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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ning 48 hours after enrollment (the intervention group) or con-
tinuous infusion of sedatives with interruption only at the discre-
tion 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 gen-
crated by computer and then concealed in sealed envelopes. Pa-
tients’ 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 mor-
phine for analgesia. The infusion of the combination of a nonan-
algesic 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 pro-
cedures at our institution (to achieve a score of 3 or 4 on the Ram-
say sedation scale, which measures sedation on a scale of [ag-
tated or restless] to 6 [asleep and unresponsive to stimuli] [10].

Base-line demographic data, Acute Physiology and Chronic
Health Evaluation (APACHE II) scores, and the reason for ad-
mission 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 hypoventila-
tion to allow an arterial carbon dioxide tension of \( >50 \text{ mm Hg} \))
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 pro-
propofol and the infusion of morphine simultaneously on a daily ba-
sis 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 dail-
ily (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 infu-
sions 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 re-
search staff, and the total daily doses of sedative drugs infused for
all patients were recorded. The total doses of either mid-
azolam 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 cura-
tive 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.

End Points

The primary end points of the study were the duration of me-
chanical ventilation, the length of stay in the intensive care unit,
and the length of stay in the hospital. The total doses of either mid-
azolam 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)

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term ventilation, withdrawal of care (a change in care from cura-
tive 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
percentile interval).
percentiles). Nominal data were analyzed by chi-square analysis with Yates’ continuity correction or by Fisher’s exact test, as appropriate. Kaplan–Meier survival analysis and Cox proportional-hazards analysis 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 baseline variables, including age, sex, weight, APACHE II score, and type of respiratory failure (acute hypoxicemic respiratory failure, such as that resulting from pulmonary edema or the acute respiratory distress syndrome; hypercapnic respiratory failure; or shock). 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 patients 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

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**Table 2. Characteristics of the Study Patients on Admission to the Intensive Care Unit.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>INTERVENTION GROUP (N=68)</th>
<th>CONTROL GROUP (N=60)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.7±12.1</td>
<td>66.0±12.1</td>
<td>0.57</td>
</tr>
<tr>
<td>Intergroup range</td>
<td>22–79</td>
<td>22–79</td>
<td></td>
</tr>
<tr>
<td>Sex (no.)</td>
<td>Male 34 (50)</td>
<td>Male 26 (43)</td>
<td>0.56</td>
</tr>
<tr>
<td>Female 34 (50)</td>
<td>Female 24 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.9±15.9</td>
<td>78.0±14.8</td>
<td>0.70</td>
</tr>
<tr>
<td>Intergroup range</td>
<td>61.0–128.0</td>
<td>60.4–78.8</td>
<td></td>
</tr>
<tr>
<td>APACHE II score*</td>
<td>21 (9–44)</td>
<td>19 (7–42)</td>
<td>0.30</td>
</tr>
<tr>
<td>Median</td>
<td>23</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Intergroup range</td>
<td>15.0–28.0</td>
<td>16–25</td>
<td></td>
</tr>
<tr>
<td>Permissive hypercapnia (no.)</td>
<td>12 (18)</td>
<td>15 (22)</td>
<td>0.42</td>
</tr>
<tr>
<td>Diagnosis (no.)</td>
<td>Acute respiratory distress syndrome/pulmonary edema</td>
<td>22 (33)</td>
<td>17 (28)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease/ventilatory failure</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Asthma</td>
<td>4 (6)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>10 (15)</td>
<td>15 (25)</td>
<td>0.21</td>
</tr>
<tr>
<td>Delirium</td>
<td>8 (12)</td>
<td>5 (8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>2 (3)</td>
<td>3 (5)</td>
<td>0.52</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*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).
**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.*

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

*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).
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. Administration of these drugs by continuous infusion offers a more consistent level of sedation than intermittent bolus administration and thus may improve patients’ comfort. 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. 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, and about 10 percent of this amount was spent on drugs. Ten to 15 percent of the drug costs resulted from the purchase of sedative drugs. Thus, a conservative estimate of the yearly cost of sedative drugs administered in intensive care units in the United States, in 1997 dollars, 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 per-
formed by the nurses caring for patients in the inten-
sive care unit. The results of neurologic assessments 
can then be relayed to physicians, and infusions of 
sedative drugs can be restarted and adjusted as need-
ed by the nurses. Our results suggest that daily in-
terruption of the sedative infusion provides accept-
able sedation while minimizing adverse effects.

In addition, in our study, daily interruption of the 
sedative infusion reduced the total dose of midazo-
lam administered by almost half. A trend toward the 
use of lower doses of benzodiazepines has previously 
been reported\textsuperscript{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,\textsuperscript{23} and this synergism may decrease 
the doses of benzodiazepines needed to achieve ad-
equate sedation. In our study, daily interruption of 
the sedative infusion did not alter the doses of pro-
propofol administered. The concentration of propofol 
in plasma declines rapidly after administration is dis-
continued,\textsuperscript{24} and this is probably the reason why the 
daily period of drug stoppage in the intervention 
group was shorter among patients assigned to pro-
propofol than among those assigned to midazolam. De-
spite this difference, the patients were awake on more 
than 80 percent of days in both subgroups of the 
tervention 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,\textsuperscript{9,25} 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 exam-
inations. 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 in-
terrupted each day than in the control group. Avoid-
ing unnecessary diagnostic studies may reduce the rate 
of complications related to the transport of pa-
tients\textsuperscript{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 com-
pares favorably with the rates of 10 to 12 percent ob-
served in previous studies.\textsuperscript{28,29} It is noteworthy that 
in no case did a patient in the intervention group re-
move his or her endotracheal tube during an inter-
ruption period. There were no differences between 
the groups in the proportions of patients who need-
ed paralytic drugs, noninvasive ventilation, tracheo-
tomy, 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 assign-
ments. We attempted to minimize this problem by 
not disclosing the end points of the study to the cli-
nicians. In the case of some patients in the control 
group, the sedative infusions were periodically inter-
rupted by the intensive care unit team. This practice 
may have interfered with the detection of differences 
in outcome between the two groups, since some pa-
tients in the control group thus received the poten-
tially beneficial intervention. This study involved pa-
tients 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 mon-
titored visible signs of physical discomfort during in-
terruptions of the sedative infusions. Whether less ob-
vious types of discomfort or psychological distress 
were present during the daily interruptions of the sed-
avtive infusions cannot be discerned from this study.

In conclusion, daily interruption of the infusion of 
sedative drugs is a safe and practical approach to treat-
ing patients who are receiving mechanical ventila-
tion. 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 dai-
ly neurologic examinations and reduces the need for 
diagnostic studies to evaluate unexplained alterations 
in mental status.

We are indebted to the nurses in the medical intensive care unit 
at the University of Chicago for helping to make this study possible.
REFERENCES


