ORIGINAL ARTICLE

Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients

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ABSTRACT

BACKGROUND

In critically ill, mechanically ventilated patients, daily interruption of sedation has been shown to reduce the time on ventilation and the length of stay in the intensive care unit (ICU). Data on whether a plan of no sedation, as compared with a plan of light sedation, has an effect on mortality are lacking.

METHODS

In a multicenter, randomized, controlled trial, we assigned, in a 1:1 ratio, mechanically ventilated ICU patients to a plan of no sedation (nonsedation group) or to a plan of light sedation (i.e., to a level at which the patient was arousable, defined as a score of −2 to −3 on the Richmond Agitation and Sedation Scale [RASS], on which scores range from −5 [unresponsive] to +4 [combative]) (sedation group) with daily interruption. The primary outcome was mortality at 90 days. Secondary outcomes were the number of major thromboembolic events, the number of days free from coma or delirium, acute kidney injury according to severity, the number of ICU-free days, and the number of ventilator-free days. Between-group differences were calculated as the value in the nonsedation group minus the value in the sedation group.

RESULTS

A total of 710 patients underwent randomization, and 700 were included in the modified intention-to-treat analysis. The characteristics of the patients at baseline were similar in the two trial groups, except for the score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, which was 1 point higher in the nonsedation group than in the sedation group, indicating a greater chance of in-hospital death. The mean RASS score in the nonsedation group increased from −1.3 on day 1 to −0.8 on day 7 and, in the sedation group, from −2.3 on day 1 to −1.8 on day 7. Mortality at 90 days was 42.4% in the nonsedation group and 37.0% in the sedated group (difference, 5.4 percentage points; 95% confidence interval [CI], −2.2 to 12.2; P=0.65). The number of ICU-free days and of ventilator-free days did not differ significantly between the trial groups. The patients in the nonsedation group had a median of 27 days free from coma or delirium, and those in the sedation group had a median of 26 days free from coma or delirium. A major thromboembolic event occurred in 1 patient (0.3%) in the nonsedation group and in 10 patients (2.8%) in the sedation group (difference, −2.5 percentage points; 95% CI, −4.8 to −0.7 [unadjusted for multiple comparisons]).

CONCLUSIONS

Among mechanically ventilated ICU patients, mortality at 90 days did not differ significantly between those assigned to a plan of no sedation and those assigned to a plan of light sedation with daily interruption. (Funded by the Danish Medical Research Council and others; NONSEDA ClinicalTrials.gov number, NCT01967680.)

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THE PRACTICE OF SEDATING PATIENTS receiving mechanical ventilation has been standard care.[1] Although advances in technology have made modern ventilators more comfortable for patients, it has generally been believed that light sedation should accompany mechanical ventilation.[2] However, trials published in the last two decades have reported that the use of sedatives may worsen outcomes in mechanically ventilated patients. A trial comparing daily interruption of sedation with no interruption showed that patients had shorter durations of mechanical ventilation and shorter stays in the intensive care unit (ICU) with daily interruption.[3] A similar trial reported in the *Journal* showed that mortality was lower and the length of hospital stay shorter among the patients who had daily interruption of sedation than among those who had no interruption.[4]

In a single-center trial, we reported that a plan of no sedation was associated with more days without mechanical ventilation and a shorter stay in the ICU or hospital than a plan of sedation with daily interruption.[5] The trial was not statistically powered to show a difference in mortality between the trial groups (the nonsedation group and the sedation group). A post hoc analysis showed a lower incidence of acute renal failure in the nonsedation group.[6] We conducted the current trial to investigate whether a plan of no sedation in patients receiving mechanical ventilation would result in a better survival outcome than a plan of light sedation with daily interruption.

METHODS

TRIAL DESIGN AND OVERSIGHT

The trial was conducted at eight centers — five in Denmark (Aarhus, Kolding, Esbjerg, Svendborg, and Odense), two in Norway (Tønsberg and Tromsø), and one in Sweden (Linköping). The first three authors and the last author designed the trial and wrote the first draft of the manuscript. The statistical analyses were performed by the authors from the Department of Business and Economics, University of Southern Denmark. All the authors had full access to data and vouch for the accuracy and completeness of the data, the fidelity of the trial to the protocol, and the complete reporting of adverse events. Approval for the trial was obtained from the national ethics committee in each of the three

participating countries. Written informed consent was obtained from either the patient or the patient's closest relatives in accordance with national regulatory requirements. If consent was withdrawn, we asked for permission to continue the registration of clinical data in order to include patients in the final analysis. The trial was funded by the Danish Medical Research Council, Danielsens Foundation, and the Scandinavian Society of Anesthesiology and Intensive Care Medicine. There was no industry involvement in the trial.

PATIENT SELECTION AND RANDOMIZATION

Patients were eligible for inclusion in the trial if they were 18 years of age or older, had undergone endotracheal intubation within 24 hours before screening, and were expected to receive mechanical ventilation for more than 24 hours. Patients were excluded if they had severe head trauma, therapeutic hypothermia, or status epilepticus, had participated in our previous trial,[5] had transferred from another ICU with a length of stay more than 48 hours, were comatose on admission (not medically induced), were brain-dead, or had a ratio of the partial pressure of arterial oxygen (measured in kilopascals) to the fraction of inspired oxygen of 9 or lower. They were also excluded if sedation was anticipated to be necessary for oxygenation or for the patient to remain in a prone position.

Within 24 hours after intubation, the patients were randomly assigned in a 1:1 ratio to a plan of no sedation (nonsedation group) or to a plan of light sedation with daily interruption (sedation group). Randomization was performed at a central location with the use of a computer-generated assignment sequence with a variable block size. Patients were stratified according to participating center, age (≤65 years or >65 years), and the presence or absence of shock on arrival (systolic blood pressure, <70 mm Hg or ≥70 mm Hg). Investigators, patients or their relatives, and physicians caring for the patients were aware of the trial-group assignments. The protocol and statistical analysis plan have been published previously[7] and are available with the full text of this article at NEJM.org.

TRIAL INTERVENTIONS

The patients in the nonsedation group did not receive any sedatives but could receive bolus doses of morphine for analgesia, as deemed

necessary by the treating team. These patients were awake and able to communicate, and it was a goal to have them sustain a natural sleep rhythm. If, despite both nonpharmacologic (reassurance or mobilization) and pharmacologic (analgesia) treatment, it became necessary to sedate a patient, the patient was given medications similar to those used in the sedation group. Crossover between trial groups was not allowed.

The patients in the sedation group received a continuous infusion of sedatives, with a goal of achieving light sedation — that is, to a level at which the patient was arousable (defined as a score of −2 to −3 on the Richmond Agitation and Sedation Scale [RASS], on which scores range from −5 [unresponsive] to +4 [combative])[8]; this intervention was consistent with international guidelines.[9] Propofol was used for sedation in the first 48 hours and was replaced by midazolam thereafter.[10] Every morning, sedation was interrupted with the aim of full wakefulness, defined as the ability to perform at least three of the following four tasks: open the eyes in response to oral commands, follow the examiner's instructions with the eyes, squeeze the examiner's hands on request, and stick out the tongue on request.[4] During the wake-up period, the patients were weaned off the ventilator. After a patient successfully performed three of the four aforementioned tasks, the infusion of sedatives was resumed at half the dose that was used before the interruption. If positive end-expiratory pressure could be reduced to 5 cm of water and the fraction of inspired oxygen could be reduced to a level below 40%, sedation was not resumed. These values did not necessarily imply that extubation was indicated. If the patient was unable to remain comfortably awake at these low settings, sedation was resumed. If the patient became uncomfortable during the wake-up period, sedation was resumed. Symptoms such as anxiety or mild agitation resulting from withdrawal of sedation could be treated with bolus doses of clonidine. The use of dexmedetomidine was discouraged in both trial groups. Both trial groups received a basic analgesic regimen that included paracetamol and opioids as bolus doses in order to keep the patients free from pain. Epidural anesthesia was used to control pain when appropriate.

Patients were assessed for delirium at least two times a day (8 a.m. and 8 p.m.) with the use of the Confusion Assessment Method for the ICU (CAM-ICU).[11] The result could be either positive (delirium), negative (no delirium), or — if in coma — unable to evaluate. If treatment was needed for delirium, the initial choice was to use nonpharmacologic measures (reassurance or mobilization). If this was not sufficient and pharmacologic treatment was needed, the protocol allowed for the use of either haloperidol or olanzapine. After extubation, patients were discharged from the ICU in accordance with the participating center's usual practice and at the discretion of the treating physician. Thromboprophylactic measures were used in both trial groups in accordance with the participating center's usual practice.

OUTCOME MEASURES

The primary outcome was all-cause mortality at 90 days after randomization. Secondary outcomes were the number of days until death up to 90 days after randomization, the number of thromboembolic events (pulmonary embolus or deep-vein thrombosis) up to 90 days after randomization; the number of days free from coma or delirium (RASS score of at least −3 and a negative CAM-ICU assessment) within 28 days after randomization; the highest score on the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) assessment, which classifies acute kidney injury according to severity, within 28 days after randomization[12]; the length of stay in the ICU up to death or 28 days after randomization, whichever occurred first; and the number of days without mechanical ventilation within 28 days after randomization. Days free from coma or delirium were recorded during the ICU stay, and days alive after discharge from the ICU up to day 28 were counted as delirium-free days.[13]

Exploratory outcomes were all-cause mortality at 28 days after randomization; the length of stay in the ICU up to death or 90 days after randomization, whichever occurred first; the number of days until the patient was no longer in need of mechanical ventilation within 90 days after randomization; the length of hospital stay within 90 days after randomization; organ failure when the patient was discharged from the ICU; the number of accidental extubations that led to reintubation within 1 hour; and the number of accidental removals of central venous catheters that led to reinsertion within 4 hours. Data for outcome measures were obtained from

patient files and from regional and national registers by the trial investigators and nurses during the 90-day observation period. Additional details of the outcome measures are provided in the protocol.[7]

STATISTICAL ANALYSIS

In a previous single-center randomized trial of sedation or nonsedation in mechanically ventilated ICU patients, mortality during hospitalization in the intention-to-treat analysis was 36% in the nonsedation group and 47% in the sedation group, findings that correspond to a 25% lower relative risk in the nonsedation group.[5] In other studies, trials, and meta-analyses, the 90-day mortality among patients receiving mechanical ventilation has been approximately 40%.[14,15] On the basis of this in-hospital mortality, we estimated that given a maximum risk of type I error of 5% and of type II error of 20%, a sample size of 700 patients (350 in each group) would provide the trial with 80% power to show that an intervention would result in a 25% lower relative risk of in-hospital death or to reject the hypothesis.[5] We used a two-sided P value for the between-group difference with respect to the primary outcome. Between-group differences were calculated as the value in the nonsedation group minus the value in the sedation group.

We performed the data analysis according to the modified intention-to-treat principle. Because the statistical analysis plan did not include a provision for correcting for multiple comparisons when conducting tests for secondary outcomes, those results are reported as point estimates and unadjusted 95% confidence intervals, from which no conclusions can be drawn regarding differences between the trial groups. All the patients were followed for 90 days, unless they withdrew consent for the investigators to acquire further data or use existing trial data, in which case the data were censored at the time consent was withdrawn. When analyzing individual variables, patients with any missing values on the variable in question were excluded. Missing data were managed with the use of multiple imputation procedures if at least 5% of the patients had missing data and Little's test was statistically significant. In the analysis of the primary outcome of all-cause mortality at 90 days, we used a multivariate logistic-regres-sion analysis. In the analysis of the secondary outcomes, we used unadjusted univariate logistic regression. In the analysis of the exploratory outcomes, we used multivariate logistic-regres-sion analysis with adjustment for the randomization stratification factors and for Simplified Acute Physiology Score (SAPS) II, Sequential Organ-Failure Assessment (SOFA) score, shock at admission, chronic kidney disease, chronic obstructive pulmonary disease, and daily use of benzodiaz-epine before randomization. We analyzed survival data using Cox proportional-hazards regression, with and without adjustment for the randomization stratification factors and for other baseline clinical variables (additional details are provided in the statistical analysis plan). A Kaplan–Meier plot was used to estimate the probability of survival at 90 days after randomization. Dichotomous and continuous outcomes were analyzed with the use of logistic regression. All statistical analyses were performed with R software (R Core Team [2013]).

RESULTS

PATIENT CHARACTERISTICS

From January 2014 through November 2017, a total of 2300 patients were assessed for eligibility, and 710 were enrolled in the trial and randomly assigned to a trial group — 354 to the nonsedation group and 356 to the sedation group. After randomization, 10 patients were excluded (reasons for exclusion are provided in Fig. 1), leaving a total of 700 patients in the modified intention-to-treat analysis. No patients were lost to follow-up, and we obtained 90-day follow-up data with respect to the primary outcome from all 700 patients. With respect to the secondary outcomes, observations were missing in less than 5% of the patients. Apart from the score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, which was 1 point higher in the nonsedation group than in the sedation group (26 vs. 25), the characteristics of the patients were similar in the two groups (Table 1).

In the sedation group, the mean RASS score was −2.3 on day 1 and increased to −1.8 on day 7, indicating a more alert state. In the nonsedation group, the mean RASS score was −1.3 on day 1 and increased to −0.8 on day 7, indicating a more alert state. The mean RASS score was
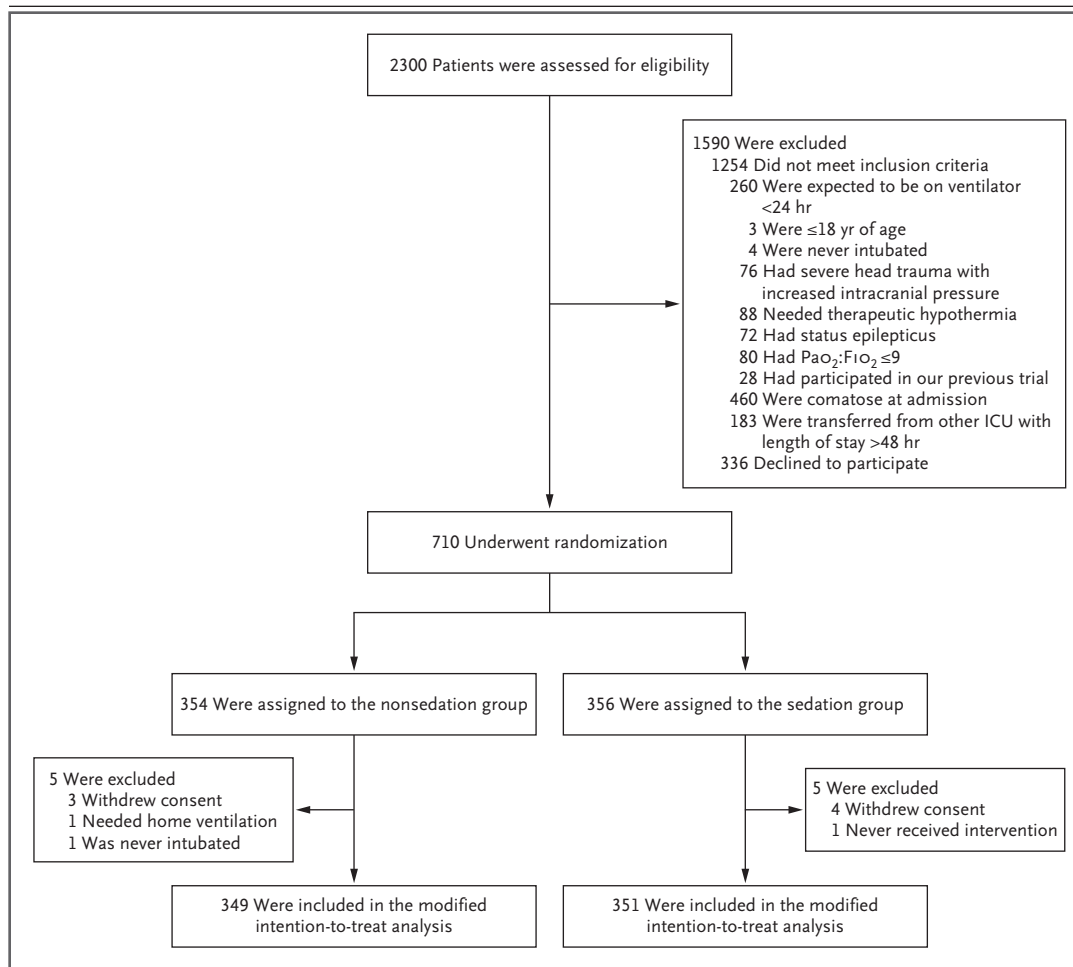
Figure 1. Enrollment, Randomization, and Analysis.

ICU denotes intensive care unit, and Pao$_2$:Fio$_2$ the ratio of the partial pressure of arterial oxygen (measured in kilopascals) to the fraction of inspired oxygen.

numerically higher in the nonsedation group than in the sedation group on each day between days 1 and 7 (Fig. 2). On day 1 of the trial, 27.0% of the patients in the nonsedation group received medication for sedation, and 38.4% received medication for sedation at some time during their ICU stay. The main reason for sedation was delirium.

OUTCOMES

In the modified intention-to-treat analysis of all-cause mortality at 90 days after randomization, 148 patients (42.4%) in the nonsedation group had died and 130 patients (37.0%) in the sedation group had died (difference, 5.4 percentage points; 95% confidence interval [CI], −2.2 to 12.2; P=0.65) (Table 2 and Fig. 3). The secondary outcome of the number of days until death up to 90 days was 13 days (interquartile range, 6 to 27) in the nonsedation group and 12 days (interquartile range, 5 to 28) in the sedation group (unadjusted difference, 1 day; 95% CI, −2 to 5). A major thromboembolic event (pulmonary embolus or deep-vein thrombosis) within 90 days after randomization occurred in 1 patient (0.3%) in the nonsedation group and in 10 patients (2.8%) in the sedation group (unadjusted difference, −2.5 percentage points; 95% CI, −4.8 to −0.7) (Table 2). All other secondary outcomes did not differ significantly between the trial groups, but no definite inferences can be drawn from these data because of the ab-

Table 1. Baseline Characteristics of the Patients at ICU Admission.*

Characteristic	Nonsedation Group	Sedation Group	Difference (95% CI)†
Age — yr			
Median	72.0	70.0	2.0 (0.1 to 3.6)
Interquartile range	63.0 to 80.0	62.8 to 78.0	
Female sex — no. (%)	126 (36.1)	147 (41.9)	−5.8 (−13.1 to 1.2)
Weight — kg			
Median	77.8	77.7	0.1 (−2.3 to 5.1)
Interquartile range	65.0 to 90.0	65.0 to 92.0	
Height — cm			
Median	173	171	2 (0 to 5)
Interquartile range	165 to 180	165 to 178	
APACHE II score‡			
Median	26	25	1 (0 to 3)
Interquartile range	22 to 30	21 to 30	
SAPS II§			
Median	49	49	0 (−2 to 3)
Interquartile range	39 to 60	40 to 59	
SOFA score at day 1¶			
Median	7	8	−1 (−3 to 0)
Interquartile range	5 to 10	6 to 11	
Type of admission — no. (%)			
Medical	244 (69.9)	235 (67.0)	2.9 (−3.8 to 9.8)
Acute surgical	94 (26.9)	95 (27.1)	−0.2 (−6.5 to 6.5)
Elective surgical	11 (3.2)	21 (6.0)	−2.8 (−6.3 to 0.1)
Diagnosis at ICU admission — no. (%)			
Pneumonia or ARDS	147 (42.1)	151 (43.0)	−0.9 (−8.2 to 6.2)
Sepsis	84 (24.1)	74 (21.1)	3.0 (−3.2 to 9.2)
Exacerbation of COPD	24 (6.9)	21 (6.0)	0.9 (−2.7 to 4.8)
Gastrointestinal bleeding	4 (1.1)	4 (1.1)	0.0 (−1.8 to 1.8)
Trauma	11 (3.2)	18 (5.1)	−1.9 (−5.1 to 1.0)
Severe acute asthma	11 (3.2)	7 (2.0)	1.2 (−1.4 to 3.6)
Postoperative complications	7 (2.0)	7 (2.0)	0.0 (−2.3 to 2.3)
Other	66 (18.9)	74 (21.1)	−2.2 (−7.9 to 3.9)

* Data on age, female sex, weight, height, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, Sequential Organ-Failure Assessment (SOFA) score, and type of admission are presented for the 700 patients in the modified intention-to-treat population (349 patients in the nonsedation group and 351 in the sedation group). Data on the diagnosis at intensive care unit (ICU) admission are presented for all 710 patients who underwent randomization (354 patients in the nonsedation group and 356 in the sedation group). ARDS denotes acute respiratory distress syndrome, and COPD chronic obstructive pulmonary disease. Percentages may not total 100 because of rounding.
† For continuous variables, the difference in medians is shown. For categorical variables, the absolute difference in percentage points is shown.
‡ APACHE II scores range from 0 to 71, with higher scores indicating more severe disease.
§ SAPS II is calculated from 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease.
¶ SOFA scores range from 0 to 4 for each organ system, with higher aggregate scores indicating more severe organ dysfunction.

sence of a prespecified plan for adjustment for multiple comparisons. The number of days free from coma or delirium was 27 in the nonsedation group and 26 in the sedation group (Table 2). During the ICU stay, the number of days free from coma or delirium was 3 (range, 1 to 6) in the nonsedation group and 1 (range, 0 to 3) in the sedation group. The highest measured RIFLE score within 28 days after randomization was 2 in both groups (scores range from 1 to 4, with 1 indicating normal kidney function, 2 risk, 3 injury, and 4 failure). The RIFLE scores are provided in Figure S2 in the Supplementary Appendix, available at NEJM.org. Exploratory outcomes are reported in Table S3.
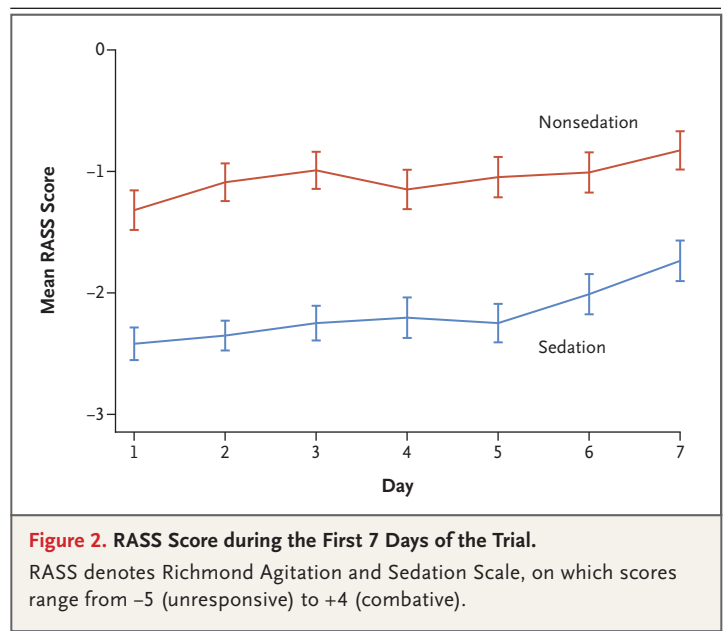
MEDICATION USE

The total doses of sedatives, including propofol and midazolam, were higher in the sedation group than in the nonsedation group (Table S1). The mean dose of morphine was 0.0073 mg per kilogram of body weight per hour (range, 0.0036 to 0.0140) in the nonsedation group, as compared with 0.0060 mg per kilogram per hour (range, 0.0027 to 0.0110) in the sedation group, over the first 3 days (unadjusted risk difference, 0.0013; 95% CI, −0.0001 to 0.0028) (Table S1). For all 7 days, the mean dose of morphine was 0.0051 mg per kilogram per hour (range, 0.0023 to 0.0110) in the nonsedation group and 0.0045 mg per kilogram per hour (range, 0.0018 to 0.0088) in the sedation group.

ADVERSE EVENTS

An accidental extubation that led to reintubation within 1 hour occurred in four patients (1.1%) in the nonsedation group and in one patient (0.3%) in the sedation group (unadjusted risk difference, 0.8 percentage points; 95% CI, −0.7 to 2.6; P=0.20). No events of accidental removal of a central venous catheter that led to reinsertion within 4 hours occurred in either trial group. Adverse events are reported in Table S2.

DISCUSSION

In this multicenter, randomized, controlled trial involving mechanically ventilated ICU patients, mortality at 90 days did not differ significantly between those who were assigned to a plan of no sedation and those who were assigned to a

Figure 2. RASS Score during the First 7 Days of the Trial.
RASS denotes Richmond Agitation and Sedation Scale, on which scores range from −5 (unresponsive) to +4 (combative).

plan of light sedation with daily interruption. Time on mechanical ventilation, length of ICU stay, and length of hospital stay did not differ significantly between the trial groups. The number of days free from coma or delirium was 1 day more in the nonsedation group than in the sedation group, and there were fewer thromboembolic events in the nonsedation group than in the sedation group. The highest measured RIFLE score did not differ significantly between the two groups. However, the lack of a plan for correction for multiple comparisons of secondary outcomes did not allow formal inferences to be made from these observations. The low numbers of thromboembolic events may be explained by the use of prophylactic low-molecular-weight heparin in all the patients in both trial groups.

Several trials have shown that lighter sedation results in shorter time on mechanical ventilation and shorter length of stay in the ICU or hospital.[3,4,16] In contrast, we did not find that time on mechanical ventilation or length of stay in the ICU or hospital differed significantly between the trial groups, perhaps because the depth of sedation did not differ between the groups as much as intended, especially on day 1. According to recent international guidelines on sedation for mechanical ventilation, a RASS score of −2 to + 1 is defined as light sedation.[2] In our trial, the sedation target in the sedation group

Table 2. Primary and Secondary Outcomes.

Outcome	Nonsedation Group (N=349)	Sedation Group (N=351)	Difference (95% CI)*
Primary outcome			
All-cause mortality at 90 days after randomization — no. (%)	148 (42.4)	130 (37.0)	5.4 (–2.2 to 12.2)†
Secondary outcomes			
No. of days until death up to 90 days after randomization			
Median	13	12	1 (–2 to 5)
Interquartile range	6 to 27	5 to 28	
Patients with a major thromboembolic event at 90 days after randomization — no. (%)	1 (0.3)	10 (2.8)	–2.5 (–4.8 to –0.7)
No. of days free from coma or delirium within 28 days after randomization			
Median	27	26	1 (0 to 2)
Interquartile range	21 to 28	22 to 28	
Highest measured RIFLE score within 28 days after randomization‡			
Median	2	2	0 (–1 to 1)
Interquartile range	1 to 4	1 to 4	
No. of days in the ICU until death or 28 days after randomization, whichever occurred first			
Median	13	14	–1 (–7 to 4)
Interquartile range	0 to 23	0 to 23	
No. of days without mechanical ventilation within 28 days after randomization			
Median	20	19	1 (–3 to 3)
Interquartile range	0 to 26	0 to 25	

* For continuous variables, the difference in medians is shown. For categorical variables, the absolute difference in percentage points is shown. The widths of the 95% confidence intervals have not been adjusted for multiple comparisons; thus, the intervals should not be used to infer treatment effects.
† P=0.65.
‡ Scores on the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) assessment range from 1 to 4, with 1 indicating normal kidney function, 2 risk, 3 injury, and 4 failure.
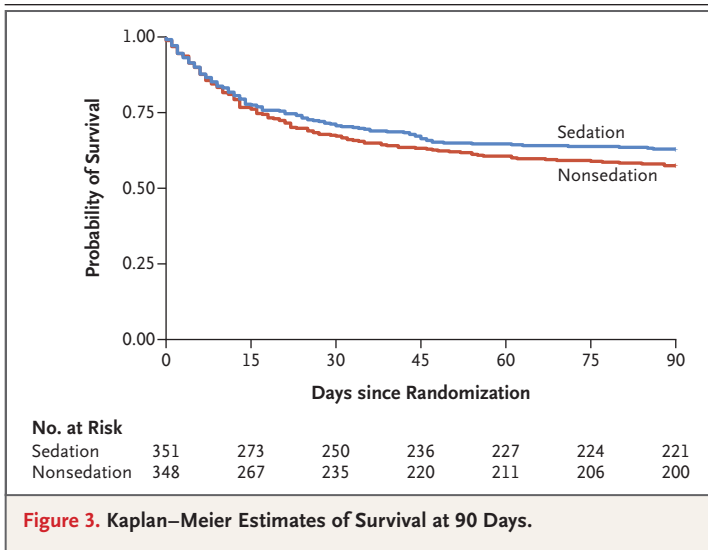

Figure 3. Kaplan–Meier Estimates of Survival at 90 Days.

No. at Risk							
Sedation	351	273	250	236	227	224	221
Nonsedation	348	267	235	220	211	206	200

was a RASS score of –2 to –3, which is light-to-moderate sedation. In the Sedation Practice in Intensive Care Evaluation (SPICE) III trial, which was recently published in the *Journal*, the sedation goal was light sedation, but the investigators reported a median RASS score of –3 to –5 for more than 40% of the patients both groups.[17] On day 1 in our trial, the mean RASS score in the sedation group was –2.3, gradually increasing to –1.8 on day 7. A higher percentage of the patients in the nonsedation group were sedated during the first week after randomization than reported in the aforementioned trial, which partly accounted for the lower-than-intended between-group difference in the degree of sedation (see the Supplementary Appendix).[18] We observed that the nonsedation group had 1 more day free from coma or delirium than the nonsedation group,

but because of the lack of adjustment for multiple comparisons, no inferences can be made from this result. This difference in the number of days free from coma or delirium is similar to the findings from a trial that compared nonsedation with sedation in postoperative care.[19] Although more events of accidental extubations occurred in the nonsedation group in our trial, few led to reintubations within 1 hour. The low number of accidental extubations in our trial might be due to the nurse-to-patient ratio of 1:1 in most of the participating ICUs.

In conclusion, among critically ill adults receiving mechanical ventilation in the ICU, mortality at 90 days did not differ significantly between those assigned to a plan of no sedation and those assigned to a plan of light sedation (i.e., to a level at which the patient was arousable) with daily interruption. The plan of no sedation resulted in no important differences in the number of ventilator-free days or in the length of ICU or hospital stay.

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