Review Article

Sedation and Delirium in the Intensive Care Unit—A Practice-Based Approach

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Abstract

Introduction: Critically ill patients often require sedation for comfort and to facilitate therapeutic interventions. Sedation practice guidelines provide an evidencebased framework with recommendations that can help improve key sedation-related outcomes. Materials and Methods: We conducted a narrative review of current guidelines and recent trials on sedation. Results: From a practice perspective, current guidelines share many limitations including lack of consensus on the definition of light sedation, optimal frequency of sedation assessment, optimal timing for light sedation and consideration of combinations of sedatives. We proposed several strategies to address these limitations and improve outcomes: 1) early light sedation within the first 48 hours with time-weighted monitoring (overall time spent in light sedation in the first 48 hours-sedation intensity-has a dose-dependent relationship with mortality risk, delirium and time to extubation); 2) provision of analgesia with minimal or no sedation where possible; 3) a goal-directed and balanced multimodal approach that combines the benefits of different agents and minimise their side effects; 4) use of dexmedetomidine and atypical antipsychotics as a sedative-sparing strategy to reduce weaning-related agitation, shorten ventilation time and accelerate physical and cognitive rehabilitation; and 5) a bundled approach to sedation that provides a framework to improve relevant clinical outcomes. Conclusion: More effort is required to develop a practical, time-weighted sedation scoring system. Emphasis on a balanced, multimodal appraoch that targets light sedation from the early phase of acute critical illness is important to achieve optimal sedation, lower mortality, shorten time on ventilator and reduce delirium.

Ann Acad Med Singapore;49:215–25 Key words: Analgesia, Benzodiazepine, Critical Care, Dexmedetomidine, Propofol

Introduction

Sedation is the depression of patients' awareness of their environment and reduction of their responsiveness to external stimuli.¹ The use of analgesia and sedation in the intensive care unit (ICU) enables patients to tolerate painful and distressing procedures such as endotracheal intubation, invasive mechanical ventilation and insertion of invasive lines.² Deep sedation is sometimes necessary to manage significant agitation and distress, ventilator synchronisation, convulsive disorders, high intracranial pressure, shivering during therapeutic hypothermia and to provide amnesia during neuromuscular blockade.

There is growing evidence that sedation practices impact delirium which may increase ICU mortality and adversely affect long-term outcomes in ICU survivors.³⁻⁶ With advancement in ventilator triggering and modes, the need for deep sedation in the critically ill has declined. There is a growing emphasis on lighter levels of sedation and early physical activity in the respective guidelines. In this report, we provide a narrative review

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and update on strategies to achieve optimal sedation and reduce the burden of coma and delirium in critically ill patients. We conclude with a brief consideration of sedation practice in Singapore.

Current Guidelines

The 2018 practice guidelines for the prevention and management of Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption (PADIS)⁷ recommend a protocol-based, stepwise assessment of pain and sedation management in critically ill adults with an analgesia-first principle (Table 1). Provision of light sedation facilitates spontaneous breathing, shortens ventilation time and early mobilisation.

Propofol or dexmedetomidine is preferred in mechanically ventilated patients while benzodiazepines should be avoided. Dexmedetomidine offers shorter median duration of mechanical ventilation,⁸ shorter time to extubation and less delirium⁹ than benzodiazepine. However, there was no difference in median duration of mechanical ventilation between propofol and dexmedetomidine.⁸ The role of benzodiazepine in specific subgroups of patients—such as alcohol withdrawal—requires further study.

Although the PADIS guidelines present contemporary evidence-based recommendations and suggestions to improve sedation-related outcomes, they are not without limitations from a practice perspective which merit consideration.

First: Lack of Consensus Definition of Light Sedation

Ideally, light sedation should induce wakeful, comfortable and calm patients who are able to sustain attention and follow commands. Patients should be oriented to their surroundings and are able to communicate and cooperate with caregivers in early rehabilitation, mobilisation and return to normal cognitive and physical functions.

Various sedation scales are used in different health settings. The Richmond Agitation and Sedation Scale (RASS) and Riker Sedation-Agitation Scale (SAS) have been well validated in ventilated patients. Although a universally accepted range for light sedation is lacking, a RASS score of between +1 (slightly restless) to -2 (awake with eye contact to voice)—which corresponds to a SAS score of between 4 (calm and cooperative) to 3 (difficult to rouse and obeys simple commands)—is generally considered as being within the acceptable range.

Table 1. Summary of Recommendations on Pain and Agitation/Sedation by PADIS

| Recommendation | Strength of Recommendation | Quality of Evidence |
|---|---------------------------------|------------------------|
| Pain | | |
| Pain in adult ICU patients should be treated before a sedative agent is considered and the management of pain should be guided by routine pain assessment (analgesia-first sedation or analgesia-based sedation) | NA (Good practice statement) | NA |
| Use a stepwise approach for pain and sedation management that is protocol-based and assessment-driven | Conditional | Moderate |
| Agitation/sedation | | |
| Use light sedation (vs deep sedation) in mechanically ventilated adults | Conditional | Low |
| Use propofol over benzodiazepine in adult ICU patients who are mechanically ventilated after cardiac surgery | Conditional | Low |
| Use either propofol or dexmedetomidine over benzodiazepines in mechanically ventilated adults | Conditional | Low |
| In intubated adults, daily sedation interruptions and nurse-led targeted sedation can achieve and maintain a light level of sedation | Ungraded | Ungraded |
| BIS monitoring appears best suited for sedative titration during deep sedation or neuromuscular blockade, although observational data also suggest lighter sedation has potential benefit | Ungraded | Ungraded |
| Sedation monitored with BIS compared with subjective scales may improve sedative titration when a sedative scale cannot be used | Ungraded | Ungraded |
| Physical restraints are frequently used to prevent self-extubation and medical device removal, avoid falls and protect staff from combative patients despite a lack of studies that demonstrated the efficacy and safety concerns associated with physical restraints | Ungraded | Ungraded |

BIS: Bispectral Index; ICU: Intensive Care Unit; NA: Not applicable; PADIS: Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption

Despite being widely accepted as the gold standard in current sedation monitoring, the subjective nature of RASS and SAS assessments predisposed both scales to variability and uncertainty on the exact level of sedation that is needed at any point in time; with lower RASS scores, variable inter-rater reliability becomes particularly glaring in different institutions.^{10–12}

Second: Optimal Frequency of Sedation Assessment is Not Known

There is a lack of consensus on the frequency of sedation assessments. The intermittent nature of these assessments makes it problematic to observe any rapid change in sedation status in response to sedative bolus.

The sedation score indicates the condition of the patient when it was taken, and often does not reflect the level of sedation the patient would be at throughout the day. This is because the clinical status of the patient fluctuates with the course of disease and ICU stay.

Third: Optimal Timing of Light Sedation is Not Defined

Although the PADIS guidelines suggest that light sedation should be provided whenever it is clinically feasible to do so, there is, however, no consideration of the early phase of critical illness. Additionally, no consideration is given to sedation targets in the first 48 hours following mechanical ventilation.

Recent reports have suggested that the first 48 hours constitute a critical period to target sedation depth and it has a significant impact on mortality.¹³ Nevertheless, many prospective observational studies continued to demonstrate low adherence to target sedation depth within the first 48 hours.^{6,14}

Fourth: Use of Sedatives with Analgesics is Not Considered

The recommendations in the PADIS guidelines were informed by randomised clinical trials (RCT), and most of them had compared the use of 1 agent against another. In contrast, clinicians often use multiple agents and these are combined with opioids that are administered through different routes and in various concentrations.

Although the benefit that accrues from the use of a combination of different agents at lower doses—rather than 1 agent at a higher dose—has not been examined, it is possible that this intervention may yield a synergistic effect whereby the desirable properties of each agent are harnessed at a lower dose and their harmful effects—seen at a higher dose—are minimised.

Strategies to Improve Sedation-Related Outcomes

Early Light Sedation

In the last decade, most sedation RCT involved patients who were on mechanical ventilation for between 48–96 hours. However, sedation depth within the first 48 hours in ICU had an impact on clinical outcomes. A meta-analysis² demonstrated lower mortality with an odds ratio (OR) of 0.34, fewer days of mechanical ventilation (-2.07 days) and shorter length of stay (LOS) in ICU (-2.98 days) for early light sedation. Hospital LOS was shorter by 5.9 days and delirium frequency was almost halved with light sedation (OR 0.5), although the results were not statistically significant.

The findings were supported by a large cohort study³ that showed a positive association between light and moderate sedation levels at day 2 of ICU admission and reduced hospital mortality (OR 0.63), ICU mortality (45.8% vs 57.0%) and ICU LOS (11 vs 12 days). These findings emphasised the importance to achieve targeted light sedation on admission to ICU.

Time-Weighted vs Point-Based Sedation Monitoring

The Sedation Index (SI) or sedation intensity score is derived by dividing the positive sum of aggregate negative RASS scores by the total number of measurements over time. SI has been suggested as a tool that can be used to perform continuous measurement of sedation depth.³ A low score on SI indicates lighter sedation and provides a measurement of the overall sedation scores of patients over a certain period of time.

SI is shown to have an independent, dose-dependent association with survival at 180 days, time to extubation and subsequent delirium. An increase of 1 point in SI increases the risk of death by nearly 30%, risk of delirium by 25% and time to extubation by 24 hours. SI readings suggest that light sedation should be close to a RASS score of 0 or -1 at most.

The duration of light sedation is important and patients should be lightly sedated continuously from the time of ICU admission. Although this measure of sedation may not be practical in sedative titration to a target, it does, however, underscores the need for continuous and objective measurement of sedation depth. Additionally, it may offer a benchmark in sedation research.

Goal-Directed vs Daily Interruption

Since the 1990s, nurse-led protocols have demonstrated a decrease in the duration of mechanical ventilation and

ICU LOS.¹⁶ A decrease in the dose of sedatives used was also found.¹⁷ Daily awakening trials have shown benefit in studies performed in small centres.^{18,19} In the Awakening and Breathing Controlled (ABC) trial,²⁰ spontaneous awakening trials were paired with spontaneous breathing trials. The findings of the study revealed that the intervention group experienced more days breathing without assistance (3.1 days) and earlier discharge from ICU (9.1 vs 12.9 days) and hospital (14.9 vs 19.2 days). Patients in the intervention group were also less likely to die at the end of the first year (hazards ratio [HR] 0.68, number needed to treat 7.4).

In their study, however, Mehta et al²¹ demonstrated that the addition of daily sedation interruption to a standard goal-directed sedation protocol did not reduce the duration of mechanical ventilation or ICU stay. Interestingly, the daily interruptions group received higher doses of benzodiazepines and opioids, and a greater number of boluses were also required to achieve adequate sedation. Since the study used a significant amount of benzodiazepines, the results could be vastly different had the investigators used a benzodiazepinefree sedation strategy instead.

Opioid-Based Sedation vs "No Sedation" Strategy

Since daily interruptions could increase the amount of sedatives used and nursing interventions needed, the way forward would be total avoidance of the use of sedative agents. In 2010, a single-centre Danish study⁴ randomised patients to a no-sedation arm (but with analgesic treatment) and a sedation arm with a daily wake-up trial. Patients who did not receive sedation were shown to have had more days without ventilation (4.2 days), shorter ICU LOS (HR 1.86) and hospital LOS (HR 3.57); there was no difference in the incidence of accidental extubations. However, an increase in the incidence of delirium (20% vs 7%) was seen. Since the study used criteria from the 4th Edition of the Diagnostic and Statistical Manual of Mental Disorders-which detects hyperactive delirium-instead of the Confusion Assessment Method for ICU (CAM-ICU), hypoactive delirium could have been underdiagnosed in the control group.

Additionally, the study involved a switch from the use of propofol to midazolam after 48 hours and the use of benzodiazepines, both of which could have confounded the study outcome. Patients in the no-sedation arm also received morphine boluses with a sedative effect and were not titrated to a pain scale. The lack of adequate staff could hinder the use of a no-sedation strategy since another person was needed to comfort 11 patients who were not sedated against 3 patients who were sedated. In the more recent multicenter NONSEDA trial,²³ no difference was found in 90-day mortality or secondary outcomes—including ventilator-free days and ICU-free days—between the no-sedation arm and light sedation group. In septic post-abdominal surgical patients,²⁴ a reduction in time to successful extubation (adjusted HR 5.2) and an increase in delirium and coma-free days were found after sedation was ceased immediately upon admission to ICU.

Multimodal Sedation

Several sedatives are currently available, but each of them offers different benefits and harmful side effects. Although an ideal sedative is lacking, the use of a combination of different sedatives at low doses can allow the benefit of each agent to be harnessed and to minimise its side effects. Consequently, patients will feel more comfortable, awake and free from delirium.

Midazolam was highly favoured for its reliability and amnesiac properties. However, the undesirable side effects associated with its use included relatively slow offset and accumulation in organ failure. Consequently, the PADIS guidelines no longer recommended its use since it may lead to increased risks of delirium and longer duration on mechanical ventilation.^{8,9}

Propofol, on the other hand, is increasingly being used since it offers better efficacy, rapid onset and offset and ease in titratability. Nevertheless, it can induce significant vasodilatory and negative inotropic effects²⁵ when it is used in high doses or in severely shocked patients.

Dexmedetomidine increases cooperativeness and effective communication,⁸ lowers the incidence of delirium^{26,27} and accelerates resolution of delirium.²⁸ It is also less easily titratable with slower onset than other sedatives. Additionally, it is known to produce bradycardia and hypotension. More insight on the efficacy and side effects of this sedative will be known after the results of the ongoing MENDS II trial—a multicenter, double-blind RCT that compares days alive without delirium or coma in the first 14 days in patients sedated with dexmedetomidine and propofol—are published.²⁹

Opioids are used to manage pain and discomfort in ICU patients. However, they can cause somnolence, gut hypomotility and respiratory depression at higher doses. With a short duration of action, fentanyl is initially more easily titratable than morphine, but it accumulates with prolonged use. Its use is preferred in patients with renal impairment since the active ingredient in morphine, metabolite morphine-6-glucuronide, accumulates in renal impairment.

Remifentanil offers organ-independent metabolism and excellent titratability with almost instantaneous onset and offset. At higher doses, however, it becomes a very potent respiratory depressant and could potentially cause hyperalgesia and haemodynamic instability. There is evidence that remifentanil can reduce duration on mechanical ventilation and ICU LOS.^{30,31} Although less commonly used than conventional opioids due to its higher cost, a study in the Netherlands showed that the use of remifentanil led to an overall reduction in total health costs at 28 days (€1494), lower ICU LOS (7.6 days vs 8.5 days) and time on mechanical ventilation (5.0 days vs 6.0 days) than other opioids.³² A recent meta-analysis of 23 RCT with 1905 patients showed a more modest reduction in duration of mechanical ventilation (mean difference [MD] -1.46 hours), time to extubation after cessation of sedation (MD -1.02 hours) and ICU LOS (MD -0.1 days) without a significant difference in costs.³³

Antipsychotic agents such as haloperidol have been used to treat delirium and agitation, but have no role in prophylaxis or treatment of hypoactive delirium.^{34,35} In a large RCT of 1789 patients in the Netherlands that compared low-dose prophylactic haloperidol to placebos, the REDUCE trial did not find a difference in incidence of undifferentiated delirium (MD 1.5%) or delirium-free and coma-free days (MD 0 days).³⁶ In their study of the treatment of delirium in patients on haloperidol, ziprasidone and placebos, the MIND-USA trial did not find a difference in duration of delirium; however, there was a heavy preponderance of patients with hypoactive delirium.³⁷ Additionally, both antipsychotic agents precipitated arrhythmias in a patient who had prolonged QTc.³⁸

Other atypical antipsychotic agents such as quetiapine have fewer side effects than haloperidol in other clinical settings. A report had demonstrated that quetiapine shortened the duration of delirium, reduced agitation and led to higher rates of discharge back home.³⁹ Based on current evidence, quetiapine could only be considered for treatment of delirium with agitation or psychotic symptoms.

The dose and number of medications used should be escalated based on patient acuity, underlying pathology and needs of individuals. For example, a patient who is on low-dose opioid infusion to manage pain and discomfort could still receive a regular dose of quetiapine for agitated delirium, low basal infusion of dexmedetomidine to accelerate delirium resolution and readily titratable infusion of propofol to finetune the level of sedation to meet a specified target.

Stepwise Approach to Multimodal Sedation

Based on the preceding discussion on the limitations of existing guidelines and insights from recent trials on strategies to improve sedation-related outcomes, an integrated stepwise approach is proposed to manage sedation or delirium in ICU patients (Fig. 1).

Upon admission to ICU, care should begin with assessment and multimodal management of pain that may include an opioid (intermittent boluses or infusion). After adequate analgesia is achieved, the need for therapeutic sedation should be evaluated and, when indicated, sedative agents with a therapeutic effect for the clinical condition can be started.

As an example, for exceptional circumstances such as when a patient presents with intracranial hypertension, a barbiturate may be administered. In another example, when a patient presents with status epilepticus, a benzodiazepine may be given to control the seizure. When more sedatives are required, propofol and dexmedetomidine may be added, individually or in combination, to achieve the sedation target indicated by the clinical condition.

When sedation is not clinically indicated, the current sedation regime of a patient should be reviewed. For example, when a patient has a RASS score ≤ -2 , any benzodiazepines that are in use should be ceased immediately, the current sedative dose reduced or a low dose of an alternative agent initiated to aid weaning until the RASS score reaches between 0 to -1. When patients are agitated (RASS ≥ 2) and are at risk of harming themselves or others, a sedative that addresses delirium-such as dexmedetomidineshould be initiated; when the delirium is hyperactive, quetiapine can be given. Propofol is useful for immediate control, but should be weaned as soon as it is safe to do so. Non-pharmacological measures that address delirium should be undertaken concurrently. When patients are calm and awake (RASS 0 to -1), delirium screening should be performed and when present, treated appropriately.

Delirium-Sparing Strategies

Many of the strategies that improve sedation-related outcomes have also been shown to reduce delirium burden. Analgesic requirements should be titrated in a timely fashion with the use of simple bedside tools such as the Visual Acuity Score in interactive patients⁴⁰ or Critical Pain Observation Tool in those who are heavily sedated or are not able to report pain.⁴¹ Early consideration of analgesic adjuncts—such as low-dose ketamine—may decrease delirium rates (21% vs 37%) and duration (2.8 days vs 5.3 days).⁴²



Fig. 1. An integrated stepwise approach to multimodal sedation. There are 5 steps in the model: 1) assess, recognise and treat pain with multimodal analgesia; 2) assess need for sedation; 3) assess current level of sedation and escalate, de-escalate or adjust choice of sedatives to achieve light sedation; 4) assess, recognise and treat delirium; and 5) continual reassessment. CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; RASS: Richmond Agitation and Sedation Scale

By targeting light sedation, patient engagement, early mobilisation and daily delirium screening can result and these outcomes can, in turn, ensure early intervention for delirium through pharmacological and non-pharmacological means. Dexmedetomidine alone, or as part of a multimodal approach, is favoured for its delirium-sparing effect in critical care and perioperative care.^{4,27,43-5} Nocturnal use of dexmedetomidine has also shown decreased delirium rates and duration without affecting sleep quality.⁴⁶

Non-pharmacological management strategies such as day-night routines, noise reduction and patient reorientation and refamiliarisation programmes are frequently instituted as part of algorithms to reduce delirium in critical care. Though reasonable in practice, these strategies lack evidence that can help to determine their effect, if any, on delirium duration or incidence.⁴⁷

Sedation Strategy as Part of ICU Bundle

A framework that outlined early implementation of patient-centred care and comfort in ICU is early Comfort using Analgesia, minimal Sedatives and maximal Humane care (eCASH). The emphasis of eCASH is on the use of analgesia first with minimal or no sedation, communication aids, noise reduction to facilitate good sleep, early mobilisation and family involvement.⁴⁸

Another framework is the ICU Liberation Bundle, which is an example of the implementation of the PADIS guidelines as a model that guides early regular assessment and intervention by bedside clinicians. The bundle encompasses the elements of Awakening and Breathing coordination, Choice of drugs, Delirium monitoring and management, Early mobility and Family engagement (ABCDEF). The programme is designed to reduce delirium and improve pain management and long-term consequences in critically ill adults. Studies have shown that adherence to even a part of the ABCDEF bundle could lead to an improvement in patient-centric outcomes.

The findings of the ICU Liberation Collaborative⁴⁹ had shown a dose-dependent relationship between compliance and hospital death within 7 days (adjusted HR 0.32), next-day mechanical ventilation (adjusted OR [AOR] 0.28), coma (AOR 0.35), delirium (AOR 0.6), use of physical restraint (AOR 0.37), ICU readmission (AOR 0.54) and discharge to a facility other than home (AOR 0.64). Another multicentre study⁵⁰ found an improvement of 7% in hospital survival and increase of 2% in days alive; for every increase of 10% in total bundle compliance, the incidence of delirium and coma is greatly reduced. In New York, the implementation

of a full ICU bundle reduced total ICU and hospital cost by 24.2% and 30.2%, respectively, compared to a partial ICU bundle.⁵¹ Trogrlić et al⁵² also found that improved mortality and ICU LOS were more statistically likely when ≥ 6 strategies that targeted delirium assessment, prevention and treatment were used.

In Australia, a quality improvement programme, Victorian Pain Agitation and Delirium, was recently developed as an algorithm for the assessment of pain, targeted sedation and delirium screening. The programme involved prescription of a RASS target twice daily, pain assessment and management at 4-hour intervals and CAM-ICU once daily.⁵³ Findings from a regular audit of the programme showed that over a 3-month period, compliance improved to >80%. The programme was sustained and maintained through ongoing audit and education. Additionally, it emphasised the need for optimal sedation and delirium prevention in ICU patients.

Consequently, a multipronged approach for optimal sedation-related outcomes (Fig. 2) in ICU patients should involve the collective use of various strategies that include an adherence to the basic premise of the PADIS guidelines with analgesia first, light sedation, multimodal sedation and analgesia, promotion of early mobility and prevention of delirium through pharmacologic and non-pharmacologic means.



Fig. 2. A multipronged approach to optimal sedation in the Intensive Care Unit.

Practice of Analgesia, Sedation and Delirium Management in Singapore ICU

In the last decade, the practice of analgesia, sedation and delirium in Singapore has changed to conform to the PADIS guidelines. Findings from 3 local studies that described sedation and delirium in ICU⁵⁴⁻⁶ throughout the city-state are shown in Table 2. In particular, the study by Lee et al⁵⁶ is a subgroup analysis of the SPICE cohort in Singapore.⁵⁵

In summary, sedation use in Singapore ICU ranged from between 25.8–70.3%; the use of fentanyl and propofol also predominated. Benzodiazepine use was

Table 2. Comparison of Major Findings from 3 Studies on Sedation Practices in Singapore

| Variable | Koh et al* | Ng et al [†] | Lee et al [‡] |
|--|---|--------------------------------------|---|
| Туре | Point-prevalence survey | Prospective, observational cohort | Prospective, observational cohort |
| Year | 2008 | 2012 | 2012 |
| Number of hospitals | 5 | 4 | 1 |
| Number of ICU | 11 | 7 | 2 |
| Number of cases | 93 | 198 | 58 |
| Sedation in ICU, % | 25.8 | 70.3 | 52.4 |
| Sedation scale usage, % | 75 | 100 | 100 |
| Choice of sedative, % | | | |
| Propofol | 50 | 36 | 44.2 |
| Morphine/fentanyl | Not reported | 56.8 | 33.8 |
| Midazolam | 41.7 | 11.4 | 6.7 |
| Sedation target prescribed, % | 20.8 | 38.7 | 11.1 |
| Light sedation, % | | | |
| Total | NA | 79.3 | 79.1 |
| Early period in ICU stay | | 70 | 64.8 |
| Subsequent period in ICU | | 83 | 84.7 |
| Use of physical restraints, % | 29 | 55.5 | NA |
| Delirium assessment | | | |
| Method | Clinical judgement | CAM-ICU | CAM-ICU |
| Compliance to assessment, % | NA | 76 | NA |
| Delirium incidence | NA | 23.7 | 22.4 |
| Difference between MICU/SICU practices | Yes | NA | Yes |
| Major differences in SICU | More propofol and less midazolam use Frequent sedation assessments | | More sedation targets and prescriptions Less midazolam use Lower sedation dose More patients in light sedation range Lower delirium incidence |

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; ICU: Intensive Care Unit; MICU: Medical Intensive Care Unit; NA: Not applicable; SICU: Surgical Intensive Care Unit

*Koh J, Tee A, Phoo JWH, et al. A national point-prevalence survey of the use of sedation, analgesia, neuromuscular blockade and delirium assessment in adult intensive care units in Singapore. Intensive Care Med 2009;4:S64.

[†]Ng SY, Phua J, Wong YL, Kalyanasundaram G, Mukhopadhyay A, Lim D, et al. Singapore SPICE: sedation practices in intensive care evaluation in Singapore—a prospective cohort study of the public healthcare system. Singapore Med J 2020;61:19–23.

*Lee YL, Kalyanasundaram G, Ti LK, Ng SY. A prospective, observational, longitudinal cohort study of sedation practices in SGH intensive care units. Proc Singapore Healthc 2018;27:103–9. mostly restricted to midazolam in patients involved in the studies, but the use of midazolam became uncommon in later studies (dropping from 41.7% in 2008 to 11.4% in 2012). Most patients were lightly sedated from the start of ICU admission.

Initially, delirium screening was rarely done; however, it became common in later studies despite the contextual and linguistic challenges faced in adapting CAM-ICU for use in local practice. Overall, the incidence of delirium in Singapore ICU is low and could be attributed to the predominant use of analgesics such as fentanyl, low use of midazolam and practice of light sedation. Additionally, efforts were made to improve delirium screening in ICU through nurse-led education initiatives.⁵⁷ Baseline compliance is high for sedation monitoring, but low for delirium screening. A comprehensive education programme that comprised didactics, patient simulation and beside-proctored interaction with real patients resulted in sustained improvement in compliance to delirium screening from 36% at baseline to 61% at 10 months.⁵⁷

Future directions for sedation, agitation and delirium research in Singapore could include identification of unique cultural beliefs or factors that aid local sedation practices and overcoming those that are harmful. An understanding of the evolution of local sedation practices over the last decade would also be beneficial to identify areas that need more emphasis. Further research could be performed on compliance to implementation of ICU care bundles such as the ABCDEF programme and other non-pharmacological methods to improve sedation and delirium-related, patient-centred outcomes. Assessment of non-pharmacologic strategies that are unique to Singapore is needed (such as a supportive family who is given access during ICU stay, availability of technology for patients to communicate and interact and for recreation/reorientation). Since sedation strategies currently recommend light to no sedation where possible, it is important to determine post ICU patient-centred outcomes-cognitive function, physical recovery, post-traumatic stress disorder, anxiety and depression, return to former quality of life-and burden of ICU care in an ageing population.

Conclusion

A multipronged approach to optimal sedation leads to improved patient outcomes in ICU. The importance of targeting light sedation early in the acute phase of critical illness and its impact on mortality, delirium and long-term outcomes must be emphasised. More effort must be devoted to the creation of a sedation scoring system that is both practical and time-weighted. A bundled approach that adheres to analgesia first with no sedation or the practice of balanced, multimodal sedation—when necessary—is essential to help patients remain alert, cooperative and delirium-free as well as to lower their mortality and duration of mechanical ventilation, facilitate early mobilisation and increase cognitive well-being.

REFERENCES

- Rowe K, Fletcher S. Sedation in the intensive care unit. Contin Educ Anaesth Crit Care Pain 2008;8:50–5.
- Cohen D, Horiuchi K, Kemper M, Weissman C. Modulating effects of propofol on metabolic and cardiopulmonary responses to stressful intensive care unit procedures. Crit Care Med 1996;24:612–7.
- Shehabi Y, Bellomo R, Kadiman S, Ti LK, Howe B, Reade MC, et al. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a multinational prospective longitudinal cohort study. Crit Care Med 2018;46:850–9.
- Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early goal-directed sedation versus standard sedation in mechanically ventilated critically III patients: a pilot study. Crit Care Med 2013;41:1983–91.
- Liu X, Xie G, Zhang K, Song S, Song F, Jin Y, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: a meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care 2017;38:190–6.
- Nassar Jr AP, Zampieri FG, Salluh JI, Bozza FA, Machado FR, Guimarães HP, et al. Organizational factors associated with target sedation on the first 48 h of mechanical ventilation: an analysis of checklist-ICU database. Crit Care 2019;23:34.
- Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825–73.
- Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151–60.
- Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489–99.
- Deol H, Minaie A, Surani S, Udeani G. P243 reliability and utility of the Ramsay sedation scale for dosing sedatives in critically ill intubated patients. Chest 2017;151:A143.
- Deol HS, Surani SR, Udeani G. Inter-rater reliability of the Ramsay sedation scale for critically-ill intubated patients. Cureus 2019;11:e6021.
- Barbato M, Barclay G, Potter J, Yeo W, Chung J. Correlation between observational scales of sedation and comfort and bispectral index scores. J Pain Symptom Manage 2017;54:186–93.
- Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med 2012; 186:724–31.
- Aragón RE, Proaño A, Mongilardi N, de Ferrari A, Herrera P, Roldan R, et al. Sedation practices and clinical outcomes in mechanically ventilated patients in a prospective multicenter cohort. Crit Care 2019;23:130.

- 15. Stephens RJ, Dettmer MR, Roberts BW, Ablordeppey E, Fowler SA, Kollef MH, et al. Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review and meta-analysis. Crit Care Med 2018;46:471–9.
- Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999;27:2609–15.
- Abdar ME, Rafiei H, Abbaszade A, Hosseinrezaei H, Abdar ZE, Delaram M, et al. Effects of nurses' practice of a sedation protocol on sedation and consciousness levels of patients on mechanical ventilation. Iran J Nurs Midwifery Res 2013;18:391–5.
- Hughes CG, Girard TD, Pandharipande PP. Daily sedation interruption versus targeted light sedation strategies in ICU patients. Crit Care Med 2013;41:S39–45.
- 19. Nassar Jr AP, Park M. Daily sedative interruption versus intermittent sedation in mechanically ventilated critically ill patients: a randomized trial. Ann Intensive Care 2014;4:14.
- 20. Girard TD, Kress JP, Fuchs BD, Thomason JWW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled Trial): a randomised controlled trial. Lancet 2008;371:126–34.
- Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985–92.
- 22. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010;375:475–80.
- Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian K, Ytrebø LM, et al. Nonsedation or light sedation in critically ill, mechanically ventilated patients. N Engl J Med 2020;382:1103–11.
- 24. Chanques G, Conseil M, Roger C, Constantin J, Prades A, Carr J, et al. Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-ventilation): a randomised, parallel-group clinical trial. Lancet Respir Med 2017;5:795–805.
- 25. Lee TL. Pharmacology of propofol. Ann Acad Med Singapore 1991;20:61-5.
- 26. Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A, et al. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis a randomized clinical trial. JAMA 2017;317:1321–8.
- Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019;380:2506–17.
- Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Cheung B, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA 2016;315:1460–8.
- 29. Pandharipande P. Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction and Mortality in Septic Patients With Acute Respiratory Failure (MENDS2). Available at: https://clinicaltrials.gov/ct2/show/NCT01739933. Accessed on 19 March 2020.
- 30. Wilhelm W, Kreuer S. The place for short-acting opioids: special emphasis on remifentanil. Crit Care 2008;12:S5.

- Futier E, Chanques G, Constantin SC, Vernis L, Barres A, Guerin R, et al. Influence of opioid choice on mechanical ventilation duration and ICU length of stay. Minerva Anestesiol 2012;78:46–53.
- 32. Al MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-based analgo-sedation vs. conventional analgesia and sedation for patients on mechanical ventilation in the Netherlands. Crit Care 2010;14:R195.
- 33. Zhu Y, Wang Y, Du B, Xi X. Could remifentanil reduce duration of mechanical ventilation in comparison with other opioids for mechanically ventilated patients? A systematic review and meta-analysis. Crit Care 2017;21:206.
- Oh ES, Needham DM, Nikooie R, Wilson LM, Zhang A, Robinson KA, et al. Antipsychotics for preventing delirium in hospitalized adults: a systematic review. Ann Intern Med 2019;doi:10.7326/M19-1859.
- 35. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. J Am Geriatr Soc 2016;64:705–14.
- 36. Van Den Boogaard M, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, et al. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE randomized clinical trial. JAMA 2018;319:680–90.
- Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. N Engl J Med 2018;379:2506–16.
- Markowitz JD, Narasimhan M. Delirium and antipsychotics: a systematic review of epidemiology and somatic treatment options. Psychiatry (Edgmont) 2008;5:29–36.
- 39. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010;38:419–27.
- 40. Klein C, Caumo W, Gélinas C, Patines V, Pilger T, Lopes A, et al. Validation of two pain assessment tools using a standardized nociceptive stimulation in critically ill adults. J Pain Symptom Manage 2018;56:594–601.
- 41. Gélinas C, Arbour C, Michaud C, Vaillant F, Desjardins S. Implementation of the critical-care pain observation tool on pain assessment/management nursing practices in an intensive care unit with nonverbal critically ill adults: a before and after study. Int J Nurs Stud 2011;48:1495–504.
- 42. Perbet S, Verdonk F, Godet T, Jabaudon M, Chartier C, Cayot S, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: a randomised double-blind control trial. Anaesth Crit Care Pain Med 2018;37:589–95.
- Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1893–1902.
- 44. Huyan T, Hu X, Peng H, Zhu Z, Li Q, Zhang W. Perioperative dexmedetomidine reduces delirium in elderly patients after lung cancer surgery. Psychiatr Danub 2019;31:95–101.
- 45. Liu X, Xie G, Zhang K, Song S, Song F, Jin Y, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: a meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care 2017;38:190–6.

- 46. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 2018; 197:1147–56.
- Herling SF, Greve IE, Vasilevskis EE, Egerod I, Mortensen CB, Møller AM, et al. Interventions for preventing intensive care unit delirium in adults. Cochrane database Syst Rev 2018;11:CD009783.
- 48. Vincent J, Shehabi Y, Walsh TS, Pandharipande P, Ball JA, Spronk P, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med 2016;42:962–71.
- 49. Pun BT, Balas MC, Barnes-Daly MA, Thompson JL, Aldrich JM, Barr J, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU Liberation Collaborative in over 15,000 adults. Crit Care Med 2019;47:3–14.
- 50. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med 2017;45:171–8.
- 51. Hsieh SJ, Otusanya O, Gershengorn HB, Hope AA, Dayton C, Levi D, et al. Staged implementation of awakening and breathing, coordination, delirium monitoring and management, and early mobilization bundle improves patient outcomes and reduces hospital costs. Crit Care Med 2019;47:885–93.

- 52. Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PHJ, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care 2015;19:157.
- 53. Breheny C. Intensive care pain, agitation and delirium standardised assessment and monitoring. Available at: https://www.bettersafercare.vic.gov.au/critical-care-network/ pain-agitiation-delirium-standardised-guidelines. Accessed on 19 December 2019.
- 54. Koh J, Tee A, Phoo JWH, et al. A national point-prevalence survey of the use of sedation, analgesia, neuromuscular blockade and delirium assessment in adult intensive care units in Singapore. Intensive Care Med 2009;4:S64.
- 55. Ng SY, Phua J, Wong YL, Kalyanasundaram G, Mukhopadhyay A, Lim D, et al. Singapore SPICE: sedation practices in intensive care evaluation in Singapore—a prospective cohort study of the public healthcare system. Singapore Med J 2020;61:19–23.
- 56. Lee YL, Kalyanasundaram G, Ti LK, Ng SY. A prospective, observational, longitudinal cohort study of sedation practices in SGH intensive care units. Proc Singapore Healthc 2018;27:103–9.
- Lieow JLM, Chen FSM, Song G, Tang PS, Kowitlawakul Y, Mukhopadhyay A. Effectiveness of an advanced practice nurse-led delirium education and training programme. Int Nurs Rev 2019;66:506–13.