Differences in efficacy and safety of midazolam vs. dexmedetomidine in critically ill patients: A meta-analysis of randomized controlled trial

WEN-JUN ZHOU[1*], MEI LIU[2*] and XUE-PENG FAN[2]

[1]Department of Anesthesiology, The Sixth Hospital of Wuhan, Affiliated Hospital of Jianghan University, Wuhan, Hubei 430015; [2]Department of Intensive Care Unit, Wuhan No. 1 Hospital, Wuhan, Hubei 430022, P.R. China

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Abstract. The present study aimed to compare the efficacy and safety of dexmedetomidine and midazolam in patients that are critically ill. Full text articles reporting the clinical effects and complications of dexmedetomidine and midazolam were retrieved from multiple databases. Review Manager 5.0 was adopted for meta-analysis, sensitivity and bias analysis. Finally, a total of 1,379 patients from 8 studies, which met the eligibility criteria, were included. The meta-analysis suggested that the length of stay at the intensive care unit [mean absolute difference (MD)=-1.80; 95% confidence interval (CI), -2.13, -1.48; P<0.00001; P-value for heterogeneity=0.41; I^2=3%], time to extubation (MD=-2.18; 95% CI, -2.66, -1.69; P<0.00001; P-value for heterogeneity=0.84; I^2=0%) and delirium (MD=0.46; 95% CI, 0.37, 0.57; P<0.00001; P-value for heterogeneity=0.65; I^2=0%) was higher following midazolam treatment compared with dexmedetomidine, while bradycardia [odds ratio (OR)=5.03; 95% CI, 3.86, 6.57; P<0.00001; P-value for heterogeneity=0.13; I^2=38%] was higher in dexmedetomidine treated patients compared with midazolam. However, no difference was observed in the incidence of hypotension (OR=0.88; 95% CI, 0.70, 1.10; P=0.26; P-value for heterogeneity=0.99; I^2=0%) and mortality (OR=0.96; 95% CI, 0.74, 1.25; P=0.77; P-value for heterogeneity=0.99; I^2=0%). Taking clinical effects and safety into account, the present study suggested dexmedetomidine to be the preferred option of anesthesia for patients that are critically ill.

Correspondence to: Dr Xue-Peng Fan, Department of Intensive Care Unit, Wuhan No. 1 Hospital, 215 Zhongshan Avenue, Wuhan, Hubei 430022, P.R. China
E-mail: fxpdoctor@sina.com

*Contributed equally

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Introduction

Due to environmental factors, patients in the Intensive Care Unit (ICU) are frequently in a state of physiological and psychological stress, which can lead to endocrine and acid-base imbalance, hemodynamic instability, increased metabolism and oxygen consumption (1-3). Effective sedation can improve the comfort of ICU patients, reduce oxygen consumption and stress response, increase tolerance to invasive operation, avoid accidental unplugging and improve the recovery rate (4-6).

Dexmedetomidine is a highly selective agonist for α2-adrenergic receptors, with an affinity ratio of 1,620:l to α2:α1 receptors (7). It acts on the adrenergic receptors in the locus coeruleus nucleus and the spinal cord, where it possesses anti-sympathetic, sedative and analgesic effects (7,8). In addition, dexmedetomidine can relieve anxiety by activating presynaptic membrane α2 receptor, inhibiting norepinephrine release and terminating pain signal transmission.

Midazolam is a benzodiazepine sedative which possesses a number of effects, including anti-anxiety, sedative and hypnotic effects, anti-convulsion, muscle relaxation and anterograde amnesia (9-11). This agent exerts sedative and hypnotic effects by stimulating 7-aminobutyric acid receptors in the central nervous system, which results in hypnotic responses (9). Midazolam has been demonstrated to prolong sedation and mechanical ventilation following long-term usage, particularly in patients with renal failure (10). However, some patients may also develop resistance to midazolam (12-14).

A number of studies have (6-9) previously compared dexmedetomidine and midazolam in critically ill patients. However, they vary in terms of research design, recruitment and exclusion criteria established and measurement methods performed. In the present study, randomized controlled trials and clinical prospective studies on dexmedetomidine and midazolam were collected. A meta-analysis was performed to comprehensively compare the efficacy and complications of dexmedetomidine and midazolam in patients that are critically ill. The present study serve as an update for the comparison between midazolam and dexmedetomidine in patients that are critically ill.

Materials and methods

Search strategy. To fully compare the clinical effects and associated complications of dexmedetomidine and midazolam, patients were sedated. References between January 2005 and October 2018 were searched in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cocharane library (https://www.cochranelibrary.com/), Embase (www.embase.com) and Chinese Journal Full-text Database (https://www.cnki.net/). Systematic reviews and meta-analysis were conducted.

Two of the authors (WZ and ML) then independently searched for articles using the following keywords: 'Critical illness', 'dexmedetomidine OR DEX', 'midazolam' and 'sedation'. All of these terms were assembled with the conjunction symbol 'AND' to search the databases for the related articles. To obtain additional research of high relevance and to improve the accuracy of subsequent analysis, the reference list of each article retrieved was also reviewed.

Citation selection. Following the initial screening, all articles were vetted further by two other authors (WZ and XF), where the titles and abstracts of these articles were independently and carefully screened. If the research article was relevant, the full-text article was then selected. There was no restriction on language and the publication period was between January 2005 and October 2018.

The inclusion criteria were as follows: i) A randomized controlled trial or a controlled clinical trial; ii) comparison of the clinical effects and mortality of dexmedetomidine and midazolam; iii) patients that are critically ill (patients whose condition is acute, critical and rapidly changing) were included; and iv) full text articles were available. Exclusion criteria were as follows: i) Non-randomized study; ii) studies on treatments other than dexmedetomidine or midazolam; iii) patients that are critically ill were not included; iv) studies lacking outcome measures or comparable results; and v) duplicated publications and incomplete data or articles.

Finally, the two researchers (ML and XF) jointly examined whether the article of interest met the aforementioned requirements. If there were any differences and no agreement could be reached, a third investigator (WZ) helped to make the decision.

Data extraction. The two reviewers (WZ and ML) read the full text, extracted the relevant data from each study and inserted them into a coding table in the Microsoft Excel software (Microsoft Corporation; version, 2013). The characteristics extracted in the present study included the name of the first author, publication year, year of onset, sample size (dexmedetomidine/midazolam), age range of patients and outcome parameters. The parameters were the clinical effects and complications of dexmedetomidine and midazolam, including length of stay in ICU, time to extubation, delirium, bradycardia, hypotension and mortality.

Statistical analysis. Meta-analysis was performed using Retrospective Manager 5.0 (2011; Cochrane Collaboration) to assess differences in clinical effects and complications between dexmedetomidine and midazolam and publication bias.

Q-statistics can be used to reflect the level of heterogeneity (3). When the heterogeneous I^2 statistic was >50%, the random effects model was used due to moderate or high heterogeneity; otherwise, the fixed effects model was selected.

Sensitivity analysis of bias was performed using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2; http://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/) tool, where the quality of the article and risk of bias in each study were assessed using the following criteria: i) Random sequence generation; ii) allocation concealment; iii) blinding of participants and researchers; iv) blinding of outcome assessment; v) incomplete outcome data; vi) selective reporting; and vii) other bias. In the present study, all parameters including length of ICU stay, time to extubation, incidence of delirium, incidence of bradycardia, hypotension and mortality were collected and the odds ratio (OR) and 95% confidence interval (CI) were calculated. Funnel plots together with Egger tests were applied to assess publication bias. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Search results. A preliminary search identified 603 related titles and abstracts in the electronic databases. After a thorough review, 8 studies (15-22) eventually met the inclusion criteria for final analysis. A total of 595 articles were excluded due to irrelevant studies (n=484), lack of a control group (n=51), incomplete data or comparisons (n=40) or review articles (n=20). Fig. 1 represents a flowchart of the search process, which summarizes the identification, inclusion and exclusion of studies for the present analysis.

Characteristics of the included studies. Table I lists the first author's name, year of publication, sample size (dexmedetomidine/midazolam), age range of patients and the study period. All included studies were published between 2004 and 2018. The sample size of included studies ranged between 24 and 798. The present study had 1,379 critically ill patients, including 750 in the dexmedetomidine group and 629 in the midazolam group.

Quality assessment. The deviation table generated using the QUADAS-2 tool under the instruction of the Review Manager 5.0 tutorial, was used to assess the risk of each study to bias by applying the criteria for evaluating design-related deviations. The risk of bias in the studies is provided in Table II. Participants and personnel in all included studies exhibited high risks of blindness bias due to the research design between dexmedetomidine and midazolam.

Results of meta-analysis

Length of ICU stay. The list of outcomes in terms of clinical effects collected include the length of ICU stay and the time to extubation. All eight studies involved patients requiring ICU stay. Fig. 2 shows a forest map of the length of ICU stay required by patients in the dexmedetomidine and the midazolam groups. All 8 studies demonstrated statistically significant differences in the length of ICU stay between dexmedetomidine and midazolam. The meta-analysis suggested that difference in

Table I. Characteristics of the included studies.

Author, year	Language	Country	Age (range), years	Sex (male/female)	Groups	n	Study period	(Refs.)
Alexopoulou *et al*, 2014	English	Greece	59±10.3 (55-69)	20/6	Dexmedetomidine Midazolam	13 13	October 2011-November 2013	(15)
Benedict *et al*, 2014	English	USA	48±5.9 (39-61)	34/24	Dexmedetomidine Midazolam	29 29	February 2011-May 2011	(16)
Ludtke *et al*, 2015	English	USA	48.7±7.8 (28-59)	27/5	Dexmedetomidine Midazolam	15 17	March 2002-April 2009	(17)
Memis *et al*, 2006	English	Turkey	46±9.4 (19-65)	15/9	Dexmedetomidine Midazolam	12 12	2001-2003	(18)
Riker *et al*, 2009	English	USA	62.1±13.4 (18-69)	246/120	Dexmedetomidine Midazolam	244 122	March 2005-August 2007	(19)
Shehabi *et al*, 2004	English	Australia	61±15 (37-77)	31/9	Dexmedetomidine Midazolam	20 20	2000-2002	(20)
Xu *et al*, 2018	English	China	57.8±13.2 (21-76)	477/321	Dexmedetomidine Midazolam	399 399	2011-2012	(21)
Xue *et al*, 2018	English	China	58.4±11.2 (19-75)	21/14	Dexmedetomidine Midazolam	18 17	2012-2014	(22)

All included samples were critically ill patients.

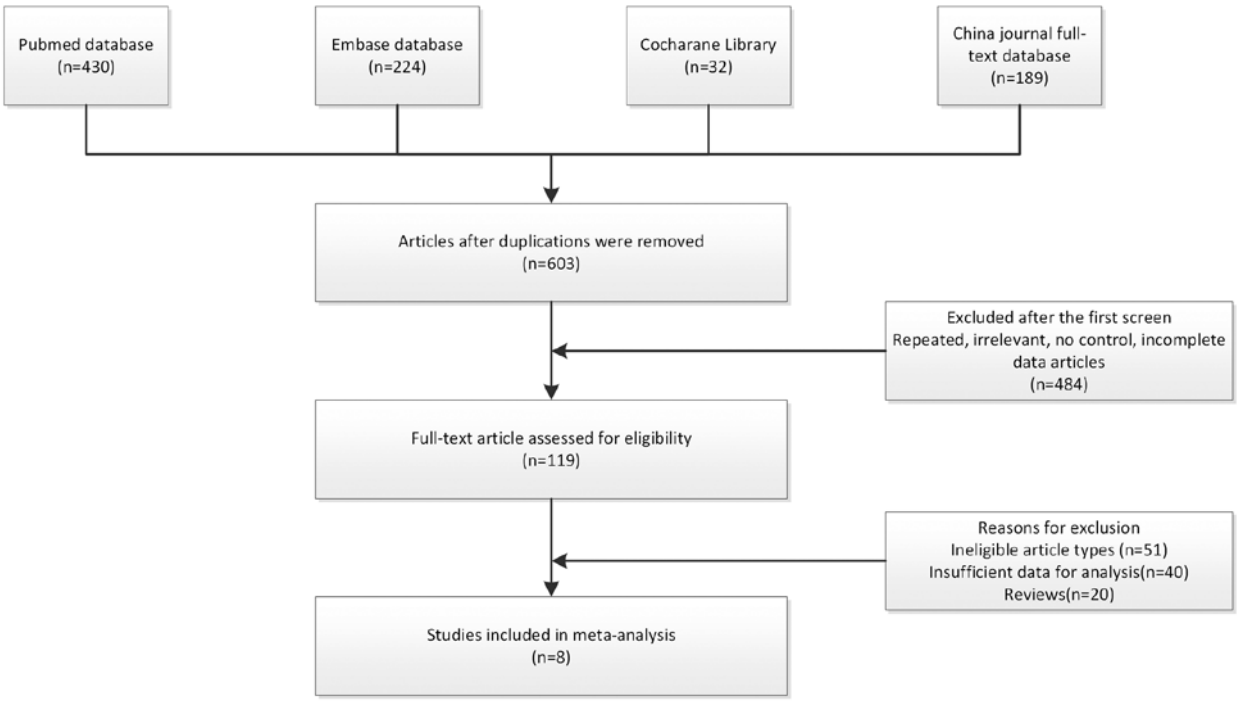

Figure 1. The flow diagram of the study identification, inclusion and exclusion process.

the length of ICU stay in dexmedetomidine and midazolam was significant [mean absolute difference (MD)=-1.80; 95% confidence interval (CI), -2.13, -1.48; P<0.00001; P-value for heterogeneity=0.41; I^2=3%]. The length of ICU stay by patients receiving midazolam (9.93 days) was longer compared with patients receiving dexmedetomidine (7.44 days).

Time to extubation. The forest plot for the meta-analysis of time to extubation is presented in Fig. 3. The results demonstrated that the time to extubation in the midazolam group (6.48 days) was higher compared with that of the dexmedetomidine group (4.01 days; MD=-2.18; 95% CI, -2.66, -1.69; P<0.00001; P-value for heterogeneity=0.84; I^2=0%).

Table II. The risk of bias table in the present study.

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	(Refs.)
Alexopoulou *et al*, 2014	Low risk	Low risk	High risk	Not clear	Not clear	High risk	Not clear	(15)
Benedict *et al*, 2014	Not clear	Low risk	High risk	Low risk	Low risk	High risk	Low risk	(16)
Ludtke *et al*, 2015	Not clear	High risk	High risk	High risk	Low risk	Not clear	Not clear	(17)
Memis *et al*, 2006	Low risk	High risk	High risk	Low risk	Not clear	Low risk	Low risk	(18)
Riker *et al*, 2009	Low risk	High risk	High risk	Low risk	Not clear	Low risk	Low risk	(19)
Shehabi *et al*, 2004	High risk	Low risk	High risk	Low risk	Low risk	Low risk	Not clear	(20)
Xu *et al*, 2018	High risk	Low risk	High risk	Low risk	Low risk	Not clear	Not clear	(21)
Xue *et al*, 2018	Low risk	Low risk	High risk	Not clear	Low risk	Low risk	Low risk	(22)

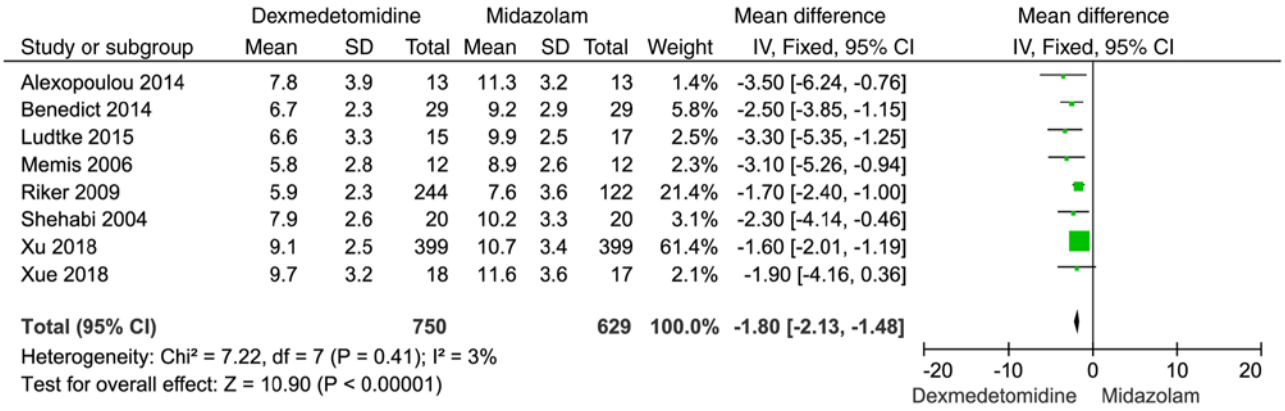

Figure 2. A forest plot comparing the length of intensive care unit stay between the dexmedetomidine and midazolam groups. IV, inverse variance; df, degrees of freedom; CI, confidence interval; SD, standard deviation.

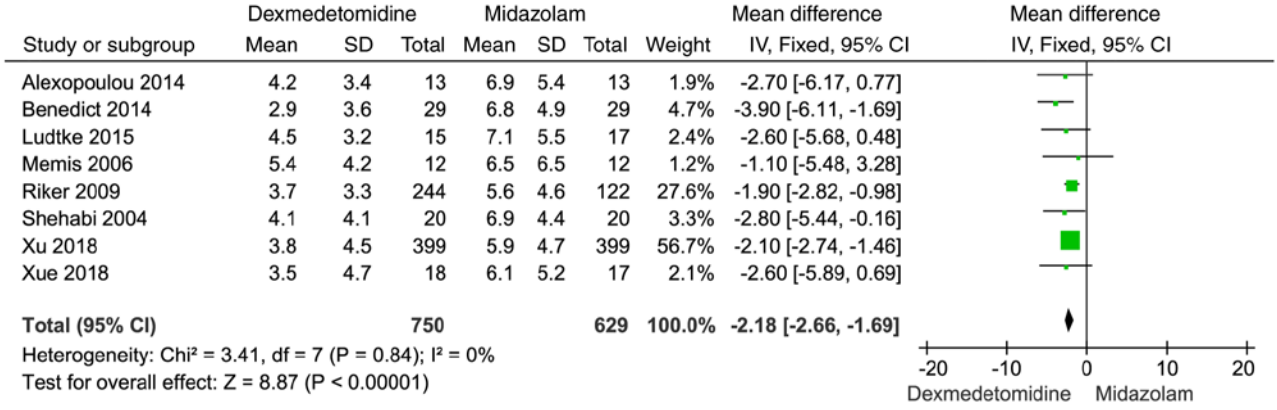

Figure 3. A forest plot comparing the time to extubation between the dexmedetomidine and midazolam groups. IV, inverse variance; df, degrees of freedom; CI, confidence interval; SD, standard deviation.

Incidence of delirium. Complications recorded included delirium, bradycardia and hypotension. The occurrence of delirium in all the included studies are shown in Fig. 4. The overall result indicated that the incidence of delirium in patients treated with midazolam was higher compared with that in patients treated with dexmedetomidine [odds ratio (OR)=0.46; 95% CI, 0.37, 0.57; P<0.00001; P-value for heterogeneity=0.65; I^2=0%].

Incidence of bradycardia. The occurrence of bradycardia reported in all eight of the studies is shown in Fig. 5. The overall result indicated that the incidence of bradycardia in the

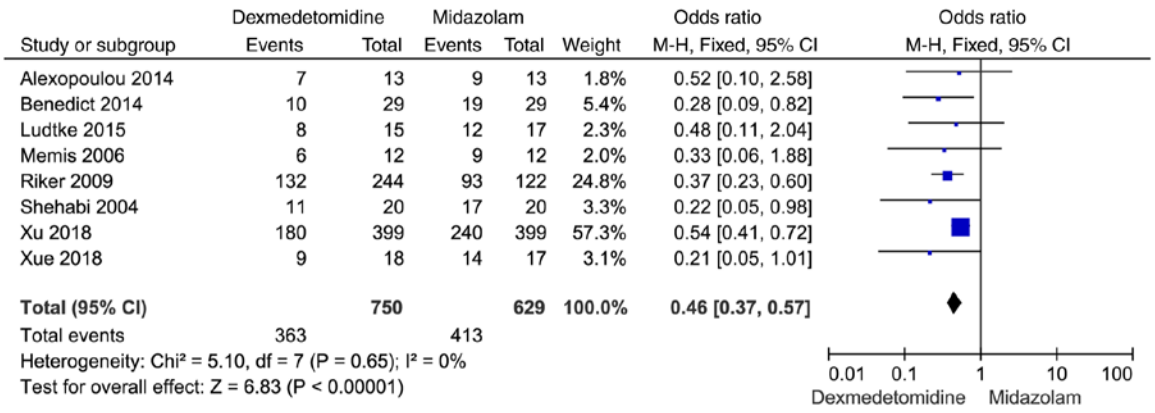

Figure 4. A forest plot comparing the incidence of delirium between the dexmedetomidine and midazolam groups. df, degrees of freedom; M-H, Mantel-Haenszel; CI, confidence interval.

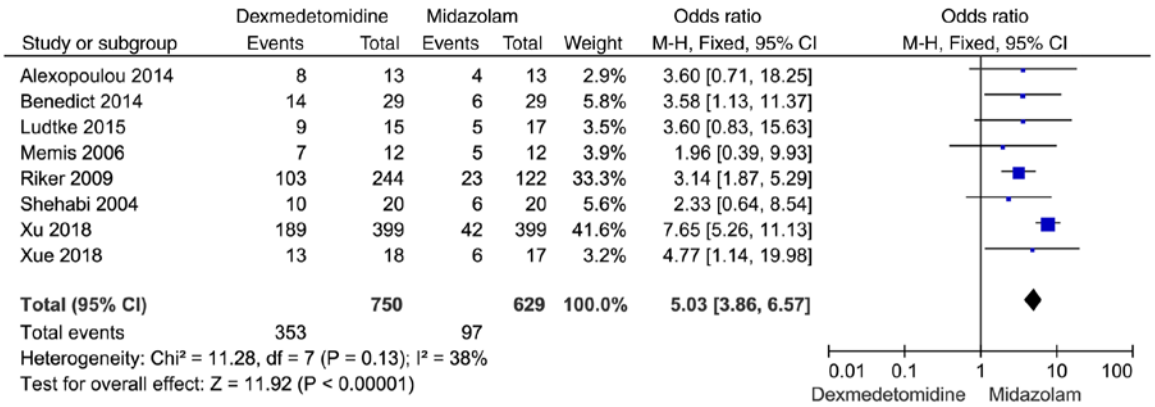

Figure 5. A forest plot comparing the incidence of bradycardia between the dexmedetomidine and midazolam groups. df, degrees of freedom; M-H, Mantel-Haenszel; CI, confidence interval.

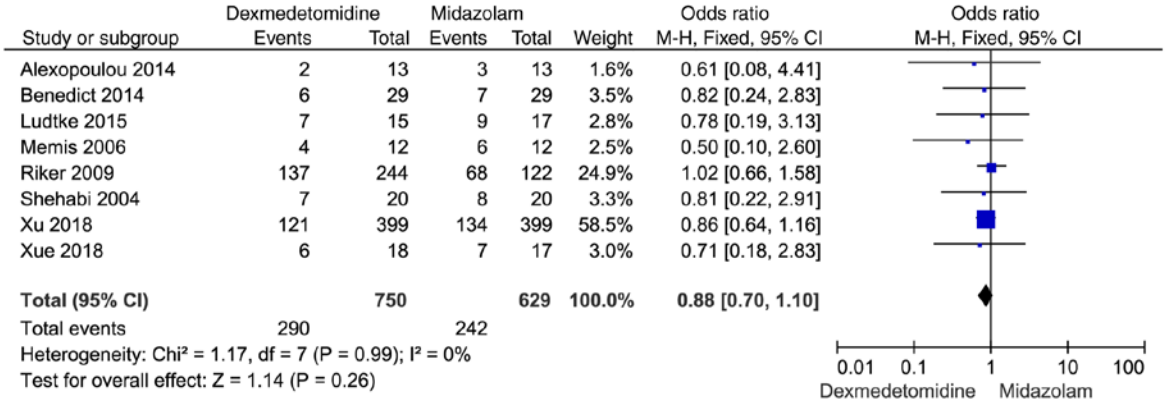

Figure 6. A forest plot comparing the incidence of hypotension between the dexmedetomidine and midazolam groups. M-H, Mantel-Haenszel; CI, confidence interval.

dexmedetomidine group was higher compared with that of the midazolam group (OR=5.03; 95% CI, 3.86, 6.57; P<0.00001; P-value for heterogeneity=0.13, I^2=38%).

Meta-analysis of hypotension. All studies with data on hypotension are presented in Fig. 6. The overall result indicated that there was no difference in the incidence of hypotension between the dexmedetomidine and the midazolam groups (OR=0.88; 95% CI, 0.70, 1.10; P=0.26; P-value for heterogeneity=0.99; I^2=0%).

Mortality. The eight studies with data on mortality are shown in Fig. 7. The overall result indicated that there was no difference in the mortality rate between the dexmedetomidine and the midazolam groups (OR=0.96; 95% CI. 0.74, 1.25; P=0.77; P-value for heterogeneity=0.99; I^2=0%).

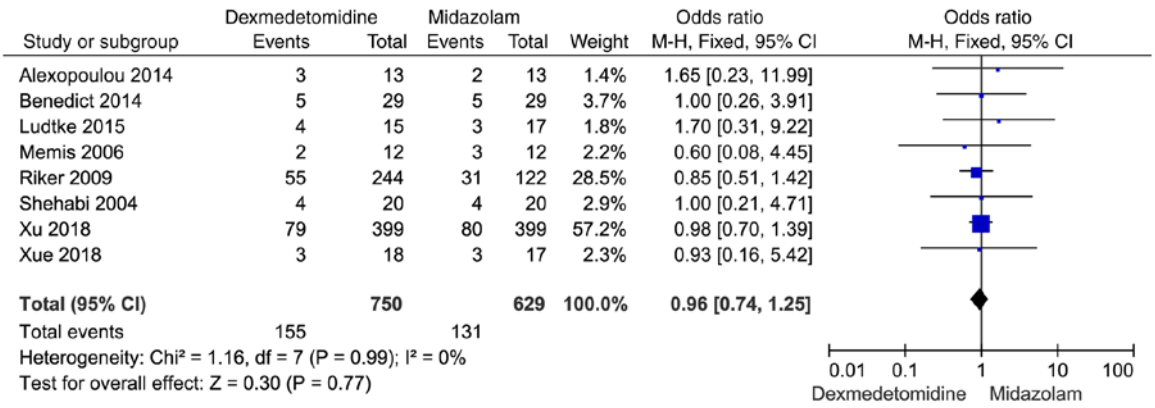

Figure 7. A forest plot comparing the incidence of mortality between the dexmedetomidine and the midazolam groups. df, degrees of freedom; M-H, Mantel-Haenszel; CI, confidence interval.

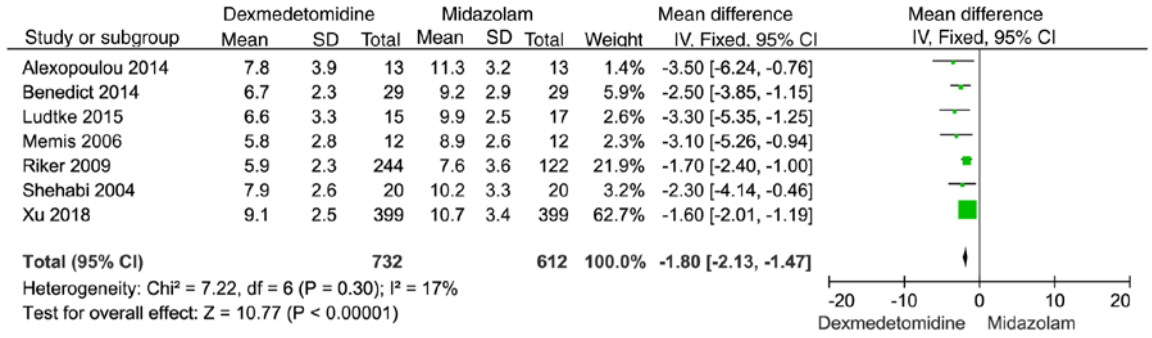

Figure 8. A forest plot for sensitivity analysis in length of intensive care unit stay. df, degrees of freedom; IV, inverse variance; CI, confidence interval; SD, standard deviation.

Sensitivity analysis. Since heterogeneity is a measure of the variation among the effect sizes of the included studies, changes in it can reflect the stability of the meta-analysis (23). According to the meta-analysis in the present study, heterogeneity of the length of ICU stay was low (I^2=3%). As shown in Fig. 8, the low heterogeneity in the length of ICU stay may be attributed to the different results of each study. Since the difference in I^2 was the most prominent following the exclusion of the study by Xue *et al* (22), this study was excluded. As such, the I^2 rose from 3 to 17%.

Bias analysis. Funnel plots of the length of ICU stay in the dexmedetomidine and the midazolam groups were performed. All studies are included in the plot. The results demonstrated that the funnel plot had medium symmetry with minimal publication bias (Fig. 9).

Discussion

Patients in critical care in the ICU experience severe stress due to underlying diseases, sleep deprivation, anxiety, pain, tracheal intubation, tracheotomy among other factors (23-25). Analgesia and sedation therapy have become an important part of patient management in the ICU.

Midazolam is a benzodiazepine sedative that is associated with effects, including anti-anxiety, sedative and hypnotic effects, anti-convulsion, muscle relaxation and anterograde amnesia (26-28). By contrast, dexmedetomidine confers advantages including sedation, cooperation and communication after awakening, such that it can reduce the demand for analgesics (27). Dexmedetomidine used for treating patients with infection, sepsis and systemic inflammatory reactions has not been demonstrated to increase the risk of side effects (29,30). In addition, it can effectively prevent the incidence of delirium and shorten the length of ICU stay (30).

In the present study, the difference in the length of ICU stay in patients receiving dexmedetomidine and midazolam was found to be significant, whilst the time to extubation in patients receiving midazolam was higher compared with patients receiving dexmedetomidine. These results demonstrated that dexmedetomidine could reduce the duration of ICU stay and extubation, suggesting that dexmedetomidine administration resulted in superior clinical outcomes and shorter recovery times compared with midazolam. Ma *et al* (31) previously reported that dexmedetomidine can significantly shorten the recovery time and extubation time of patients, which may be related to the reduction of propofol and fentanyl dosage by dexmedetomidine. Results from the present study is consistent with those observed by Ma *et al* Additionally, Romagnoli *et al* (32) stated previously that dexmedetomidine represents an optimal choice for sedation of patients that are critically ill due to its unique properties in calming patients and increasing cooperativity by providing (light) sedation and analgesia. It can be used as an effective drug to induce light sedation,

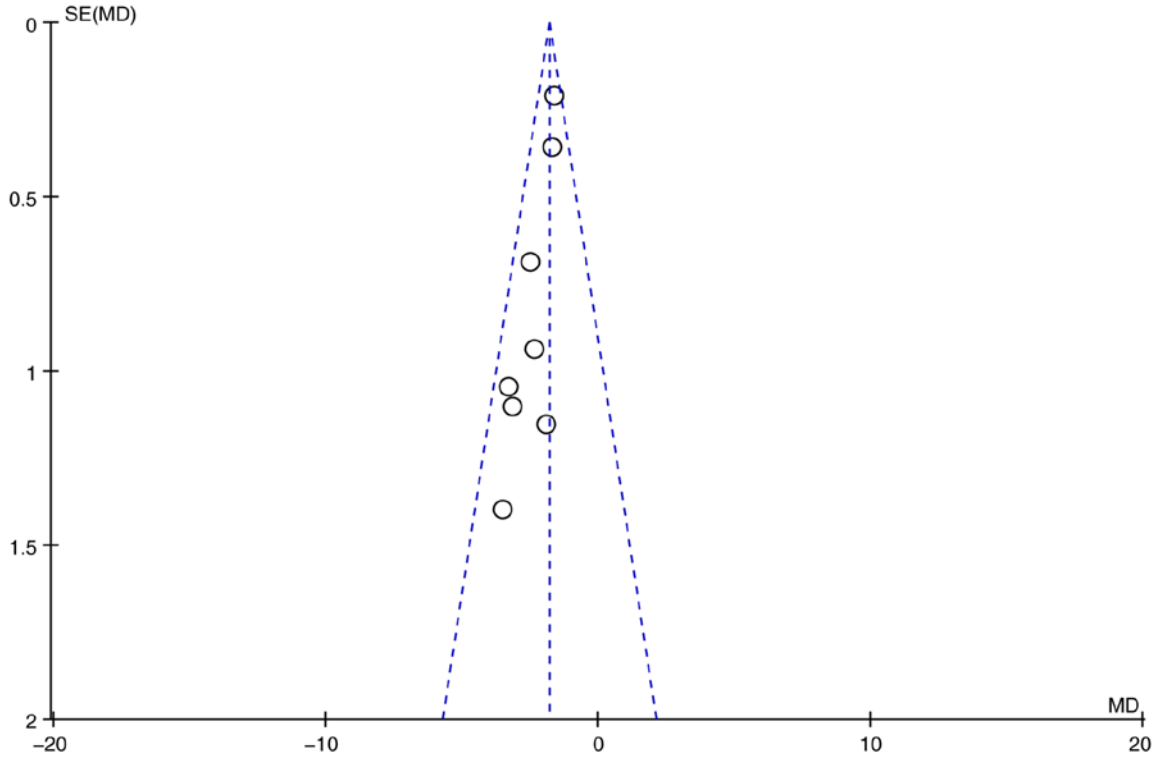

Figure 9. Begg's funnel plot of publication bias. SE, standard error; MD, mean absolute difference.

analgesia and quasi-physiological sleep in patients that are critically ill. Considering the results of ICU stay and time to extubation, the results demonstrated that dexmedetomidine is effective for inducing light sedation for patients that are critically ill.

The incidence of delirium in patients receiving midazolam was found to be higher compared with that in patients receiving dexmedetomidine, whilst the incidence of bradycardia in patients receiving dexmedetomidine was higher compared with that in patients receiving midazolam. This observation is consistent with that reported by the study of Yao *et al* (33), which demonstrated that dexmedetomidine, is a novel and highly selective agonist of the α2 adrenergic receptor resulting in analgesic effects. Sedation for severe patients can shorten the length of ICU stay, reduce the incidence of delirium and improve the outcome of patients that are critically ill (30). Romagnoli *et al* (32), also reported that dexmedetomidine can provide a fundamental support for the prevention and treatment of delirium in patients that are critically ill, demonstrating that dexmedetomidine can prevent adverse effects.

The overall results of the present study indicated that the occurrence of hypotension and mortality in patients receiving dexmedetomidine and midazolam did not differ. The results of mortality and complications indicated that dexmedetomidine and midazolam exerted little difference in terms of the safety of sedation in patients that are critically ill. This consistent with previous studies (4,6).

The present study has a number of limitations. Additional indicators, such as recovery time in both the dexmedetomidine and midazolam groups could have been analyzed, which should be evaluated in the future. Furthermore, additional articles should also be included for further research.

In the present study, low heterogeneities were obtained in the meta-analysis. According to the funnel plots, no publication bias was observed, further validating the results. Compared with midazolam, dexmedetomidine is the preferred anesthetic for patients that are critically ill. The present study can facilitate anesthesiologists in the selection of anesthetic agents for patients that are critically ill.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

WZ and XF made substantial contributions to conception and design of the study. WZ, ML and XF searched literature, extracted data from the collected literature and analyzed the data. WZ wrote and XF revised the manuscript. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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