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Daily Sedation Interruption in Mechanically Ventilated Critically Ill Patients Cared for With a Sedation Protocol

A Randomized Controlled Trial

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Context Protocolized sedation and daily sedative interruption are 2 strategies to minimize sedation and reduce the duration of mechanical ventilation and intensive care unit (ICU) stay. We hypothesized that combining these strategies would augment the benefits.

Objective To compare protocolized sedation with protocolized sedation plus daily sedation interruption in critically ill patients.

Design, Setting, and Patients Randomized controlled trial of 430 critically ill, mechanically ventilated adults conducted in 16 tertiary care medical and surgical ICUs in Canada and the United States between January 2008 and July 2011.

Intervention Continuous opioid and/or benzodiazepine infusions and random allocation to protocolized sedation (n=209) (control) or to protocolized sedation plus daily sedation interruption (n=214). Using validated scales, nurses titrated infusions to achieve light sedation. For patients receiving daily interruption, nurses resumed infusions, if indicated, at half of previous doses. Patients were assessed for delirium and for readiness for unassisted breathing.

Main Outcome Measure Time to successful extubation. Secondary outcomes included duration of stay, doses of sedatives and analgesics, unintentional device removal, delirium, and nurse and respiratory therapist clinical workload (on a 10-point visual analog scale [VAS]).

Results Median time to successful extubation was 7 days in both the interruption and control groups (median [IQR], 7 [4-13] vs 7 [3-12]; interruption group hazard ratio, 1.08; 95% CI, 0.86-1.35; *P*=.52). Duration of ICU stay (median [IQR], 10 [5-17] vs 10 [6-20]; *P*=.36) and hospital stay (median [IQR], 20 [10-36] vs 20 [10-48]; *P*=.42) did not differ between the daily interruption and control groups, respectively. Daily interruption was associated with higher mean daily doses of midazolam (102 mg/d vs 82 mg/d; *P*=.04) and fentanyl (median [IQR], 550 [50-1850] vs 260 [0-1400]; *P*<.001) and more daily boluses of benzodiazepines (mean, 0.253 vs 0.177; *P*=.007) and opiates (mean, 2.18 vs 1.79; *P*<.001). Unintentional endotracheal tube removal occurred in 10 of 214 (4.7%) vs 12 of 207 patients (5.8%) in the interruption and control groups, respectively (relative risk, 0.82; 95% CI, 0.36-1.84; *P*=.64). Rates of delirium were not significantly different between groups (53.3% vs 54.1%; relative risk, 0.98; 95% CI, 0.82-1.17; *P*=.83). Nurse workload was greater in the interruption group (VAS score, 4.22 vs 3.80; mean difference, 0.41; 95% CI, 0.17-0.66; *P*=.001).

Conclusion For mechanically ventilated adults managed with protocolized sedation, the addition of daily sedation interruption did not reduce the duration of mechanical ventilation or ICU stay.

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CRITICALLY ILL PATIENTS WEAN more quickly from mechanical ventilation, with lower risk of delirium, when clinicians use specific strategies to reduce excessive sedation.[1-3] A nursing-implemented sedation titration protocol that specifies clear targets for level of awareness is one approach to minimize sedation.[4] Daily interruption of sedative infusions may achieve the same goal if infusions are resumed only when necessary and at half the

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previous dose.[5] Early clinical trials evaluating each strategy led to strong recommendations for their use in practice.[6] However, results of subsequent clinical trials varied,[7-10] and use of these strategies in clinical practice has been inconsistent.[11,12] Concerns about daily interruption of sedation include patient discomfort, unintentional device removal, and increased clinician workload.[13,14] A systematic review of 5 trials that evaluated daily interruption highlighted the need for further research.[15]

Avoiding excessive sedation is intuitively appealing. In light of the observed and potential benefits of both protocolized sedation and daily interruption in some settings, we hypothesized that mechanically ventilated adults managed with both strategies would receive less sedation and have a shorter duration of mechanical ventilation than patients managed with protocolized sedation alone.

METHODS

We conducted this multicenter randomized controlled trial in 16 centers from January 2008 to July 2011, after approval from local institutional review boards. In preparation, we completed a 65-patient, 3-center pilot randomized trial.[16]

Participants

Eligible critically ill adults were those expected by the intensive care unit (ICU) team to require mechanical ventilation for at least 48 hours after enrollment and for whom the ICU team had decided to initiate continuous sedative and/or opioid infusion(s). Patients admitted to the ICU after cardiac arrest or traumatic brain injury were excluded, as were patients receiving neuromuscular blocking agents, those enrolled in another trial, those previously enrolled in the current trial, or those for whom there was a lack of commitment to maximal treatment. Legally authorized surrogates provided written informed consent.

Randomization and Masking

Research staff randomized patients to protocolized sedation plus daily interruption (interruption group) or protocolized sedation alone (control group), using an automated telephone system that stratified by center with undisclosed variable block sizes. None of the participants, study personnel, clinicians, or investigators analyzing data was masked to group assignment.

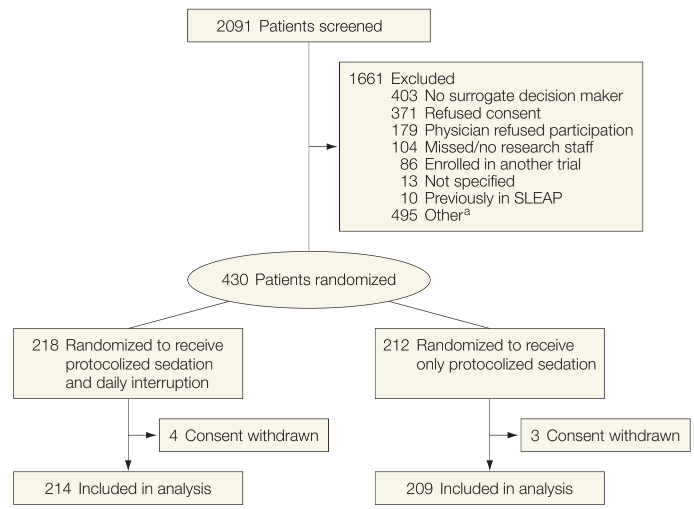
Procedures

Bedside nurses titrated analgesic and sedative infusions according to a protocol that prioritized pain assessment (eFigures 1 and 2, available at http://www.jama.com). Morphine, fentanyl, or hydromorphone was administered for analgesia; midazolam or lorazepam, for sedation. Nurses used the Sedation-Agitation Scale[17] (8 sites) (eTable 1) or the Richmond Agitation Sedation Scale[18] (8 sites) (eTable 2) to assess sedation needs hourly and titrated infusions to maintain, ideally, a comfortable yet rousable state equivalent to a Sedation-Agitation Scale score of 3 or 4 or Richmond Agitation Sedation Scale score of −3 to 0. When the sedation score directed an increase in medication, the bedside nurse judged whether to increase the opioid and/or benzodiazepine infusions. When patients were oversedated, nurses alternately reduced opioid and benzodiazepine infusions. Midazolam and morphine were reduced in 1- to 2-mg decrements, fentanyl in 12.5- to 25-μg decrements, and hydromorphone in 0.1- to 0.5-mg decrements at 15- to 30-minute intervals. If doses of midazolam, lorazepam, or morphine were less than 3 mg/h, 0.5-mg decrements could be used. If Sedation-Agitation Scale score was 1 to 2 (Richmond Agitation Sedation Scale score −4 or −5), yet the patient showed signs of agitation or distress, bolus doses were administered as needed. When patients were extremely agitated (Sedation-Agitation Scale score 7; Richmond Agitation Sedation Scale score 3 or 4), nurses could deviate from this protocol. For both groups, infusions were discontinued when a patient was oversedated (Sedation-Agitation Scale score 1 or 2; Richmond Agitation Sedation Scale score −4 or −5) while receiving 0.5 to 1 mg/h of midazolam or morphine (or fentanyl, 12.5-25 μg/h). Intermittent dosing was permitted for procedures. Propofol, ketamine, and dexmedetomidine infusions were not permitted.

In the interruption group, bedside nurses interrupted benzodiazepine and opioid infusions daily and assessed hourly for wakefulness, defined as Sedation-Agitation Scale score 4 to 7 (Richmond Agitation Sedation Scale score −1 to 4) and ability to perform at least 3 of the following on request: eye opening, tracking, hand squeezing, and toe moving. If the bedside nurse and a physician agreed that infusions were no longer required (the patient was free of discomfort and agitation and the Sedation-Agitation Scale score was between 2 and 5 or the Richmond Agitation Sedation Scale score was between −4 and 1), oral or bolus intravenous therapy was used at their discretion. Alternatively, if they judged that ongoing benzodiazepine or opioid infusions were required, nurses resumed infusions at half of the previous dose and titrated to achieve the target level of light sedation. If a patient became agitated (Sedation-Agitation Scale score 6 or 7 or Richmond Agitation Sedation Scale score 2 to 4) or exhibited signs of discomfort (respiratory rate >35/min, oxygen saturation as measured by pulse oximetry <90%, heart rate >140/min or a change in heart rate of 20% in either direction, systolic blood pressure >180 mm Hg, or increased anxiety and diaphoresis) before the physician's assessment, nurses promptly resumed infusions at half the previous rate. Daily interruption could be delayed for procedures. When an interruption was not performed or infusions were not restarted at 50% of the previous dosage, the primary reason was documented. We also recorded any interruption of benzodiazepine and opioid infusions among control patients.

Patients were weaned from mechanical ventilation at the discretion of the ICU team. To standardize the assessment of a patient's extubation readiness, respiratory therapists evaluated patients daily at their current ventilator settings for the following criteria: awake, adequate cough with suctioning, PaO_2 greater than 60 mm Hg, oxygen saturation greater than or equal to 90%, fraction of inspired oxygen less than or equal to 0.4, positive end expiratory pressure less than or equal to 10 cm H_2O, respiratory rate less than or equal to 35/min, ventilation less than or equal to 15 L/minute, no inotrope or vasopressor infusions, mean arterial pressure greater than 60 mm Hg, and no evidence of acute myocardial ischemia (ie, chest pain, consistent electrocardiogram findings, elevated biomarker levels, or new arrhythmia). If all criteria were met, a 1-hour trial of unassisted breathing was initiated, during which ventilatory support was withdrawn and the patient breathed spontaneously at the previous fraction of inspired oxygen through a t-tube circuit, a tracheostomy mask, or the ventilator circuit with continuous positive airway pressure of 5 cm H_2O. The breathing trial could be terminated if any of the following signs of failure persisted for more than 5 minutes: respiratory rate greater than 35/min, oxygen saturation less than 90%, heart rate greater than 140/min or a change in heart rate of 20% in either direction, systolic blood pressure less than 90 or greater than 180 mm Hg, or increased anxiety and diaphoresis. A breathing trial was successful if the patient could breathe without mechanical assistance for 1 hour. When patients passed a trial of unassisted breathing, respiratory therapists notified a physician with a view to extubation. Research staff recorded reasons for delayed extubation, and daily screening continued until extubation. If the patient did not pass the unassisted breathing trial, the previous ventilator settings were resumed and the screening and breathing trials were repeated daily until extubation. If reintubation occurred within 48 hours, study sedation procedures resumed.

Figure 1. Flow of Patients in the Trial



[a] Other includes 362 patients receiving propofol, 39 with open abdomen or chest, 33 needing ongoing deep sedation (because of a plan to return to the operating room, severe agitation, chronic pain, precarious airway, or hemodynamic instability), and 23 receiving high-frequency ventilation. For the remainder, please see the supplemental eAppendix.

Bedside nurses also assessed daily for delirium with the Intensive Care Delirium Screening Checklist.[19] Patients in both groups were managed "off protocol" during periods of neuromuscular blockade, high-frequency oscillation, or palliative care.

Outcomes

The primary study outcome was time to successful extubation, defined as time from randomization to extubation (or tracheostomy mask) for 48 hours. Secondary outcomes included unintentional device removal (eg, endotracheal tubes), physical restraint use, delirium, neuroimaging in the ICU, tracheostomy, barotrauma, total doses of sedatives and analgesics during mechanical ventilation, organ dysfunction, ICU and hospital lengths of stay, and death. Twice daily, nurses and respiratory therapists recorded their additional clinical workload attributed to study procedures, using a 10-point visual analog scale (VAS), with 1 corresponding to "very easy" and 10 to "difficult." For patients assigned to daily interruption, we measured the proportion of days during which sedation was interrupted.

Statistical Analysis

The sample size estimate assumed a median time to successful extubation of 7 days among controls and a 2-day reduction with the addition of daily interruption (hazard ratio 1.4). We determined that 205 patients per group would provide a power of 90%, with an α level of 5%.

Our primary analysis was based on an intention-to-treat principle whereby all patients were analyzed according to their original group allocation, regardless of whether they received the allocated treatment. We used the Kaplan-Meier method to estimate and plot the distributions of time to successful extubation and an unadjusted Cox proportional hazards model to estimate a hazard ratio. For the time-to-extubation analysis, the event occurred when a patient was extubated within 28 days from randomization and remained extubated for more than 48 hours. Patients who died before extubation or who were transferred to another institution before 28 days were censored at death or transfer. Patients undergoing withdrawal of life support were censored when that decision was made.

We also conducted a per-protocol analysis of patients who had interruptions on more than 75% of eligible study days and 1 prespecified subgroup analysis, according to classification of a patient's ICU admission as medical vs surgical/trauma. We hypothesized that medical patients would benefit more than surgical patients from daily interruption, given their anticipated longer durations of mechanical ventilation and sedative infusions.

Table 1. Baseline Characteristics

Characteristics	No. (%) Protocolized Sedation and Daily Interruption (n = 214)	No. (%) Protocolized Sedation (n = 209)
Age, median (IQR), y	57 (46-70)	60 (49-70)
Women	93 (43.5)	92 (44.0)
Type of admission[a]		
Medical	175 (81.8)	179 (86.1)
Surgical	30 (14.5)	22 (11.0)
Trauma	8 (3.7)	6 (2.9)
BMI, median (IQR)	28.2 (23.8-34.2)	28.6 (25.0-33.2)
APACHE II score, median (IQR)[b]	24.0 (18-28)	23.0 (19-29)
SOFA at day 1, median (IQR)[c]	7 (5-10)	6 (4-9)
Mechanical ventilation, median (IQR), d	2 (1-4)	2 (1-4)
Opioid infusions		
No. (%)	184 (87)	186 (89)
Days of infusion, median (IQR)	1 (1-3)	1 (1-3)
Benzodiazepine infusions		
No. (%)	169 (81)	163 (80)
Days of infusion, median (IQR)	1 (1-3)	1 (1-3)
ICU admission diagnosis[d]		
Bacterial/viral pneumonia	39 (18.2)	47 (22.5)
Nonurinary sepsis	40 (18.7)	36 (17.2)
Other respiratory disease	22 (10.3)	21 (10.0)
Aspiration pneumonia	11 (5.1)	4 (1.9)
COPD	4 (1.9)	10 (4.8)
Postoperative respiratory disease	7 (3.3)	7 (3.3)
Urinary sepsis	3 (1.4)	9 (4.3)
Gastrointestinal perforation/rupture	6 (2.8)	5 (2.4)
Hepatic failure	6 (2.8)	4 (1.9)
Noncardiogenic pulmonary edema	5 (2.3)	4 (1.9)
Other	71 (33.2)	62 (29.7)
Pre-ICU conditions[e]		
Alcohol use	49 (23.0)	44 (21.2)
Tobacco use	48 (22.5)	40 (19.3)
Any psychiatric condition	42 (19.6)	29 (14.4)
Any neurologic condition	33 (15.4)	36 (17.2)
Respiratory disease	17 (8.0)	26 (12.4)
Renal dysfunction	20 (9.4)	16 (7.7)
Habitual drug use	14 (6.6)	10 (4.8)
Liver disease	12 (5.6)	11 (5.3)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

[a] Surgical refers to admission from an operating room or postoperative recovery area.

[b] APACHE II score may range from 0 to 71, with higher scores indicating more severe disease.

[c] SOFA score may range from 0 to 24 points, with higher scores indicating more severe disease.

[d] Diagnoses in this category are mutually exclusive. The 10 most frequent diagnoses are listed, and the remainder are categorized as "other."

[e] Pre-ICU conditions are listed in descending frequency: neurologic condition defined as stroke, seizure disorder, dementia, neuromuscular disease, Parkinson disease, or other neurologic condition; psychiatric condition includes depression, bipolar disorder, schizophrenia, anxiety disorder, or other psychiatric condition; respiratory disease defined as home oxygen, carbon dioxide retention at baseline, or home ventilation; renal dysfunction defined as chronic renal failure with creatinine level greater than 180 µmol/L or chronic dialysis; liver disease defined as Child Pugh Grade C or known esophageal varices; and habitual drug use other than tobacco or alcohol.

Descriptive data are presented as percentages, means with standard deviations for normally distributed variables, and medians with interquartile ranges for nonnormally distributed variables. Sedative and opioid doses are presented as midazolam and fentanyl equivalents, respectively.[20] We converted Richmond Agitation Sedation Scale values to Sedation-Agitation Scale scores for analyses (eTable 3).

To examine between-group differences in categorical variables, we used χ^2 or Fisher exact tests, as appropriate. For dichotomous outcomes, we present relative risks or hazard ratios and their 95% CIs. If all assumptions were met for parametric analyses of the continuous variables, we used a 2-sample *t* test; otherwise, we used a 2-sample Wilcoxon rank sum test. Mean Sedation-Agitation Scale and VAS scores per patient and mean differences with 95% CIs were calculated. All statistical tests were 2-sided and considered statistically significant at $\alpha < .05$. SAS version 9.2 and S-Plus version 7.0 were used for statistical analysis.

An independent data and safety monitoring committee reviewed trial progress and adverse events after randomization of 67, 117, and 292 patients. They also reviewed blinded data for 1 planned interim analysis after enrollment of 211 patients.

RESULTS

Participants

Patients were enrolled in 14 Canadian and 2 US centers. Of 2091 eligible patients, 1661 were not enrolled, primarily because of lack of an authorized decision maker (24.3%), consent refusal (22.3%), or physician refusal (10.8%) (FIGURE 1). Among 430 randomized patients, 7 withdrew consent in the first 3 days of the study and were excluded from the analysis.

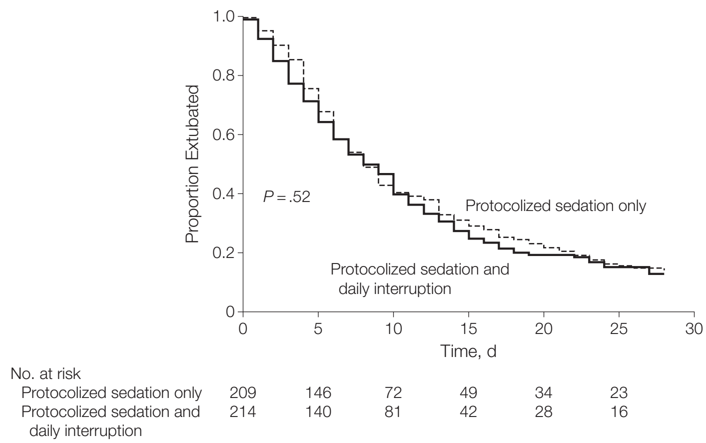
Patient characteristics were similar in the 2 groups (TABLE 1). Eighty-four percent received medical diagnoses. At enrollment, 359 (84.9%) patients were receiving midazolam infusions; 334 (79.0%), fentanyl; 71 (16.5%), morphine; and 41 (9.5%), propofol. Propofol infusions were discontinued at enrollment according to the study protocol.

Outcomes

The median time to successful extubation was 7 days in both groups (hazard ratio, 1.08; 95% CI, 0.86-1.35; *P*=.52) (FIGURE 2). Adjustment for age, body mass index, Acute Physiology and Chronic Health Evaluation II score, and admission type gave consistent results (adjusted hazard ratio, 1.04; 95% CI, 0.83-1.31). Similarly, in a per-protocol analysis of patients who had interruptions on more than 75% of eligible study days, there was no difference in time to successful extubation between groups. There were no between-group differences in ICU or hospital lengths of stay, hospital mortality, rates of unintentional device removal, delirium, ICU neuroimaging, barotrauma, tracheostomy, or organ dysfunction (TABLE 2).

TABLE 3 summarizes data related to sedative and opioid administration. Pa-

Figure 2. Kaplan-Meier Curves for Time to Successful Extubation



P value calculated from log-rank statistic.

Table 2. Patient Outcomes

	Protocolized Sedation and Interruption (n = 214)	Protocolized Sedation (n = 209)	Measure of Effect (95% CI)	*P* Value
Days to successful extubation, median (IQR)[a]	7 (4 to 13)	7 (3 to 12)	HR, 1.08 (0.86 to 1.35)	.52
Days in ICU,[b] median (IQR)[a]	10 (5 to 17)	10 (6 to 20)	Mean difference, −3.17 (−6.89 to 0.55)	.36
Days in hospital, median (IQR)[a]	20 (10 to 36)	20 (10 to 48)	Mean difference, −8.2 (−17.64 to 1.19)	.42
ICU mortality, No. (%)	50 (23.4)	52 (24.9)	RR, 0.94 (0.67 to 1.32)	.72
Hospital mortality, No. (%)	63 (29.6)	63 (30.1)	RR, 0.98 (0.73 to 1.31)	.89
ICU-acquired organ failure and supportive therapies, No. (%)				
ARDS	89 (41.8)	78 (37.3)	RR, 1.12 (0.88 to 1.42)	.35
Vasopressors/inotropes	121 (56.8)	130 (62.2)	RR, 0.91 (0.78 to 1.07)	.26
Renal replacement	50 (23.5)	37 (17.7)	RR, 1.33 (0.91 to 1.94)	.14
Neuromuscular blockade	20 (9.7)	21 (10.2)	RR, 0.94 (0.53 to 1.69)	.84
Unintentional device removal, No. (%)				
Gastric tube	18 (8.5)	29 (13.9)	RR, 0.61 (0.35 to 1.07)	.08
Endotracheal tube	10 (4.7)	12 (5.8)	RR, 0.82 (0.36 to 1.84)	.64
Urinary catheter	6 (2.8)	13 (6.2)	RR, 0.45 (0.17 to 1.17)	.09
Central venous or arterial catheter	17 (8.0)	10 (4.8)	RR, 1.68 (0.79 to 3.57)	.18
Neuroimaging in ICU, No. (%)				
Computed tomography	29 (13.6)	33 (15.9)	RR, 0.85 (0.54 to 1.35)	.53
Magnetic resonance imaging	9 (4.2)	7 (3.4)	RR, 1.25 (0.47 to 3.29)	.64
Physical restraint				
Patients, No. (%)	166 (76.4)	166 (79.4)	RR, 0.96 (0.87 to 1.07)	.46
Study days, mean (SD)	4.71 (5.67)	5.36 (6.14)	Mean difference, −0.70 (−1.84 to 0.43)	
Delirium, No (%)[b]	113 (53.3)	113 (54.1)	RR, 0.98 (0.82 to 1.17)	.83
Reintubation within 48 h, No. (%)	12 (5.6)	16 (7.7)	RR, 0.73 (0.35 to 1.50)	.39
Tracheostomy, No (%)	49 (23.2)	54 (26.3)	RR, 0.88 (0.63 to 1.23)	.46

Abbreviations: ARDS, acute respiratory distress syndrome; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; RR, relative risk.
[a] Analyses are measured from enrollment.
[b] Patients who ever had a score of 4 or more on the Intensive Care Screening Delirium Checklist.[19]

tients in the interruption group received higher mean daily benzodiazepine doses (102 vs 82 mg/d midazolam equivalents; median, 8 [IQR, 0-86 vs median, 0 [IQR, 0-50]; $P=.04$) and a greater number of boluses per day (mean, 0.253 vs 0.177; $P=.007$). They also received higher daily opioid doses (1780 vs 1070 μg/d fentanyl equivalents; $P<.001$), both as infusion and boluses, and a greater number of opioid boluses per day (mean, 2.18 vs 1.79; $P<.001$).

Protocol Adherence and Clinician Workload

Adherence with daily interruption was 72.2% of all eligible study days for an average patient and 85.6% for all eligible patient-days. Fifty-three percent of patients missed at least 1 daily interruption, and 6 patients missed every scheduled interruption. The most common reasons for noninterruption were related to mechanical ventilation (38.5%), agitation or pain (16.3%), and first day of study (14.6%) (eTable 4). Infusions were reinitiated at a dose exceeding 50% of the previous dose for 30 patients (14.1%) on a total of 47 days. Propofol infusions were administered to 28 patients, accounting for 3.0% of study days.

In the control group, 34 patients (16.4%) had infusions interrupted on 54 occasions, accounting for 2.3% of study days. Forty patients receiving propofol infusions accounted for 2.1% of study days.

Overall, mean Sedation-Agitation Scale scores per patient were similar in the 2 groups (3.28 [95% CI, 2.92 to 3.85] in the interruption group vs 3.23 in controls; 95% CI, 3.0 to 3.71, respectively; mean difference, 0.05; 95% CI, −0.10 to 0.19; $P=.52$). However, nurse workload was significantly higher in the interruption group (mean VAS score, 4.22 vs 3.80; 95% CI, 3.30 to 5.0 vs 2.98 to 4.40; mean difference, 0.41; 95% CI, 0.17 to 0.66; $P=.001$). Respiratory therapist workload was similar in the 2 groups (mean VAS score, 3.69 in the interruption group vs 3.61 in controls; 95% CI, 2.62 to 4.67 vs 2.70 to 4.33, respectively; mean difference, 0.08; 95% CI, −0.20 to 0.36; $P=.57$). Adherence with the performance of spontaneous breathing trials and with extubation after a successful spontaneous breathing trial was similar in the 2 groups (eTable 5).

Subgroup Analysis

Contrary to our hypothesis, surgical and trauma patients randomized to daily interruption had significantly shorter time to successful extubation than those randomized to protocolized sedation alone (6 vs 13 days; hazard ratio 2.55; 95% CI, 1.40 to 4.55), whereas there was no difference among medical patients (9 vs 8 days; hazard ratio, 0.92; 95% CI, 0.72 to 1.18; P value for the interaction=.004). Baseline characteristics and outcomes of the surgical/trauma patients by randomization group are presented in the supplementary appendix (eTables 6 to 8).

Table 3. Benzodiazepine and Opioid Administration[a]

	Protocolized Sedation and Interruption (n = 214)	Protocolized Sedation (n = 209)	Measure of Effect, Mean Difference (95% CI)	P Value
Midazolam equivalents				
Total dose/patient, mg	1087 (4297) 222 (50 to 734)	1038 (4592) 237 (57 to 599)	48.4 (−804.4 to 901.2)	.91
Dose/patient/d, mg	102 (326) 8 (0 to 86)	82 (287) 0 (0 to 50)	19.23 (2.37 to 37.07)	.04
Dose/patient/d, infusion, mg	101 (325) 6 (0 to 86)	82 (287) 0 (0 to 50)	19.22 (1.92 to 36.53)	.03
Dose/patient/d, bolus, mg	0.99 (5.9) 0 (0 to 0)	0.49 (2.65) 0 (0 to 0)	0.50 (0.23 to 0.76)	<.001
Infusion, d	5.73 (6.42) 4 (2 to 7)	5.58 (5.91) 4 (2 to 7)	0.15 (−1.04 to 1.33)	.81
Boluses/d, No.	0.253 (1.145) 0 (0 to 0)	0.177 (0.808) 0 (0 to 0)	0.077 (0.020 to 0.134)	.007
Fentanyl equivalents				
Total dose/patient, μg	18 997 (59 928) 5286 (1512 to 16 437)	13 532 (23 219) 5936 (2056 to 15 236)	5464.6 (−3236.0 to 14 165.2)	.22
Dose/patient/d, μg	1780 (4135) 550 (50 to 1850)	1070 (2066) 260 (0 to 1400)	709.3 (522.0 to 897.7)	<.001
Dose/patient/d, infusion, μg	1664 (4070) 420 (0 to 1725)	984 (2002) 80 (0 to 1260)	679.7 (495.3 to 864.1)	<.001
Dose/patient/d bolus, μg	116 (215) 0 (0 to 100)	86 (169) 40 (0 to 150)	30.13 (19.15 to 41.11)	<.001
Infusion, d	6.44 (6.86) 5 (2 to 9)	6.61 (6.20) 5 (3 to 9)	−0.17 (−1.42 to 1.09)	.79
Boluses/d, No.	2.18 (2.87) 1 (0 to 4)	1.79 (2.67) 0 (0 to 3)	0.395 (0.239 to 0.551)	<.001

Conversion factors: For conversion of lorazepam to midazolam, 1 mg midazolam=0.5 mg lorazepam. For conversion of opioids to fentanyl equivalents, 10 mg morphine=2 mg hydromorphone=0.1 mg fentanyl.
[a] Doses are presented as mean (SD) in the first row and median (interquartile range) in the second row.

COMMENT

In this multicenter randomized trial, we found that among mechanically ventilated patients receiving continuous sedation, the combined use of protocolized sedation and daily sedative interruption did not improve on the clinical outcomes observed with protocolized sedation alone. Patients in the daily interruption group received more opioids and benzodiazepines, and self-assessed nursing workload was higher for patients in the daily interruption group than the control group; however, these findings are of uncertain clinical importance.

Our results contrast with those of 2 earlier trials supporting daily interruption of sedative infusions in mechanically ventilated adults.[5,21] In the original single-center trial comparing daily interruption with usual care in 128 mechanically ventilated patients receiving sedative and opioid infusions, daily interruption was associated with shorter mechanical ventilation and ICU stay and less neuroimaging.[5] In that trial, research personnel were always present for sedation interruption and had decisional authority regarding resumption of infusions. In a 4-center study, investigators randomized 336 ICU patients receiving ventilation to daily interruption (with up to 4 hours of monitoring by research personnel) or to usual care without a sedation protocol or additional monitoring.[21] Patients assigned to daily interruption had shorter durations of mechanical ventilation and ICU and hospital stay; however, unintentional extubation occurred more frequently.

Our study is distinct from these earlier trials. First, we compared a sedation strategy adding daily interruption to a control group strategy of protocolized sedation that targeted light sedation, which is likely superior to "usual care" of an earlier era. Second, in this pragmatic trial, sedation was not directed by research staff but was managed by bedside ICU staff with their usual patient assignments, according to well-tested study protocols. Third, the multicenter design reflects actual practice in ICUs with variable workloads and ICU staffing models. Finally, we enrolled surgical patients in addition to medical patients; in this small prespecified subgroup, daily interruption was unexpectedly associated with shorter time to extubation.

The potential benefit of nurse-directed sedation titration protocols to minimize sedation is recognized,[6] although early trials testing this strategy have been conflicting. A nurse-directed sedation protocol compared with usual care among 322 medical patients resulted in shorter durations of mechanical ventilation and ICU and hospital stay.[4] In contrast, no clinical benefits were found with a different nurse-directed protocol in another center, potentially related to advanced-practice nurses managing ventilators who were already routinely using sedation-minimization strategies.[7] The effectiveness of any new intervention to minimize sedation likely depends on the local usual care.

In this trial, adherence with sedation interruption of 72% compares favorably with that achieved in previous trials (ranging from 25% to 70%) when research personnel were not managing patient sedation.[16,22,23] Reluctance to interrupt sedation infusions is expressed clearly in clinician surveys and practice audits.[11,12,24] Common clinical concerns include the potential for patient discomfort, respiratory distress, patient safety, and additional workload.[13,14,25,26] These reservations may reflect our unexpected findings of greater opioid and benzodiazepine doses, more bolus doses, and greater nurse workload among patients in the daily interruption group.

Strengths of this trial, in addition to the multicenter pragmatic design, include a broad mix of patients and an assessment of perceived additional nursing workload associated with daily sedation interruption. This trial also has limitations. Blinding of caregivers was not feasible, we did not screen for drug withdrawal, and our results may not be applicable to patients receiving shorter-acting agents such as propofol or dexmedetomidine or to patients requiring deeper levels of sedation.

In conclusion, for critically ill patients receiving mechanical ventilation, when nurses implemented a sedation protocol that targeted light sedation, daily sedation interruption did not reduce the duration of mechanical ventilation, offered no additional benefits for patients, and may have increased both sedation and analgesic use and nurse workload.

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Supplementary Online Content

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eAppendix. SLEAP clinical collaborators and SLEAP statistical analysis plan
eFigure 1. Protocol for nursing management of analgesia and sedation during mechanical ventilation for patients in the protocolized sedation group, who were receiving fentanyl.
eFigure 2. Protocol for nursing management of analgesia and sedation during mechanical ventilation for patients in the daily interruption group, who were receiving receiving morphine
eTable 1. Sedation-Agitation Scale (SAS)
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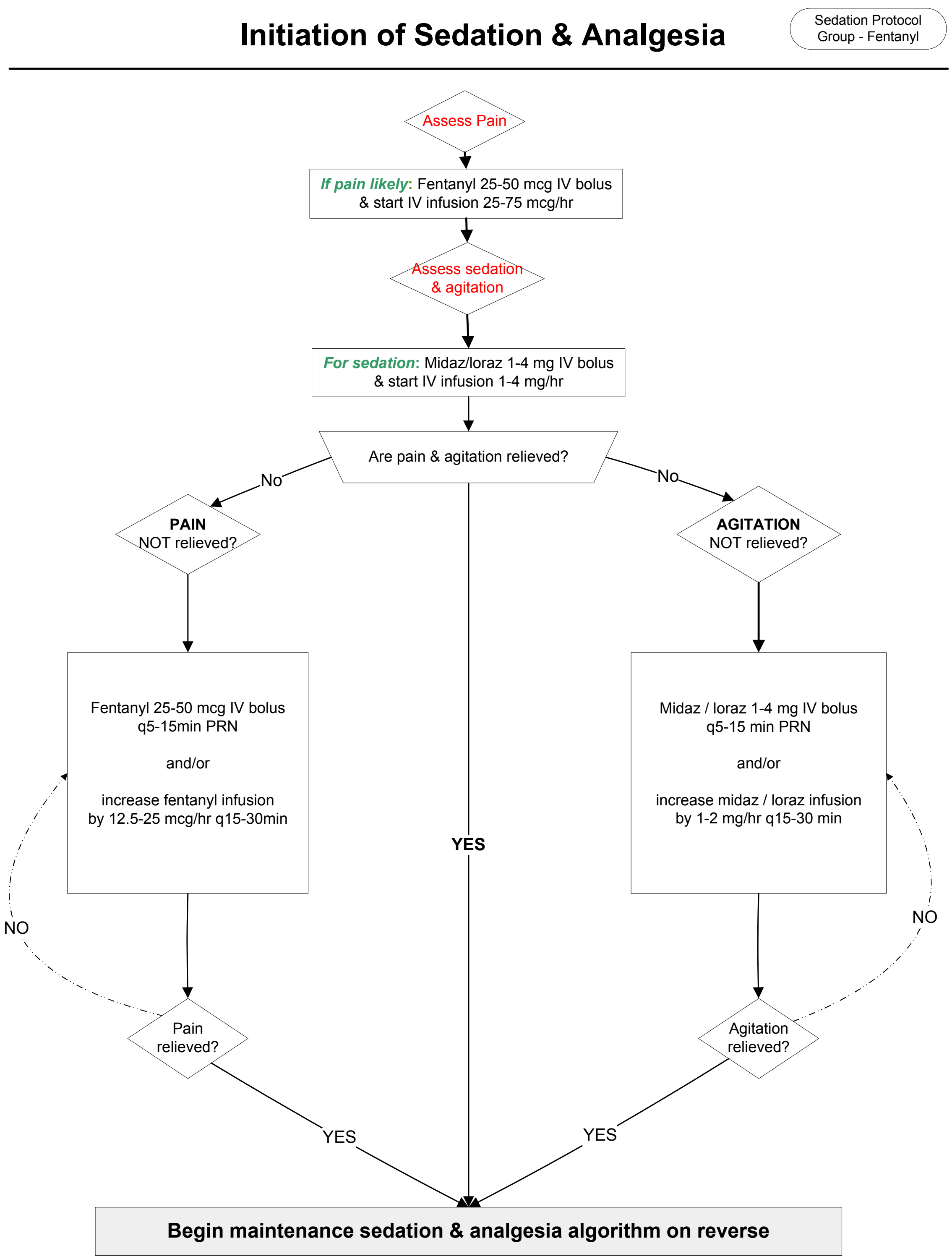
eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Protocol for nursing management of analgesia and sedation during mechanical ventilation for patients in the protocolized sedation group, who were receiving fentanyl. Separate protocols were provided for patients receiving morphine or hydromorphone. Opioid and benzodiazepine infusions were initiated using the first page of the protocol; and managed thereafter using the second page of the protocol. Midaz= midazolam, loraz=lorazepam; midazolam or lorazepam could be administered within the protocol.



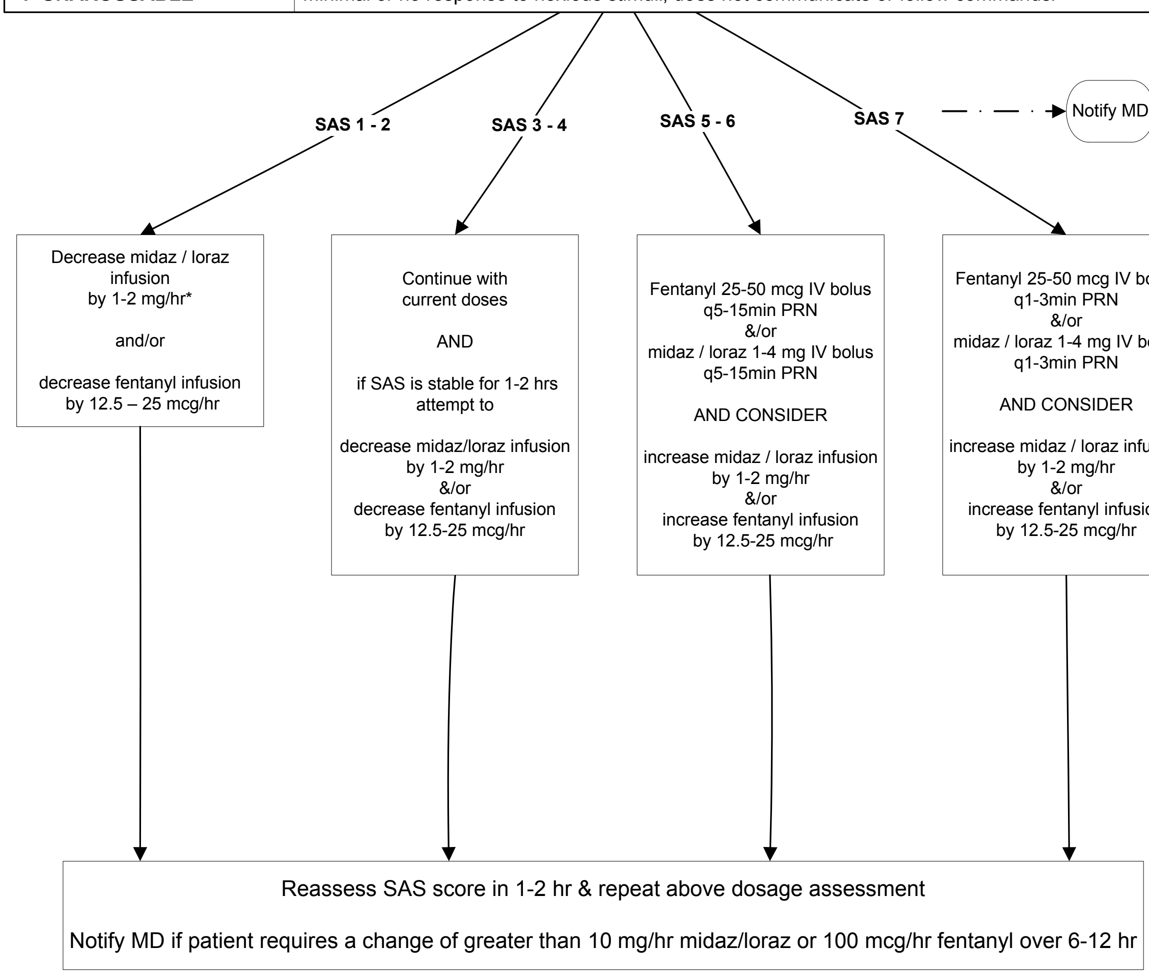
Maintenance Sedation & Analgesia Algorithm

Sedation Protocol Group - Fentanyl

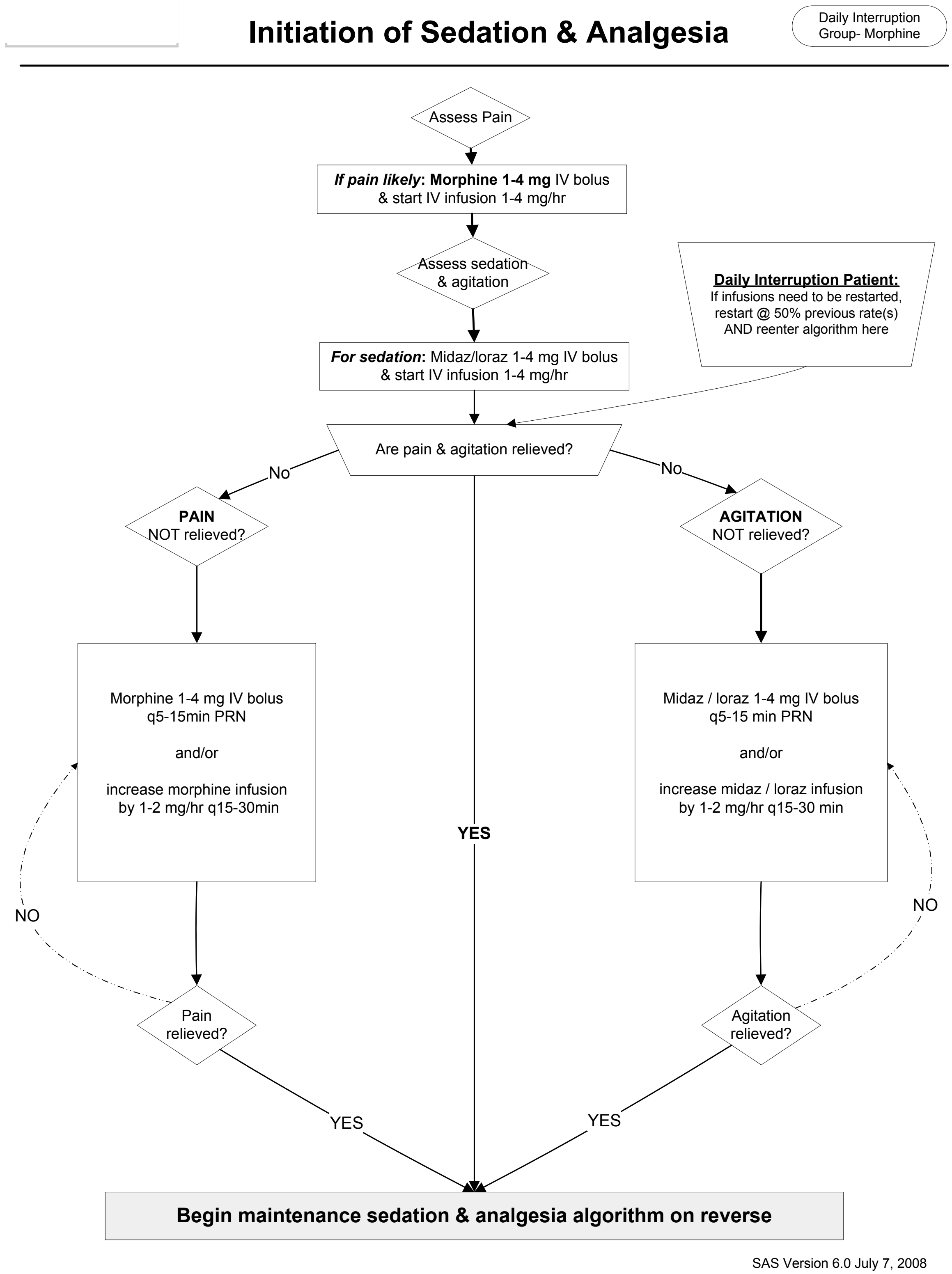
1. No minimum or maximum doses.
2. Patients do not have to receive both midaz/loraz AND fentanyl, assess pain and anxiety independently.
3. Use bolus doses as needed (no minimum and no maximum number of doses).

What is the current SAS score?

7 DANGEROUS AGITATION	Pulls at ETT, tries to remove catheters, climbs over bed rails, strikes at staff, thrashes side-to-side.
6 VERY AGITATED	Does not calm, despite frequent verbal reminders; requires verbal reminding of limits, physical restraints; bites ETT.
5 AGITATED	Anxious or mildly agitated, attempts to sit up, calms down to verbal instructions.
4 CALM & COOPERATIVE	Calm, awakens easily, follow commands.
3 SEDATED	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands.
2 VERY SEDATED	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously.
1 UNAROUSABLE	Minimal or no response to noxious stimuli, does not communicate or follow commands.



*NOTE: if 2 mg/hr or less of midaz/loraz, may decrease by 0.5 – 1mg/hr as per SAS score eFigure 2. Protocol for nursing management of analgesia and sedation during mechanical ventilation for patients in the daily interruption group, who were receiving receiving morphine. Separate protocols were provided for patients receiving fentanyl or hydromorphone. Opioid and benzodiazepine infusions were initiated using the first page of the protocol; and managed thereafter using the second page of the protocol. Midaz=midazolam, loraz=lorazepam; midazolam or lorazepam could be administered within the protocol.



Maintenance Sedation & Analgesia Algorithm

Daily Interruption Group- Morphine

1. No minimum or maximum doses.
2. Patients do not have to receive both midaz/loraz AND morphine, assess pain and anxiety independently.
3. Use bolus doses as needed (no minimum and no maximum number of doses).

What is the current SAS score?

7 DANGEROUS AGITATION	Pulls at ETT, tries to remove catheters, climbs over bed rails, strikes at staff, thrashes side-to-side.
6 VERY AGITATED	Does not calm, despite frequent verbal reminders; requires verbal reminding of limits, physical restraints; bites ETT.
5 AGITATED	Anxious or mildly agitated, attempts to sit up, calms down to verbal instructions.
4 CALM & COOPERATIVE	Calm, awakens easily, follow commands.
3 SEDATED	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands.
2 VERY SEDATED	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously.
1 UNAROUSABLE	Minimal or no response to noxious stimuli, does not communicate or follow commands.

SAS 1 - 2

Decrease midaz / loraz infusion by 1-2 mg/hr*

and/or

decrease morphine infusion by 1-2 mg/hr*

SAS 3 - 4

Continue with current doses

AND

if SAS is stable for 1-2 hrs attempt to

decrease morphine infusion by 1-2 mg/hr
&/or
decrease midaz/loraz infusion by 1-2 mg/hr

SAS 5 - 6

Morphine 1-4 mg IV bolus q5-15min PRN
&/or
midaz/loraz 1-4 mg IV bolus q5-15min PRN

AND CONSIDER

increase morphine infusion by 1-2 mg/hr
&/or
increase midaz/loraz infusion by 1-2 mg/hr

SAS 7 → Notify MD

Morphine 1-4 mg IV bolus q1-3min PRN
&/or
midaz/loraz 1-4 mg IV bolus q1-3min PRN

AND CONSIDER

increase morphine infusion by 1-2 mg/hr
&/or
increase midaz/loraz infusion by 1-2 mg/hr

Reassess SAS score in 1-2 hr & repeat above dosage assessment

Notify MD if patient requires a change of greater than 10 mg/hr midaz/loraz or morphine over 6-12 hr

*NOTE: if patient on 2 mg/hr or less, may decrease by 0.5 - 1 mg/hr as per SAS score

eTable 1. Sedation-Agitation Scale (SAS)[1]

7	Dangerous agitation	Pulling ET tube, trying to remove catheters, climbing bed rail, striking staff, thrashing
6	Very agitated	Not calm, despite verbal reminding; requires physical restraints, biting ET tube
5	Agitated	Mildly agitated, attempting to sit up, calms with verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows command
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate nor follow commands

eTable 2. Richmond Agitation Sedation Scale (RASS)[2]

+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive, vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (≥ 10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (< 10 seconds)
-3	Moderate Sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

eTable 3. RASS/SAS Conversions

RASS	SAS
+4	7
+3	6
+2	5
+1	5
0	4
-1	4
-2	3
-3	3
-4	2
-5	1

eTable 4. Reasons for non-interruption of infusions in the daily interruption group

Reason	n	%
Ventilation	124	38.7
Agitation/pain	54	16.9
Day 1 of study	44	13.8
Missed	34	10.6
Hemodynamics	18	5.6
Airway hemorrhage	13	4.1
Physician request	13	4.1
Palliative	9	2.8
Other (no reason, unable to tolerate, procedures)	11	3.4

eTable 5. Compliance with Spontaneous Breathing Trial (SBT) and extubation

	Protocolized Sedation and Daily Interruption	Protocolized Sedation	p-value
Days SBT not done, when criteria met, N (%)	109 (17.61)	146 (17.61)	0.999
Days not extubated, when passed SBT, N (%)	215 (59.56)	298 (64.09)	0.183
Days extubated, after first passed SBT, N (%)	67 (44.97)	70 (46.36)	0.8089
Days extubated, after second passed SBT, N (%)	42 (52.50)	39 (45.35)	0.357

Surgical/Trauma subgroup

In the small pre-specified surgical/trauma subgroup, daily interruption was unexpectedly associated with shorter time to extubation. This subgroup fulfilled the following credibility criteria: the variable was a baseline characteristic, the hypothesis was specified a priori, the subgroup analysis was one of three hypotheses tested, and the effect was suggested by a within-study comparison[3]. However, the observed subgroup effect was inconsistent with our pre-specified direction, the subgroup was small (N=68), and there were baseline imbalances. Given these reservations, we are unable to make any firm conclusions regarding the use of daily interruption in surgical patients, and further large trials in this population are necessary. The tables below show baseline characteristics (eTable 6), patient outcomes (eTable 7), and benzodiazepine and opioid administration (eTable 7) in the surgical/trauma patients, by group.

eTable 6. Baseline Characteristics of Surgical/Trauma patients, by randomization group

Characteristics	Protocolized Sedation and Daily Interruption N=39	Protocolized Sedation N=29	p-value
Age, years	48 (39,64)	65 (56,76)	0.0082
Female Sex – no. (%)	17 (43.6)	8 (27.6)	0.1759
Type of admission - no. (%)[a]			0.9858
Surgical	31 (79.5)	23 (79.3)	
Trauma	8 (20.5)	6 (20.7)	
Body-mass index, kg/m^2 [b]	28.3 (25.3,33.6)	27.9 (26.3,30.5)	0.6270
APACHE II score[c]	21 (16,27)	26 (20,32)	0.0370
SOFA (at day 1) [d]	7 (3,10)	7 (3,9)	0.9950
Days of mechanical ventilation	2 (1,5)	3 (1,4)	0.6481
Opioid infusions			
No. (%)	37 (94.9)	28 (96.6)	1.0
Days of infusion	2 (1,4)	2 (1,3)	0.9674
Benzodiazepine infusions			
No. (%)	24 (63.2)	15 (60)	0.8006
Days of infusion	1 (1,2)	1 (0,3)	0.5175
ICU[e] admission diagnosis - no. (%)[f]			
Bacterial/viral pneumonia	0 (0.0)	0 (0.0)	NA
Non-urinary sepsis	0 (0.0)	0 (0.0)	NA
Other respiratory disease	0 (0.0)	0 (0.0)	NA
Aspiration pneumonia	0(0.0)	0 (0.0)	NA
COPD[g]	0 (0.0)	0 (0.0)	NA
Post operative respiratory disease	7 (18.0)	7 (24.1)	0.5325
Urinary sepsis	0 (0.0)	0 (0.0)	NA
Gastrointestinal perforation/rupture	6 (15.4)	5 (17.2)	1.0
Hepatic failure	0 (0.0)	0 (0.0)	NA
Non-cardiogenic pulmonary edema	0 (0.0)	0 (0.0)	NA
Pre-ICU conditions - no. (%)[h]			
Alcohol use	8 (32.0)	9 (47.4)	0.2997
Tobacco use	10 (34.5)	4 (17.4)	0.1676
Any psychiatric condition	6 (15.4)	3 (10.3)	0.7225
Any neurological condition	2 (5.1)	4 (13.8)	0.3898
Respiratory disease	2 (5.1)	4 (13.8)	0.3898
Renal dysfunction	0 (0.0)	0 (0.0)	NA
Habitual drug use	3 (12.0)	1 (6.2)	1.0
Liver disease	1 (2.6)	0 (0.0)	1.0

This table shows baseline characteristics of the 2 groups.
Data presented as median (IQR) or no. (%).
[a]Surgical refers to admission from an operating room or postoperative recovery area.
[b]The body-mass index is the weight in kilograms divided by the square of the height in meters.
[c]APACHE (Acute Physiology and Chronic Health Evaluation) II Score may range from 0 to 71, with higher scores indicating more severe disease.
[d]Sequential Organ Failure Assessment (SOFA) score may range from 0 to 24 points, with higher scores indicating more severe disease.
[e]ICU = Intensive Care Unit
[f]Diagnoses in this category are mutually exclusive. The 10 most frequent diagnoses are listed, and the remainder are categorized as "Other".
[g]COPD = Chronic obstructive pulmonary disease
[h]Pre-ICU conditions listed in descending frequency: neurological condition defined as stroke, seizure disorder, dementia, neuromuscular disease, Parkinson's disease, or other neurological condition; psychiatric condition includes depression, bipolar disorder, schizophrenia, anxiety disorder, or other psychiatric condition; respiratory disease defined as home oxygen, CO_2 retention at baseline, or home ventilation; renal dysfunction defined as chronic renal failure with creatinine > 180 umol/L, or chronic dialysis; liver disease defined as Child Pugh Grade C or known esophageal varices; habitual drug use other than tobacco or alcohol.

eTable 7. Patient Outcomes in Surgical/Trauma patients, by randomization group

	Protocolized sedation and interruption N=39	Protocolized sedation N=29	Measure of effect	P value
Days to successful extubation, median (IQR) [a]	6 (3,12)	13 (5,20)	HR:2.55 (1.4,4.55)	0.0015
Days in ICU[b], median (IQR)	10 (7,21)	22 (15,30)	MD:-17.7 (-32.0,-3.4)	0.0170
Days in hospital, median (IQR)	32 (18,52)	39 (21,67)	MD:-12.6 (-49.7,24.4)	0.4992
ICU mortality - no.(%)	2 (5.1)	3 (10.3)	RR:0.50 (0.09,2.78)	0.6441
Hospital mortality - no.(%)	4 (10.3)	6 (20.7)	RR:0.50 (0.15,1.60)	0.3050
ICU-acquired organ failure and supportive therapies - no.(%)				
ARDS[c]	5 (13.2)	9 (31.0)	RR:0.42 (0.16,1.13)	0.0745
Vasopressors/inotropes	22 (57.9)	20 (69.0)	RR:0.84 (0.58,1.21)	0.3532
Renal replacement	7 (18.4)	3 (10.3)	RR:1.78 (0.50,6.30)	0.4952
Neuromuscular blockade	4 (10.8)	3 (10.3)	RR:1.04 (0.25,4.31)	1.00
Accidental device removal - no.(%)				
Gastric tube	4 (10.5)	4 (13.8)	RR:0.76 (0.21,2.80)	0.7188
Endotracheal tube	1 (2.6)	0 (0.0)	NA	1.00
Urinary catheter	1 (2.6)	1 (2.6)	RR:0.76 (0.05,11.69)	1.00
Central venous or arterial catheter	4 (10.5)	1 (3.4)	RR:3.05 (0.36,25.88)	0.3794
Neuro-imaging in ICU - no.(%)				
Computed tomography	6 (15.8)	5 (17.2)	RR:0.92 (0.31,2.71)	1.00
Magnetic resonance imaging	1 (2.6)	3 (10.3)	RR:0.25 (0.03,2.32)	0.3084
Physical restraint				
Patients - no.(%)	27 (71.1)	22 (75.9)	RR:0.94 (0.70,1.25)	0.6599
Study days, mean (SD)	4.76 (5.04)	4.34 (4.68)	MD:0.42 (-1.99,2.83)	0.7297
Delirium - no. (%)[d]	26 (68.4)	22 (75.9)	RR:0.90 (0.67,1.22)	0.5032
Reintubation within 48 hours - no.(%)	1 (2.6)	3 (10.3)	RR;0.25 (0.03,2.26)	0.3051
Tracheostomy - no.(%)	13 (34.2)	14 (48.3)	RR:0.71 (0.40,1.27)	0.2448

This table shows primary and secondary outcomes of the 2 groups.
Data are presented as no. (%), mean (standard deviation, SD), or median (IQR, interquartile range)
HR = hazard ratio, Mean Diff = mean difference, RR = relative risk
[a]'Time-to' analyses are measured from the time of enrolment
[b]ICU = Intensive Care Unit
[c]ARDS = Acute respiratory distress syndrome
[d]Patients who ever had a score of 4 or more on the Intensive Care Screening Delirium Checklist[19]

eTable 8. Benzodiazepine and Opioid Administration in Surgical/Trauma patients, by randomization group

	Protocolized sedation and interruption N=39	Protocolized sedation N=29	Measure of effect Mean Diff (95% CI)	P value
Midazolam equivalents				
Total dose/pt (mg)	434.2 (1231.3) 86.0 (1, 435)	284.3 (493.7) 148.6 (32.5, 274.5)	149.8 (-291.4,591.0)	0.4985
Dose/pt/day (mg)	52.9 (123.7) 3.5 (0, 50)	17.5 (50.5) 0 (0, 2)	35.3 (20.8,49.8)	<0.0001
Dose/pt/day, infusion (mg)	52.5 (123.7) 3 (0, 49.5)	17.3 (50.4) 0 (0, 0)	35.2 (20.7,49.7)	<0.0001
Dose/pt/day, bolus (mg)	0.38 (2.1) 0 (0, 0)	0.25 (1.5) 0 (0, 0)	0.13 (-0.14,0.40)	0.3474
Infusion, days	4.4 (4.4) 3.5 (0, 6)	4.0 (3.6) 3 (1, 5)	0.4 (-1.6,2.4)	0.6716
Boluses/day, no	0.13 (0.71) 0 (0, 0)	0.11 (0.59) 0 (0, 0)	0.02 (-0.07,0.12)	0.6538
Fentanyl equivalents				
Total dose/pt (mcg)	15410 (30322) 4150 (2475, 12388)	11356 (11566) 7560 (3990, 14765)	4055 (-6725,14835)	0.4535
Dose/pt/day (mcg)	1877 (3394) 562 (100, 1878)	701 (1221) 75 (0, 750)	1176 (782,1570)	<0.0001
Dose/pt/day, infusion (mcg)	1770 (3401) 500 (0, 1802.5)	616 (1169) 0 (0, 650)	1154 (761,1547)	<0.0001
Dose/pt/day, bolus (mcg)	107 (142) 50 (0,155)	84 (166) 20 (0, 100)	22 (0.4,44)	0.0462
Infusion, days	5.1 (4.1) 4 (2, 6)	6.1 (3.7) 6 (3, 8)	-0.96 (-2.9,0.97)	0.3240
Boluses/day, no.	2.4 (2.8) 1 (0, 4)	2.0 (2.9) 1 (0, 3)	0.4 (-0.03,0.80)	0.0694

This table shows doses of sedatives and opioids administered to patients in both groups.
Doses presented as mean (SD), and median (IQR). Mean diff = mean difference
For conversion of lorazepam to midazolam, 1 mg midazolam = 0.5 mg lorazepam
For conversion of opioids to fentanyl equivalents, 10 mg morphine = 2 mg hydromorphone = 0.1 mg fentanyl

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