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Sedation in the Critically Ill

Evidence Based Medicine Guideline

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SUMMARY
Sedation is an essential component of care for critically ill patients. Each sedative medication possesses specific properties, risks and benefits, which must all be considered in choosing an appropriate therapy. The primary goal should be addressing patient comfort through adequate pain control followed by anxiolysis through an appropriate sedation regimen. Propofol and dexmedetomidine should be used as first line agents for sedation over benzodiazepines in critically ill, mechanically ventilated adult patients.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Pain management should be guided by routine pain assessment and addressed before a sedative agent is considered.**
    - **Continuous infusion opioids, such as fentanyl, may be used as part of an analgesia-first sedation strategy prior to adding additional sedative agents.**
    - **Opioids may also be used as an adjunct to a first line sedative agents in order to achieve the desired level of analgosedation.**
  - **Sedatives should be titrated to the appropriate level of desired sedation based on the Richmond Agitation Sedation Scale (RASS).**
  - **Propofol or dexmedetomidine should be used as first line agents over benzodiazepines in critically ill, mechanically ventilated adults.**
  - **Ketamine, at sedative doses (0.5-5 mg/kg/hr), may also be an alternative for patients without contraindications (noted below).**
  - **Ketamine, at sub-dissociative doses (<0.5 mg/kg/hour IV), may be considered in patients with moderate to severe pain to decrease opioid requirements.**
  - **Benzodiazepines should be used as a last line sedative agent, in most patients, due to the high correlation with ICU delirium.**
- **Level 3**
  - **Propofol is the sedative of choice when rapid neurologic assessment is needed, or intracranial hypertension is present.**
  - **Ketamine should be avoided in patients with coronary artery disease, arrhythmias, inability to tolerate an increase in blood pressure/heart rate, severe pulmonary secretions, glaucoma, or psychiatric history (see "Ketamine for Analgesia" guideline).**
  - **Benzodiazepines are the treatment of choice in patients with alcohol withdrawal or seizures/status epilepticus (see "Alcohol Withdrawal" guideline).**

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Sedation is an essential component of care for the critically ill patient. The goal for sedation in the ICU is to provide comfort in the form of anxiolysis and facilitate mechanical ventilation or invasive procedures. Anxiety is a psychophysiological response to real or imagined danger, while agitation refers to excitement accompanied by motor restlessness. An ideal regimen should control anxiety and agitation and provide amnesia while minimizing adverse effects. Selection of drug therapy should be based on identification and differentiation of pain, anxiety, agitation, and delirium. Monitoring tools frequently include subjective assessments by caregivers or sedation scales. Inappropriate therapy may result in adverse drug reactions, prolonged mechanical ventilation, extended ICU stays, and increased costs. Sedatives routinely used in the ICU setting include propofol, dexmedetomidine, benzodiazepines, and ketamine. When determining which sedative agent to use, it is important to understand the properties, pharmacokinetics, and adverse effects of each agent. This includes onset and offset of action, ease of administration, mode of metabolism and excretion, side effect profile, drug interactions, and cost-effectiveness.

LITERATURE REVIEW

Sedation Assessment

Prior to initiation of sedation, it is important for health care providers to determine the indication for using these agents. Providers must also frequently reassess a patient's condition to determine the duration and level of sedation appropriate for the patient. Several sedation assessment scales have been developed to objectify a patient's need for sedation as well as determine their current level of sedation in order to titrate appropriate agents. Per SCCM guidelines, all ICU patients should be assessed routinely using the Richmond Agitation-Sedation Scale (RASS).

The Richmond Agitation-Sedation Scale (RASS) is a 10-point scale used to determine a patient's level of anxiety and/or agitation versus depth of sedation. The 10-point scale is further divided into four levels of agitation (+1 to +4), one level to represent a calm and alert state (0), and five levels of light to deep sedation (-1 to -5). In a trained individual, this assessment can be completed in 30-60 seconds using three components: observation, response to verbal stimulus, and response to physical stimulus. According to Sessler and colleagues, there is a high inter-rater reliability among nurse educators and RASS trained bedside nurses (r = 0.964) (1). This robust inter-rater reliability was demonstrated for patients from medical, surgical, cardiac surgery, and neuroscience ICUs in patients with and without mechanical ventilation (2).

Richmond Agitation-Sedation Scale (RASS)

Scale	Score	Description
Combative	4	Combative, violent towards staff
Very agitated	3	Pulls at tubes and/or catheters, aggressive towards others
Agitated	2	Frequent non-purposeful movement
Restless	1	Anxious, restless movements
Alert & calm	0	Awake and alert, calm
Drowsy	-1	Not fully alert, sustained awakening
Light sedation	-2	Awakens for < 10 seconds
Moderate sedation	-3	Movement and eye opening to voice
Deep sedation	-4	No response to voice, but opens eyes to physical stimulation
Cannot be aroused	-5	No response to verbal or noxious stimulus

Sedation Agents

Propofol is an anesthetic agent with sedative-hypnotic and anticonvulsant properties. It is commonly used due to its rapid onset and offset of action. Like benzodiazepines, this agent exerts its effects on the GABA receptor in the central nervous system via an alternate binding site. Propofol is metabolized through the liver by conjugating to inactive metabolites and is ultimately excreted through the renal system (3-4). The most common adverse effect associated with propofol is hypotension secondary to its vasodilatory effects. Other potential effects include hypertriglyceridemia and pancreatitis, which are associated with prolonged infusions of high dose propofol. Propofol infusion syndrome (PRIS) is a rare but potentially fatal adverse effect characterized by arrhythmias, metabolic acidosis, rhabdomyolysis, hyperkalemia and cardiac arrest (3-5). This is typically seen with infusion rates >5mg/kg/hr for a prolonged duration (>48 hours) with a mortality rate reaching up to 85% (6).

Dexmedetomidine is an anesthetic agent which acts as an alpha-2-agonist and carries both sedative and analgesic properties but lacks anti-convulsant properties (3-5). This agent is unique in that it has eight times the affinity to alpha-2 receptors when compared to clonidine, however, it does not appear to cause significant effects on respiratory drive. As a result, it is commonly used in non-ventilated patients and mechanically ventilated patients near extubation. It is not necessary to discontinue this agent prior to extubation (4). During continuous infusion, dexmedetomidine can cause vasodilation resulting in hypotension. Therefore, a bolus prior to continuous infusion is not recommended.

Benzodiazepines function by binding to gamma-aminobutyric acid type A ($GABA_a$) within the central nervous system. As a result, these agents have sedative, amnestic, anxiolytic, and anticonvulsant properties (3,4, 6-8). The most commonly used benzodiazepines used in the ICU setting are midazolam (Versed), lorazepam (Ativan), and diazepam (Valium). Midazolam is metabolized through the cytochrome P_{450} system within the liver to produce the active metabolite, 1-hydroxymethylmidazolam (3,4). This compound is excreted in the urine and can accumulate in patients with renal failure. In addition, due to its metabolism via the cytochrome P450 enzymes, the potential for drug interactions must be considered when using this agent. Lorazepam is a long-acting agent that is metabolized in the liver to its inactive form. High dose lorazepam is associated with the risk of toxicity from propylene glycol which results in an anion gap metabolic acidosis (3-5). While both agents can be used for sedation, Barr and colleagues found that during maintenance sedation, midazolam and propofol were superior in achieving optimal levels of sedation overall when compared to lorazepam. This study also demonstrated prolonged intubation time in patients who received lorazepam (5).

Ketamine is a dissociative agent that acts through antagonism of N-methyl-D-aspartate (NMDA) receptors causing functional and electrophysiological dissociation. It is believed to block afferent impulses associated with pain from returning to the central nervous system. Through NMDA receptor antagonism, ketamine attenuates centrally-mediated pain processes to reduce the development of opioid tolerance and opioid-induced hyperalgesia. In addition to action on NMDA receptors, ketamine also acts as a weak opioid receptor agonist, alpha-1 and beta-2 receptor agonist and muscarinic acetylcholine receptor inhibitor (6). The analgesic properties of ketamine are observed at subanesthetic doses (<1 mg/kg IV bolus dose and <0.5 mg/kg/hr IV continuous infusion). Higher dosing of ketamine is required to achieve sedation. When used for sedation, ketamine continuous infusion should be initiated at 0.5 to 1 mg/kg/hr and then titrated to an upper dose range of 4 to 5 mg/kg/hr. Ketamine has sedative, amnesic, and analgesic properties without causing respiratory depression or hypotension (7). Adverse effects include neurologic (psychotomimetic effects), cardiovascular (hypertension and tachyarrhythmias), and respiratory (hypersalivation and laryngospasm). Psychotomimetic effects are dose-dependent; therefore, the risk of development is higher with increased doses. Psychotomimetic effects occur in 7-8% of patients given sub-dissociative doses compared to 3.6-5% in placebo patients (6).

Selecting Sedative Agents

Several trials have compared various sedative agents in an effort to determine whether one is superior to the rest. Jakob and colleagues compared the effects of dexmedetomidine and midazolam and propofol in mechanically ventilated patients requiring long term sedation. This study concluded that dexmedetomidine was comparable to midazolam and propofol in maintaining light to moderate sedation and ultimately reduced duration of mechanical ventilation (13, 14). Both the SEDCOM and MENDS trials found a greater incidence of bradycardia in the dexmedetomidine group, but neither study found a significant intervention was required for the bradycardia (15, 16). The MENDS trial evaluated short term sedation (</=120 hour) comparing dexmedetomidine and lorazepam in a mixed medical and surgical ICU population. Patients receiving dexmedetomidine had significantly less delirium and coma time compared to the lorazepam group (16). Delirium itself is an independent risk factor for prolonged length of stay, greater neuropsychological dysfunction, and increased mortality and therefor all efforts should be made to avoid using agents that worsen delirium (17). The MENDS trial did not evaluate time to extubation, ICU or hospital length of stay (16). Another prospective, double blind, randomized trial reported that patients spent similar time within target sedation level between dexmedetomidine and midazolam. However, the dexmedetomidine group had shorter time to extubation than midazolam treated group (3.7 vs. 5.6 days) (18).

Table 1: Commonly used Sedatives in the ICU

Drug	MOA	Loading	Rate	Onset	Duration	Pharmacokinetics	Side effects
Propofol	GABA agonist, alternate binding site	Do NOT bolus	10mcg/kg/min Range: 5-50 mcg/kg/min	<1 minute	5 - 10 minutes	$T_{1/2}$ 30-60 min after infusion; longer with prolonged infusion due to lipophilic properties; metabolized by hepatic glucoronidation	Hypotension due to vasodilation, PRIS, pancreatitis, hypertriglyceridemia, green urine (8, 9)
Dexmed-etomidate (Precedex)	Alpha-2-agoinst	Do NOT bolus	0.2mcg/kg/hr Range: 0.2-1.5 mcg/kg/hr	5-10 minutes	60-120 minutes	$T_{1/2}$ 2hr, accumulates with prolonged infusion, metabolized by hepatic glucoronidation and oxidation, no active metabolites	Transient hypertension followed by hypotension, bradycardia, dry mouth, nausea (9)
Ketamine	NMDA antagonist	0.5mg/kg	0.5mg/kg/hr Range: 0.5-5 mg/kg/hr	<1 min	1-2 hours	$T_{1/2}$ 2.5 hours Metabolized via the CYP450 enzyme system in the liver with renal excretion	Dose dependent; dissociative state, nausea, vomiting, respiratory depression at high doses (6, 9)
Midazolam (Versed)	GABAa agonist	2-6mg	1mg/hr Range: 1-15 mg/hr	1-5 min	1-2 hours	$T_{1/2}$ 3-11hr; metabolized by hepatic cytochrome p450; renal excretion of active metabolites; lipophilic	Delirium, respiratory depression, hypotension (10)
Lorazepam (Ativan)	GABAa agonist	1-4mg	1mg/hr Range: 0.5-8 mg/hr	5-20 minutes	2-6 hours	$T_{1/2}$ 8-15hr; metabolized by hepatic glucoronidation, no active metabolites, offset more predictable	Delirium, respiratory depression, hypotension (10)

Table 2: Commonly used Analgesics in the ICU

Drug	MOA	Loading	Rate	Onset	Duration	Pharmacokinetics	Side effects
Fentanyl	Mu-selective opioid agonist	1-2 mcg/kg	Titrate to CPOT>2 Range: 0-500mcg/hr	1-2min	30-60 mins	$T_{1/2}$ 1.5 hours Highly lipid soluble Accumulation in liver impairment No active metabolites Minimal vasodilatory effects	Respiratory depression, drowsiness, euphoria, narcotic ileus (11, 12)
Ketamine	NMDA antagonist	0.5mg/kg	0.5mg/kg/ hr Range: 0.5-5 mg/kg/hr	<1 min	1-2 hours	$T_{1/2}$ 2.5 hours Metabolized via the CYP450 enzyme system in the liver with renal excretion	Dose dependent; dissociative state, nausea, vomiting, respiratory depression at high doses (6)
Hydro-morphone (Dilaudid)	Mu-selective opioid agonist	0.025 – 0.05mg/kg	Titrate to CPOT>2	5-15min	2-4 hours	$T_{1/2}$ 2-3 hours Moderately lipid soluble, delayed effects Accumulation in liver impairment Metabolites: Hydromorphone-3-glucuronide - neuroexcitatory	depression, drowsiness, euphoria, narcotic ileus (8, 9)
Morphine	Mu, Kappa , delta opioid agonist	0.1mg/kg	Titrate to CPOT>2	5-10min	3-4hours	$T_{1/2}$ 1.5-2 hours Vasodilatory effects Metabolites: Morphine 3-glucuronide – neuroexcitatory, no analgesia Morphine 6-glucuronide - analgesic	Hypotension Respiratory depression Narcotic ileus (12)

CPOT = Critical Care Patient Observation Tool

Ketamine is emerging as another of the newer agents being used for sedation and analgesia in the ICU population. Perbet and colleagues conducted a double-blind placebo-controlled randomized trial involving mechanically ventilated ICU patients receiving low doses of ketamine in addition to either midazolam or propofol to assess the potential for decreased opiate consumption and the impact on decreasing delirium. This study found that ketamine use did not decrease opiate use in ICU patients, however, it did demonstrate a decreased incidence of delirium and duration (5). This can have a profound impact on ICU patients as it has been found that ICU patients that develop delirium are three-times more likely to die by 6 months than those who do not, with each additional day of delirium being associated with a 10% increase in the risk of death (19). Larger randomized controlled trials comparing the use of ketamine as the primary sedative with other common sedatives are limited. Umunna and colleagues conducted a single center, retrospective yearlong study of patients requiring sedation for >24 hours in which ketamine was utilized as the primary agent. The study was limited in its sample size, however, it revealed similar rates of adverse effects with other common sedatives such as propofol and benzodiazepines (20,21). Larger comparative studies are needed but ketamine is promising due to its proven decrease in delirium, ability to use with hypotensive patients, amnestic and analgesic properties.

For Analgosedation of a specific injury type, please reference the guideline for the specific injury.

- Burn Injuries: “Ketamine for Anesthesia: Analgesia in Trauma Patients and Analgesia in Burn Dressings”.
- Traumatic Brain Injuries: “Severe Traumatic Brain Injury Management”

Other related analgesia guidelines on SurgicalCriticalCare.net:

- “Alcohol Withdrawal”
- “Pain Management in Surgery”
- “Gabapentin for Post Operative Pain”
- “Delirium management in the Surgical Patient”

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