Sedation and Analgesia in the Intensive Care Unit

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Introduction
Critically ill patients in the intensive care unit (ICU) requiring mechanical ventilation frequently experience pain, anxiety, sleep deprivation and distress. Sedation and analgesics are commonly used to provide comfort and relieve pain. Commonly used agents include benzodiazepines, propofol, opioids and the newer agents, remifentanil and dexmedetomidine.

There is now an increasing awareness that important complications from sedative agents and the way they are used, can occur.1 Oversedation can prolong weaning from ventilation and ICU duration of stay.2 Undersedation may contribute to increased sympathetic activity, myocardial ischaemia, poor ventilator synchrony, hypercatabolism, immunosuppression and accidental dislodgements of lines and tubes. Finally, sedation and analgesia may increase delirium, which can occur in up to 80% of ICU patients, without achieving increased comfort.

Current practice varies widely.1,3 New trends and research are therefore focused not only on which is the best pharmacological agent, but also on monitoring the depth and adequacy of sedation and protocols sedation use.

Indications for Sedation
Appropriate evaluation and management of causes of distress are essential to optimal management of sedation. Preexisting medical conditions such as alcohol or substance abuse, chronic sedative use, psychiatric illness, alzheimers, gout, chronic pain may contribute to the experience of distress and influence choice of agent.4 Identifying new causes of pain related to the acute illness is also crucial. Management of root causes such as bedsores, wound infections and changing medical conditions should not be masked by use of sedatives. Simple measures such as frequent turning, removing restraints if possible, or minimizing light and noise to allow night time sleep patterns may also improve patient comfort. Communication and explanation to the patient during interventions can significantly allay anxiety.

Pharmacological intervention should be considered only after treatable predisposing and precipitating factors have been managed, prior psychiatric and pain medications have been resumed, and the ICU environment has been optimized for patient comfort.

Monitoring of Sedation and Analgesia
Pain evaluation in the ICU is generally poorly done. Patient self reporting with a visual analogue scale (VAS) is most preferred, although often difficult in the ICU setting. Table 1 shows the Critical Care Pain Observation Tool.5

Sedation scales such as the Ramsay Sedation Scale, The Richmond Agitation Sedation Scale (RASS), Sedation Agitation Score, and Motor Activity Assessment Scale are shown in Table 2 and have all been validated for use in the ICU.6 Whilst such sedation scales allow better documentation, reduced sedation and analgesic use, and shorter duration of ventilation, widespread use has not yet been adopted.6,7

Objective measures of depth of sedation include the use of electroencephalograms (EEG), bispectral index (BIS) and the Narkotrend index.6 None of these are commonly employed.

Sedative and Analgesic Agents
Drugs used for analgesia and sedation in the ICU are compared in Table 3. Choices of sedative agents are determined by the underlying cause of discomfort, the sensitivity of patients to the agents and the likely length of sedation required. Optimal strategies match the patients needs with a particular drugs’ pharmacokinetic and pharmacodynamic profile. The context sensitive half times indicate the change in half time clearance of a drug, when the preexisting duration of infusion is considered. During prolonged infusions, drugs are redistributed to saturate body compartments, and when stopped, clearance is prolonged.

IV Induction Agents
Propofol had been extensively used as an ICU sedative infusion. With a high clearance, propofol sedative infusions allowed shorter times between termination of infusion and extubation. A recent meta-analysis8 concluded using propofol infusion reduced duration of mechanical ventilation and length of ICU stay only when compared with long acting benzodiazepines, but not when compared with midazolam.

Side effects include myocardial depression, reduced systemic vascular resistance, hypertriglyceridaemia, elevated amylase levels and green urine.
Opioids produce analgesia, narcosis and anxiolysis. Side effect concerns include respiratory depression, histamine release, bradycardia, hypotension, nausea and vomiting and poor gastric motility. Withdrawal agitation is also a concern.

There are differences in specific agents. Morphine's histamine release contribute to increased pruritis and potential bronchospasm, compared with fentanyl. Accumulation after continuous drug infusion can lead to prolonged drug effects.

Remifentanil is an ultrashort acting ester opioid commonly used in anaesthesia. It's metabolism is non organ dependant and is by nonspecific blood and tissue esterases to an inactive metabolite. This means it has a stable context sensitive half time (3-10 mins). Offset is therefore independent of length of preceding infusion. Studies have shown shorter weaning from mechanical ventilation and duration of ICU stay compared with other opioids. Increased relative costs is a concern. Concerns include increased delirium, dependence and withdrawal agitation.

Benzodiazepines

Benzodiazepines bind to the GABAA ligand gated Cl-channel to produce sedation and hypnosis. Midazolam has the highest clearance, and minimal haemodynamic effects and is the most commonly used sedative infusion.  Concerns include increased delirium, dependence and withdrawal agitation.

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Loading dose is 1 g/kg over 1 minute. Infusion concentrations are commonly 20, 25 or 50 g/ml. Infusion rates of 0.1-0.15 g/kg/min can be continued and increased by 0.025 g/kg/min at 5 min intervals to a maximum rate of 0.2 g/kg/min.

2 Agonists

Dexmedetomidine is a new potent 2 agonist acting in the locus cereuleus, causing inhibiting sympathetic stimulation, analgesia, sedation, without causing respiratory depression. Studies have shown improved weaning in patients with agitation from opioid or benzodiazepine withdrawal.  Dexmedetomidine was compared with midazolam in 375 mechanically ventilated ICU patients for up to 30 days of continuous infusion. RASS scores were kept between -1 to +1.  Riker et al. found less delirium, (54% in demedetomidine group vs 76.6% in midazolam group, p<0.01) in less tachycardia and hypertension, and less time on ventilators (3.7days in dexametomidine group vs 5.6days in midazolam group p<0.05). Delirium has been independently associated with cognitive impairment and 6 month mortality. Concerns include hypotension, bradycardia, and absence of approval for infusions longer than 24 hours. There is a study underway by the US NIH clinical trials group comparing dexametomidine and propofol for sedation of ICU patients.

Infusion concentrations are commonly 4 g/ml with a loading dose of 1 g/kg recommended over 10 minutes. Infusion rates of 0.2-0.7 g/kg/hr can be continued for 24 hours. In the study, infusions were continued up to 30 days.

Antipsychotic Agents

Haloperidol is effective in the management of delirium and has been recommended by the SCCM guidelines.  Boluses of 1-5mg are useful in conjunction with other sedative anxiolytics. Side effects can include QT prolongation, hypotension and extrapyramidal movement tics.

Neuromuscular Blocking Agents

Neuromuscular blocking agents are used sparingly in today's ICU. Concerns include critical illness myopathy, and awareness from inadequate sedation. Current indications are reserved for patients with difficult ventilation from high airway pressures, prevention of shivering in patients undergoing hypothermia, and malignant intracranial hypertension. Cisatracurium and rocuronium are the commonly used non depolarizing muscle relaxants, because of their relative cardiostability. Cisatracurium undergoes hoffman's degradation and similar to remifentanil is metabolized by tissue and plasma esterases.

Sedations Use

Although new drugs continue to become available, it is increasingly recognized that it is how sedatives are used that requires a new approach.

Choices in Usage Include:
1. Continuous infusion
2. Bolus
3. Daily stop sedation trials
4. Sleep aids
5. Sedation protocols
6. Monitoring of sedation
A number of studies have shown the benefit of daily stop of sedation trials over continuous infusions. Kress et al. demonstrated a reduction in duration of mechanical ventilation, length of ICU stay and fewer investigations to look for cause of unexplained changes of mental status.\textsuperscript{12,13}

Most recently, the ABC trial randomized 335 ventilated patients to a protocol that paired spontaneous awakening trials (SATs)-ie, daily interruption of sedatives-with spontaneous breathing trials (SBTs) versus SBTs alone.\textsuperscript{14} Patients in the intervention group spent more days breathing without assistance than the control group (14.7 days vs 11.6 days; mean difference 3.1 days, 95% CI 0.7 to 5.6; \( p = 0.02 \)) and were discharged from intensive care (median time 9.1 days vs 12.9 days; \( p = 0.01 \)) and the hospital earlier (median time 9.6 days vs 19.2 days; \( p = 0.04 \)). More patients in the intervention group self-extubated. (16 patients vs six patients; 6.0% difference, 95% CI 0.6% to 11.8%; \( p = 0.03 \)), but the reintubation rates were similar. Patients in the intervention group were less likely to die than were patients in the control group (HR 0.68, 95% CI 0.50 to 0.92; \( p = 0.01 \)). For every seven patients treated with the intervention, one life was saved. (NNT 7.4, 95% CI 4.2 to 35.5) They concluded daily wake and breath trials improve outcomes and should be employed universally.

Nurse driven protocols have been validated and involve nurse assessment of:\textsuperscript{5,6}

1. Sedation/Agitation Scale
2. Haemodynamic stability
3. Titration of sedation agent selected
4. Daily stop of Sedation

**Conclusions**

Critically ill ventilated patients benefit from the optimization of their sedation and analgesia management. Sedation strategies must incorporate a recognition and management of causes and precipitants for pain and anxiety in ICU patients. Using sedation scales can improve sedation titration and minimize over and undersedation. Newer agents for sedation infusion such as dexmedetomidine and remifentanil add to the armament of the intensive care physician. The use of daily sedation interruption together with daily spontaneous wean protocols has been shown to decrease mortality in the critically ill.

**References**


**Table 1 Critical Care Pain Observational Tool**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial expression</strong></td>
<td>No muscular tension observed</td>
<td>Relaxed, neutral: 0</td>
</tr>
<tr>
<td></td>
<td>Presence of frowning, brow lowering, orbit tightening, and levator contraction</td>
<td>Tense: 1</td>
</tr>
<tr>
<td></td>
<td>All of the above facial movements plus eyelid tightly closed</td>
<td>Griming: 2</td>
</tr>
<tr>
<td><strong>Body movements</strong></td>
<td>Does not move at all (does not necessarily mean absence of pain)</td>
<td>Absence of movements: 0</td>
</tr>
<tr>
<td></td>
<td>Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements</td>
<td>Protection: 1</td>
</tr>
<tr>
<td></td>
<td>Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed</td>
<td>Restlessness: 2</td>
</tr>
<tr>
<td><strong>Muscle tension</strong></td>
<td>No resistance to passive movements</td>
<td>Relaxed: 0</td>
</tr>
<tr>
<td></td>
<td>Resistance to passive movements</td>
<td>Tense, rigid: 1</td>
</tr>
<tr>
<td></td>
<td>Strong resistance to passive movements, inability to complete them</td>
<td>Very tense or rigid: 2</td>
</tr>
<tr>
<td><strong>Compliance with the ventilator</strong></td>
<td>Alarms not activated, easy ventilation</td>
<td>Tolerating ventilator or movement: 0</td>
</tr>
<tr>
<td></td>
<td>Alarms stop spontaneously</td>
<td>Coughing but tolerating: 1</td>
</tr>
<tr>
<td></td>
<td>Asynchrony: blocking ventilation, alarms frequently activated</td>
<td>Fighting ventilator: 2</td>
</tr>
<tr>
<td><strong>OR Vocalisation (extubated patients)</strong></td>
<td>Talking in normal tone or no sound</td>
<td>Talking in normal tone or no sound: 0</td>
</tr>
<tr>
<td></td>
<td>Sighing, moaning</td>
<td>Sighing, moaning: 1</td>
</tr>
<tr>
<td></td>
<td>Crying out, sobbing</td>
<td>Crying out, sobbing: 2</td>
</tr>
</tbody>
</table>

Scores for each of the four domains are summed, with a total score of 0 to 8 [34].

### Table 2: Four Subjective Sedation Assessment Scales: A Comparison of Their Scoring

<table>
<thead>
<tr>
<th>Agitated</th>
<th>Calm</th>
<th>Sedated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Anxious, agitated, both</td>
<td>2 Cooperative, orientated &amp; tranquil</td>
<td>4 Brisk response to light glabella tap</td>
</tr>
<tr>
<td>7 Dangerously agitated</td>
<td>4 Calm and cooperative</td>
<td>3 Patient responds to command only</td>
</tr>
<tr>
<td>6 Very agitated</td>
<td>0 Alert and calm</td>
<td>5 sluggish response to light glabella tap</td>
</tr>
<tr>
<td>5 Agitated</td>
<td>3 Calm and cooperative</td>
<td>6 No response</td>
</tr>
<tr>
<td>1 Restless</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Source:**
- Sessler CN et al. AJRCCM 2002;166(10):1338-44
- Devlin JW et al. CCM 1999;27(7):1271-5

### Table 3: A Comparison of Commonly Used ICU Sedative and Analgesic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination</th>
<th>Duration</th>
<th>Dosing IV</th>
<th>Concentration</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Relative Cost</th>
</tr>
</thead>
</table>
| Midazolam | Cyt P450 Active metabolite | 1-4h longer if elderly liver/renal failure | LD 2-5mg MD 1-10mg/hr | 10mg/ml Undiluted | Short acting, Cardiac stable | Propofol infusion syndrome, BP, lipid, amylase | $$$
| -Benzodiazepine | Conjugation | 3-10 mins | | | | | $$
| Propofol | Conjugation | 3-10 mins | LD 5-150 µg/kg/min | 1mg/ml Undiluted | Short Acting, Rapid offset, ↓ ICP, ↓ wean time | Resp depression, BP, withdrawal, ↓ Gl absorption | $|
| Morphine | Conjugation Active metabolite | 2-4hr if long infusion liver/renal failure | LD 2-4mg MD 1-20mg/hr | 1mg/ml | Anxiolytic, ↓ HR, ↓ RR, Cheap | Delirium, Dependence, Withdrawal, ICP, high cost | $$$
| -Opioid | Conjugation | 10-20 mins | LD 1 g/kg-1min, MD 0.6-1.5 µg/kg/hr | 20, 25, 50 µg/min | No accumulation rapid offset, ↓ wean time | HR, ↓BP, ↓ICP, acute withdrawal | $$$
| Remifentanil | Tissue Esterases | 6min in liver failure | LD 1 g/kg-10nm MD 0.2-0.7 µg/kg/hr for 24hr | 2 µg/ml | Rapid offset, No respiratory depression, Withdrawal Mx, ↓ wean time, ↓ delirium | HR, ↓BP, Not > 24hrs, expensive | $$$$