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Evolving concepts of sedation in the critically ill

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Sedatives are an integral tool in the management of critically ill patients (Table 1). However, we are only starting to appreciate that the level of sedation we provide, and when and how to stop it, are important factors in determining patient outcome in the ICU. In one study, the use of a sedation protocol that allowed bedside nurses to adjust sedative and analgesic doses reduced the duration of mechanical ventilation and length of ICU stay by 1.5 days.¹⁻³ Similarly, Kress et al found an improvement in outcome when patients were awakened daily by interrupting their sedative infusions.⁴ Use of such strategies may not only improve patient outcome, but also result in significant cost savings and improved efficiency of patient flow in the ICU.

Despite the promising results of these studies, important questions remain. The primary issue is whether patients managed with a combination of both of these strategies (protocolized sedation and daily awakening) have an even better outcome than patients managed with only a single strategy. In addition, it is not clear how much additional workload is imposed on caretakers by stopping sedatives daily. Another significant concern is whether daily awakening may traumatize patients and have long-term psychological effects.

Risks of under- and over-sedation

Both inadequate and excessive sedation may have deleterious effects on the critically ill patient (Table 2). Undertreated pain results in physiologic responses (hypercoagulability, immunosuppression, persistent catabolism) that are associated with poor outcomes.⁵ Pain increases the levels of sympathetic nervous system activity and catecholamine release, placing additional demands on the cardiovascular system in the critically ill. Prolonged pain can result in the development of severe anxiety and even delirium. Anxiety and agitation associated with insufficient sedation may increase the risk of adverse events such as self-extubation, loss of central lines, and self-injury or injury to caretakers. In addition, inadequate sedation may leave patients with traumatic memories of their ICU stay.

On the other hand, excessive sedation can lead to respiratory depression, hypotension, bradycardia, ileus, and venous stasis. Excessive sedation can make evaluation of a patient's neurological status very difficult, thus interfering with the recognition and diagnosis of acute neurologic events that may occur in the ICU. Observational studies have identified sedation as an independent risk factor for ventilator-associated pneumonia.⁶ In addition, delayed recovery related to over-sedation may prolong the duration of mechanical ventilation, as well as durations of ICU and hospital stay. Finally, over-sedation may also have long-term emotional effects; one study has suggested that an inability to recall experiences during a critical illness leads to psychological distress after recovery.⁷ Partly because of the complications associated with over-sedation, the goals of sedation have now changed. In a survey of 34 ICUs in Great Britain published in 1981, the majority of respondents wanted to keep most patients well-sedated and completely detached from the ICU.⁸ Today, in contrast, the target is a sleepy, yet rousable, cooperative patient who is pain- and anxiety-free.



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Table 1: Goals of sedative use

- Reduce respiratory muscle oxygen requirements
- Reduce patient-ventilator asynchrony
- Anxiolysis
- Amnesia
- Facilitate sleep
- Facilitate invasive tests or procedures

Practice variability

Guidelines for intravenous (IV) sedation produced by a multidisciplinary task force from the Society of Critical Care Medicine (SCCM) have recently been published.¹ These guidelines include recommendations regarding the preferred agents for analgesia and sedation in the ICU. Midazolam and propofol are the preferred agents for short-term sedation (< 24 hours) and lorazepam for long-term sedation (≥ 24 hours).¹ For analgesia, morphine is the preferred agent, with fentanyl as an alternative for patients with hemodynamic instability or morphine allergy. However, these guidelines are based on contradictory results from a few randomized trials that have compared different sedative agents in varied ICU patient populations.⁹ Moreover, there are multiple acceptable alternative medications available for both analgesia and sedation. The choice of medications is determined by multiple factors, including patient-specific factors, physician preference, drug interactions, and cost. It is clear that wide variations in clinical practice exist even when guidelines based on reputable evidence are available.¹⁰ Surveys of sedation and analgesic administration in US and British ICUs reveal widely varying practice patterns with regard to type of medications, route of administration (intermittent versus continuous IV), and sedation monitoring.¹¹⁻¹⁴

In a recent survey at Mount Sinai Hospital, critical care nurses were asked about their satisfaction with current sedation and analgesia practices in the ICU. Of the 28 respondents, 59% were dissatisfied and cited physician inconsistency in choice of sedative agents and dosing as the major reasons for their dissatisfaction (unpublished data).

In summary, there is no consensus regarding a preferred sedation regimen in mechanically-ventilated patients and a wide variability in practice patterns exists, even within a single ICU. This variability contributes to nurse dissatisfaction with the current sedative administration practice.

Continuous infusions versus bolus administration

Because intermittent bolus injection of sedatives results in peaks and troughs of effect, as well as potential periods of anxiety and agitation, many intensivists believe that continuous infusion of sedatives produces a more predictable and reliable anxiolysis, maximizing the therapeutic benefit and minimizing side effects.¹⁵ Conversely, time-to-awakening after discontinuing sedative infusions can occasionally be delayed for > 24 hours,¹⁵ presumably due to drug accumulation. In addition, one retrospective study found a correlation between the use of continuous sedative infusions and prolonged durations of mechanical ventilation, as well as ICU stay.¹⁶ However, given the retrospective nature of this study,

Table 2: Potential pitfalls of sedation practice

Dangers of undersedation

- Agitation
- Recall
- Myocardial ischemia
- Ventilator asynchrony
- Self-extubation

Dangers of oversedation

- Prolonged alteration of consciousness
- Increased duration of mechanical ventilation
- Increased duration of ICU stay
- Increase in mortality?
- Increase in nosocomial infections?
- Increased medication costs

it is difficult to draw any conclusions regarding cause and effect. It is feasible that patients with greater illness severity (and thus more likely to have a longer length of stay) were given sedatives by continuous infusion, and those who were less ill were given sedatives by bolus dosing.

In practice, continuous infusions are very frequently used in mechanically-ventilated patients, as revealed in surveys of US,^{12,14} British,¹⁷ and Danish¹³ intensivists, for the following reasons: many patients have difficulty communicating their sedative/analgesic requirements because of an endotracheal tube or an altered level of consciousness; the maintenance of an adequate, continuous, opioid blood concentration improves patients' analgesia;¹⁸ there is increasing evidence that the continuous versus intermittent administration of opioid decreases morbidity rate¹⁹ and may decrease mortality.²⁰

Choice of sedative and analgesic agents

The importance of sedation in the ICU has recently been addressed in the executive report of practice variables for intravenous sedation by a multidisciplinary task force from the SCCM.¹ This guideline includes recommendations regarding the preferred agents for analgesia and sedation in the ICU. Benzodiazepines are the most commonly used medications for anxiolysis and the relief of agitation; butyrophenones (eg, haloperidol) or the non-analgesic sedative propofol are also used for this purpose, and opiates remain the usual drug of choice for analgesia. However, even within each of these classes, there is a tremendous choice of drugs and published studies are conflicting regarding the "best" agent. Clearly, the choice of the "best" agent is determined by individual patient characteristics, including age, comorbidities, drug interactions, and anticipated duration of mechanical ventilation.

McCollam et al compared the efficacy, safety, and cost of continuous infusions of lorazepam, midazolam, and propofol in critically ill trauma/surgery patients and found that although lorazepam was the most cost-effective, over-sedation (based on assessment of the Murray scale) occurred more commonly than with the other 2 agents.²¹ He concluded that midazolam is the most titratable drug, avoiding both oversedation and undersedation. Similar results were observed in an elegant prospective study that used sophisticated modeling techniques to compare the pharmacokinetics

and pharmacodynamics of lorazepam and midazolam administered as continuous infusions in 24 patients.²² These investigators found significant delays in emergence from sedation with lorazepam as compared with midazolam.

Despite the widespread use of sedative agents in all ICUs, there are few rigorous studies of the comparative usefulness of the various sedative drugs. This was highlighted by a systematic review that attempted to determine which drugs are associated with optimal sedation, shortest time to extubation, and shortest ICU stay.⁹ The authors identified 32 studies that fulfilled the following criteria: the enrolment of adults requiring mechanical ventilation and short- or long-term sedation; the comparison of at least 2 sedative drugs; outcomes that included quality of sedation, time to extubation, or length of ICU stay; a randomized study design. The most striking finding of this overview was the paucity of data available on the choice of sedatives in the ICU. The authors concluded that only a minority of sedative agents used in the ICU had been evaluated rigorously by more than 1 or 2 randomized controlled trials, most were not double-blind, most compared midazolam with propofol and, of the 32 studies, only 14 followed patients for > 24 hours. With the exception of trials evaluating post-cardiac surgery patients, no data were available about the effect of sedative choice on the duration of mechanical ventilation or length of ICU stay.

Sedation scoring systems

Within the SCCM guidelines for IV sedation, there are recommendations regarding the choice of analgesic and sedative agents; however, there are no reliable guidelines addressing their adequacy.¹ Although there are validated methods for the subjective scoring of the presence of pain (linear scale or visual analog scale), a standard scoring system for sedation has been difficult to develop and implement.² In a study evaluating factors affecting ICU nurses' delivery of sedative therapy, Weinert and colleagues found that conflicts arose between physicians and nurses when explicit and shared goals of sedation were lacking.²³ A more uniform way to approach sedation in critically ill patients would be to agree on a common terminology for describing depth of sedation and the patient's apparent level of comfort.

Assessment of the degree of sedation may be difficult, especially in patients undergoing mechanical ventilation when communication is restricted. The use of sedation scales is one of the most frequently used methods of quantifying the degree of sedation in the ICU. Although many scales have been described, none is universally accepted or used. A recently published systematic review highlights the need for more information regarding the measurement properties of sedation effectiveness instruments.²⁴ De Jonghe et al identified 25 studies describing sedation instruments. Of these, only 1 pediatric ICU scale (the Comfort Scale²⁵) and 3 adult ICU scales (the Ramsay scale,²⁶ the Sedation-Agitation Scale,²⁷ and the Motor Activity Assessment Scale²⁸) have been tested for reliability and validity. Moreover, none have been tested for their ability to detect change in sedation status over time (responsiveness).

The goal of sedation scales is to avoid both excessive and inadequate sedation. However, oversedation is more difficult

to detect and avoid than undersedation. While an undersedated patient shows signs of agitation and distress, an oversedated patient may look comfortable and well cared for because the adverse effects are more subtle. In addition, deeply sedated patients are less demanding both physically and emotionally. Perhaps most disturbing is the observation that, in some hospitals, the intensity of sedation varies inversely with the number of nurses on a shift suggesting that "compliant" patients permit understaffing of ICUs.²⁹ A sedation scale can document oversedation and be used to trigger changes in drug dose. Indeed, Detriche et al found that the number of excessively sedated patients was significantly reduced with the introduction of a simple 5-point sedation scale in their ICU.³⁰

Despite the availability of easy-to-use sedation scales, their use is not widespread. A recent British survey revealed that 67% and 47% of adult and pediatric ICUs, respectively, employ scoring systems.¹¹ However, a Danish survey found that only 16% of respondents use a sedation scale (Ramsay scale).¹³ A US survey published in abstract form revealed that 78% of intensivists believe that they "monitor sedative use,"¹⁴ however, 43% use the Glasgow Coma Score, which does not qualify as a sedation scoring system.

The use of sedation scales reduces the risk of oversedation, yet none of the published scales fulfills the requisite criteria of validity, reliability, and responsiveness. Nonetheless, what appears to be important is not so much the precise method of measurement (eg, the Ramsay scale) as the routine incorporation of a measurement tool into sedation practice.

Sedation protocols

The use of explicit detailed protocols to manage complex clinical problems is becoming more common in the ICU.¹⁰ Currently, protocols are being used to help manage mechanical ventilation, ventilator weaning,^{31,32} and antibiotic decision-making.³³ Protocols promote a multidisciplinary approach to patient care and enhance efficiency by making the clinical plan explicit to all providers. Nurses, therapists, and physicians, thereby, achieve a level of uniformity of approach and goals, thus reducing within-patient variability in decision-making. Protocols may also enhance efficiency by allowing non-physician providers to make clinical decisions without continuous physician input. In this regard, protocol-directed weaning from mechanical ventilation by nurses and respiratory therapists has been shown to lead to more rapid extubation than physician-directed weaning, as well as significant cost-savings.³¹ Other potential benefits include a reduction in medical errors and increased compliance with evidence-based treatments.¹⁰

Sedation protocols are algorithms that nurses can use to adjust sedative and analgesic doses (based upon written guidelines) and to assess the patient's level of sedation, potentially avoiding both under- and over-sedation. Sedation protocols have been shown to decrease the duration of mechanical ventilation, promote the judicious use of therapeutic agents, reduce variability in prescribing, and decrease sedative costs in critically ill patients.^{3,31,34-38}

In a recent study, Brook et al performed a single-centre, non-blinded, randomized-controlled trial that compared a

nursing-implemented sedation protocol with usual sedation care in 322 adults requiring mechanical ventilation.³ Patients assigned to the intervention group were managed by a protocol, in which sedative/analgesic agents were titrated according to the patient's level of sedation as measured by the Ramsay scale. The patient's sedation level was assessed every 4 hours. The infusion rate was turned down if the level was adequate or the patient was rebolused if it was inadequate. In the control group, all decisions regarding sedation were made by the ICU team.

The primary outcome was the duration of mechanical ventilation, while secondary outcomes included ICU and hospital length of stay, tracheostomy rate, and hospital mortality. The authors performed an intention-to-treat analysis and controlled for important cointerventions with a weaning protocol. They found that the sedation protocol significantly reduced the duration of mechanical ventilation by 1.5 days ($p=0.003$) compared with the usual-care group. They also demonstrated a reduction in hospital stay (5.7 vs. 6.5 days; $p=0.013$) and ICU length of stay (14.0 vs. 19.9 days; $p<0.001$), a reduced duration of continuous sedative infusions, and a lower tracheostomy rate; all statistically significant and in favour of the treatment group. There was no significant difference in the mortality rate between the two groups.

This study was generally methodologically sound, but had several limitations that should be addressed in future studies. It is recognized that "blinding" is very difficult in this type of study; however, the lack of blinding may have resulted in a bias favouring the treatment group. That is, physicians making sedation decisions (or nurses making suggestions) for the control group may not have been as aggressive with weaning as they might have been under usual circumstances. The performance of this study in a single centre with previous experience in sedation research raises the issue of generalizability. Additionally, this study enrolled only medical ICU patients, and thus the applicability of this protocol to surgical patients is unknown.

Despite compelling evidence that sedation protocols improve outcome and reduce costs in critically ill patients, they are used in only a minority of ICUs. A recent paper revealed that, outside the setting of a trial, adherence to sedation protocols may only be moderate and it seems clear that the degree of adherence will affect the efficacy of any protocol.³⁹ A multicentre survey of critical care pharmacists regarding sedative, analgesic, and paralytic practices in their respective ICUs found that protocols were used in only 26% and health professional-generated pain/sedation scores were used to assess dosing needs in only 25%.⁴⁰ Although many institutions monitor paralytic doses, few use dosing or monitoring protocols for sedation or pain management. Just as the administration of vaso-active agents is titrated to patient-specific pathophysiology, administration of sedative drugs should be titrated to patient-specific objectives. In summary, guidelines that

minimize unnecessary variability in practice, prevent excessive medication, and emphasize management based on individual patient characteristics will improve the effective utilization of sedative and analgesic medications.

Daily interruption of sedative infusions

Daily interruption of sedative drug infusions, allowing patients to awaken daily, has recently been shown to have notable advantages.⁴ Kress et al performed a single-centre, randomized trial in a medical ICU that enrolled 128 mechanically-ventilated patients who were considered to require continuous IV sedation. Patients randomized to the intervention group had their sedative infusion interrupted on a daily basis starting 48 hours after enrolment. While sedation was held, patients were observed closely by a research nurse who contacted a study physician when patients either awakened or became agitated. The physician then decided whether or not to resume the sedative infusion, and if so, it was restarted at half the previous rate and re-titrated to achieve sedation at a Ramsay score of 3-4. The control group was managed by the ICU team in a usual care fashion.

With this simple intervention, the authors demonstrated a significant reduction in the duration of mechanical ventilation in the treatment group (median 4.9 vs 7.3 days, $p=0.004$) and an accompanying decrease in length of stay in the ICU (median 6.4 vs 9.9 days, $p=0.02$) and in hospital (median 13.3 vs 16.9, $p=0.19$). The mortality, tracheostomy, and reintubation rates were not different between the groups; however, fewer patients in the intervention group required neurological diagnostic testing to assess changes in mental status. No increase in complications (eg, unplanned extubation) was observed in the intervention group.

The main concern with the internal validity of this trial lies in the area of cointerventions. A standardized ventilator weaning protocol was not used and no details regarding weaning are provided. This, along with the lack of blinding raises the possibility that bias may have been inadvertently introduced if the intervention group was weaned from the ventilator more aggressively than the control group. This would tend to diminish the size of the demonstrated effect to some degree. The other issue with this trial is its generalizability. This study only enrolled medical ICU patients, and therefore, the applicability of this protocol to surgical patients is unknown. In addition, while the intervention in this trial may be technically easier to reproduce than the sedation protocol used in the Brook study,³ it is also significantly more demanding in terms of human resources. A dedicated nurse who observed the patient for signs of awakening or agitation was present whenever the infusions were stopped in the intervention group. The safety and efficacy of this protocol in the average ICU where many additional demands are placed upon nurses' time are unclear. One final concern is whether daily sedative interruption may have long-

term psychological effects on patients. Perceptions of distress by patients during daily awakenings or recollections of discomfort after their stay in the ICU were not studied. Long-term follow-up of patients, in this study and others like it, is needed to determine the residual impact, if any, of this sedation strategy.

Delirium in ICU patients

Agitated behaviour is a common and worrisome problem in the ICU, and often influences the dose of sedation and analgesia. Delirium, with a described incidence of 20%, is of particular concern to the intensivist because of its associated morbidity.⁴² In one study, the presence of delirium clearly increased the incidence of self-extubation and removal of catheters.⁴¹ Opiate use is one risk factor associated with delirium development.⁴¹ In the ICU population, the frequent inability to conduct an interview makes determination of the presence of delirium criteria difficult. Until recently, there was no easily applicable assessment tool for delirium in this patient population. Bergeron and colleagues recently developed and evaluated a screening checklist of 8 items based on DSM criteria and features of delirium.⁴² The sensitivity and specificity of this checklist for the diagnosis of delirium were 99% and 64%, respectively. The screening checklist can easily be applied by a clinician or nurse in < 5 minutes. Delirium screening in all ICU patients may be important because of its “confounder” influence (delirium itself increases length of stay and alters sedation and possible analgesia use); and because a decrease in the incidence of delirium may accompany one of the newer management strategies.

The impact of sedation strategies on health-related quality of life

The target effect of sedation in the majority of mechanically-ventilated patients has recently changed, for all the reasons presented above. Whereas intensivists previously strove to achieve a deeply sedated, unresponsive state, the current preference is for a sleepy patient who is easily awakened and who is pain- and anxiety-free. To add to the drawbacks of deep sedation mentioned above, one study has suggested that an inability to recall experiences during a critical illness leads to psychological distress after recovery.⁷ However, the psychological ramifications of keeping patients lightly sedated are not known and need to be better evaluated in future studies.

Patients surviving their ICU stay often have reduced health-related quality of life, especially if acute lung injury was present.⁴³ Post-traumatic stress disorder (PTSD) has also been observed in these patients.⁴⁴ However, there is very limited information available regarding the impact of sedation and neuromuscular blockade on health-related quality of life outcomes. In this regard, Nelson et al observed a significant correlation between the number of days of sedative administration in the ICU and both depressive symptoms and PTSD at follow-up.⁴⁵ However, because of the small

sample size and retrospective nature of the study, they were unable to draw any conclusions about cause-and-effect relationships.

Daily interruption of sedative infusions has been shown in a randomized controlled trial to result in a decreased duration of mechanical ventilation by 2.4 days and ICU length of stay by 3.5 days.⁴ However, the long-term psychological impact of “daily awakening” on patients has yet to be assessed. A potential concern is whether patients in the intervention group may experience undue anxiety or discomfort when their sedative and analgesic infusions are interrupted daily that may have longstanding psychological repercussions. Future studies should evaluate the psychological impact of different sedation strategies on ICU patients and include items such as pain, anxiety, and recall of daily sedative discontinuation.

Conclusion

It is clear that the manner in which sedatives are used in the ICU is important, in terms of meaningful clinical and cost-related outcomes such as duration of mechanical ventilation and length of hospital or ICU stay. The process of implementing sedation in critically ill patients may be equally or more important than the choice of which sedative drug to use. Because there is no risk-free sedative drug, recent efforts to improve outcomes for patients in the ICU have shifted toward investigations of the manner in which sedatives are administered.

Many important questions regarding sedation in the ICU remain unanswered. It is clear that intensivists need better methods of ensuring that the lowest effective doses of the most appropriate sedative, analgesic, and tranquilizing drugs are given for the shortest required time to critically ill patients receiving mechanical ventilation.

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Websites of interest

Canadian Critical Care Society
www.canadiancriticalcare.org

Canadian Association of Critical Care Nurses
www.caccn.ca

Society of Critical Care Medicine
sccm.org

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