

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

SEDATION AND AGITATION MANAGEMENT

SUMMARY

Sedation is an essential component of care for critically ill patients necessitating appropriate selection and monitoring of drug therapy. Each sedative agent possesses specific risks, benefits, and economic cost, which must all be considered in choosing an appropriate therapy. It is important to recognize that while sedative agents may provide anxiolytic, amnestic, sedative-hypnotic, anticonvulsant, and muscle relaxant effect, they do not have an analgesic effect. Midazolam and propofol are appropriate where short-term sedation is necessary, while lorazepam and diazepam are appropriate for long-term sedation. Due to its cost and risk profile, propofol should be reserved for patients in whom conventional sedation has failed, rapid assessment of neurologic function is necessary, or intracranial hypertension is present.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Sedatives should be titrated to a Riker Sedation-Agitation Scale (SAS) score of 3 to 4.**
 - **Midazolam is the drug of choice for short-term anxiolysis (<= 72 hours) in ventilated patients. Intermittent administration is preferred.**
 - **Lorazepam is the anxiolytic of choice for patients anticipated to be ventilated for 24 hours to 5 days.**
 - **Propofol should be reserved for the following patient populations:**
 - **Failure of conventional sedation**
 - **Need for rapid neurologic assessment**
 - **Presence of intracranial hypertension**
- **Level 3**
 - **Oral diazepam can be used for long-term anxiolysis (anticipated time on ventilator greater than 5 days).**
 - **Dexmedetomidine may have a role in the ICU sedation, however, it should be evaluated on a case by case basis.**

INTRODUCTION

Sedation is an essential component of care for the critically ill patient. The goal for sedation in the ICU is to provide comfort and anxiolysis, and facilitate mechanical ventilation or procedures. An ideal regimen should control anxiety and agitation, and provide amnesia while minimizing adverse effects. Practices of ICU sedation vary widely. Monitoring tools frequently include subjective assessments by caregivers or sedation scales that are not validated. Inappropriate therapy may result in adverse drug reactions, prolonged mechanical ventilation, extended ICU stays, and increased costs.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

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.

Selection of drug therapy is based on identification and differentiation of pain, anxiety, agitation, and delirium. Anxiety is a psychophysiologic response to real or imagined danger, while agitation refers to excitement accompanied by motor restlessness. Benzodiazepines and propofol have been extensively studied in critically ill patients. Benzodiazepines are considered first-line agents for the management of anxiety and agitation (Table). Midazolam has a short half-life and undergoes hepatic metabolism to an active metabolite. Substantial accumulation may occur with high doses or prolonged infusions. Lorazepam has an intermediate half-life and is glucuronidated in the liver, but has no active metabolites to accumulate. Diazepam has a long half-life and is hepatically metabolized to several active metabolites. Propofol is classified as a short acting sedative-hypnotic agent and is useful in the management of refractory intracranial hypertension; however, its ability to reduce ICP is dose dependent (>50 mcg/kg/min). Its use has been associated with hypotension, metabolic acidosis, rhabdomyolysis, methemoglobinemia, and potentially life-threatening bradyarrhythmias (see Propofol guideline).

LITERATURE REVIEW

Sedation Assessment

Despite the widespread use of sedatives, there are few well-designed trials addressing optimal drug therapy. Most existing studies did not use a validated sedation scale. Many were not blinded and confounding variables (analgesic use and neuromuscular blockade) were not controlled. Endpoints were variable and the “ideal” level of sedation was not consistent among studies.

Riker and colleagues performed a study to test the Riker Sedation-Agitation Scale (SAS) for reliability and validity in adult ICU patients (1). The SAS includes seven levels of agitation, ranging from dangerous agitation to unarousable. Paired evaluators (experienced ICU nurses) simultaneously and independently scored patients using the SAS, Ramsey, and Harris scales. Reliability was confirmed for all scales by the high interrater proportion of agreement (0.95). Validity was established based on a high correlation with the Ramsey and Harris scales.

Sedative Agents

Ostermann and colleagues conducted a systematic review in ventilated ICU patients to determine which sedatives were associated with optimal sedation, shortest time to extubation, and shortest length of ICU stay (2). Studies assessing short term sedation were analyzed separately from those assessing long term sedation. Nine trials evaluating short-term sedation (less than 24 hours) in surgical or mixed ICU patients were identified. Six compared midazolam with propofol. Propofol provided a better quality of sedation in three trials, while the remainder reported no difference. Only three trials evaluated time to extubation and reported propofol to be superior. Length of ICU stay was not addressed. Of the studies assessing long-term sedation (greater than 24 hours), seven compared midazolam with propofol and one compared midazolam with lorazepam. Quality of sedation for both midazolam and propofol was comparable. Time to extubation was shorter with propofol, although this was not statistically significant in all trials. A single study reported no difference in length of stay between midazolam and propofol. No difference in quality of sedation was found in the trial comparing midazolam with lorazepam.

A recent systematic review further examined randomized trials of sedative agents in patients with respiratory failure who required mechanical ventilations (3). Findings are similar to the previous review where both propofol and midazolam provide adequate level of sedation. Although not statistically significant, propofol appears to have faster time to recovery than midazolam. No significant difference was detected between lorazepam and midazolam in terms of level of sedation and time to recovery. Due to a lack of rigorous clinical trials, no conclusive statement can be made regarding a preferred sedative agent in the ICU and therapeutic decisions are left to individual clinicians.

In search for an ideal sedative therapy, dexmedetomidine, an alpha-2 agonist, has generated much interest in the ICU setting. Dexmedetomidine has eight times stronger affinity to alpha-2 receptor compared to clonidine, and does not appear to cause respiratory depression compared to other sedatives such as benzodiazepine or propofol. These properties suggest that dexmedetomidine may be an ideal sedating agent for those who are mechanically ventilated, and may lead to shorter ventilator days and ICU days. However, conflicting results have been reported on the role of dexmedetomidine in the ICU.

The MENDS trial evaluated short term sedation (<=120 hr) comparing dexmedetomidine and lorazepam in a mixed medical and surgical ICU population (Grade 1) (4). Patients receiving dexmedetomidine had significantly less delirium and coma time compared to the lorazepam group. However, the study did not evaluate time to extubation, ICU or hospital length of stay. MacLaren et al. retrospectively assessed dexmedetomidine as an adjunctive sedation agent in mixed ICUs (Grade 2) (5). While dexmedetomidine reduced other sedative requirements, it failed to alter analgesic requirements and reduce agitation. Interestingly, adequate sedation was achieved less frequently during dexmedetomidine administration compared to prior to its initiation (47.9% vs. 64.6%; p=0.001). Another prospective, double blind, randomized trial reported that patients spent similar time within target sedation level between dexmedetomidine and midazolam (6). However, the dexmedetomidine group had shorter time to extubation than midazolam treated group (3.7 vs. 5.6 days).

Dexmedetomidine has also been investigated for management of ICU-induced delirium and shivering control during therapeutic hypothermia therapy. Reade et al. evaluated dexmedetomidine vs. haloperidol infusion in 20 mechanical ventilated patients in an open label trial (7). Patients received standard interventions such as propofol, midazolam, or morphine during the study. The dexmedetomidine group had significantly shorter time to extubation than the haloperidol group, however, no assessment of incidence of delirium was described. Several studies suggest dexmedetomidine with or without meperidine may reduce shivering threshold, however, these studies were done primarily in a postanesthesia setting or in healthy volunteers (8-12). Therefore, its usage in therapeutic hypothermia is based on extrapolation. While preliminary data appear to be promising, randomized trials are needed to justify the routine use of this agent in these settings.

Further references regarding the use of sedative agents in the ICU can be found in the American College of Critical Care Medicine / Society of Critical Care Medicine practice parameters for ICU sedation (13).

Drug	Onset	DOA	T1/2	Special considerations
Lorazepam	3-7 min	120 min	10-20 hr	<ul style="list-style-type: none"> • IV and PO liquid formulation contain propylene glycol • Average cost \$15.6/24 hr (@ 2mg/hr)
Midazolam	1-5 min	15-60 min	2-11 hr	<ul style="list-style-type: none"> • Active metabolites; lipophilic • Prolonged sedation likely in obese patients or >72 hour infusion • Average cost \$18.6/24 hr (@ 5mg/hr)
Diazepam	<2 min	15-60 min	20-120 hr	<ul style="list-style-type: none"> • Active metabolite; highly lipophilic • Average cost \$3.54 (20mg/day)
Propofol	<1 min	5-10 min	~24 hr	<ul style="list-style-type: none"> • Propofol infusion syndrome is likely associated with high dose and prolonged infusion (>48 hr) • Average cost \$22.8/24 hr (@ 30mcg/kg/min)
Dexmedetomidine	---	2.5-4 hr	2-4 hr	<ul style="list-style-type: none"> • Possess analgesic sparing effect; potential anxiolytic and anti-shivering effect • Average cost \$358.68/24 hr (@ 0.7 mcg/kg/hr)
Ketamine	20-60 sec	10-15 min	2-3 hr	<ul style="list-style-type: none"> • Minimal effect on respiratory drive • May increase HR/BP and ICP • Average cost \$90.42/24 hr (@ 10 mcg/kg/min)

* Cost are based on intravenous dose and 70 kg body weight

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