Use of dexmedetomidine in patients with sepsis: a systematic review and meta-analysis of randomized-controlled trials

Ting Zhang
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
Qimin Mei
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
Shabai Dai
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
Yecheng Liu (ptcaliu@sina.com)
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
Huadong Zhu
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences

Research Article

Keywords: Dexmedetomidine, sepsis, intensive critical care, meta-analysis, sedatives

Posted Date: April 20th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1562230/v1

Abstract

Purpose

Dexmedetomidine is widely used in patients with sepsis. However, its effect on septic patients remains controversial. Therefore, the objective of this study is to summarize all randomized-controlled trials examining the use of dexmedetomidine in patients with sepsis.

Methods

In this systematic review and meta-analysis, we searched for randomized-controlled trials comparing dexmedetomidine with other sedatives in adults with sepsis. We generated pooled relative risks and mean differences, and performed trial-sequential-analysis as well as cumulative meta-analysis. The primary outcome was mortality, whereas the secondary outcomes were ICU stays, duration of mechanical ventilation and ventilation-free days, incidence of total adverse events, incidence of delirium and levels of IL-6, TNF-α, alanine transaminase.

Results

Twenty-three randomized-controlled trials with 2,293 involved patients were identified. Compared to other sedatives, dexmedetomidine could decrease the all-cause mortality (RR 0.81; 95% Confidence Interval (CI) 0.71–0.93; P < 0.05) and inflammatory response (levels of IL-6 and TNF-α at 24 h: SMD: -1.46; 95% CI -2.10, -0.83 , p 0.05 SMD: -1.20; 95% CI -1.78, -0.62 , p 0.05, respectively). Trial-sequential-analysis showed that it is not up to required information size but the cumulative Z curve crossed the trial sequential monitoring boundary for benefit. Using cumulative meta-analysis, a steady reduction in mortality was observed after 2020. Risks of total adverse events were similar between dexmedetomidine and the other sedatives (OR = 1.06, 95% CI 0.50, 2.25, p = 0.87), but dexmedetomidine increases the risk of arrhythmias (OR 2.36, 95% CI 1.15, 4.8; P = 0.02; I2 = 0%). ICU stays (SMD: −0.26; 95% CI −0.70,0.18, p = 0.24), duration of mechanical ventilation, incidence of delirium (RR 0.89; 95% CI 0.66 to 1.19, low certainty; P = 0.43) the levels of alanine transaminase and creatinine changes at 24 h (Respectively: p = 0.17 and 0.30) were all not significantly reduced.

Conclusion

The use of dexmedetomidine in comparison to other sedative agent reduces significantly the all-cause mortality and inflammatory response in patients with sepsis. Dexmedetomidine might lead to an increased incidence of arrhythmias, but its safety profile did not show significant differences in the incidence of the total adverse events.

Introduction

Sepsis is the systemic inflammatory response syndrome caused by infection affecting millions of patients per year and carrying a high risk of mortality, which has become a major global health problem [1] [2]. According to the Global Burden of Diseases Study, sepsis is affecting at least 49 million patients every year, causing 11 million deaths and accounting for 19.7% of all global deaths [3] [4]. Epidemiological data showed that over 20% of the septic patients required mechanical ventilation [5].

Sedative medications are frequently used for patient comfort and safety, which is an integral component of the therapy concept for mechanically ventilated patients to reduce the anxiety and stress level associated with tracheal intubation and other invasive interventions [6] [7].

Basic and translational studies showed that among the recommended sedatives, dexmedetomidine (alpha2 receptor agonist) has anti-inflammatory and anti-bacterial effects which are superior to those of gamma-aminobutyric acid (GABA) agonists, as for example, benzodiazepines and propofol. Furthermore, it also reduces neuronal apoptosis and promotes biomimetic sleep — all of which could improve clinical outcomes [6]. As potential risk factors, existing data suggested a loading dose might cause arrythmia. Therefore, despite extensive research, its potential benefits and risks in patients with sepsis remain a controversy.

Recently, existing meta-analyses have shown discrepancies, from which two [8] [9] suggesting a positive effect of dexmedetomidine on mortality in sepsis patients, while the others [10] [11] did not find a significant difference on mortality between dexmedetomidine and the other sedative agents. However, these conclusions are limited by the numbers of included studies, whereas there is still controversy in terms of the effects of dexmedetomidine on the incidence of delirium, adverse events and the duration of ICU stays. Furthermore, Trial Sequential Analysis (TSA) [12] and cumulative meta-analyses have never been performed in the previous systematic reviews and meta-analyses.

Methods

Protocol and registration

The protocol of this study was pre-registered on PROSPERO (CRD42022303354) and findings are reported by using the PRISMA checklist (attached in the Supplementary File).

Systematic search

We conducted a comprehensive search on PubMed, EMBASE, Web of Science, Google Scholar, and unpublished sources including PROSPERO, Clinicaltrials.gov, and the Cochrane Library with inception until February 28, 2022 for randomized-controlled trials (RCTs) investigating the role of

dexmedetomidine comparing with placebo or other sedative agents as therapy in adult sepsis patients. We did not apply language restrictions. We included three search terms: 'Dexmedetomidine', 'sepsis' and 'Randomized Controlled Trials' (see supplementary appendix for search strategy, appendix 1–5). We used the Medical Subject Headings database for the identification of the synonyms and examined the reference list of full-text articles for additional relevant studies. We also considered the conference proceedings such as the American Association for the Surgery of Trauma (AAST), the Critical Care Medicine (SCCM) and the European Society of Intensive Care and Emergency Medicine (ESICM).

Study selection

We included RCTs investigated patients with sepsis who were randomized to intravenous dexmedetomidine administration comparing to propofol or other sedatives. We included studies of adult patients with sepsis received dexmedetomidine at any dose. We included studies reported the following outcomes: mortality, length of stay in intensive care units, duration of mechanical ventilation and ventilator-free days, incidence of adverse events as well as the levels of inflammatory cytokine (as IL-6, TNF-α), creatinine (Cr) and alanine transaminase (ALT). For outcomes reported at multiple timepoints, we mostly chose the longest reported follow-up timepoint.

After the implementation of the search strategy, two reviewers screened all potentially relevant citations independently and in duplicate. Citations deemed as potentially relevant by any screener was proceeded to the second-stage full-text review. Full texts were subsequently reviewed for the eligibility. In case of disagreements among the reviewers, a third-party adjudication was claimed. We captured reasons for exclusion at the full-text screening stage.

Data collection process and data items

Two reviewers (Zhang and Mei) aggregated data independently and in duplicate by using a pre-specified standardized data abstraction form. A third reviewer (Liu) adjudicated disagreements. We collected data on trial characteristics, demographic data, interventions, and control procedures as well as outcomes of interest.

Risk of bias assessment in individual studies

We assessed the risk of bias independently and in duplicate by using the Cochrane Risk of Bias 2.0 tool for RCTs. We used the tool to assess the risk of bias (RoB) in the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. We ranked each domain as "low", "some concerns" or "high". We determined overall RoB for each trial based on the highest risk attributed to any one domain. We assessed certainty of evidence for each outcome by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [13]. In accordance with the GRADE methods, we used the terminology consistent with the overall certainty of evidence, which includes the stronger language for high certainty evidence, and the less certain language ('probably' or 'may') for moderate or low certainty evidence. We used the Guideline Development Tool (https://www.gradepro.org) to formulate the Summary of Findings Table.

Summary measures and synthesis of results

Statistical analyses were performed by using the Review Manager Software 5 (Review Manager [RevMan] Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) and STATA software V.16.0 (STATA Corporation, College Station, TX, USA). We performed both fixed-effects analysis by using the Mantel–Haenszel method, and random-effects analyses by using the DerSimonian and Laird estimator [14]. We developed study weights by using the inverse variance method. We used relative risks (RRs) or odds ratios (ORs) for presenting results of dichotomous outcomes, and mean differences (MDs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs) for outlining continuous outcomes. We also presented absolute differences with 95% CIs, which we used for GRADE ratings. By reporting medians and interquartile ranges (IQR), means and standard deviations (SDs) were determined according to the methods described by McGrath et al. [15].

We assessed the heterogeneity between the selected trials by using visual inspection of the forest plots, the Chi-squared test for homogeneity (where $p < 0.1$ indicates important heterogeneity), and the I^2 statistic (for which a value of 50% or greater was considered as reflective of potentially important heterogeneity) [16]. For investigating publication biases, we created the funnel plot in which the log RRs were plotted against their standard errors. We performed a predefined subgroup analysis comparing studies with high RoB to those with low RoB and APACHE II scores.

We conducted a cumulative meta-analysis according to publication year and sample size, by updating the pooled risk ratio when the result of a new trial was published for the primary outcome [17]. This statistical method was used to detect the dynamic trend of the association result, and it further stabilize the meta-analysis conclusion. We conducted trial sequential analysis (TSA) [12] using a fixed-effects model for mortality. For the TSA, we used the statistical significance level of 5%, the power of 80%, and a relative risk reduction of 15%. We used a model variance-based heterogeneity correction and did this analysis by using Trial Sequential Analysis v.0.9.5.10 beta software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, https://www.ctu.dk/tsa).

Results

Study selection

Of the 263 studies identified in the search (see Fig. 1), we excluded 121 duplicates and further 74 citations after title and abstract screening. We assessed 78 full texts and included 23 RCTs in review [18-40]. There were 2,293 patients included in this study. Baseline characteristics of included trials are summarized in Table 1.

Study description

The selected studies were published between 2009 and 2020. The number of included participants from each study were ranged from 40 to 422. The mean age of participants ranged from 47 to 73 years. All participants met the sepsis criteria. Dexmedetomidine dose varied apparently among studies. The dosage of dexmedetomidine was similar across included trials with the most common regimen including a loading dose of 1 μg/kg·h, followed by a maintenance dose of 0.2 to 1 μg/kg·h. Eight of the included trials [21, 27, 28, 31, 33, 36, 37, 40] were judged to be at high RoB, while the remainder of the trials were judged either at low ROB or certain concerns. (see Fig. 2 and e-Fig. 1 for all RoB judgements). Table 2 and e-Table 1-7 depict the pooled outcomes with associated GRADE certainty of evidence.

Primary outcomes

Table 2 shows the summary of findings for all outcomes including the certainty of evidence. Pooled analysis outlined the dexmedetomidine group had a lower occurrence of mortality (RR 0.81; 95% Confidence Interval (CI) 0.71–0.93; risk difference (RD) 6% reduction; 95% CI 2% reduction to 10% reduction; P < 0.05;high certainty), with no significant heterogeneity (I^2 = 27%, P = 0.14) (see Fig. 3). There was no obvious asymmetry in funnel plots by the visual inspection (see e-Fig. 2). The TSA results demonstrated that the information size needed for detecting an intervention effect, was 3398 patients. The cumulative Z curve crossed both, the conventional boundary for benefit and the trial sequential monitoring boundary for benefit (see Fig. 4), suggesting that current evidence is sufficient, while further studies are unlikely to change the current conclusion of the benefit with dexmedetomidine. A cumulative meta-analysis was conducted to assess changes over the time and sample size (see Fig. 5 and e-Fig. 3). A statistically significant reduction in mortality was observed in the studies performed from 2009 to 2019 (RR = 0.58 95% CI 0.45–0.75). After the addition of further recent RCTs[22, 24, 25, 32, 36], a significant reduction in 28-day mortality was still observed (RR 0.81; 95% CI 0.71–0.93).

Secondary Outcomes

ICU Stays

While 15 studies [18-33, 35-40] included ICU stays in their evaluation index, the results indicated that the dexmedetomidine group could not reduce ICU stays in comparison with the other sedation groups (SMD: −0.26; 95% CI −0.70,0.18, p = 0.24, high certainty]) (see e-Fig. 4).

Duration of Mechanical Ventilation

There were eight studies [18, 20, 22, 24, 26, 29-31] explored the impact of dexmedetomidine on the duration of mechanical ventilation. We selected the fixed effect model since there was no heterogeneity in both subgroups (I^2 = 0%). The meta-analysis did not find a reduction of mechanical ventilation time under dexmedetomidine use compared to other sedation (MD: −0.4; 95% CI -1.12,0.31, p= 0.27, high certainty) (see e-Fig. 5).

Duration of Ventilator-free Days

There were three studies [19, 20, 25] included the ventilator-free days as indicator, whereby the results indicated that the dexmedetomidine group could not increase the ventilator-free days in comparison with other sedation group (MD: 1.68; 95% CI −1.5,4.85, p = 0.3, very low certainty])(see e-Fig. 6).

Levels of IL-6, TNF-α, Alanine Transaminase and Creatinine changes at 24 h

Random effect models were utilized in the four outcomes, whereby the results showed a significant lower levels of IL-6 and TNF-α at 24 h in the dexmedetomidine group in comparison with the groups of the other sedatives (SMD: -1.46; 95% CI -2.10, -0.83 , p□0.05, low certainty; SMD: -1.20; 95% CI -1.78, -0.62 , p□0.05, moderate certainty; see e-Fig. 7 and e-Fig. 8). However, random model analysis indicated that dexmedetomidine did not lead to a significant change in ALT and Cr at 24 h (Respectively: p = 0.17 and 0.30, low certainty; see e-Fig. 9).

Incidence of delirium

Three studies [20, 30, 31] explored the incidence of delirium for dexmedetomidine. In total, 50/162 (30.86%) patients in the dexmedetomidine group were reported as having experienced delirium, versus 57/165 (34.55%) patients in the control group. Following the meta-analysis, dexmedetomidine was not significantly associated with lower risk of delirium compared to control group: 327 patients; risk ratio 0.89; 95% CI 0.66 to 1.19, low certainty; P = 0.43(see e-Fig. 10). However, considering there were only three studies were included, this result need be interpreted prudently.

Incidence of Total Adverse Events

Eight studies [19, 20, 22, 24, 30, 32, 36, 39] included the incidence of adverse events, which was evidenced by 831 participants. The results demonstrated that there was no difference in the incidence of adverse events between the group of dexmedetomidine and propofol (OR = 1.06, 95% CI 0.50, 2.25, p = 0.87, moderate certainty; see e-Fig. 11a). In terms of arrhythmia and hypotension, the pooled odds ratios (ORs) were 2.36 (95% CI 1.15, 4.8; P = 0.02; I^2 = 0%, high certainty; see e-Fig. 11b) and 0.82 (95% CI 0.22, 3.09; P = 0.76; I^2 = 47%, low certainty; see e-Fig. 11c). According to the research findings, dexmedetomidine was significantly associated with higher risk of arrhythmia, but did not show significant differences in the incidence of hypotension in comparation with other sedative medications.

Subgroup analyses and sensitivity analyses

From the subgroup analyses of the primary outcome, we found that the APACHE II scores of patients in each study (> 20 or ≤ 20) and the risk of bias had no significant effect on all-cause mortality. (see e-Fig. 12 and e-Fig. 13). Among the majority of the studies, the heterogeneity results were not obviously altered after sequentially omitting each study, indicating that our results were statistically reliable (see e-Fig. 14).

Discussion

This systematic review and meta-analysis demonstrate that dexmedetomidine sedation in sepsis patients could decrease mortality and the level of IL-6 TNF-α at 24 h compared to other sedations, but is associated with a significant increase in risk of arrhythmia. There were no significant differences in ICU stays, duration of mechanical ventilation, incidence of total adverse events, incidence of delirium, and levels of ALT or creatinine at 24 h.

Research findings of several systematic reviews and meta-analyses on the research topic were presented [8] [9] [10] [41] [11]. Among previous meta-analyses, Huang's study was the most comprehensive one [10], included 15 RCTs totaling 1871 patients for analysis, found that dexmedetomidine use was not significant in reducing mortality (RR 0.79; =0.97, 95% confidence interval (CI) = 0.83–1.13, p = 0.70). Unfortunately, due to a gap in the literature review resulted insufficient information size, Huang's study couldn't conclude with a high level of certainty, unlike our analysis. One of the strengths of the present systematic review and meta-analysis is the large sample size, which effected a high level of certainty, as demonstrated by the TSA analysis by assessing whether dexmedetomidine could improve mortality. Our cumulative meta-analysis for the primary outcomes showed that mortality in the dexmedetomidine group was lower than conventional sedatives, while new studies added lead consistently to improvements in mortality. From a statical perspective, despite the RR value has been changing over the time, the conclusion was relatively stable with the increase of sample size and the passage of time, and the advantage of dexmedetomidine group was obvious.

Comparing the safety profile of dexmedetomidine with those of the other sedations, there were no significant differences in the incidence of the total adverse events in sepsis patients, though the incidence of arrhythmia was significantly increased. This finding has not been reported in previous studies. Theoretically, dexmedetomidine is an α2-adrenoceptor agonist causing vasodilation, decreasing sympathetic response [42] and therefore potentially inducing hemodynamic side-effects. A possible explanation for our research findings is that only three [30, 36, 39] out of the six [19, 20, 22, 30, 36, 39] studies administered a loading dose of dexmedetomidine, which is associated with higher risk for arrhythmia due to a fall in cardiac output (following the loading infusion secondary to a transient afterload increase after α2 adrenoceptor-mediated vasoconstriction) [43]. Avoiding giving a loading dose of dexmedetomidine may reduce the incidence of arrhythmia, while close hemodynamic monitoring therefore is still recommended.

Accumulated evidences have demonstrated the stimulating effect of dexmedetomidine on the central and peripheral receptors, causing a reduction of the sympathetic nerve activity and plasma catecholamine concentration [44]. Its ability to reduce sympathetic tone and indirectly increase the parasympathetic activity is of great importance to inhibit the release of inflammatory factors and to reduce cell apoptosis, resulting the reduction of the occurrence of inflammation and sepsis [45]. Results of our meta-analysis also suggest that after 24 hours of receiving dexmedetomidine, the levels of TNF-α and IL-6 were significantly lower than the control group. But our meta-analysis did not confirm the previous reports [46, 47] that dexmedetomidine prevents liver and kidney damage resulting from sepsis. Further research is needed to study it in the future, as the included sample size was small.

This systematic review and meta-analysis have several strengths including a pre-registered protocol, a comprehensive literature search including unpublished sources, independent screening and data abstractions, and the GRADE assessment of certainty of evidence as method instrument. However, there are also limitations. First, due to a lack of individual patient data, we were unable to conduct pre-planned subgroup analyses according to the patient baseline characteristics, as for example, the underlying etiology of sepsis. Second, the study population and the used dexmedetomidine regimens varied among studies, which might result clinical heterogeneity. More data are needed to evaluate the impact of dexmedetomidine regimen on the clinical outcomes. Third, seven trials were judged to be at high risk of performance, which might compromise the reliability of our results.

Conclusions

Considering optimizing treatment of sepsis patients and improving their outcomes is an endeavor among worldwide research work, the findings of this study are extremely valuable for the clinical work on sepsis patients. Based on the current evidence, this meta-analysis showed that dexmedetomidine could significantly decrease the mortality and the levels of inflammatory cytokines in sepsis patients than other sedatives. More clinical RCTs are needed to verify the efficacy and safety of dexmedetomidine on the length of the hospital stay and mechanical ventilation time. Dexmedetomidine might lead to an increased incidence of arrhythmias, but it did not lead to an increased incidence of total adverse events.

Abbreviations

CI: confidence interval

TSA: Trial Sequential Analysis

RCT: randomized-controlled trial

ALT: alanine transaminase

Cr: creatine

RoB: risk of bias

RR; relative risk

OR: odds ratio

MD: mean difference

SMD: standardized mean difference

IQR: interquartile ranges

SD: standard deviation

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors have read the manuscript and consented for this manuscript to be published by Critical Care.

Availability of data and materials

All data associated with this manuscript are inculded in the main text and supplementary materials.

Competing interests

The authors declare that they have no competing interests.

Funding

Supported by the Non-Profit Central Research Institute Fund of Chinese Academy of Medical Sciences (Grant Number: 2019XK320035).

Authors' contributions

YCL, HDZ and TZ conceived of the study idea. TZ and YCL coordinated the systematic review. QMM and SBD designed the search strategy. QMM and SBD screened abstracts and full texts. TZ and QMM acquired the data and judged risk of bias in the studies. TZ verified the data and performed the analyses. TZ and SBD created the GRADE evidence profiles. All authors interpreted the data analyses. All authors cowrote and revised the manuscript for intellectual content. All authors provided their final approval for manuscript submission. All authors agree to be accountable for all aspects of the work.

Acknowledgements

Not applicable

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC, (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama 315: 801–810
2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K, (2016) Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med 193: 259–272
3. Alliance ES, (2021) European Sepsis Report 2021
4. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M, (2020) Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet 395: 200–211
5. Vincent JL, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y, (2014) Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med 2: 380–386

6. Reade MC, Finfer S, (2014) Sedation and delirium in the intensive care unit. N Engl J Med 370: 444–454
7. Patel SB, Kress JP, (2012) Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med 185: 486–497
8. Zhang WQ, Xu P, Zhan XH, Zheng P, Yang W, (2019) Efficacy of dexmedetomidine for treatment of patients with sepsis: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 98: e15469
9. Chen P, Jiang J, Zhang Y, Li G, Qiu Z, Levy MM, Hu B, (2020) Effect of Dexmedetomidine on duration of mechanical ventilation in septic patients: a systematic review and meta-analysis. BMC Pulm Med 20: 42
10. Huang P, Zheng X, Liu Z, Fang X, (2021) Dexmedetomidine Versus Propofol for Patients With Sepsis Requiring Mechanical Ventilation: A Systematic Review and Meta-Analysis. Front Pharmacol 12: 717023
11. Wang C, Chen Q, Wang P, Jin W, Zhong C, Ge Z, Xu K, (2021) The Effect of Dexmedetomidine as a Sedative Agent for Mechanically Ventilated Patients With Sepsis: A Systematic Review and Meta-Analysis. Frontiers in Medicine 8
12. Wetterslev J, Jakobsen JC, Gluud C, (2017) Trial Sequential Analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 17: 39
13. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 336: 924–926
14. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C, (2014) Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol 14: 120
15. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A, Collaboration DESD, (2020) Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. Stat Methods Med Res: 962280219889080
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG, (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557–560
17. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC, (1992) Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 327: 248–254
18. Tasdogan M, Memis D, Sut N, Yuksel M, (2009) Results of a pilot study on the effects of propofol and dexmedetomidine on inflammatory responses and intraabdominal pressure in severe sepsis. J Clin Anesth 21: 394–400
19. Pandharipande PP, Sanders RD, Girard TD, McGrane S, Thompson JL, Shintani AK, Herr DL, Maze M, Ely EW, investigators M, (2010) Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. Crit Care 14: R38
20. 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 Trial I, (2017) Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial. JAMA 317: 1321–1328
21. Zhou F, (2017) Study on organ protection value of dexmedetomidine in patients with septic myocardial injury. Knowledge of prevention and treatment of cardiovascular diseases: 73–74
22. 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, Group ACT, the SIIII, (2020) 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. Crit Care 24: 441
23. Memis D, Kargi M, Sut N, (2009) Effects of propofol and dexmedetomidine on indocyanine green elimination assessed with LIMON to patients with early septic shock: a pilot study. J Crit Care 24: 603–608
24. Liu J, Shi K, Hong J, Gong F, Mo S, Chen M, Zheng Y, Jiang L, Xu L, Tu Y, Hu B, Yang X, Sun R, (2020) Dexmedetomidine protects against acute kidney injury in patients with septic shock. Ann Palliat Med 9: 224–230
25. 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, Investigators MS, (2021) Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. N Engl J Med 384: 1424–1436
26. Mark B. Sigler MD EAIMP, Kenneth M. Nugent MD, (2018) Comparison of dexmedetomidine and propofol in mechanically ventilated patients with sepsis: A pilot study. THE SOUTHWEST RESPIRATORY AND CRITICAL CARE CHRONICLES 6 NO 22 (2018)
27. Yu-xin LXyL, (2016) Study of organ protective effects in sepsis patients with myocardial injury with dexmedetomidine and propofol in ICU. Journal of Community Medicine 14: 11–14
28. cai RD, LMr, XXj, LJd, (2017) Effect of dexmedetomidine on expression of inflammation related genes in patients with sepsis. Contemporary Medicine 23: 1–4
29. Meng Jianbiao ZGSFSHLB, (2014) Comparative study of propofol and dexmedetomidine on inflammatory responses in patients with sepsis. Chinese Journal of Critical Care Medicine 7: 19–23
30. Cai Jian, Llu shu chang QX, song, LI Li,YE Ying., (2019) Therapeutic effect of dexmedetomidine in sepsis patients with mechanical ventilation China Journal of Emergency Resuscitation and Disaster Medicine 14: 442–445
31. Wang Yifei XW, Li Guofa, Li Yue, Zhou Yang, Ma Huanggang, Zhu Weidong,, Yunhua. Z, (2019) Effect of Dexmedetomidine -based early goal-oriented sedation strategy on gastrointestinal function in patients with sepsis. Chinese Journal of Critical Care & Intensive Care Medicine 5: 317–324
32. Wei Guowen LB, (2020) Effects of dexmedetomidine on perioperative hemodynamics, lactate clearance rate,and hepatic and renal function in patients with septic shock. Guangxi Medical Journal 42: 1219–1223

33. Zhu Weisheng WJ, LiuYu, Lou Qunbing, Chen Xiaozheng, (2017) Effects of dexmedetomidine hydrochloride on perioperative serum cytokines and high mobility group protein B1 in patients with sepsis. Chinese Journal of Nosocomiology 27: 650–652,666
34. Chun Z, (2019) Effects of Dexmedetomidine on the Plasma hs-CRP PCT IL-6 TFC levels and Oxygenation of Patients with ARDS Induced by Sepsis. Hebei Medicine 25: 94–98
35. Chen Xianfeng HJ, Zhang Chi, Pan Yiping, Tian Diansheng, Kuang Fafa, Tang, Zhanhong, (2018) Effect and mechanism of dexmedetomidine on lungs in patients of sepsis complicated with acute respiratory distress syndrome. Chinese Critical Care Medicine 30: 151–155
36. Zhang LinNa GX, (2020) Effects of dexmedetomidine on inflammatory response and S100 beta protein in patients with sepsis associated encephalopathy. Chinese Journal of Multiple Organ Diseases in 19: 115–118
37. Zhang C, Wu X, Jiang Z, Yu G, (2013) Effects of dexmedetomidine sedation on immunomodulation and cytokine release in mechanically ventilated septic shock patients. JOURNAL OF HEBEI MEDICAL UNIVERSITY 34: 33–36
38. Wu Xiandan WP, Zhang Jinbo et al., (2018) Effects of dexmedetomidine sedation on inflammatory factors in patients with mechanical ventilation sepsis Chinese Journal of General Practice 16: 675–677
39. Wang Lu Y, Zou Handong, Zhou Chengliang, (2016) Effects of dexmedetomidine and propofol on agitation and inflammatory response in patients with sepsis associated encephalopathy Modern Journal of Integrated Traditional Chinese and Western Medicine 544–545
40. Jue QX-eZMW, (2017) Effects of dexmedetomidine on perioperative intestinal barrier function in patients with sepsis. Chinese Journal of General Practice 15: 876–878
41. Liu Z, Zeng Y, Yang B, Liao P, (2021) Efficacy and safety of dexmedetomidine in sepsis patients requiring mechanical ventilation: a systematic review and meta-analysis. J Clin Pharm Ther
42. Gerlach AT, Murphy CV, Dasta JF, (2009) An updated focused review of dexmedetomidine in adults. Ann Pharmacother 43: 2064–2074
43. Venn M, Newman J, Grounds M, (2003) A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. Intensive Care Med 29: 201–207
44. Barends CR, Absalom A, van Minnen B, Vissink A, Visser A, (2017) Dexmedetomidine versus Midazolam in Procedural Sedation. A Systematic Review of Efficacy and Safety. PLoS One 12: e0169525
45. Flanders CA, Rocke AS, Edwardson SA, Baillie JK, Walsh TS, (2019) The effect of dexmedetomidine and clonidine on the inflammatory response in critical illness: a systematic review of animal and human studies. Crit Care 23: 402
46. Miyamoto K, Nakashima T, Shima N, Kato S, Ueda K, Kawazoe Y, Ohta Y, Morimoto T, Yamamura H, (2018) Effect of Dexmedetomidine on Lactate Clearance in Patients With Septic Shock: A Subanalysis of a Multicenter Randomized Controlled Trial. Shock (Augusta, Ga) 50: 162–166
47. Kang K, Gao Y, Wang SC, Liu HT, Kong WL, Zhang X, Huang R, Qi ZD, Zheng JB, Qu JD, Liu RJ, Liu YS, Wang HL, Yu KJ, (2018) Dexmedetomidine protects against lipopolysaccharide-induced sepsis-associated acute kidney injury via an α7 nAChR-dependent pathway. Biomed Pharmacother 106: 210–216

Tables

Table 1

Study author and year	Study design	No. of patients DEX/control	Mean or median age in years DEX/control	Mean or median APACHE II scores DEX/control	Mean or median SOFA scores DEX/control	Sedation goals	DEX group
Tasdogan et al., 2009	Single site RCT	20/20	58 (21-78)/50 (19-74)	19 ± 5/18 ± 4	4.2 ± 1.8/4.0 ± 2.5	N/A	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-2 μg/kg/h
Pandharipande et al., 2010	Single site RCT	31/32	60□46,65)/58□44,66□	30 (26, 34)/29 (24, 32)	10 (9,13)/9 (8,12)	RASS score of-4 to -2	maximum 1. mcg/kg/hr
Kawazoe et al., 2017	Multisite RCT	100/101	68□14.9)/69□13.6□	23□18,29□/22□16,29.5□	8□6,11□/9□5,11□	RASS score of -2 to 0	m [IQR], mcg the First wee 81 [11, 154.5]~228 408.5]
Zhou et al., 2017	Single site RCT	40/40	48.54±4.79/48.45±4.82	18.07±4.09/17.89±4.32	N/A	Ramsay score of 2 to 3	loading dose 1 ug/kg/hr o 10 minutes followed by maintenance dose of 0.2-0 mg/kg/h
Cioccari et al., 2020	Multisite RCT	44/39	67.7±12.4/62.9±16.8	24.9 ± 6.7/25.3 ± 7.0	6□5,10□/9□5,14□	RASS score of-2 to -4	During Entire Study:1.12 (0.06–8.0) μg/kg/d; Duration(Da 0.75(1.7)
Memiş et al., 2009	Single site RCT	20/20	60 (31-80)/54 (25-78)	22 ± 5/20 ± 8	4.5 ± 2.8/4.0 ± 2.9	N/A	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-2 μg/kg/h
Liu et al., 2020	Single site RCT	100/100	57□31-66/54(35-71)	29□26,37□/29(22,36)	10□8,13)/11(8,12)	RASS score of -2 to 0	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-0 μg/kg/h
Hughes et al., 2021	Single site RCT	214/208	59 (48–68)/60 (50–68)	27 (21,32)/27 (22,32)	10 (8,13)/10 (8,12)	RASS score of -2 to 1	maintenance dose of 0.2-1 μg/kg/h
Sigler et al.,	Single	17/19	62.5/59	19(13, 20)/16(12, 19)	11(7, 14)/10(8, 13)	RASS	initiated at 0

2018	site RCT					score of -2 to 2	mcg/kg/hou and titrated every 5 minu by 0.1 mcg/kg/hou a maximum dose of 1.4 mcg/kg/hou
Lei et al., 2016	Single site RCT	29/29	46.5±18.4/47.5±15.2	17.9±4.9/18.3±4.2	N/A	Ramsay score of 2 to 3	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-(μg/kg/h
Ren et al., 2017	Single site RCT	25/25	73.96±8.41/	19.84±6.12/18.8±6.01	N/A	N/A	loading dose 2.5 μg/kg followed by maintenance dose of 0.2-(μg/kg/h
Meng et al., 2014	Single site RCT	20/20	56±18/51±14	18±4/19±4	4.2±1.7/4.1±2.4	Ramsay score of 2 to 3	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-2 μg/kg/h
Cai et al., 2019	Single site RCT	30/30	54±17.55/58.6±14.95	20.3±4.76/21.43±4.52	8.67±1.54/8.8±2.36	RASS score of -2 to 0	loading dose 1 μg/kg followed by maintenance dose of 0.2-1 μg/kg/h
Wang et al., 2019	Single site RCT	31/32	74.13±10.69/	20.97±5.64/20.7±5.85	8.23±1.23/8.07±1.46	RASS score of -2 to 0	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-1 μg/kg/h
Wei et al., 2020	Single site RCT	60/59	43. 45 ± 7. 86/45. 21 ± 8. 35	26. 43 ± 5. 24/25. 12 ± 5. 89	12. 37 ± 2. 82/11. 82 ± 2. 53	SAS score of 1 to 2	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-(μg/kg/h
Zhu et al., 2017	Single site RCT	47/47	54.37±12.53/55.35±13.21	N/A	N/A	N/A	maintenance dose of 0.6μg/kg/h
Zheng et al., 2019	Single site RCT	32/30	46.05±8.52/45. 76 ± 7. 93	14.25±4.81/14.61±4.35	N/A	N/A	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-(μg/kg/h
Chen et al., 2018	Single site RCT	80/80	47.57±4.48/46.21±4.22	17.74±1.19/17.26±1.12	N/A	RASS score of -1 to 0	maintenance dose of 0.2-(μg/kg/h
Zhang et al., 2020	Single site RCT	25/25	59. 0±4. 8/58. 8±4. 8	21±4/20±5	8. 8±1. 6/8. 6±1. 8	N/A	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-(μg/kg/h
Zhang et al., 2013	Single site RCT	50/50	62.9±1.8/61.5±2.8	18.7±5.9/19.1±7.3	N/A	RASS score of	loading dose 0.3 μg/kg ov

						-2 to 1	15 minutes followed by maintenance dose of 0.3 μg/kg/h
Wu et al., 2018	Single site RCT	48/48	47±10/51±8	21.11±3.73/19.96±4.08	3.15±0.86/4.83±1.07	RASS score of -2 to 1	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-(μg/kg/h
Wang et al., 2016	Single site RCT	28/28	47.32±14.86/51.11±15.159	11.21 ±3.994/11.86 ±6.878	10.68±5.15/11.39±5.19	Ramsay score of 3 to 4	loading dose 1 μg/kg over minutes followed by maintenance dose of 0.2-(μg/kg/h
Qian et al., 2017	Single site RCT	60/60	57.48±7.28/57.85±7.66	17.47±3.11/17.11±3.02	N/A	N/A	loading dose 0.6 μg/kg ov 10 minutes followed by maintenance dose of 0.5 μg/kg/h

DEX dexmedetomidine□N/A not applicable, IAP intraabdominal pressure, APACHE II acute physiology and chronic health evaluation, SOFA sequential organ fa creatinine, BUN blood urea nitrogen
*Mean (SD)

Table2

Question: Dexmedetomidine compared to Other sedatives for Patients with sepsis

Certainty assessment							№ of patients		Effect	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomidine	Other sedatives	Relative (95% CI)	Absolu (95% CI)
All-cause mortality at longest follow-up										
18	randomised trials	not serious	not serious	not serious	not serious	none	241/906 (26.6%)	295/897 (32.9%)	**RR 0.81** (0.71 to 0.93)	**62 few per 1,000** (from 95 few to 23 fewer)
High Risk of Bias										
11	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	108/448 (24.1%)	135/448 (30.1%)	**RR 0.80** (0.66 to 0.97)	**60 few per 1,000** (from 102 fewer t 9 fewe
Low Risk of Bias										
7	randomised trials	not serious	not serious	not serious	serious[b]	none	133/458 (29.0%)	160/449 (35.6%)	**RR 0.82** (0.68 to 0.98)	**64 few per 1,000** (from 114 fewer t 7 fewe
APACHE II ≤20										
9	randomised trials	serious	not serious	not serious	serious[b]	none	39/276 (14.1%)	62/276 (22.5%)	**RR 0.64** (0.45 to 0.90)	**81 few per 1,000** (from 124 fewer t 22 fewer)
APACHE II >20										
9	randomised trials	not serious	not serious	not serious	not serious	none	202/630 (32.1%)	233/621 (37.5%)	**RR 0.85** (0.74 to 0.99)	**56 few per 1,000** (from 98 few to 4 fewer)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Of the 11 included studies, five are at high risk of bias and six has some concerns.

b. Wide confidence intervals do not exclude important benefit or harm which lowers our certainty in effect

Figures

Fig.1 Study flowchart

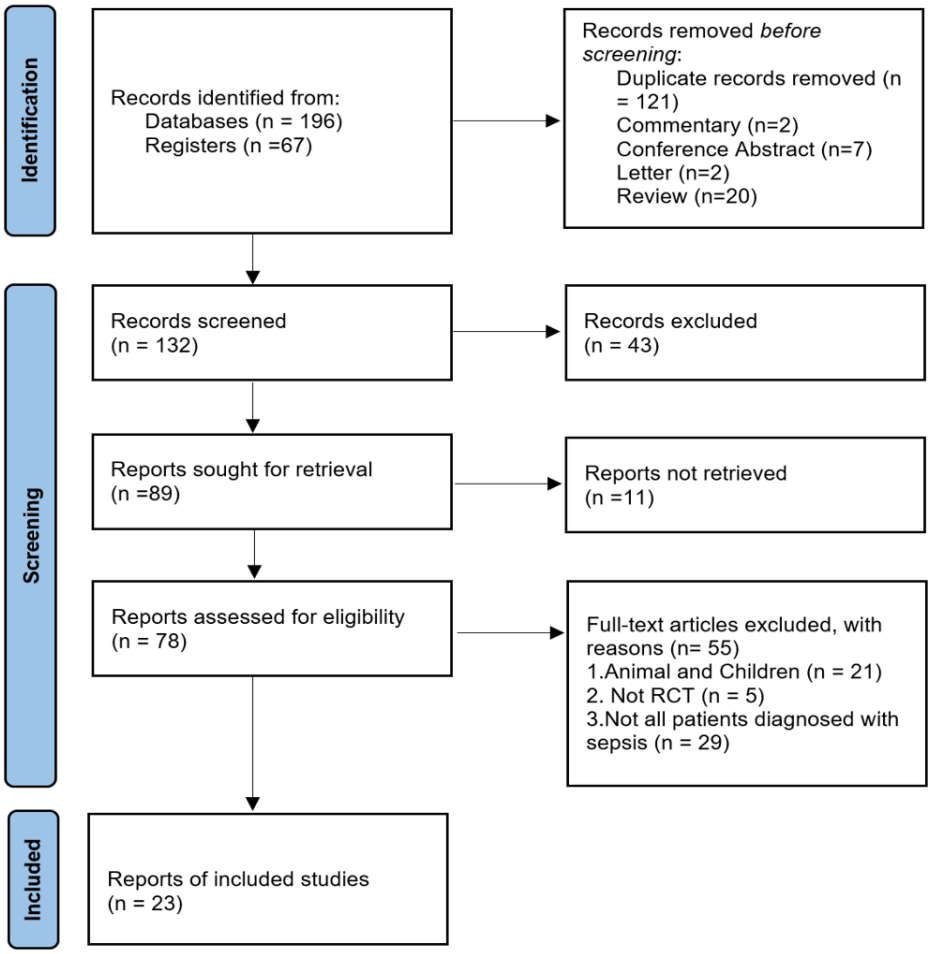


Figure 1

See image above for figure legend.

Fig. 2 Risk of bias assessment

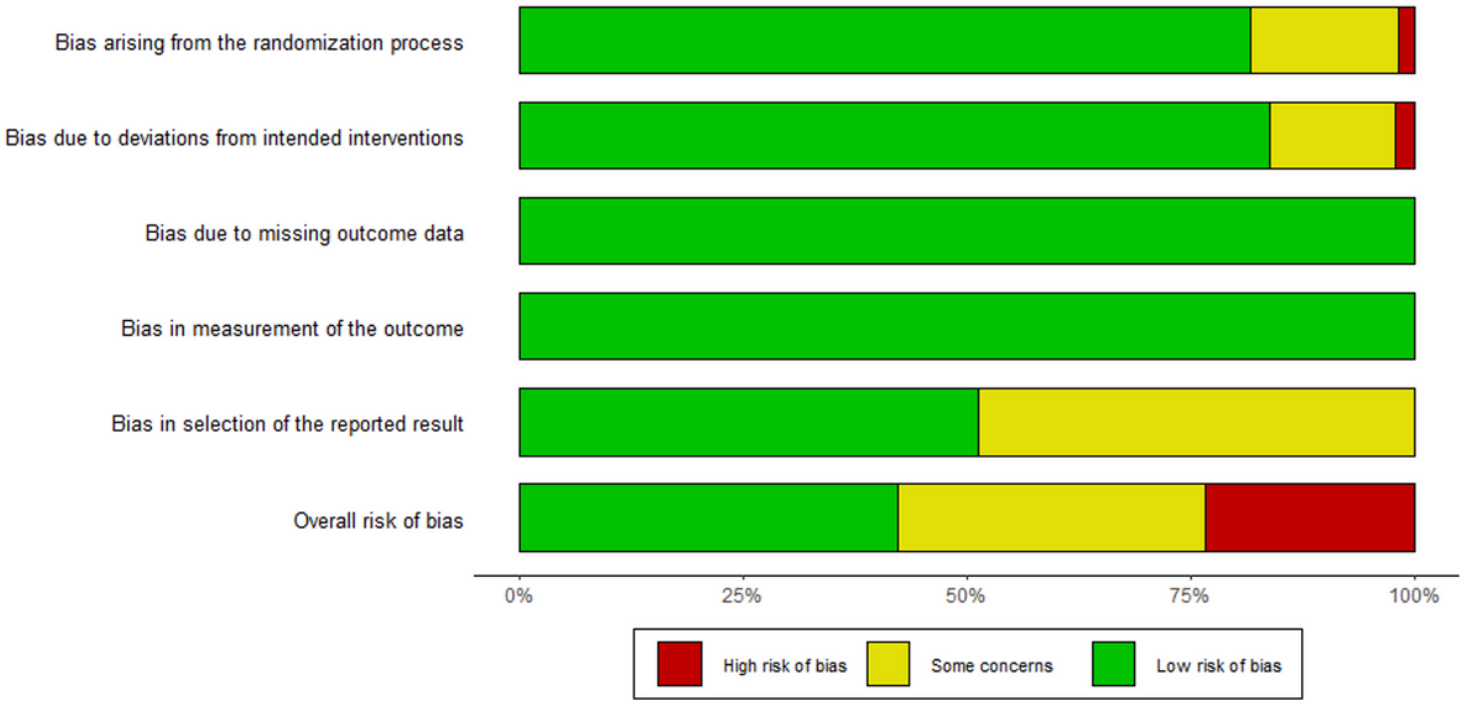
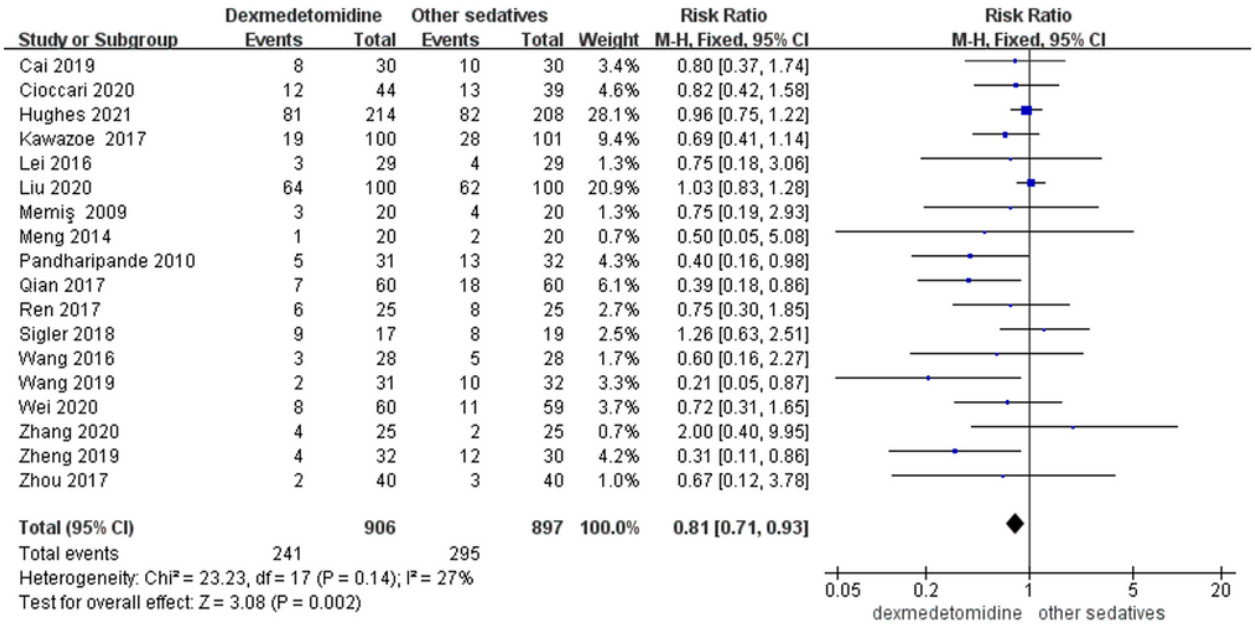


Figure 2

See image above for figure legend.

Fig. 3 Effect of dexmedetomidine on mortality. *DF* degrees of freedom



Study or Subgroup	Dexmedetomidine Events	Total	Other sedatives Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cai 2019	8	30	10	30	3.4%	0.80 [0.37, 1.74]
Cioccari 2020	12	44	13	39	4.6%	0.82 [0.42, 1.58]
Hughes 2021	81	214	82	208	28.1%	0.96 [0.75, 1.22]
Kawazoe 2017	19	100	28	101	9.4%	0.69 [0.41, 1.14]
Lei 2016	3	29	4	29	1.3%	0.75 [0.18, 3.06]
Liu 2020	64	100	62	100	20.9%	1.03 [0.83, 1.28]
Memiş 2009	3	20	4	20	1.3%	0.75 [0.19, 2.93]
Meng 2014	1	20	2	20	0.7%	0.50 [0.05, 5.08]
Pandharipande 2010	5	31	13	32	4.3%	0.40 [0.16, 0.98]
Qian 2017	7	60	18	60	6.1%	0.39 [0.18, 0.86]
Ren 2017	6	25	8	25	2.7%	0.75 [0.30, 1.85]
Sigler 2018	9	17	8	19	2.5%	1.26 [0.63, 2.51]
Wang 2016	3	28	5	28	1.7%	0.60 [0.16, 2.27]
Wang 2019	2	31	10	32	3.3%	0.21 [0.05, 0.87]
Wei 2020	8	60	11	59	3.7%	0.72 [0.31, 1.65]
Zhang 2020	4	25	2	25	0.7%	2.00 [0.40, 9.95]
Zheng 2019	4	32	12	30	4.2%	0.31 [0.11, 0.86]
Zhou 2017	2	40	3	40	1.0%	0.67 [0.12, 3.78]
Total (95% CI)		**906**		**897**	**100.0%**	**0.81 [0.71, 0.93]**
Total events	241		295			

Heterogeneity: Chi² = 23.23, df = 17 (P = 0.14); I² = 27%
Test for overall effect: Z = 3.08 (P = 0.002)

Figure 3

See image above for figure legend.

Fig. 4 Trial sequential analysis.

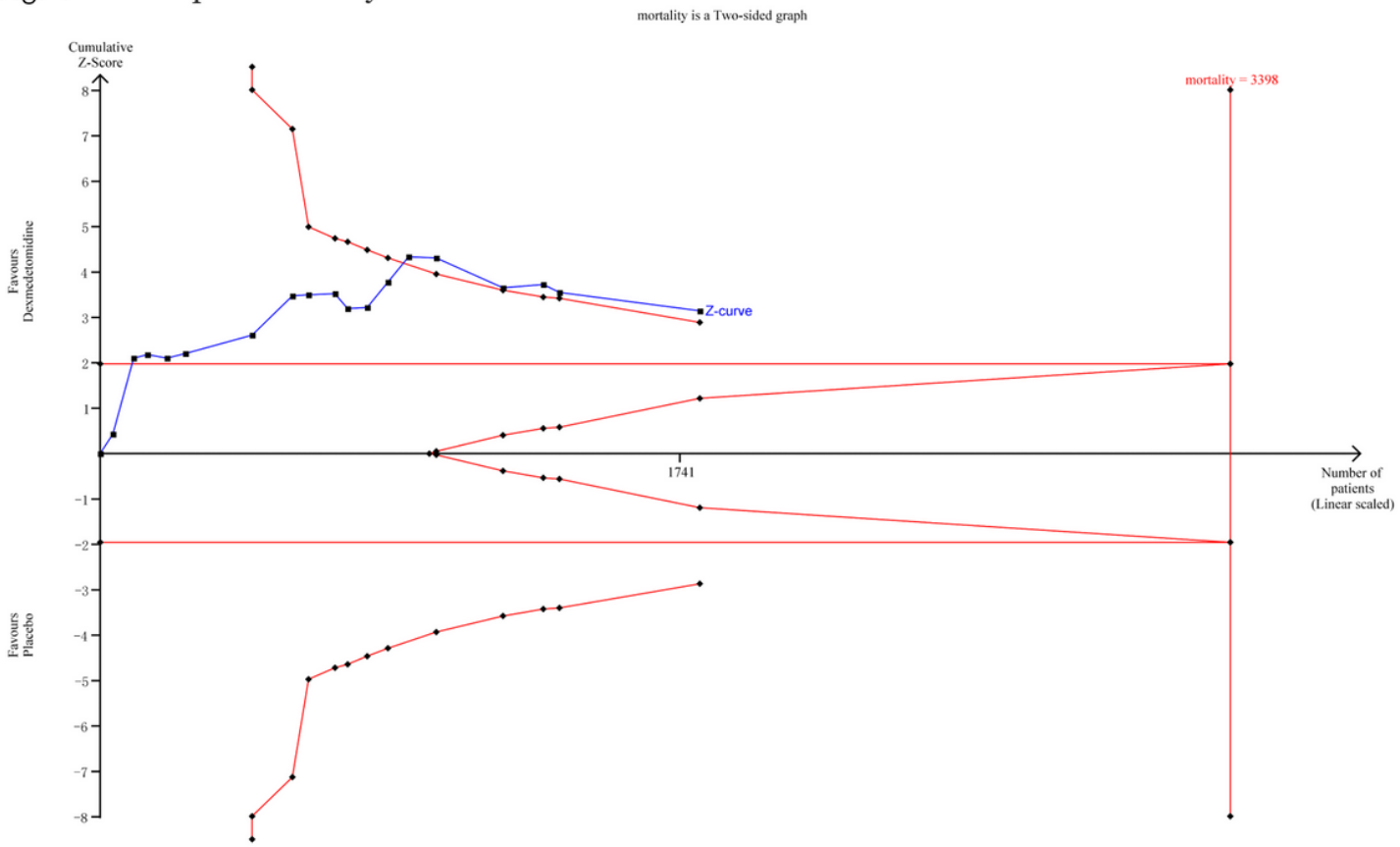


Figure 4

See image above for figure legend.

Fig. 5 Cumulative meta-analysis. Pooled risk ratios are updated each time a new study was published.

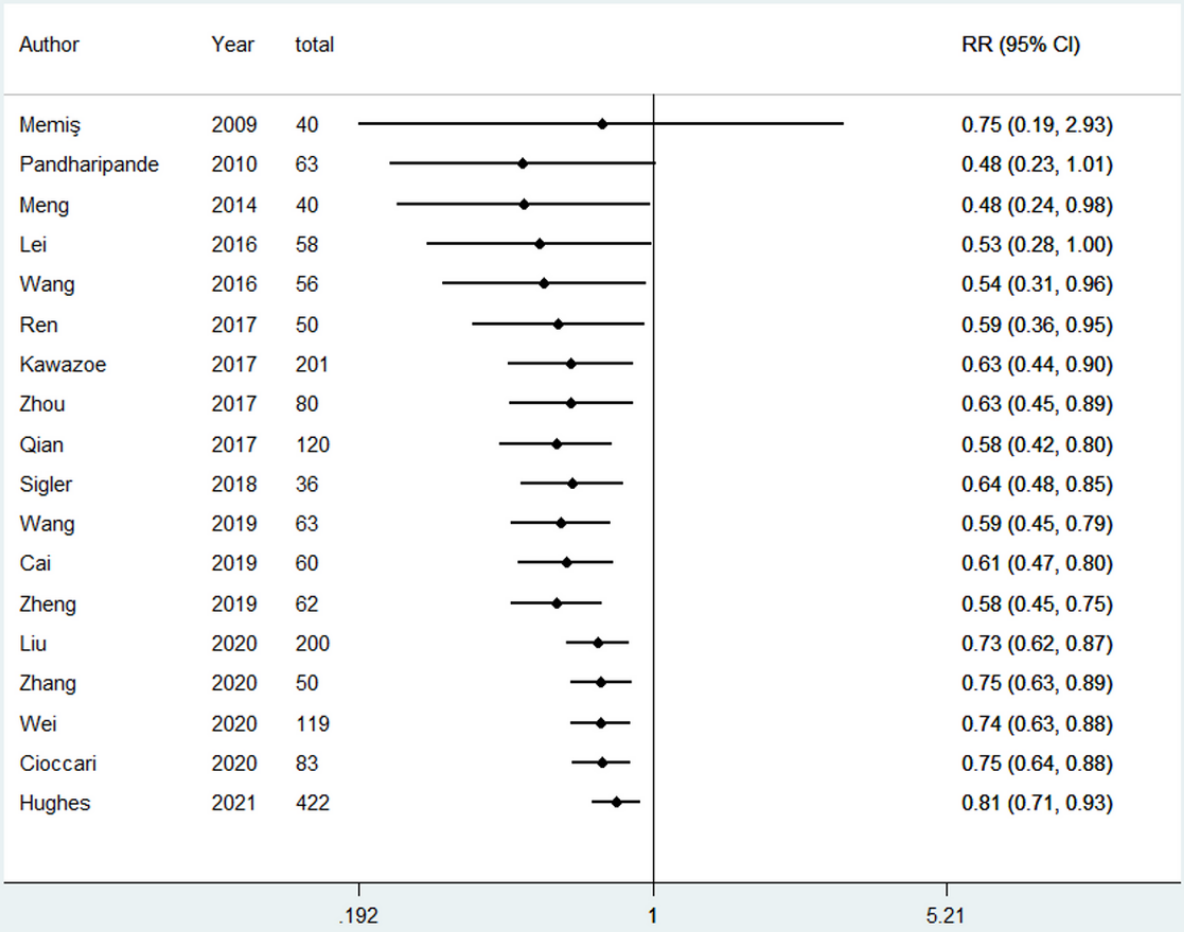


Figure 5

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile.docx