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Meta-analysis review

Sedation management in mechanically ventilated intensive care unit patients: Meta-analysis review

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ABSTRACT

Sedation is crucial for managing mechanically ventilated intensive care unit (ICU) patients, but agents differ in their effects. Propofol, benzodiazepines and α_2-agonists are commonly used, yet their comparative impact remains unclear. This review searched OVID MEDLINE and Embase from January 2006 to June 2025 for randomised controlled trials in adult ICU patients. The primary outcome was duration of mechanical ventilation; secondary outcomes were ICU length of stay, delirium and mortality. Twenty-six trials (N = 4,993) were included. Dexmedetomidine significantly shortened mechanical ventilation (mean difference [MD] –0.60 days; 95 % CI –0.89 to –0.31), with larger effects *versus* midazolam (MD –1.25 days) and mixed comparators (MD –1.23 days), but not *versus* propofol (MD –0.34 days). ICU stay was also reduced (MD –0.94 days; 95 % CI –1.49 to –0.39). Delirium risk decreased (odds ratio [OR] 0.58; 95 % CI 0.38–0.87). No mortality difference was found. Dexmedetomidine is therefore associated with a modest but clinically meaningful reduction in ventilation time, ICU stay and delirium, particularly when compared with benzodiazepines, though benefits over propofol are less certain.

Keywords: dexmedetomidine, sedation, mechanical ventilation, intensive care unit, midazolam

INTRODUCTION

Sedation is a fundamental component of care for critically ill patients receiving invasive mechanical ventilation (MV) in the intensive care unit (ICU) (1). While it is necessary to alleviate pain, reduce anxiety, and facilitate ventilator synchrony, excessive or inappropriate sedation has been associated with adverse outcomes, including prolonged ventilation, increased incidence of delirium and higher mortality (2–4). Evidence from trials and guideline recommendations consistently supports the use of the minimum possible level of sedation to reduce the risks of prolonged ventilation, delirium and adverse outcomes (5, 6).

A variety of sedative agents are currently used in intensive care units, most commonly propofol, benzodiazepines such as midazolam and lorazepam, and alpha-2 adrenergic receptor agonists, including dexmedetomidine and clonidine (1). Propofol and midazolam remain the most frequently administered agents in many countries due to familiarity, ease of titration and cost considerations (1, 7). However, concerns have been raised about benzodiazepines given their association with increased rates of delirium and

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prolonged sedation. Dexmedetomidine, a selective alpha-2 agonist, has emerged as a widely used alternative and is recommended particularly when light sedation or delirium prevention (8). Previous studies suggest that dexmedetomidine may reduce the risk of delirium compared with propofol and benzodiazepines, although it does not show a clear benefit on major clinical outcomes such as mortality and duration of mechanical ventilation (9, 10). Clonidine, another alpha-2 agonist with broader receptor activity, is used in some ICUs due to its lower cost and availability in both intravenous and enteral formulations. However, high-quality comparative data on clonidine are limited, and its role in ICU sedation remains less defined (11).

Despite numerous studies and systematic reviews, prescribing patterns remain heterogeneous, and the optimal sedative regimen continues to be debated. Previous reviews were conducted prior to the publication of recent large-scale trials, and few have directly compared multiple agents with a consistent focus on clinically meaningful outcomes (12–14).

To address this gap, we conducted this meta-analysis to provide an updated summary of current evidence about sedation strategies in mechanically ventilated ICU patients. We aimed to assess the effect of different sedative regimens on the duration of mechanical ventilation, with secondary analyses of ICU stay, mortality, delirium and adverse events.

EXPERIMENTAL

Search strategy and selection criteria

This report followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15) (Table SI). The following electronic databases were searched: OVID MEDLINE and Embase from January 2006 to June 2025. Full details of the search strategy are provided in Supplementary Table SII.

We included randomised controlled trials (RCTs) that evaluated sedation strategies for adults (≥ 18 years old) receiving invasive mechanical ventilation in intensive care unit settings. To be included, studies needed to report the primary clinical outcome, which is the duration of MV, at least. Results were limited to the English language. Conference abstracts were excluded due to insufficient data for quality assessment, along with inaccessible studies, case reports, and editorials. Studies focusing on perioperative sedation or without reporting the duration of MV were excluded.

Titles and abstracts of all identified studies were independently reviewed by three reviewers using eligibility criteria. Studies included for full-text screening were also reviewed by independent reviewers. Disagreements were resolved through consensus discussion, with consultation of an additional reviewer if needed.

Data extraction

Authors independently extracted the following data from each article using a standardized study form: (*i*) study information, including geographic location, publishing year, research design, sample size, length of following up and number of institutions included; (*ii*) characteristics of participants, including mean/median age, percentage of women, specialties, ethnicity, sedatives used, sedation scale, and (*iii*) weaning protocol use outcomes, including all clinical outcomes mentioned below, and data for calculating effect size (*e.g.*, days, number of events, mean, odds ratio).

The primary outcome is the duration of MV. Secondary outcomes are ICU length of stay, all-cause mortality, and delirium at ICU admission. Two authors independently reviewed each trial for risk of bias, using the second version of the Cochrane risk of bias tool for randomised trials (RoB2).

Statistical analysis

The effect sizes were measured using odds ratio (OR) and mean difference (MD) for binary and continuous outcomes, resp., with respective 95 % confidence interval (CI) and *p*-value. A random-effects model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Heterogeneity among studies was evaluated by the I^2 test (16), with values greater than 50 % suggesting substantial heterogeneity. Subgroup analyses, defined *a priori* (sedative agents), were done to explore potential sources of heterogeneity. Cochrane Collaboration's tool for assessing risk of bias in RCTs (RoB 2) (17) was used to assess study quality (Table SII). Bias secondary to small study effects was investigated using funnel plots and the Egger test. We used R, version 4.4.1 (R Foundation for Statistical Computing, Austria) for all analyses. Statistical tests were 2-sided and used a significance threshold of $p < 0.05$.

RESULTS AND DISCUSSION

The search strategy defined in the protocol found 4,682 publications. We included a total of 27 trials, randomising 4,993 participants from 26 studies (18–43). The results of the search and reasons for study exclusion are detailed in Fig. 1. Studies were conducted across

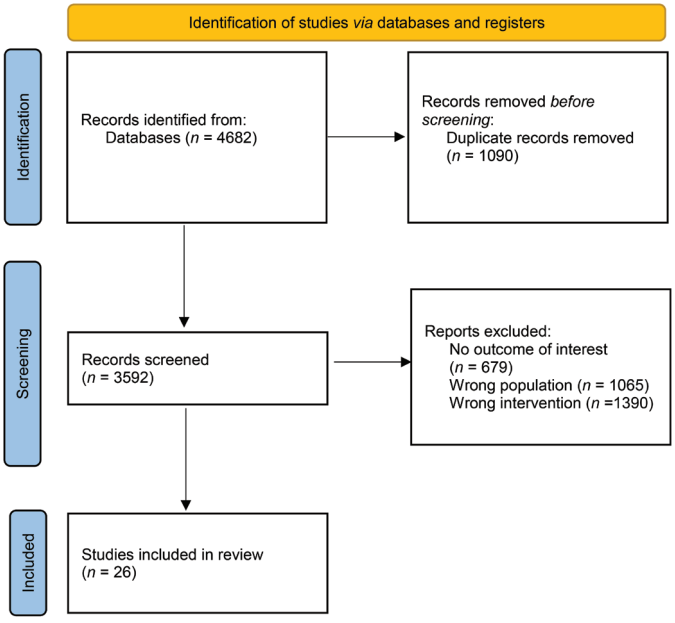

Fig. 1. PRISMA diagram.

Table I. Summary of the included papers

Report outcome	Agent for sedation	Sample size	Country	Ref.
MV duration + mortality + ICU LOS	Dexmedetomidine *vs.* midazolam/ propofol	70	Switzerland	26
MV duration + mortality + ICU LOS	Lorazepam *vs.* propofol	132	USA	19
MV duration + delirium + ICU LOS	Dexmedetomidine *vs.* propofol	200	China	31
MV duration + ICU LOS	Dexmedetomidine *vs.* propofol	72	India	36
MV duration + ICU LOS	Dexmedetomidine *vs.* midazolam	60	Egypt	18
MV duration + delirium + mortality + ICU LOS	Ciprofol *vs.* propofol	135	China	32
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* control	90	South Korea	29
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* midazolam/ propofol	37	Australia/ New Zealand	41
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* lorazepam	106	USA	35
MV duration + delirium + ICU LOS	Dexmedetomidine *vs.* propofol	60	Taiwan	20
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* midazolam/ propofol	85	Europe	40
MV duration + mortality + ICU LOS	Dexmedetomidine *vs.* propofol	80	China	30
MV duration + ICU LOS	Sevoflurane *vs.* propofol	99	Sweden	25
MV duration + ICU LOS	Dexmedetomidine *vs.* midazolam	40	India	24
MV duration + ICU LOS	Dexmedetomidine *vs.* midazolam	500	Europe	27
MV duration + ICU LOS	Dexmedetomidine *vs.* propofol	498	Europe	27
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* midazolam	23	USA	33
MV duration + delirium + ICU LOS	Dexmedetomidine *vs.* midazolam/ propofol	85	Switzerland	40
MV duration + mortality + ICU LOS	Dexmedetomidine *vs.* placebo	20	Australia	38
MV duration + mortality + ICU LOS	Dexmedetomidine *vs.* placebo	71	Australia	37
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* midazolam	366	USA	39
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* placebo	299	Australia	42
MV duration + ICU LOS	Dexmedetomidine *vs.* ketofol	24	Egypt	23
MV duration + delirium + ICU LOS	Dexmedetomidine *vs.* propofol	183	Canada	22
MV duration + mortality + ICU LOS	Dexmedetomidine *vs.* clonidine *vs.* propofol	1,404	UK	43
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* propofol	89	USA	21
MV duration + delirium + mortality + ICU LOS	Dexmedetomidine *vs.* midazolam	101	Iran	34
MV duration	Dexmedetomidine *vs.* propofol	64	Turkey	28

ICU – intensive care unit, MV – mechanical ventilation, LOS – length of stay

a broad range of clinical and geographical settings. Most of the trials were developed in North America (n = 6) and Europe (n = 7). Most studies enrolled mixed medical-surgical ICU populations, though several focused on post-cardiac surgery or trauma patients. Detailed study characteristics are provided in Table I.

Duration of mechanical ventilation

There are 25 RCTs comparing dexmedetomidine with other sedatives in adult patients receiving invasive mechanical ventilation (Fig. 2) (18, 20–24, 26–31, 33–43). In the primary random-effects meta-analysis, dexmedetomidine was associated with a modest but statistically significant reduction in MV duration (mean difference [MD] –0.60 days; 95 % CI –0.89 to –0.31; $p < 0.001$), though with substantial heterogeneity (I^2 = 99 %).

Group analyses revealed variation by the comparator agent applied. Compared with midazolam (6 studies), dexmedetomidine significantly reduced ventilation time (MD –1.25 days; 95 % CI –2.30 to –0.20; p = 0.028; I^2 = 98.1 %) (Fig. 3). No significant difference was observed *versus* propofol (8 studies, MD –0.34 days; 95 % CI –0.74 to 0.07; p = 0.090; I^2 = 99.6 %) (Fig. S1). In studies with mixed comparators (4 studies), dexmedetomidine again showed a significant benefit (MD –1.23 days; 95 % CI –2.41 to –0.04; p = 0.046; I^2 = 17.8 %) (Fig. S2).

Three additional trials evaluated other sedative comparisons outside the scope of the main analysis. Liu *et al*. (32) reported in 2023 a mean ventilation duration of 4.8 days (standard deviation, SD, 0.9 days) with ciprofol, compared to 5.3 days (SD 1.1 days) with propofol. Hellström *et al*. in 2012 (25) found similar durations in post-cardiac surgery patients receiving sevoflurane (mean 0.13 ± 0.05 days) and propofol (0.15 ± 0.05 days). In contrast, Shannon *et al*. in 2006 (19) observed substantially longer ventilation in patients sedated with lorazepam (mean 16.8 days) compared to those receiving propofol (7.7 days).

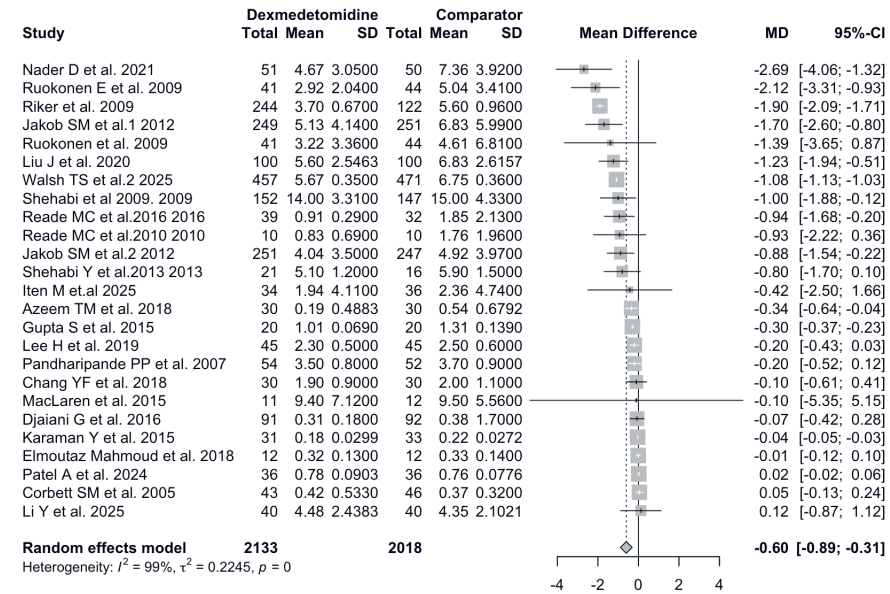

Fig. 2. Forest plot of duration of MV comparing dexmedetomidine to other sedative agents

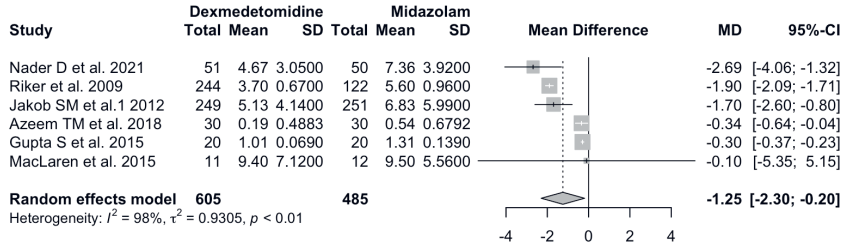

Fig. 3. Forest plot of duration of MV comparing dexmedetomidine to midazolam.

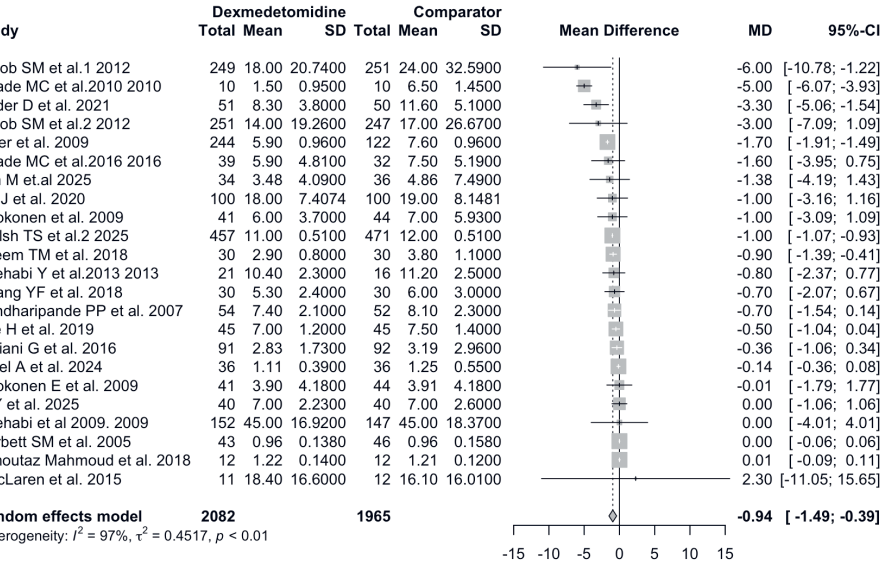

Fig. 4. Forest plot of length of ICU stay comparing dexmedetomidine to other sedative agents.

Length of ICU stay

A meta-analysis of 23 randomised controlled trials evaluating dexmedetomidine *versus* other sedatives reported a pooled mean difference in ICU length of stay of –0.94 days (95 % CI –1.49 to –0.39; p = 0.002), indicating a statistically significant reduction in ICU length of stay associated with dexmedetomidine use. Substantial between-study heterogeneity was observed (I^2 = 97.2 %), suggesting variability in effect estimates across trials (Fig. 4).

Mortality and delirium

A total of 15 trials reported mortality data comparing dexmedetomidine with alternative sedative agents. Meta-analysis demonstrated no statistically significant difference in all-cause mortality between groups (odds ratio [OR], 0.84; 95 % CI 0.70 to 1.01; p = 0.062) (Fig. S3).

The association with delirium was reported in 13 trials. Dexmedetomidine was associated with a significantly lower odds of developing delirium (OR, 0.58; 95 % CI 0.38 to 0.87; $p = 0.0137$; $I^2 = 44.7$ %) (Fig. S4).

A funnel plot of the included trials for the primary outcome (duration of mechanical ventilation) is shown in Fig. S5. Egger's regression test did not indicate statistically significant asymmetry (intercept = –3.27, $p = 0.138$), suggesting no strong evidence of publication bias.

This meta-analysis synthesises evidence from 26 randomised controlled trials evaluating the clinical effects of dexmedetomidine compared with other sedative agents in mechanically ventilated adult ICU patients. The findings demonstrate that dexmedetomidine is associated with a modest but statistically significant reduction in the duration of mechanical ventilation and ICU stay. It was also associated with a significantly lower incidence of delirium, although no difference in all-cause mortality was observed compared with other sedatives.

Our findings are broadly consistent with prior evidence suggesting that dexmedetomidine, through its selective α_2-adrenoceptor agonism, facilitates a lighter, more rousable sedation state that may support earlier weaning and reduced ventilator dependence. Randomised trials, such as those by Jakob *et al*. (27) and Riker *et al*. (39), reported significantly shorter time to extubation with dexmedetomidine compared to midazolam, and these results have been reinforced by meta-analyses demonstrating reduced ventilation duration and ICU stay, particularly when compared with benzodiazepines. These benefits have been attributed to preserved respiratory drive, reduced risk of oversedation, and improved patient-ventilator synchrony. However, such effects are not consistently observed in comparisons with other sedatives like propofol. Trials focusing on dexmedetomidine, including the SPICE III trial (44) and the MENDS 2 trial (45), have shown minimal differences. These neutral findings may reflect the similar pharmacokinetic properties of dexmedetomidine and propofol, and their shared capacity to facilitate light, titratable sedation with rapid offset, in contrast to the prolonged effects seen with benzodiazepines.

The observed benefits of dexmedetomidine appear more distinct when compared with benzodiazepines, particularly midazolam, a finding supported by previous studies (46, 47). Benzodiazepines have been associated with delayed emergence from sedation, prolonged ventilation, and increased risk of ICU-acquired delirium, especially when used continuously and without protocolised light sedation targets. These pharmacological effects (46, 47) are largely attributable to their longer half-lives, active metabolites, and gamma-aminobutyric acid-related (GABAergic) mechanisms, which can impair arousal and cognitive recovery. In contrast, dexmedetomidine promotes a lighter, more rousable sedation without respiratory depression, which may support earlier assessment for extubation (48). However, this comparative advantage is context-dependent. When compared with propofol, the differences in clinical outcomes like ventilation duration and delirium appear attenuated (49, 50). While dexmedetomidine may offer advantages in specific populations or settings, especially where preservation of cognitive function or communication is prioritised, propofol remains a mainstay of ICU sedation due to its tiltability and hemodynamic profile (49, 50). These findings highlight the need for individualised sedative selection, tailored to patient condition, therapeutic goals, and care setting, rather than generalised assumptions about drug superiority.

It is important to note that our meta-analyses of secondary outcomes, including ICU length of stay, delirium and mortality, were restricted to studies that reported the primary outcome of mechanical ventilation duration. As a result, several trials that may have provided relevant data on these secondary endpoints were not included. This introduces the possibility of selective outcome availability, which could influence pooled estimates and limit the comprehensiveness of our synthesis for these outcomes. While the decision to focus on studies reporting the primary outcome ensured consistency in the study population and intervention comparison, it may have excluded valuable information from otherwise rigorous trials that did not report ventilation duration. Future reviews may consider a broader inclusion framework when addressing secondary endpoints.

Limitations of the study

This study has several limitations. First, heterogeneity in ventilation duration was moderate to high, reflecting variation in ICU protocols, sedation targets, comparator drugs, and patient populations. Subgroup analyses by comparator class addressed some of this, but residual variation remains. Second, many included studies were small and single-centred, which may limit generalisability and inflate effect size estimates. Additionally, pooling of continuous outcomes such as ventilation duration and ICU stay required conversion from medians and interquartile ranges to means and standard deviations using statistical approximations. These conversions assume normal distributions and may bias results, particularly in skewed datasets. Finally, extubation-related outcomes such as ventilator-free days or predefined extubation windows were not consistently reported, limiting our ability to assess more nuanced measures of ventilator liberation. Future trials should aim to adopt uniform sedation and extubation endpoints and ensure comprehensive reporting of outcomes.

CONCLUSIONS

This meta-analysis provides updated evidence that dexmedetomidine, when compared with other commonly used sedatives in adult ICU patients receiving mechanical ventilation, is associated with modest reductions in ventilation duration and ICU stay, and a significantly lower incidence of delirium. These benefits were most evident in comparisons with benzodiazepines, while differences were attenuated when compared with propofol. These findings reinforce current guideline recommendations favouring non-benzodiazepine sedatives and suggest that dexmedetomidine may be a useful component of light-sedation strategies in selected ICU populations. Further large-scale trials are warranted to clarify its role across diverse clinical settings, especially in comparison with propofol and in patient groups at high risk of sedation-related complications.

Acronyms, abbreviations, symbols. – CI – confidence interval, GABA – gamma-aminobutyric acid, ICU – intensive care unit, LOS – length of stay, MD – mean difference, MV – mechanical ventilation, OR – odds ratio, PRISMA – preferred reporting items for systematic reviews and meta-analyses, RCT – randomised controlled trial, RoB 2 – risk of bias 2 tool (Cochrane), SD – standard deviation.

Availability of data and materials. – All data generated or analyzed during this study are included in the published article.

Competing interests. – The authors declare that they have no competing interests.

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Authors contributions. – Conceptualisation, D.L.; methodology, D.L.; investigation, F.Y.; formal analysis, F.Y.; visualisation, F.Y.; validation, D.L.; writing, original draft preparation, F.Y.; writing, review and editing, D.L.; funding acquisition, F.Y. Both authors have read and agreed to the published version of the manuscript.

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