

# Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients\*

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**Objective:** In critically ill patients receiving mechanical ventilation, daily interruption of sedative infusions decreases duration of mechanical ventilation and intensive care unit length of stay. Whether this sedation strategy reduces the incidence of complications commonly associated with critical illness is not known.

**Design:** Blinded, retrospective chart review.

**Setting:** University-based hospital in Chicago, IL.

**Patients:** One hundred twenty-eight patients receiving mechanical ventilation and continuous infusions of sedative drugs in a medical intensive care unit.

**Interventions:** None.

**Measurements and Main Results:** We performed a blinded, retrospective evaluation of the database from our previous trial of 128 patients randomized to daily interruption of sedative infusions vs. sedation as directed by the medical intensive care unit team without this strategy. Seven distinct complications associated with mechanical ventilation and critical illness were identified: a)

ventilator-associated pneumonia; b) upper gastrointestinal hemorrhage; c) bacteremia; d) barotrauma; e) venous thromboembolic disease; and f) cholestasis or g) sinusitis requiring surgical intervention. The incidence of complications was evaluated for each patient's hospital course.

One hundred twenty-six of 128 charts were available for review. Patients undergoing daily interruption of sedative infusions experienced 13 complications (2.8%) vs. 26 (6.2%) in those subjected to conventional sedation techniques ( $p = .04$ ).

**Conclusions:** Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation reduces intensive care unit length of stay and, in turn, decreases the incidence of complications of critical illness associated with prolonged intubation and mechanical ventilation. (Crit Care Med 2004; 32:1272-1276)

**KEY WORDS:** sedatives; respiration, artificial; critical illness; drug administration schedule; intensive care units; complications

Critically ill patients undergoing mechanical ventilation frequently require sedation and analgesia. The drugs used to achieve these end points are well established, including benzodiazepines, propofol, and haloperidol for sedation and opiates for analgesia. The strategies by which these drugs are administered are quite variable. Awareness of the potential detrimental effects of oversedation (1) has led to the development of protocols aimed at minimizing complications associated with accumulation of these drugs and prolongation of their effects (2, 3). We previously published results of a

prospective, randomized, controlled trial comparing a protocol of daily interruption of continuous sedative infusions to a regimen of sedation and analgesia directed by intensive care unit (ICU) physicians without mandated daily interruption. Implementation of daily sedative interruption until patients were awake and able to follow commands led to a reduction in average duration of mechanical ventilation (MV) of 2.4 days as well as a reduction in average ICU length of stay (LOS) of 3.5 days. These results were achieved without an increased rate of adverse events potentially linked to less sedation, including patient removal of endotracheal tubes or central venous catheters (3).

Reducing duration of MV and reducing ICU LOS are important outcomes in the care of critically ill patients. Mechanical ventilation and critical illness may translate into nosocomial complications commonly seen in ICU patients. For instance, the duration of MV has been previously linked to increasing risk of developing ventilator-associated pneumonia (VAP) (4, 5). Logically, it would seem that

other complications of critical illness would be more likely to occur with increasing duration of MV and ICU LOS; however, outcomes data are lacking for many such intuitive assumptions.

Accordingly, we identified seven common complications of critical illness frequently seen in mechanically ventilated patients: a) ventilator-associated pneumonia; b) upper gastrointestinal hemorrhage; c) bacteremia; d) barotrauma; e) venous thromboembolic disease; f) cholestasis; and g) sinusitis. We then sought to determine whether a strategy of daily interruption of sedative infusions was associated with a reduction in these important complications.

## METHODS

**Patients and Study Design.** After approval by the Institutional Review Board at the University of Chicago Hospitals, the database of our previously published, prospective, randomized-controlled study of daily sedative interruption in critically ill patients undergoing mechanical ventilation was accessed. This database of 128 patients was provided to investigators (WS, BG) who had no previous knowl-

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edge of patient randomization and who were not involved in the original study evaluating daily sedative interruption. No documentation of study arm was present within data records (including written chart and the hospital's computerized patient database) accessible to these investigators. Information from charts was logged onto a standardized computer data collection form. All charts were reviewed independently. In the event of an ambiguous clinical scenario, a panel of three blinded critical care physicians was presented with the clinical data to ensure accurate assignment.

**Data Collection and Definition of Variables.** Demographic data [age, gender, weight, Acute Physiology and Chronic Health Evaluation II severity of illness score (6)], use of a ventilator strategy utilizing permissive hypercapnia (intentional hypoventilation to allow an arterial carbon dioxide tension of  $\geq 50$  mm Hg), ICU LOS, and duration of mechanical ventilation were recorded for all patients. To establish the presence of the identified seven complications associated with mechanical ventilation and critical illness (ventilator-associated pneumonia, upper gastrointestinal hemorrhage, bacteremia, barotrauma, venous thromboembolic disease, cholestasis, and sinusitis), predefined clinical criteria were established (outlined in detail subsequently). Complications were selected based on clinical importance, frequency, and reliability of disclosure from a retrospective chart review.

Complications of critical illness were required to be new and distinct from the ICU admitting diagnoses. To meet the diagnosis of VAP, the patient was required to have a new lung parenchymal opacity on chest radiograph and simultaneous presentation of (at least) two of the following three criteria: a) temperature  $< 36^{\circ}\text{C}$  or  $> 38^{\circ}\text{C}$ ; b) white blood cell count  $< 4 \text{ K}/\mu\text{L}$  or  $> 10 \text{ K}/\mu\text{L}$ ; c) purulent secretions from the endotracheal tube. Upper gastrointestinal hemorrhage was confirmed by esophagogastroduodenoscopy, mesenteric angiography, or the combination of grossly visualized blood from an enterally-placed tube (e.g., Salem Sump) and subsequent transfusions of two or more units of packed red blood cells. Bacteremia required the presence of positive blood cultures; however, cultures of coagulase negative *Staphylococcus* species required serial demonstration (blood cultures positive on more than one occasion). Barotrauma was defined as a pneumothorax requiring chest tube insertion. The presence of venous thromboembolic disease required one of the following: venous thrombosis proven by Doppler ultrasonography, venography, or infused computed tomography (CT); or pulmonary embolus proven by pulmonary angiogram or infused spiral CT of the thorax. Cholestasis required all of the following: a) elevated alkaline phosphatase and total bilirubin; b) imaging study (CT/ultrasound) confirming the presence of cholestasis; and c) the need for procedural intervention (surgical or percutaneous drainage by an interventional

radiologist). Sinusitis required either gross purulence from the nares or sinus fluid present on sinus CT scan and subsequent endoscopic drainage.

The incidence of deep venous thrombosis prophylaxis and gastric stress ulcer prophylaxis was assessed. Deep venous thrombosis prophylaxis was defined as the daily administration of subcutaneous unfractionated or low molecular weight heparin or intermittent pneumatic compression devices for a time period  $\geq 75\%$  of the time spent in the ICU. Stress ulcer prophylaxis was defined as the daily administration of a proton pump inhibitor, histamine (H<sub>2</sub>) antagonist, or sucralfate therapy for a time period  $\geq 75\%$  of the time spent in the ICU.

**Statistical Analysis.** Demographic data are summarized as mean (SD) or median (interquartile range) as appropriate for parametric and nonparametric distributions, respectively. Comparisons of demographic data were made by unpaired Student's *t*-test (parametric data) or Mann-Whitney U test (nonparametric data) as appropriate. If a patient suffered a specific complication multiple times (e.g., multiple pneumothoraces), only the first was counted. In addition, complications were required to have all defining criteria fulfilled in chronological proximity to the institution of MV. This was defined as the time period beginning no earlier than 48 hrs after initiation of MV and extending to a period no later than 48 hrs following discontinuation of MV. Comparisons of complication incidence between groups used the general estimating equation regression model (7). Kaplan-Meier and log rank analyses were used to assess the effect of daily interruption of sedative infusion on the time to first complication from both MV and ICU admission (8).

## RESULTS

One hundred twenty-eight patients from the database were eligible for evaluation; 126 had medical records available (66 patients in the sedative interruption group and 60 patients in the control group; Fig. 1).

As previously noted, the demographic characteristics, Acute Physiology and

Chronic Health Evaluation II scores, and frequency of use of permissive hypercapnia ventilation strategy were similar in the two groups (3) (Table 1).

Deep venous thrombosis prophylaxis was administered for 90.2% of patients in the daily sedation interruption group vs. 92.5% in the control group ( $p = 1.0$ ). Gastric stress ulcer prophylaxis was administered to 90.5% of patients in the daily sedation interruption group vs. 96.3% in the control group ( $p = 1.0$ ).

**Outcomes.** After blinded assessment for all potential complications, the sedative interruption group experienced a total of 13 complications in 12 patients (2.8%). In contrast, the patients in the control group experienced a total of 26 complications among 19 patients (6.2%;  $p = .04$  by generalized estimating equation). Six of the seven prospectively sought complications occurred more frequently in the control group (all except upper gastrointestinal hemorrhage). Individual complications in each group are detailed in Table 2.

The Kaplan-Meier analysis of time from intubation to first complication according to study group is depicted in Figure 2. The same analytical technique was applied to time from ICU admission to first complication as well (Fig. 3). Although not statistically significant, the Kaplan-Meier curves demonstrate a trend toward decreased incidence of first complication in the daily sedative interruption group vs. the control.

Table 3 summarizes the rates of measured individual complications in comparison with previously published rates (9–23).

## DISCUSSION

Pain and anxiety are common among patients admitted to ICUs. These symptoms may be attributed to the discomfort of procedures such as endotracheal intubation and mechanical ventilation, isolation from familiar surroundings, lack of control or autonomy, and uncertainty regarding prognosis. Sedatives and analgesics are frequently administered to patients during mechanical ventilation to alleviate this pain and anxiety, decrease excessive oxygen consumption, and facilitate nursing care. As a result, the bedside nursing role of careful monitoring of sedatives and analgesia is extremely important (24–26). The use of sedation protocols mandating daily interruption of continuous sedative infusions or a nurs-

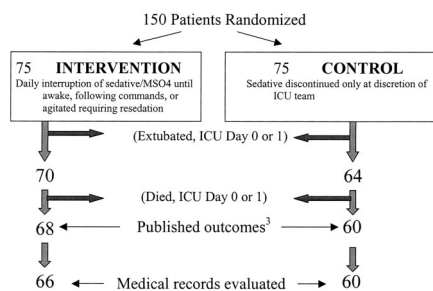


Figure 1. Schematic of patient recruitment characteristics. ICU, intensive care unit.

Table 1. Characteristics of study patients

	Intervention	Control	p Value
Patients reviewed, no.	66	60	
Age, yrs	55.5 (41.0–71)	61 (40.0–73.5)	.59
Gender, no.			.69
Male	32	26	
Female	34	34	
Weight, kg	69.4 (58.8–90.3)	66 (60.4–78.8)	.77
APACHE II	20.1 ± 6.4	21.2 ± 6.1	.34
Permissive hypercapnia	12	15	.48
Mortality rate, %	36.3	46.7	.16
Duration of mechanical ventilation, days	4.8 (2.4–8.0)	7.3 (3.4–16.1)	.003
Length of stay, days			
Intensive care unit	6.2 (3.9–11.3)	9.9 (4.7–17.9)	.01
Hospital	13.3 (7.3–20.5)	16.9 (8.5–26.6)	.15

APACHE, Acute Physiology and Chronic Health Evaluation (8).

The APACHE II is an assessment of the severity of illness, with possible scores ranging from 0 to 71 (increasing scores correlated with an increasing risk of in-hospital death). Data are expressed as mean ± standard deviation or median (interquartile range).

Table 2. Summary of complications

Complication	Intervention, No.	Control, No.
VAP	2	5
Upper gastrointestinal hemorrhage	5	4
Bacteremia	4	7
Barotrauma	0	3
VTE	2	5
Cholestasis	0	1
Sinusitis	0	1
Total (No.)	13	26

VAP, ventilator-associated pneumonia; VTE, venous thromboembolic event.

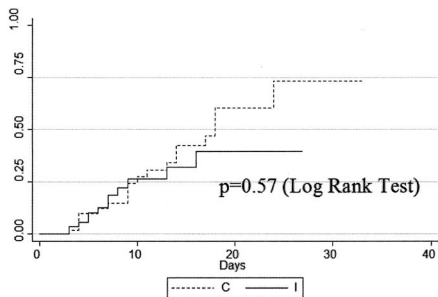


Figure 2. Kaplan-Meier plot, time from intubation to first complication. I, intervention arm (daily sedation interruption); C, control arm.

ing-directed protocol targeting reduction in sedative dosing has been shown to shorten duration of MV and ICU LOS (2, 3). We previously reported that such reductions in sedation could be implemented without increasing adverse events such as patient removal of endotracheal tubes and central venous catheters (3).

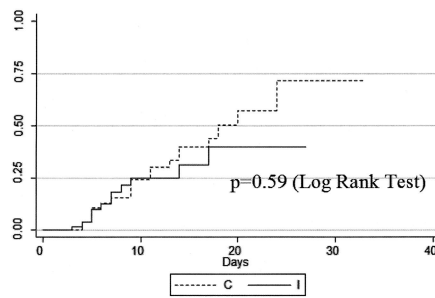


Figure 3. Kaplan-Meier plot, time from intensive care unit admission to first complication. I, intervention arm (daily sedation interruption); C, control arm.

For the purpose of this investigation, we sought to determine whether a protocol of daily interruption of sedative infusions would affect the incidence of common complications associated with critical illness. Complications were selected based on clinical importance, frequency, and reliability of disclosure from a retrospective chart review.

Complications of critical illness are routinely studied individually; however, studying such complications in aggregate can create a risk of possible interrelationships not immediately recognized (e.g., venous thromboembolic events undergoing anticoagulation therapy with subsequent gastrointestinal hemorrhage). As a result of this concern, the comparison between groups was analyzed using the general estimating equation (7). This method of analysis permits comparisons of the sum of complications while accounting for the possibility of interrelationships between multiple complications among individual patients.

The data for the time to first complication are also illustrated by Kaplan-Meier curves (Figs. 2 and 3). These curves demonstrate some disparity later in the ICU course (approximately 2 wks postintubation), suggesting that ICU time may increase the chance of a complication. Unlike the general estimating equation, which evaluates the sum of all complications and their potential interrelationships, the Kaplan-Meier curves evaluate only the first complication in each patient. There were no differences between these two groups using this method of analysis.

The seven prospectively defined complications are well-described in critical illness (4, 5, 9–23, 27–32). Some complications, such as VAP, have been clearly linked to duration of MV (4, 5). Cook et al. (5) reported that cumulative risk of VAP increased over time, even though the daily hazard rate decreased after day 5 of MV. They noted a risk of VAP per day of 3.3% at MV day 5, 2.3% at MV day 10, and 1.3% at MV day 15. Other complications such as bacteremia may be associated with the presence of venous catheters (15, 31). Since these catheters are more likely to be present when patients are intubated and mechanically ventilated and/or in the ICU, a higher incidence in the control group is understandable.

Critically ill patients are frequently immobilized and subjected to procedures involving invasive instrumentation. It is in this immobilized state that they may fall prey to complications such as venous thromboembolic events (20), even when established prophylactic measures are instituted (21).

At least four of our prospectively defined complications may occur as a direct result of invasive instrumentation. Bacteremia (venous catheters) and VAP (endotracheal intubation) have already been discussed previously. It seems logical that reducing intubation time should reduce the incidence of barotrauma, although convincing data to support this supposition are lacking. As discussed, shortening the duration of MV and ICU LOS may reduce the need for and duration of venous catheter placement. Conceivably, iatrogenic pneumothorax during central catheter placement is another complication that could be avoided. Nasoenteral tubes and supine positioning may predispose patients to sinusitis (23, 32). Shortening ventilator and ICU time may decrease the need for these invasive devices.

Table 3. Review of published rates of complications

Complication	Source	Incidence	Intervention	Control
VAP	Cook et al. (5)	17.5	3	8.3
	Rello et al. (9)	9.3		
	Rello et al. (10)	21.9		
Upper GI hemorrhage	Cook et al. (11)	1.5	7.6	6.7
	Cook et al. (12)	2.6		
	Schuster et al. (13)	14		
Bacteremia	Hugonnet et al. (14)	3.2–4.3	6	11
	Pittet et al. (15)	2.7		
	Vincent et al. (16)	12		
Barotrauma	Schnapp et al. (17)	13	6	5
	Gammon et al. (18)	11.9		
	Petersen et al. (19)	8		
VTE	Hirsch et al. (20)	33	3	8.3
	Ibrahim et al. (21)	23.6		
Cholestasis	Mutlu et al. (22)	0.2–3	0	1.7
Sinusitis	Holzappel et al. (23)	18	0	1.7

VAP, ventilator-associated pneumonia; GI, gastrointestinal; VTE, venous thromboembolic event. All values are percentages.

This study has limitations worth noting. Although the database was prospectively randomized to daily sedative interruption vs. control groups, the described complications were not prospectively defined and followed in the original investigation. Because of the potential for bias in our retrospective evaluation, the database was reviewed by investigators blinded to each patient's assignment (daily sedative interruption vs. control). These investigators had never seen the database before this study and indeed were not present when the original investigation was undertaken. This blinding minimizes, but does not fully eliminate, the potential for bias.

Because we did not prospectively seek to identify these complications in the original study, it is possible that some were undetected (e.g., venous thrombosis). However, a potential difference in incidence of undetected complications seems quite unlikely, given the prospective randomization of the patients to two groups. In addition, many of the complications (e.g., ventilator-associated pneumonia, bacteremia) are routinely sought in critically ill patients and/or were only identified for purposes of this investigation by the need for an intervention (e.g., barotrauma leading to chest tube placement, cholecystitis or sinusitis leading to surgery), further reducing the likelihood of underrecognition of these complica-

tions as defined. Finally, retrospective evaluations based on medical charting have inherent limitations. Subtleties such as central venous catheter manipulation and exact ventilator settings at the time when barotrauma occurred were not reliably documented in our medical records.

The complications of critical illness vary widely according to previously published epidemiologic studies. As can be seen in Table 3, our incidences of complications compare reasonably well with the incidences reported in prior publications. However, as noted in Table 3, our incidences of sinusitis and venous thromboembolic disease are lower than reported in prior publications. These differences are likely due to differences in methodology. For example, the incidence of venous thromboembolic events in the study by Ibrahim et al. (21) included patients only if duration of mechanical ventilation exceeded 7 days, and duplex ultrasonography for venous thromboembolic events was performed even in the absence of symptoms. This is different from our study, where duration of mechanical ventilation averaged 4.8 and 7.3 days for the intervention and control group, respectively. In addition, only those with clinical presentations that merited evaluation were included. The study by Holzappel et al. (23) only involved patients nasotracheally intubated,

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a known risk factor for sinusitis (33). None of the patients in our study were nasotracheally intubated.

The relatively small sample size from this single-center investigation limits our ability to determine the relative impact and importance of each individual complication evaluated. Larger studies are needed to overcome this important limitation.

## CONCLUSIONS

We have demonstrated that common complications of critical illness are reduced when intubated, mechanically ventilated patients are subjected to a protocol of daily sedative interruption. These improved outcomes are likely the result of reduced duration of mechanical ventilation and length of stay in the ICU.

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