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Singapore SPICE: Sedation Practices in Intensive Care Evaluation in Singapore – a prospective cohort study of the public healthcare system

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ABSTRACT

Introduction: A study was conducted to describe the sedation practices of Singapore intensive care units (ICUs) in terms of drug use, sedation depth and the incidence of delirium in both early (< 48 hours) and late (> 48 hours) periods of ICU admission.

Methods: A prospective multicentre cohort study was conducted on patients who were expected to be sedated and ventilated for over 24 hours in seven ICUs (surgical ICU, n = 4; medical ICU, n = 3) of four major public hospitals in Singapore. Patients were followed up to 28 days or until ICU discharge, with four hourly sedation monitoring and daily delirium assessment by trained nurses. Richmond Agitation and Sedation Score (RASS) and Confusion Assessment Method for Intensive Care (CAM-ICU) were used.

Results: We enrolled 198 patients over a five-month period. Mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 25.3 ± 9.2 and 90.9% of hospital admissions were emergency. Patients were followed up for 1,417 ICU patient days, of which 396 days were in the early period and 1,021 days were in the late period. There were 7,354 RASS assessments performed. Propofol and fentanyl were the sedative agents of choice in the early and late periods, respectively. Patients were mostly in the light sedation range, especially in the late period. At least one episode of delirium was seen in 23.7% of patients.

Conclusion: Sedation practices in Singapore ICUs are characterised by light sedation depth and low incidence of delirium. This may be due to the drugs used.

Keywords: delirium, intensive care unit, sedation

INTRODUCTION

Delirium is a common complication associated with worse long-term outcomes in critically ill patients.[1,2] The causes of delirium are multifactorial and may be associated with sedation practices.[3,4] Although there are updated guidelines for sedation and analgesia in the intensive care unit (ICU),[5] compliance has typically been low.[6]

The Australian New Zealand Sedation Practice in Intensive Care Evaluation (ANZ SPICE) study informed that early sedation depth independently predicts delayed extubation and increased mortality in the ICU,[4] and early goal-directed sedation may be a feasible intervention to improve outcomes.[7]

To our knowledge, data on sedation and delirium in critically ill patients in Singapore is limited. A point prevalence survey done in 2010 showed that sedation was administered in 25.8% of patients; in 75% of patients, there was use of sedation scales. However, sedation protocols were used only in 20.8% of patients. No delirium screening was performed.[8]

In view of this, we conducted a prospective multicentre cohort study to comprehensively describe the sedation practices of Singapore ICUs in terms of drug use, sedation depth and incidence of delirium in both the early and late periods of ICU admission.

METHODS

All surgical and medical adult ICUs in the Singapore public healthcare system (five hospitals; surgical ICU, n = 5; medical ICU, n = 5) were invited to participate in the study. Seven ICUs (surgical ICU, n = 4; medical ICU, n = 3) from four hospitals eventually agreed to participate. The ANZ SPICE protocol[4] was used. All study centres follow a closed model of care led by attending intensivists. There was an on-duty specialist registrar at all times and the nursing ratio was 1:1–2 in all ICUs.

Ethics approval was obtained at all the individual participating centres. The requirement for informed consent was waived due to the observational nature of the study.

All consecutively sedated, intubated and mechanically ventilated adult ICU patients who were expected to remain intubated for another day were included. Patients with suspected or proven dementia, neurological impairment, psychiatric illnesses or those who were unable to communicate with the investigators were excluded. To avoid over-representation by any one centre, no centre recruited more than 30 patients.

Prior to commencement of the study, the investigators, research staff and ICU nurses were trained in the ANZ SPICE protocol,[4] including assessment of patients using the Richmond Agitation and Sedation Score (RASS)[9] and Confusion Assessment Method for Intensive Care (CAM-ICU).[10] The local languages (i.e. English, Mandarin, Malay, Tamil and local dialects) were used to communicate with the patients. We used the ANZ SPICE study protocol[4] with a streamlined standardised case report form for data entry. A trained research coordinator collected the data from electronic and paper clinical notes.

Upon enrolment into the study, relevant demographic data, including age, gender, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II[11] scores and admission sources, were collected. RASS and pain scores were assessed at baseline and every four hours subsequently by the trained nurses. Patients' sedation level was recorded according to the RASS, as light sedation (score range −2 to +1), deeply sedated (score range −3 to −5) and agitated (score ≥ 2). Daily CAM-ICU assessments were only performed for lightly sedated patients. A patient was diagnosed with delirium if CAM-ICU was positive. For patients who were able to communicate, Visual Analogue Scale (VAS) > 3 was used for pain assessment. For those who were unable to communicate, the Critical Care Pain Observation Tool (CPOT) descriptors[12] were used.

The first 48 hours of ICU admission was considered as the early period. A patient was considered to have early deep sedation if a RASS score of −3 to −5 was recorded during this period. The period after the first 48 hours of ICU admission was considered as the late period.

Data on all cumulative sedative medication infusions and doses were collected. Daily sedation cessations and indications were noted. Adjunct therapies, such as the use of physical restraints, renal replacement therapy and vasopressors, were recorded as well.

The patients were followed up for up to 28 days or until discharge from hospital. We recorded outcomes of development of delirium, tracheostomy performed, ventilation duration, ICU mortality and length of stay, and hospital mortality and length of stay.

Statistical analysis was performed using SPSS Statistics version 17 (SPSS Inc, Chicago, IL, USA). Comparisons of categorical data and proportion were performed using chi-square or Fisher's exact test, as appropriate. Parametric continuous variables were compared using Student's *t*-test. Non-parametric variables were compared using the Wilcoxon rank sum test. All tests were two-sided and $p < 0.05$ was considered to be statistically significant. Data was presented as mean ± standard deviation or median (interquartile range), as appropriate. Missing data was handled by multiple imputations.

RESULTS

We enrolled 198 patients over a period of five months in 2012. A majority of patients were admitted from the ward (n = 79, 39.9%), followed by the emergency department (n = 56, 28.3%) and emergency operating rooms (n = 45, 22.7%). Together, this group of patients was considered as emergency hospital admissions (n = 180, 90.9%). The baseline demographics of our primary cohort are presented in Table I.

Table I. Patient demographics (n = 198).

Variable	No. (%)
Age (yr)*	62.3 ± 16.9
Male gender	109 (55.1)
Weight (kg)*	62.3 ± 15.1
APACHE II score*	25.3 ± 9.2
Cause of hospital admission	
Ward	79 (39.9)
Emergency department visit	56 (28.3)
Emergency operation	45 (22.7)
Elective operation	10 (5.1)
Intensive care unit transfer	7 (3.5)
Interhospital transfer	1 (0.5)

**Data presented as mean ± standard deviation. APACHE: Acute Physiology and Chronic Health Evaluation*

Of the 162 patients who were admitted for more than 48 hours, 49 (30.2%) patients were lightly sedated during the first 48 hours. All patients recruited were followed up to the end of study – our cohort was followed up for 1,417 ICU patient days, of which 396 patient days were in the early period (first 48 hours) and 1,021 patient days were in the late period (after 48 hours).

The overall drug regimen, and the drug regimens of the early and late periods are presented in Table II. In the early period, the most commonly used sedation drug was propofol, which was administered for 260 (65.7%) patient days, followed by fentanyl (n = 193, 48.7%). In the late period, the reverse trend was observed, with fentanyl being more commonly administered than propofol (fentanyl: n = 384, 37.6%; propofol: n = 251, 24.6%). While the proportion of patients receiving sedation drugs decreased from the early period to late period, the mean dose of drug per patient day increased.

Table II. Drug regimens in the early and late periods of ICU patient days.

Drug	ICU patient days (no. [%])		
	Total (n = 1,417)	**Early period (n = 396)**	**Late period (n = 1,021)**
Fentanyl			
No. of patient days	577 (41)	193 (49)	384 (38)
Dose (μg)	401,319	112,159	289,160
Dose/patient day (μg)*	696 ± 403	581 ± 451	753 ± 489
Propofol			
No. of patient days	511 (36)	26 (66)	251 (25)
Dose (μg)	528,369	244,432	283,937
Dose/patient day (μg)*	1,034 ± 726	940 ± 783	1,131 ± 872
Morphine			
No. of patient days	228 (16)	76 (19)	152 (15)
Dose (μg)	5,185	1,370	3,815
Dose/patient day (μg)*	23 ± 13	18 ± 18	25 ± 15
Midazolam			
No. of patient days	162 (11)	77 (19)	85 (8)
Dose (μg)	5,542	1,972	3,570
Dose/patient day (μg)*	34 ± 32	26 ± 36	42 ± 37
Dexmedetomidine			
No. of patient days	57 (4)	17 (4)	40 (4)
Dose (μg)	166	32	134
Dose/patient day (μg)*	2.9 ± 1.8	1.9 ± 1.3	3.4 ± 2.1
Ketamine	2		
Haloperidol	1		
Diazepam	1		

**Data presented as mean ± standard deviation. ICU: intensive care unit*

Sedation holidays were practised in about one-fifth (22.1%) of our patients, for which extubation was taken as the main indication (55.6%; Table III).

Table III. Sedation holidays.

Variable	No. (%)
No. of patient days	1,417 (100.0)
Deliberate cessation	313 (22.1)
Indication (n = 313)	
Extubation	174 (55.6)
Deep sedation not required	22 (7.0)
Routine daily interruption	13 (4.2)
Other	110 (35.1)

There were 7,354 RASS assessments performed during 1,417 ICU patient days. For 2,849 (38.7%) RASS assessments, the ICU team prescribed a sedation target, which was met most of the time (82.5%).

Overall, 5,836 (79.3%) of the sedations performed were in the light sedation range. This occurred more often in the late period when compared to the early period (late period: 82.9%; early period: 69.8%). In contrast, there were more deep sedations in the early period when compared to late period (early period: 28.8%; late period: 15.7%). The range of sedation levels achieved according to RASS scores over the early and late periods are presented in Fig. 1.

Out of 198 patients, 47 (23.7%) patients had at least one episode of delirium during the ICU stay. There were 164 (11.6%) patient days of CAM-ICU being positive, with more occurring in the late period when compared to the early period (late period: n = 137, 13.4%; early period: n = 27, 6.8%). The overall incidence of pain was 8.4%. Data for intensive care sedation, delirium and pain are presented in Table IV.

Table IV. RASS assessments, CAM-ICU and pain during the early and late periods of ICU patient days.

Drug	**No. (%)**		
	Total	**Early period**	**Late period**
No. of patient days	1,417 (100.0)	396 (100.0)	1,021 (100.0)
With ≥ 1 assessment of light sedation	1,075 (75.9)	240 (60.6)	835 (81.8)
With positive CAM-ICU	164 (11.6)	27 (6.8)	137 (13.4)
RASS assessments	7,354 (100.0)	1,863 (100.0)	5,491 (100.0)
Assessments with prescribed sedation target	2,849 (38.7)	727 (39.0)	2,122 (38.6)
Assessments that met prescribed sedation target	2,351 (82.5)	566 (77.9)	1,785 (84.1)
Assessments where patient could			
Communicate that he was in pain	269 (3.7)	57 (3.1)	212 (3.9)
Not communicate but appeared to be in pain	351 (4.8)	91 (4.9)	260 (4.7)

CAM-ICU: Confusion Assessment Method for Intensive Care; RASS: Richmond Agitation and Sedation Score

Patient outcomes are presented in Table V. The overall ICU and hospital mortality were 12.1% and 24.2%, respectively. The median ICU and hospital lengths of stay were 4 (IQR 3–8) days and 21 (IQR 11–37) days, respectively. The median days on the ventilator was 3 (IQR 2–6) days, and 14 (7.1%) patients received a tracheostomy.

Table V. Patient outcomes (n = 198).

Outcome	**No. (%)**
Hospital mortality	48 (24.2)
Hospital LOS (day)*	21 (11–37)
ICU mortality	24 (12.1)
ICU LOS (day)*	4 (3–8)
Ventilation days (day)*	3 (2–6)
Tracheostomy	14 (7.1)
Time to tracheostomy (day)*	9 (6–15)
Vasopressor	131 (66.2)
Renal replacement therapy	51 (25.8)

**Data presented as median (interquartile range). ICU: intensive care unit; LOS: length of stay*

DISCUSSION

Over a period of five months, we observed the sedation practices for 198 ICU patients in the Singapore public healthcare system. Propofol and fentanyl were the sedative agents of choice in the early and late periods, respectively. Mostly, patients were in the light sedation range and this occurred more commonly in the late period. About one-quarter of our patients had at least one episode of delirium.

Patients in Singapore had a sedation depth profile comparable to that of two previous SPICE studies in Australian/New Zealand (ANZ SPICE) and Malaysia (MY SPICE),[4,13] with a greater proportion of deep sedation scores occurring in the early period when compared to the late period. In Australia, 61.9% of RASS assessments in the early period was in the deep sedation range when compared to 23.7% in the late period;[4] the corresponding proportion was 58% in the early period and 34% in the late period for Malaysia,[13] and 28.8% in the early period and 15.7% in the late period for Singapore in our study. This is to be expected, as in the

early course of critical illness, patients may be more acutely ill and hence require deeper sedation to facilitate critical care interventions.

In general, our patients were more lightly sedated than the other two cohorts. In the early period, 69.8% of our patients were in the light sedation range when compared to 35.5% and 39.3% in ANZ SPICE and MY SPICE, respectively. In the late period, 15.7% of our patients were in the deep sedation range when compared to a range of 23.7%–34% of patients in the other two studies.

CAM-positive delirium occurred at least once in 23.7% of our patients, which was lower than a range of 44%–50.7% in the other two SPICE studies. In a North American BRAIN-ICU study,[14] 74% of critically ill patients developed delirium during the hospital stay.

Differences in findings related to the incidence of delirium between these studies may be attributed to the different profiles of their study populations. In addition, the different sedation practices adopted in these hospitals may also have contributed to this. Midazolam was the most common sedative administered in MY SPICE (39.6% of patient days) and second most common in ANZ SPICE (36.6% of patient days). In contrast, in our study, propofol and fentanyl were the most common sedative agents administered, with midazolam used only for 11.4% of patient days.

Midazolam, as a benzodiazepine, has been associated with increased incidence and duration of delirium in previous studies.[15,16] The reduced use of midazolam in our practice may have been associated with the lower incidence of delirium observed in our patients.

Due to limited sample size, while we did characterise a difference in sedation depth between the early and late periods of ICU patient days, we did not analyse the effect of this exposure on clinical outcomes.

To our knowledge, this is the first prospective longitudinal multicentre study of sedation practices in the surgical and medical ICUs of the Singapore public healthcare system.

The study protocol was detailed and comprehensive, and data collection was supported by an experienced research team. This data would form an invaluable baseline for further studies on sedation and delirium in the Singapore ICUs.

Due to the research protocol, the completeness of monitoring in our study was very high and may not reflect the true practice in a busy ICU. A quality improvement study in Singapore found that compliance to sedation monitoring and delirium screening was 79% and 36%, respectively.[17] Barriers cited for compliance included difficulty in performing and interpreting delirium screening as well as a lack of appropriate physician response. However, an educational programme in the ICU was able to increase compliance of delirium screening to 61% at ten months.[17]

Hence, future pragmatic research, in this context, should take into account the effectiveness and sustainability of sedation and delirium monitoring. Interventions in sedation/delirium monitoring and treatment should be aimed at improving clinically relevant outcomes. Changes to practices must be implementable across different critical practices.

The limitations of our study were that we were unable to document the screening process and comprehensively describe the numbers and reasons for exclusion of patients. Selection bias may have resulted, as a consequence, and thus the external validity and generalisability of our study and its findings was weakened.

Current sedation randomised controlled trials have not looked at the impact of early sedation depth on outcome. A pilot study has suggested that delivery of early goal-directed sedation was feasible, appeared safe, achieved early light sedation, minimised benzodiazepines and propofol, and decreased the need for physical restraints.[7] Completion of SPICE III will provide us with data and insight for translation into practice that is measurable and sustainable.

While the development of ICU delirium is associated with worse outcomes, it is not known whether pharmacological treatment of ICU delirium would result in improved outcome.[18] The MINDS-USA trial should shed more light on the subject.

The modern practice of ICU sedation is embodied in the concept of eCASH – early Comfort using Analgesia, minimal Sedatives and maximal Humane care.[19] Our understanding and practice of sedation and delirium management in the ICU will continue to evolve with more data.

In conclusion, we found that the sedation practices in our Singapore ICUs differ from other centres by having a lower use of benzodiazepines, lighter depth of sedation and less delirium. Data from future studies will further guide our practice.

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FIGURE

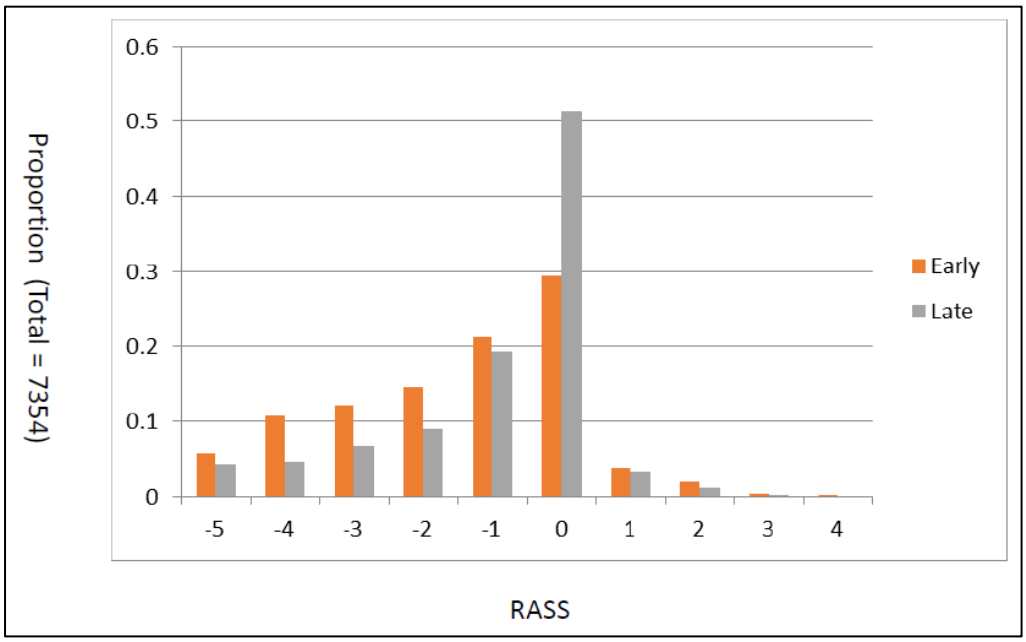

Fig. 1 Comparative sedation levels, according to RASS assessments, during the early and late periods of ICU admission. ICU: intensive care unit; RASS: Richmond Agitation and Sedation Score