Benzodiazepine Versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated, Critically Ill Adults: A Systematic Review and Meta-Analysis of Randomized Trials

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Background: Use of dexmedetomidine or propofol rather than a benzodiazepine sedation strategy may improve ICU outcomes. We reviewed randomized trials comparing a benzodiazepine and nonbenzodiazepine regimen in mechanically ventilated adult ICU patients to determine if differences exist between these sedation strategies with respect to ICU length of stay, time on the ventilator, delirium prevalence, and short-term mortality.

Methods: We searched CINAHL, MEDLINE, the Cochrane databases, and the American College of Critical Care Medicine's Pain, Agitation, Delirium Management Guidelines' literature database from 1996 to 2013. Citations were screened for randomized trials that enrolled critically ill, mechanically ventilated adults comparing an IV benzodiazepine-based to a nonbenzodiazepine-based sedative regimen and reported duration of ICU length of stay, duration of mechanical ventilation, delirium prevalence, and/or short-term mortality. Trial characteristics and results were abstracted in duplicate and independently, and the Cochrane risk of bias tool was used for quality assessment. We performed random effects model meta-analyses where possible.

Results: We included six trials enrolling 1,235 patients: midazolam versus dexmedetomidine ($n = 3$), lorazepam versus dexmedetomidine ($n = 1$), midazolam versus propofol ($n = 1$), and lorazepam versus propofol ($n = 1$). Compared to a benzodiazepine sedative strategy, a nonbenzodiazepine sedative strategy was associated with a shorter ICU length of stay ($n = 6$ studies; difference = 1.62 d; 95% CI, 0.68–2.55; $I^2 = 0\%$; $p = 0.0007$) and duration of mechanical ventilation ($n = 4$ studies; difference = 1.9 d; 95% CI, 1.70–2.09; $I^2 = 0\%$; $p < 0.00001$) but a similar prevalence of delirium ($n = 2$; risk ratio = 0.83; 95% CI, 0.61–1.11; $I^2 = 84\%$; $p = 0.19$) and short-term mortality rate ($n = 4$; risk ratio = 0.98; 95% CI, 0.76–1.27; $I^2 = 30\%$; $p = 0.88$).

Conclusions: Current controlled data suggest that use of a dexmedetomidine- or propofol-based sedation regimen rather than a benzodiazepine-based sedation regimen in critically ill adults may reduce ICU length of stay and duration of mechanical ventilation. Larger controlled studies are needed to further define the impact of nonbenzodiazepine sedative regimens on delirium and short-term mortality. (*Crit Care Med* 2013; 41:S30–S38)

Key Words: critical illness; delirium; dexmedetomidine; length of stay; lorazepam; midazolam; mechanical ventilation; meta-analysis; mortality; propofol; systematic review

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Dr. Devlin has received grants, honoraria, and payment for the development of educational presentations from Hospira. Dr. Barr has received an honorarium and travel expenses from SCCM and payment for lectures from Cynosure Health. Mr. Dasta has disclosed consultancies with Hospira, Cadence Pharmaceuticals, and Pacira Pharmaceuticals; he is also a member of the France Foundation Speaker Program, sponsored by Hospira. Dr. Kress has received honoraria from Hospira. Dr. Davidson has received honoraria from Hospira and the France Foundation. Dr. Spencer has disclosed that his institution has received grants from the National Institutes of Health and Ontario Heart and Stroke. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3182a16898

The 2013 American College of Critical Care Medicine's (ACCM) Pain, Agitation and Delirium (PAD) Clinical Practice Guidelines (1) made several evidence-based recommendations surrounding sedation in critically ill adults. During the guideline development process, the premise that sedative choice influences patient outcome stimulated substantial debate among task force members. The PAD guidelines subsequently offered a weak recommendation favoring the use of IV nonbenzodiazepine sedatives (either dexmedetomidine or propofol) over benzodiazepine sedatives (either lorazepam or midazolam) in mechanically ventilated adults. This recommendation was based on an evaluation of 13 studies published between 1997 and 2010 that compared IV benzodiazepine sedative regimens with either IV dexmedetomidine or propofol (2–14).

The authors of the PAD guidelines also performed a limited meta-analysis of the effect of sedative choice on ICU length of stay. Using six of the 13 studies that formed the basis of the recommendation cited above, they found that a benzodiazepine-based sedative regimen was associated with an approximately half-day longer ICU length of stay (2, 4, 5, 11–13). However, some of the outcomes of potentially greatest importance to clinicians and patients, such as duration of mechanical ventilation, prevalence of delirium, and short-term mortality, were not considered in this analysis. In addition, this PAD guideline meta-analysis contained data from studies evaluating postoperative sedative choice in cardiac surgery patients, a patient population with distinct clinical practices and outcomes (11–13).

In an effort to address these limitations, we sought to expand the previous analysis by including additional controlled studies published between 2010 and 2013, eliminating studies evaluating cardiac surgery patients, and considering other factors, such as use of daily sedation interruption and protocolization of sedation as well as ventilator weaning, that could confound patient outcomes. We reviewed randomized trials comparing a benzodiazepine and nonbenzodiazepine regimen in mechanically ventilated adult ICU patients to determine if differences exist between these sedation strategies in terms of ICU length of stay, duration of mechanical ventilation, delirium prevalence, and short-term mortality.

METHODS

Trial Identification

With the guidance of experienced medical librarians, we searched for eligible studies published in the English language with the following key words: "benzodiazepines" or "diazepam" or "midazolam" or "lorazepam" and "dexmedetomidine" or "propofol" and "intensive care" or "critical care" or "ICU." Relevant trials for the default time period published between December 1996 and February 2013 were identified using MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and CINAHL. We also reviewed the literature database created by the ACCM PAD Guideline Task Force with approximately 19,000 citations (1), reference lists of review articles and meta-analyses, and personal files, and we questioned experts in the field to determine if study identification was complete.

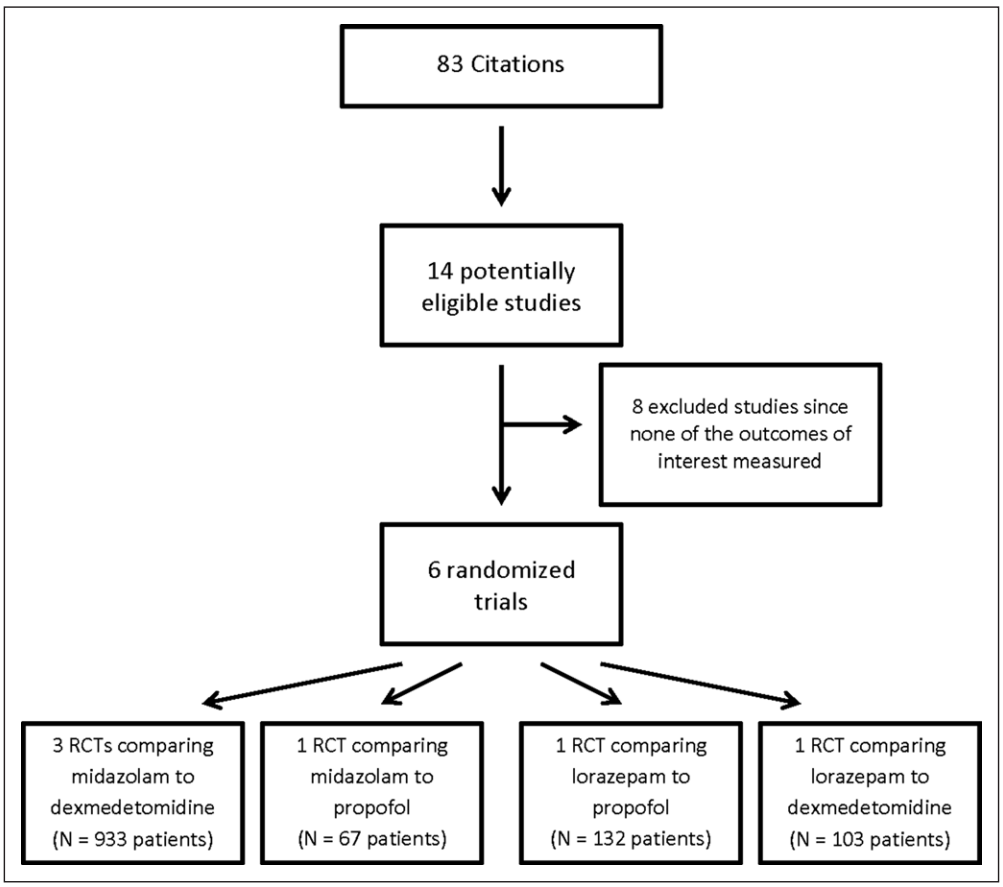

Figure 1. Article identification; six trials were included in the qualitative and quantitative analysis. RCTs = randomized controlled trials.

Eligibility Criteria

Study inclusion criteria were based on the following attributes: 1) design: randomized controlled parallel group trial; 2) population: adult (≥ 19 yr) medical or surgical ICU patients receiving invasive mechanical ventilation and administration of IV pharmacologic sedation; 3) intervention: the use of IV dexmedetomidine or 1% propofol regardless of dose or duration compared to a control group receiving IV lorazepam or midazolam regardless

of dose, duration, or frequency; and 4) predefined outcomes: ICU length of stay, duration of mechanical ventilation, delirium prevalence, and all-cause, short-term mortality occurring within 45 days after the time of randomization or during hospitalization.

Studies that evaluated cardiac surgery or critically ill obstetrical patients were excluded from this analysis given that sedation practices, ventilation strategies, and ICU throughput are generally different in these patient populations (15). Studies available only in abstract form or not published in English were also excluded.

Citations were screened independently by two reviewers for potentially relevant studies. These were rescreened in duplicate in full-text form if the titles and abstracts indicated that they fulfilled the inclusion criteria.

Data Abstraction

Using a custom-made data collection form, two reviewers independently abstracted data regarding trial design, patient population, the intervention and the comparison, and clinical outcomes. The primary outcome of interest was the duration of ICU length of stay, with secondary outcomes including duration of mechanical ventilation, delirium prevalence (where delirium was evaluated at least daily using a validated screening tool), and all-cause, short-term mortality (i.e., ≤ 45 d after randomization or during hospital stay).

Risk of Bias Assessment

Methodological quality was independently assessed by at least two reviewers using the Cochrane Collaboration risk for bias tool that considered seven different domains: adequacy of sequence generation; allocation sequence concealment; blinding of participants and caregivers; blinding for outcome assessment; incomplete outcome data; selective outcome reporting; and the presence of other potential sources of bias not accounted for in the other six domains (16). Because of difficulties in blinding propofol use, and its associated risk of influencing subjective outcomes such as ICU length of stay and ventilator dependency, we considered other aspects of trial design, such as the absence of protocolization of sedative goals and ventilator weaning, that may amplify the impact of lack of blinding when assigning a risk of bias score for this domain. We also considered the influence of pharmaceutical industry in our assessments of risk of bias. If a pharmaceutical sponsor was involved in trial design, data analysis, or article preparation, but other categories of risk of bias were low, an unclear risk for bias was assigned in the "other" category; otherwise the study was deemed to be at a high risk for bias. The estimated overall risk of bias for each trial was categorized was "low" (if the risk of bias was low in all key domains), "unclear" (if there is low or unclear risk of bias for all key domains), or "high" (if the risk of bias was high in one or more key domains).

TABLE 1. Characteristics of Randomized Studies Evaluating the Effect of Benzodiazepine Versus Nonbenzodiazepine-Based Sedation on Clinical Outcomes

Trial (*n*)	Trial Design	Patient Population (Severity of Illness)	Intervention[a]
Carson et al (2) (132)	Randomized open-label, multicenter	Medical (22)[b]	Lorazepam by intermittent bolus
			Propofol
Jakob et al (27) (500)[c]	Randomized double-blind, double-dummy multinational, multicenter	Mixed[d] (45)[e]	Midazolam
			Dexmedetomidine
Pandharipande et al (4) (103)	Randomized, double-blind, multicenter	Mixed[d] (28)[b]	Lorazepam
			Dexmedetomidine
Riker et al (5) (366)	Randomized, double-blind, multicenter	Mixed[d] (19)[b]	Midazolam
			Dexmedetomidine
Ruokonen et al (6) (67)	Randomized, double-blind, double-dummy, multicenter	Mixed[d] (2.5)[g]	Midazolam
			Dexmedetomidine
Weinbroum et al (3) (67)	Randomized, unblinded	Mixed[d] (17)[b]	Midazolam
			Propofol

LOS = length of stay, RASS = Richmond Agitation-Sedation Scale, CAM-ICU = Confusion Assessment Method for the ICU.

[a]Continuous IV infusion unless otherwise stated.

[b]Average Acute Physiology and Chronic Health Evaluation II score across all study groups.

[c]Based on intention to treat.

[d]Mixed = mixed medical/surgical population.

[e]Average Simplified Acute Physiology Score-2 across all study groups.

[f]Delirium assessment with CAM-ICU 48 hr after sedation discontinuance.

[g]Mean organ failure.

Disagreements across any methodological step were resolved through group discussion and consensus.

The quality of evidence resulting from this systematic review was evaluated using the GRADE (Grades of Recommendation Assessment, Development and Evaluation) methodology (17).

Data Synthesis and Statistical Analysis

Descriptive statistics were reported as proportions for categorical variables and mean/median for continuous variables. We combined data from trials to estimate the pooled risk ratio (RR) and associated 95% CIs for binary outcomes. Pooled RRs were calculated using random effects models, applying inverse variance weighting and the methods of DerSimonian and Laird (18). Weighted mean difference was used to summarize the effect measure for continuous outcomes. Data were pooled using inverse variance and a random effects model. Most trials reported median as the measure of treatment effect, with accompanying interquartile range (IQR), SEM, or range. For the purpose of analysis, medians were assumed to be equivalent to means and SDs estimated from IQR/SEMs/or range as follows: SD = IQR × 0.74; SD = SEM × square root of n; SD = range/4. Statistical heterogeneity was assessed by the I^2 statistic; substantial heterogeneity was interpreted as an I^2 of greater than 50%. Analyses were performed using RevMan version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Trial Identification

Our search yielded 83 publications; all but two of these were identified from the electronic database search (**Fig. 1**). We excluded 69 articles based on reviews of the title and abstract, leaving 14 articles for full review. Of these 14 studies, eight were excluded because they did not evaluate any of the outcomes of interest (19–26). The remaining six randomized trials, which enrolled 1,235 patients, were included in this systematic review (2–6, 27). One study evaluated midazolam versus propofol (3), one study evaluated lorazepam versus propofol (2), one study evaluated lorazepam versus dexmedetomidine (4), and three studies evaluated midazolam versus dexmedetomidine (5, 6, 27).

Trial Characteristics

Table 1 describes the characteristics of the six studies including patient enrollment; presence of blinding; study design; patient mix and baseline severity of illness; control and experimental interventions; the methods, frequency, and goals for sedative therapy; use of daily sedation interruption and ventilator weaning protocols; delirium assessment using a validated instrument; and the period over which short-term mortality was evaluated. With the exception of one, all trials enrolled patients from more than one center (3). The four dexmedetomidine studies (4–6, 27) were blinded, whereas none of the propofol trials were

Method and Frequency of Sedation Assessment/Sedation Goal	Daily Sedation Interruption	Ventilator Weaning Protocol Used	Daily Delirium Assessment	Defined Outcome Data Available
Ramsay every 2 hr Ramsay of 2–3	Yes	Yes	No	ICU LOS, ventilator days, hospital mortality
RASS every 2 hr RASS of 0 to −3	Yes	Not stated	No[f]	ICU LOS, ventilator days, 45-d mortality
RASS (frequency not stated) RASS target determined by team	No	No	Yes with CAM-ICU	ICU LOS, ventilator days, 28-d mortality, delirium
RASS every 4 hr RASS of −2 to +1	Yes	Not stated	Yes with CAM-ICU	ICU LOS, ventilator days, delirium, 30-d mortality
RASS (frequency not stated) RASS target determined by team	Yes	Not stated	Yes, but no details provided	ICU LOS
Unique scoring system developed for study (frequency of assessment not provided) Target light sedation	No	No	No	ICU LOS

blinded (2, 3). On average, patients were older (mean age = 59 yr), severely ill (average Acute Physiology and Chronic Health Evaluation II score = 21), and mostly (75%) medical (28). Sedative protocols, which included an established goal for sedative titration, were in place for four of the six studies (2, 3, 5, 27). While two other studies routinely monitored sedation, caregivers were allowed to establish the target level of sedation for each patient (4, 6).

Trial Bias and Quality of Evidence

The Cochrane risk of bias score for each citation is included in **Figure 2**. Only one (3) of the six studies has a high overall Cochrane risk of bias score (**Fig. 3**).

Because of the small number of trials included in this meta-analysis, we could not reliably examine funnel plots for publication bias. Using GRADE methodology, we assessed evidence for pooled data for ICU length of stay, duration of mechanical ventilation, mortality, and delirium to be moderate, moderate, moderate, and low, respectively (**Table 2**).

Clinical Outcomes

All six trials reported ICU length of stay as an outcome (n = 1,235 patients). The use of a nonbenzodiazepine IV sedative regimen was associated with a shorter ICU length of stay (mean difference = 1.65 d; 95% CI, 0.72–2.58; I^2 = 0%; p = 0.0005) (2–6, 27) (**Fig. 4**). Data from Weinbroum et al (3) were removed in post hoc fashion from the analysis because of an extraordinarily long length of ICU stay of the patients (average =26 d), but this did not alter the results of our analysis (mean difference = 1.62 d; 95% CI, 0.68–2.55).

Data from four trials (n = 1,101 patients) found that use of a nonbenzodiazepine-sedative regimen was associated with a shorter duration of mechanical ventilation (mean difference, 1.9 d; 95% CI, 1.70–2.09; I^2 = 0%; $p < 0.00001$) (2, 4, 5, 27) (**Fig. 5**).

The definition of delirium varied across studies. In two trials (n = 469 patients), delirium was clearly defined and evaluated on a daily basis (4, 5). The prevalence of delirium varied even between these two studies (approximately 81% and 61%, respectively). Pooling the data from these two studies did not confirm or refute a difference between delirium prevalence with these two sedation strategies (RR = 0.83; 95% CI, 0.61–1.11; I^2 = 84%; p = 0.19) (**Fig. 6**).

Short-term, all-cause mortality (reported as either hospital mortality or as mortality ≤ 45 d after randomization) was available from four trials involving 1,101 patients (4–6, 27). Risk for death (RR, 0.98; 95% CI, 0.76–1.27; I^2 = 30%; p = 0.94) was similar between benzodiazepine and nonbenzodiazepine regimens (**Fig. 7**).

DISCUSSION

The results of this meta-analysis suggest that the use of nonbenzodiazepine sedation in medical and surgical adult ICU patients (excluding cardiac surgery and obstetrical patients) is associated with 1.65 day shorter length of ICU stay and 1.9 day shorter duration of mechanical ventilation compared to patients receiving benzodiazepines for sedation. No significant difference in mortality was found in our analysis, and data on delirium prevalence were insufficient to draw clear conclusions. These results both expand and support the weak recommendation made in the 2013 ICU PAD guidelines that nonbenzodiazepine sedative options may be preferred over benzodiazepine-based sedative regimens (1). Although ICU length of stay and duration of mechanical ventilation are important outcomes, they do not fully characterize the entire gamut of benefits and the burdens to patients, caregivers, and healthcare institutions associated with sedative choice. Ultimately, therapeutic decisions should always be guided by patient context and by available financial and clinical resources.

The greater decrease in ICU length of stay associated with nonbenzodiazepine sedative use in this meta-analysis compared to the PAD guideline meta-analysis (~1.6 vs 0.5 d) is likely related to two factors: the addition of data from the recently published trial by Jakob et al (27) and the exclusion of studies enrolling cardiac surgery patients (11–13). In general, cardiac surgery represents a unique subset of ICU patients because they have much shorter durations of mechanical ventilation and ICU length of stay (often < 24 hr) (29). It follows that sedative choice in this setting is unlikely to significantly influence outcomes that involve duration (30).

Most ICU clinicians perceive that use of a benzodiazepine sedative regimen will result in a higher prevalence of delirium based on the results of cohort studies that have used regression techniques to demonstrate this relationship (31–33). However, the results of one recent ICU pharmacokinetic/pharmacodynamic study challenges this assumption, and the importance of the confounding factors that can influence this relationship have increasingly been highlighted (34). Among the two studies that evaluated delirium status during the period of sedative administration, the relationship between sedative choice and delirium prevalence differed; however, heterogeneity of these results could be due, in part, to differences in study methodology. It should be appreciated that sedation-induced delirium is complex and that our current understanding rests on a foundation composed of a number of assumptions (35). Artifact stemming from delirium assessment in patients receiving moderate sedation is possible and represents a potentially significant confounder (36, 37). This highlights the importance of using standardized approaches in future comparative studies to further define the relationship between sedative choice and delirium and its influence on other pertinent outcomes.

Underlying pharmacologic differences between sedatives and the presence of patient factors including genetic predisposition, end-organ dysfunction and the use of interacting medications will influence how patients respond and recover from sedative use (34, 38). The ability to titrate and prevent oversedation with benzodiazepines is more challenging than with dexmedetomidine and propofol given the longer context sensitive half-lives, and in the case of midazolam, reliance on the cytochrome P-450 enzyme system for metabolism and the renal function for active metabolite clearance (39). These

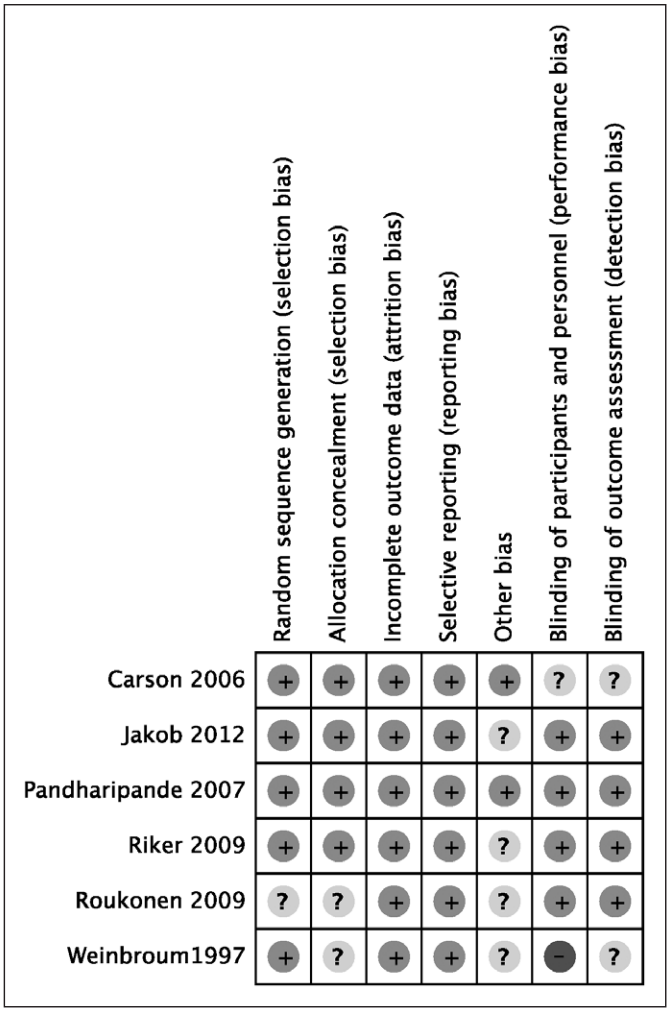

Figure 2. Methodologic quality of trials using the Cochrane risk of bias tool. *(+)* = low risk of bias, *(?)* = unclear, *(-)* = high risk of bias..

features may, in part, help explain the shorter ICU length of stay and duration of mechanical ventilation observed with propofol and dexmedetomidine. Yet, despite a decrease in ICU length of stay and duration of mechanical ventilation with use of nonbenzodiazepine sedatives, mortality was not affected. This is not surprising given the complexity of ICU patients and the various underlying factors such as severity of illness and comorbidities that will influence mortality.

This study has a number of strengths. To avoid selection bias, we searched multiple databases and reviewed citations independently and in duplicate. Data abstraction and the evaluation of risk of bias were performed in the same manner. We incorporated explicit inclusion and exclusion criteria as well as the Cochrane risk of bias assessment for each study.

Potential limitations in our meta-analysis are not only related to issues with individual study design but also difficulties extracting and pooling relevant data (Table 2). Individual studies varied in the use of protocols for ventilator weaning, sedation titration, and sedation interruption. As these protocols likely play an important role in ICU length of stay and duration of mechanical ventilation, isolating the impact of sedation type on these outcomes is difficult. In addition, the generalization of available data may be compromised by "practice misalignment" of the control group with the current standard of care (40). Identified issues include the use of continuous lorazepam without bolus administration (4) and the use of continuous moderate dose midazolam infusion without mandated daily sedation interruption or standardized ventilator weaning protocols (5).

The risk of bias imposed by lack of blinding in the propofol trials (2, 3) must also be considered. It is uncertain whether this may have impacted the observed findings in these two studies. This was particularly of concern for the Weinbroum et al trial (3), in which there was no ventilator weaning or sedation interruption protocol. However, a post hoc analysis of ICU length of stay that did not include this study did not appreciably affect our results.

Pooling of ICU length of stay and duration of mechanical ventilation data was hindered by individual study data reporting. Median duration and ranges (IQR, SEM, or overall range) were reported rather than mean duration and SD, suggesting that data were not distributed normally. Our assumption that median approximated mean (and estimates of SD from provided ranges) requires that we consider our study results an estimate of the potential benefit associated with nonbenzodiazepines.

Finally, despite a comprehensive search strategy, we could not assess for publication bias due to the small number of trials in this meta-analysis and the exclusion of abstracts and non-English articles. In addition, significant unexplained heterogeneity was observed for mortality and delirium outcomes, lowering our confidence in these estimates.

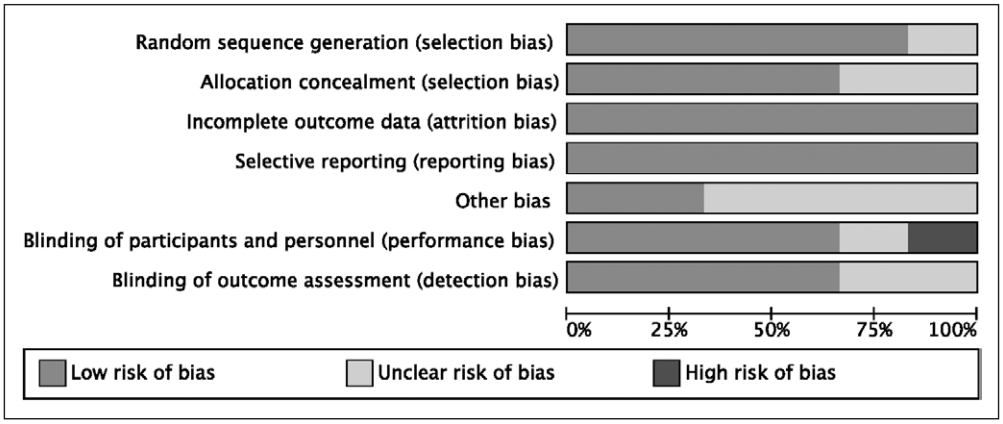

Figure 3. Overall risk of bias using the Cochrane risk of bias tool.

In summary, this meta-analysis of randomized trials in noncardiac surgery critically ill, mechanically ventilated adults indicates that the benzodiazepines are associated with a longer ICU length of stay and prolonged dependence on mechanical ventilation when compared with

TABLE 2. Nonbenzodiazepine- Versus Benzodiazepine-Based Strategy for Sedation of Adult Mechanically Ventilated Patients

Outcomes	Participants (Studies) Follow-Up	Quality of the Evidence (Grades of Recommendation Assessment, Development and Evaluation)	Estimated Benefit With Nonbenzodiazepine
ICU Length of stay	1,235 (6)	⊗⊗⊗○	−1.64 d (−2.57, −0.70)
	Up to 45 d	Moderate due to imprecision[a]	
Duration of mechanical ventilation	1,101 (4)	⊗⊗⊗○	−1.87 d (−2.51, −1.22)
	Up to 45 d	Moderate	
All-cause mortality	1,101 (4)	⊗⊗⊗○	1.01 (0.78, 1.30)
	Up to 45 d	Moderate due to imprecision[b]	
	Control rate: 25%		
Delirium	469 (2)	⊗⊗○○	0.82 (0.61, 1.11)
	During ICU stay	Low due to imprecision, inconsistency[c,d]	
	Control rate: 70%		

[a]95% CI from −2.57 d to −0.70 d: clinical impact at the end of these two extremes differs. In addition, we had to assume that median length of stay reported in studies was similar to mean and had to convert interquartile range (IQR)/SEM/range to SD using estimation formulas. This decreases confidence in the estimate and CI.

[b]Borderline decision to rate down. We had to assume that median length of stay reported in studies was similar to mean and had to convert IQR/SEM/range to SD using estimation formulas. This decreases confidence in the estimate and the 95% CI.

[c]95% CI includes clinically important benefit as well as harm.

[d]Only two studies reporting inconsistent results ($I^2 = 84\%$).

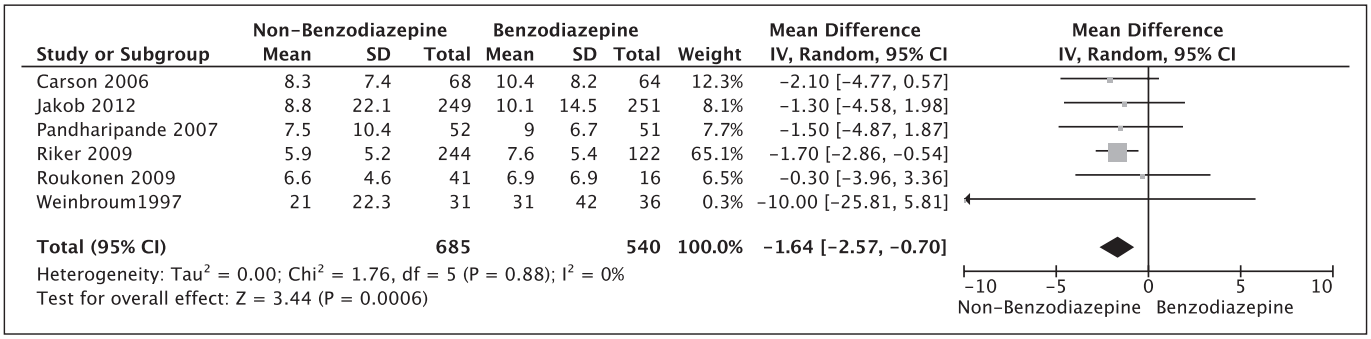

Figure 4. Forrest plot for ICU length of stay. Nonbenzodiazepine sedative use was associated with a significantly shorter ICU length of stay compared with benzodiazepine sedative use. *df* = degrees of freedom.

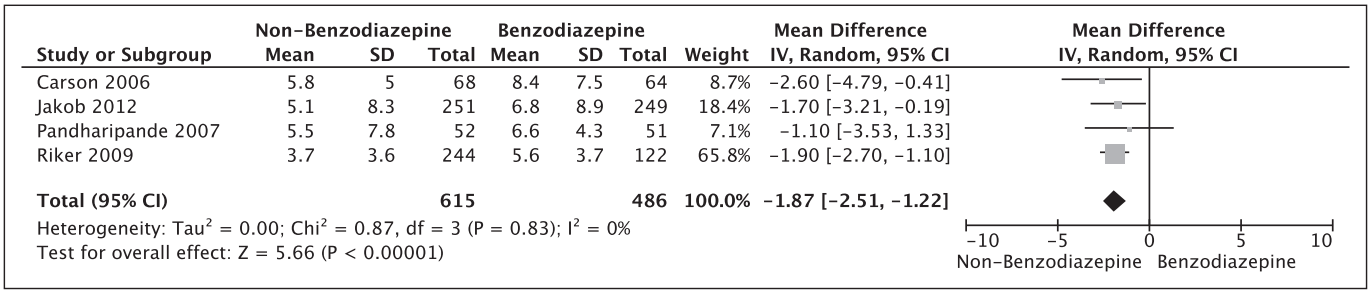

Figure 5. Forrest plot for duration of mechanical ventilation. Nonbenzodiazepine sedative use was associated with a significantly shorter duration on mechanical ventilation compared with benzodiazepine sedative use. *df* = degrees of freedom.

nonbenzodiazepine alternatives (i.e., propofol and dexmedetomidine). There is no clear difference between the groups in terms of short-term mortality, and the relationship between sedative choice and delirium requires further investigation.

ACKNOWLEDGMENTS

We appreciate the expertise of medical librarians Maryanne Lamont, MLS, and Charles P. Kishman, Jr, MSLS, for their assistance in searching the literature.

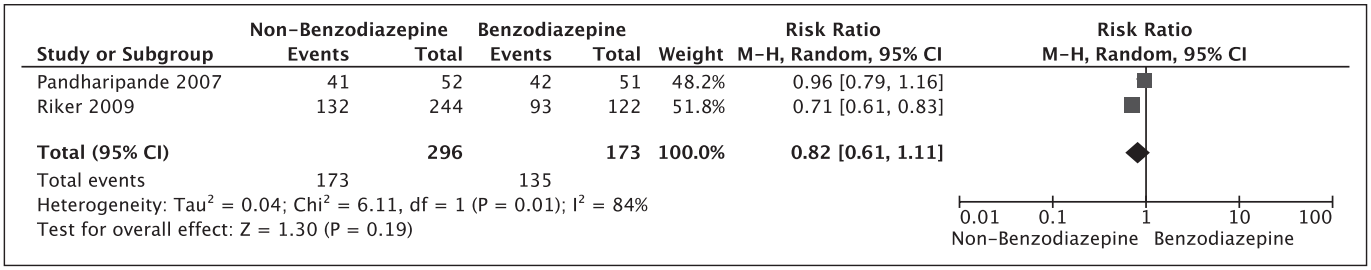

Figure 6. Forrest plot for delirium prevalence. Delirium prevalence was similar in both groups with significant heterogeneity in the analysis. *df* = degrees of freedom, M-H = Mantel-Haenszel.

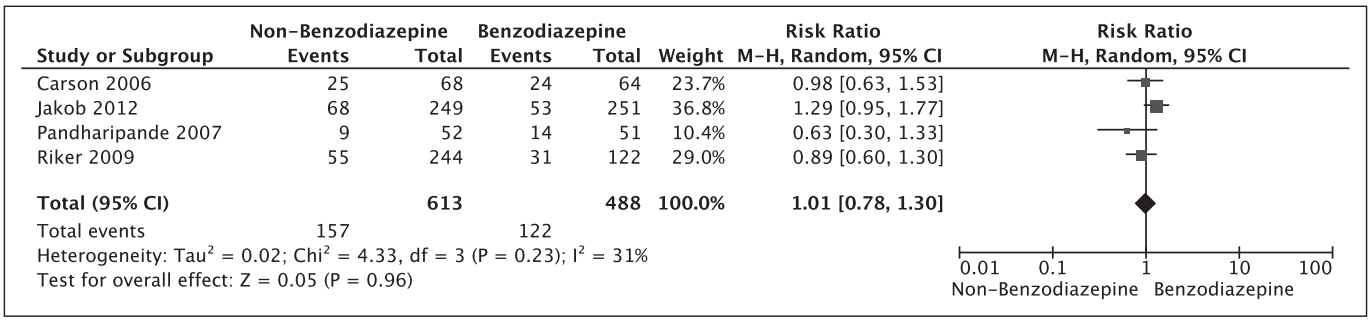

Figure 7. Forrest plot for all-cause short-term mortality. There was no significant difference between groups. *df* = degrees of freedom, M-H = Mantel-Haenszel.

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