

DAILY INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

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ABSTRACT

Background Continuous infusions of sedative drugs in the intensive care unit may prolong the duration of mechanical ventilation, prolong the length of stay in the intensive care unit and the hospital, impede efforts to perform daily neurologic examinations, and increase the need for tests to assess alterations in mental status. Whether regular interruption of such infusions might accelerate recovery is not known.

Methods We conducted a randomized, controlled trial involving 128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs in a medical intensive care unit. In the intervention group, the sedative infusions were interrupted until the patients were awake, on a daily basis; in the control group, the infusions were interrupted only at the discretion of the clinicians in the intensive care unit.

Results The median duration of mechanical ventilation was 4.9 days in the intervention group, as compared with 7.3 days in the control group ($P=0.004$), and the median length of stay in the intensive care unit was 6.4 days as compared with 9.9 days, respectively ($P=0.02$). Six of the patients in the intervention group (9 percent) underwent diagnostic testing to assess changes in mental status, as compared with 16 of the patients in the control group (27 percent, $P=0.02$). Complications (e.g., removal of the endotracheal tube by the patient) occurred in three of the patients in the intervention group (4 percent) and four of the patients in the control group (7 percent, $P=0.88$).

Conclusions In patients who are receiving mechanical ventilation, daily interruption of sedative-drug infusions decreases the duration of mechanical ventilation and the length of stay in the intensive care unit. (N Engl J Med 2000;342:1471-7.)

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CRITICALLY ill patients who require mechanical ventilation are often given continuous intravenous infusions of sedative drugs to treat anxiety and agitation and to facilitate their care. Benzodiazepines are the agents most commonly given,^{1,2} but some patients are given other nonanalgesic sedatives, such as propofol^{3,4} or haloperidol.⁵ Opiates are often given as well, since non-opiate sedatives have no analgesic properties. New approaches to mechanical ventilation, often involving the use of permissive hypercapnia (i.e., allowing the

partial pressure of arterial carbon dioxide to reach 50 mm Hg or higher), can cause patients substantial discomfort, necessitating high levels of sedation.^{6,7}

In many intensive care units, sedatives are infused continuously.^{1,2} As compared with intermittent bolus infusion, this approach provides a more constant level of sedation and may increase patients' comfort.^{8,9} However, administration of sedatives by continuous infusion has been identified as an independent predictor of a longer duration of mechanical ventilation as well as a longer stay in the intensive care unit and in the hospital.¹⁰

Continuous infusion of sedatives has other disadvantages. Extended sedation may limit clinicians' ability to interpret physical examinations. It may be difficult to distinguish changes in mental status that are due to the action of a sedative from those that are due to neurologic injury. Therefore, clinicians may be compelled to order diagnostic studies to rule out new neurologic injury when patients do not awaken rapidly after the sedative infusion is discontinued.

The benefit of administering sedatives by continuous infusion must be balanced against these disadvantages. Daily interruption of sedative infusions to allow patients to "wake up" may improve the situation by allowing clinicians to streamline the administration of sedatives while ensuring optimal comfort for patients. We undertook this study to determine whether daily interruption of sedative infusions in critically ill patients receiving mechanical ventilation would decrease the duration of mechanical ventilation and the length of stay in the intensive care unit and in the hospital.

METHODS**Patients**

We studied patients in the medical intensive care unit who were intubated and receiving mechanical ventilation and who were deemed by the intensive care unit team to require sedation by continuous intravenous infusion. Included among these patients were all those who showed agitation or discomfort after recovering from the effects of the drugs used to facilitate endotracheal intubation (e.g., thiopental or etomidate). The exclusion criteria were pregnancy, transfer from an outside institution where sedatives had already been administered, and admission after resuscitation from cardiac arrest. The patients were randomly assigned to one of two strategies: daily interruption of the infusion of sedatives begin-

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ning 48 hours after enrollment (the intervention group) or continuous infusion of sedatives with interruption only at the discretion of the intensive care unit team (the control group). Within each group, the patients were then randomly assigned to receive either midazolam or propofol. The random assignments were generated by computer and then concealed in sealed envelopes. Patients' assignment to the intervention group or the control group was known only to the study investigators, but the sedatives were given on an open-label basis.

All four subgroups simultaneously received an infusion of morphine for analgesia. The infusion of the combination of a nonanalgesic sedative drug (propofol or midazolam) and morphine will henceforth be referred to as the infusion of sedative drugs. The protocols for the infusion of sedatives are shown in Table 1. Nurses adjusted the dosage and rate of infusion according to standard procedures at our institution (to achieve a score of 3 or 4 on the Ramsay sedation scale, which measures sedation on a scale of 1 [agitated or restless] to 6 [asleep and unresponsive to stimuli]¹¹).

Base-line demographic data, Acute Physiology and Chronic Health Evaluation (APACHE II) scores,¹² and the reason for admission to the intensive care unit were recorded for all patients. The number of patients with pulmonary edema, acute respiratory distress syndrome, or status asthmaticus who underwent ventilation with the use of permissive hypercapnia (intentional hypoventilation to allow an arterial carbon dioxide tension of ≥ 50 mm Hg) was also recorded. The paralytic drug cisatracurium was given to patients with the acute respiratory distress syndrome or status asthmaticus whose ventilation was deemed ineffective while they were receiving the sedative infusions.

The study was approved by the institutional review board at the University of Chicago. The requirement for consent from patients was waived because the intervention, though not routinely applied, was within the established standard of care at our institution.

Study Protocol

In the intervention group, an investigator not directly involved in the patients' care interrupted the infusion of midazolam or propofol and the infusion of morphine simultaneously on a daily basis until the patients were awake and could follow instructions or until they became uncomfortable or agitated and were deemed to require the resumption of sedation. If a patient was receiving a paralytic drug, the sedative infusion was not interrupted. A research nurse who was not directly involved in the patients' care evaluated the patients each day throughout the period when infusions were stopped until the patients were either awake or uncomfortable and in need of resumed sedation. This nurse immediately contacted a study physician when a patient awakened, at which time the study physician examined the patient and decided whether to resume the infusions. For the patients in the intervention group who were receiving paralytic drugs, the sedative infusions were stopped daily (after administration of the paralytic drug had been stopped) in a manner identical to that for the patients in the intervention group who were not receiving paralytic drugs. The sedative infusions were started again after the patient was awake or, if agitation prevented successful waking, at half the previous rates and were adjusted according to the need for sedation.

The patients in the control group were monitored each day by research staff, and the total daily doses of sedative drugs infused were recorded. The adjustment of the dosage of sedative drugs in the control group was left to the discretion of the intensive care unit team. Apart from daily interruption and resumption of sedative-drug infusions in the intervention group, all other decisions regarding patient care were made by the intensive care unit team.

Each day, we assessed each patient's mental status with respect to wakefulness. A patient was considered "awake" if he or she was able to perform at least three of the following four actions, which could be assessed objectively: open the eyes in response to a voice, use the eyes to follow the investigator on request, squeeze a hand on request, and stick out the tongue on request.¹³ The percentage of days on which the patient was classified as awake (the number of days awake divided by the total number of days during which

TABLE 1. PROTOCOLS FOR THE INFUSION OF SEDATIVE DRUGS IN THE STUDY PATIENTS.*

ASSIGNED SEDATIVE DRUG	PROTOCOL
Midazolam	Midazolam: initial intravenous bolus of 0.5–5 mg every 1–5 min as needed
	Midazolam: continuous infusion at 1–2 mg/hr; dosage to be increased in increments of 1–2 mg/hr until adequate sedation is achieved
	Morphine: initial intravenous bolus of 2–10 mg as needed Morphine: continuous infusion at 1–5 mg/hr
Propofol	Propofol: continuous infusion at 5 $\mu\text{g}/\text{kg}$ of body weight/min; dosage to be increased in increments of 5–10 $\mu\text{g}/\text{kg}/\text{min}$ every 2 min until adequate sedation is achieved
	Morphine: initial intravenous bolus of 2–10 mg as needed
	Morphine: continuous infusion at 1–5 mg/hr

*The doses of sedatives and morphine were adjusted to achieve a score of 3 or 4 on the Ramsay sedation scale (on which 1 denotes anxious and agitated or restless or both; 2 cooperative, oriented, and tranquil; 3 responsive to commands only; 4 asleep, with a brisk response to a light glabellar tap or loud sound; 5 asleep, with a sluggish response to a light glabellar tap or loud sound; and 6 asleep, with no response to a light glabellar tap or loud sound). Morphine was given to ensure adequate analgesia; it was administered to all patients "as needed," according to the nurse's assessment of the level of analgesia (on a scale on which 1 denotes extreme pain, 2 severe pain, 3 moderate pain, 4 slight pain, and 5 no pain). Morphine was administered in response to a score of 1 to 4 and was continued until the pain was considered to be adequately controlled.

sedative-drug infusions were given) was recorded. Patients were considered to have been awake on any given day if they had been awake at any time during that day.

End Points

The primary end points of the study were the duration of mechanical ventilation, the length of stay in the intensive care unit, and the length of stay in the hospital. The total doses of either midazolam or propofol and of morphine administered were recorded, as were the average rates of infusion (calculated as total milligrams of drug per kilogram of body weight, divided by the total number of hours from the start of the infusion to its termination).

The use of neurologic tests (e.g., computed tomography [CT] of the brain, magnetic resonance imaging [MRI] of the brain, and lumbar puncture) was recorded, as were the numbers of patients requiring paralytic drugs, reintubation, noninvasive ventilation, or tracheostomy. Adverse events (e.g., removal of the endotracheal tube by the patient), transfer to a facility equipped to provide long-term ventilation, withdrawal of care (a change in care from curative measures to measures aimed at comfort), and death in the hospital were also recorded. The specific end points to be studied were not disclosed to any of the caregivers.

Statistical Analysis

Data were analyzed on an intention-to-treat basis. Patients who died during the first or second day in the intensive care unit and those from whom the endotracheal tube was successfully removed during the first or second day, before the sedative infusion could be interrupted, were not included in the analysis. All patients were followed until discharge from the hospital.

Nonparametric data were analyzed with Mann–Whitney U tests. These data are presented as median values (with 25th and 75th

percentiles). Nominal data were analyzed by chi-square analysis with Yates' continuity correction or by Fisher's exact test, as appropriate. Kaplan-Meier survival analysis¹⁴ and Cox proportional-hazards analysis¹⁵ were used to assess the effects of daily interruption of the sedative infusion on the duration of mechanical ventilation and on the length of stay in the intensive care unit and in the hospital. Cox proportional-hazards analysis was used to assess differences between the intervention group and the control group after adjustment for base-line variables, including age, sex, weight, APACHE II score, and type of respiratory failure (acute hypoxic respiratory failure, such as that resulting from pulmonary edema or the acute respiratory distress syndrome; hypercapnic respiratory failure; or shock).¹⁶ All statistical tests were two-sided.

RESULTS

Patients

A total of 150 patients were enrolled in the study; 75 were randomly assigned to the intervention group and 75 to the control group. Seven patients in the intervention group and 15 in the control group were excluded because either the endotracheal tube was removed or they died on the first or second day in the intensive care unit. Thus, 68 patients in the intervention group and 60 in the control group were included in the analyses. The demographic characteristics, APACHE II scores, rate of use of permissive hypercapnia during ventilation, and diagnoses on admission to the intensive care unit were similar in the two groups (Table 2). In the intervention group, 37 patients received midazolam and 31 received propofol, and in the control group 29 received midazolam and 31 received propofol. There were no demographic differences between these subgroups in either group (data not shown).

Outcomes

In 18 of the 60 patients in the control group, the sedative infusions were stopped temporarily on days other than the final day of administration, and the percentage of days (other than the final day) on which the drugs were stopped ranged from 0 to 54 percent. The daily interruption of sedative infusions in the intervention group was associated with a significant decrease in the duration of mechanical ventilation; the median duration of mechanical ventilation in this group was 2.4 days shorter than it was in the control group (Table 3). Mechanical ventilation was discontinued earlier in the intervention group than in the control group (relative risk of extubation, 1.9; 95 percent confidence interval, 1.3 to 2.7; $P < 0.001$) (Fig. 1). The median length of stay in the intensive care unit in the intervention group was shorter than it was in the control group by 3.5 days (relative risk of discharge, 1.6; 95 percent confidence interval, 1.1 to 2.3; $P = 0.02$) (Fig. 2). The length of stay in the hospital did not differ between the two groups (Table 3).

Among the patients receiving midazolam, the total dose of this sedative was lower in the intervention group than in the control group, as was the total dose of morphine (Table 3). In contrast, among the pa-

TABLE 2. CHARACTERISTICS OF THE STUDY PATIENTS ON ADMISSION TO THE INTENSIVE CARE UNIT.

VARIABLE	INTERVENTION GROUP (N=68)	CONTROL GROUP (N=60)	P VALUE
Age (yr)			0.57
Median	57	61	
Interquartile range	42-71	40-74	
Sex (no.)			0.56
Male	34	26	
Female	34	34	
Weight (kg)			0.70
Median	69.9	66.0	
Interquartile range	58.9-90.2	60.4-78.8	
APACHE II score*			0.30
Median	20	22	
Interquartile range	15-25	16-25	
Permissive hypercapnia (no.)	12	15	0.42
Diagnosis (no.)			
Acute respiratory distress syndrome or pulmonary edema	20	15	0.72
Chronic obstructive pulmonary disease or ventilatory failure	22	17	0.76
Asthma	4	3	0.86
Sepsis	10	15	0.21
Delirium	8	5	0.73
Hemorrhagic shock	1	3	0.52
Cardiogenic shock	2	2	0.70
Drug overdose	1	0	0.95

*APACHE II denotes Acute Physiology and Chronic Health Evaluation. The APACHE II is an assessment of the severity of illness, with possible scores ranging from 0 to 71 (increasing scores correlate with an increasing risk of in-hospital death).

tients receiving propofol, there were no significant differences between the intervention and the control groups in the total dose of propofol or the total dose of morphine.

The percentage of days during which patients were awake while receiving a sedative infusion was greater in the intervention group than in the control group (85.5 percent vs. 9.0 percent, $P < 0.001$). Fewer diagnostic tests to assess changes in mental status were performed in the intervention group (6 CT scans of the brain) than in the control group (13 CT scans of the brain, 2 MRI scans of the brain, and 1 lumbar puncture; $P = 0.02$). Only 4 of the 16 tests in the control group and 3 of the 6 tests in the intervention group provided an explanation (e.g., intracranial hemorrhage) for the changes in mental status.

Only 7 patients in the intervention group never awakened during their stay in the intensive care unit, as compared with 15 patients in the control group ($P = 0.05$). Of these patients, 6 in the intervention group and 13 in the control group died in a coma; the others were transferred to facilities equipped to provide long-term ventilation. There were no significant differences between the two groups in the number of other adverse events (in the intervention group, two patients removed the endotracheal tube and one

TABLE 3. THE DURATION OF MECHANICAL VENTILATION, LENGTH OF STAY IN THE INTENSIVE CARE UNIT AND THE HOSPITAL, AND DOSES OF SEDATIVE DRUGS AND MORPHINE, ACCORDING TO STUDY GROUP.*

VARIABLE	INTERVENTION GROUP (N=68)	CONTROL GROUP (N=60)	P VALUE
	median (interquartile range)		
Duration of mechanical ventilation (days)	4.9 (2.5–8.6)	7.3 (3.4–16.1)	0.004
Length of stay (days)			
Intensive care unit	6.4 (3.9–12.0)	9.9 (4.7–17.9)	0.02
Hospital	13.3 (7.3–20.0)	16.9 (8.5–26.6)	0.19
Midazolam subgroup (no. of patients)	37	29	
Total dose of midazolam (mg)	229.8 (59–491)	425.5 (208–824)	0.05
Average rate of midazolam infusion (mg/kg/hr)	0.032 (0.02–0.05)	0.054 (0.03–0.07)	0.06
Total dose of morphine (mg)	205 (68–393)	481 (239–748)	0.009
Average rate of morphine infusion (mg/kg/hr)	0.027 (0.02–0.04)	0.05 (0.04–0.07)	0.004
Propofol subgroup (no. of patients)	31	31	
Total dose of propofol (mg)	15,150 (3983–34,125)	17,588 (4769–35,619)	0.54
Average rate of propofol infusion (mg/kg/hr)	1.9 (0.9–2.6)	1.4 (0.9–2.4)	0.41
Total dose of morphine (mg)	352 (108–632)	382 (148–1053)	0.33
Average rate of morphine infusion (mg/kg/hr)	0.035 (0.02–0.07)	0.043 (0.02–0.07)	0.65

*Average rates of infusion were calculated as milligrams of drug per kilogram of body weight divided by the number of hours from the start of the infusion to its termination.

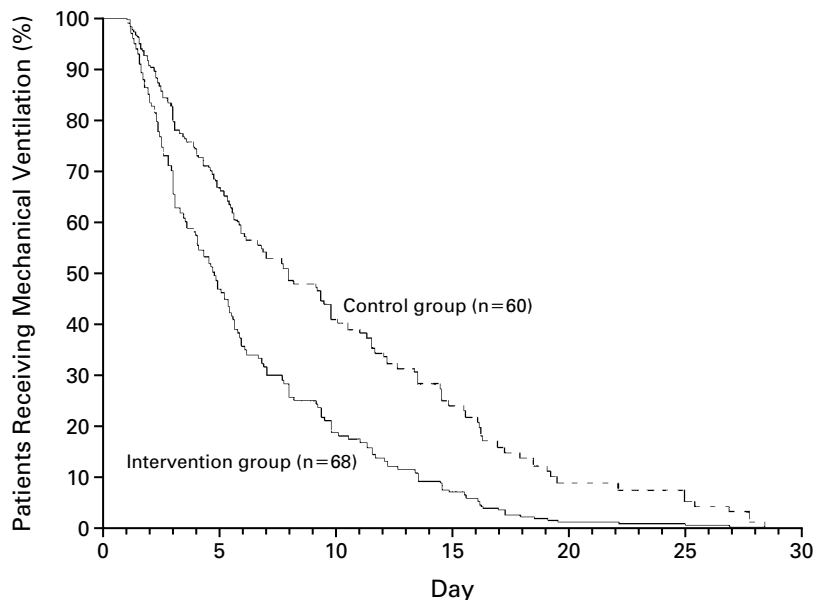


Figure 1. Kaplan–Meier Analysis of the Duration of Mechanical Ventilation, According to Study Group. After adjustment for base-line variables (age, sex, weight, APACHE II score, and type of respiratory failure), mechanical ventilation was discontinued earlier in the intervention group than in the control group (relative risk of extubation, 1.9; 95 percent confidence interval, 1.3 to 2.7; $P < 0.001$).

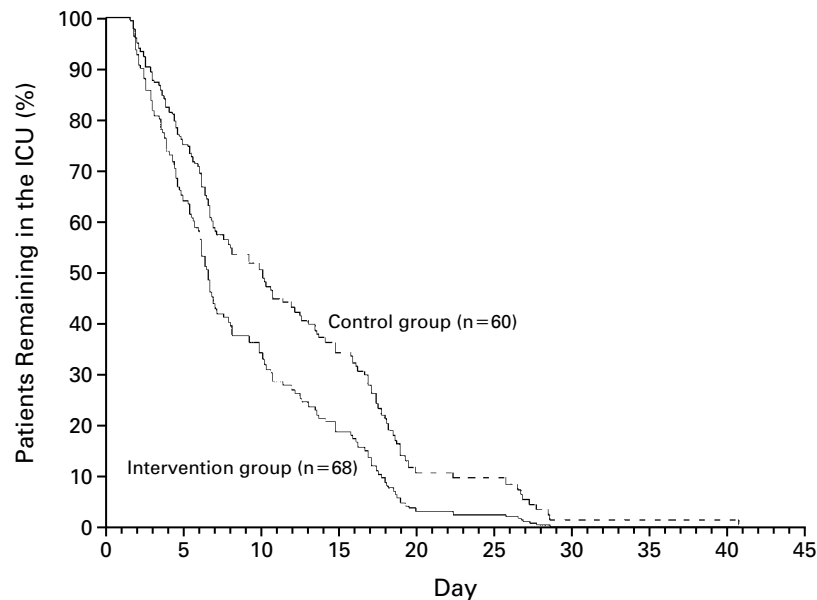


Figure 2. Kaplan–Meier Analysis of the Length of Stay in the Intensive Care Unit (ICU), According to Study Group.

After adjustment for base-line variables (age, sex, weight, APACHE II score, and type of respiratory failure), discharge from the intensive care unit (ICU) occurred earlier in the intervention group than in the control group (relative risk of discharge, 1.6; 95 percent confidence interval, 1.1 to 2.3; $P=0.02$).

pulled out a central venous catheter; in the control group, four patients removed the endotracheal tube ($P=0.88$). Seven patients in each group were given cisatracurium ($P=0.78$), and five in each group required noninvasive ventilation after extubation ($P=0.74$). Twelve patients in the intervention group and 18 patients in the control group required reintubation ($P=0.17$), and 12 and 16, respectively, underwent tracheostomy ($P=0.31$). Nine patients in the intervention group and 12 in the control group were transferred to a facility equipped to provide long-term ventilation ($P=0.43$). The in-hospital mortality rate did not differ significantly between the two groups (36.0 percent in the intervention group and 46.7 percent in the control group, $P=0.25$), and care was withdrawn from 24 and 25 patients, respectively ($P=1.00$). Fifty-nine percent of the patients in the intervention group were discharged to their homes, as compared with 40 percent of the patients in the control group ($P=0.06$).

When the primary end points of the study (the duration of mechanical ventilation, the length of stay in the intensive care unit, and the length of stay in the hospital) were evaluated according to whether midazolam or propofol was given, no significant differences between the intervention and control groups were found (data not shown). In the intervention group, the average number of hours per day that patients received the sedative infusion was 22.8 among

those given propofol, as compared with 18.7 among those given midazolam ($P=0.05$).

DISCUSSION

Sedatives are often given to patients who are receiving mechanical ventilation to alleviate their anxiety, decrease excessive oxygen consumption, and facilitate nursing care.¹⁷ Administration of these drugs by continuous infusion offers a more consistent level of sedation than intermittent bolus administration and thus may improve patients' comfort.⁹ In our experience, sedation is often difficult with intermittent administration, and such regimens can be taxing on nurses and can hamper other aspects of patient care.¹⁷ However, a potential drawback to continuous infusions is the accumulation of the drug and accompanying delays in the improvement of mental status. We hypothesized that daily interruption of the sedative infusion would decrease these problems.

Care of critically ill patients is costly. In the United States in 1997, approximately \$80.8 billion was spent on intensive care,¹⁸ and about 10 percent of this amount was spent on drugs.¹⁹ Ten to 15 percent of the drug costs resulted from the purchase of sedative drugs.²⁰ Thus, a conservative estimate of the yearly cost of sedative drugs administered in intensive care units in the United States, in 1997 dollars,²¹ is between \$0.8 billion and \$1.2 billion, and the costs may be higher than that if the use of sedative drugs

increases the duration of mechanical ventilation and the length of stay in the intensive care unit.

In this study, daily interruption of the infusion of sedative drugs shortened the duration of mechanical ventilation by more than 2 days and the length of stay in the intensive care unit by 3.5 days. Reducing the duration of mechanical ventilation will probably cut costs — both monetary costs and those related to complications of mechanical ventilation, such as ventilator-associated pneumonia and barotrauma. Daily interruption of the sedative infusion is a practical, cost-effective intervention that can be readily performed by the nurses caring for patients in the intensive care unit. The results of neurologic assessments can then be relayed to physicians, and infusions of sedative drugs can be restarted and adjusted as needed by the nurses. Our results suggest that daily interruption of the sedative infusion provides acceptable sedation while minimizing adverse effects.

In addition, in our study, daily interruption of the sedative infusion reduced the total dose of midazolam administered by almost half. A trend toward the use of lower doses of benzodiazepines has previously been reported^{13,22} and is at least partly related to the concomitant administration of opiates such as morphine. Benzodiazepines may enhance the analgesic effects of morphine,²³ and this synergism may decrease the doses of benzodiazepines needed to achieve adequate sedation. In our study, daily interruption of the sedative infusion did not alter the doses of propofol administered. The concentration of propofol in plasma declines rapidly after administration is discontinued,²⁴ and this is probably the reason why the daily period of drug stoppage in the intervention group was shorter among patients assigned to propofol than among those assigned to midazolam. Despite this difference, the patients were awake on more than 80 percent of days in both subgroups of the intervention group, and this percentage did not differ according to the sedative agent used. In addition, there were no differences in the duration of mechanical ventilation or the length of stay in the intensive care unit when patients were grouped according to the sedative they received.

One drawback to continuous intravenous sedation is impaired mental status,^{8,25} which may prevent the early detection of neurologic dysfunction resulting from new insults. Stopping the sedative infusion for a period during each day is a simple way to improve clinicians' ability to perform daily neurologic examinations. In our study, most of the diagnostic tests performed to assess changes in mental status were not helpful, but fewer of these tests were performed in the group in which the sedative infusion was interrupted each day than in the control group. Avoiding unnecessary diagnostic studies may reduce the rate of complications related to the transport of patients^{26,27} and may reduce costs.

The incidence of adverse events, such as removal of the endotracheal tube by the patient, was low and did not differ significantly between the intervention group and the control group. Because such events were uncommon, the power of this study to detect a difference between the groups may not have been adequate. Nevertheless, the 5 percent overall rate at which patients removed the endotracheal tube compares favorably with the rates of 10 to 12 percent observed in previous studies.^{28,29} It is noteworthy that in no case did a patient in the intervention group remove his or her endotracheal tube during an interruption period. There were no differences between the groups in the proportions of patients who needed paralytic drugs, noninvasive ventilation, tracheostomy, reintubation, or transfer to another facility for long-term ventilation, or in the proportion from whom care was withdrawn. The percentage of patients successfully discharged to their homes was greater in the group assigned to daily interruption of infusions than in the control group.

This study has several limitations. We cannot be certain that the clinicians involved in patient care were completely unaware of the study-group assignments. We attempted to minimize this problem by not disclosing the end points of the study to the clinicians. In the case of some patients in the control group, the sedative infusions were periodically interrupted by the intensive care unit team. This practice may have interfered with the detection of differences in outcome between the two groups, since some patients in the control group thus received the potentially beneficial intervention. This study involved patients receiving medical intensive care; whether our results can be extrapolated to other groups of critically ill patients (e.g., those receiving intensive care after surgery or trauma) is not clear. In addition, we monitored visible signs of physical discomfort during interruptions of the sedative infusions. Whether less obvious types of discomfort or psychological distress were present during the daily interruptions of the sedative infusions cannot be discerned from this study.

In conclusion, daily interruption of the infusion of sedative drugs is a safe and practical approach to treating patients who are receiving mechanical ventilation. This practice decreases the duration of mechanical ventilation, the length of stay in the intensive care unit, and the doses of benzodiazepines used. It also improves the ability of clinicians to perform daily neurologic examinations and reduces the need for diagnostic studies to evaluate unexplained alterations in mental status.

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