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Effect of Protocolized Sedation on Clinical Outcomes in Mechanically Ventilated Intensive Care Unit Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Objective: To assess the effects of protocolized sedation (algorithm or daily interruption) compared with usual care without protocolized sedation on clinical outcomes in mechanically ventilated adult intensive care unit (ICU) patients via a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: We searched Ovid MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov from their inception to February 28, 2013. A random-effects model was used to synthesize risk ratios (RRs) and weighted mean differences (WMDs).

Results: Of 4782 records screened, 6 RCTs including 1243 patients met the inclusion criteria. Protocolized sedation was associated with significant reductions in overall mortality (RR, 0.85; 95% CI, 0.74 to 0.97; $P=.02$; number needed to treat, 20; $P=.11$), ICU length of stay (WMD, -1.73 days; 95% CI, -3.32 to -0.14 days; $P=.03$), hospital length of stay (WMD, -3.55 days; 95% CI, -5.98 to -1.12 days; $P=.004$), and tracheostomy (RR, 0.69; 95% CI, 0.50 to 0.96; $P=.03$; number needed to treat, 16.6; $P=.04$; 5 RCTs) compared with usual care. Protocolized sedation produced no significant differences in duration of mechanical ventilation (WMD, -1.04 days; 95% CI, -2.54 to 0.47 days; $P=.18$), reintubation (RR, 0.78; 95% CI, 0.52 to 1.15; $P=.21$; 3 RCTs), and self-extubation (RR, 1.49; 95% CI, 0.46 to 4.82; $P=.51$; 4 RCTs) compared with usual care. Included studies did not report delirium incidence.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>.

Data Previously Presented: An outdated abstract of this paper titled “Do Sedation Protocols Decrease Mortality in the ICU: A Systematic Review & Meta-analysis” was presented at the 43rd Critical Care Congress in San Francisco, CA.

Conclusion: In mechanically ventilated adults in closed, nonspecialty ICUs, protocolized sedation seems to decrease overall mortality (15%), ICU and hospital lengths of stay (1.73 and 3.55 days, respectively), and tracheostomy (31%) compared with usual care without protocolized sedation.

More than 790,000 patients require mechanical ventilation each year in the United States.¹ Sedation is commonly used in the intensive care unit (ICU) to facilitate the use of mechanical ventilation and mitigate the symptoms of pain and agitation.² However, there is considerable variation in what constitutes optimal sedation; consequently, variation in sedation practice may lead to undersedation or, more likely, oversedation.³ Inappropriate sedation, for example, oversedation, is associated with adverse clinical outcomes, including a longer duration of mechanical ventilation, prolonged ICU length of stay (LOS), episodes of delirium, and increased mortality.^{4,5}

Protocolized sedation (algorithm or daily interruption) intends to reduce variation in clinical care by reducing subjectivity in clinical decision making, thus replacing ICU staff discretion with evidence-based protocols that standardize sedation management.⁶ In 1999 and 2000, 2 landmark randomized controlled trials (RCTs) by Brook et al⁷ and Kress et al,⁸ respectively, suggested that protocolized (standardized) sedation significantly improved several clinical outcomes, including duration of mechanical ventilation, compared with usual care without protocolized (standardized) sedation. Between 2008 to 2011, 4 more RCTs^{9–12} were published; chief among them was the study by Girard et al,¹¹ which reported more ventilator-free days; however, most studies had varying, and sometimes conflicting, results for common clinical outcomes reported across studies (eg, ICU LOS). To our knowledge, a quantitative summary of RCTs examining standardized vs nonstandardized discretionary sedation management does not exist.

We conducted a systematic review and meta-analysis of the current body of literature to summarize RCTs that evaluated protocolized sedation vs usual care without protocolized sedation in mechanically ventilated adult ICU patients and that reported 1 or more of the prespecified clinical outcomes.

METHODS

This systematic review and meta-analysis was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.¹³

Study Eligibility Criteria

We included RCTs that studied the effect of protocolized sedation vs usual care without protocolized sedation in mechanically ventilated adult (> 18 years old) ICU patients and reported 1 or more of the following clinical outcomes: mortality, duration of mechanical ventilation, ICU or hospital LOS, and incidence of tracheostomy, reintubation, self-extubation, and delirium. We defined protocolized sedation as either of the following 2 standardized sedation management strategies used to treat ICU patients: a sedation algorithm or a daily sedation interruption. We defined usual care as nonprotocolized, discretion-based sedation management (eg, clinician-directed sedation).

Search Methods

We searched the following databases from inception through February 28, 2013: Ovid MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov. We used Cochrane's Highly Sensitive Search Strategy for RCTs in MEDLINE.¹⁴ No search had language or other limitations. One reviewer (M.A.M.) excluded duplicate articles and clearly ineligible studies based on title and abstract. Two reviewers (M.A.M. and A.G.V.) independently screened the remaining articles in full text to determine review eligibility based on the inclusion criteria. In all cases, a third reviewer (A.K.), or group consensus, resolved disagreements. Last, the reference section of included studies was searched. The Supplemental Appendix (available online at <http://www.mayoclinicproceedings.org>) provides full details of the Ovid MEDLINE search strategy.

Data Extraction

Two reviewers (M.A.M. and A.G.V.) independently conducted unblinded data extraction for each included study using standardized pro forma. Discrepancies were resolved via group discussion. Information extracted from each study included publication date, hospital location, sample size, ICU type and setup, sedatives used, sedation scale and weaning protocol use, follow-up, patient characteristics, inclusion and exclusion criteria, and clinical outcomes listed under study eligibility criteria.

Assessment of Bias Risk

We assessed methodological quality using Cochrane's domain-based risk of bias tool (Supplemental Figure; available online at <http://www.mayoclinicproceedings.org>).¹⁵ Two reviewers (M.A.M. and A.K.) independently extracted data from each included study for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias risk. A third reviewer (A.G.V.) resolved assessment disagreements.

Data Synthesis and Analysis

We used Cochrane Review Manager version 5.2 software to calculate summary risk ratios (RRs) and the number needed to treat (NNT) for dichotomous outcomes and weighted mean differences (WMDs) for continuous outcomes, along with their respective 95% CIs. A random effects model was used to account for variations in protocol design among the included studies.

Overall mortality was analyzed as follows: we pooled the longest followed mortality measure reported in each study, to avoid double counting. For example, Bucknall et al¹² reported both ICU and hospital mortality, but only hospital mortality was included in the overall mortality summary estimate.

Missing Data

We emailed all 6 study corresponding authors for missing or supplemental data. Girard et al¹¹ provided mean duration of mechanical ventilation data, and 5 authors⁷⁻¹¹ provided

supplemental data. However, Bucknall et al¹² did not reply to requests for supplemental data. When means and standard deviations were not published, we estimated those values from other information contained in the published report as follows: if the study provided a median, we used that value as an appropriate estimate of central tendency and estimated the standard deviation from the interquartile range^{8,9,11,12} or, if the interquartile range was not provided, the range,^{10,12} using established formulas.^{14,16}

In the study by Girard et al,¹¹ the upper quartile for hospital LOS was not quantifiable in the control group because 75% or less of patients had been discharged by the end of the 28-day hospital follow-up. We imputed a worst-case estimate for the upper quartile by extrapolating the control arm of the outcome's published Kaplan-Meier curve.¹¹ The aforementioned methods were applied to the interquartile range.

Identifying and Addressing Heterogeneity

We identified the presence of between-study heterogeneity in studies contributing to each outcome's summary estimate via a standard χ^2 test, where $P < .10$ indicated significant heterogeneity. Owing to the low power of this test, we also quantified between-study inconsistency via the I^2 statistic, which ranges from 0% to 100% and assesses what percentage of the variation in the effect estimates is due to heterogeneity. An $I^2 \geq 50\%$ indicated substantial heterogeneity.¹⁴ We addressed heterogeneity by examining, in full text, individual studies contributing to a summary estimate and excluded the single most outlying study in a sensitivity analysis. All other statistical tests were considered significant at 2-tailed $P \leq .05$.

Assessment of Reporting Bias

We aimed to assess for publication bias by plotting each included RCT's effect size by its sample size for duration of mechanical ventilation. The resulting funnel plot was to be visually inspected for symmetry and evidence of publication bias.¹⁷ However, the meta-analysis included fewer than 10 studies; therefore, funnel plots to assess for publication bias were not produced because they would be inadequately powered to detect real asymmetry—and evidence of publication bias.¹⁴

Subgroup Analyses

We did not perform any subgroup analyses.

Sensitivity Analyses

We performed a sensitivity analysis to explore the impact that a single excluded study had on I^2 , if $I^2 \geq 50\%$ in studies contributing to an outcome with a heterogeneous summary estimate.

RESULTS

Identification and Selection of Studies

As outlined in Figure 1, the initial search produced 4782 studies; of these, 894 duplicates were removed. We further excluded 3720 studies on the basis of title and abstract and

retrieved 168 studies for full-text review. Ultimately, 6 RCTs with 1243 randomized patients reporting 461 nonduplicated deaths met the inclusion criteria.^{7–12}

Characteristics of the Included Studies

Characteristics of the included studies are summarized in the Table. Three studies were conducted in the United States,^{7,8,11} 2 in Australia,^{9,12} and 1 in Greece.¹⁰ The first 2 studies evaluating sedation protocols were published in 1999 and 2000; the remaining 4 were published between 2008 and 2011. Only 2 of the 6 studies were multicentered.^{9,11} Three studies had medical ICUs,^{7,8,11} 2 had medical ICUs combined with 1 or more specialties,^{9,10} and 1 had a general ICU.¹² Girard et al¹¹ used both open and closed ICUs, and the remaining studies had closed ICUs. Follow-up was variable and ranged from hospital discharge to 1 year. Follow-up was unclear in the study by Bucknall et al,¹² so we estimated duration based on the longest followed mortality measure.

The total number of patients per study ranged from 50 to 335; US trials generally enrolled more patients. The mean age ranges of the intervention and control groups of the included studies were 52.1 to 65.1 years and 56.1 to 69.1 years, respectively. The percentages of males in the intervention and control groups were 50.0% to 71.4% and 43.3% to 72.9%, respectively. The mean APACHE II (Acute Physiology and Chronic Health Evaluation II) score ranges of the intervention and control groups were 17.4 to 26.0 and 18.9 to 26.5, respectively. Except for the study by Anifantaki et al,¹⁰ in which trauma was more prominent, most patients were admitted to the ICU for medical reasons.

Sedatives varied, but the most commonly used drugs were fentanyl, midazolam, and propofol. All the studies used sedation assessment scales, the most common being the Ramsay sedation scale, which was used in 3 studies.^{7,8,10} Three studies used weaning protocols.^{7,8,11} Sedation strategies varied in design (algorithm vs daily interruption) and implementation (nurse vs non-nurse) but were consistent in their intention to standardize sedation management. Four studies used daily interruption,^{8–11} and the remaining 2 used an algorithm.^{7,12} Similarly, 4 studies were nurse implemented,^{7,10–12} and 2 were not.^{8,9} Studies varied in reporting clinical outcomes (Table); the duration of mechanical ventilation and ICU and hospital LOSs were universally reported, whereas the incidence of delirium was not reported at all.

Risk of Bias Assessment

The risk of bias for included studies is summarized in the Supplemental Figure. The overall quality of evidence was moderate. Five of the 6 studies provided sufficient information to assess 5 or more bias categories. Two studies described participant randomization but did not discuss the technique.^{7,12} Except for Anifantaki et al,¹⁰ all the studies adequately described allocation concealment, and only the study by Weisbrodt et al⁹ was double blinded. Two studies^{8,10} provided insufficient attrition information to assess for incomplete outcome data. Only 2 studies^{11,12} published their protocols, allowing for selective outcome reporting assessment; however, most reported the expected clinical outcomes. The basis for “other bias” varied, but the most common reason for high risk included aberrations in ICU bed and nurse supply.

Study Outcomes

Overall Mortality.—After pooling the longest followed mortality from each included study, protocolized sedation was associated with a significant reduction in overall mortality compared with usual care without protocolized sedation (RR, 0.85; 95% CI, 0.74 to 0.97; $P=.02$; $I^2=0\%$; NNT, 20; $P=.11$) (Figure 2).

Duration of Mechanical Ventilation.—Among the included studies, protocolized sedation produced no significant difference in mean days of mechanical ventilation compared with usual care without protocolized sedation (WMD, -1.04 days; 95% CI, -2.54 to 0.47 days; $P=.18$; $I^2=74\%$) (Figure 3).

ICU and Hospital LOSs.—Among the included studies, protocolized sedation was associated with a significant reduction in mean ICU LOS (WMD, -1.73 days; 95% CI, -3.32 to -0.14 days; $P=.03$; $I^2=60\%$) and mean hospital LOS (WMD, -3.55 days; 95% CI, -5.98 to -1.12 days; $P=.004$; $I^2=12\%$) compared with usual care without protocolized sedation (Figure 3).

Tracheostomy.—Among the 5 reporting studies^{7–9,11,12} protocolized sedation was associated with a significant reduction in tracheostomy compared with usual care without protocolized sedation (RR, 0.69; 95% CI, 0.50 to 0.96; $P=.03$; $I^2=30\%$; NNT, 16.6; $P=.04$; 5 RCTs) (Figure 4).

Reintubation.—Among the 3 reporting studies,^{7,8,11} protocolized sedation produced no significant difference in reintubation compared with usual care without protocolized sedation (RR, 0.78; 95% CI, 0.52 to 1.15; $P=.21$; $I^2=21\%$; 3 RCTs) (Figure 4).

Self-extubation.—Among the 4 reporting studies,^{8,11,12} protocolized sedation produced no significant difference in self-extubation compared with usual care without protocolized sedation (RR, 1.49; 95% CI, 0.46 to 4.82; $P=.51$; $I^2=43\%$; 4 RCTs) (Figure 4).

Delirium.—The included studies did not report the incidence of delirium; however, Girard et al¹¹ reported no significant difference in days of delirium between groups in their trial.

Sensitivity Analysis

The summary estimates for duration of mechanical ventilation and ICU LOS showed $I^2=50\%$. We suspected that Bucknall et al¹² were causing substantial heterogeneity because of their lack of respiratory therapists and (contrary to Weisbrodt et al's⁹ similar lacking) their large sample size. A sensitivity analysis excluding the study by Bucknall et al¹² from both outcome summary estimates resolved the heterogeneity; the mean duration of mechanical ventilation was significantly reduced (WMD, -1.72 days; 95% CI, -2.64 to -0.81 days; $P=.0002$; $I^2=0\%$; 5 RCTs), and mean ICU LOS was further reduced (WMD, -2.37 days; 95% CI, -3.84 to -0.90 days; $P=.0002$; $I^2=32\%$; 5 RCTs) (figures not shown).

DISCUSSION

This systematic review and meta-analysis included 6 RCTs involving 1243 patients and 461 deaths. Although we summarized multiple clinical outcomes, only 3 outcomes were reported by all 6 studies. Pooled analysis suggests that among mechanically ventilated adults treated in closed, nonspecialty ICUs, standardized sedation management via protocolized sedation (algorithm or daily interruption) is associated with a significant decrease in overall mortality, ICU and hospital LOSs, and tracheostomy compared with usual care without protocolized sedation. Self-extubation, reintubation, and duration of mechanical ventilation were not significantly different; however, the latter had a heterogeneous summary estimate; a sensitivity analysis excluding the study by Bucknall et al¹² resolved heterogeneity, and duration of mechanical ventilation was significantly reduced. The incidence of delirium was not reported in the included studies.

To our knowledge, this study is the first to summarize RCTs comparing protocolized sedation (algorithm or daily interruption) with usual care without protocolized sedation (nonstandardized, discretionary sedation). However, these results are comparable with the 2011 meta-analysis by Augustes et al¹⁸ of 5 RCTs comparing daily interruption with no daily interruption. The summary estimates for most reported clinical outcomes were similar to ours in effect size, statistical significance, and heterogeneity. The similarities are likely due to the fact that of the 5 RCTs included in that meta-analysis, the 3 largest^{8,10,11} were also included in the present study. In sharp contrast, their ICU and hospital LOS summary estimates were remarkably heterogeneous and small in effect size compared with our results. These stark differences can partly be ascribed to the remaining 2 RCTs,^{19,20} which were excluded from the present study because the control groups also had protocolized sedation.¹⁸

A subsequent Cochrane review by Burry et al²¹ included 9 RCTs and investigated the same question. Our reviews shared 4 studies^{8–11}; the remaining 5 studies^{19,20,22–24} were excluded because the control groups also had protocolized sedation via algorithm. Although the Cochrane review included 3 more studies than the present review, the total number of patients included was almost the same. Again, most reported clinical outcomes were similar except ICU and hospital LOSs—particularly with respect to effect for each outcome. Square size is proportional to study weight in this random effects meta-analysis. IV indicates inverse variance. size and statistical significance. For example, whereas the present results indicated a significant 1.72-day reduction in ICU LOS, the Cochrane review found a nonsignificant 0.5-day reduction.²¹ This repeated discrepancy—regarding ICU and hospital LOSs—between the present findings and those of the 2 previously published reviews^{18,21} may partly be explained by the fact that both previous reviews also included RCTs in which the control group received protocolized sedation via algorithm instead of discretion. Evidence that choice of control group affects results comes from a subgroup analysis in the Cochrane review in which the duration of mechanical ventilation was significantly attenuated in the summary estimate of RCTs in which the control group was a sedation algorithm (as opposed to discretionary sedation).²¹ Interestingly, sedation dose is reduced by a larger margin when discretionary sedation is compared with protocolized sedation¹¹ as opposed to comparing differing methods of the latter strategy.²²

A recent review suggested that clinical outcomes in the ICU improve as sedation is minimized.² The review incorporated evidence from 2 large RCTs^{8,11} included in this study; however, the strongest line of evidence supporting this hypothesis comes from a 2010 study by Strom et al²⁵ in which mechanically ventilated adults randomized to a protocol of no sedation had significantly more ventilator-free days and fewer ICU and hospital days compared with a protocol of sedation with daily interruption. Given the apparent inverse relationship between sedation and clinical benefit, we suspected that sedation reduction was part of the mechanism of protocolized sedation, which, in the present meta-analysis, was associated with several improved clinical outcomes. A post hoc analysis of this study showed that 3 of the 6 included RCTs had significantly less sedation (lower total benzodiazepine dose^{8,11} and fewer days of continuous infusion⁷) in the protocolized sedation group. Seemingly, standardization reduces sedative use compared with discretionary sedation. However, this does not seem to be the case when comparing 2 standardized sedation strategies; a large 2012 multicenter RCT by Mehta et al²² found that daily interruption plus a sedation protocol (vs a sedation protocol alone) resulted in significantly more total sedation and no clinical benefit. The true mechanism is likely multifaceted, and we caution against the assumption that decreased sedation is a corollary of standardized sedation management.

Despite widespread consensus supporting the use of standardized sedation management, adoption has been suboptimal.^{26,27} The 2013 pain, agitation/sedation, and delirium (PAD) guidelines explicitly recommend light sedation via “daily sedative interruption or a light target level.”⁵ These guidelines were published in January 2013 and cited a 2009 survey by Patel et al²⁸ that showed that 71% of health care professionals used a sedation protocol. To understand current practice patterns, we conducted a small survey in September 2014, approximately 19 months after the guidelines were published. We called 123 hospitals—a 3% random sample of 4089 acute care hospitals the United States in 2010—and asked whether protocolized sedation was used in the ICU. The response rate was 72% after excluding 40 hospitals without an ICU. Of 60 responding hospitals, 71% used protocolized sedation via daily interruption (63%), algorithm (47%), or both (12%). The present findings—the same as those of Patel et al²⁸—are not encouraging for 2 reasons: first, the present results are self-reported, and actual vs self-reported use of protocolized sedation has been shown to be a conservative 20% lower²⁷; and second, it seems that the 2013 PAD guidelines have not compelled protocolized sedation adoption, at least not in the first 19 months after publication. A survey of perceived barriers found unplanned extubation to be a major concern preventing daily interruption adoption.²⁹ This concern may be warranted as we found that protocolized sedation increased self-extubation risk by 49%; although nonsignificant, this result is underpowered. However, this review does suggest that the benefits of protocolized sedation outweigh the harms, and we hope that this work will provide the remaining 29% of health care professionals more confidence in adopting the previously mentioned recommendations from the 2013 PAD guidelines. In addition, we hope that this impartial meta-analysis might convince skeptical clinicians to standardize sedation management, particularly clinicians who are skeptical of the objectivity of clinical practice guidelines that may be formulated by researchers with financial or intellectual conflicts of interest.³⁰

The overall quality of evidence was moderate; in other words, there is a need for further high-quality research. Five of the 6 included studies were not blinded; patients in either group may have received more or less diligent care, especially if providers cared for patients in both study arms. Consequently, particular attention should be given to minimizing performance and detection bias. The study by Weisbrodt et al⁹ was the most recently conducted, and despite claims of the impossibility of a blinded study from investigators of several included RCTs, the authors demonstrated the feasibility of a double-blinded RCT. Their method provides a framework for future investigators to curtail these critical biases.

This study has several limitations. First, the results are not applicable to specialty ICUs or to patients with severe illness. Most included patients were treated for medical conditions. Thus, these results are best generalized to adults admitted to medical ICUs with an APACHE II range of approximately 18 to 26. Second, these results are not applicable to children; however, recent randomized evidence supported protocolized sedation use in the pediatric population.^{31,32} Third, we did not search abstracts from conference proceedings, which may have introduced bias into this review. Last, although we found a significant 15% reduction in overall mortality, the results should be interpreted cautiously because the analytical method does not account for variable follow-up, which is better analyzed using hazard ratios. In addition, statistical significance in overall mortality was driven by the study by Girard et al,¹¹ which had a weight of 43.4% (Figure 2). We do not find this particularly concerning because their study was the largest and highest-quality RCT included in this review. Hospital mortality was the most consistently reported mortality measure (reported by 4 of 6 RCTs), and although there was no difference between groups, it provides a more conservative, albeit underpowered, estimate of the direction of mortality benefit (Figure 2).

CONCLUSION

Protocolized sedation (algorithm or daily interruption) is associated with a 15% reduction in overall mortality, a 1.73-day reduction in ICU LOS, a 3.55-day reduction in hospital LOS, and a 31% reduction in tracheostomy compared with usual care without protocolized sedation. In other words, a standardized approach to sedation management seems better than a nonstandardized, discretionary approach. This conclusion is most generalizable to older mechanically ventilated adults who are not severely ill and are being treated for medical conditions in a closed, nonspecialty ICU. Given the unsatisfactory implementation rate found in these survey results and the apparent benefits of protocolized sedation suggested by this review, we recommend that ICUs strongly consider implementing either daily sedation interruption or a sedation algorithm. Further research investigating protocolized sedation should quantify delirium incidence, as it was not reported in the included RCTs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

APACHE II	Acute Physiology and Chronic Health Evaluation II
C	control
COPD	chronic obstructive pulmonary disease
I	intervention
ICU	intensive care unit
LOS	length of stay
NNT	number needed to treat
NR	not reported
PAD	pain, agitation/sedation, and delirium
RASS	Richmond Agitation Sedation Scale
RCT	randomized controlled trial
RR	risk ratio (relative risk)
SAS	Riker Sedation-Agitation Scale
WMD	weighted mean difference

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FIGURE 1.
Study selection flowchart.

FIGURE 2.

Forest plot of the effect of protocolized sedation compared with usual care without protocolized sedation on overall mortality. Diamond summary estimate pooling the longest followed mortality from each study (ie, pooled subtotals) is presented last. Square size is proportional to study weight in this random effects meta-analysis. M-H indicates Mantel-Haenszel.

FIGURE 3.

Forest plot of the effect of protocolized sedation compared with usual care without protocolized sedation on days of mechanical ventilation and intensive care unit (ICU) and hospital lengths of stay (LOSs). Diamond summary estimate is presented last for each outcome. Square size is proportional to study weight in this random effects meta-analysis. IV indicates inverse variance.

FIGURE 4.

Forest plot of the effect of protocolized sedation compared with usual care without protocolized sedation on tracheostomy, reintubation, and self-extubation. Diamond summary estimate is presented last for each outcome. Square size is proportional to study weight in this random effects meta-analysis. M-H indicates Mantel-Haenszel.

TABLE.

Characteristics of Included Randomized Controlled Trials Comparing Protocolized Sedation vs Usual Care Without Protocolized Sedation on Clinical Outcomes in Mechanically Ventilated Adult ICU Patients^a

Reference, year, location	Sample size	ICU type (setup)	Age (y), mean		Male sex (%)		APACHE II score, Mean			Most cases	Drugs used	Sedation scale (Weaning protocol)	Intervention	Control	Follow-up	Reported outcomes ^b
			I	C	I	C	I	I	C							
Brook et al, ⁷ 1999 Single center United States	321	Medical (closed)	57.8	58.1	51.2	47.2	23.1	23.2	23.2	Pneumonia	Diazepam, fentanyl, lorazepam, midazolam, morphine, haloperidol	Ramsay (Yes)	Nurse-implemented continuous sedation algorithm (n=162)	Physician-directed continuous sedation (n=159)	Hospital discharge ^c	1, 3–7
Kress et al, ⁸ 2000 Single center United States	128	Medical (closed) ^c	57 ^d	61 ^d	50	43.3	20 ^d	22 ^d	22 ^d	COPD or ventilatory failure	Midazolam, morphine, propofol	Ramsay (Yes) ^c	Daily interruption of sedation until patients were awake (n=68)	ICU physician—directed sedative interruption (n=60)	Hospital discharge	1, 3–8
Bucknall et al, ¹² 2008 Single center Australia	312	General (closed)	58.2	56.1	64	58	18.6	19.5	19.5	Medical	Diazepam, haloperidol, fentanyl, midazolam, morphine, propofol	SAS (No)	Nurse-implemented sedation algorithm (n=159)	Sedation medication type and dose limits for infusion and boluses prescribed by ICU medical staff (n=153)	Hospital discharge ^e	0, 1, 3–6, 8
Girard et al, ¹¹ 2008 Multicenter United States	335	Medical (mixed) ^c	60 ^d	64 ^d	54	51	26 ^d	26.5 ^d	26.5 ^d	Sepsis/ARDS	Benzodiazepines, ^f haloperidol, ^f opiates, ^f propofol	RASS (Yes)	Nurse-implemented daily interruption of sedation plus a daily spontaneous breathing trial	Sedation per usual care plus a daily spontaneous breathing trial (n=168)	1 y	2, 3 ^c , 4, 5 ^d , 6–8

Reference, year, location	Sample size	ICU type (setup)	Age (y). mean		Male sex (%)		APACHE II score, Mean			Most cases	Drugs used	Sedation scale (Weaning protocol)	Intervention	Control	Follow-up	Reported outcomes ^b
			I	C	I	C	I	C								
Anifantaki et al. ¹⁰ 2009 Single center Greece	97	Medical; surgical (closed) ^c	52.1	56.1	71.4	72.9	17.4	18.9	Trauma	Fentanyl, midazolam, morphine, propofol, remifentanyl	Ramsay (NR)	(n=167) Nurse- implemented daily interruption of sedation (n=49)	ICU medical staff— directed sedation (n=48)	Hospital discharge	1, 3–5	
Weisbrodt et al. ⁹ 2011 Multicenter Australia	50	Medical surgical trauma (closed) ^c	65.1	69.1	54	71	23.4	21.4	Respiratory	Fentanyl, midazolam, propofol	RASS (No)	Daily interruption of fentanyl or midazolam infusions for up to 6 h (n=26)	Usual management of sedation in Australia (n=24)	6 mo ^c	0, 2–6	

^a APACHE II = Acute Physiology and Chronic Health Evaluation II; ARDS = acute respiratory disease syndrome; C = control; COPD = chronic obstructive pulmonary disease; I = intervention; ICU = intensive care unit; NR = not reported; RASS = Richmond Agitation Sedation Scale; SAS = Riker Sedation-Agitation Scale.

^b 0 = ICU mortality, 1 = hospital mortality 2 = 6- to 12-month mortality, 3 = duration of mechanical ventilation, 4 = ICU length of stay, 5 = hospital length of stay, 6 = incidence of tracheostomy, 7 = incidence of reintubation, 8 = incidence of self-extubation, 9 = incidence of delirium.

^c Reported via email.

^d Values are medians not means.

^e Estimated based on the longest followed mortality measure.

^f Benzodiazepines as lorazepam and opiates as fentanyl equivalents.

^g Median hospital length of stay is reported; however, interquartile range is missing in the control group.