

A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial



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Summary

Background Standard treatment of critically ill patients undergoing mechanical ventilation is continuous sedation. Daily interruption of sedation has a beneficial effect, and in the general intensive care unit of Odense University Hospital, Denmark, standard practice is a protocol of no sedation. We aimed to establish whether duration of mechanical ventilation could be reduced with a protocol of no sedation versus daily interruption of sedation.

Methods Of 428 patients assessed for eligibility, we enrolled 140 critically ill adult patients who were undergoing mechanical ventilation and were expected to need ventilation for more than 24 h. Patients were randomly assigned in a 1:1 ratio (unblinded) to receive: no sedation (n=70 patients); or sedation (20 mg/mL propofol for 48 h, 1 mg/mL midazolam thereafter) with daily interruption until awake (n=70, control group). Both groups were treated with bolus doses of morphine (2.5 or 5 mg). The primary outcome was the number of days without mechanical ventilation in a 28-day period, and we also recorded the length of stay in the intensive care unit (from admission to 28 days) and in hospital (from admission to 90 days). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00466492.

Findings 27 patients died or were successfully extubated within 48 h, and, as per our study design, were excluded from the study and statistical analysis. Patients receiving no sedation had significantly more days without ventilation (n=55; mean 13.8 days, SD 11.0) than did those receiving interrupted sedation (n=58; mean 9.6 days, SD 10.0; mean difference 4.2 days, 95% CI 0.3–8.1; p=0.0191). No sedation was also associated with a shorter stay in the intensive care unit (HR 1.86, 95% CI 1.05–3.23; p=0.0316), and, for the first 30 days studied, in hospital (3.57, 1.52–9.09; p=0.0039), than was interrupted sedation. No difference was recorded in the occurrences of accidental extubations, the need for CT or MRI brain scans, or ventilator-associated pneumonia. Agitated delirium was more frequent in the intervention group than in the control group (n=11, 20% vs n=4, 7%; p=0.0400).

Interpretation No sedation of critically ill patients receiving mechanical ventilation is associated with an increase in days without ventilation. A multicentre study is needed to establish whether this effect can be reproduced in other facilities.

Funding Danish Society of Anesthesiology and Intensive Care Medicine, the Fund of Danielsen, the Fund of Kirsten Jensa la Cour, and the Fund of Holger og Ruth Hess.

Introduction

...But what I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise...

Thomas Petty¹

These lines were written in an editorial linked to a follow-up study of mechanically ventilated patients, in which Kollef and colleagues² reported that continuous infusion of sedatives lengthened the duration of ventilation compared with bolus doses of sedatives. In 2000, Kress and colleagues³ showed that daily interruption of sedative infusions until patients were awake reduced the duration of mechanical ventilation. One major disadvantage of sedation for critically ill patients is that clinicians are unable to assess the patient's mental status; Kress and colleagues also recorded fewer CT scans of the brain in patients who were woken up daily than in the control group in which infusions were interrupted at the clinicians' discretion.

In a further study of daily sedative interruption, Kress and colleagues⁴ showed that daily interruption kept post-

traumatic stress disorder to a minimum, although, at the follow-up interview, few patients recalled being woken up daily. Real memories of the intensive care stay have been shown to reduce the severity of post-traumatic stress disorder.⁵ Also the risk of several well known complications—ventilator-associated pneumonia, haemorrhage in the upper gastrointestinal tract, bacteraemia, barotraumas, venous thromboembolic disease, cholestasis, and sinusitis requiring surgical intervention—is reduced by daily interruption of sedation.⁶

Despite these findings, standard practice is to sedate critically ill patients needing intubation and mechanical ventilation.^{7–9} A natural development for sedation strategies would be to try to keep the amount and duration of sedation to a minimum, with the expectation that this strategy could further reduce the duration of mechanical ventilation.¹⁰ In the general intensive care unit in the Department of Anesthesia and Intensive Care Medicine at Odense University Hospital, Denmark, we have used the standard treatment of no sedation for intubated patients receiving mechanical ventilation since June, 1999. Patients receive

Lancet 2010; 375: 475–80

Published Online

January 29, 2010

DOI:10.1016/S0140-

6736(09)62072-9

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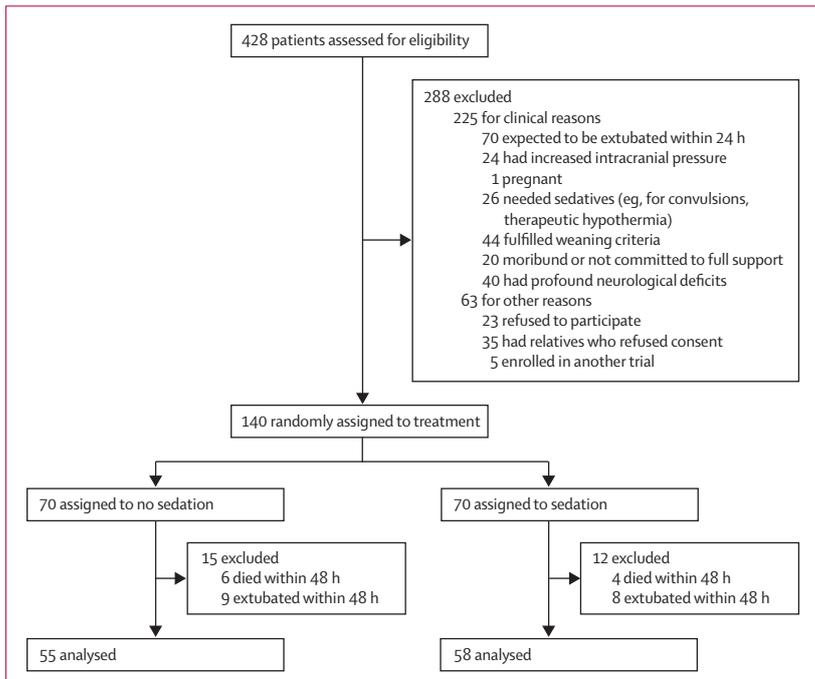


Figure 1: Trial profile

intravenous morphine as bolus doses but no infusion of sedatives or analgesics. To our knowledge, this strategy has not been used in other departments or described in published reports. We undertook a prospective randomised study to establish whether no sedation versus sedation with daily interruption reduced the duration of mechanical ventilation.

Methods

Participants

We studied critically ill adult patients undergoing mechanical ventilation. Patients in Odense University Hospital, Denmark, were admitted to an 18-bed multi-disciplinary, closed intensive care unit from both medical and surgical departments. The intensive care unit has at least two physicians present (one intensive care specialist and one specialist trainee) at all times. The patient to nurse ratio is 1:1, which allows the nurse to manage several tasks in addition to patient care (eg, renal replacement therapy).

Eligible patients were expected to need mechanical ventilation for more than 24 h. Patients were excluded if they were younger than 18 years, had increased intracranial pressure, needed sedation (eg, for status epilepticus, or hypothermia after cardiac arrest), were pregnant, met our criteria for weaning from ventilation ($\text{FiO}_2 \leq 40\%$ and positive end-expiratory pressure of 5 cm H_2O), or had no cerebral contact (ex coma hepatica). We decided a priori to exclude patients with no cerebral contact because these patients would not be offered long-term sedation. Patients transferred intubated from other intensive care departments were also eligible for the study. For these

patients, the study period started within 24 h of arrival in our intensive care unit; no restrictions were placed on the duration for which patients had received mechanical ventilation before they were transferred to our unit.

The study was approved by the local scientific ethics committee, and written informed consent was obtained from every patient or their representatives. If permission was given by the patients representatives, information and consent was obtained from the patient after the study.

Randomisation and masking

Within 24 h after intubation, patients were randomly assigned in a 1:1 ratio to receive no sedation with intravenous analgesics alone (intervention group) or sedation with daily interruption until awake (control group). Attending doctors enrolled and randomly assigned patients, and started the assigned treatment. Treatment allocation was concealed by random selection of opaque sealed envelopes for consecutive patients from a box of 140 envelopes. Every envelope contained a number that the investigators had manually assigned to each treatment group before the start of the study. None of the participants, investigators analysing data, or personnel giving interventions or assessing outcomes was masked to group assignment for practical reasons.

Procedures

The intervention group received intravenous morphine in bolus doses (2.5 or 5 mg) as needed. If patients were uncomfortable, a doctor was consulted, and any possible causes for patient discomfort were investigated (eg, hypoxia, tube obstruction, pain). If needed, a person was assigned to verbally comfort and reassure the patient. Physical restraints were never used. For cases in which delirium was suspected, intravenous haloperidol was given as bolus doses (1, 2.5, or 5 mg), but if the patient still seemed uncomfortable after this treatment, the patient was sedated with propofol for 6 h. Afterwards, a new trial to manage the patient without sedation was started; if sedation had to be started three times, the patient was kept sedated, with daily interruption of sedation, according to the protocol for the control group. However, crossover between the groups was not allowed, and patients who needed sedation as per the control group protocol remained in the intervention group for analysis by intention to treat.

The control group received intravenous morphine in bolus doses (2.5 or 5 mg) as needed, and were sedated with an infusion of propofol (20 mg/mL) titrated to reach a Ramsay score of 3–4.¹¹ The Ramsay score was recorded every 2–3 h to ensure correct titration of the sedative infusion. Every day, sedation was interrupted until patients were awake, starting the day after enrolment. The sedative infusion was stopped in the morning, and patients were judged to be awake when they could do three out of four simple tasks on request: open their eyes, look at the investigator, squeeze the hand, or put out their tongue. After testing, the sedative infusion was started at half the

previous dose and titrated to a Ramsay score of 3–4. After 48 h, the sedative was changed to an infusion of midazolam (1 mg/mL) titrated to a Ramsay score of 3–4. Thereafter, daily interruption of sedation, and titration of midazolam to a Ramsay score of 3–4 was continued as for treatment with propofol. Daily interruption of sedation and testing was done by a nurse, and checked by the attending doctor; if the nurse and attending doctor were in doubt of whether the patient could be judged as awake, the investigators assessed the patient.

If possible, both groups of patients were mobilised daily to a chair, despite mechanical ventilation, as per our standard routine; patients from the control group were mainly mobilised during daily interruption of sedation. The standard ventilation method was pressure support. Patients were only put on controlled ventilation in the case of severe prolonged hypoventilation. We decided a priori to stop infusion of sedatives in the control group when ventilator settings reached an FiO_2 of 40% and a positive end-expiratory pressure of 5 cm H_2O ; after this point, patients were not sedated and treatment was identical to that of the intervention group. Sedation was started again if patients in the control group needed increased respiratory support ($\text{FiO}_2 > 50\%$ and positive end-expiratory pressure > 8 cm H_2O). All patients were weaned from the ventilator according to our local weaning protocol, starting once patients were stable (FiO_2 of 40%, positive end-expiratory pressure of 5 cm H_2O , spontaneous breathing effort with rate < 35 breaths per min, heart frequency < 140 beats per min, systolic blood pressure > 90 mm Hg, no substantial use of vasopressors or inotropics, and $\text{pH} > 7.3$).

The primary outcome measure was the number of days without mechanical ventilation (after successful extubation, or removal of ventilator support for patients with tracheostomies) in a 28-day period, as recommended by the ARDSnetwork;¹² the 28-day period began at intubation, or, for patients transferred to our intensive care unit while intubated, at admission to our unit. Patients who were intubated again within 24 h, or were dependent on non-invasive ventilation after extubation, were judged to have been receiving mechanical ventilation. Patients dying or dependent on mechanical ventilation for more than 28 days had zero days without ventilation. We also recorded the total length of stay in the intensive care unit and in hospital, where data were available, and mortality in the intensive care unit and hospital.

Secondary endpoints were occurrences of need for CT or MRI brain scans, accidental removal of endotracheal tube, and ventilator-associated pneumonia. Ventilator-associated pneumonia was defined as a new lung parenchymal opacity on a chest radiograph of a patient who had been intubated for more than 48 h, and simultaneous presentation of two or more of: temperature of less than 36°C or more than 38°C ; white blood cell count of less than $4 \times 10^9/\text{L}$ or more than $10 \times 10^9/\text{L}$; or purulent secretions from the endotracheal tube.⁶ Study personnel screened the patients for delirium once daily using criteria from the

	No sedation (n=55)	Sedation (n=58)
Age (years)	67 (54–74)	65 (54–74)
Women	13 (24%)	24 (41%)
Weight (kg)	80.0 (74.0–92.0)	78.5 (70.0–91.0)
APACHE II	26 (19–30)	26 (22–31)
SAPS II	46 (36–56)	50 (43–63)
SOFA (at day 1)	7.5 (5.0–11.0)	9.0 (5.5–11.0)
Diagnosis at admission to intensive care unit		
Respiratory disorder*	26 (47%)	27 (47%)
Sepsis	15 (27%)	19 (33%)
Pancreatitis	2 (4%)	3 (5%)
Peritonitis	0	1 (2%)
Gastro-intestinal bleeding	5 (9%)	0
Liver and biliary disease	2 (4%)	0
Trauma	2 (4%)	3 (5%)
Other	3 (5%)	5 (9%)

Data are in number (%) or median (IQR). APACHE II=acute physiology and chronic health evaluation. SAPS II=simplified acute physiology score. SOFA=sequential organ-failure assessment. *Pneumonia, chronic obstructive pulmonary disease, and asthma.

Table 1: Baseline characteristics on admission to the intensive care unit

diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV).¹³

Statistical analysis

We calculated that to provide 80% power with p values of less than 0.05 judged to be significant, a sample of size of 100 patients would be needed to detect a mean difference of 1.5 days of mechanical ventilation, a SD of 5,¹⁴ and a median ventilation time of 5–7.5 days, according to Kress and colleagues.³ We anticipated that some patients would be severely ill on the basis of the acute physiology and chronic health evaluation (APACHE II), and therefore we chose a sample size of 140 patients.

Analysis of patient data was by intention to treat. Patients who had their endotracheal tube removed or died during the first 48 h were not included in the analysis. To adjust primary outcome data for baseline variables—age, sex, weight, APACHE II, simplified acute physiology score (SAPS II), and sequential organ-failure assessment (SOFA) at day 1—we applied a multiple linear regression using the robust Huber-White sandwich estimator of the variance-covariance matrix. This analysis needs correct specification of the fixed effects part of the model only, and was checked by inspection of the corresponding residual plot. The number of days without ventilation was also compared without correction for baseline variables with the Wilcoxon rank sum test.

We used Kaplan-Meier plots to present length of stay in the intensive care unit (from admission to 28 days) and in hospital (from admission to 90 days); patient data recorded after the specified periods were right censored. Cox proportional-hazards analysis was used to assess differences between the study groups from hazards ratios

	No sedation (n=55)	Sedation (n=58)	p value
Days without mechanical ventilation (from intubation to day 28)	13.8 (11.0); 18.0 (0–24.1)	9.6 (10.0); 6.9 (0–20.5)	0.0191*†
Length of stay (days)			
Intensive care unit	13.1 (5.7–∞)‡	22.8 (11.7–∞)‡	0.0316*§
Hospital	34 (17–65)	58 (33–85)	0.0039*§¶
Mortality			
Intensive care unit	12 (22%)	22 (38%)	0.06
Hospital	20 (36%)	27 (47%)	0.27
Drug doses (mg/kg)			
Propofol (per h of infusion)**	0 (0–0.515)	0.773 (0.154–1.648)	0.0001
Midazolam (per h of infusion)	0 (0–0)	0.0034 (0–0.0240)	<0.0001
Morphine (per h of mechanical ventilation)	0.0048 (0.0014–0.0111)	0.0045 (0.0020–0.0064)	0.39
Haloperidol (per day of mechanical ventilation)	0 (0–0.0145)	0 (0–0)	0.0140
Tracheostomy	16 (29%)	17 (29%)	0.98
Ventilator-associated pneumonia	6 (11%)	7 (12%)	0.85

Data are mean (SD), median (IQR), or number (%). ∞=data not available because of censoring at day 28. *Corrected for baseline variables: age, sex, weight, acute physiology and chronic health evaluation (APACHE II), simplified acute physiology score (SAPS II), and sequential organ-failure assessment (SOFA) at day 1. †Calculated from multiple linear regression. ‡More than 25% of patients remained in the intensive care unit for more than 28 days (figure 2). §Calculated from Cox regression analysis. ¶Calculated for the first 30 days to agree with the proportional hazards assumption. ||Drug dose (mg) as a proportion of bodyweight (kg). **Maximum dose during 48 h of treatment.

Table 2: Outcome data

(HRs), after adjustment for the baseline variables mentioned previously. Patient data were right censored in case of death. No violation against the proportional hazard assumption was detected in the test for length of stay in the intensive care unit. However, the proportional hazards assumption was uncertain with regard to analysis of total length of hospital stay: the score process test was significant with $p=0.01$, thus rejecting the Cox model.^{15,16} We therefore allowed the effect of this variable to change after an initial period of 30 days, and this revised model was accepted. For all remaining indicators, categorical data were analysed with the χ^2 test or Fisher's exact test, and continuous data were analysed with the Wilcoxon-Mann-Whitney test.

All tests were done with Stata/IC (version 10.1) for Windows, apart from the score process test, for which we used R project for statistical computing (version 2.7.2). This study is registered with ClinicalTrials.gov, number NCT00466492.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

428 patients were assessed for eligibility during April, 2007–December, 2008, of whom 140 were enrolled and randomly assigned to treatment (figure 1). Overall, a higher proportion of men ($n=76$ patients, 67%) than women ($n=37$, 33%) were included in the study, and the ratio of men to women was higher in the intervention group than in the control group (table 1). 27 patients were excluded from the statistical analysis because mechanical ventilation

was stopped within 48 h (figure 1). An extra person was needed to comfort and reassure 14 patients ($n=11$ in intervention group vs $n=3$ in control group, $p=0.0247$), and was present for a mean of 2.5 days (SD 2.3) in both groups.

The no sedation strategy was associated with a significantly higher number of days without ventilation than was the sedation strategy. The mean difference after correction for baseline variables was 4.2 days (95% CI 0.3–8.1; table 2); without correction for baseline variables the difference remained significant ($p=0.0350$).

Length of stay in the intensive care unit was significantly shorter in the no sedation group than in the sedation group, with a difference of 9.7 days (figure 2 and table 2). Cox regression analysis, with adjustment for baseline variables, showed that sedation increased length of stay (HR 1.86, 95% CI 1.05–3.23). Length of hospital stay was substantially shorter in the no sedation group than in the sedation group, with a difference of 24 days (figure 3 and table 2). The proportional hazards assumption was uncertain, so we allowed the effect of this variable to change after an initial period of 30 days. During the initial period, sedation significantly increased length of stay (HR 3.57, 1.52–9.09), and for days 31–90, sedation had no effect (0.76, 0.35–1.72; $p=0.54$). Mortality in the intensive care unit and in hospital overall was higher in the sedation group than in the no sedation group, but none of the differences reached significance (table 2).

Between the intervention and control groups, no difference was recorded in the occurrence of complications: accidental removal of the endotracheal tube ($n=7$ vs $n=6$; $p=0.69$); need for CT or MRI brain scans ($n=5$ vs $n=8$; $p=0.43$); ventilator-associated pneumonia ($n=6$ vs $n=7$; $p=0.85$); and need for intubation again within 24 h ($n=7$ vs $n=11$; $p=0.37$).

Mean doses of propofol and midazolam are shown in table 2. The protocol was deviated for ten (18%) patients in the intervention group, who received continuous sedation on more than two occasions. In most cases, sedation was needed to permit sufficient oxygenation in severe acute respiratory distress syndrome (eg, prone ventilation), but one patient was sedated after request from relatives. These ten patients account for most of the sedative drugs used in the intervention group, but use of these sedatives was significantly lower in the intervention group than in the control group. Difference in morphine dose between the two groups was not significant.

Delirium was recorded in 11 (20%) patients in the intervention group and 4 (7%) in the control group ($p=0.0400$). Haloperidol was used more frequently in the intervention group ($n=19$) than in the control group ($n=8$; $p=0.0100$), but the doses were very low for both groups (table 2).

Discussion

Findings from our study show that in critically ill patients receiving mechanical ventilation, a protocol of no sedation significantly increased the number of days without ventilation in a 28-day period compared with daily interruption of sedation. Use of no sedation was also associated with a significant reduction in the length of stay in the intensive care unit and in hospital. No difference in complications such as accidental removal of the endotracheal tube, ventilator-associated pneumonia, or need for CT and MRI brain scans were recorded. Mortality was increased in the group receiving sedation, but the difference compared with the group receiving no sedation did not reach significance. The occurrence of agitated delirium was increased in the group receiving no sedation.

Our study responded to calls in editorials and review articles for randomised trials aiming to reduce routine use of sedation, as practised in most intensive care units.¹⁷⁻¹⁹ We included both medical and surgical patients, since a limitation of previous studies has been inclusion of medical patients only.^{3,20} However, our study is limited by being single centre and unblinded, which holds a risk of bias. For practical reasons, masking of participants, investigators, and personnel could not be used for this study. The generalisability of results is limited by the fact that we had a standard nurse to patient ratio of 1:1, which is not possible in many intensive care units, and we used an extra person to calm patients, although this person was seldom needed and was used for very short periods. Further, 18% of the intervention group did not tolerate the no sedation strategy. However, in view of the disease severity in the population studied, including acute respiratory distress syndrome, and the fact that analysis was by intention to treat, with no crossover allowed, the results are very promising.

Several factors could have reduced the effect of no sedation versus daily interruption of sedation. First, morphine has a sedative effect, and therefore both groups received some sedation. We did not restrict or use a pain

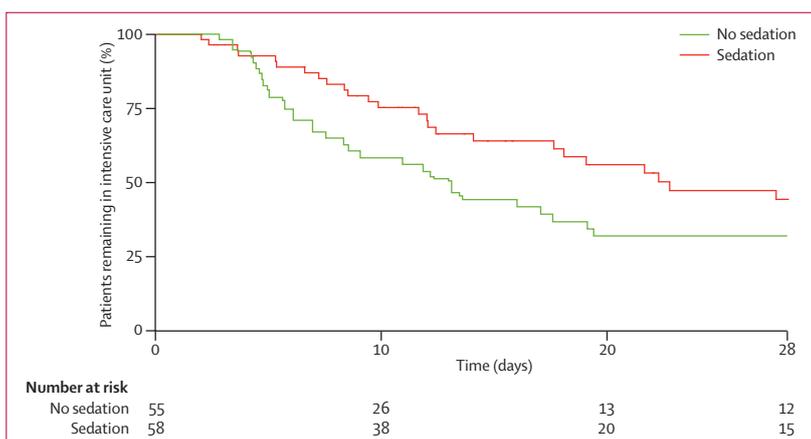


Figure 2: Kaplan-Meier plot of length of stay in the intensive care unit and number at risk from admission to 28 days

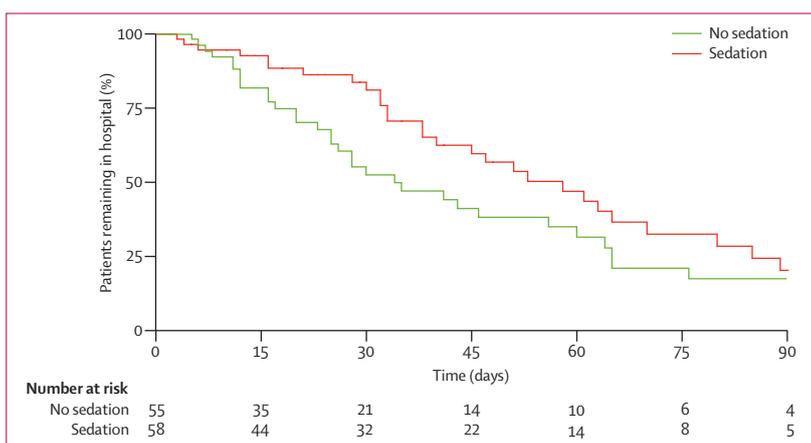


Figure 3: Kaplan-Meier plot of length of stay in hospital and number at risk from admission to 90 days

scale to guide the use of morphine, but use of morphine was very low in both groups with no significant difference between the groups. Use of morphine was probably low because patients included in the study were severely ill, reducing the need for sedation or analgesics.²¹

Second, in the control group, the first interruption of sedation until patients were awake was done the day after randomisation (within 24 h). Interruption of sedation at this early stage might have increased the number of patients who were extubated within 48 h, and were therefore excluded from statistical analysis of the control group. In Kress and colleagues' study,³ the first interruption of sedation was done after 48 h. We expected that interruption of sedation within 24 h would shorten the time for which patients received mechanical ventilation. To avoid underestimation of the effect of no sedation, we excluded patients expected to be extubated within 24 h and those with very low ventilator settings ($FiO_2 \leq 40\%$ and positive end-expiratory pressure of 5 cm H_2O). Furthermore, as per our standard routine, both groups of patients were mobilised daily to a chair, which might have prevented occurrence of ventilator-associated pneumonia in both

groups, and thereby reduced the difference in ventilation time between the two groups.

Third, we included severely ill patients who were dependent on mechanical ventilation for longer than 28 days. Girard and colleagues' study²⁰ excluded patients who were dependent on mechanical ventilation for more than 2 weeks. When patients cannot be weaned from mechanical ventilation, other factors such as comorbidity, age, overall health before start of mechanical ventilation, and inability to gain focus control in infection, are probably more determinant of outcome than is sedation.

Another limitation of the study is that if patients still needed mechanical ventilation after 48 h, we changed the sedative from propofol to midazolam to avoid propofol infusion syndrome,^{22,23} but use of midazolam could increase duration of mechanical ventilation. However, in Kress and colleagues' study,³ patients were randomly assigned to receive either midazolam or propofol, and no difference was recorded in ventilation time between the groups; the time taken to wake the patient did increase with midazolam compared with propofol.

Detection of delirium was not one of our primary endpoints. We used DSM-IV criteria,¹³ which detected hyperactive delirium, but use of the confusion assessment method for the intensive care unit^{24,25} would have been more appropriate to also detect hypoactive delirium. We detected far fewer cases of delirium in the group receiving interrupted sedation than in the group receiving no sedation, which emphasises the difficulty of detection of delirium in sedated patients even if they are routinely woken up. To address the long-term psychological effects of the intervention, we are inviting all patients from the study to participate in a follow-up interview about 1 year after they completed the study.

Results from this single-centre study suggest that a strategy of no sedation is promising, but a multicentre trial is needed to show that the benefits of this strategy can be reproduced in other facilities. A multicentre study should be powered to detect outcome measures from our study—ventilation time, and length of stay in the intensive care unit and in hospital—and should use the confusion assessment method for the intensive care unit to detect silent forms of delirium.

Contributors

TS and PT conceived and designed the study, recruited patients, and collected data. All authors had full access to all data, and contributed to data analysis and interpretation. TS and PT drafted the report. All authors contributed to review and revision of the report, and have seen and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

PT and TS received research grants from the Fund of Danielsen; and TS received research grants from the Danish Society of Anesthesiology and Intensive Care Medicine, the Fund of Kirsten Jensa la Cour, and the Fund of Holger og Ruth Hess. None of these funding organisations affected the trial or publication. We thank the nurses and our colleagues in the Department of Anesthesia and Intensive Care Medicine at Odense University Hospital for their participation and support in the study.

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