Early Intensive Care Sedation Predicts Long-Term Mortality in Ventilated Critically Ill Patients

Yahya Shehabi1,2, Rinaldo Bellomo3,4,5,6, Michael C. Reade7,8, Michael Bailey5, Frances Bass5, Belinda Howe3, Colin McArthur9, Ian M. Seppelt10, Steve Webb11,12, and Leonie Weisbrodt13;

Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the ANZICS Clinical Trials Group*

1Clinical School of Medicine, University of New South Wales, Randwick, Australia; 2Intensive Care Research, Prince of Wales Hospital, Randwick, Australia; 3Faculty of Medicine, University of Melbourne, Melbourne, Australia; 4Faculty of Medicine, Monash University, Melbourne, Australia; 5Australian New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; 6Intensive Care Research, Austin Hospital, Heidelberg, Australia; 7Burns, Trauma & Critical Care Research Centre, University of Queensland, Brisbane, Queensland, Australia; 8Australian Defence Force, Brisbane, Queensland, Australia; 9Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand; 10Department of Intensive Care Medicine, Nepean, University of Sydney, Sydney Medical School Nepean, Kingswood, Australia; 11Intensive Care Unit, Royal Perth Hospital, Perth, Australia; 12School of Medicine and Pharmacology and School of Population Health, University of Western Australia, Perth, Australia; 13Sydney Nursing School, University of Sydney, Nepean Hospital, Kingswood, Australia

Objectives: To investigate the relationships between early sedation and time to extubation, delirium, and hospital and 180-day mortality among ventilated critically ill patients in the intensive care unit (ICU).

Methods: Multicenter (25 Australia and New Zealand hospitals) prospective longitudinal (ICU admission to 28 d) cohort study of medical/surgical patients ventilated and sedated 24 hours or more. We assessed administration of sedative agents, ventilation time, sedation depth using Richmond Agitation Sedation Scale (RASS, four hourly), delirium (daily), and hospital and 180-day mortality. We used multivariable Cox regression to quantify relationships between early deep sedation (RASS, −3 to −5) and patients’ outcomes.

Measurements and Main Results: We studied 251 patients (mean age, 61.7 ± 15.9 yr; mean Acute Physiology and Chronic Health Evaluation [APACHE] II score, 20.8 ± 7.8), with 21.1% (53) hospital and 25.8% (64) 180-day mortality. Over 2,678 study days, we completed 14,736 RASS assessments. Deep sedation occurred in 191 (76.1%) patients within 4 hours of commencing ventilation and in 171 (68%) patients at 48 hours. Delirium occurred in 111 (50.7%) patients with median (interquartile range) duration of 2 (1–4) days. After adjusting for diagnosis, age, sex, APACHE II, operative, elective, hospital type, early use of vasopressors, and dialysis, early deep sedation was an independent predictor of time to extubation (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.87–0.94; \( P = 0.001 \)), hospital death (HR, 1.11; 95% CI, 1.02–1.20; \( P = 0.01 \)), and 180-day mortality (HR, 1.08; 95% CI, 1.01–1.16; \( P = 0.026 \)) but not delirium occurring after 48 hours (\( P = 0.19 \)).

Conclusions: Early sedation depth independently predicts delayed extubation and increased mortality, making it a potential target for interventionstrial studies.

Keywords: ventilation; mortality; sedation; delirium; intensive care

* A complete list of members may be found before the beginning of the REFERENCES.

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Correspondence and requests for reprints should be addressed to Yahya Shehabi, M.B.B.S., E.M.B.A., University of New South Wales Clinical School and Prince of Wales Hospital, Program of Acute Care, Department of Intensive Care Services, Barker Street, Randwick, NSW 2031, Australia. E-mail: y.shehabi@unsw.edu.au

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delirium assessment scales has standardized patient assessment, making sedation more reproducible and comparable, potentially improving the quality of clinical trials (4, 5). Studies using such tools have raised concern that the choice of sedative drugs and depth of sedation may influence the subsequent development of delirium and other key patient outcomes, including mortality (6–9). None, however, have explored the possible association of sedation depth with long-term outcome.

The outcome of mechanically ventilated patients is determined by factors present at the initiation of ventilation as well as by management decisions made during mechanical ventilation, including sedation strategy (choice of sedative agents and sedation depth) (10). It is plausible that the long-term outcome of mechanically ventilated adult patients could be influenced by the initial management of sedation (early sedation). Until now, sedation trials have enrolled patients mostly after 48 hours after the initiation of ventilation, during which time patients receive non–protocol-based sedation, during which time patients receive non–protocol-based sedation with unknown impact on outcomes. In addition, surveys of sedation practice, so far, have not longitudinally assessed the choice and the depth of early sedation and its association with relevant and long-term clinical outcomes (11–15). As a result, modern early ICU sedation practice is inadequately characterized and its effects poorly understood.

We performed a multicenter, prospective longitudinal cohort study of sedation practice in ventilated adults in Australia and New Zealand (ANZ), including early (first 48 h) and subsequent sedation. The objectives of this study were to characterize the pattern of early sedation practice in ANZ ICUs and assess its relationship with relevant clinical outcomes, including time to extubation, delirium, and hospital and 180-day mortality. We hypothesized that the choice of sedative agents and the intensity of sedation depth in the first 48 hours would be associated with these outcomes.

Some of the results of this study have been previously reported in the form of an abstract (16).

METHODS

Study Design and Eligible Patients

Each participating center’s Human Research and Ethics Committee approved this study with a waiver of consent. We recruited patients from 25 ICUs in ANZ, including tertiary, metropolitan, and rural hospitals. Over 3 months, (June to September 2010) each unit recruited up to a maximum of 20 patients. Patients were eligible for inclusion if they were ventilated within the previous 24 hours, were receiving continuous or intermittent intravenous sedative and/or analgesic drugs, and were expected to stay in ICU and remain sedated or ventilated for longer than 24 hours. Exclusion criteria were age less than 18 years, proven or suspected neurological impairment, burns, dementia or psychiatric illness, palliative care or treatment limitations, or inability to communicate in English.

Study Procedures

We conducted the study in collaboration with the ANZ Intensive Care Research Centre (ANZIC RC) and the Monash University Centre of Clinical Research Excellence in Therapeutics. We designed a streamlined data case report form for optical recognition scanning. We trained senior clinicians and all research coordinators on study procedures, including practical sessions and bedside training on performing the Richmond Agitation Sedation Score (RASS), performed by bedside nurses, and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), performed by research coordinators (4, 5, 17).

Measurements, Definitions, and Data Collection

At enrollment, we collected demographic data, including age, sex, body weight, admission source, date and time of hospital and ICU admission, and date and time of first intubation. We recorded Acute Physiology and Chronic Health Evaluation II (APACHE II) score at the conclusion of 24 hours in the ICU, APACHE III admission diagnosis (18), and key interventions, including vasopressor and inotropic agents and renal replacement therapy (newly initiated or ongoing).

We followed patients daily from admission until ICU discharge, death, or 28 days in the ICU, whichever came first. During this time we assessed and recorded sedation level using the RASS scale every 4 hours (4). A RASS of −2 to +1 was considered “light sedation” and a RASS of −3 to −5 “deep sedation.” A RASS between +2 to +4 was considered “agitation.” For the daily RASS assessments over the 28 days, patients may fall into more than one RASS category on the same day; however, no duplicate ranges were counted (i.e., a patient with three RASS assessments in deep sedation range had one RASS in deep sedation only counted for that day). Presence of pain was assessed by the bedside nurses with every RASS assessment. The visual analog scale was used in patients who were able to report pain, whereas in patients unable to report pain, Critical Care Pain Observation (19) descriptors were used to guide nursing assessment for the presence or absence of pain.

CAM-ICU was assessed daily and only during light sedation (RASS, −2 to +1) to avoid overdiagnosis. Patients were considered delirious if their CAM-ICU (5) assessment was positive (when the RASS was −2 to +1).

We collected daily cumulative dose of sedative, analgesic, and antipsychotic medications and the number of days prescribed. Only sedatives given in the ICU were collected. Data on sedatives given outside the ICU during surgery or other out-of-ICU interventions were not collected. To examine the pattern of sedative and analgesic administration, we divided the cohort into quartiles of ICU length of stay (<4, 4–8, >8–14, and >14 d).

We defined successful extubation as cessation of mechanical ventilation without further requirements for ventilation, including continuous noninvasive ventilation within the next 24 hours. We recorded survival status at ICU and hospital discharge or 28 days. We obtained 180-day survival from medical records or data linkage with the Australian and New Zealand National Death Registries.

Statistical Plan

Sample size. The number of times a patient was deeply sedated during the first 48 hours is anticipated to be approximated by a normal distribution with an SD of about 4. Based on a mortality rate of 25%, with 250 patients, this study will have a 90% power (two-sided P value of 0.05) to detect a difference of 2 in the number of times deep sedation occurred in the first 48 hours between alive and deceased. A difference of this magnitude is perceived to be clinically relevant. Furthermore, with 250 patients we have a 78% power to identify a point estimate to within 5% of the true value for an event, such as a particular pattern of sedation, when that event truly occurred in at least 10% of patients.

Statistical analysis. All patients were included in the analysis. Comparisons of proportions were performed using chi-square tests for equal proportion or Fisher exact tests where appropriate. Nonnormally distributed continuous variables were compared using Student t tests and presented as means (SDs). Normally distributed variables were compared using Wilcoxon rank-sum tests and presented as median (interquartile range [IQR]).

Early deep sedation was defined by the number of times RASS assessments (collected every 4 h) were between −3 and −5 during the first 48 hours of ICU stay. Deep sedation was treated as a continuous variable. Early deep sedation was the primary exposure variable in the time-to-event analysis of outcomes occurring after 48 hours: time to extubation, time to subsequent delirium, time to hospital death, and 180-day mortality. Time-to-event analysis was performed using Cox proportional hazard regression and reported as hazard ratio (HR) and 95% confidence interval (CI) and as Kaplan-Meier curves with a corresponding log-rank test. Adjustment of observed effects due to known or suspected potential confounders was undertaken using multivariable analysis using a list of a priori defined covariates comprising APACHE III diagnosis (cardiac, respiratory, gastrointestinal, sepsis, or other), age, sex, APACHE II score,
operative admission (surgical), elective admission, hospital type (rural, metropolitan, or tertiary), and early use of vasopressors and dialysis within the first 48 hours of admission. All patients with ICU lengths of stay less than 48 hours were excluded from the multivariate analysis. A two-sided P value of 0.05 was considered to be statistically significant.

Analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patients’ Characteristics

We studied 251 patients (Figure 1). Their characteristics are shown in Table 1. The use of vasopressors was common (more than 70%), whereas just under one-quarter of subjects received renal replacement therapy or a tracheostomy. The most common APACHE III admission diagnosis was respiratory failure (96 [38.5%]) followed by gastrointestinal disorder (46 [18.5%]), cardiovascular disorder (45 [18.1%]), sepsis (31 [12.5%]), and miscellaneous (31 [12.3%]). Hospital and 180-day mortality rates were 21.1% (53 hospital deaths) and 25.8% (64 deaths by 180 d). We assessed a total of 2,678 ICU days, of which 1,944 (72.6%) were ventilated days.

Sedative and Analgesic Drug Choices

At the time of the first assessment (within 4 h of enrollment), propofol was administered to 142 (56.6%) patients and midazolam to 137 (54.6%), both simultaneously in 46 (18.3%), and fentanyl and morphine in 116 (46.2%) and 111 (40.2%) patients, respectively. Over the first 48 hours 156 (62.2%) and 153 (56.6%) patients received propofol and midazolam, respectively. Over the first 48 hours 156 (62.2%) and 153 (56.6%) patients received propofol and midazolam, respectively, with fentanyl administered to a higher proportion of patients (108 [44.6%]) than morphine (86 [35.5%]) (P = 0.044) at 48 hours (Table 2). Midazolam was used more frequently than propofol in patients with longer ICU stay (>8 d) (Table 3). Fentanyl was used more commonly than morphine after 48 hours and became the predominant analgesic agent for longer ICU stay patients (P = 0.003).

Of the 2,678 study days, patients received sedatives on 1,956 (73%) days, mainly during the first few days of critical illness and ICU stay. Patients received midazolam on 716 of 1,956 (36.6%) and propofol on 706 of 1,956 (36.1%) days. Fentanyl was given on 996 (50.9%) and morphine on 588 (30%) days. Dexmedetomidine was administered on 189 (9.7%) days and prednisolone in patients staying in ICU longer than 4 days (Table 3). Combinations of drugs were more frequent than single agents. The most common combination was midazolam and an opioid given on 471 (49.3%) days followed by propofol with an opioid given on 241 (25.2%) days. Propofol and fentanyl were the agents most commonly used as a single agent on 157 (31.2%) and 147 (29.2%) days, respectively.

Pain was reported to be present in 18 (7.2%) patients at the time of their first assessment and in 57 (23.5%) patients during the first 48 hours.

Prevalence of Delirium

Within the first 24 hours of study commencement 67 of 251 (26.7%) patients were within RASS −2 to +1, and among these, 58 patients had a CAM-ICU assessment, of which 18 (31%) were positive. Within the first 48 hours, 124 of 250 (49.6%) patients were assessable (RASS, −2 to +1), and among these, 30 of 124 (24.2%) had been delirious for at least 1 day. Throughout the study, 111 of 219 (50.7%) of assessed patients (RASS, −2 to +1) were delirious at least 1 day with a median (IQR) duration of delirium of 2 (1–4) days. The proportion of patients with delirium increased with increasing ICU stay (P = 0.002), with more than 67% of patients staying in ICU longer than 14 days experiencing at least 1 day of delirium (Figure 2).

The percentage of positive CAM-ICU of all assessed days, however, were not different among the four categories of ICU stay (16 of 114 [14%] vs. 48 of 302 [15.9%] vs. 62 of 416 [14.9%] vs. 178 of 1,024 [17.4%], respectively). Agitation (RASS, +2 to +4) was rare (0.5% of patients at the first assessment, 72 of 2,653 [2.7%] with the first 48 h, and 2.8% overall).

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**TABLE 1. PATIENT DEMOGRAPHICS AND KEY INTERVENTIONS AND OUTCOMES**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 251</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), yr</td>
<td>61.7 (±15.9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>154 (61.4)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>83.5 (±23.6)</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)</td>
<td>20.8 (±7.8)</td>
</tr>
<tr>
<td>Operative admission diagnosis, n (%)</td>
<td>90 (35.9)</td>
</tr>
<tr>
<td>Ventilated &gt; 24 h, n (%)</td>
<td>243 (96.8)</td>
</tr>
<tr>
<td>Ventilation days, median (IQR)</td>
<td>5.1 (2.6–10)</td>
</tr>
<tr>
<td>Vasopressors infusions, n (%)</td>
<td>179 (70.4)</td>
</tr>
<tr>
<td>Renal replacement therapy, n (%)</td>
<td>58 (23.1)</td>
</tr>
<tr>
<td>Tracheostomy after ICU admission, n (%)</td>
<td>60 of 250 (24.0)</td>
</tr>
<tr>
<td>ICU length of stay, median (IQR), d</td>
<td>8.9 (6.5–12.5)</td>
</tr>
<tr>
<td>Hospital length of stay, median (IQR), d</td>
<td>20.0 (11.6–37.0)</td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
<td>42 (16.7)</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>53 (21.1)</td>
</tr>
<tr>
<td>180-d mortality, n (%)</td>
<td>64 (25.8)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; ICU = intensive care unit; IQR = interquartile range.

*Mutually exclusive APACHE III diagnosis.
Choice of Antidelirium and Agitation Agents

Throughout the study period, haloperidol, dexmedetomidine, or diazepam were prescribed to 67.3% (haloperidol 20.7%, dexmedetomidine 30.6%, and diazepam 18%) of delirious or agitated patients. In patients without the diagnosis of delirium or agitation, these drugs were prescribed to 27.8% (only 5.7% were given haloperidol, 17.1% were given dexmedetomidine, and 5% diazepam). Virtually all (114 of 116) patients who received one of these drugs were ventilated for more than 4 days (Table 3).

Sedation Targets

Clinicians prescribed sedation targets (RASS range) for only 3,602 (24.9%) of all RASS assessments. Only one-third (34.7%) of assessments met the prescribed target. Deliberate cessation of all sedatives and analgesics occurred in 34 of 251 (13.5%) during the first 48 hours and in 56 of 248 (22.6%) patients on study Day 2; however, routine sedation interruption was rarely practiced (3.1% of all study days). Overall sedation was interrupted for specific indications, such as weaning from mechanical ventilation and/or unplanned deep sedation on 288 of 608 (47.4%) and 216 of 608 (35.5%) study days, respectively.

Depth of Sedation

At 4 hours after starting mechanical ventilation, most patients (191 [76%]) were deeply sedated (RASS, −3 to −5). Deep sedation continued throughout the first 48 hours in 171 (68%) patients. Of 2,656 RASS assessments within the first 48 hours, 1,642 (61.9%), 942 (35.5%), and 72 (2.7%) were deeply sedated, lightly sedated, or agitated, respectively. Throughout the study period, deep sedation occurred in 5,137 of 14,637 (35.1%) of total assessments, primarily during the early ICU days. However, in 181 patients who had admissions of 5 or more days’ duration, the majority of assessments were in light sedation range with only 578 of 2,432 (23.7%) in the deep sedation range. The median time to the first assessment for which light sedation was recorded was 2 (IQR, 1–3) days. The number of daily RASS categories recorded for every patient up to Day 28 is shown in Figure 3.

Depth of Sedation and Outcomes

Cox proportional hazard multivariable regression modeling, adjusting for a priori defined covariates comprising APACHE III diagnosis (cardiac, respiratory, gastrointestinal, sepsis, or other), age, sex, APACHE II score, operative admission (surgical), elective admission, hospital type (rural, metropolitan, or tertiary), and early use of vaspressors and dialysis within the first 48 hours of admission, showed that early sedation depth was predictive of time to extubation, with the occurrence of each additional deep sedation increasing time to extubation by (12.3 h), after adjustment for potential covariates (HR, 0.90; 95% CI, 0.87–0.94) (Table 4). Male sex, respiratory admission diagnosis, and the need for vaspressors were also predictors of time to extubation. The median (IQR) time to extubation was significantly longer in patients deeply sedated early (at 48 h) (7.7 [6.0–8.6] vs. 2.4 [1.9–4.0] d; P < 0.001), and their probability of death at 180 days was significantly higher (P = 0.048) (Figures 4A and 4B).

Using multiple regression, the cumulative dose of midazolam and fentanyl given in the first 48 hours also predicted time to extubation independent of sedation depth (P = 0.001 and P = 0.010, respectively). Neither propofol nor morphine cumulative dose given in the first 48 hours was independently predictive of time to extubation.

### Table 2. Administration of Sedatives, Analgesics, and Antidelirium Medications

<table>
<thead>
<tr>
<th>Drugs Given</th>
<th>During the First 48 h</th>
<th>During Entire Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Rx</td>
<td>Dose*</td>
</tr>
<tr>
<td>Midazolam</td>
<td>153</td>
<td>0.71 (0.37-1.41) mg kg⁻¹ d⁻¹</td>
</tr>
<tr>
<td>Propofol</td>
<td>156</td>
<td>13.56 (4.25-31.7) mg kg⁻¹ d⁻¹</td>
</tr>
<tr>
<td>Morphine</td>
<td>115</td>
<td>0.53 (0.21-0.98) mg kg⁻¹ d⁻¹</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>133</td>
<td>8.33 (3.05-18.0) μg kg⁻¹ d⁻¹</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>19</td>
<td>0.027 (0.004-0.11) μg kg⁻¹ d⁻¹</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1</td>
<td>0.13 (0.13-0.13) mg d⁻¹</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5</td>
<td>0.42 (0.09-0.48) mg d⁻¹</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: Rx = prescription.*

### Table 3. Administration of Sedatives, Analgesics, and Antidelirium Medications According to Intensive Care Unit Length of Stay

<table>
<thead>
<tr>
<th>Drugs Given, %</th>
<th>&lt;4 d (N = 45)</th>
<th>4-8 d (N = 73)</th>
<th>&gt;8-14 d (N = 63)</th>
<th>&gt;14 d (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>48.9</td>
<td>58.9</td>
<td>77.8</td>
<td>80.9</td>
</tr>
<tr>
<td>Propofol</td>
<td>75.6</td>
<td>82.2</td>
<td>74.6</td>
<td>88.2</td>
</tr>
<tr>
<td>Morphine</td>
<td>60.0</td>
<td>53.4</td>
<td>49.2</td>
<td>47.1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>57.8</td>
<td>52.1</td>
<td>66.7</td>
<td>77.9</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>2.2</td>
<td>26</td>
<td>25.4</td>
<td>30.9</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.0</td>
<td>5.5</td>
<td>17.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2.2</td>
<td>6.8</td>
<td>6.3</td>
<td>25.0</td>
</tr>
<tr>
<td>RASS −3 to −5, %</td>
<td>34.6</td>
<td>38.7</td>
<td>37.7</td>
<td>32.3</td>
</tr>
<tr>
<td>Ventilation time, d*</td>
<td>1.84 (1.26-2.13)</td>
<td>3.66 (2.6-4.9)</td>
<td>6.69 (4.9-8.6)</td>
<td>15.36 (10.9-22.9)</td>
</tr>
<tr>
<td>ICU length of stay, d*</td>
<td>2.71 (2.04-3.65)</td>
<td>5.66 (4.8-6.5)</td>
<td>9.88 (9.0-11.0)</td>
<td>22.69 (16.8-33.7)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: ICU = intensive care unit; RASS = Richmond Agitation Sedation Scale. *Median (interquartile range).
Most patients with delirium after 48 hours (86 of 96 [89.6%]) had early deep sedation (at 48 h) compared with those without delirium (relative risk, 1.7; 95% CI, 1.00–3.02; \( P = 0.046 \)). However, in multivariable analysis, early deep sedation was not predictive of time to subsequent delirium occurring after 48 hours (HR, 1.033; 95% CI, 0.98–1.08; \( P = 0.19 \)) (Table 4).

Almost all patients (39 of 40 [97.5%]) who died between Day 2 and Day 28 had deep sedation in the first 48 hours (relative risk, 7.61; 95% CI, 1.44–43.6; \( P = 0.009 \)). Using multivariable Cox proportional hazard regression and adjusting for APACHE III diagnosis (including cardiac, respiratory, gastrointestinal, and sepsis), age, male sex, APACHE II, operative admission (surgical), elective admission, hospital type (rural or metropolitan), use of vasopressors, and dialysis within the first 48 hours of admission, each additional occurrence of deep sedation in the first 48 hours remained associated with death in hospital (HR, 1.107; 95% CI, 1.022–1.200; \( P = 0.0126 \)). Deep sedation was also associated with long-term mortality, with every additional RASS assessment in the deep sedation range being independently associated with increased hazard of death at 6 months (HR, 1.083; 95% CI, 1.01–1.16; \( P = 0.026 \)) (Table 4). The above associations (occurrence of deep sedation with time to extubation and mortality) were approximately linear with trend analysis (0.03) using Cochran-Mantel-Haenszel test. There was no independent association between choice of sedative agents in the first 48 hours and hospital death or 6-month mortality.

**DISCUSSION**

**Key Findings**

We found a significant relationship between early sedation depth and major clinical outcomes. Early deep sedation was a significant independent predictor of death and time to extubation. Every additional RASS assessment in the deep sedation range in the first 48 hours was associated with delayed time to extubation of 12.3 hours, a 10% increased risk of hospital death, and an 8%
increased risk of death at 6 months. These associations remained significant after adjusting for illness severity and other relevant potential confounders. We believe this is the first study to report this important association between early ICU sedation practice and clinically important outcomes.

**Relationship with Previous Studies**

Previous studies have shown that the presence of deep sedation (coma) in ICU patients substantially increased the probability of death at 6 months long after its occurrence (20–22). Our study identified the novel finding that early sedation depth is independently associated with time to extubation and long-term mortality. The early ICU period is the time when decisions about sedation choice and depth are made, and sedation depth is typically least monitored and deeper sedation is accepted by many clinicians. Although early deep sedation may be clinically necessary, the intensity of sedation often exposes patients to unwarranted lengthy deep sedation by the “overshoot phenomenon.” Trials limiting sedation depth have shown a beneficial effect. For example, ventilated patients randomized to a protocol of no sedation had significantly more ventilation-free days and lower hospital mortality (23). Sedation algorithms targeting light sedation were also shown to have similar benefits (8, 24). This suggests that the first 48 hours of sedation may be a key period for effectiveness trials, when interventions are most likely to have an impact on outcomes assessed. To date, major controlled trials of sedation randomized subjects up to 96 hours after initiation of mechanical ventilation, missing the impact of early sedation on important outcomes (8, 25–27). Finally, early deep sedation is a potentially modifiable risk factor. Our findings suggest that trials that do not include early intervention may fail to detect a treatment effect.

Our cohort shares many characteristics with patients in previous observational and interventional studies, including a high APACHE II score, a mix of medical and surgical patients.

### Table 4. Time to Extubation, Delirium, and 180-Day Mortality Versus Early Sedation Depth (Richmond Agitation Sedation Scale, –3 to –5) As Primary Exposure Variable, Multivariable Proportional Hazard Cox Regression

<table>
<thead>
<tr>
<th></th>
<th>Time to Extubation</th>
<th>Delirium after 48 h</th>
<th>180-d Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>RASS, –3 to –5*</td>
<td>0.90</td>
<td>0.87–0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II</td>
<td>0.99</td>
<td>0.97–1.02</td>
<td>0.79</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.98–1.00</td>
<td>0.71</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.63</td>
<td>0.46–0.87</td>
<td>0.02</td>
</tr>
<tr>
<td>Operative</td>
<td>0.77</td>
<td>0.48–1.24</td>
<td>0.33</td>
</tr>
<tr>
<td>Elective</td>
<td>1.25</td>
<td>0.74–2.11</td>
<td>0.36</td>
</tr>
<tr>
<td>Cardiac†</td>
<td>0.83</td>
<td>0.45–1.56</td>
<td>0.88</td>
</tr>
<tr>
<td>Respiratory†</td>
<td>0.48</td>
<td>0.30–0.77</td>
<td>0.01</td>
</tr>
<tr>
<td>Sepsis†</td>
<td>0.66</td>
<td>0.35–1.24</td>
<td>0.18</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>1.11</td>
<td>0.62–1.98</td>
<td>0.86</td>
</tr>
<tr>
<td>Vasoppressors</td>
<td>0.69</td>
<td>0.49–0.97</td>
<td>0.02</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.59</td>
<td>0.36–0.95</td>
<td>0.03</td>
</tr>
<tr>
<td>Rural hospital</td>
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<td>0.85–2.77</td>
<td>0.14</td>
</tr>
<tr>
<td>Metro hospital</td>
<td>1.00</td>
<td>0.67–1.49</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; RASS = Richmond Agitation Sedation Scale.

* For each additional episode of early deep sedation, the chance of achieving a desirable outcome (shorter time to extubation) was reduced by 10% (6–13%).
† APACHE III admission diagnostic codes.
‡ Continuous venovenous hemofiltration within first 48 hours.

**Figure 4.** Kaplan-Meier curves for time to extubation and mortality at 180 days. (A) Time to extubation was significantly longer among patients who were deeply sedated early in the intensive care unit compared with those who were not. Median (interquartile range), 7.7 (6.0–8.6) vs. 2.4 (1.9–4.0) days (log-rank, \( P < 0.001 \)). (B) Those who were deeply sedated early (first 48 h) showed significantly reduced survival (log-rank \( P = 0.048 \)) compared with patients who were not deeply sedated.
Nevertheless, the results of this study generate a premise that severity for which APACHEII score was inadequate to adjust. It is unlikely that sedation depth and outcomes observed in our study are unique to ANZ ICUs. Distinct features of ANZ ICUs, such as 1:1 patient to nurse ratio, direct coordinated nurse-led sedation management with frequent titration of sedative infusions as clinically desired, twice-daily intensivist-led rounds, and common use of sedation scales and algorithms, suggest that ANZ standard practice is not inferior to other published algorithms (11, 28, 29). Daily interruption of sedation was uncommon, as previously reported in ANZ ICUs (25, 30). However, the generalizability of the benefit of this practice has been questioned (31–34). Furthermore, the original published sedation interruption protocol was applied 48 hours after commencement of mechanical ventilation (35, 36). Although a systematic review found deep sedation to extend up to 6 days in most published trials (37), other studies found a high prevalence of deep sedation at enrollment (5, 20, 22, 26). This is consistent with our finding that most of our patients were deeply sedated early in their ICU admission. Similarly, the incidence and duration of delirium (50.7%) was comparable to previously published data (15, 16, 38). All these findings suggest broad relevance for our observations.

Finally, the cumulative dose of midazolam and fentanyl predicted delayed extubation, whereas propofol and morphine did not. This concurs with reduced midazolam, but not propofol, exposure and sedation depth seen with daily sedative interruption (35). Although the role of dexmedetomidine in ICU sedation is still evolving, it was mostly used for delirious and/or agitated patients once these conditions developed, rather than as a primary sedative agent early in a patient’s ICU stay. This reflects published reports showing reduced delirium and/or delirium duration (22, 25, 39, 40). Although the use of dexmedetomidine as a sedative agent seems to be increasing, the use of traditional sedatives remains more common (41–43).

Study Strengths and Limitations
This study has many strengths, including prospective and detailed multicenter longitudinal assessment in a broad range of critically ill patients and the use of CAM-ICU by trained research coordinators. Daily delirium assessment was only done during light sedation to avoid overdiasnosis. A small percentage of patients did not have delirium assessment, which may have slightly reduced the true incidence of delirium. Patients who were not receiving intravenous sedative medications were not included. Although the multivariable analysis adjusted for known confounders, adjustment for other confounders, such as dynamic changes in illness severity, presence or absence of sepsis/septic shock, and individual and genetic variability, could not be performed. Cohort studies cannot establish causality, and early depth of sedation may, at least partly, be a marker of illness severity for which APACHEII score was inadequate to adjust. Nevertheless, the results of this study generate a premise that needs to be tested in adequately powered well-designed trials.

Implications for Clinicians and Investigators
The association between early sedation depth and important outcomes suggests that this aspect of sedation management is a major unobserved confounder in trials of ICU sedation. Early randomization in future sedation trials can be achieved through a hierarchy of consent that includes delayed consent, consistent with trials of emergency interventions. This may increase the ability of an intervention to influence outcome, be more informative to clinicians, and have a greater power to detect an effect on important outcomes such as mortality and long-term outcomes. On the other hand, the lack of association between depth of sedation and delirium seen in our study challenges the view that the intensity of early sedation might contribute to its subsequent development. However, the incidence of delirium in our cohort, despite CAM-ICU assessment during light sedation only, was high, reaching nearly 70% in patients staying in the ICU longer than 14 days. This supports the need for universal monitoring of delirium.

Conclusions
Early deep sedation is an independent predictor of delayed time to extubation and increased long-term mortality. The prevalence of early deep sedation presents a modifiable risk factor that is a candidate for future intervention (44, 45). Future trials should be designed to deliver interventions at the time of or within a few hours of the initiation of sedation.

Author disclosures are available with the text of this article at www.atjjournals.org.

The ANZICS Clinical Trial Group endorsed the study, which was conducted in collaboration with the ANZ Intensive Care Research Centre (ANZIC RC) and the Monash University Centre of Clinical Research Excellence in Therapeutics. The SPICE Study site investigators are as follows (in alphabetical order; all in Australia unless specified as New Zealand [NZ]):

Albury Base Hospital, Albury: E. Ibrum, C. Maher, C. Mhashonganyika, H. McKeen; The Alfred Hospital, Melbourne: V. Bennett, D. J. Cooper, S. Vallance; Auckland City Hospital/CVICU, Auckland, NZ: J. Brown, E. Gilders, R. Parke; Auckland City Hospital DCCM, Auckland, NZ: C. McArthur, L. Newby, C. Simmonds; Austin Health, Melbourne: R. Bellomo, G. Eastwood, L. Peck, M. Reade, H. Young; Box Hill Hospital, Melbourne: S. Elliott, I. Mercer, J. Sidhu, A. Whittfield; Calvary Hospital, Canberra: G. Ding, P. Hatfield, K. Smith; Central Gippsland Health Service, Sale: T. Coles, J. Dennett, T. Summers; Christchurch Hospital, Christchurch, NZ: S. Henderson, J. Mehrtens; Concord Hospital, Sydney: R. Anderson, E. Jones, D. Milliss, H. Wong; Frankston Hospital, Melbourne: J. Botha, S. Allisp; Lyell McEwin Hospital, Adelaide: M. Kanhere, J. Wood; Wollongong Hospital, Wollongong: R. Smith; St. Vincent’s Hospital, Sydney: C. Reynolds; Tauranga Hospital, Tauranga, NZ: C. Hogan, J. Tai, T. Williams; Nambour Hospital, Nambour: A. Buckley, P. Gamett, S. McDonald; Nepean Hospital, Sydney: C. Czumer, I. Serpell, L. Weisbrond; Prince of Wales Hospital, Sydney: F. Bass, P. Edhouse, M. Sana, Y. Shehab; Royal Perth Hospital, Perth: J. Chamberlain, S. Webb; Sir Charles Gardiner Hospital, Perth: A. Bicknell, B. Roberts; St George Hospital, Sydney: E. Casey, A. Cheng, D. Inskipp, S. Myburgh; St. Vincent’s Hospital, Melbourne: J. Holmes, J. Santamaria, R. Smith; St. Vincent’s Hospital, Sydney: P. Nair, C. Reynolds; Tauranga Hospital, Tauranga, NZ: T. Browne, D. Cubis, J. Goodson, S. Nelson; Wellington Hospital, Wellington, NZ: D. Mackle, S. Pecher; Wollongong Hospital, Wollongong: B. Johnson, M. Sterba.

References


