



# DAILY INTERRUPTION OF SEDATION IN PATIENTS RECEIVING MECHANICAL VENTILATION

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**Background** Daily interruption of continuous infusion of sedatives has improved outcomes in patients receiving mechanical ventilation in open-label studies.

**Objectives** To assess the feasibility of a protocol for a double-blind, randomized, controlled trial study on the impact of routine daily interruption of sedation in patients receiving mechanical ventilation.

**Methods** A total of 50 patients receiving mechanical ventilation were randomized to daily interruption of fentanyl and/or midazolam infusions for up to 6 hours or to usual management of sedation. Blinding was achieved by using replacement infusions (saline or active drug in saline).

**Results** The recruitment target of 80 patients was not met in an extended time frame. Propofol was used outside the protocol in 27% of patients in the intervention group and 17% of patients in the control group ( $P = .10$ ). A total of 15% of the intervention group and 12% of the control group never had replacement infusions started ( $P = .77$ ), and replacement infusions were started on only approximately one-third of eligible days in patients who received replacement infusions. The mean doses of fentanyl and midazolam were similar. The blinding strategy was safe and effective: no patients had unplanned extubations, and the most frequent reason for ending replacement infusions was completion of the maximum 6-hour period.

**Conclusions** The double-blinded design for assessment of sedation interruption in patients receiving mechanical ventilation was safe and effective. Slow recruitment of patients and frequent noncompliance with the protocol suggest that modifications to the protocol are needed. (*American Journal of Critical Care*. 2011;20:e90-e98).

**A**ppropriate sedation is an integral part of the care of critically ill patients<sup>1</sup> and has been described as the challenge of providing comfort without inducing coma.<sup>2</sup> Assessing a patient's level of sedation, defining the appropriate level, and finding the balance between undersedation and oversedation add to the complexity of caring for patients in intensive care.<sup>3</sup> In some studies, sedation scoring systems,<sup>4-6</sup> sedation algorithms,<sup>4,7,8</sup> and a routine, daily interruption in continuous infusions<sup>9</sup> have been associated with improved outcomes, such as reduced duration of mechanical ventilation, reduced length of stay in the intensive care unit (ICU), and better psychological recovery.<sup>10</sup> However, in other studies in different settings,<sup>11-15</sup> improvement in patients' outcomes did not occur.

In a randomized study<sup>9</sup> in a single medical ICU in North America, adult patients were assigned to daily interruption of sedation or to standard care; no protocol for weaning from mechanical ventilation was used in either group. Patients in the intervention group had a significant reduction in the median duration of mechanical ventilation of 2.4 days. Primarily on the basis of this study, recommendations to adopt daily interruption of sedation as a standard of care are a component of several clinical practice guidelines.<sup>16-20</sup> A recent review<sup>21</sup> of research on daily interruption of sedation indicated that the practice is widespread despite limited published data and the methodological limitations of studies to date, particularly lack of blinding. Attempts to replicate the benefits of daily interruption of sedation have been

inconclusive.<sup>11,13,22</sup> A lack of consistent findings in these studies may be associated with shortfalls in study design, most importantly, the lack of blinding investigators to the study intervention. A possible way for blinding in a study of sedation interruption is random assignment of patients to either a placebo solution or a solution identical to their prescribed sedative during the period of interruption.

Because of anticipated complexity and a lack of information on the anticipated treatment effect size, we conducted a pilot study to assess the feasibility of a protocol for a double-blind, randomized, controlled examination of the impact of a routine, daily interruption in sedation vs standard care in adults receiving mechanical ventilation in Australian ICUs. Feasibility was assessed by determining the ability to recruit patients to the study and apply the protocol in the context of local clinical practice.

Appropriate sedation should provide comfort without inducing coma.

#### About the Authors

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#### Methods

##### Patients

Patients included in the study were recruited from 2 level-3 ICUs<sup>23</sup> in New South Wales, Australia. During the recruitment period, the Nepean Hospital ICU had 12 intensive care beds, and the Royal North Shore Hospital had 29. Admissions to both units included a mix of medical, surgical, and trauma patients. As is standard in Australian ICUs, the admission and care of patients in each unit were directed by a trained ICU physician responsible for all treatment decisions.<sup>24</sup> Patients care was reviewed daily by a team of medical officers, led by the intensive care staff specialist, and treatment decisions, including sedation management plans, were made in consultation with the bedside nurses. One-to-one nursing care was standard for patients receiving mechanical ventilation.<sup>24</sup> Adjustments in treatments, including continuous infusion of sedatives, by bedside nurses

was based on a patient's response and occurred within prescribed limits throughout the day.

All patients receiving mechanical ventilation for more than 12 hours were screened daily and considered for inclusion in the study if they were receiving continuous infusions of fentanyl and/or midazolam and were expected to require these infusions for 48 hours or more. Patients were excluded if they had a neurological or neurosurgical diagnosis (Acute Physiology and Chronic Health Evaluation III definitions<sup>25</sup>) at admission, had taken a drug overdose, could not comprehend English, or had limitations to treatment, such as do-not-resuscitate orders. The study was conducted in accordance with the Helsinki Declaration of 1975. Institutional ethics approval was obtained, and prospective informed consent was sought from each patient's next of kin.

### Study Treatments

Patients were randomized 1:1 with variable block sizes by using a computer sequence and sequentially numbered, sealed, opaque envelopes. In the absence of contraindications, every patient was given a replacement infusion in place of his or her prescribed sedative for a defined period each day. These infusions consisted of physiological saline for patients in the intervention group and fentanyl and/or midazolam in physiological saline for patients in the control group. Thus, the intervention group had a daily interruption in sedation and the control group continued to receive their current dose of sedative.

Replacement infusions in both groups appeared identical and were labeled "study drug." For easy identification, colored tubing was used for intravenous administration of the study drug infusions in both groups. A team of nonclinical senior nurses in the ICU were responsible for randomizing patients to the 2 groups and for preparing the study drug. Patients, researchers, bedside nurses, and treating physicians had no knowledge of the treatment given (ie, were blinded). If a patient required reintubation during the ICU stay or was readmitted to an ICU during the same hospitalization, daily replacement infusions were recommenced consistent with previous group assignments.

Sedation with fentanyl and/or midazolam was prescribed by the medical staff responsible for the

clinical care of each patient according to the usual practice in each ICU. The use of propofol or any drug other than midazolam or fentanyl for other than extreme agitation or procedures was considered a violation of the protocol. Ad hoc interruption of continuous sedation (eg, assessment of readiness for weaning) was permitted in both groups of patients at the discretion of the clinical medical team. The Richmond Agitation-Sedation Scale (RASS)<sup>6</sup> was used to assess the level of sedation each morning of mechanical ventilation and again at the restart of the patient's prescribed sedative after cessation of the study drug. According to standard care in the participating units, sedation prescriptions were not targeted to a prespecified RASS score.

The appropriateness of starting infusion of the study drug was assessed each morning for each patient, starting on the second morning of mechanical ventilation. The study drug was not started if the patient was scheduled for invasive procedures or investigations requiring in-hospital transport within the next 2 hours; infusion of the study drug was started after the procedure was completed. Before starting infusion of the study drug, the bedside nurse determined the patient's RASS score, and if the patient was sufficiently oriented and awake to interact with the instruments or otherwise communicate with the nurse, assessed pain by using a 0 to 10 numeric rating scale, with 0 = pain-free and 10 = "worst pain ever experienced,"<sup>26</sup> and anxiety by using the Faces Anxiety Scale.<sup>27</sup> Patients were exempt from infusion of the study drug that day if their pain was considered marked, they were scheduled for surgery within the study drug infusion period, or the treating clinicians deemed the infusion inappropriate because of clinical need, such as neuromuscular blockade.

Infusion of the study drug was stopped if the patient met any of the following criteria: increased levels of pain, unstable hemodynamic status, a 1-point increase in the score on the Faces Anxiety Scale, a score of +2 or more on the RASS, ventilator dyssynchrony, any procedure or event requiring an increase in sedation, and infusion of the study drug for 6 hours. As soon as infusion of the study drug was stopped for any of the criteria, infusion of the prescribed sedative was restarted. The 6-hour maximum duration was included to preserve the blinding in patients in the control group who might not have met any of the other criteria for stopping the study drug for several days. Infusion of the study drug could be decreased or stopped by the clinical team if they thought that the level of sedation should be reduced. The clinical team also controlled all other aspects of patient care.

Daily sedation interruption practice is widespread despite limited published data.

Every patient was given a replacement infusion (some with sedation, some without) for a defined period each day.

## Strategies to Promote Adherence to the Protocol

The study protocol was developed according to the current standard practices for the management of sedation, with the exception that nonstudy sedatives could only be prescribed after consultation with a senior medical officer. Research nurses were continually available to consult with the clinical team, provide one-to-one support for the bedside nurses, and monitor protocol adherence daily. Education from senior clinicians was provided when deviations in protocol occurred.

## Outcomes and Data Collection

The primary goal of the study was to assess the safety, feasibility, and effectiveness of the study protocol. Safety was defined as the number of unplanned extubations during the study intervention and the percentage of patients with agitation (RASS score greater than +2). Feasibility was defined as being able to enroll at least 80 patients in the 2 ICUs in a 12-month period and the ability to apply the protocol as evidenced by compliance with protocol requirements by clinicians. Effectiveness was defined as the ability of the investigators, patients, or clinicians to ascertain treatment assignment on the basis of a patient's response during infusion of the study drug.

Demographic and clinical data, scores on the Acute Physiology and Chronic Health Evaluation II,<sup>28</sup> diagnostic classification according to scores on the Acute Physiology and Chronic Health Evaluation III,<sup>25</sup> and number of unplanned extubations and tracheostomies were collected from the patients' records. The bedside nurse recorded sedation scores before and at the end of infusion of the study drug, duration of the infusion, and the reasons to restart the prescribed sedative. The total doses of study and nonstudy sedatives and the number of ad hoc interruptions were recorded. Nondrug outcomes included duration of mechanical ventilation and ventilator-free survival at 28 days,<sup>29</sup> duration of ICU and hospital stays, and survival at hospital discharge and 6 months after ICU discharge.

## Data Analysis

Data were analyzed by using SPSS, version 14.0 (SPSS Inc, Chicago, Illinois). Blinded analysis of clinical end points was performed by using the intention-to-treat principle. Mean daily doses of fentanyl and midazolam were calculated by dividing the total doses given via continuous infusion by the number of days of mechanical ventilation overall. Normally distributed data were compared by using *t* tests. Data that were not normally distributed were

logarithmically transformed to base 10 and were compared by using *t* tests (drug doses, duration of mechanical ventilation, ICU and hospital stay). If the transformed distributions were not normal, the untransformed data were compared by using the Mann-Whitney test (days study drug given and ad hoc interruption, adjusted for number of days of mechanical ventilation). Nominal variables were compared by using  $\chi^2$  analysis. A significance level of  $P = .05$  was set for all statistical tests. This pilot study did not have sufficient power to detect significant differences in clinical end points. It was determined a priori that the recruitment of 80 patients during a 1-year period, from both centers, would indicate the feasibility of a phase 3 study.

## Results

### Patient Characteristics

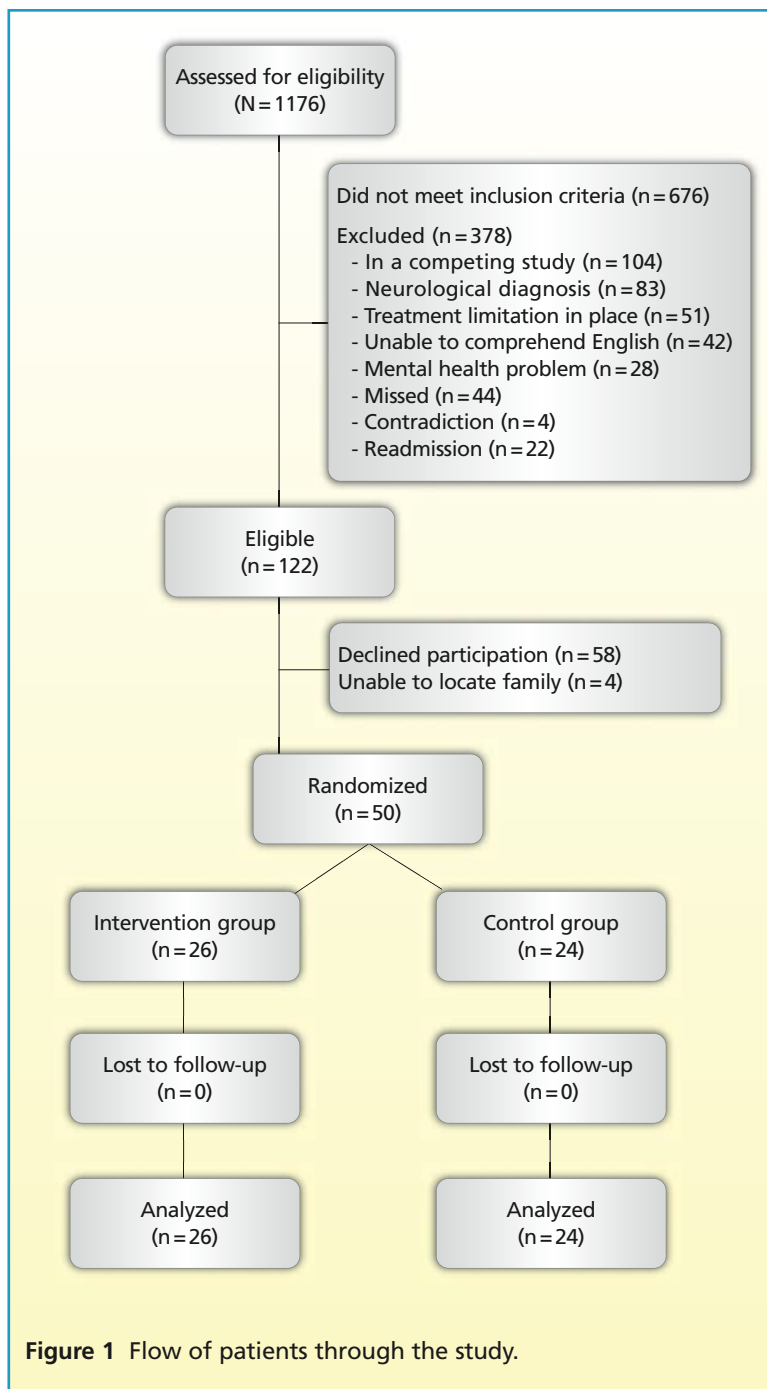
Of 1176 patients receiving mechanical ventilation who were screened between September 2005 and December 2007, 122 were eligible (Figure 1). Reasons for noneligibility were recorded. The study was terminated before recruitment of 80 patients because of slow recruitment rates. Informed written consent was not obtained for 72 patients who were otherwise eligible for the study; for 58 of the 72 (47.5% of the 122 eligible), the next of kin declined to provide consent. Data on 50 patients randomly assigned to the intervention group ( $n = 26$ ) or the control group ( $n = 24$ ) were included in the analysis. The groups had equivalent baseline characteristics (Table 1) and had similar RASS scores before infusions of the study drug were started (Table 2).

### Use of Sedatives

Data on administration of the study drug and ad hoc interruptions are shown in Table 3. Each day, as indicated by the study protocol, clinicians' judgment was used to determine contraindications, such as poorly controlled pain, recent extreme agitation, and palliative care, before infusion of the study drug was started. Clinical staff considered that starting infusion of the study drug was never appropriate for several patients in each group (15% of the intervention group and 13% of the control group), and infusion of the study drug was started for other patients on approximately one-third of

The Richmond Agitation-Sedation Scale was used to assess the level of sedation each morning of ventilation.

The use of replacement infusion to deliver blinded sedation interruption is feasible, safe, and effective.



**Figure 1** Flow of patients through the study.

possible days. In addition to the planned interruption in the intervention group, ad hoc interruption of infusions of sedatives was implemented in many patients in both groups. Propofol was the most common additional agent used, sometimes in violation of the study protocol (Table 4). The median doses of fentanyl or midazolam did not differ significantly between the 2 groups of patients.

### Effects of Sedation

A total of 239 morning RASS scores and 153 restart RASS scores were recorded (Table 2). The range

of scores was similar for both groups at both times. Approximately 50% of patients in both groups had RASS scores greater than +1 at the time the prescribed sedative was restarted. The percentages of RASS scores of +2 or greater (ie, very agitated) immediately before the prescribed sedative was restarted were low in both groups. The reasons for stopping infusion of the study drug are presented in Figure 2. The most common reason in both groups was completion of the 6-hour period of infusion of the study drug; the next most common reason was agitation, which was similar between groups.

### Clinical End Points

This pilot study was not designed to be adequately powered to detect significant differences in clinical outcomes. The 2 groups did not differ significantly (Table 5), and no unplanned extubations occurred during the study.

### Discussion

This study was designed to assess the feasibility of conducting a randomized, double-blind, controlled clinical examination of a routine daily interruption to continuous sedation in patients receiving mechanical ventilation. The number of eligible patients and the number of patients receiving mechanical ventilation were low. Clinical staff often mistakenly anticipated that their patients would be ready for weaning from mechanical ventilation within 48 hours. More than a quarter of otherwise eligible patients were already enrolled in other clinical trials within the study units, and enrollment in our study was not possible. This problem of coenrollment was encountered in a similar study<sup>22</sup> and probably will become more prevalent in Australian ICUs.<sup>30</sup> The number of eligible patients was reduced further when nearly 50% of patients' next of kin declined to provide consent. The reasons for these refusals were not recorded, but possibly the concept of discontinuing drugs being given to promote comfort was considered too objectionable, despite assurances that the drugs would be recommenced at the first sign of discomfort. Concerns about insufficient sedation were expressed by some family members in another study<sup>13</sup> on interruption of sedation.

Adherence to the study protocol was a problem, particularly for use of propofol, which is used at least as commonly as midazolam in Australia.<sup>31,32</sup> The frequency of propofol use was unexpected, and because of its milky appearance, incorporating its use into the protocol would have increased the challenge of blinding allocation. The low percentage of days on mechanical ventilation that infusions of

**Table 1**  
Baseline characteristics according to group

Characteristic	Group		P
	Intervention (n = 26)	Control (n = 24)	
Age, mean (95% CI), y	65.1 (58.4-71.6)	69.1 (63.7-74.5)	.35 <sup>a</sup>
Male sex, No. (%) of patients	14 (54)	17 (71)	.21 <sup>b</sup>
APACHE II score, mean (95% CI)	23.4 (20.3-26.4)	21.4 (18.4-24.4)	.36 <sup>a</sup>
Nonoperative diagnosis, No. (%) of patients	22 (85)	18 (75)	.40 <sup>b</sup>
Reason for admission to intensive care unit, No. of patients			.17 <sup>c</sup>
Cardiac	0	2	
Respiratory	10	12	
Gastrointestinal	6	8	
Sepsis	7	2	
Metabolic	2	0	
Renal	1	0	

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval.  
<sup>a</sup> Independent samples t test.  
<sup>b</sup> Fisher exact test.  
<sup>c</sup> Pearson  $\chi^2$  test.

the study drug were given and the prevalence of ad hoc interruption of sedation diluted the effect of the intervention, as suggested by the lack of difference in the doses of fentanyl and midazolam. In another pilot study,<sup>22</sup> the percentage of study days on which infusions were interrupted was higher (82%) than the percentage we were able to achieve. In a survey<sup>31</sup> of Australian and New Zealand intensive care practice, 62% of the respondents used daily interruption of sedation to manage some patients. However, this finding was inconsistent with the subsequent report<sup>32</sup> of a 1-day point prevalence study of 234 patients in which only 9.5% had had a deliberate interruption in their sedation in the previous 12 hours. In our 2 ICUs, the regular interruption of

**Table 2**  
Sedation scores

Scores on Richmond Agitation Sedation Scale (RASS)	% of total number of RASS assessments	
	Intervention (n = 114)	Control (n = 125)
Each morning		
Between -3 and -5 (no eye contact)	36.0	43.2
Between -2 and 0 (eye contact)	55.3	40.0
$\geq +1$ (spontaneous movement)	8.8	16.8
At restart of prescribed sedative after cessation of study drug		
Intervention (n = 72)		Control (n = 81)
Between -3 and -5 (no eye contact)	13.8	32.0
Between -2 and 0 (eye contact)	38.8	19.7
$\geq +1$ (spontaneous movement)	47.2	48.1
$\geq +2$ (very agitated)	13.9	7.4

**Table 3**  
Study drug infusions and ad hoc interruptions during study participation

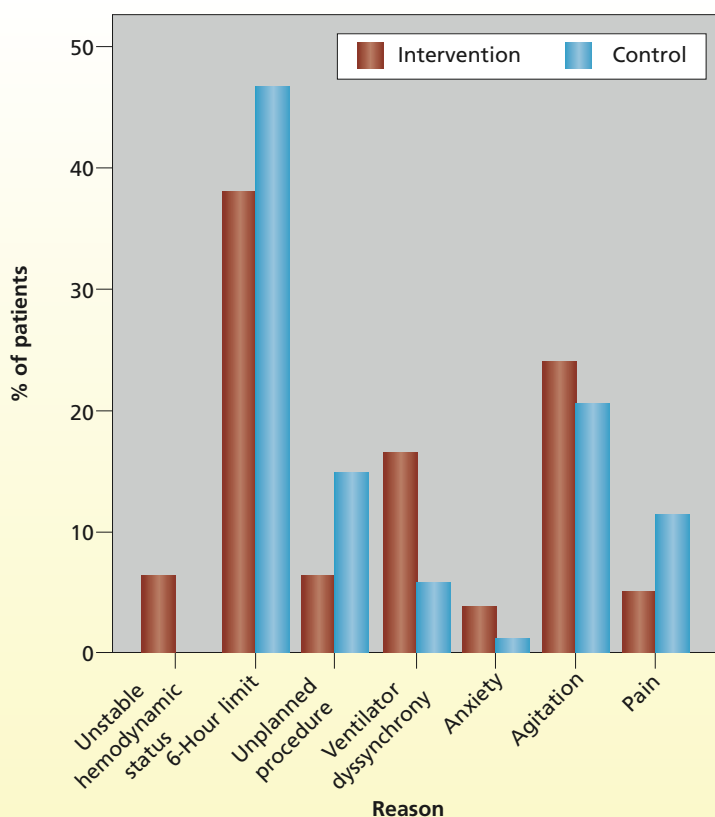
Infusions and interruptions	Group		P
	Intervention (n = 26)	Control (n = 24)	
Study drug infusions			
No. (%) of patients receiving study drug infusion	22 (85)	21 (88)	.77 <sup>a</sup>
No. of study drug infusions per patient, median (range)	2 (0-12)	3 (0-13)	
Proportion of infusions per day of mechanical ventilation, median (range)	25 (0-80)	35 (0-99)	.17 <sup>b</sup>
Duration of infusion, mean (SD), h	3.4 (1.7)	4.6 (1.7)	.20 <sup>c</sup>
Ad hoc interruptions			
No. (%) of patients experiencing	16 (62)	12 (50)	.41 <sup>a</sup>
No. of interruptions per patient, median (range)	1 (1-4)	1 (1-5)	
Proportion of interruptions per day of mechanical ventilation, median (range)	19 (0-82)	11 (0-68)	.23 <sup>b</sup>

<sup>a</sup> Fisher exact test.  
<sup>b</sup> Mann-Whitney test.  
<sup>c</sup> Independent samples t test.

**Table 4**  
Doses of fentanyl, midazolam, and propofol during mechanical ventilation

Drug dose and violations	Group		P
	Intervention (n=26)	Control (n=24)	
Fentanyl dose per day of mechanical ventilation, median (IQR), µg	721.1 (555-1063)	986.3 (451-2305)	.99 <sup>a</sup>
Midazolam dose per day of mechanical ventilation, median (IQR), mg	31.9 (18-47)	33.23 (13-95)	.41 <sup>a</sup>
No. (%) of patients prescribed propofol	12 (46)	15 (62)	.25 <sup>b</sup>
No. (%) of patients given propofol in violation of study protocol	7 (27)	4 (17)	.10 <sup>b</sup>
Total propofol dose, mean (CI), mg	117 (10.0-224.7)	92.9 (15.8-170.0)	.71 <sup>c</sup>

<sup>a</sup> Fisher exact test.  
<sup>b</sup> Mann-Whitney test.  
<sup>c</sup> Independent samples t test.



**Figure 2** Principal reason patient was returned to prescribed sedation.

sedation appears to be more common than the point prevalence estimate.

Our blinding strategy was feasible, safe, and apparently effective. Similar numbers of patients in the intervention and control groups experienced spontaneous movement at the end of infusion of the study drug, and the most frequent reason for ending infusion was the elapse of the maximum 6-hour period. This finding suggests that a patient's

response generally did not indicate his or her group assignment. The safety of the blinding strategy is supported by the low numbers of agitated patients immediately before the prescribed sedative was restarted and the absence of unintended extubation in either group. Other studies<sup>9,11,13,22</sup> of daily interruption in sedation have been open label, with the intervention managed by the investigators. In the randomized study by Kress et al,<sup>9</sup> clinical staff were not informed of group allocation, but an investigator openly interrupted the sedative infusions in the intervention group, and a research nurse evaluated patients in whom sedatives were ceased until the patients were awake or agitated. Therefore it seems likely that the clinical staff in the study by Kress et al were aware of the group allocation. In another study, Mehta et al<sup>22</sup> argued that blinding after randomization was not possible.

Our protocol would have been improved by less reliance on an accurate prediction for duration of mechanical ventilation from the clinicians; a simpler inclusion question would be "Is this patient going to be receiving mechanical ventilation tomorrow?" during the first 24 hours of admission. Including propofol as a primary agent of sedation would complicate blinding because of the need for a white liquid placebo, such as lipid, but use of propofol for interim sedation (for whatever reason) should be included in future protocols. The number of ad hoc interruptions in sedation provides support for waived or delayed consent but, on the other hand, also suggests that clinicians are adopting daily interruption of sedation despite a lack of evidence suggesting a benefit of this practice in the Australian context.

## Conclusion

We found that a double-blinded strategy for the study of sedation in patients receiving mechanical ventilation can be safe and effective. Slow recruitment and protocol violations, with the low proportion of

**Table 5**  
**Clinical outcomes**

Characteristic	Group		P
	Intervention (n = 26)	Control (n = 24)	
Duration of mechanical ventilation, median (IQR)	8.0 (3.6-14.5)	8.4 (4.4-14.3)	.93 <sup>a</sup>
28-day ventilator-free survival, mean (CI)	11.9 (7.6-16.1)	10.6 (6.2-14.9)	.66 <sup>b</sup>
Duration of ICU stay in days, median (IQR)	8.2 (6.4-17.3)	11.3 (7.4-18.6)	.83 <sup>a</sup>
Duration of hospital stay in days, median (IQR)	20.1 (11.0-41.7)	18.5 (11.5-31.2)	.87 <sup>a</sup>
ICU mortality, number (%)	5 (19.0)	8 (33.0)	.30 <sup>c</sup>
Six-month mortality, number (%)	13 (50.0)	11 (45.8)	.77 <sup>c</sup>
Tracheostomy, number (%)	8 (31.1)	13 (54.2)	.99 <sup>d</sup>
Days from mechanical ventilation start to tracheostomy, mean (CI)	5.3 (4.09-6.41)	5.8 (3.96-7.71)	.61 <sup>b</sup>

Abbreviations: CI, 95% confidence interval; ICU, intensive care unit; IQR, interquartile range.  
<sup>a</sup> Independent samples t test for log<sub>10</sub> transformed data.  
<sup>b</sup> Independent samples t test.  
<sup>c</sup> Fisher exact test.  
<sup>d</sup> Pearson  $\chi^2$  test.

days that the planned interruption of sedation actually occurred and frequent ad hoc interruptions suggest that use of the current protocol in a large multicenter study might be difficult.

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#### FINANCIAL DISCLOSURES

Leonie Weisbrodt and Ian Seppelt were members of the Sedation Advisory Board in Intensive Care for Hospira Inc, Lake Forest, Illinois, and have received honoraria, which were donated to the hospital research fund, for attending board meetings. These 2 authors are also members of the management committee for the SPICE (Sedation Practices in Intensive Care) investigators, who have been awarded an unrestricted grant from Hospira Inc to support conduct of the study. This study (clinical trial registration number ACTRN1260-5000043639) was supported by grants from the Intensive Care Foundation and Australian College of Critical Care Nurses.

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