

included: narrowing to one agent if *P aeruginosa* was not identified; focusing the antimicrobial spectrum of activity on susceptibility data; and limiting the course of therapy to 5 days in patients remaining afebrile for 48 h. With this protocol, de-escalation occurred in 31.4% of patients.

In a randomised trial, patients with clinically diagnosed ventilator-associated pneumonia were assigned to have the duration of antibiotic therapy decided by the clinical judgment of the treating physician (standard therapy) or by a formalised discontinuation protocol.⁶ Patients assigned to the discontinuation protocol were monitored Monday to Friday by a clinical pharmacist, who made recommendations to stop one or more antibiotics if a non-infectious cause for pulmonary infiltrates was identified or if all of the following criteria were met: temperature less than 38.3°C; white-cell count less than 10×10⁹ cells per L or decreased 25% from peak value; improvement or insufficient progression of the chest radiograph; absence of purulent sputum; and ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen greater than 250. 89% of patients managed with the discontinuation protocol had at least one antibiotic discontinued within 48 h of recommendation. The overall duration of treatment was also significantly shorter in the discontinuation group than in the standard therapy group (6.0 [SD 4.9] vs 8.0 [5.6] days, p=0.001). Similar results were found with

a pneumonia score to assist in setting an endpoint for empiric treatment of ventilator-associated pneumonia.⁷

Experience so far suggests that unnecessary antibiotic use can be curtailed in the hospital setting, particularly within intensive-care units. Whether the ideal strategy involves the use of a serum marker such as procalcitonin or a locally applied practice protocol remains to be established.

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I declare that I have no conflicts of interest.

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Less sedation in intensive care: the pendulum swings back

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In *The Lancet* today, Thomas Strøm and colleagues¹ report the use of a protocol of no sedation for patients receiving mechanical ventilation in the intensive care unit. How much sedation is needed in the intensive care unit has become a major issue, overlapping with many aspects of mechanical ventilation, its duration, and the weaning period. Sedation for mechanically ventilated patients aims to reduce distress, ease adaptation to the ventilator, reduce oxygen consumption and carbon dioxide production, and protect patients with brain injury from development of oedema or ischaemia. However, clinical observations, epidemiological studies, and intervention trials have suggested that sedation is often overused.²

Use of adjusted sedation and analgesia has been an important advance in the care of critically ill patients.

Physicians often judge that both sedation and analgesia are needed, so continuous intravenous delivery of sedative and analgesic drugs has become standard for mechanically ventilated patients, especially at the early stage when severe hypoxaemia is present. To avoid misuse, however, this practice should be repeatedly reviewed for every patient from at least four standpoints. First, are both sedative and analgesic drugs needed upfront? Second, does the patient have one or several pathological disorders that result in drug accumulation? Third, could a different ventilator setting help adaptation and reduce or eliminate the need for drug treatment? Fourth, if treatment with both sedative and analgesic drugs is needed on initial examination, does the patient continue to need both drugs at the same doses?

Such a rigorous approach is difficult to implement, and so evidence for frequent overuse of sedation in the intensive care unit has led clinicians to propose new ways of administering these drugs. A major breakthrough was the finding that daily full interruption of continuous intravenous infusion of sedative shortened the duration of mechanical ventilation without induction of adverse effects.³ Further, interruption of sedation reduced the number of brain scans ordered for unexplained lack of awakening. The rationale for daily interruption of sedation was to target inappropriate use of sedative drugs relative to their progressive accumulation in the body, especially in the many patients with some degree of kidney insufficiency, interstitial fluid accumulation, or liver insufficiency. Such accumulation leads to substantial delay in awakening and prolonged mechanical ventilation. Daily interruption of sedation was subsequently combined with systematic use of spontaneous breathing trials to hasten separation from the ventilator with impressive results.⁴ This pragmatic approach was a response to failure to correctly manage sedation with continuous intravenous infusion, despite the development of bedside sedation scores for drug titration.

Strøm and colleagues' protocol of no sedation is even simpler than daily interruption of sedation, and was associated with major benefits. No sedation meant that patients received intravenous morphine as bolus doses (2.5 or 5 mg) with no infusion of sedatives or analgesics, but many patients were excluded because of medical indications for profound sedation (eg, increased intracranial pressure, status epilepticus, or hypothermia after cardiac arrest) or because they already met criteria for weaning from ventilation. Although most patients were ventilated for respiratory disorders, it seems that, initially, no patient was excluded for severe hypoxaemia. Thus only 140 of the 428 patients assessed for eligibility were eventually randomly assigned. No sedation was associated with significantly more days without ventilation (4.2 days, 95% CI 0.3–8.1 days), a significantly shorter stay in intensive care, and a shorter stay in hospital by 24 days, than was daily interruption of sedation.

Was there a price to pay for these major benefits? Occurrences of accidental removal of the endotracheal tube or similar complications did not differ between



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groups. Delirium was, however, recorded more frequently in patients in the intervention group than in the control group (20% vs 7%), and haloperidol was used more frequently in the intervention group than in the control group (35% vs 14%). An extra person was needed at the bedside to comfort and reassure patients more often in the intervention group than in the control group (20% vs 5%) for 2–3 days. The protocol was also deviated from for ten (18%) patients receiving no sedation, who were continually sedated on more than two occasions, mostly to permit sufficient oxygenation in severe acute respiratory distress syndrome. Despite mechanical ventilation, patients in both groups were mobilised daily to a chair, which was probably easier to undertake in the intervention group since patients from the control group were mainly mobilised during daily interruption of sedation.

A protocol of no-sedation strategy implies more than simply not giving patients sedatives. First, in the selection of patients and during the course of mechanical ventilation, clinicians need to search for medical indications for sedation. Boluses of morphine as needed provide some sedation, and although the total dose in today's study was low, initial doses can be higher and need careful clinical monitoring. The study also suggested that patients not receiving sedation might need appropriate supplemental drugs because they had an increased probability of developing delirium, and they might need an extra person for reassurance. Long-term follow-up of these patients will be important to

assess the occurrence of post-traumatic stress disorder or painful recollections. Therefore the protocol of no sedation seems to be associated with a need for more frequent individual assessment of the patient's pain, fear, anxiety, agitation or confusion, and adaption to the ventilator. Moreover, early and frequent mobilisation of patients could have contributed to improved outcome,⁵ but such a strategy might have increased the workload for personnel.

This single centre study has some limitations. Furthermore, the slight imbalance in patients' severity could have favoured the group receiving no sedation, so the strategy needs to be repeated in different populations by different groups. The overall results, however, are impressive and promising. Use of this strategy will mean that more attention needs to be paid in the daily care of patients, and caregivers will need increased empathy towards patients. Hopefully, these findings will prove beneficial to patients.

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My research laboratory has received research grants from several ventilator companies (Maquet, Dräger, Philips Respironics, General Electric), but has no relationship to disclose for the use of sedation in intensive care.

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W Survival in people with type 2 diabetes as a function of HbA_{1c}

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Since publication of the troubling results from the ACCORD trial¹ in mid-2008, which showed that intensive treatment of type 2 diabetes was associated with a higher all-cause mortality than was conventional therapy, an explanation has been sought. The goal for people intensively treated was a glycated haemoglobin (HbA_{1c}) of less than 6.0%. At the end of 3.5 years, when the trial was prematurely terminated, the HbA_{1c} achieved was 6.4% in the intensively treated and 7.5% in the conventionally treated groups; HbA_{1c} was 8.1% at inclusion. The most plausible explanation for these results is hypoglycaemia: the treatment target was probably too low, or glucose lowering was too rapid, or the combinations of treatments led to hypoglycaemia.

By contrast, researchers from the ADVANCE² and VADT³ studies reported no increase in mortality in intensively treated patients. Meta-analyses of the three trials, and of the UKPDS and the PROactive trials,⁴⁻⁶ had sufficient power to conclude that although intensive treatment was associated with a lowered rate of major cardiovascular events and myocardial infarctions, it had no effect on mortality. Results were homogeneous between trials, but ACCORD¹ was the only one that showed a significant increase in mortality.

Findings from the UKPDS,⁷ which included younger (median age 54 years), newly diagnosed patients, showed a substantially lowered all-cause mortality and rate of myocardial infarction in the 10-year post-trial follow-up for those originally allocated to intensive therapy. This outcome suggests a legacy of early intensive treatment. In all studies,⁵ hypoglycaemia was more frequent in the intensively treated than in the conventionally treated group.

In *The Lancet* today, some light is thrown on this issue by Craig Currie and colleagues⁸ with data from the large and statistically powerful General Practice Research Database, which has gathered data electronically from general practitioners in the UK. In this study of 48 000 patients with type 2 diabetes (cohort 1 changed from monotherapy to combination oral therapy with metformin and a sulphonylurea; cohort 2 changed to insulin treatment), the main result is that the 10% of patients with lowest HbA_{1c} values (<6.7%) had a higher death rate than all but those in the top 10%, who had an HbA_{1c} of 9.9% or higher. Furthermore, cardiovascular disease was more frequent in this low HbA_{1c} group than in any other decile. Similar results were reported in the two cohorts analysed with different definitions

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



Thomas Strøm, Torben Martinussen, Palle Toft

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.

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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

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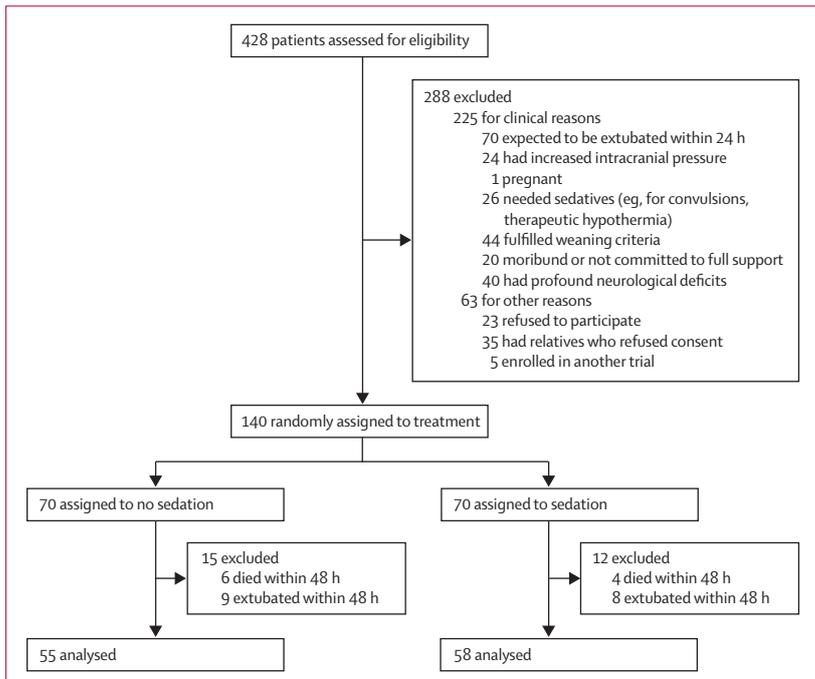


Figure 1: Trial profile

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 $p=0\cdot01$, 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, $p=0\cdot0247$), 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 ($p=0\cdot0350$).

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; $p=0\cdot54$). 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 $n=6$; $p=0\cdot69$); need for CT or MRI brain scans ($n=5$ vs $n=8$; $p=0\cdot43$); ventilator-associated pneumonia ($n=6$ vs $n=7$; $p=0\cdot85$); and need for intubation again within 24 h ($n=7$ vs $n=11$; $p=0\cdot37$).

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

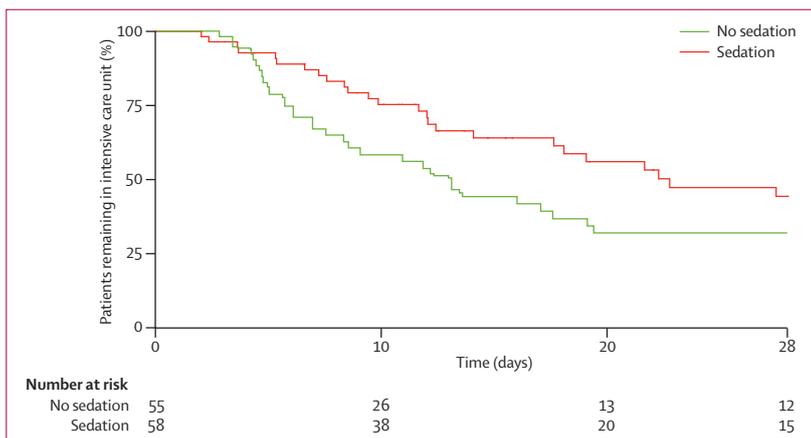


Figure 2: Kaplan-Meier plot of length of stay in the intensive care unit and number at risk from admission to 28 days

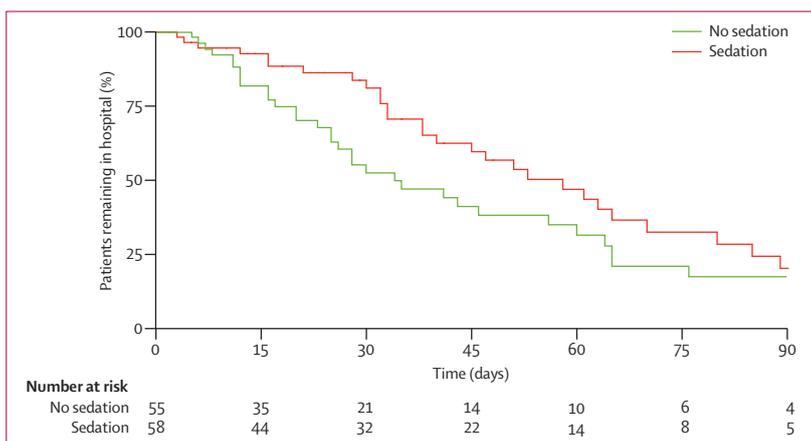


Figure 3: Kaplan-Meier plot of length of stay in hospital and number at risk from admission to 90 days

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.

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Less sedation in intensive care: the pendulum swings back



In *The Lancet* today, Thomas Strøm and colleagues¹ report the use of a protocol of no sedation for patients receiving mechanical ventilation in the intensive care unit. How much sedation is needed in the intensive care unit has become a major issue, overlapping with many aspects of mechanical ventilation, its duration, and the weaning period. Sedation for mechanically ventilated patients aims to reduce distress, ease adaptation to the ventilator, reduce oxygen consumption and carbon dioxide production, and protect patients with brain injury from development of oedema or ischaemia. However, clinical observations, epidemiological studies, and intervention trials have suggested that sedation is often overused.²

Use of adjusted sedation and analgesia has been an important advance in the care of critically ill patients. Physicians often judge that both sedation and analgesia are needed, so continuous intravenous delivery of sedative and analgesic drugs has become standard for mechanically ventilated patients, especially at the early stage when severe hypoxaemia is present. To avoid misuse, however, this practice should be repeatedly reviewed for every patient from at least four standpoints. First, are both sedative and analgesic drugs needed upfront? Second, does the patient have one or several pathological disorders that result in drug accumulation? Third, could a different ventilator setting help adaptation and reduce or eliminate the need for drug treatment? Fourth, if treatment with both sedative and analgesic drugs is needed on initial examination, does the patient continue to need both drugs at the same doses?

Such a rigorous approach is difficult to implement, and so evidence for frequent overuse of sedation in the intensive care unit has led clinicians to propose new ways of administering these drugs. A major breakthrough was the finding that daily full interruption of continuous intravenous infusion of sedative shortened the duration of mechanical ventilation without induction of adverse effects.³ Further, interruption of sedation reduced the number of brain scans ordered for unexplained lack of awakening. The rationale for daily interruption of sedation was to target inappropriate use of sedative drugs relative to their progressive accumulation in the body, especially in the many patients with some degree of kidney insufficiency, interstitial fluid

accumulation, or liver insufficiency. Such accumulation leads to substantial delay in awakening and prolonged mechanical ventilation. Daily interruption of sedation was subsequently combined with systematic use of spontaneous breathing trials to hasten separation from the ventilator with impressive results.⁴ This pragmatic approach was a response to failure to correctly manage sedation with continuous intravenous infusion, despite the development of bedside sedation scores for drug titration.

Strøm and colleagues' protocol of no sedation is even simpler than daily interruption of sedation, and was associated with major benefits. No sedation meant that patients received intravenous morphine as bolus doses (2.5 or 5 mg) with no infusion of sedatives or analgesics, but many patients were excluded because of medical indications for profound sedation (eg, increased intracranial pressure, status epilepticus, or hypothermia after cardiac arrest) or because they already met criteria for weaning from ventilation. Although most patients were ventilated for respiratory disorders, it seems that, initially, no patient was excluded for severe hypoxaemia. Thus only 140 of the 428 patients assessed for eligibility were eventually randomly assigned. No sedation was associated with significantly more days without ventilation (4.2 days, 95% CI 0.3–8.1 days), a significantly shorter stay in intensive care, and a shorter stay in hospital by 24 days, than was daily interruption of sedation.

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Was there a price to pay for these major benefits? Occurrences of accidental removal of the endotracheal tube or similar complications did not differ between groups. Delirium was, however, recorded more frequently in patients in the intervention group than in the control group (20% vs 7%), and haloperidol was used more frequently in the intervention group than in the control group (35% vs 14%). An extra person was needed at the bedside to comfort and reassure patients more often in the intervention group than in the control group (20% vs 5%) for 2–3 days. The protocol was also deviated from for ten (18%) patients receiving no sedation, who were continually sedated on more than two occasions, mostly to permit sufficient oxygenation in severe acute respiratory distress syndrome. Despite mechanical ventilation, patients in both groups were mobilised daily to a chair, which was probably easier to undertake in the intervention group since patients from the control group were mainly mobilised during daily interruption of sedation.

A protocol of no-sedation strategy implies more than simply not giving patients sedatives. First, in the selection of patients and during the course of mechanical ventilation, clinicians need to search for medical indications for sedation. Boluses of morphine as needed provide some sedation, and although the total dose in today's study was low, initial doses can be higher and need careful clinical monitoring. The study also suggested that patients not receiving sedation might need appropriate supplemental drugs because they had an increased probability of developing delirium, and they might need an extra person for reassurance. Long-term follow-up of these patients will be important to assess the occurrence of post-traumatic stress disorder or painful recollections. Therefore the protocol of no sedation seems to be associated with a need for more

frequent individual assessment of the patient's pain, fear, anxiety, agitation or confusion, and adaption to the ventilator. Moreover, early and frequent mobilisation of patients could have contributed to improved outcome,⁵ but such a strategy might have increased the workload for personnel.

This single centre study has some limitations. Furthermore, the slight imbalance in patients' severity could have favoured the group receiving no sedation, so the strategy needs to be repeated in different populations by different groups. The overall results, however, are impressive and promising. Use of this strategy will mean that more attention needs to be paid in the daily care of patients, and caregivers will need increased empathy towards patients. Hopefully, these findings will prove beneficial to patients.

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