BMJ Open

Effects of dexmedetomidine on delirium and mortality during sedation in ICU patients: a systematic review and meta-analysis protocol

Rao Sun, Shuo Wang, Shiyong Li, Chun Yang, Yilin Zhao, Ailin Luo

To cite: Sun R, Wang S, Li S, *et al*. Effects of dexmedetomidine on delirium and mortality during sedation in ICU patients: a systematic review and meta-analysis protocol. *BMJ Open* 2019;**9**:e025850. doi:10.1136/bmjopen-2018-025850

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-025850).

Received 5 August 2018
Revised 22 November 2018
Accepted 12 February 2019

Department of Anesthesiology, Tongji Medical College, Huazhong University of Science and Technology, Tongji Hospital, Wuhan, China

Correspondence to
Dr Ailin Luo;
alluo@tjh.tjmu.edu.cn

ABSTRACT

Introduction Delirium is very common in patients admitted to intensive care unit (ICU), and may worsen survival in these patients. Several meta-analyses have evaluated the antidelirium effects of dexmedetomidine in ICU patients, but their findings were inconsistent. Recently, several large multicentre randomised clinical trials (RCTs) were published, but they have not yet to be included in any meta-analysis. We will conduct a meta-analysis adding these data to evaluate the effects of dexmedetomidine on delirium and mortality in ICU patients, aiming to terminate controversy and provide robust evidence for guiding clinical practice.

Methods and analysis The Cochrane Central Register of Controlled Trials, PubMed, Embase, ISI Web of Science will be searched from inception to 31 December 2018 for relevant RCTs. Two reviewers will independently screen the identified citations. After quality appraisal and data extraction of included studies, we will conduct meta-analyses for outcomes of interest, including delirium, mortality, length of ICU/hospital stay, time to extubation, ICU costs and adverse effects. The statistical heterogeneity among studies will be assessed by the χ^2 test and quantified by the I^2 statistics. We will undertake subgroup analyses to explore heterogeneity and sensitivity analyses to evaluate whether the results are robust. Potential publication bias will be assessed by funnel plot and Egger's test. At last, the quality of evidence of the main outcomes will be rated using the Grading of Recommendations Assessment, Development and Evaluation system.

Ethics and dissemination The present study is a meta-analysis based on published studies, thus ethical approval is not needed. Our review will elucidate whether dexmedetomidine could decrease the incidence of delirium and improve survival in ICU patients. Our findings may help clinicians to choose optimal sedative agents for ICU patients. The results of this meta-analysis will be submitted to a peer reviewed journal for publication.

PROSPERO registration number CRD42018095358.

Strengths and limitations of this study

- We will conduct a comprehensive literature search. Several large multicentre RCTs that are not integrated in any meta-analysis to date will be included.
- This systematic review will systematically evaluate the effects of dexmedetomidine on delirium and mortality in ICU patients.
- Our findings may provide evidence and guidance for clinical practice.
- Our results may be limited by heterogeneity due to variations across individual RCTs in patient population, follow-up duration, treatment duration and dosage of dexmedetomidine.

INTRODUCTION

Delirium is an acute brain illness involving changes in consciousness, attention, cognition and perception[1] It is very common in critically ill patients[2 3] and is a serious complication because the occurrence of delirium has been associated with higher morbidity, prolonged hospital stay, worse functional recovery and long-term decline in cognitive function.[4–6] Moreover, recent studies demonstrated that delirium was associated with increased short- and long- term mortality in patients admitted to intensive care unit (ICU).[7–9]

Patients in the ICU need sedation to reduce discomfort from care interventions, facilitate mechanical ventilation, prevent accidental removal of instrumentation and reduce oxygen demands.[10 11] For decades, γ-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines) have been standard of care for sedation in the ICU.[10] However, emerging studies suggested that these sedatives could increase the prevalence of delirium.[12 13] Although a proportion of sedation-related delirium is rapidly reversible and may not worsen the prognosis of patients,[14] sedatives could reduce the prevalence of delirium that are still needed.

Dexmedetomidine, a highly selective α2-adrenoreceptor agonist, has increasingly been used for sedation in ICU patients.[15] Dexmedetomidine exerts sedative property via the receptors within the locus ceruleus.[16]

Recent studies demonstrated that the sedative effects of dexmedetomidine, unlike other sedative agents, were achieved through the modulation of an endogenous sleep-promoting pathway without disruption of sleep architecture.[17–19] Moreover, dexmedetomidine could also provide analgesia via receptors in the spinal cord,[16] and attenuate stress response with minimal respiratory depression.[20] Because of its unique mechanism of action, dexmedetomidine has been shown to overcome the limitations of the GABA-mimetic sedatives and thus reduce the incidence of delirium[21 22] and improve survival.[23 24]

Several meta-analyses have evaluated the antidelirium effects of dexmedetomidine in ICU patients. Constantin *et al*[25] showed that dexmedetomidine-based sedation was associated with decreased incidence of delirium. However, a Cochrane systematic review concluded that dexmedetomidine did not reduce the prevalence of delirium when used for long-term sedation.[26] The results of a network meta-analysis also showed no effects of dexmedetomidine on prevention of delirium.[27] These findings were so inconsistent that it may become confusing to clinicians in the choice of the best sedative agents for ICU patients. Moreover, previous meta-analyses have not systematically evaluated whether dexmedetomidine could improve survival in ICU patients. Therefore, there is an urgent need to conduct a meta-analysis. Several large multicentre randomised clinical trials (RCTs)[28–33] that are not integrated in any meta-analysis to date will be included. Hopefully, our findings may provide evidence and guidance for clinical practice.

The objective of this systematic review is to evaluate the effects of dexmedetomidine on delirium and mortality during sedation in ICU patients.

METHODS AND ANALYSIS

This systematic review protocol was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist.[34]

Eligibility criteria

- Study designs: this review will include only RCTs. Cluster RCTs and RCTs with cross-over design will be excluded.
- Participants: adult patients (aged 18 years or older) requiring sedation in the ICU.
- Interventions: a comparison between dexmedetomidine and placebo or other sedative agents (including benzodiazepines, propofol, opioid and other sedatives) will be included. We will only include studies that initiates infusion of study drugs after ICU admission.

Outcomes

Primary outcomes

Incidence of delirium, using a validated diagnostic method.

Secondary outcomes

1. All-cause mortality within 30 days after ICU admission; if mortality was assessed at other follow-up times (eg, ICU mortality, hospital mortality) or the follow-up times was not reported, we arbitrarily consider them as 30 day mortality and conduct subgroup analysis.
2. Duration of delirium.
3. Length of ICU stay.
4. Length of hospital stay.
5. Duration of mechanical ventilation.
6. Time to extubation.
7. ICU costs.
8. Patients' and family experience during ICU sedation. For example, using the Intensive Care Experience Questionnaire[35] for patients; using the Family Satisfaction in the Intensive Care Unit Questionnaire[36] for family members.
9. Safety outcomes.
10. Hypotension.
11. Hypotension with intervention.
12. Bradycardia.
13. Bradycardia with intervention.
14. Hypoxaemia.
15. Hypoxaemia with intervention.

Study search

The following databases will be searched: the Cochrane Central Register of Controlled Trials , PubMed, Embase, ISI Web of Science from inception to 31 December 2018. The search strategies will be developed using Medical Subject Heading terms and corresponding text words and no language restrictions will be imposed. Details of the search strategy for each database are shown in online supplementary appendix 1.

Ongoing studies will be searched on the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), International Standard Randomised Controlled Trials Number registry (www.isrctn.com), and the clinicaltrials.gov database.

We also handsearched the reference lists of included studies and previously published meta-analyses in relation to this topic for relevant studies

Study selection

We will include the following studies: (1) the design was an RCT; (2) the study participants were adult patients (aged 18 years or older) requiring sedation in ICU; (3) compared dexmedetomidine and placebo or other sedative agents, and the drugs were infused after ICU admission; (4) reported the incidence of delirium and/or mortality. Citations identified with electronic and manual searches will be saved and deduplicated in EndNote. Two reviewers (RS and SL) will scan the titles and abstracts of these citations independently and in duplicate against the inclusion criteria. The full text of the studies that pass the first eligibility screening will be obtained to make a final decision whether they were eligible for inclusion.

All disagreements were resolved by consensus or by a third reviewer (AL). A flow chart of study selection will be detailed in a PRISMA flow chart.[37]

Data extraction

Two reviewers (SL and YZ) independently will extract data from the articles using a predesigned data extraction form, and any disagreement will be resolved by consulting a third reviewer (AL). When a study either overlapped or was a duplicate of another study, we will contact the study authors for clarification and, if confirmed, will use the publication with the more detailed data for this meta-analysis and combined the additional data.

The following information will be extracted:

- Basic information: title, publication year, name of authors, centres (single-centre, multi-centre), registration identification, funding.
- Participants: sample size, country/countries, mean age, gender distribution, ICU types (mixed ICU, medical ICU, surgical ICU, coronary care unit (CCU), respiratory care unit, burn unit, other), target sedation range, sedation duration.
- Interventions: loading dose, maintenance infusion dose, treatment duration.
- Comparator: placebo or other sedative agents, loading dose, maintenance infusion dose, treatment duration.
- Outcomes: incidence of delirium, the definition of delirium and the time assessed, duration of delirium, mortality and the follow-up time assessed, length of ICU stay, length of hospital stay, duration of mechanical ventilation, time to extubation, ICU costs and safety outcomes, such as hypotension, bradycardia and hypoxaemia.

Methodological quality appraisal

The Cochrane risk of bias tool[38] will be used to evaluate the methodological quality of included studies. The Cochrane risk of bias tool includes seven domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias, and each domain will be classified as either 'low', 'high' or 'unclear' risk of bias. Two reviewers (RS and SW) will independently perform the methodological quality assessment, with disagreements being resolved by discussion or a third reviewer (AL).

Data synthesis

Meta-analysis will be performed using Review Manager Software V.5.2. For the outcomes in the present systematic review, dichotomous data and continuous data will be calculated as risk ratios and standardised mean difference with the corresponding 95% CIs, respectively. The statistical heterogeneity among studies will be assessed by the χ^2 test (statistically significant at $p<0.05$)[39] and quantified by the I^2 statistics (25%, 50% and 75% is considered as low, moderate and high heterogeneity, respectively).[40] Assuming the existence of variations across individual RCTs in patient population, follow-up duration, treatment duration and dosage of dexmedetomidine, the random-effects model will be used to pool the data. When substantial heterogeneity is detected, we will explore possible explanations in subgroup analyses. If there is not enough available data (less than two studies) for any comparison, we will conduct a narrative, qualitative description instead of a meta-analysis.[38]

Continuous data that presented as medians and IQR or ranges will be converted to means and SD as the instruction of Cochrane Handbook.[38] The median value will be equivalent to the mean, and the SD will be estimated as 'IQR/1.35' or 'range/4' (small studies, n<70) or 'range/6' (larger studies, n>70).[41] We will conduct sensitive analysis by excluding these estimated data to evaluate the robustness of results.

Sample size calculation

In a previous meta-analysis,[4] the overall incidence of delirium in ICU patients was 31.8%. We assume 20% of the reduction in incidence of delirium as clinically important. With a significance and power set at 0.05 (two-sided) and 80%, respectively, the sample sizes required to detect differences is 1584 patients. With a significance and power set at 0.05 (two-sided) and 90%, the required sample size is 2120 patients.

Subgroup analysis and investigation of heterogeneity

If there are adequate data, we will perform subgroup analyses for the primary outcomes as follows.

For incidence of delirium and mortality:

1. Age of participants: aged >60 years or <60 years.
2. Type of ICU: mixed ICU, medical ICU, surgical ICU, CCU, respiratory care unit, burn unit, others.
3. Target sedation range: deep sedation or light sedation.
4. Sedation duration: short term (<24 hours) or long term (>24 hours).
5. Infusion rate of dexmedetomidine: high infusion rate or low infusion rate.
6. Infusion regimen of dexmedetomidine: with loading does or without loading dose.
7. Timing of infusion: at night or at daytime.
8. Comparator: placebo, benzodiazepines, propofol, opioids, other sedatives.

For incidence of delirium: delirium assessment tools used.

For mortality: follow-up duration.

Sensitivity analysis

To evaluate whether the results of the systematic review are robust, we will conduct sensitivity analyses for the primary outcomes by excluding studies with small sample sizes, studies of low methodological quality (did not clearly report methods for blinding and allocation concealment) and studies with high percentage of withdrawals (above 10%).[42] We will perform sensitive analyses for the continuous outcomes excluding studies reporting data other than mean deviation and SD.

Assessment of reporting biases

For the primary outcomes, if there are 10 or more studies in an analysis, a funnel plot will be drawn to explore the possibility of publication bias.[43] Statistically, we will also assess publication bias by Egger's test[44] using Stata V.11.0. We will base evidence of asymmetry on p<0.05.

Summary of findings table

We will assess the quality of evidence for each outcome with Grading of Recommendations Assessment, Development and Evaluation approach.[45] We will provide a summary of findings table in five domains (risk of bias, inconsistency, indirectness, imprecision, and publication bias) for each outcome. For each downgrade factor, a judgement of 'no', 'serious (downgrade the quality of evidence by one level)' or 'very serious (downgrade the quality of evidence by two levels)' was assigned. Before rating, we classified all the outcomes as at' high' quality by default, and after rating, each outcome could receive a grade of either' 'high', 'moderate', 'low' or 'very low' quality.

Patient and public involvement

Patients and public were not involved in development of the research question or the design of this study.

Ethics and dissemination

The present study is a meta-analysis based on published studies, thus ethical approval is not needed. The systematic review will be conducted and reported according to the PRISMA statement. The results of this meta-analysis will be submitted to a peer reviewed journal for publication.

Contributors RS and AL conceived and designed the protocol. SW and YZ participated in the development of the search strategy. SL and YZ planned the data extraction. SW, SL, CY and AL tested the feasibility of the study. RS drafted the manuscript. AL and CY revised the manuscript. All authors approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Oh ES, Fong TG, Hshieh TT, *et al*. Delirium in older persons: advances in diagnosis and treatment. *JAMA* 2017;318:1161–74.
2. Mehta S, Cook D, Devlin JW, *et al*. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015;43:557–66.
3. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med* 2014;370:444–54.
4. Salluh JI, Wang H, Schneider EB, *et al*. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015;350:h2538.
5. Ely EW, Gautam S, Margolin R, *et al*. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 2001;27:1892–900.
6. van den Boogaard M, Schoonhoven L, Evers AW, *et al*. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med* 2012;40:112–8.
7. Witlox J, Eurelings LS, de Jonghe JF, *et al*. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304:443–51.
8. Ely EW, Shintani A, Truman B, *et al*. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753–62.
9. van den Boogaard M, Peters SA, van der Hoeven JG, *et al*. The impact of delirium on the prediction of in-hospital mortality in intensive care patients. *Crit Care* 2010;14:R146.
10. Shehabi Y, Bellomo R, Mehta S, *et al*. Intensive care sedation: the past, present and the future. *Crit Care* 2013;17:322.
11. Oldham M, Pisani MA. Sedation in critically ill patients. *Crit Care Clin* 2015;31:563–87.
12. Pandharipande P, Shintani A, Peterson J, *et al*. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104:21–6.
13. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. *Crit Care Clin* 2006;22:313–27.
14. Patel SB, Poston JT, Pohlman A, *et al*. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *Am J Respir Crit Care Med* 2014;189:658–65.
15. Wunsch H, Kahn JM, Kramer AA, *et al*. Dexmedetomidine in the care of critically ill patients from 2001 to 2007: an observational cohort study. *Anesthesiology* 2010;113:386–94.
16. Hall JE, Uhrich TD, Barney JA, *et al*. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000;90:699–705.
17. Alexopoulou C, Kondili E, Diamantaki E, *et al*. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. *Anesthesiology* 2014;121:801–7.
18. Wu XH, Cui F, Zhang C, *et al*. Low-dose Dexmedetomidine Improves Sleep Quality Pattern in Elderly Patients after Noncardiac Surgery in the Intensive Care Unit: A Pilot Randomized Controlled Trial. *Anesthesiology* 2016;125:979–91.
19. Nelson LE, Lu J, Guo T, *et al*. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003;98:428–36.
20. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000;4:302–8.
21. Pandharipande PP, Pun BT, Herr DL, *et al*. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007;298:2644–53.
22. Riker RR, Shehabi Y, Bokesch PM, *et al*. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009;301:489–99.
23. Pandharipande PP, Sanders RD, Girard TD, *et al*. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care* 2010;14:R38.
24. Zhang DF, Su X, Meng ZT, *et al*. Impact of Dexmedetomidine on Long-term Outcomes After Noncardiac Surgery in Elderly: 3-Year Follow-up of a Randomized Controlled Trial. *Ann Surg* 2018.
25. Constantin JM, Momon A, Mantz J, *et al*. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. *Anaesth Crit Care Pain Med* 2016;35:7–15.
26. Chen K, Lu Z, Xin YC, *et al*. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *Cochrane Database Syst Rev* 2015;1:CD010269.
27. Zhang Z, Chen K, Ni H, *et al*. Sedation of mechanically ventilated adults in intensive care unit: a network meta-analysis. *Sci Rep* 2017;7:44979.
28. Deiner S, Luo X, Lin HM, *et al*. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. *JAMA Surg* 2017;152:e171505.
29. Li X, Yang J, Nie XL, *et al*. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *PLoS One* 2017;12:e0170757.

30. Reade MC, Eastwood GM, Bellomo R, *et al*. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. *JAMA* 2016;315:1460–8.
31. Kawazoe Y, Miyamoto K, Morimoto T, *et al*. Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial. *JAMA* 2017;317:1321–8.
32. Skrobik Y, Duprey MS, Hill NS, *et al*. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium. A Randomized, Placebo-controlled Trial. *Am J Respir Crit Care Med* 2018;197:1147–56.
33. Shehabi Y, Forbes AB, Arabi Y, *et al*. The SPICE III study protocol and analysis plan: a randomised trial of early goaldirected sedation compared with standard care in mechanically ventilated patients. *Crit Care Resusc* 2017;19:318–26.
34. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
35. Rattray J, Johnston M, Wildsmith JA. The intensive care experience: development of the ICE questionnaire. *J Adv Nurs* 2004;47:64–73.
36. Wall RJ, Engelberg RA, Downey L, *et al*. Refinement, scoring, and validation of the Family Satisfaction in the Intensive Care Unit (FS-ICU) survey. *Crit Care Med* 2007;35:271–9.
37. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
38. Higgins JPT, Green S. (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration. 2011. Available: http://handbook.cochrane.org
39. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997;127:820–6.
40. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
41. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
42. Sun R, Jia WQ, Zhang P, *et al*. Nitrous oxide-based techniques versus nitrous oxide-free techniques for general anaesthesia. *Cochrane Database Syst Rev* 2015;11:CD008984.
43. Peters JL, Sutton AJ, Jones DR, *et al*. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991–6.
44. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
45. Atkins D, Best D, Briss PA, *et al*. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.