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Sedation in the Critical Care Unit

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Those familiar with the care of critically ill patients know that anxiety and agitation is expected in these patients due to the stress they are suffering. This major stress arises directly from their underlying illness and is compounded by the necessary treatment they are receiving (eg, mechanical ventilation and invasive monitoring) and the environment in which they receive it (bright, loud, and full of unfamiliar faces). Appropriate sedation of the critically ill patient has become an integral part of their care. However, too much sedation can lead to prolonged mechanical ventilation and the associated risk of ventilator-associated pneumonia¹ or ventilator-associated lung injury.² Too little sedation can lead to excessive patient stress and potential harm, including barotrauma, self-extubation, myocardial ischemia, and dysrhythmias.

A variety of sedative and analgesic agents are used to relieve the anxiety and agitation in these patients. For those with pain, an analgesic is the initial agent of choice. Sedative medications are used in conjunction with analgesics to treat anxiety and agitation beyond that due to pain alone. The number of agents available to provide sedation for critically ill patients is vast, as reflected in surveys in North America and in the United Kingdom. In a survey of 164 American intensive care units (ICUs), 18 different agents were being used for sedation.³ A similar survey of 348 ICUs in the UK found that a total of 11 different sedative agents were administered.⁴ While it is useful to have a wide choice of agents, it can lead to some confusion and the tendency to quickly jump from agent to agent rather than optimizing the use of initial agents. Different clinicians within the same ICU may develop favourite “cocktails” that differ from each other, leading to further confusion in patient care. The objective of this review is to summarize a stepwise approach to sedation of the critically ill patient. The approach presented relies on information gleaned from the literature and from direct discussions. Although high-level evidence is sparse in this area, it has been reviewed where available.

Which sedative agents are available?

Prior to outlining an approach to sedation of the critically ill patient, it is useful to define the taxonomy used to group the sedative agents available. For this review, the taxonomy in Table 1 is proposed.

A stepwise approach to sedation of the critically ill patient.

Step 1. For each patient, establish the goal for sedation

Critically ill patients are a heterogeneous group with different underlying co-morbid diseases, severity of illness, life support requirements, and monitoring needs. The level of sedation considered to be optimal varies among this diverse population and also within individual patients over time. At one end of the spectrum, very deep levels of sedation are required for a severely head-injured patient with precarious intracranial pressure or another with severe acute respiratory distress syndrome who requires complete control of ventila-



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Table 1: Taxonomy for sedative agents

- Benzodiazepines (eg, diazepam, lorazepam, midazolam)
 - Opiates (eg, morphine, fentanyl)
 - Neuroleptics (eg, haloperidol, methotrimeprazine)
 - Anesthetic agents (eg, propofol, inhalational agents such as isoflurane)
 - Alpha 2 agonists (eg, clonidine, dexmedetomidine)
-

tion and minimal oxygen consumption. At other times, our goal is an awake, but relatively calm patient, (eg, the patient about to undergo weaning from mechanical ventilation). While we all approach each patient with these differences in mind, it is useful to make the target level of sedation explicit for each patient.

Step 2. Use a sedation scoring system

Following the objective to be explicit in the desired level of sedation for a specific patient, I suggest that a “sedation measuring system” be adopted to guide sedation. Sedation measuring systems may be either objective or subjective in nature. Examples of the former are well summarized in a recent narrative review by Dr. Carrasco⁵ and include such measurements as continuous electroencephalography and auditory-evoked potentials. Subjective sedation measurement systems are widely recognized and utilized and rely on the judgment of the observer.

Regardless of the measurement, the objective of such a system is to provide an instrument to achieve a reliable, valid, and responsive measure of a patient’s level of sedation. Reliability refers to the ability of the scoring system to be reproducible among different observers at one point in time (inter-rater reliability), and within the

same observer over time (intra-rater reliability). This is a highly desired quality of the scoring system as many health care professionals will care for the same patient during his/her stay, necessitating a system that is consistent across users. The validity of an instrument can be defined as the extent to which the instrument truly measures the degree of sedation. Finally, responsiveness is the extent to which an instrument can detect important changes in sedation over time.⁶

While one would generally consider an objective assessment to be preferred over that of a subjective one, the fact remains that objective measurements of sedation in the critically ill patient have not yet been demonstrated to be reliable and valid. Table 2 summarizes a number of those that have been investigated to date and their associated limitations.⁵ Work continues in this area, and as technology evolves, a more useful objective measurement may emerge.

In a recent excellent systematic review, De Jonghe and co-workers identified 25 subjective scoring systems reported in the literature.⁶ The most commonly used subjective sedation scoring system is the Ramsay scale, first described in 1974.⁷ It consists of a single categorical item that measures the level of sedation with a numerical scale. It has been demonstrated to be highly reliable. Other scoring systems, including the Glasgow Coma Scale modified by Cook and Palma,⁸ the Sedation-Agitation-Scale,⁹ the New Sheffield Sedation Scale¹⁰ and the Motor Activity Assessment Scale¹¹ were also been found to be highly reliable in adults.⁶ The first includes 4 items that would theoretically improve its’ sensitivity, while the other 3 comprise a single item, similar to the Ramsay scale. Interestingly, all validation of sedation scoring systems has been conducted by comparing them against other scoring systems.⁶ No gold standard exists. The Ramsay scale has been validated against the modified Glasgow Coma Scale and the Sedation-Agitation-Scale and vice-versa. These

Table 2: Objective measurements of sedation in the critically ill patient ⁵

Measuring system	Advantages and limitations
Plasma drug concentration	Lack of agreement with level of sedation
Frontalis electromyography	Inter-individual variation
Lower esophageal contractility	Low sensitivity
Continuous electroencephalography	Difficult interpretation Inter-agent variation
Cerebral function monitor	Complex and difficult to interpret
Cerebral function analyzing monitor	Complex and difficult to interpret
Power spectral analysis	Not available for clinical use
AEP’s	Limited reliability in light sedation Adequate for research

Scales appear to measure the same construct as reflected by high correlation coefficients. The Motor Activity Assessment Scale has been validated against a visual analogue scale with good results.¹¹ No sedation scoring systems have been tested for their ability to accurately detect changes in sedation level over time within the same patient (responsiveness).

Overall, no sedation scoring system has been evaluated so thoroughly that it would be considered ideal⁶ and there are a number that appear to be equally useful. When choosing a specific scoring system, consultation with nursing staff should be conducted. In the end, of the scoring systems considered to be reliable and similar in terms of validity testing, the one that is most acceptable to the staff should be chosen. Interestingly, a recent study describing the introduction of a sedation scoring system (The Brussels sedations scale), using a before-after design, demonstrated that use of a sedation scoring system resulted in a reduction in the incidence of oversedation in the ICU.¹²

Step 3. Choose the appropriate sedative agent(s) for your patient

An ideal sedative agent would have a rapid onset of action, be effective at providing adequate sedation, allow rapid recovery after discontinuation, be easy to administer, lack drug accumulation, have few adverse effects, interact minimally with other drugs, and be inexpensive.¹³

A recent systematic review of the literature summarized all randomized controlled trials published until June, 1998, that compared at least two sedative agents.¹³ The objective of this review was to determine the relative effectiveness of sedative agents on quality of sedation, time to extubation, and length of ICU stay. A total of 32 trials fulfilled inclusion and exclusion criteria. The majority of trials (20 of 32) compared the relative effectiveness of midazolam and propofol, so that relatively few trials evaluated the numerous other agents. No trials evaluated haloperidol or the more recent agent, methotrimeprazine. A major concern raised by the reviewers was the validity of many of the identified trials. None of the trials documented masking of allocation, only 16% were blinded, just over 20% described co-interventions adequately (eg, weaning strategy, anesthesia for post-operative patients, use of analgesia and neuromuscular blockers), almost 60% provided baseline data sufficient to compare patient groups, and 81% used intention-to-treat analysis. The poor quality of many of the trials made it difficult to have confidence in drawing strong inferences from the reported results. The review suggested, however, that propofol appeared to be at least as good a sedative agent as midazolam, and that it appeared to allow a faster time to extubation. Beyond this, no firm conclusions of the relative effectiveness of the various studied agents could be made.

The authors concluded that this is clearly an area of research for extensive future study.

Since that review, further trials have been published and continue to appear in abstract format. A Medline search strategy, similar to the one used in the systematic review, revealed only 3 new randomized controlled trials.¹⁴⁻¹⁶ In one blinded trial, lorazepam was compared to midazolam in 75 patients ventilated over 72 hours.¹⁴ The authors reported favourable results for lorazepam (greater time spent at target sedation level and lower cost). However, 11 patients were excluded (death, neuromuscular blocker use, other sedative use), and while the amount of fentanyl was recorded, no other co-interventions were standardized.

In a small, unblinded study of 31 surgery or trauma patients, lorazepam, midazolam, and propofol were compared.¹⁵ These authors reported a greater time at the desired level of sedation for midazolam when compared to lorazepam (more over sedation) and lorazepam (more under sedation). However, the cost of lorazepam was significantly less than the other two, leading the authors to speculate that this may be the preferred drug. Again, weakness of study design, including the fact that it was not blinded and co-interventions were not well described, makes interpretation of the results difficult. To date, there is no ideal sedative, although both midazolam and propofol have been considered highly desirable except for their associated cost. However, an accompanying editorial highlighted the exciting fact that both midazolam and propofol are now off patent;¹⁷ hopefully, we should be seeing the economic benefit of this within the next few years.

A third very interesting, randomized, placebo-controlled trial described the use of a highly selective alpha₂-adrenergic agonist as a sedative agent, dexmedetomidine, in postoperative cardiac and general surgery patients requiring ventilation in the ICU.¹⁶ These investigators found a decreased need for other sedative (midazolam) and analgesic (morphine) agents in the treatment arm. Further study is underway with this sedative agent, but it must be considered to be in the experimental stage for the present.

Therefore, the ideal sedative agent(s) is still not clear. Within Canada, an informal email survey using the Canadian Critical Care Society list (cccs@critcare.lhsc.on.ca) identified variation among centers in their approach. However, most of the physicians who replied said that midazolam or lorazepam would be their first choice of sedative agent. Lorazepam was generally only considered in the setting of longer-term sedation (days versus hours). In addition, most physicians would also include some form of analgesic agent (usually morphine). Propofol was generally reserved for patients whose target sedation level was deep coma, but who also required frequent neurological assessment (gener-

Table 3: Clinical outcomes of a nursing implemented protocol²⁰

Outcome	Protocol directed sedation (n=162)	Non-protocol directed sedation (n=159)	p
Duration of mechanical ventilation (hrs)	89.1 ± 133.6	124.0 ± 153.6	.003
Length of ICU stay (days)	5.7 ± 5.9	7.5 ± 6.5	.13
Length of hospital stay (days)	14.0 ± 17.3	19.9 ± 6.5	<0.01
Mortality, No. (%)	49 (30.3)	57 (35.9)	.342
Acquired organ system derangements	2.8 ± 1.4	2.9 ± 1.5	.737
Reintubation, No. (%)	14 (8.6)	21 (13.2)	.213
Tracheostomy, No. (%)	10 (6.2)	21 (13.2)	.038

ally neurosurgical patients). For patients who do not settle easily on some combination of these due to excessive agitation, most doctors would suggest administering either haloperidol (especially if suppression of ventilatory drive is a major concern) or methotrimeprazine.

Step 4. Create a standardized approach: the use of clinical practice guidelines

In the past decade, there has been an increased interest in the adoption of clinical practice guidelines to standardize patient care. The critically ill patient requires very complex care, including ongoing monitoring of hemodynamic and respiratory parameters, titration of life support measures, administration of prophylactic and therapeutic pharmacological agents, and non-pharmacological technologies. In addition, each patient is also unique with different major issues in their care. When we add into this mix, multiple consultants, nurses, respiratory therapists, and other health care professionals with varying backgrounds and opinions, it is not surprising that over time the potential for some confusion in care arises. In order to improve consistency of care, clinical practice guidelines have been developed for various aspects of patient care including feeding, deep venous thrombosis prophylaxis, weaning patients, and sedation. While on the surface these guidelines appear to be a good idea, they must be evaluated to ensure they are truly effective.

Devlin and colleagues reported on the evaluation of a sedation guideline designed to shift the use of midazolam to lorazepam for all ICU patients requiring more than 24 hours of ventilation.¹⁸ These authors used a before-after design and did not report the use of a sedation scoring system (the general goal being to maintain each patient in a calm and relaxed state while being awake or just slightly asleep), limiting their evalu-

ation to cost and time-to-weaning from mechanical ventilation. They reported no difference in the duration of mechanical ventilation, time-to-wean, or length of ICU stay. They did find a reduction in cost coincident with a successful increased use of lorazepam in preference to midazolam. MacLaren and associates used a similar before-after design that included the protocol-based use of both analgesics and sedative agents and incorporating the Ramsay sedation scale.¹⁹ They reported a similar reduction in cost and also an improvement in the quality of sedation. Interestingly, they also found a trend towards a delay in time to extubation with a greater use of lorazepam; however, this did not reach statistical significance.

While before-after trials are the standard for guideline evaluation, they are open to significant bias. Two randomized controlled trials evaluated the use of alternative approaches to sedating the critically ill patient. Brook and co-workers randomized patients to either a nursing-implemented sedation protocol or a “traditional non-protocol approach” within a 19-bed medical ICU.²⁰ Their target sedation level was a Ramsay score of 3 (patient awake, responds to commands only). 328 patients were randomized, but 7 were excluded as they were surgical patients awaiting transfer to the surgical ICU. Baseline characteristics were similar between the two groups and co-interventions were reasonably well standardized. The major findings of this study were a decrease in the duration of ventilation and length of ICU and hospital stay (Table 3). There was also a decrease in the rate of tracheostomies (6.2% versus 13.2%). While mortality was lower in the protocol group, it did not reach statistical significance.

A second trial, recently reported by Kress and co-workers, was designed to determine the effect of

Table 4: The duration of mechanical ventilation, length of stay in the intensive care unit and the hospital, and doses of sedative drugs and morphine,* according to study group.²¹

Variable	Intervention group (n=68) median (interquartile range)	Control group (n=60)	p value
Duration of mechanical ventilation (days)	4.9 (2.5-8.6)	7.3 (3.4-16.1)	0.004
Length of stay (days)			
Intensive care unit	6.4 (3.9-12.0)	9.9 (4.7-17.9)	0.02
Hospital	13.3 (7.3-20.0)	16.9 (8.5-26.6)	0.19
Midazolam subgroup (no. of patients)	37	29	
Total dose of midazolam (mg)	229.8 (59-491)	425.5 (208-824)	0.05
Total dose of morphine (mg)	205 (68-393)	481 (239-748)	0.009
Propofol subgroup (no. of patients)	31	31	
Total dose of propofol (mg)	15,150 (3983-34,125)	17,588 (4769-35,619)	0.54
Total dose of morphine (mg)	352 (180-632)	382 (148-1053)	0.33

*Average rates of infusion were calculated as milligrams of drug per kilogram of body weight divided by the number of hours from the start of the infusion to its termination.

daily interruption of sedative infusions on duration of mechanical ventilation and length of ICU stay.²¹ In a medical intensive care unit, 150 patients were randomized to the protocol group or usual care. Of these, 22 were excluded since they were either extubated or died within the first 48 hours. The sedative infusions received by the patients were midazolam or propofol, patient allocation of sedative agent was determined by randomization. The investigators found that the intervention group had a shorter length of mechanical ventilation, a shorter length of ICU stay and, in the midazolam group, a lower dose of sedative agent (Table 4). In addition, fewer diagnostic tests to assess mental status were performed in the intervention group (6 CT scans in the intervention group versus 13 CT scans, 2 MRIs, and one lumbar puncture in the control group, $p = 0.02$). There were no differences found in adverse events such as self-extubation or removal of central lines. However, concerns have been raised regarding the negative impact of other adverse events that were not recorded, including the cardiovascular and psychological effects of daily wakening of critically ill patients.

These interesting trials highlight some of the difficulties in studying a process such as the implementation of a clinical practice guideline, rather than a more discrete intervention such as a pharmacological agent. The first potential problem is that of contamination. There is the potential for contamination in the non-protocol group who are being treated by the same people within the same work area, to be treated more and more like the protocol group. In the study by Kress and co-workers, 18 patients had sedation interrupted on

days other than the final day of administration²¹ consistent with a contamination effect. Contamination biases the results in such a way that differences between study groups become more difficult to detect. The fact that differences were found between groups in both these trials favouring the intervention group, despite a systematic bias working against this, suggests that the benefits seen were real. The other potential concern has to do with how one should analyze the introduction of a “process” rather than a specific new treatment such as a new drug or mode of ventilation. Implementing a guideline is a system-wide change and some would argue that patients within an area adopting a new guideline couldn’t be considered completely independent. If this is accepted, then the degrees of freedom used in the analysis should be fewer than the standard approach to analysis and the ability to demonstrate a difference more difficult. The ideal approach to analyzing the introduction of a clinical practice guideline involves the randomization of centers rather than individual patients (cluster randomization). Obviously, such a study is difficult to perform, requiring considerable resources and organization. It is for this reason that before-after designs are generally used.

Summary

In this short review of sedation in the intensive care unit, I have attempted to outline one approach to achieving adequate sedation for critically ill patients. I have suggested that one should be explicit in defining the level of sedation desired for each patient and that one should use a sedation scoring system and a clinical practice guideline to

aid this process. There is evidence to suggest that such a systematic approach is potentially beneficial for patients. However, it is important to recognize that while these studies suggesting benefit¹⁸⁻²¹ are internally valid, their external validity (generalizability) remains to be demonstrated. Adopting this approach is most likely to be successful if current practice within a specific ICU is felt to be less than optimal by those working there. Furthermore, all those involved (nurses, respiratory therapists, pharmacists and physicians) must see the merit in adopting such an approach or it is likely to fail in its objective. I suspect that there are many ICUs where an informal, yet relatively systematic, approach to sedation is in place with which staff are pleased. While there may be potential for improvement even in this setting, it will be harder to achieve without careful planning and widespread consultation with and education of staff on why any change is required. In some cases it may not be. If a decision is made to adopt a clinical practice guideline, evaluation of its impact and follow-up assessment of compliance and benefit should ideally be conducted.

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