A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients*

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Objective: **To compare duration of mechanical ventilation for patients randomized to receive lorazepam by intermittent bolus administration vs. continuous infusions of propofol using protocols that include scheduled daily interruption of sedation.**

Design: **A randomized open-label trial enrolling patients from October 2001 to March 2004.**

Setting: **Medical intensive care units of two tertiary care medical centers.**

Patients: **Adult patients expected to require mechanical ventilation for >48 hrs and who required ≥10 mg of lorazepam or a continuous infusion of a sedative to achieve adequate sedation.**

Interventions: **Patients were randomized to receive lorazepam by intermittent bolus administration or propofol by continuous infusion to maintain a Ramsay score of 2–3. Sedation was interrupted on a daily basis for both groups.**

Measurements and Main Results: **The primary outcome was median ventilator days. Secondary outcomes included 28-day ventilator-free survival, intensive care unit and hospital length of stay, and hospital mortality. Median ventilator days were significantly lower in the daily interruption propofol group compared with the intermittent bolus lorazepam group (5.8 vs. 8.4, $p = .04$). The difference was largest for hospital survivors (4.4 vs. 9.0, $p = .006$). There was a trend toward greater ventilator-free survival for patients in the daily interruption propofol group (median 18.5 days for propofol vs. 10.2 for lorazepam, $p = .06$). Hospital mortality was not different.**

Conclusions: **For medical patients requiring >48 hrs of mechanical ventilation, sedation with propofol results in significantly fewer ventilator days compared with intermittent lorazepam when sedatives are interrupted daily. (Crit Care Med 2006; 34:1326–1332)**

Key Words: conscious sedation; respiratory failure; mechanical ventilator weaning; intensive care units

To minimize patient discomfort in the intensive care unit (ICU), sedation and analgesia have become an integral part of critical care practice. Sedation and analgesia reduce the stress response, provide anxiolysis, improve tolerance of ventilator support, and facilitate nursing care. Unfortunately, sedatives and analgesics have adverse effects including respiratory depression and delirium that can prolong mechanical ventilation. This problem can worsen patient outcome and substantially increase health care costs (1, 2). Deliberate approaches to the administration of sedatives including defined nurse-directed protocols (3, 4) and daily interruption of continuous infusions of sedatives (5) can lead to significant decreases in duration of mechanical ventilation. Important complexity remains, however, regarding the choice of appropriate sedative medications and methods of administration (6). A number of effective sedative agents are available, but they differ considerably with regard to adverse effects and costs.

Clinical practice guidelines (7) assembled by the American College of Critical Care Medicine of the Society of Critical Care Medicine (SCCM) recommend the use of lorazepam given as intermittent intravenous bolus or continuous intravenous infusion for most patients. This recommendation is based in part on lower drug acquisition costs for lorazepam compared with other benzodiazepines such as midazolam, with equal or better levels of sedation in patients requiring long-term sedation (8, 9). Many physicians and pharmacists prefer intermittent bolus dosing of lorazepam rather than continuous infusions because of high levels of drug accumulation and oversedation associated with continuous infusions (10), and because of concerns regarding precipitation of drug in intravenous tubing (9, 11).

*See also p. 1544.

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Because some studies have demonstrated more rapid awakening and extubation with propofol compared with benzodiazepines (12–19), SCCM clinical practice guidelines recommend the use of propofol for patients who require rapid awakening (e.g., for neurologic assessment or extubation). None of those studies reported overall duration of mechanical ventilation. It is possible that more rapid and reliable awakening throughout the course of mechanical ventilation will facilitate earlier liberation from mechanical ventilation. Despite calls for such a comparison (20), to date there have been no clinical trials comparing lorazepam to propofol for sedation of patients requiring mechanical ventilation for >48 hrs. In addition, there have been no trials comparing continuous infusion of sedatives to an intermittent bolus dosing regimen including daily interruption of sedatives.

We sought to compare a strategy of sedation with continuous infusions of propofol to a strategy of intermittent bolus dosing of lorazepam, including daily interruption of sedatives until patients were awake and able to follow simple commands. We conducted a randomized, open-label trial at two medical centers comparing ventilator days for patients expected to require ≥48 hrs of mechanical ventilation who were randomized to either drug regimen.

MATERIALS AND METHODS

The protocol was approved by the Institutional Review Boards at each institution.

Patients. The study population comprised patients admitted to the medical intensive care units of the University of North Carolina Hospitals and the University of Chicago Hospitals between October 2001 and March 2004. Patients were screened for eligibility by study team members daily. Inclusion criteria included age ≥18, anticipated requirement of mechanical ventilation for >48 hrs based on assessments of respiratory strength and gas exchange during the first 24 hrs, and requirement of six or more doses or a total of 10 mg of lorazepam within 24 hrs or, in the judgment of the primary ICU team, requirement of continuous sedation due to agitation or ventilator asynchrony. If patients did not meet these criteria within the first 4 days after intubation, they were no longer eligible. Exclusion criteria included known hypersensitivity to lorazepam or propofol, benzodiazepine dependence, high risk of alcohol withdrawal, known history of pancreatitis or clinical evidence of active pancreatitis, pregnancy or breastfeeding, resuscitation from cardiac arrest without recovery of mental status, head trauma or acute neurologic injury with Glasgow Coma Scale score <8, transfer from an outside institution where sedatives had already been administered for >24 hrs, or death was expected within 24 hrs.

After we obtained informed written consent from patients' legally authorized surrogates, patients were randomized by a study team member. A simple computer-generated randomization scheme stratified by institution determined the patients' group assignments. Each assignment was indicated on a piece of paper enclosed in a consecutively numbered sealed opaque envelope. Because of differences in the time to onset of sedation between the two drugs, it was not possible to blind caregivers to study drug assignment. Therefore, the study was conducted in an open-label fashion.

Study Protocol. After group assignment, initial sedatives provided by the primary ICU teams were held and patients were monitored. If patients developed clinical evidence of discomfort, they were assessed for pain and treated at the discretion of the primary ICU service. If patients continued to show signs of anxiety and/or agitation despite assessment and treatment of pain, the study sedative regimen was initiated and maintained as follows: Patients assigned to the intermittent bolus lorazepam group were given intravenous lorazepam in doses ranging from 2 mg every 4 hrs to 4 mg every 4 hrs (~0.044 mg/kg) depending on their requirements before randomization and the amount of time required to arouse from their previously sedated state. Additional doses of 2 mg or 4 mg of lorazepam were allowed per the discretion of the bedside nurse. Patients assigned to the daily interruption propofol group were started on a 1% propofol with EDTA (21) infusion at 5 μg/kg/min. The infusion rate was increased every 10 mins as needed with a maximum allowable dose of 80 μg/kg/min. In both cases, a Ramsay score (22) of 2–3 was targeted, and sedatives were titrated to achieve this level of sedation. This corresponded to the patient being cooperative, oriented and tranquil, or able to respond to commands. A Ramsay score of 4 (brisk response to light glabellar tap or loud auditory stimulus) was accepted in cases of clinically significant ventilator asynchrony. In both groups, patient arousal was reassessed at least every 2 hrs by a bedside nurse, and lorazepam doses or propofol infusion rates were adjusted to maintain the target Ramsay score. If the primary physicians believed that acute hyperactive delirium was a cause of agitation, intermittent doses of haloperidol were permitted.

Patients in both groups received ≥2 mg of morphine sulfate or an equivalent opiate every 4 hrs to ensure that undetected pain was being treated. When periods of patient discomfort were detected, opiate doses were increased in 2-mg increments along with sedative doses, especially when pain or dyspnea was believed to be contributing. Continuous morphine infusions were used when high doses of sedatives were required, especially if significant ventilator asynchrony was present.

If patients in the intermittent bolus lorazepam group did not maintain adequate sedation with the maximum dose of 8 mg every 4 hrs and continuous morphine, they were considered a treatment failure and switched to an alternative sedation regimen. If patients in the propofol group required >80 μg/kg/min to achieve adequate sedation despite continuous morphine, they were considered treatment failures and switched to an alternative sedation regimen. Patients assigned to the propofol group had serum triglyceride measurements on the day of enrollment and every 4 days afterward. Patients were considered treatment failures if serum triglycerides increased to >500 mg/dL, and they were switched to the intermittent bolus lorazepam protocol. Patients in the daily interruption propofol group were also monitored for bradycardia and hypotension not explained by other causes. If present, they were switched to the lorazepam protocol.

Each morning, propofol infusions or the subsequent doses of lorazepam were stopped to allow patients to wake up until they were able to follow simple commands including tracking with their eyes, squeezing fingers, and moving their tongue (5). Morphine was held as well unless it was indicated for pain. Sedation was not interrupted if the patients required F_{IO_2} >0.80. Sedation was held as long as patients remained free from discomfort. Sedative administration was resumed when patients showed signs of agitation or discomfort, including asynchrony with the ventilator. On resumption of sedation, doses were reduced to half the previous dose if the time to achieve awakening was >6 hrs. If patients required only occasional small doses of sedatives to maintain comfort after awakening, their study regimens were stopped and they were maintained with lorazepam at doses of 1 or 2 mg in intervals of ≥8 hrs given at the discretion of the bedside nurse. This occurred in two patients in the daily interruption propofol group, one after 5 days and the other after 21 days.

Mechanical ventilation was managed by the primary ICU services. Because of the heterogeneous causes of respiratory failure for patients in the study, a single ventilator management protocol was not used. However, the approach to weaning mechanical ventilation was uniform for all patients. Based on standard practice at both institutions, patients received spontaneous breathing trials when they met the following screening criteria: a) Pa_{O_2}/F_{IO_2} ratio ≥200; b) positive end-expiratory pressure ≤5; c) cough/airway reflexes intact; d) 1-min frequency/tidal volume <105; e) no vasopressor agents (23).

Baseline and Follow-Up Data. Demographic information was collected on all patients at the time of randomization. Acute

Physiology and Chronic Health Evaluation II scores (24) and Glasgow Coma Scale scores were calculated based on variables recorded from the first 24 hrs of ICU admission. Sequential Organ Failure Assessment scores (25) were measured on the day of randomization. Ramsay scores as documented by the bedside nurse were recorded every 2 hrs until extubation. Eye opening and motor response components of the Glasgow Coma Scale were assessed and documented by bedside nurses every 8 hrs. Peak heart rate on each nursing shift was recorded during the period of mechanical ventilation.

Outcome Measures. The primary outcome for the study was defined *a priori* as median ventilator days. Ventilator days were measured from the time of intubation to the initial time that a patient became free from mechanical ventilation (by extubation or removal of ventilatory support for patients with tracheostomies) for a period lasting ≥72 consecutive hours. Secondary outcomes included 28-day ventilator-free survival, ICU length of stay, hospital length of stay, and hospital mortality. Twenty-eight-day ventilator-free survival was defined as the number of days within the first 28 days of the study period that patients were alive and off mechanical ventilation. Patients were monitored for daily administration of sedatives and analgesics, use of soft wrist restraints, and complications including self-extubations, reintubations, and tracheostomies.

We performed an analysis of approaches to liberation from mechanical ventilation to determine whether weaning efforts were similar for patients in each group. Each day of mechanical ventilation (up to day 21) was reviewed to determine when patients passed spontaneous breathing trial (SBT) screening criteria (23), which days SBTs were performed, frequency/tidal volume during SBTs, reasons for withholding extubation if SBTs were passed, and hours of noninvasive positive pressure ventilation received after extubation. Reviewers were blinded to study drug protocol for this evaluation.

Statistical Analysis. Using data from a pilot survey of duration of ventilation in one of the study ICUs, we performed a simulation study to determine the sample size needed to show a 2-day difference in median ventilator days with power of 0.9 and $\alpha = .05$. This analysis indicated that a sample size of 130 patients would be required.

Data were analyzed using an intention-to-treat approach. All patients were followed until discharge from the hospital. Ventilator days and length of stay were compared using the Wilcoxon rank-sum test. The Student's *t*-test for unequal variances (Satterthwaite approximation) was used to compare continuous variables. Categorical outcomes were compared using the chi-square test or Fisher's exact test. All statistical tests were two-sided. Data are reported as mean ± SD or median (25th, 75th percentiles). The statistician was blinded to study drug for the analysis.

RESULTS

Five hundred forty-six patients met inclusion criteria. Forty-three patients did not have an identifiable surrogate, and 106 refused consent. Two hundred sixty-five patients met other exclusion criteria. Sixty-four patients were randomized to the intermittent bolus lorazepam group, and 68 patients were randomized to the propofol group. Patients were enrolled an average of 1.5 days after intubation. All randomized patients completed the study and were included in the analysis.

Patient characteristics of each group are shown in Table 1. Sixty-two percent of patients in each group were mechanically ventilated for pneumonia, acute respiratory distress syndrome, or septic shock. Patients were similar in age, gender, and illness severity. At the time of randomization, 13 patients in the lorazepam group had renal failure compared with seven patients in the propofol group. The amount of sedatives received before randomization was similar between groups.

Sedation. Following randomization, patients in the intermittent bolus lorazepam group received a median of 11.5 (3.8, 22.7) mg of lorazepam per ventilator day. The mean rate of propofol infusions in patients in the daily awakening propofol group was 24.4 ± 16.3 μg/kg/min. Patients in the propofol group were more likely to be changed from intermittent morphine to morphine infusions (44 patients in the propofol group vs. 21 in the lorazepam group), and this resulted in higher morphine doses per ventilator day (median 31.6 [16.2, 71.6] mg for propofol vs. 10.7 [5.4, 25.8] mg for lorazepam, $p < 0.001$). Two patients in the propofol

Table 1. Patient characteristics

	Lorazepam	Propofol
No.	64	68
Age, mean ± SD	51.0 ± 16.8	54.0 ± 7.7
Female, n (%)	34 (53)	34 (50)
Race, n (%)		
Caucasian	34 (54)	35 (52)
African American	25 (40)	32 (47)
Other	4 (6)	1 (1.0)
Diagnosis, n (%)		
Pneumonia and/or ARDS	27 (42)	30 (43)
Septic shock	13 (20)	13 (19)
Other shock	3 (5)	5 (7)
Hemoptysis/alveolar hemorrhage	2 (3)	2 (3)
Sickle cell chest syndrome	3 (5)	0 (0)
COPD/asthma	4 (6)	5 (7)
Upper airway obstruction	1 (2)	4 (6)
Cystic fibrosis	4 (6)	1 (2)
Interstitial lung diseases	4 (6)	1 (2)
Other diagnoses[a]	3 (5)	7 (10)
APACHE II, mean ± SD	22.9 ± 7.7	20.7 ± 7.3
SOFA, mean ± SD	9.2 ± 4.0	8.3 ± 3.6
PaO_2/FIO_2, mean ± SD	186 ± 115	190 ± 111
GCS, ICU admission, mean ± SD	13.1 ± 3.0	12.4 ± 3.8
Chronic liver disease,[b] n (%)	3 (5)	2 (3)
Renal failure,[c] n (%)	13 (20)	7 (10)
University of North Carolina, n (%)	41 (64)	39 (57)
University of Chicago, n (%)	23 (36)	29 (43)
Sedatives prior to randomization		
Lorazepam, mg, mean ± SD	26.9 ± 21.2 n = 38	31.0 ± 23.2 n = 36
Propofol, mg, mean ± SD	3501 ± 2751 n = 34	3405 ± 5470 n = 40
Morphine, mg, mean ± SD	52.2 ± 48.7 n = 52	61.4 ± 98.4 n = 57

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; ICU, intensive care unit.

[a]Other diagnoses include diabetic ketoacidosis (1), renal failure (2), meningitis (2), seizures (1), congestive heart failure (2), bowel obstruction (1), obstructive sleep apnea (1); [b]chronic liver disease: Child-Pugh Class C at randomization; [c]renal failure: requiring hemodialysis at the time of randomization.

group did not receive opiates. Two patients in the lorazepam group received fentanyl, one patient received dilaudid, and one patient did not receive opiates. Six patients (9%) in the propofol group received haloperidol for agitated delirium compared with eight patients (12%) in the lorazepam group ($p = .80$), with median total doses of 40 mg and 20 mg, respectively.

Patients in both groups spent similar numbers of hours at different levels of sedation measured as percentage of recorded Ramsay scores, and they were equally as likely to have sedation held until the patients were able to follow simple commands (Table 2). There were no differences in the eye opening or motor response categories of the Glasgow Coma Scale or mean peak heart rate. Five patients (8%) in the intermittent bolus lorazepam group failed therapy, all due to inadequate sedation on the lorazepam protocol. Three of them received supplementation with diazepam and two with propofol. Three patients (4%) in the daily interruption propofol group failed therapy ($p = .50$ compared with lorazepam). One patient developed bradycardia not attributable to other causes, one patient developed hypotension not attributable to other causes, and one patient developed hypertriglyceridemia. There were no adverse outcomes associated with these occurrences. The mean triglygeride levels for the patients receiving propofol were 184 ± 154 mg/dL at baseline, 195 ± 105 mg/dL on day 6, and 166 ± 103 mg/dL on day 10.

Outcomes. Median ventilator days were significantly lower in the propofol group compared with the intermittent bolus lorazepam group (5.8 vs. 8.4, $p = .04$, Table 3). This overall difference in median ventilator days was due to the difference between groups for hospital survivors (4.4 vs. 9.0, $p = .006$), whereas there was no difference in median ventilator days between groups for nonsurvivors (7.2 vs. 7.5, $p = .66$). There was also a trend toward greater ventilator-free survival for patients in the daily interruption propofol group (median 18.5 days for propofol vs. 10.2 for lorazepam, $p = .06$). Because of the greater number of patients with renal failure in the lorazepam group at randomization (seven propofol vs. 13 lorazepam), a secondary analysis of ventilator days was performed excluding patients with renal failure. This did not substantially change the differences in ventilator days for all patients (5.8 propofol vs. 8.5 lorazepam, $p = .07$) or for hospital survivors (4.9 propofol vs. 9.1 lorazepam, $p = .01$).

Table 2. Levels of sedation

	Lorazepam	Propofol	p Value
Ramsay score[a]			
1 = agitated or restless	15.1	11.5	.15
2 = cooperative, oriented and tranquil	20.6	21.1	.88
3 = responds to command only	26.4	28.8	.48
4 = brisk response to light glabellar tap or loud auditory stimulus	16.4	16.3	.97
5 = sluggish response to light glabellar tap or loud auditory stimulus	11.4	12.7	.73
6 = no response to light glabellar tap or loud auditory stimulus	10.1	9.6	.88
Sedation held until patient able to follow simple commands, % of ventilator days	82.8	81.9	.86
GCS eye opening,[b] mean ± SD	2.7 ± 0.9	2.6 ± 0.8	.49
GCS motor response,[c] mean ± SD	4.4 ± 1.3	4.2 ± 1.2	.38
Peak heart rate, mean ± SD	105.0 ± 15.0	106.1 ± 18.9	.72
Percent of time on ventilator with soft wrist restraints, mean ± SD	47.4 ± 37.5	52.8 ± 37.1	.39

GCS, Glasgow Coma Scale.

[a]Reported as % of recorded hours of mechanical ventilation at each level of sedation; [b]eye opening response per GCS (1–4), assessed every 8 hrs; [c]motor response per GCS (1–6), assessed every 8 hrs.

Table 3. Outcomes

	Lorazepam	Propofol	p Value
No.	64	68	
Ventilator days for all patients, median	8.4 (4.6, 14.7)	5.8 (3.5, 10.3)	.04
Ventilator days for survivors, median	9.0 (5.3, 16.8)	4.4 (3.0, 8.7)	.006
	n = 40	n = 43	.006
Ventilator days for nonsurvivors, median	7.5 (4.0, 11.4)	7.2 (4.2, 13.2)	.66
	n = 24	n = 25	
28-day ventilator-free survival, median	10.2 (0, 20)	18.5 (0, 24)	.06
ICU LOS for all patients, median	10.4 (6.7, 16.8)	8.3 (5.2, 15.2)	.20
ICU LOS for survivors, median	12.7 (7.8, 19.1)	8.6 (5.0, 14.7)	.05
	n = 40	n = 43	
ICU LOS for nonsurvivors, median	9.5 (5.3, 12.0)	9.3 (6.0, 18.1)	.68
	n = 24	n = 25	
Hospital LOS for all patients, median	20 (12, 30)	18 (12, 29)	.55
Hospital LOS for survivors, median	22.5 (14, 33)	19 (10, 32)	.16
Hospital mortality, n (%)	24 (38)	25 (37)	.82
Approaches to weaning and patient responses			
Percent of days an SBT was performed when a screen was passed, mean ± SD	90 ± 26	89 ± 24	.85
f/V_T during SBTs, mean ± SD	64.9 ± 31.0	48.8 ± 26.7	.009
Patients for whom an SBT or extubation was withheld because of oversedation, n (%)	9 (14)	5 (7)	.21
Patients who received NPPV after extubation, n (%)	8 (13)	7 (10)	.69
Reintubations, n (%)	9 (16)	7 (12)	.59
Self-extubations, n (%)	1 (2)	3 (5)	.62
Tracheostomies, n (%)	12 (19)	12 (18)	.90

ICU, intensive care unit; LOS, length of stay; SBT, spontaneous breathing trial; f/V_T, frequency to tidal volume ratio; NPPV, noninvasive positive pressure ventilation.

Median values presented with (25th, 75th percentiles). SBT screen criteria: a) Pa_{O_2} ratio ≥200; b) positive end-expiratory pressure ≤5; c) cough/airway reflexes intact; d) 1-min frequency to tidal volume ratio <105; e) no vasopressor agents (Ref. 23).

ICU length of stay was not significantly different overall (8.3 days propofol vs. 10.4 days lorazepam, $p = .20$); however, for hospital survivors, ICU length of stay was shorter for the propofol group (8.6 vs. 12.7, $p = .05$). Hospital length of stay was not significantly different, and hospital mortality was the same for both groups.

Physicians were equally compliant in performing SBTs when screening criteria were met, and there were no differences in how many patients had SBTs or extubations withheld because of oversedation

(14% in the lorazepam group vs. 7% in the propofol group, $p = .21$). However, the ratio of frequency to tidal volume ratio during SBTs was lower for patients in the propofol group (64.9 ± 31.0 vs. 48.8 ± 26.7, $p = .009$). There were no differences in the number of reintubations or the number of patients who received noninvasive positive pressure ventilation after extubation.

DISCUSSION

In this randomized trial, sedation using continuous infusions of propofol resulted in nearly 3 fewer days of mechanical ventilation compared with intermittent bolus dosing of lorazepam. This result was more notable for survivors. There was also a significant decrease in ICU days for survivors associated with propofol sedation. It is not surprising that study drug assignment led to differences in ventilator days in survivors and not in nonsurvivors since the amount of time that passes before a dying patient has mechanical ventilation withdrawn is often determined by the pace of end-of-life decision making, and this should not be affected by which sedatives the patient is receiving.

There are number of possible explanations for the differences in outcomes between the study groups. Propofol has a rapid decline in plasma concentration when infusions are held (26, 27). Lorazepam is metabolized by hepatic glucuronidation, and the inactive metabolites are excreted by the kidney (28). Pharmacokinetics are stable with prolonged administration (29, 30), but the clearance rate is slower than that of propofol. The lipid solubility of lorazepam is limited, so it crosses the blood-brain barrier slowly. Therefore, it has a slower onset and prolonged duration of effect. Sedatives were held daily for patients in both groups, but because of differences in drug clearance, patients in the propofol group may have had more rapid or effective awakening, which resulted in better performance on spontaneous breathing trials and earlier extubation. This is supported by the lower frequency to tidal volume ratios recorded for patients in the propofol group during spontaneous breathing trials. Lower frequency to tidal volume ratios in the propofol group may have been impacted by higher morphine doses, but morphine was usually held during SBTs.

Higher opiate requirements with the use of propofol compared with benzodiazepines have been reported in previous studies (11, 15). The reason for this may be explained by previous observations that benzodiazepines enhance the analgesic effects of opiates leading to lower opiate requirements (31). Better pain control in the propofol group could have led to lower sedation requirements; however, pain assessments were made frequently for patients receiving lorazepam, and pain control with narcotics was the first priority in the sedation regimens.

A recent observational study of delirium in critically ill patients noted that lorazepam is associated with a higher incidence of delirium than other sedatives including propofol (32). It is possible that patients in the bolus dose lorazepam group had more agitated delirium during periods of awakening, possibly leading to earlier resumption of sedation. Such was our anecdotal observation during this trial, although it was not formally tested. We did measure Richmond Agitation Sedation Scale scores for a subgroup of patients (n = 52) enrolled in the trial after the Richmond Agitation Sedation Scale validation study was published (33). In this subgroup, patients in the intermittent lorazepam group were more likely than patients in the propofol group to have Richmond Agitation Sedation Scale scores increase from levels indicating adequate sedation (0 to −3) in the morning before scheduled interruption of sedatives, to levels consistent with agitation (1 to 4) in the afternoon ($p = .01$). When this study was designed, a validated measure of delirium such as the Confusion Assessment Method for the Intensive Care Unit (34) was not published, so we did not measure delirium specifically. This should be a component of similar studies in the future.

To our knowledge, this is the first randomized clinical trial comparing intermittent bolus dosing of lorazepam to propofol infusions including daily sedative interruption for patients mechanically ventilated for >48 hrs. Continuous infusions of lorazepam have been compared with propofol in at least one study involving surgical and trauma patients (11). In that study, continuous infusions of lorazepam were associated with more episodes of oversedation and fewer episodes of undersedation compared with propofol. Precipitation of drug in the intravenous administration set was reported in 18% of lorazepam infusion preparations. Duration of mechanical ventilation was not reported. Another study published as an abstract demonstrated that serum lorazepam levels were ten-fold higher in patients receiving continuous infusions of lorazepam compared with those receiving intermittent bolus dosing (10). In a randomized comparison of lorazepam intermittent bolus dosing vs. midazolam infusions for short-term (8-hr) sedation, bolus dosing with lorazepam was found to be as safe and effective as midazolam infusions (35). Duration of mechanical ventilation for patients requiring longer sedation was not reported.

Kollef et al. (36) conducted a prospective observational study assessing the influence of sedative administration strategy on the duration of mechanical ventilation. After adjusting for multiple confounders including illness severity, age, and number of organ failures, the authors found that continuous administration of sedative drugs was associated with prolongation of mechanical ventilation when compared with intermittent dosing or use of no sedatives at all. However, sedation regimens in the Kollef study may not have included daily interruptions of continuous infusions. A previous study has shown that scheduled daily interruption of continuous infusions of propofol or midazolam is associated with significantly fewer ventilator days compared with interruption of infusions at the discretion of the physician (5). Without daily interruption of propofol infusions, our results likely would have been quite different. This study also provides further validation of the safety of daily interruption of sedative infusions as self-extubations were minimal.

The implications of these results relate to patient comfort and outcome and hospital costs. Fewer days of mechanical ventilation for survivors of critical illness are associated with shorter ICU stays and fewer complications such as ventilator-associated pneumonia (37, 38). Earlier removal of endotracheal tubes results in less exposure to noxious stimuli, quicker advancement to regular nutrition and rehabilitative services in the hospital, and enhanced interaction with the patients' families and health care providers. Propofol has been associated with higher drug acquisition costs than lorazepam; however, propofol costs are now lower with generic formulations that have become available. Higher drug costs are also likely offset by lower hospital costs associated with fewer ventilator days and ICU days. A formal economic analysis is required to confirm this.

The absence of blinding for nurses and physicians is a limitation of this study.

Propofol has a noticeably faster onset of effect than lorazepam, and this difference made blinding impossible. Biases could have affected nurses' decisions regarding drug administration or physicians' decisions about when to extubate patients. However, the formal protocols for sedative administration kept levels of sedation uniform, and we have demonstrated that physicians were equally aggressive in performing spontaneous breathing trials and extubations when indicated. A major strength of the study is that it was performed within the standard clinical setting of two different hospitals and included a heterogeneous patient population, which enhances generalizability to other medical ICUs.

CONCLUSIONS

For medical ICU patients requiring >48 hrs of mechanical ventilation and intravenous sedation, use of propofol infusions with daily sedative interruption results in significantly fewer ventilator days compared with intermittent bolus dosing of lorazepam. The shorter duration of mechanical ventilation is associated with fewer ICU days for survivors. Contrary to published clinical guidelines (7), this study supports the use of propofol for patients who require significant amounts of sedation for prolonged periods of mechanical ventilation, as long as daily interruption of the propofol infusion is part of the sedation strategy.

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