Altering Intensive Care Sedation Paradigms to Improve Patient Outcomes

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SEDATION ALGORITHMS: A HISTORY

The clinical approach to sedation for intensive care unit (ICU) patients has evolved significantly during the last 30 years, as new medications have emerged, and clinicians have embraced systematic and evidence-based approaches to care. One of the first studies to address this issue was published in 1974 by Ramsay and colleagues; it was a report ahead of its time in many ways: sedation was titrated to a scale, a subset of patients was monitored with electroencephalography, sedation medication was interrupted, and a relatively light level of sedation was targeted (Ramsay scale of 2–4).\textsuperscript{1} Reports describing different approaches to ICU sedation began to appear in the 1980s and early 1990s. Although highly variable, they generally reported deep levels of sedation, frequent use of neuromuscular blockade, and no standard approach to medication selection or strategy for administration.\textsuperscript{2} Simpson and colleagues\textsuperscript{3} reported the advantages of lorazepam relative to the lasting effects of diazepam, and continuous infusion etomidate initially gained popularity, until it was recognized not to be as safe as originally believed.\textsuperscript{4,5} Patient perceptions and recall of the ICU experience were a novel consideration,\textsuperscript{6} and the impact of organ dysfunction on drug and metabolite elimination was described.\textsuperscript{7} Early reports of continuous sedation with midazolam and propofol appeared,\textsuperscript{8,9} and innovative approaches to avoid prolonged sedation from continuous infusions were proposed.\textsuperscript{10} Reports of lingering

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neuromuscular dysfunction after prolonged ICU neuromuscular blockade first appeared in 1990, leading to a reevaluation of that approach.\textsuperscript{11}

As attention to the practice of sedation and analgesia for ICU patients grew, the Society of Critical Care Medicine published the first sedation practice guideline in 1995, summarized in a five-page document with 13 references.\textsuperscript{12} A follow-up report published in 2002 (but reflecting literature published up to 2000) was a much-expanded effort, encompassing 23 pages, 235 references, and 28 recommendations.\textsuperscript{13} In the few years after the publication of these guidelines, the volume of evidence available to guide ICU sedation, analgesia, and delirium has increased significantly, as shown in Fig. 1.

**SHOULD WE CHANGE STANDARD PRACTICE?**

As additional clinical research results have accumulated, the quality of research has varied, results have often conflicted (even among seemingly similar studies), diagnostic and treatment approaches have been inconsistent, and many important areas have not been studied. Many significant findings have been identified, several with consistent results in multiple research reports. It is apparent that changes in the clinical practice of ICU sedation are warranted. Before describing the authors’ approach to these changes (which the author’s are not defining as comprehensive), it is important to characterize the existing approach to sedation, if possible.

Sedation practice depends on several factors, including geographic location, approved and available drugs within that region, and the type of ICU patient population served. Given these multiple factors, the few available reports, and the many different approaches used, a common pattern for ICU sedation is difficult to construct, but several observations can be made. Various surveys of practice have been completed in the United States,\textsuperscript{14,15} Germany,\textsuperscript{16,17} Australia,\textsuperscript{18} and Canada.\textsuperscript{19,20} Although sedation protocols and sedation scales (21\% vs 46\%) are being incorporated in care protocols more frequently, more than half the responders still do not use these tools. When used, the Ramsay scale,\textsuperscript{1} Sedation-Agitation Scale (SAS),\textsuperscript{21} and Richmond Agitation and Sedation Scale (RASS)\textsuperscript{22} appear to be the most common sedation assessment tools. Across all time frames of sedation (short [<24 hours],

![Fig. 1. PubMed citations (accessed Mar 19, 2009) for (sedation OR analgesia OR delirium) AND (intensive OR critical) care, grouped by specific publication dates. Note that the first 2 periods are 10-year intervals, and the last period (2005–9) is not a full 5 years.](image-url)
intermediate [24–72 hours], and long [>72 hours]), the gamma-aminobutyric acid (GABA) agonists remain the most commonly prescribed sedatives, essentially limited to midazolam (Versed), lorazepam (Ativan), and propofol (Diprivan). Daily sedation interruptions are incorporated by roughly a third of responders, and less than half the clinicians routinely assess pain and delirium (most commonly with the Confusion Assessment Method for the ICU [CAM-ICU] or the Intensive Care Delirium Screening Checklist [ICDSC]).

Several important breakthroughs have been made in the last 10 years that should guide future practice in the ICU. These are summarized in Box 1.

**Analgesia**

As part of the American Association of Critical Care Nurses Thunder II project, Puntillo and colleagues assessed the level of pain during six ICU procedures in 6000 adults. Their findings were surprising in that patients reported the greatest level of discomfort with the simple procedures that occur frequently in the ICU, such as suctioning and repositioning. This fits well with earlier data that 90% of patients have unpleasant recall of their ICU experience, including pain. Despite many years of focused attention on pain as an important clinical issue in the ICU, the desired outcomes have not yet been attained. Gélinas reported that 64% of open heart surgery patients experienced moderate or severe pain, similar to earlier data from 17 years ago.

Caring for critically ill patients who cannot verbalize their analgesic needs remains a common clinical problem. In the absence of patient self-report of pain, behavioral indicators have traditionally been used to assess analgesic needs and response to therapy. Two reliable and valid pain assessment tools based on these behaviors, in conjunction with other patient features (such as compliance with mechanical ventilation), have now been validated. Although the Critical Care Pain Observation Tool and the Behavioral Pain Scale represent significant improvements for monitoring pain in these challenging patients, data linking these scores with patient self-report of pain severity and improved outcomes have yet to be published.

Several papers have focused on improving the approach to ICU sedation by employing a strategy the authors call “analgesia-first” or “A1.” This strategy, in which sedating medications are given only after aggressive analgesic strategies

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**Box 1**

**Important research findings that should guide ICU sedation practice**

1. Routine daily ICU care procedures are among the most painful or stressful events reported by patients.

2. Providing analgesia before sedation may reduce sedation requirements and shorten ventilator time.

3. Dangerous adverse effects associated with sedative medications are better understood, including prolonged effects of midazolam, propylene glycol toxicity with lorazepam, delirium with benzodiazepines, propofol infusion syndrome, and bradycardia associated with dexmedetomidine.

4. Dexmedetomidine reduces the incidence of delirium, shortens ventilator time, and appears cost-effective, relative to the GABA agonists.

5. New monitoring tools help detect ICU delirium and better define pain among nonverbal ICU patients.

6. Cognitive sequelae among critical illness survivors are beginning to be characterized.
have been used, compares favorably to traditional propofol or benzodiazepine-based regimens for sedation. Patients receiving A1 therapy consistently achieve comfort goals, and less than 50% require sedating medications. There are no overwhelming data to support use of one analgesic over another, but the extremely short half-life of remifentanil may be beneficial for patients requiring frequent neurologic evaluations. Breen and colleagues randomized patients to either remifentanil first (supplemented by midazolam as needed: an A1 approach) or midazolam first, supplemented by fentanyl or morphine. The A1 approach reduced the time of mechanical ventilation by 54 hours and the time from start of weaning to extubation by 27 hours. An open-label study by Rozendaal and colleagues randomized medical and surgical ICU patients to remifentanil-based sedation (with propofol as required) versus a GABA-based regimen supplemented with fentanyl or morphine. Patients treated with the A1 approach weaned from mechanical ventilation faster, and they were almost twice as likely to be extubated and discharged from the ICU during the first 3 days. Dahaba and colleagues randomized patients to two different medications, both using an A1 strategy (remifentanil or morphine), with midazolam supplementation as needed to maintain a SAS of four. This sedation target was attained more commonly in patients in the remifentanil group (78.3% vs 66.5%), who also spent less time on ventilators and left the ICU sooner after extubation. Mullejeans and colleagues similarly randomized patients to remifentanil or fentanyl, with propofol supplementation as needed. Optimal sedation approached 90% in both groups, and less than 40% of patients required propofol. The rapid offset of analgesia when remifentanil was stopped was associated with a slightly greater incidence of pain.

Sedation

The benzodiazepines, midazolam and lorazepam, are the most commonly used ICU sedative drugs in the United States. The major adverse effects specific to these two medications, prolonged sedative effect for midazolam and propylene glycol toxicity with lorazepam, are now better understood. Midazolam has a rapid onset and short duration of action with single dose administration, and it is recommended because it works quickly. It is not recommended for sustained sedation because prolonged administration results in extended pharmacologic activity, caused by accumulation of parent drug, especially in patients who are obese, have low serum albumin, or have renal impairment. Prolonged sedative activity from midazolam may also be related to accumulation of its active metabolite, alpha-hydroxymidazolam, especially in patients with renal insufficiency. In addition, because it is metabolized by cytochrome P450 3A4, this drug is subject to significant interactions with several inhibitors and substrates of this enzyme system, including fluconazole, fentanyl, and propofol.

Propylene glycol is used as a diluent in many medications, but parenteral formulations of lorazepam contain a substantial amount that can accumulate and cause toxicity in patients receiving large lorazepam doses. Although initially thought to accumulate only with very high lorazepam doses in the 15 to 25 mg/h range, data suggest that total daily lorazepam doses (including infusion and bolus administration) as low as 1 mg/kg are associated with toxic propylene glycol concentrations and adverse effects such as acute kidney injury and metabolic acidosis. These clinical features of propylene glycol toxicity occur so frequently from other causes in critically ill patients that it is easy to overlook that lorazepam administration may cause these events. Because most hospitals do not have the ability to quickly measure propylene glycol concentrations, the serum osmol gap has been used as a reliable screening and surveillance tool. An osmol gap greater than 10 to 12 may help identify patients
accumulating this toxic substance, and some physicians have recommended screening patients at least every other day when lorazepam doses approximate 1 mg/kg/d.  

The other major GABA agonist commonly used to provide ICU sedation is propofol. Popular for its quick onset of sedation and rapid elimination when discontinued, propofol has several adverse effects that are well defined and expected, including hypotension, respiratory depression, hypertriglyceridemia, and pancreatitis. The least understood, least predictable, and most dangerous adverse effect is the propofol infusion syndrome (PRIS). Possible mechanisms for this life-threatening syndrome include inhibition of enzymes in the mitochondrial respiratory chain, impaired fatty acid oxidation, diversion of carbohydrate metabolism to fat substrates, and metabolite accumulation.

The associated signs and symptoms of PRIS vary by report but generally include worsening metabolic acidosis (sometimes specifically identified as lactic acidosis), triglyceride elevations, worsening hypotension and pressor requirements, and arrhythmias (tachycardia, bradycardia, and bundle branch block), with variable inclusion of renal failure, hyperkalemia, rhabdomyolysis, and liver dysfunction. An analysis of more than 1100 cases (including 342 fatalities) suggested that death was more likely if patients were younger than 18 years, or if cardiac symptoms, hypotension, rhabdomyolysis, renal dysfunction, or metabolic acidosis were present. Although usually associated with prolonged, high-dose administration greater than 70 μg/kg/min, several cases have been reported with short duration and lower doses, including surgical anesthesia or sedation for nonoperative cardiac procedures.

Early recognition of possible PRIS is of critical importance, and management remains empiric but must include stopping propofol. Additional treatment options include supporting the hemodynamic and cardiac dysfunction with fluids and pressors or inotropes and even extracorporeal devices, and consideration for hemodialysis or hemofiltration.

The alpha-2 agonists clonidine and dexmedetomidine represent the major alternative to the GABA-agonist drug class for ICU sedation. Clonidine is available for intravenous use in many countries. Dexmedetomidine, first approved in 1999 by the FDA, is the only intravenous alpha-2 agonist available in the United States. Both medications bind to noradrenergic receptors in the brain, spinal cord, and throughout the body. Distinct from GABA agonists, alpha-2 agonists provide analgesic effects and sedation, with little or no respiratory depression. The analgesic component of dexmedetomidine provides patient comfort simultaneously with sedation, possibly similar to the A1 philosophy, although this has not been directly studied. Sympatholytic effects lower heart rate and blood pressure, which may be beneficial (reducing tachycardia and hypertension) or undesirable (hypotension and bradycardia).

Several randomized studies have compared the benzodiazepines (lorazepam or midazolam) or propofol to dexmedetomidine. The major benefits with dexmedetomidine include a reduction in the incidence of delirium, a reduction in time on mechanical ventilation, and a reduction in tachycardia and hypertension. The incidence of delirium was reduced with dexmedetomidine in three of the four studies reporting this outcome, complementing earlier data that benzodiazepines may be deliriogenic in the dose range commonly used among adult ICU patients. The pilot study that did not show a delirium reduction compared dexmedetomidine with standard care rather than a protocol-controlled comparator medication, and it used a composite definition of delirium (Fig. 2). The incidence of adverse effects varied between studies, but hypotension appeared to be similar between benzodiazepines and dexmedetomidine. Tachycardia and hypertension were more frequent with
benzodiazepines, whereas bradycardia was more common with dexmedetomidine. The definitions for bradycardia varied by study, but treatment for the bradycardia was rarely required. Two studies allowed clinicians to select different sedation target goals for their patients; post hoc analysis suggested that deep sedation levels may be attained less easily with dexmedetomidine than with benzodiazepines.

The 2 blinded, randomized controlled studies that compared dexmedetomidine with benzodiazepines (Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction [MENDS] and Safety and Efficacy of Dexmedetomidine Compared With Midazolam [SEDCOM]) showed similar findings. The MENDS study compared dexmedetomidine (in doses up to 1.5 μg/kg/h) and lorazepam infusions (in doses up to 10 mg/h) among 106 medical and surgical ICU patients at two centers for up to 5 days. Target sedation levels were defined by the clinical team for each patient. Patients who received dexmedetomidine had a higher number of days alive without delirium or coma and were within their target sedation range more often. The SEDCOM multicenter study compared dexmedetomidine (in doses up to 1.4 μg/kg/h) and midazolam infusions (in doses up to 0.1 mg/kg/h) among 375 medical and surgical ICU patients for up to 30 days with a common light sedation target for all patients (RASS of −2 to +1) and a required daily arousal assessment. Patients receiving dexmedetomidine had a lower prevalence of delirium (54% vs 76.6%, P < .001) and a shorter duration of ventilatory support (3.7 days vs 5.6 days, P = .01).

**Delirium**

A major advancement in patient monitoring during the last decade includes the development and validation of delirium-screening tools. ICU delirium is a clinically important, but commonly undetected, problem affecting as many as 80% of critically ill patients. Underrecognition may relate to the complex nature of this syndrome, to the variability of symptoms, and to the fact that the most common form of delirium, the hypoactive subtype, is easy to overlook unless routine assessment is performed. Two assessment tools were published in 2001 to facilitate recognition of delirium: CAM-ICU and the ICDSC. These tools have improved identification of ICU delirium, but it is not yet confirmed that these tools improve outcomes, nor how best to treat delirium. These questions remain the next challenges for clinical researchers.

![Forest plot showing the incidence of delirium in 4 randomized studies that compared dexmedetomidine with midazolam or propofol after cardiac surgery, with lorazepam, with midazolam, or with standard care. The cumulative odds ratio shows a dramatic reduction (0.45) of delirium with dexmedetomidine use.](Data from Refs. 38,44,45,46)

![Table showing the results of the study and the odds ratio for delirium with dexmedetomidine use.](Weight | Odds Ratio | Weight | Odds Ratio)

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<tr>
<th>Study or Subgroup</th>
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<th>Study or Subgroup</th>
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<tbody>
<tr>
<td>Maldonado 2009 M</td>
<td>15.0%</td>
<td>0.15 [0.04, 0.50]</td>
<td>Maldonado 2009 P</td>
<td>14.8%</td>
<td>0.14 [0.04, 0.47]</td>
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<tr>
<td>Pandharipande 2007</td>
<td>8.8%</td>
<td>0.80 [0.30, 2.13]</td>
<td>Riker 2009</td>
<td>55.6%</td>
<td>0.37 [0.23, 0.60]</td>
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<tr>
<td>Ruokenen 2009</td>
<td>5.8%</td>
<td>2.35 [0.94, 5.89]</td>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>0.45 [0.32, 0.64]</td>
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Heterogeneity: Chi² = 21.07, df = 4 (P = 0.0003); I² = 81%
Test for overall effect: Z = 4.54 (P < 0.00001)
Cognitive Sequelae

After surviving their stay in the ICU, many patients will suffer from cognitive deficits, such as memory impairments, difficulty maintaining attention or concentrating, reduced processing speed, and general intellectual decline. The prevalence of these impairments varies from 25% to 78% and they are a major determining factor in whether patients return to work and regain productivity. More subtle cognitive impairments can affect driving, money management, the ability to perform activities of daily living, and family interactions. There is growing data that the sedation approach clinicians choose in the ICU is associated with these outcomes.

RECOMMENDATIONS FOR CHANGES IN PRACTICE

Based on the above evidence, several important changes supported in multiple studies can now be recommended when providing sedation for ICU patients. These are summarized in Box 2.

Consider providing analgesia first before initiating sedative therapy, guided by patient self-report or validated pain tools, such as the Critical-Care Pain Observation Tool or the Behavioral Pain Scale. Analgesics such as remifentanil, fentanyl, morphine, and dexmedetomidine may allow patient comfort and wakefulness to coexist. Many ICU patients can remain awake or lightly sedated if they are comfortable. If lightly sedated but pain-free patients are still not able to tolerate their care, additional sedation may be needed. Consider dexmedetomidine because of its beneficial effects to

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<td><strong>A recommended approach for ICU sedation</strong></td>
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1. Provide analgesia first, with remifentanil, fentanyl, morphine, or possibly dexmedetomidine. Monitor analgesia adequacy with patient self-report if possible, or, if not possible, with a validated assessment tool.

2. Propofol and dexmedetomidine may be beneficial compared with benzodiazepines, if a sedative is needed. Consider dexmedetomidine for ICU patients because of its beneficial effects on delirium, cost-effectiveness, and mechanical ventilation, unless

   A. Deep sedation is required

   B. The patient has bradycardia or severe left ventricular dysfunction

3. Avoid the adverse effects commonly associated with standard sedative medications.

   A. Avoid midazolam accumulation by limiting the duration of use; practice at least daily interruption of drug or awakening the patient, and targeting the lightest level of sedation possible.

   B. If lorazepam is used, avoid continuous infusion if possible; monitor the serum osmol gap if daily doses approach 1 mg/kg. If lorazepam is infused continuously, interrupt drug or awaken the patient at least daily, and target the lightest level of sedation possible.

   C. If propofol is used, avoid prolonged use or doses greater than 70 mg/kg/min, and monitor triglycerides, creatine kinase, arterial blood gases, liver and renal function, and electrocardiogram. Be aware of the signs of PRIS, and discontinue propofol if these appear.

4. Monitor all patients for delirium, even those who are calm and not agitated.

5. Before hospital discharge, assess cognitive function in patients, and consider neuropsychiatric follow-up for anyone who needs it.
reduce delirium and duration of mechanical ventilation, and its cost-effectiveness.\textsuperscript{47,48} There is no evidence to identify which patients require deep sedation (SAS of 1 or 2, RASS of $-4$ or $-5$, Ramsay of 4–6), but if patients remain intolerant of their care despite analgesia and light or moderate sedation, dexmedetomidine may require supplementation. If GABA agonists, such as midazolam, lorazepam, or propofol, are added or substituted, avoid prolonged sedation with daily awakenings or dose-reduction strategies, especially with the benzodiazepines. A multicenter study showed reductions in duration of mechanical ventilation, ICU time, and mortality when daily awakening is linked to spontaneous breathing trials.\textsuperscript{62}

When using the GABA agonists, understand the common adverse effects that can occur and the less common but life-threatening adverse effects. Many of these are dose-related, so strategies to reduce sedative doses may reduce the incidence of adverse effects. Avoid midazolam accumulation by dose-reduction protocols or daily awakening.\textsuperscript{44,63,64} Avoid propylene glycol toxicity with lorazepam dosing by monitoring the osmol gap serially as daily doses approach or exceed 1 mg/kg.\textsuperscript{36} Recognize the signs of PRIS associated with death (age <18 years, dysrhythmias, hypotension, rhabdomyolysis, renal dysfunction, or metabolic acidosis) and substitute other medications for propofol if these develop or progress.\textsuperscript{43} Finally, routine monitoring of all patients for delirium using the CAM-ICU or ICDSC allows clinicians to identify patients with delirium and to develop specific treatment plans for this disorder.\textsuperscript{23–26} This may identify a cohort of patients at very high risk for prolonged cognitive impairments for whom neuropsychiatric testing and counseling may be beneficial, although even non-delirious patients may suffer from these cognitive sequelae.\textsuperscript{65}

SUMMARY

Providing sedation and comfort for intensive care patients has evolved in the last 30 years but remains difficult for clinicians. As research has focused on this challenging area, the authors have identified ways to improve practice, including providing analgesia before sedation, strategies to help recognize dangerous adverse effects associated with the medications that are used, and better ways to monitor pain and delirium in patients. Dexmedetomidine and propofol have become the preferred sedatives for many ICU situations, and creative ways to administer them, such as linking awakening and breathing trials, are emerging. Finally, screening survivors for cognitive impairments may allow clinicians to refer them for the focused rehabilitation they require.

REFERENCES


