Use of sedatives in the critically ill

Marcus Peck
Jim Down

Abstract
Sedation is necessary for the care of most critically ill patients and yet it is not without risk. No agent is ideal and each has potentially deleterious sequelae, particularly in the context of organ dysfunction. Tailoring the regimen to each individual patient is essential but certain strategies such as the protocolized use of sedation scoring systems and daily interruptions have been shown to enhance patient outcome. Here, we review these subjects and the evidence that underscores current clinical practice.

Keywords daily interruptions; goals; holds; protocol; Ramsay; RASS; SAS; SAT; sedation; scoring

The goals of sedation

Analgesia
Analgesia must be the primary concern. Surgical wounds, line insertion and tracheal suctioning can make life very uncomfortable for critically ill patients. In addition to unnecessary suffering, untreated pain may result in neurohumoral stress, pulmonary dysfunction (secondary to guarding of chest wall and/or abdomen), inadequate sleep, agitation, exhaustion and potentially long-term psychological damage.

The relief of dyspnoea
The feeling of not being able to breathe is intensely frightening. The resulting increased respiratory drive has the potential for ventilator dyssynchrony and worsening hypoxaemia. In health, coughing is an important reflex that is essential for sputum clearance but, in a critically ill, mechanically ventilated patient, coughing can compromise gas exchange and risks barotrauma. This reflex can be suppressed by deep sedation.

To permit mechanical ventilation
Un-physiological strategies such as inverse-ratio, low tidal volume, pressure-control ventilation with permissive hypercapnia and prone positioning are all intolerable without adequate levels of sedation.

To permit nursing care
Routine nursing care requires the observation of frequent vital signs and regular rolling and repositioning of the patient. Adequate analgesia and sedation can relieve the resulting discomfort, improve endotracheal tube tolerance and reduce the risk of unplanned extubation.

To reduce oxygen consumption
Sedation may be used to help moderate global oxygen consumption in conditions when delivery is compromised. In patients with traumatic brain-injury, sedation may be required to minimize cerebral oxygen consumption.

To control delirium
Acutely confused patients are a potential risk to themselves and their caregivers. Patients with hyperactive delirium may make an injurious attempt to climb out of bed, assault staff or inadvertently remove airways, catheters and devices essential for their care. It is also pertinent to mention, however, that some sedatives (e.g. benzodiazepines) are also causes of delirium.

If sedation is not administered carefully the patient can be put at considerable risk (see Box 1).

The hazards of under- and over-sedation

Risks of under-sedation
- Severe anxiety and agitation
- Cardiovascular instability (hypertension, tachycardia, increased oxygen consumption)
- Stress response (hypercoagulability, immunosuppression, catabolism)
- Ventilator dyssynchrony
- Hypoxaemia
- Inadvertent removal of essential devices and catheters
- Unplanned extubations

Risks of over-sedation
- Drug-induced coma
- Undetected intracranial, intrathoracic or intra-abdominal catastrophes
- Unnecessary investigations (e.g. CT brain)
- Cardiovascular instability (hypotension, bradycardia)
- Drug accumulation
- Prolonged mechanical ventilation
- Prolonged ICU length of stay

Box 1

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Non-pharmacological adjuncts to sedation

Non-pharmacological techniques that allow reduced use of chemical sedation should always be explored. The patient’s environment is crucial in this regard and should be minimally intrusive. Comfortable room temperature and minimal noise levels must be maintained at all times as well as the provision of natural light in all bays during the daytime to help to preserve normal circadian rhythm. Excessive physical stimulation (vital signs, repositioning, etc.) should be avoided and frequent patient re-orientation used to re-establish a degree of understanding and control for the patient. Modern ventilator modes are increasingly tolerable to lightly sedated patients and there is the option of using gentle physical restraint in patients with hyperactive delirium to avoid excessive polypharmacy.

Sedative agents

Each agent has advantages and disadvantages in both pharmako-kinetics and pharmacodynamics, which are summarized in Table 1.

Unsurprisingly, no agent is ideal and a knowledge of why is essential when deciding which to use on an individual patient.

Route of drug administration

The intravenous route has the most predictable pharmacokinetic profile and, for this reason, it is by far the most commonly used route for drug administration in the critically ill patient. Intermittent bolus dosing is possible and suits agents with longer elimination times such as diazepam, lorazepam and haloperidol. However, it does risk periods of over-sedation and under-sedation and increases demands on nursing time.

Continuous infusions provide, in theory, more consistent levels of sedation and greater levels of patient comfort. No prospective work has been done comparing patient outcomes of intermittent bolus sedation dosing versus continuous infusion. However, continuous infusions were shown to be an independent predictor of prolonged time on a ventilator, length of ICU and hospital stay in addition to increased organ failure and re-

<table>
<thead>
<tr>
<th>Agent</th>
<th>Benefits</th>
<th>Drawbacks</th>
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| Opioids (e.g. morphine, fentanyl, remifentanil) | CNS: potent analgesic  
RS: excellent at attenuating the cough reflex  
CVS: good cardiovascular stability in euvolaemic patients | CNS: deliriogenic  
RS: dose-dependent depression (characterized by preserved tidal volume and low respiratory rate)  
CVS: hypotension in hypovolaemic patients  
GIT: nausea/vomiting and gastric hypomotility |
| Benzodiazepines (e.g. midazolam, lorazepam, diazepam) | CNS: dose-dependent sedation throughout spectrum, potent anxiolytic, amnestic and anticonvulsant properties | CNS: deliriogenic  
RS: dose-dependent depression (characterized by low tidal volume and high respiratory rate)  
CVS: hypotension in hypovolaemic patients |
| Propofol                     | CNS: excellent dose-dependent sedation throughout spectrum, potent anxiolytic, amnestic and anticonvulsant properties, readily titratable by infusion | CNS: deliriogenic, not analgesic  
RS: readily induces apnoea  
CVS: significant hypotension mainly due to preload reduction and some myocardial depression  
Metabolic: hypertriglyceridaemia and syndrome of dysrhythmias, heart failure, metabolic acidosis, hyperkalaemia and rhabdomyolysis in adults on high doses |
| Haloperidol                  | CNS: induces a dissociative mental indifference to the environment in those with hyperactive delirium, potentiates analgesic effects of opioids  
GIT: has anti-emetic properties | CNS: cataleptic immobility is possible, extra-pyramidal effects can occur, may reduce seizure threshold  
RS: mild depression with opioids  
CVS: prolonged QT interval with torsades de pointes  
Metabolic: rarely causes neuroleptic malignant syndrome |
| Alpha 2 agonists (e.g. clonidine, dexmedetomidine) | CNS: strong analgesic and good anxiolytic effects, not deliriogenic  
RS: no significant depression | CVS: initial hypertension followed by prolonged hypotension, rebound hypertension possible on withdrawal  
GIT: reduced gastric motility |

CNS: central nervous system; RS: respiratory system; CVS: cardiovascular system; GIT: gastrointestinal tract.

Table 1
intubation rates when compared with bolus dosing in one un-randomized, retrospective study.1

**Maintaining goals of sedation**

Establishing and maintaining clear goals are essential for the management of sedation in critically ill patients.

Analgesia is the primary concern but assessment of analgesia is often crude and subjective (e.g. looking for facial grimacing) or indirect (e.g. looking for signs of sympathetic stimulation). In lightly sedated patients, it can be enhanced by the use of numerical or visual analogue pain scales. Mechanically ventilated patients who are unable to communicate provide a challenge in this regard. However, a psychometric scoring system known as the Behavioural Pain Scale has been validated to monitor pain behaviours in this group and it evaluates facial expression, upper limb movements and compliance with ventilation each on a 4-point scale.

Once analgesia has been optimized, other physiological causes of agitation must be excluded or corrected. These might include hypoxaemia, hypoglycaemia, hypotension and withdrawal from alcohol or other substances. A pre-defined sedation goal or endpoint should then be set and regularly monitored. Recognition of failure to meet these goals should lead to drug titration or a change in regimen.

**Sedation scoring systems**

This approach to sedation management recognizes that different patients have differing needs for sedation and that these needs also vary over time for an individual patient. Sedation scoring systems are tools that can be performed rapidly at the bedside and used to enhance titration of therapy and improve patient comfort, physiology, understanding and communication.

In 1999, Brook and colleagues demonstrated that a nurse-led, protocol-driven approach to the sedation of patients with respiratory failure reduced their time on the ventilator, tracheostomy rate, and ICU and hospital length of stay.2 They used the Ramsay scale (see Table 2), which was first published in 1974 and remains un-validated but still in widespread use largely because of its simplicity.3 It is limited, however, in that it doesn’t assess the degree of agitation, which is a frequent observation in critically ill patients and if unrecognized has potentially injurious consequences.

Interest in protocolized sedation led to the multidisciplinary development of several sedation scoring systems that were validated in terms of reliability, validity, and responsiveness across samples, settings and observers. The most widely used are the Sedation Agitation Scale (SAS; Table 3) and the Richmond Agitation Sedation Scale (RASS; Table 4); both are similar in that they have discreet numerical scales with the central position representing a calm and cooperative state and escalating degrees of sedation or agitation on either side.3,4

**Sedation holds**

This approach encourages focused down-titration of infusion rates in a timely manner to reduce the complications of drug accumulation.

The daily interruption of sedative infusions was shown by Kress and colleagues in 2000 to significantly reduce days on mechanical ventilation, days on ICU and the number of diagnostic studies to investigate alterations in mental status when compared with those managed without interruptions.5 They also increased patient-days spent awake and able to follow commands, enhanced physician—patient communication and improved physical examination. To achieve this, the sedation infusions were switched off (usually in the morning) and patient allowed to emerge until they responded to commands (a Ramsay score 3 in the Kress study). If the patient required re-sedation at any time, the infusion was restarted at half of its former rate.

Sedation holds or ‘spontaneous awakening trials’ (SATs) risk abrupt waking with agitation, cardiopulmonary instability and self-extubation, and the practice requires adequate training of the

### The Sedation Agitation Scale (SAS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation</td>
<td>Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
<td>Does not calm despite frequent verbal reminding of limits, requiring physical restraints, biting ETT</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Anxious or physically agitated, calms to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative</td>
<td>Calm, easily rousable, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
<td>Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
<td>Aroused to physical stimuli but does not communicate or follow commands, may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unrousable</td>
<td>Minimal or no response to noxious stimuli, does not communicate or follow commands</td>
</tr>
</tbody>
</table>

**Table 2**

**Table 3**
nursing staff to deal with these consequences. However, in centres that practice SATs, the process is led by senior nurses who preserve safety by staggering the sedation holds and maintaining appropriate staffing levels.

SATs have also been shown to facilitate spontaneous breathing trials (SBTs). In their 2008 ABC trial, Girard and colleagues demonstrated that SATs together with SBTs resulted in significant reductions in time on the ventilator, ICU and hospital length of stay when compared with SBT alone and the phrase ‘wake up and breathe’ was coined. There were more self-extubations in the SAT arm of the study but no difference in the need for re-intubation between the groups. Patients in the SAT group were also less likely to die in the year following enrolment, with one life saved for every seven patients treated.

Table 4

<table>
<thead>
<tr>
<th>The Richmond Agitation Sedation Scale (RASS)</th>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overtly combative, violent, immediate danger to staff</td>
<td></td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls or removes tube(s) or catheter(s); aggressive</td>
<td></td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent non-purposeful movement, fights ventilator</td>
<td></td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious but movements not aggressive vigorous</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (&gt;10 s)</td>
<td></td>
</tr>
<tr>
<td>–1</td>
<td>Drowsy</td>
<td>Briefly awakens with eye contact to voice (&lt;10 s)</td>
<td></td>
</tr>
<tr>
<td>–2</td>
<td>Light sedation</td>
<td>Movement or eye opening to voice (but no eye contact)</td>
<td></td>
</tr>
<tr>
<td>–3</td>
<td>Moderate sedation</td>
<td>No response to voice, but movement or eye opening to physical stimulation</td>
<td></td>
</tr>
<tr>
<td>–4</td>
<td>Deep sedation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>–5</td>
<td>Unrousable</td>
<td>No response to voice or physical stimulation</td>
<td></td>
</tr>
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</table>

Table 4

Conclusion

Sedation is both necessary and problematical in critically ill patients. It has many goals, and failure to achieve them may result in significant morbidity. Much can be done to optimize sedation non-pharmacologically and the shift towards a more judicious approach, using scoring systems or daily interruptions, has been shown to reduce the time patients spend both on a ventilator and in the unit. These strategies have improved the quality of patient care and become an essential part of modern critical care practice.

REFERENCES


FURTHER READING


