atypical antipsychotics in comparison to haloperidol and to one another. The few existing studies suggest similarity in efficacy and safety of oral atypical antipsychotics compared with haloperidol [52,54,55]. Further studies are needed to validate the role of haloperidol or oral atypical antipsychotics in sedation of critically ill patients.

Ketamine: Ketamine is an intravenous anesthetic agent with analgesic and bronchodilator properties in smaller doses. It exerts its action by non-competitive blocking of NMDA receptors in the sensory ending. Other actions in sub-anesthetic doses include opioid and muscarinic agonist activities, and nicotinic receptor antagonist [56]. Ketamine stimulate the sympathetic autonomic system and thus

does not cause cardiovascular depression. Normal blood pressure is preserved or even could be elevated. Hence, it is contraindicated in patients at risk of elevated blood pressure. Ketamine is highly lipophilic, thus has a very rapid onset of action is of one minute and a duration of action of 10 to 15 minutes. Ketamine is rarely used in the adult intensive care unit (ICU) and it is not approved for that. However, off-label use in the ICU include procedural sedation or analgesia, or as adjunct to opioid analgesia for non-neuropathic pain are off-label use [49]. Ketamine produces what called a “dissociated anesthesia”, in which conscious level, spontaneous breathing, and intact brain stem reflexes are preserved. Randomized studies on patients with burns have suggested that oral ketamine provides better analgesia during painful procedure than dexmedetomidine or the combination of midazolam, acetaminophen, and codeine [57,58]. Some experts suggested that ketamine use reduce the amount of opioid need in postoperative patients [58]. More studies are needed to examine the roles of Ketamine in sedation of critically ill patients in the intensive care unit.

Conclusion

In critically ill patients, distress is caused by various reasons: pain, fear/anxiety, dyspnea, or delirium are common among these patients; this is especially obvious if patients who are intubated or having difficulty communicating with their caregivers. Agitation due to distress may manifest clinically with ventilator asynchrony and vital sign abnormalities. Physicians’ goal is to comfort patients who are in distress by attenuating their sympathetic tone. There is no single best sedative agent that is always superior in all clinical situations. Benzodiazepines as midazolam and lorazepam are among the best sedative agents used in the intensive care unit (ICU). A higher doses of benzodiazepine have sedative, anticonvulsant, muscle relaxation effects. Propofol is a common intravenous anesthetic that used as a sedative in agitated critically ill adults. Dexmedetomidine is alpha-2-agonist agents that is highly selective and centrally acting. Its central effects leads to anxiolytic and sedative outcomes. Antipsychotics, as haloperidol, is widely used to treat delirium in these patients whereas Ketamine is rarely used in the ICU.

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