South African National Department of Health
Brief Report of Rapid Review

Component: Tertiary and Quaternary Hospital Level

TITLE: Dexmedetomidine compared to standard of care for sedation in mechanically ventilated patients

Date: July 2023

Key findings

- Several agents are available on the Essential Medicines List for sedation of intensive care patients including midazolam IV, morphine IV, propofol IV, ketamine IV, and lorazepam IV. The agents have differing side effect profiles, including delirium; and it has been proposed that dexmedetomidine may be more efficacious and a preferable agent for reducing the risk of delirium in this group of patients.
- We conducted a rapid search of the literature to explore the safety and efficacy of dexmedetomidine compared to standard of care for sedation in mechanically ventilated intensive care patients .
- We included one systematic review and one RCT and their quality was assessed using AMSTAR 2 and the Cochrane Risk of Bias tool, respectively. Quality of the systematic review was rated as high and the RCT was considered to have a high risk of bias.
- A meta-analysis was conducted to pool estimates from the studies included in the systematic review and the RCT.
- Effects of the intervention
  - Outcome 1.1. Duration of mechanical ventilation days
    Dexmedetomidine likely reduces the duration of mechanical ventilation (days) (Mean difference -0.92, 95% CI -1.71 to -0.07, 4 trials , n=4982, p=0.02, I^2=0%, moderate certainty evidence).
  - Outcome 1.2. Length of stay in intensive care unit
    Dexmedetomidine may increase the length of stay {LOS} (days) in ICU (MD 0.03, 95% CI -3.46 to 3.51, 5 trials, n=5104 participants, p=0.99, i2=16%, low certainty evidence).
  - Outcome 1.3 Risk of delirium
    There is very uncertain evidence regarding the effects of dexmedetomidine on the risk of delirium (RR 0.89, 95% CI 0.74 to 1.08, 7 trials, n=5502 participants, p=0.25, i^2=72%, very low certainty evidence).
  - Outcome 1.4. Mortality
    Dexmedetomidine likely results in little to no difference in mortality (RR 1.00, 95% CI 0.92 to 1.09, 7 trials, n=5495 participants, p=0.99, i2=0%, moderate certainty evidence).
  - Outcome 1.6. Adverse events (risk of bradycardia)
    Dexmedetomidine may result in an increase in the risk of bradycardia (RR 3.31, 95% CI 1.65 to 6.66, 7 trials, n=5505 participants5,6, p=0.0008, I2=81%, low certainty evidence).
  - Outcome 1.7. Adverse events (risk of hypotension)
    Dexmedetomidine may result in an increase in the risk of hypotension (RR 1.76, 95% CI 0.98 to 3.17, 7 trials, 5505 participants5,6, p=0.06, i2=84%, low certainty evidence).
- Certainty of evidence ranged from Very Low to Moderate
- Dexmedetomidine is more resource intensive than alternative options on the EML.

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

Rationale: The Tertiary and Quaternary Hospital Level Committee suggests not to use dexmedetomidine for sedation in patients in intensive care requiring mechanical ventilation.

Dexmedetomidine is likely to reduce mechanically ventilated days slightly (less than a day) compared to standard of care, however little or no difference was found for mortality, or length of stay in intensive care, and the evidence was very uncertain for risk of delirium. Dexmedetomidine may result in an increase in risk of bradycardia and hypotension.

Dexmedetomidine is more resource intensive that other options on the EML available for sedation in the intensive care.

Level of Evidence: Certainty of evidence ranged from Very low (Risk of delirium), Low (Length of stay in ICU, Bradycardia, Hypotension), to Moderate (Duration of mechanical ventilation, Mortality).

(Refer to appendix 1 for the evidence to decision framework)

Table 1: Summary of findings

Dexmedetomidine compared to traditional sedatives for critically ill mechanically ventilated patients

Patient or population: critically ill mechanically ventilated patients
Setting: ICU/Intensive care
Intervention: Dexmedetomidine
Comparison: traditional sedatives

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with traditional sedatives	**Risk with Dexmedetomidine**				
Duration of mechanical ventilation	The median duration of mechanical ventilation ranged from **3.3-6.8** days	MD **0.92 days fewer** (1.72 fewer to 0.12 fewer)	-	4982 (4 RCTs)	⊕⊕⊕◯ Moderate[a]	Dexmedetomidine likely reduces duration of mechanical ventilation slightly.
LOS in ICU	The median LOS in ICU ranged from **5.7-10.1** days	MD **0.03 days more** (3.46 fewer to 3.51 more)	-	5104 (5 RCTs)	⊕⊕◯◯ Low[a,b]	Dexmedetomidine may increase length of stay ICU slightly.
Risk of delirium	380 per 1,000	**339 per 1,000** (282 to 411)	**RR 0.89** (0.74 to 1.08)	5502 (7 RCTs)	⊕◯◯◯ Very low[b,c,d]	The evidence is very uncertain about the effect of dexmedetomidine on risk of delirium.
Mortality follow-up: range 30 days to 90 days	267 per 1,000	**267 per 1,000** (245 to 291)	**RR 1.00** (0.92 to 1.09)	5495 (7 RCTs)	⊕⊕⊕◯ Moderate[c]	Dexmedetomidine likely results in little to no difference in mortality.
Risk of bradycardia	28 per 1,000	**92 per 1,000** (46 to 185)	**RR 3.31** (1.65 to 6.66)	5505 (7 RCTs)	⊕⊕◯◯ Low[c,d]	Dexmedetomidine may result in a large increase in the risk of bradycardia.
Risk of hypotension	53 per 1,000	**93 per 1,000** (52 to 167)	**RR 1.76** (0.98 to 3.17)	5505 (7 RCTs)	⊕⊕◯◯ Low[c,d]	Dexmedetomidine may result in a large increase in the risk of hypotension.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgrade by 1 level due to serious risk of bias: all studies at high overall risk of bias

b. Downgraded by 1 level due to imprecision: effect ranges from significant benefit to significant harm

c. Downgraded by 1 level due to risk of bias: Six of seven studies at high risk of bias

d. Downgraded by 1 level due to inconsistency: Moderate heterogeneity present

BACKGROUND

Patients who are critically ill in intensive care often undergo uncomfortable procedures such as mechanical ventilation. In order to minimise pain, anxiety and prevent potential adverse effects such as delirium, sedation is recommended.[1] Several sedative agents are available in the public sector's intensive care setting; namely midazolam IV, morphine IV, propofol IV, ketamine IV, and lorazepam IV however with differing side effect profiles, including delirium. Dexmedetomidine, an α2-agonist, is proposed to have a better side effect profile in terms of prevention of delirium and respiratory effects.[2] [3] Literature and guidelines vary in evidence and recommendations for dexmedetomidine[4], thus a medicine review was conducted assess the evidence for ICU patients who require mechanical ventilation.

RESEARCH QUESTION

How effective and safe is dexmedetomidine compared to standard of care for sedation in mechanically ventilated, intensive care patients?

ELIGIBILITY CRITERIA FOR REVIEW

Table 2: PICO for medicine review

Population:	Mechanically ventilated, intensive care, **adult (≥ 18 years) patients requiring sedation**
Intervention:	Dexmedetomidine IV
Comparators:	Midazolam IV, morphine IV, propofol IV, ketamine IV, lorazepam IV
Outcomes:	Outcomes: • Reduction in mechanical ventilation days • Reduction in intensive care length of stay • Incidence of delirium • ICU mortality • Cardiovascular stability • Adverse events within ICU (self-extubation or reintubation) • Reduction in length of hospital stay • Total dose of sedation • Total opioid use
Study designs:	Systematic reviews of RCTs (meta-analysis), RCTs

METHODS

A search of the evidence (systematic reviews) was conducted in PubMed, Cochrane Library, and Epistemonikos in November 2022. The search strategy is outlined in Appendix 2. Screening and selection of articles were conducted independently by two reviewers (MM and PS). Another search was carried out in February 2023 to identify RCTs published after the publication of the most recent systematic review identified. Data extraction was conducted by two reviewers (MM and PS) and reviewed by the ERC. The methodological quality of included systematic reviews was conducted using AMSTAR 2[5] by two reviewers (SD and KM). The risk of bias of primary studies was assessed using the Cochrane risk of bias tool; assessed by one reviewer (SD) and checked by a second reviewer (KM). For studies included in the selected systematic reviews, the risk of bias assessments carried out by the review authors were used. The overall risk of bias for each study was assessed as: i) Low risk of bias: low risk of bias for all key domains; ii) Unclear risk of bias: unclear risk of bias for one or more key domains. , or iii) High risk of bias: high risk of bias for one or more key domains.

Where possible data from individual studies included in the selected systematic reviews and other primary studies were pooled using random effects meta-analysis in RevMan 5.4.1. For dichotomous outcomes, RR was used and mean difference (MD) utilised for continuous outcomes. Where necessary

and possible, medians and IQRs were transformed into means and standard deviations using the quantile estimation methodology described by McGrath and colleagues.[6]

The certainty of the evidence was assessed for key outcomes (duration of mechanical ventilation, LOS in ICU, risk of delirium, mortality, risk of bradycardia, and risk of hypotension) using the GRADE approach[7]. Initially, the GRADE assessment carried out for the studies in included systematic reviews was used after which one reviewer (SD) reviewed the judgements considering the addition of data from the included trial to the pool of studies informing key outcomes. Another reviewer checked the GRADE assessment changes (KM).

RESULTS

The search for systematic reviews retrieved 220 studies, of which 64 were duplicates and removed. After title and abstract screening 27 records remained. Full text review was undertaken, and one study met the eligibility criteria (See Appendix 3 – Table 1 for full list of excluded SRs). The search for eligible RCTs conducted post publication of the selected systematic review retrieved 427 records. Fifteen records remained after screening, and after full text review one RCT was included (See Appendix 3 – Table 2 for excluded RCTs). Table 3 below describes the characteristics of the include SR and RCT.

Internal Validity

The included systematic review (Chen 2015) was rated as high quality (see Appendix 5 for details of AMSTAR 2 assessment). A detailed summary of risk of bias assessments for primary studies is provided in Appendix 4 and in figure 1 below. All but two studies (Riker 2009, Pandharipande 2007) were at high overall risk of bias, due to high risk of bias in at least one key domain.

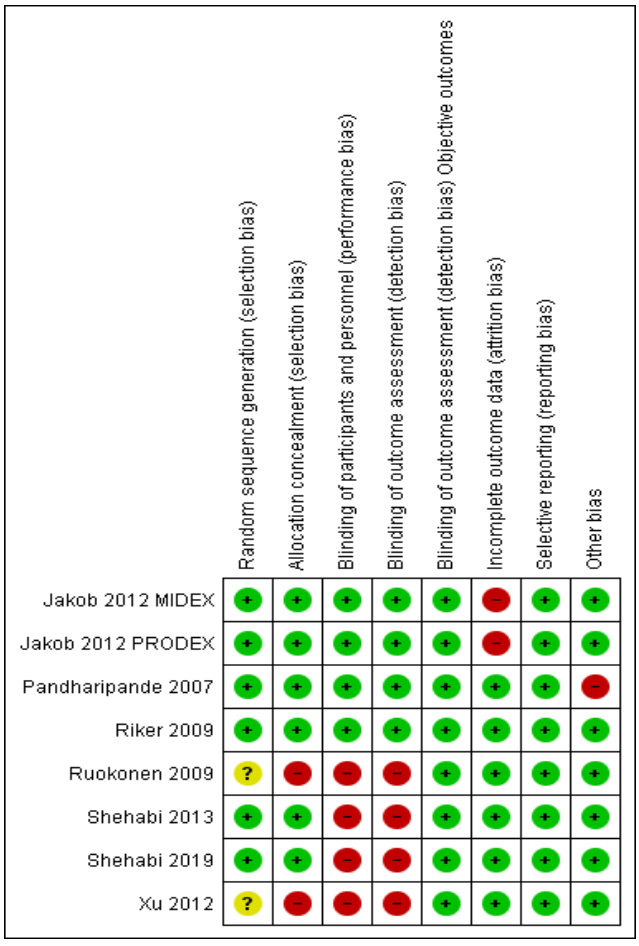


Figure 1. Risk of bias judgements about included study. *summary: review authors' each risk of bias item for each*

Description of included studies

One Cochrane review (Chen *et al*. 2015[Error! Bookmark not defined.]), including seven trials, and one RCT (Shehabi *et al*. 2019[8]) were included; they are described in Table 3 below.

Table 3. Summary of included studies

Study	Study design	Nr of included trials/ participants	Types of participants	Study designs included	Interventions	Outcomes reported
Chen 2015[Error! Bookmark not defined.]	Systematic review	7 trials (1624 participants)	Adults; critically ill patients on mechanical ventilation needing long-term sedation (more than 24 hours)	randomized and quasi-randomized controlled trials	dexmedetomidine versus alternative/ traditional sedatives (propofol, midazolam and lorazepam)	Duration of mechanical ventilation: Relative decrease 22% in the geometric mean (95% CI 10% to 33%) Risk of delirium: RR 0.85 (0.63 to 1.14) Risk of coma: RR 0.69 (0.55 to 0.86) (1 trial, n=103) Adverse events: incidence of bradycardia - RR 2.11 (1.39 to 3.2); 6 RCTs, n=1587 ICU LOS: Relative decrease 14% in the geometric mean (95% CI 0.01% to 24%); 5 RCTs, n=1223 Mortality: RR 0.99 (0.79 to 1.24); 6 RCTs, n=1584
Shehabi 2019[8]	Open-label RCT Setting: Multinational; 74 ICUs in eight countries (Australia, Ireland, Italy, Malaysia, New Zealand, Saudi Arabia, Switzerland, and the United Kingdom)	N=1948 in intervention group N=1956 in control group	Critically ill adults who had been undergoing ventilation through an endotracheal tube for less than 12 hours in the ICU and were expected to continue to receive ventilatory support for longer than the next calendar day	n/a	Intravenous dexmedetomidine started at a dose of 1 µg/kg of body weight/ hour without a loading dose and adjusted (max dose, 1.5 µg /kg/ hour) to achieve a RASS score in the target range (RASS score of −2 (lightly sedated) to +1 (restless), **vs.** usual care (propofol, midazolam, or other sedatives)	90-day all-cause mortality: 566/1948 in intervention vs 569/1956 in usual care group. Adjusted risk difference, 0.0 percentage points; 95% CI −2.9 to 2.8; P = 0.98. 180-day mortality: 609/1935 (31.5%) vs 610/1946 (31.3%); Adj RD 0.1 (−2.8 to 3.1) Cognitive function- (Mean score on Short IQCODE at 180 days: 3.14 (3.11 to 3.17) vs 3.08 (3.05 to 3.11). Adj RD: 0.06 (0.02 to 0.11) Quality of life - Mean score on the EQ-5D-3L questionnaire: 69.8 (68.5 to 71.1) vs 70.2 (69.0 to 71.5). Adj RD: −0.4 (−2.2 to 1.3) Median no. of days free from coma or delirium (IQR): 24.0 (11.0 to 26.0) vs 23.0 (10.0 to 26.0). adj RD 1.0 (0.5 to 1.5) Median no. of ventilator-free days (IQR): 23.0 (0.0 to 26.0) vs 22.0 (0.0 to 25.0) Adj. RD 1.0, 95% CI 0.4 to 1.6

Certainty of the evidence

In the review by Chen 2015, they had downgraded all outcomes because "6 of the 7 studies received funding support from pharmaceutical firms and thus publication bias was strongly suspected". However, this is not a criterion for assessing publication bias, therefore we did not downgrade the certainty of the evidence for any outcome on this basis. There were fewer than 10 studies included in meta-analysis therefore funnel plots for assessing publication bias could not be done. In other instances, the outcomes had been downgraded for imprecision, which with the addition of the Shehabi 2019 trial was not an issue anymore.

Effects of interventions

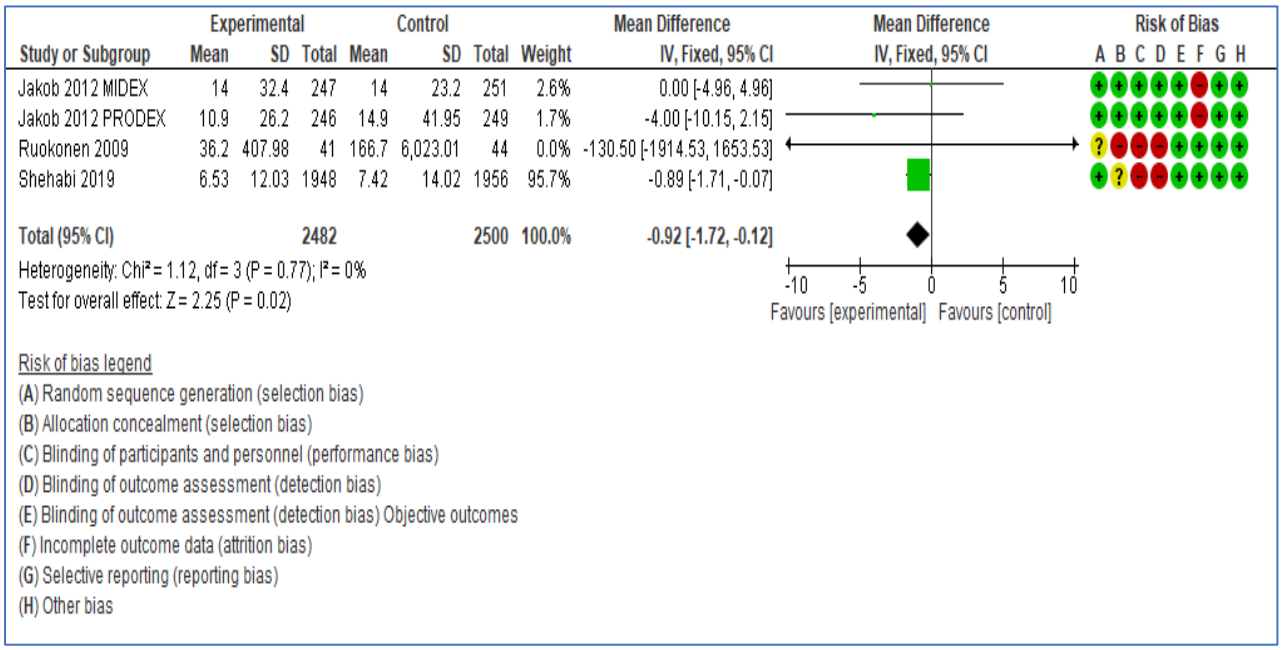
The summary of findings on key outcomes are presented in Table 1.

Data for Shehabi *et al.* 2013[9] trial could not be included for duration of mechanical ventilation or duration of ICU LOS. The only data available for these outcomes were the geometric means, which the Chen et al.[Error! Bookmark not defined.] review authors calculated based on the study obtained from trial authors. Some of the outcomes were not reported on in the included studies such as adverse events (self-extubation or reintubation), reduction in length of hospital stay, total dose of sedation and total opioid use.

Comparison 1: Dexmedetomidine compared to traditional sedatives (propofol, midazolam and lorazepam)

Outcome 1.1 - Duration of mechanical ventilation

Dexmedetomidine likely reduces the duration of mechanical ventilation (days) by less than 1 day (MD -0.92, 95% CI -1.71 to -0.07, 4 trials , n=4982[Error! Bookmark not defined.,8], p=0.02, I^2=0%, moderate certainty evidence)



(Figure 2).

Figure 2. Forest plot of comparison 1: Dexmedetomidine vs. traditional sedatives, outcome: 1.1 Duration of mechanical ventilation (days)

Shehabi *et al.* 2019[8] also reported that the median no. of ventilator-free days in the Dexmedetomidine group was higher than in the usual care group [Median (IQR): 23.0 (0.0 to 26.0) vs 22.0 (0.0 to 25.0) – in favour of dexmedetomidine; Adj. RD 1.0, 95% CI 0.4 to 1.6].

Outcome 1.2 - ICU Length of stay (LOS)

Dexmedetomidine may increase the LOS (days) in ICU (MD 0.03, 95% CI -3.46 to 3.51, 5 trials, n=5104 participants[Error! Bookmark not defined.,Error! Bookmark not defined.], p=0.99, i^2=16%, low certainty evidence, *not statistically significant* – See Figure 3).

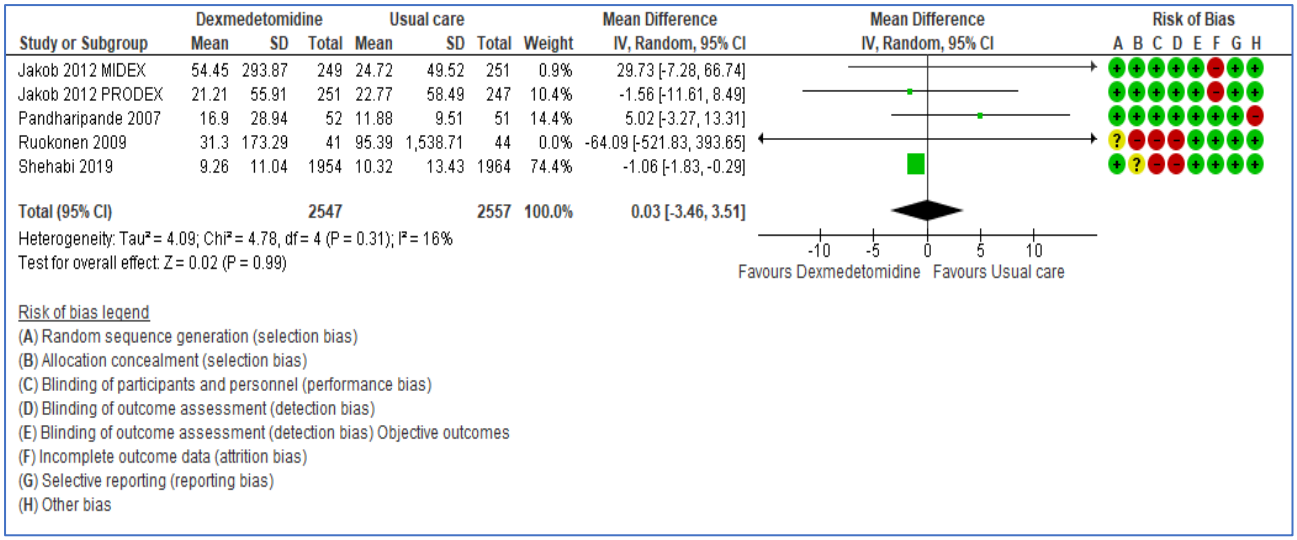


Figure 3. Forest plot of comparison1: Dexmedetomidine vs. traditional sedatives, outcome: 1.2 ICU LOS (days)

Outcome 1.3 - Risk of delirium

The evidence is very uncertain regarding the effects of dexmedetomidine on the risk of delirium (RR 0.89, 95% CI 0.74 to 1.08, 7 trials, n=5502 participants[Error! Bookmark not defined.,Error! Bookmark not defined.], p=0.25, i^2=72%, very low certainty evidence, *not statistically significant* – See Figure 4)

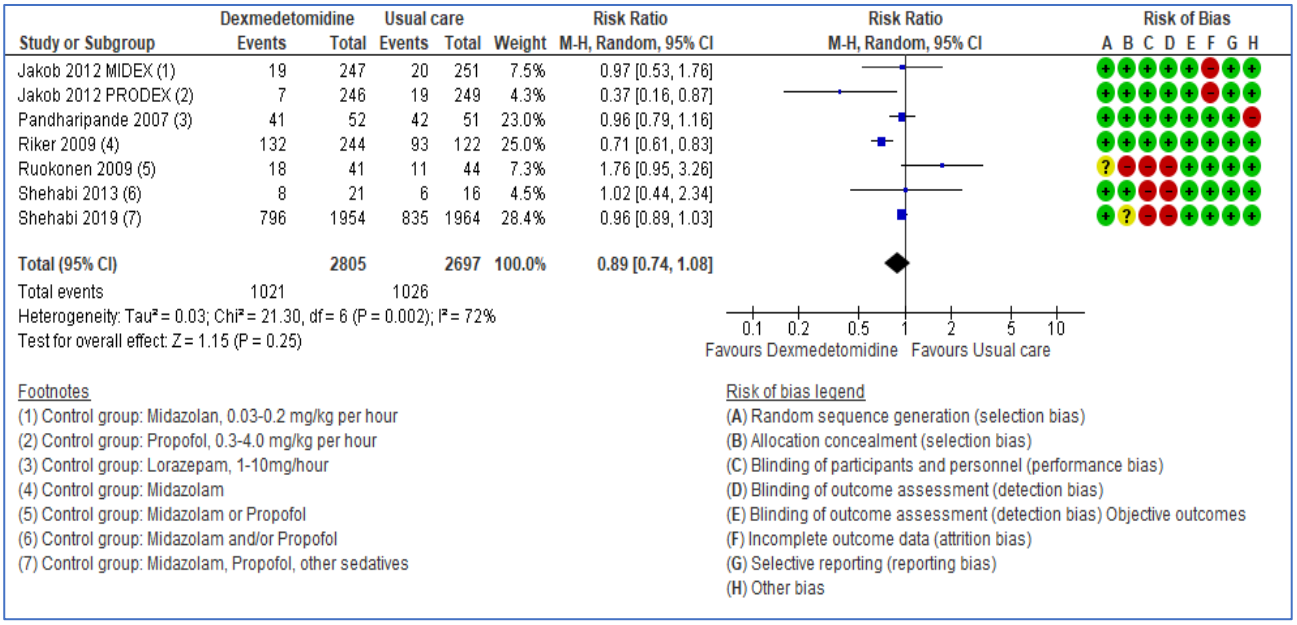


Figure 4. Forest plot of comparison 1: Dexmedetomidine vs. traditional sedatives, outcome: 1.3 Risk of delirium.

Outcome 1.4 - Mortality

Dexmedetomidine likely results in little to no difference in mortality (RR 1.00, 95% CI 0.92 to 1.09, 7 trials, n=5495 participants[Error! Bookmark not defined.,Error! Bookmark not defined.], p=0.99, i^2=0%, moderate certainty evidence, *not statistically significant* – See Figure 5).

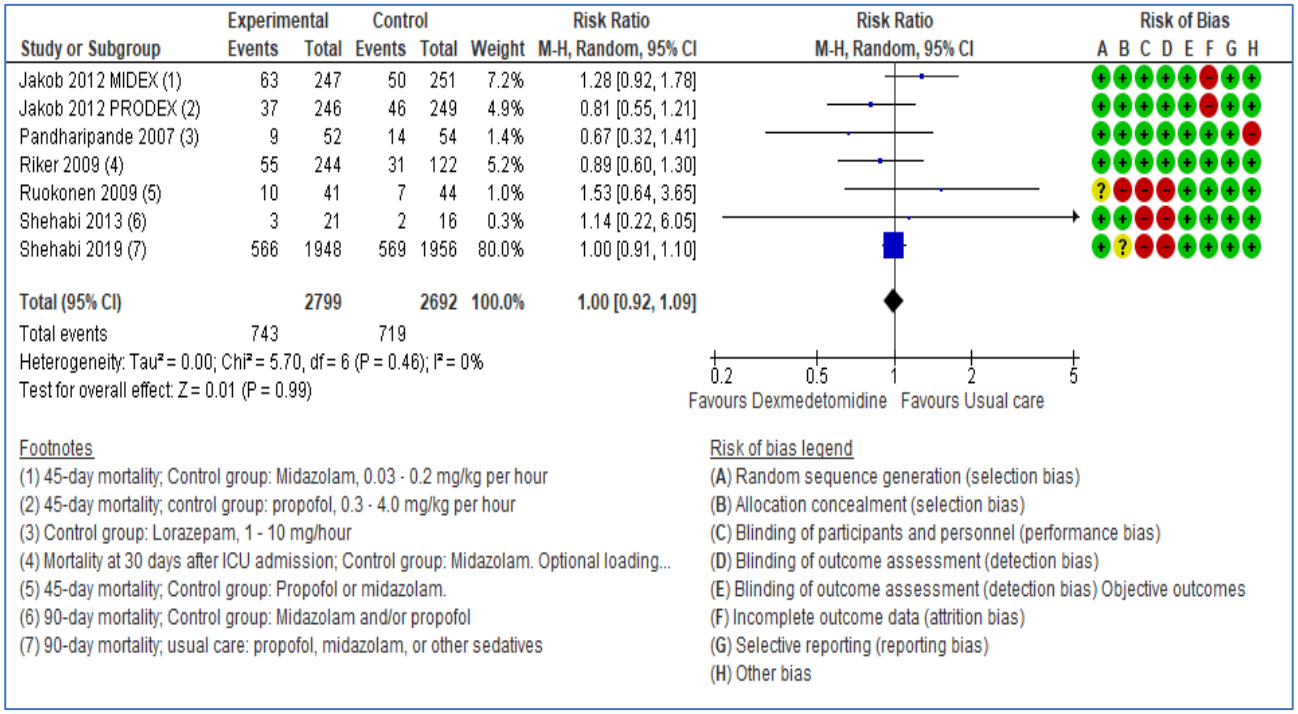


Figure 5. Forest plot of comparison 1: Dexmedetomidine vs. traditional sedatives, outcome: 1.4 Mortality.

In Shehabi *et al.* 2019[Error! Bookmark not defined.], 180-day mortality was also reported. There was no difference between the groups (609/1935 (31.5%) vs 610/1946 (31.3%); Adjusted Risk Difference 0.1, 95% CI −2.8 to 3.1.

Outcome 1.5 - Risk of coma

One trial (Shehabi *et al.* 2019[Error! Bookmark not defined.]) reported on median number of days free from coma. Those in the dexmedetomidine group had 1 more day free from coma compared to those in the usual care group [Median (IQR): 25 (14-27) vs 24 (14-26)].

Outcome 1.6 - Adverse events (bradycardia)

Dexmedetomidine may result in a large increase in risk of bradycardia (RR 3.31, 95% CI 1.65 to 6.66, 7 trials, n=5505 participants[Error! Bookmark not defined.,Error! Bookmark not defined.], p=0.0008, I^2=81%, low certainty evidence, Figure 6).

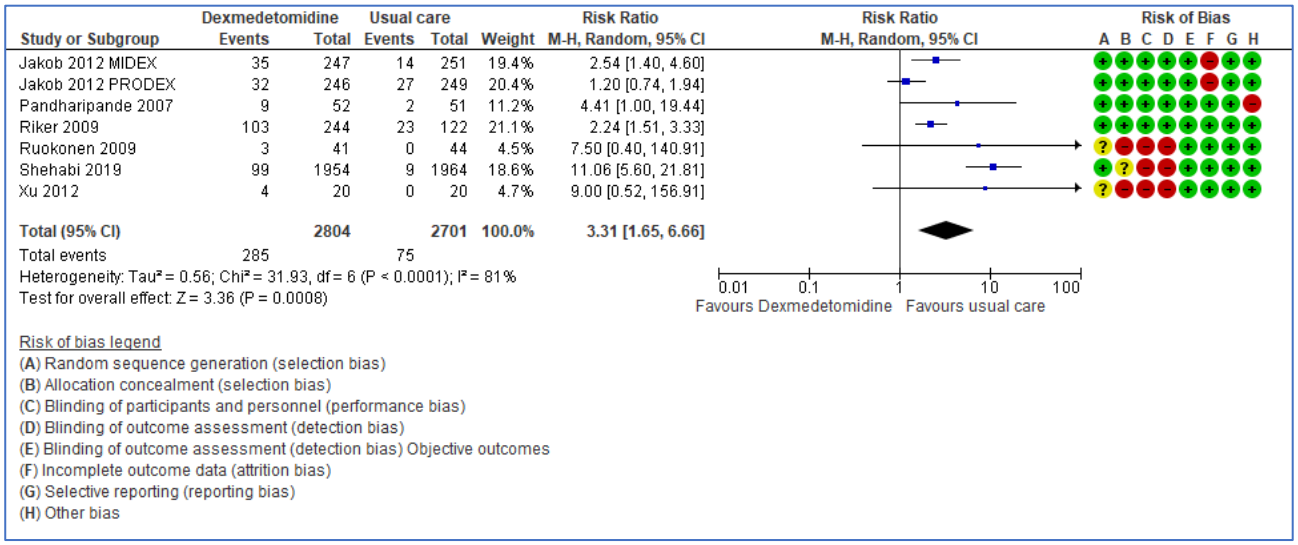


Figure 6. Forest plot of comparison 1:Dexmedetomidine vs. traditional sedatives, outcome: 1.6 Risk of bradycardia.

Outcome 1.7 - Adverse events (hypotension)

Dexmedetomidine may result in a large increase in risk of hypotension (RR 1.76, 95% CI 0.98 to 3.17, 7 trials, 5505 participants[Error! Bookmark not defined.,Error! Bookmark not defined.], p=0.06, i^2=84%, low certainty evidence, Figure 7).

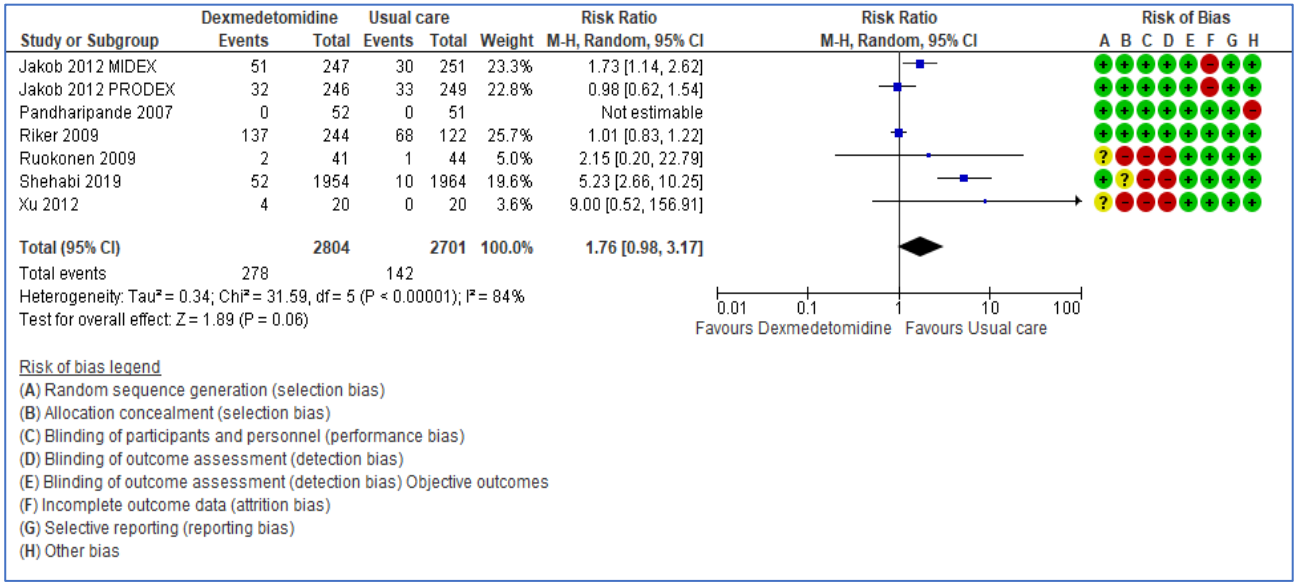


Figure 7. Forest plot of comparison 1: Dexmedetomidine vs. traditional sedatives, outcome: 1.7 Risk of hypotension.

COSTING

Table 4: Cost per day comparison

Agent	Description	mg/ vial	Price	Price per mg	Dose	Dose/ hour (70kg patient)	Cost per dose/ hour	Cost per day
Dexmedetomidine	200mcg/2ml; injection; 2 ml[i]	0,2	R228,44	R1 424,20	0.0008 mg/ kg/ hour	0,056mg	R63,96	R1 535,12
Midazolam	5mg/5ml; injection; 5 ml[ii]	5	R5,75	R1,15	0.05 mg/ kg/ hour	3,5mg	R4,03	R96,60
	50mg/10ml; injection; 10 ml[iii]	50	R19,92	R0,40	0.05 mg/ kg/ hour	3,5mg	R1,39	R33,47
Propofol	10mg/ml; injection; 20 ml[iv]	200	R13,36	R0,07	4 mg/ kg/ hour	280mg	R18,70	R448,90
Fentanyl	100mcg/2ml; injection; 2 ml[v]	0,1	R4,74	R47,40	0.0005 mg/ kg/ hour	0,035mg	R1,66	R39,82
	500mcg/10ml; injection; 10 ml	0,5	R10,35	R20,70	0.0005 mg/ kg/ hour	0,035mg	R0,72	R17,39

CONCLUSION

Standard of care for sedation of intensive care patients in need of mechanical ventilation include midazolam IV, morphine IV, propofol IV, ketamine IV, and lorazepam IV. The agents have differing side effect profiles, including delirium; and dexmedetomidine is alternative agent for the indication. A rapid review was conducted to explore the safety and efficacy of dexmedetomidine compared to standard of care for this indication. One high quality systematic review and one RCT (low risk of bias) were included in the review.

[i] Pfizer – Precedex – contract price July 2023
[ii] Accord Midazolam – contract price July 2023
[iii] Phama-Q midazolam – contract price July 2023
[iv] Biotech Laboratories – Milsia – contract price July 2023
[v] Pharma-Q fentanyl – contract price – July 2023

Meta-analysis was undertaken to pool the results of the RCT and trials from the systematic review. Dexmedetomidine is likely to reduce mechanically ventilated days slightly (less than one day) compared to standard of care, however little or no difference was found for mortality, risk of delirium or length of stay in intensive care. Dexmedetomidine may result in an increased in risk of bradycardia and hypotension and is more resource intensive than other options on the EML (midazolam, propofol and fentanyl). It is thus recommended that standard of care (agents already listed) be utilised rather than dexmedetomidine due to a much higher expense for a small or uncertain benefit and increased risk of harm.

Reviewers: Phumla Sinxadi, Malcom Miller, Solange Durao, Kim MacQuilkan

Declaration of interests:

- Phumla Sinxadi (Division of Clinical Pharmacology, Department of Medicine, University of Cape Town) – no interests to declare
- Malcolm Miller (Department of Anaesthesia and Perioperative Medicine, University of Cape Town) – no conflict of interest to declare
- Solange Durao (SAMRC, Health Systems Research Unit)*
- Kim MacQuilkan (Right to Care) has no interests to declare.
- Jane Riddin (Essential Drugs Programme) has no interests to declare

* Affiliation: South African Medical Research Council, Health Systems Research Unit. Funding: Partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: ☐ Moderate: X Low: ☐ Very low: ☐	**Outcome 1.1** - Duration of mechanical ventilation – Moderate certainty of evidence – Downgraded by 1 level due to risk of bias
	What is the certainty/quality of evidence? High: ☐ Moderate: ☐ Low: X Very low: ☐	**Outcome 1.2** – LOS in ICU (days) – Low certainty evidence - Downgraded by 1 level due to risk of bias and Downgraded by 1 level due to imprecision
	What is the certainty/quality of evidence? High: ☐ Moderate: ☐ Low: ☐ Very low: X	**Outcome 1.3** – Risk of Delirium Very Low certainty evidence - Downgraded by 1 level due to imprecision Downgraded by 1 level due to risk of bias Downgraded by 1 level due to inconsistency: Moderate heterogeneity present
	What is the certainty/quality of evidence? High: ☐ Moderate: X Low: ☐ Very low: ☐	**Outcome 1.4** – Mortality Moderate certainty of evidence – Downgraded by 1 level due to risk of bias
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☐ Small: X None: ☐	**Outcome 1.1** - Duration of mechanical ventilation Dexmedetomidine likely reduces the duration of mechanical ventilation (days) slightly MD -0.92, 95% CI -1.71 to -0.07, 4 trials , n=4982, p=0.02, I^2=0.

	What is the size of the effect for beneficial outcomes? Large: ☐ Moderate: ☐ Small: ☒ None: ☐	**Outcome 1.2** – LOS in ICU (days) Dexmedetomidine may increase the LOS (days) in ICU slightly MD 0.03, 95% CI -3.46 to 3.51, 5 trials, n=5104, p=0.99,i^2=16% .
	What is the size of the effect for beneficial outcomes? Large: ☐ Moderate: ☐ Small: ☒ None: ☐	**Outcome 1.3** – Risk of Delirium The evidence is very uncertain regarding the effects of dexmedetomidine on the risk of delirium RR 0.89, 95% CI 0.74 to 1.08, 7 trials, n=5502, p=0.25, i^2=72%.
	What is the size of the effect for beneficial outcomes? Large: ☐ Moderate: ☐ Small: ☐ None: ☒	**Outcome 1.4** – Mortality Dexmedetomidine likely results in little to no difference in mortality RR 1.00, 95% CI 0.92 to 1.09, 7 trials, n=5495, p=0.99, i^2=0%.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☒ Very low: ☐	**Outcome 1.6** – Adverse events (bradycardia) – Low Certainty evidence – Downgraded by 1 level due to risk of bias. Downgraded by 1 level due to inconsistency: Moderate heterogeneity present.
	What is the certainty/quality of evidence? High: ☐ Moderate: ☐ Low: ☒ Very low: ☐	**Outcome 1.7** – Adverse events (hypotension) – Low Certainty evidence – Downgraded by 1 level due to risk of bias. Downgraded by 1 level due to inconsistency: Moderate heterogeneity present.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☒ Moderate: ☐ Small: ☐ None: ☐	**Outcome 1.6** – Adverse events (bradycardia) Dexmedetomidine may result in a large increase in risk of bradycardia RR 3.31, 95% CI 1.65 to 6.66, 7 trials, n=5505, p=0.0008, I2=81%. Number needed to harm 1 patient = 13 patients, 95% CI 11 to 16.
	What is the size of the effect for harmful outcomes? Large: ☒ Moderate: ☐ Small: ☐ None: ☐	**Outcome 1.7** – Adverse events (hypotension) Dexmedetomidine may result in a large increase in risk of hypotension RR 1.76, 95% CI 0.98 to 3.17, 7 trials, n=5505, p=0.06, i2=84%.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: ☐ Favours control: ☒ Intervention = Control *or* Uncertain: ☐	Slight or no increase in benefits and potential large harm in terms of bradycardia

<table>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?

Yes [X] No [ ] Uncertain [ ]</td><td>.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)/day</th></tr><tr><td>Dexmedetomidine</td><td>R1 535,12</td></tr><tr><td>Midazolam</td><td>R33,47</td></tr><tr><td>Propofol</td><td>R448,90</td></tr><tr><td>Fentanyl</td><td>R17,39</td></tr></table>Additional resources:</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?

Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?

Yes [ ] No [ ] Uncertain [X]</td><td></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [ ] Uncertain [ ]</td><td>None anticipated</td></tr>
</table>

Appendix 2: Search strategy

PUBMED – November 2022 and re-run for RCTs in February 2023

Search No.	Query	Search Details	Results
6	#1 AND #2 Filters: Meta-Analysis and Systematic Review	(("critical illness"[MeSH Terms] OR "critical care"[MeSH Terms] OR "intensive care units"[MeSH Terms] OR "critically ill"[Title/Abstract] OR "critically illness*"[Title/Abstract] OR "acutely ill"[Title/Abstract] OR "critical care"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "ICU"[Title/Abstract] OR "high care"[Title/Abstract]) AND ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[Title/Abstract] OR "MPV1440"[Title/Abstract] OR "mpv 1440"[Title/Abstract] OR "Precedex"[Title/Abstract])) AND (meta-analysis[Filter] OR systematicreview[Filter])	108
5	#3 AND #4	("critical illness"[MeSH Terms] OR "critical care"[MeSH Terms] OR "intensive care units"[MeSH Terms] OR "critically ill"[Title/Abstract] OR "critically illness*"[Title/Abstract] OR "acutely ill"[Title/Abstract] OR "critical care"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "ICU"[Title/Abstract] OR "high care"[Title/Abstract]) AND ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[Title/Abstract] OR "MPV1440"[Title/Abstract] OR "mpv 1440"[Title/Abstract] OR "Precedex"[Title/Abstract]) AND (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	November 2022 = 377 February 2023 = 422
4	RCTs	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms:noexp] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	1 395 438
3	#1 AND #2	("critical illness"[MeSH Terms] OR "critical care"[MeSH Terms] OR "intensive care units"[MeSH Terms] OR "critically ill"[Title/Abstract] OR "critically illness*"[Title/Abstract] OR "acutely ill"[Title/Abstract] OR "critical care"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "ICU"[Title/Abstract] OR "high care"[Title/Abstract]) AND ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[Title/Abstract] OR "MPV1440"[Title/Abstract] OR "mpv 1440"[Title/Abstract] OR "Precedex"[Title/Abstract])	1 295
2	dexmedetomidine	"dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[Title/Abstract] OR "MPV1440"[Title/Abstract] OR "mpv 1440"[Title/Abstract] OR "Precedex"[Title/Abstract]	7 976
1	Intensive care	"critical illness"[MeSH Terms] OR "critical care"[MeSH Terms] OR "intensive care units"[MeSH Terms] OR "critically ill"[Title/Abstract] OR "critically illness*"[Title/Abstract] OR "acutely ill"[Title/Abstract] OR "critical care"[Title/Abstract] OR "intensive care"[Title/Abstract] OR "ICU"[Title/Abstract] OR "high care"[Title/Abstract]	312 075

COCHRANE – November 2022

search	Query	Results
#1	Dexmedetomidine	**6621**
#2	MeSH descriptor: [Hypnotics and Sedatives] explode all trees	**3 946**
#3	MeSH descriptor: [Critical Care] explode all trees	**2 232**
#4	#1 AND #2 AND #3	**101**
#5	#4 in Cochrane Reviews	**2**

EPISTEMONIKOS – November 2022 and February 2023

(title:((title:("intensive care") OR abstract:("intensive care")) OR (title:("critical care") OR abstract:("critical care")) OR (title:("ICU") OR abstract:("ICU")) AND (title:(dexmedetomidine) OR abstract:(dexmedetomidine))) OR abstract:((title:("intensive care") OR abstract:("intensive care")) OR (title:("critical care") OR abstract:("critical care")) OR (title:("ICU") OR abstract:("ICU")) AND (title:(dexmedetomidine) OR abstract:(dexmedetomidine)))) AND (title:(sedat*) OR abstract:(sedat*))

All studies - 119

Filtered for RCTs – 5 – same for February 2023

Filtered for systematic reviews - 42

Appendix 3. List of excluded studies

Table 2: Excluded systematic reviews and meta-analyses

Study	Reason for exclusion
Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. Intensive Care Med. 2010 Jun;36(6):926-39. doi: 10.1007/s00134-010-1877-6.	Incorrect population
Lin YY, He B, Chen J, Wang ZN. Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients? a meta-analysis. Crit Care. 2012 Sep 27;16(5):R169. doi: 10.1186/cc11646.	Incorrect population
Adams R, Brown GT, Davidson M, Fisher E, Mathisen J, Thomson G, Webster NR. Efficacy of dexmedetomidine compared with midazolam for sedation in adult intensive care patients: a systematic review. Br J Anaesth. 2013 Nov;111(5):703-10. doi: 10.1093/bja/aet194.	Incorrect population
Xia ZQ, Chen SQ, Yao X, Xie CB, Wen SH, Liu KX. Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. J Surg Res. 2013 Dec;185(2):833-43. doi: 10.1016/j.jss.2013.06.062.	Incorrect population
Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, Isella F, Zangrillo A. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically Ill patients: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2014 Dec;28(6):1459-66. doi: 10.1053/j.jvca.2014.03.010.	Only one outcome delirium
Nelson S, Muzyk AJ, Bucklin MH, Brudney S, Gagliardi JP. Defining the Role of Dexmedetomidine in the Prevention of Delirium in the Intensive Care Unit. Biomed Res Int. 2015;2015:635737. doi: 10.1155/2015/635737.	Only one outcome delirium
Serafim RB, Bozza FA, Soares M, do Brasil PE, Tura BR, Ely EW, Salluh JI. Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review. J Crit Care. 2015 Aug;30(4):799-807. doi: 10.1016/j.jcrc.2015.04.005..	Only one outcome delirium
Turunen H, Jakob SM, Ruokonen E, Kaukonen KM, Sarapohja T, Apajasalo M, Takala J. Dexmedetomidine versus standard care sedation with propofol or midazolam in intensive care: an economic evaluation. Crit Care. 2015 Feb 19;19(1):67. doi: 10.1186/s13054-015-0787-y.	Incorrect study type
Woods AD, Giometti R, Weeks SM. The use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy to decrease the severity of delirium in alcohol withdrawal in adult intensive care unit patients: a systematic review. JBI Database System Rev Implement Rep. 2015 Jan;13(1):224-52. doi: 10.11124/jbisrir-2015-1602.	Incorrect population
Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, Kress JP, Davidson JE, Spencer FA. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2013 Sep;41(9 Suppl 1):S30-8. doi: 10.1097/CCM.0b013e3182a16898.	Incorrect intervention
Caroff DA, Szumita PM, Klompas M. The Relationship Between Sedatives, Sedative Strategy, and Healthcare-Associated Infection: A Systematic Review. Infect Control Hosp Epidemiol. 2016 Oct;37(10):1234-42. doi: 10.1017/ice.2016.129.	Incorrect outcome
Constantin JM, Momon A, Mantz J, Payen JF, De Jonghe B, Perbet S, Cayot S, Chanques G, Perreira B. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med. 2016 Feb;35(1):7-15. doi: 10.1016/j.accpm.2015.06.012	Incorrect population
Cruickshank M, Henderson L, MacLennan G, Fraser C, Campbell M, Blackwood B, Gordon A, Brazzelli M. Alpha-2 agonists for sedation of mechanically ventilated adults in intensive care units: a systematic review. Health Technol Assess. 2016 Mar;20(25):v-xx, 1-117. doi: 10.3310/hta20250.	Incorrect population

Study	Reason for exclusion
Tsaousi GG, Lamperti M, Bilotta F. Role of Dexmedetomidine for Sedation in Neurocritical Care Patients: A Qualitative Systematic Review and Meta-analysis of Current Evidence. Clin Neuropharmacol. 2016 May-Jun;39(3):144-51. doi: 10.1097/WNF.0000000000000151.	Incorrect study type
Zamani MM, Keshavarz-Fathi M, Fakhri-Bafghi MS, Hirbod-Mobarakeh A, Rezaei N, Bahrami A, Nader ND. Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review. J Crit Care. 2016 Apr;32:93-100. doi: 10.1016/j.jcrc.2015.11.013.	Incorrect population
Liu X, Xie G, Zhang K, Song S, Song F, Jin Y, Fang X. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: A meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care. 2017 Apr;38:190-196. doi: 10.1016/j.jcrc.2016.10.026..	Incorrect population
Zhang Z, Chen K, Ni H, Zhang X, Fan H. Sedation of mechanically ventilated adults in intensive care unit: a network meta-analysis. Sci Rep. 2017 Mar 21;7:44979. doi: 10.1038/srep44979.	Incorrect population
Nguyen J, Nacpil N. Effectiveness of dexmedetomidine versus propofol on extubation times, length of stay and mortality rates in adult cardiac surgery patients: a systematic review and meta-analysis. JBI Database System Rev Implement Rep. 2018 May;16(5):1220-1239. doi: 10.11124/JBISRIR-2017-003488.	Incorrect population
Pavone KJ, Cacchione PZ, Polomano RC, Winner L, Compton P. Evaluating the use of dexmedetomidine for the reduction of delirium: An integrative review. Heart Lung. 2018 Nov;47(6):591-601. doi: 10.1016/j.hrtlng.2018.08.007.	Incorrect study type
Tran A, Blinder H, Hutton B, English SW. A Systematic Review of Alpha-2 Agonists for Sedation in Mechanically Ventilated Neurocritical Care Patients. Neurocrit Care. 2018 Feb;28(1):12-25. doi: 10.1007/s12028-017-0388-5.	Incorrect population
Wu M, Liang Y, Dai Z, Wang S. Perioperative dexmedetomidine reduces delirium after cardiac surgery: A meta-analysis of randomized controlled trials. J Clin Anesth. 2018 Nov;50:33-42. doi: 10.1016/j.jclinane.2018.06.045.	Incorrect population
Pan H, Liu C, Ma X, Xu Y, Zhang M, Wang Y. Perioperative dexmedetomidine reduces delirium in elderly patients after non-cardiac surgery: a systematic review and meta-analysis of randomized-controlled trials. Can J Anaesth. 2019 Dec;66(12):1489-1500. English. doi: 10.1007/s12630-019-01440-6.	Incorrect population
Abowali HA, Paganini M, Enten G, Elbadawi A, Camporesi EM. Critical Review and Meta-Analysis of Postoperative Sedation after Adult Cardiac Surgery: Dexmedetomidine Versus Propofol. J Cardiothorac Vasc Anesth. 2021 Apr;35(4):1134-1142. doi: 10.1053/j.jvca.2020.10.022.	Incorrect population
Burry LD, Cheng W, Williamson DR, Adhikari NK, Egerod I, Kanji S, Martin CM, Hutton B, Rose L. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. Intensive Care Med. 2021 Sep;47(9):943-960. doi: 10.1007/s00134-021-06490-3.	Incorrect intervention
Kyo M, Shimatani T, Hosokawa K, Taito S, Kataoka Y, Ohshimo S, Shime N. Patient-ventilator asynchrony, impact on clinical outcomes and effectiveness of interventions: a systematic review and meta-analysis. J Intensive Care. 2021 Aug 16;9(1):50. doi: 10.1186/s40560-021-00565-5.	Incorrect intervention
Lewis K, Alshamsi F, Carayannopoulos KL, Granholm A, Piticaru J, Al Duhailib Z, Chaudhuri D, Spatafora L, Yuan Y, Centofanti J, Spence J, Rochwerg B, Perri D, Needham DM, Holbrook A, Devlin JW, Nishida O, Honarmand K, Ergan B, Khorochkov E, Pandharipande P, Alshahrani M, Karachi T, Soth M, Shehabi Y, Møller MH, Alhazzani W; GUIDE group. Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials. Intensive Care Med. 2022 Jul;48(7):811-840. doi: 10.1007/s00134-022-06712-2.	Incorrect population
Wu J, Li B, Ma K, Li H, Shao X. A systematic review and meta-analysis of the clinical efficacy of the intravenous injection of dexmedetomidine in ICU patients with hyperactive brain syndrome. Ann Palliat Med. 2022 Jan;11(1):299-308. doi: 10.21037/apm-21-3762.	Incorrect population

Table 2: Excluded randomised controlled trials

Study	Reason for exclusion
Sequential use of midazolam and dexmedetomidine for long-term sedation may reduce weaning time in selected critically ill, mechanically ventilated patients: a randomized controlled study. Zhou Y, Yang J, Wang B, Wang P, Wang Z, Yang Y, Liang G, Jing X, Jin X, Zhang Z, Deng Y, Hu C, Liao X, Yin W, Tang Z, Tian Y, Tao L, Kang Y. Crit Care. 2022 May 3;26(1):122. doi: 10.1186/s13054-022-03967-5.	Primary outcomes not included, incorrect intervention
Incidence, risk factors, and outcomes for sepsis-associated delirium in patients with mechanical ventilation: A sub-analysis of a multicenter randomized controlled trial. Yamamoto T, Mizobata Y, Kawazoe Y, Miyamoto K, Ohta Y, Morimoto T, Yamamura H. J Crit Care. 2020 Apr;56:140-144. doi: 10.1016/j.jcrc.2019.12.018. Epub 2019 Dec 24	Incorrect population
Dexmedetomidine versus propofol for prolonged sedation in critically ill trauma and surgical patients. Winings NA, Daley BJ, Bollig RW, Roberts RF Jr, Radtke J, Heidel RE, Taylor JE, McMillen JC. Surgeon. 2021 Jun;19(3):129-134. doi: 10.1016/j.surge.2020.04.003. Epub 2020 Apr 25.	Incorrect population
Early sedation with dexmedetomidine in ventilated critically ill patients and heterogeneity of treatment effect in the SPICE III randomised controlled trial. Shehabi Y, Serpa Neto A, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, Kadiman SB, McArthur CJ, Reade MC, Seppelt IM, Takala J, Wise MP, Webb SA; SPICE III Study Investigators. Intensive Care Med. 2021 Apr;47(4):455-466. doi: 10.1007/s00134-021-06356-8. Epub 2021 Mar 8.	Post hoc analysis, specific sub-group only.
Sleep quality and quantity determined by polysomnography in mechanically ventilated critically ill patients randomized to dexmedetomidine or placebo. Oxlund J, Knudsen T, Sörberg M, Strøm T, Toft P, Jennum PJ. Acta Anaesthesiol Scand. 2023 Jan;67(1):66-75. doi: 10.1111/aas.14154. Epub 2022 Oct 21.	Incorrect outcome
A randomized, double-blind pilot study of dexmedetomidine versus midazolam for intensive care unit sedation: patient recall of their experiences and short-term psychological outcomes. MacLaren R, Preslaski CR, Mueller SW, Kiser TH, Fish DN, Lavelle JC, Malkoski SP. J Intensive Care Med. 2015 Mar;30(3):167-75. doi: 10.1177/0885066613510874. Epub 2013 Nov 12.	Incorrect outcome
Dexmedetomidine versus midazolam for sedation during endobronchial ultrasound-guided transbronchial needle aspiration: A randomised controlled trial. Kim J, Choi SM, Park YS, Lee CH, Lee SM, Yoo CG, Kim YW, Lee J. Eur J Anaesthesiol. 2021 May 1;38(5):534-540. doi: 10.1097/EJA.0000000000001370.	Incorrect population
Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial. Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A, Koami H, Beppu S, Katayama Y, Itoh M, Ohta Y, Yamamura H; Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) Trial Investigators. JAMA. 2017 Apr 4;317(13):1321-1328. doi: 10.1001/jama.2017.2088.	Incorrect population
Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. Hughes CG, Mailloux PT, Devlin JW, Swan JT, Sanders RD, Anzueto A, Jackson JC, Hoskins AS, Pun BT, Orun OM, Raman R, Stollings JL, Kiehl AL, Duprey MS, Bui LN, O'Neal HR Jr, Snyder A, Gropper MA, Guntupalli KK, Stashenko GJ, Patel MB, Brummel NE, Girard TD, Dittus RS, Bernard GR, Ely EW, Pandharipande PP; MENDS2 Study Investigators. N Engl J Med. 2021 Apr 15;384(15):1424-1436. doi: 10.1056/NEJMoa2024922. Epub 2021 Feb 2.	Incorrect population
Impact of dexmedetomidine on hemodynamic changes during and after coronary artery bypass grafting. Hashemian M, Ahmadinejad M, Mohajerani SA, Mirkheshti A. Ann Card Anaesth. 2017 Apr-Jun;20(2):152-157. doi: 10.4103/aca.ACA_76_16.	Incorrect population
Sedation effects by dexmedetomidine versus propofol in decreasing duration of mechanical ventilation after open heart surgery. Elgebaly AS, Sabry M. Ann Card Anaesth. 2018 Jul-Sep;21(3):235-242. doi: 10.4103/aca.ACA_168_17.	Incorrect population
The effect of dexmedetomidine on vasopressor requirements in patients with septic shock: a subgroup analysis of the Sedation Practice in Intensive Care Evaluation [SPICE III] Trial. Cioccari L, Luethi N, Bailey M, Shehabi Y, Howe B, Messmer AS, Proimos HK, Peck L, Young H, Eastwood GM, Merz TM, Takala J, Jakob SM, Bellomo R; ANZICS Clinical Trials Group and the SPICE III Investigators. Crit Care. 2020 Jul 16;24(1):441. doi: 10.1186/s13054-020-03115-x.	Incorrect population
Comparison of dexmedetomidine versus propofol on hemodynamics in surgical critically ill patients. Chang YF, Chao A, Shih PY, Hsu YC, Lee CT, Tien YW, Yeh YC, Chen LW; NTUH Center of Microcirculation Medical Research (NCMMR). J Surg Res. 2018 Aug;228:194-200. doi: 10.1016/j.jss.2018.03.040. Epub 2018 Apr 11.	Incorrect population
Stress response during early sedation with dexmedetomidine compared with usual-care in ventilated critically ill patients. Moore JPR, Shehabi Y, Reade MC, Bailey M, Fraser JF, Murray L, Anstey C, Singer M. Crit Care. 2022 Nov 22;26(1):359. doi: 10.1186/s13054-022-04237-0.	Incorrect outcome

Appendix 4. Risk of bias assessments of studies

Jakob 2012 MIDEX (assessment as in Chen 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified for study centre in blocks of 4."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible study participants were randomized 1:1 by a central interactive voice-response system funded by the sponsor to either continue their current standard care (midazolam [MIDEX trial] or propofol [PRODEX trial]) or switch to dexmedetomidine
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments."
Blinding of outcome assessment (detection bias)	Low risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, ICU length of stay (LOS), mortality Quote: "Treatments were administered in a double-dummy design, with 0.9% sodium chloride as dummy for all treatments."
Incomplete outcome data (attrition bias)	High risk	Dexmedetomidine group: 249 included in intention-to-treat analyses; 60/249 withdrawals (23 due to 'lack of efficacy'; 23 due to 'adverse or serious adverse event'; 2 due to 'protocol violation'; 16 due to 'other reasons'); 227 included in per-protocol analyses, 22 excluded (8 due to 'missing inclusion criteria'; 8 due to 'incorrect dosing'; 1 due to 'received excluded medication'; 5 due to 'missing assessments'); Midazolam group: 251 included in intention-to-treat analyses, 1 excluded due to 'withdrew consent'; 51/252 withdrawals (10 due to 'lack of efficacy'; 19 due to 'adverse or serious adverse event'; 2 due to 'protocol violation'; 21 due to 'other reasons'); 233 included in per-protocol analyses, 18 excluded (7 due to 'missing inclusion criteria'; 1 due to 'met exclusion criteria'; 6 due to 'incorrect dosing'; 2 due to 'received excluded medication'; 2 due to 'missing assessments') Comment: > 20% participants in each group withdrew. Reasons for withdrawal and exclusion were not balanced between study groups. These missing data would inevitably bias the results.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Jakob 2012 PRODEX (assessment as in Chen 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified for study centre in blocks of 4."
Allocation concealment (selection bias)	Low risk	Quote: "Eligible study participants were randomized 1:1 by a central interactive voice-response system funded by the sponsor to either continue their current standard care (midazolam [MIDEX trial] or propofol [PRODEX trial]) or switch to dexmedetomidine."

Blinding of participants and personnel (performance bias)	Low risk	Quote: "Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors."
Blinding of outcome assessment (detection bias)	Low risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, ICU length of stay (LOS), mortality Quote: "Propofol and propofol dummy were prepared, connected, and removed by independent personnel and infused with nontransparent black syringes, infusion tubings, and connectors."
Incomplete outcome data (attrition bias)	High risk	Dexmedetomidine group: 251 included in intention-to-treat analyses; 71/251 withdrawals (36 due to 'lack of efficacy'; 29 due to 'adverse or serious adverse event'; 1 due to 'Nonpharmacological intervention'; 1 due to 'protocol violation'; 7 due to 'other reasons'); 223 included in per-protocol analyses, 28 excluded (3 due to 'missing inclusion criteria'; 1 due to 'met exclusion criteria'; 7 due to 'incorrect dosing'; 1 due to 'received excluded medication'; 16 due to 'missing assessments') Propofol group: 247 included in intention-to-treat analyses, 2 excluded due to 'withdrew consent'; 60/249 withdraws from propofol group (13 due to 'lack of efficacy'; 28 due to 'adverse or serious adverse event'; 4 due to 'nonpharmacological intervention'; 3 due to 'protocol violation'; 16 due to 'other reasons'); 214 included in per-protocol analyses, 33 excluded (7 due to 'missing inclusion criteria'; 2 due to 'met exclusion criteria'; 10 due to 'incorrect dosing'; 6 due to 'received excluded medication'; 8 due to 'missing assessments') Comment: > 20% participants in each group withdrew. Reasons for withdrawal and exclusions were not balanced between study groups. These missing data would inevitably bias the results.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Pandharipande 2007 (assessment as in Chen 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized using computer-generated, permuted block randomization (known only to the investigational pharmacists) and stratified by site to receive sedation with either dexmedetomidine or lorazepam."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized using computer-generated, permuted block randomization (known only to the investigational pharmacists) and stratified by site to receive sedation with either dexmedetomidine or lorazepam."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "We used infusion instead of bolus dosing to preserve the blinding and to minimize potential adverse events. The study drug was prepared in clear bags containing either dexmedetomidine (prepared for a final concentration of 0.15 dg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1 mL/h (0.15 dg/kg per hour dexmedetomidine or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 dg/ kg per hour dexmedetomidine or 10 mg/h lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS)."
Blinding of outcome assessment (detection bias)	Low risk	Subjective outcome: risk of delirium, risk of coma, proportion of sedation time spent at target sedation level Quote: "We used infusion instead of bolus dosing to preserve the blinding and to minimize potential adverse events. The study drug was prepared in clear bags containing either dexmedetomidine (prepared for a final concentration of 0.15 dg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1

		mL/h (0.15 dg/kg per hour dexmedetomidine or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 dg/ kg per hour dexmedetomidine or 10 mg/h lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS)."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: ventilator-free days, adverse effects, ICU LOS, mortality Quote: "We used infusion instead of bolus dosing to preserve the blinding and to minimize potential adverse events. The study drug was prepared in clear bags containing either dexmedetomidine (prepared for a final concentration of 0.15 dg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1 mL/h (0.15 dg/kg per hour dexmedetomidine or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 dg/kg per hour dexmedetomidine or 10 mg/h lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS)."
Incomplete outcome data (attrition bias)	Low risk	completed study protocol; 1 withdrawal from lorazepam group (due to 'withdrawn by family'), 51 completed study protocol. Comment: Reasons for withdrawal were explicitly reported and balanced across study groups.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	High risk	Comment: This study used continuous infusion of lorazepam as a comparator, did not mandate daily interruption, and assessed sedation level infrequently. Such a study design might potentially increase the risk of coma in the control group and was considered to be a source of bias.

Riker 2009 (assessment as in Chen 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 2:1 to receive dexmedetomidine to obtain more comprehensive safety data during prolonged dexmedetomidine use."; "All patients were centrally randomized using an interactive voiceresponse system and a computer-generated schedule."
Allocation concealment (selection bias)	Low risk	Quote: "All patients were centrally randomized using an interactive voice-response system and a computer-generated schedule."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind"; "Optional blinded loading doses (up to 1 dg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 dg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the mid-point of the allowable infusion dose range."
Blinding of outcome assessment (detection bias)	Low risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Optional blinded loading doses (up to 1 dg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 dg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the mid-point of the allowable infusion dose range."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, ICU LOS, mortality Quote: "Optional blinded loading doses (up to 1 dg/kg dexmedetomidine or 0.05 mg/kg midazolam) could be administered at the investigator's discretion. The starting maintenance infusion dose of blinded study drug was 0.8 dg/kg per hour for dexmedetomidine and 0.06 mg/kg per hour for midazolam, corresponding to the mid-point of the allowable infusion dose range."

Incomplete outcome data (attrition bias)	Low risk	Quote: "A total of 375 eligible patients were randomized and 366 patients received study drug, comprising the primary analyses study population (244 patients received dexmedetomidine, 122 received midazolam). Nine patients randomized (6 in the dexmedetomidine group, 3 in the midazolam group) never received study drug" 194 included in long-term use analyses in dexmedetomidine group, 50 excluded (received study drug f 24 hours) (21 due to "extubated"; 17 due to "adverse event"; 7 due to "lack of efficacy"; 3 due to "withdrew consent"; 1 due to "entry criteria" (patient had new information after consent that identified an exclusion criterion (e.g., need for general anaesthesia, unexpected liver or cardiac disease)); 1 due to "investigator opinion" (investigator felt that patient no longer met entry criteria (e.g., extubated, no longer required sedation, required deeper sedation)); 103 included in long-term use analyses in midazolam group, 19 excluded (5 due to "adverse event"; 5 due to "lack of efficacy"; 4 due to "withdrew consent"; 4 due to "entry criteria"; 1 due to "investigator opinion") Comment: Reasons for withdrawal and exclusion were explicitly reported and balanced across study groups
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Ruokonen 2009 (assessment as in Chen 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified for study centre, current sedative, sedation target (Richmond Agitation–Sedation Scale; RASS) 0 to -3 vs. RASS -4, and admission type (medical vs. postoperative/trauma)." Comment: The authors reported they used stratified randomization, but did not state how they randomly divide participants in detail
Allocation concealment (selection bias)	High risk	Comment: The authors did not explicitly state how they concealed randomization sequence
Blinding of participants and personnel (performance bias)	High risk	Quote: "double-blind"; "Dexmedetomidine and dexmedetomidine dummy (0.9% NaCl), propofol 2% and propofol dummy (0.9% NaCl) and midazolam (0.1%) and midazolam dummy (0.9% NaCl) were prepared by personnel not involved in the study or the patient's care; infusion systems for propofol and its dummy were nontransparent."; "Depending on standard care at time of randomization, midazolam was given either as intravenous boluses (1–2 mg), starting at 3 boluses per hour for 1 h, and thereafter 1–4 boluses per hour, and if not sufficient as continuous infusion of 0.2 mg/kg/h, or as a continuous infusion at 0.12 mg/kg/h for 1 h, followed by adjustments at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/h." Comment: Bolus injection of midazolam usually acts much faster than continuous infusion of dexmedetomidine and therefore blinding could be easily broken. It is therefore possible that the investigators' decisions and actions could have been influenced.
Blinding of outcome assessment (detection bias)	High risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level Quote: "Dexmedetomidine and dexmedetomidine dummy (0.9% NaCl), propofol 2% and propofol dummy (0.9% NaCl) and midazolam (0.1%) and midazolam dummy (0.9% NaCl) were prepared by personnel not involved in the study or the patient's care; infusion systems for propofol and its dummy were nontransparent."; "Depending on standard care at time of randomization, midazolam was given either as intravenous boluses (1–2 mg), starting at 3 boluses per hour for 1 h, and thereafter 1–4 boluses per hour, and if not sufficient as continuous infusion of 0.2 mg/kg/h, or as a continuous infusion at 0.12 mg/kg/h for 1 h, followed by adjustments at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/h."

		Comment: Blinding could be easily broken. Lack of blinding might bias the assessment of subjective outcomes.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: duration of mechanical ventilation, adverse events, duration of weaning, ICU LOS, mortality Comment: Objective outcomes were not likely to be biased by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	Quote: "85 were randomized (intention-to-treat patients) to receive dexmedetomidine (DEX; n = 41) or to continue their previous standard care (SC; n = 44)"; 31 completed study treatment in dexmedetomidine group, 10 withdraws (6 due to "lack of efficacy"; 3 due to "adverse event"; 1 due to "discharge to another hospital"); 37 completed study treatment in standard group, 7 withdraws (1 due to "lack of efficacy"; 5 due to "adverse event"; 1 due to "protocol violation") Imputation roles: • If ICU discharge date exists but end of mechanical ventilation (MV) is missing MV end date is set equal to ICU discharge and participant is assumed to have been weaned from any mechanical ventilation. • If ICU discharge date and end of MV are missing g length of ICU stay and duration of MV are set to 45 days. • If ICU discharge date is missing but end of MV exists g length of ICU stay is set to 45 days and duration of MV is as observed. Comment: Reasons for withdrawal were explicitly reported and generally balanced across study groups. Conservative imputation rules were applied
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported
Other bias	Low risk	The study appears to be free of other sources of bias.

Shehabi 2013 (assessment as in Chen 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Block randomization was undertaken with concealed envelopes.”
Allocation concealment (selection bias)	Low risk	Quote: “Block randomization was undertaken with concealed envelopes.”
Blinding of participants and personnel (performance bias)	High risk	Quote: “unblinded” Comment: It was possible that the investigators’ decisions and actions could have been influenced.
Blinding of outcome assessment (detection bias)	High risk	Subjective outcome: rate of delirium, proportion of sedation time spent at target sedation level Quote: “unblinded” Comment: Lack of blinding might influence the subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: ICU LOS, mortality Comment: Objective outcomes were not likely to be biased by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study and there were no losses to follow-up, no treatment withdrawals, no trial group changes and no major adverse events.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported
Other bias	Low risk	The study appears to be free of other sources of bias.

Shehabi 2019 (assessed by SD and KM)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned in a 1:1 ratio to receive dexmedetomidine or usual care, as described below. Block randomization with a variable block size was implemented by means of a password-protected website. Randomization was stratified according to trial site and the presence or absence of suspected or proven sepsis,20 as determined by the treating clinician."
Allocation concealment (selection bias)	Low risk	From protocol: "protocol - Randomisation will be conducted through a password-protected, secure website using a central, computer-based randomisation program" .
Blinding of participants and personnel (performance bias)	High risk	"The administration of medications in our trial was unblinded" Comment: It was possible that the investigators' decisions and actions could have been influenced.
Blinding of outcome assessment (detection bias)	High risk	Subjective outcome: rate of delirium, proportion of sedation time spent at target sedation level Trial was unblinded and lack of blinding might influence the assessment of subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: ICU LOS, mortality Objective outcomes were not likely to be biased by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	53/ 2001 (2.6%) patients randomised to the Dex group and 43/1999 (2.2%) patients randomised to the usual care group were LTFU or withdrew consent. Missing data was similar between the groups and reasons provided.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported
Other bias	Low risk	The study appears to be free of other sources of bias.

Xu 2012 (assessment as in Chen 2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The authors stated that they used stratified randomization, but they did not state how they did this
Allocation concealment (selection bias)	High risk	Comment: The authors did not state how they concealed their randomization sequence. Allocation concealment was probably not done.
Blinding of participants and personnel (performance bias)	High risk	Subjective outcome: risk of delirium, proportion of sedation time spent at target sedation level. Comment: The authors did not state they used blinded methods. It was possible that the investigators' decisions and actions could have been influenced
Blinding of outcome assessment (detection bias)	High risk	Comment: The authors did not state they used blinded methods. Lack of blinding might bias the assessment of subjective outcomes, but not objective outcomes.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Objective outcome: adverse events. Comment: Objective outcomes were not likely to be biased by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	All the participants completed the study protocol.
Selective reporting (reporting bias)	Low risk	All the outcomes listed in Methods section are reported

Other bias	Low risk	The study appears to be free of other sources of bias.

Appendix 5. AMSTAR 2 review of Chen *et al.* 2015

Chen 2015 is a High quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	YesYesYesYesYesYesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Yes Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	Yes
NRSI	0 Yes Yes Yes Yes

10. Did the review authors report on the sources of funding for the studies included in the review?	Yes Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	Yes
NRSI	Yes Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes

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