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RESEARCH

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Dexmedetomidine for delirium prevention in adult patients following cardiac surgery: a meta-analysis of randomized controlled trials

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Abstract

Objectives To determine whether perioperative administration of dexmedetomidine reduces the incidence of postoperative delirium in adult patients undergoing cardiac surgery.

Methods We searched the PubMed, Embase and Cochrane Library databases for randomized controlled trials from the last 10 years up to March 10, 2024. We then conducted a meta-analysis to evaluate the effectiveness and safety of dexmedetomidine in preventing delirium after cardiac surgery in adults. This meta-analysis followed the steps in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA2020) guidelines. This study is registered with INPLASY under number INPLASY202430132.

Results A total of 2689 patients were included in our analyses. All included studies were randomized controlled trials. Dexmedetomidine can reduce the occurrence of delirium in patients after cardiac surgery(OR 0.75, 95%CI 0.57–0.98, $I^2=12\%$, $P=0.04$). In terms of other end events, length of intensive care unit(ICU) stay(MD -0.16, 95%CI -1.85-1.53, $I^2=0\%$, $P=0.85$) and mortality(OR 1.59, 95%CI 0.74–3.42, $I^2=0\%$, $P=0.23$) were not statistically different with dexmedetomidine compared with placebo. Bradycardia (OR 0.85, 95%CI 0.54 ~ 1.34, $I^2=72\%$, $P=0.49$) and hypotension (OR 1.97, 95%CI 0.96 ~ 4.03, $I^2=84\%$, $P=0.06$) were not significantly different between the two groups.

Conclusions Dexmedetomidine is safe for cardiac surgery patients and to some extent reduces the incidence of delirium in cardiac surgery patients, which is more important in preoperative use.

Keywords Dexmedetomidine, Delirium, Cardiac surgery

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Introduction

Delirium is an acute, fluctuating cognitive disorder characterized by a reduced ability to sustain attention, disorientation to time and place, memory loss, and disrupted sleep and wake cycles [1]. Cardiac surgery-induced changes in cardiac output, intracranial blood perfusion, and release of inflammatory factors can lead to postoperative delirium(POD), prolong hospital stay, and have significant adverse effects on patients' prognosis. The pathophysiological logic behind the different phenotypes of delirium may be more complex [2–4]. According to statistics, the incidence of postoperative delirium is about 12–55%, which shows that this phenomenon seriously affects the patient population after cardiac surgery [5]. Unfortunately, there is currently no specific treatment for POD [6]. Prevention of POD relies mainly on repositioning the patient, controlling pain, and maintaining nerve rhythm [7].

Dexmedetomidine is an alpha-2 A adrenergic receptor agonist commonly used to sedate patients in anesthesia and intensive care settings. Experimental studies have shown that dexmedetomidine has a neuroprotective effect by reducing stress responses to surgery, reducing the need for opioid analgesics, and restoring more natural sleep patterns [8]. Despite these theoretical advantages, the ability of dexmedetomidine to reduce the incidence of delirium after cardiac surgery remains controversial. Turan et al. investigated the preventive effect of dexmedetomidine on POD and upper ventricular arrhythmias after cardiac surgery, but did not find that dexmedetomidine had a positive effect on the prevention of POD [9]. Huet found that overnight infusion of dexmedetomidine did not reduce postoperative delirium in patients recovering from elective cardiac surgery [10]. Qu reported that single overnight administration of dexmedomide reduced the incidence of delirium on the first day after cardiac surgery [11]. Priye [12] conducted a small sample study and found that dexmedetomidine can provide safe and effective adjuvant analgesia for patients undergoing cardiac surgery and that the incidence of delirium tends to decrease without adverse hemodynamic effects. The contradictory results of these studies may be explained by the significant heterogeneity between study designs and the lack of consistency of POD definitions, making it impossible to draw definitive conclusions about the benefit-risk ratio of the use of dexmedetomidine infusions in this context.

In recent years, scholars have paid more attention to the impact of delirium on the prognosis of patients. Our study investigated the value of dexmedetomidine in the prevention of postoperative delirium events after cardiac surgery by including randomized controlled trials over the past 10 years [9–15], which were divided into three subgroups for analysis based on differences in drug use in the studies. We also examined differences in length of ICU stay and mortality after surgery.

Methods

This meta-analysis followed the steps in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16]. Our meta-analyses were pre-registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols database (number: INPLASY202430132) and were fully available on inplasy.com (https://inplasy.com/inplasy-2024-3-0132). Ethical approval was not required for this study.

Search strategy

Three researchers were independent (Chang Meng, Duo Wang and Yue Zhao). They each conducted an extensive electronic search for articles published in the field between January 1, 2014 and March 10, 2024. Researchers searched databases, including PubMed, Embase and Cochrane databases, and manually selected relevant randomized controlled trials. Specific literature search strategies can be found in the appendix(Supplement File: Table S1).

Inclusion and exclusion

The document management process utilizes EndNote (X9) software, and two investigators conduct an independent assessment of the project's qualifications. In the first phase of the process, the title and abstract are reviewed, after which the article in question is subjected to a comprehensive review. The studies included in this review were only randomized controlled trials. The following inclusion criteria were met: (1) Adult patients following cardiac surgery. (2) Patients with dexmedetomidine or placebo (normal saline). (3) Outcomes Indicators: Delirium incidence, ICU-days, Mortality. We excluded animal trials, studies that included patients < 18 years of age, and insufficient data to be extracted, such as summaries, reviews, pharmacological presentations, and other literature. If we need relevant research data, we will contact the authors. Non-intravenous administration, unreasonable control group settings, and inaccurate data extraction were also excluded. The studies included in this meta-analysis were evaluated for delirium. POD assessment during cardiac surgery intensive care Unit was performed every 12 h using ICU confusion assessment (CAM-ICU) [17], while delirium assessment in the ward was performed using CAM. The evaluation process is administered by a separate researcher for CAM-ICU or CAM measurements.

Bias & quality assessment

The two researchers conducted independent evaluation, preliminary selection and verification of the literature

in accordance with a unified and standardized method, and included the literature in strict accordance with the inclusion and exclusion criteria, and then collected data. The quality of the selected articles was evaluated according to the Cochrane Reviewer Handbook 5.1.0 [18].

Data synthesis and analysis

Meta-analysis was performed using RevMan5.4. Data that met homogeneity ($P > 0.10$, $I^2 \leq 50\%$) in the heterogeneity test were analyzed using the fixed-effect model. If uniformity ($P \leq 0.10$ or $I2 > 50\%$) was not met and heterogeneity cannot be excluded, a random effects model can be used to combine effects [19]. Results were expressed as odds ratios (OR) of 95% confidence intervals (CI) for discontinuous outcomes. We used mean difference (MD) and 95% CI to express continuous results. A p value of less than 0.05 was considered statistically significant.

Results

The flowchart (Fig. 1) summarizes the search and research selection process. A total of 446 literatures were searched, of which 220 were excluded due to duplicates. 144 studies were also excluded after reading the title and abstract. The remaining 82 studies were evaluated by reading the full text. Data from seven clinical trials evaluating the effectiveness and safety of dexmedetomidine in preventing delirium after cardiac surgery in adults.

The main features of included trials are presented in Table 1. A total of 2689 patients were included in our analyses. All included studies were randomized controlled trials. All of the studies were comparing the efficacy and safety of dexmedetomidine for delirium prevention in adult patients following cardiac surgery. Dexmedetomidine was statistically different from placebo in the prevention of postoperative delirium (Fig. 2)(OR 0.75, 95%CI 0.57–0.98, $I^2 = 12\%$, $P = 0.04$). In terms of other end events, length of ICU stay (Fig. 3)(MD -0.16, 95%CI -1.85-1.53, $I^2 = 0\%$, $P = 0.85$) and mortality (Fig. 4)(OR 1.59, 95%CI 0.74–3.42, $I^2 = 0\%$, $P = 0.23$) were not statistically different with dexmedetomidine compared with placebo. In terms of drug-related adverse events, there was no statistically significant difference between bradycardia (Fig. 5)(OR 0.85, 95%CI 0.54–1.34, $I^2 = 72\%$, $P = 0.49$) and

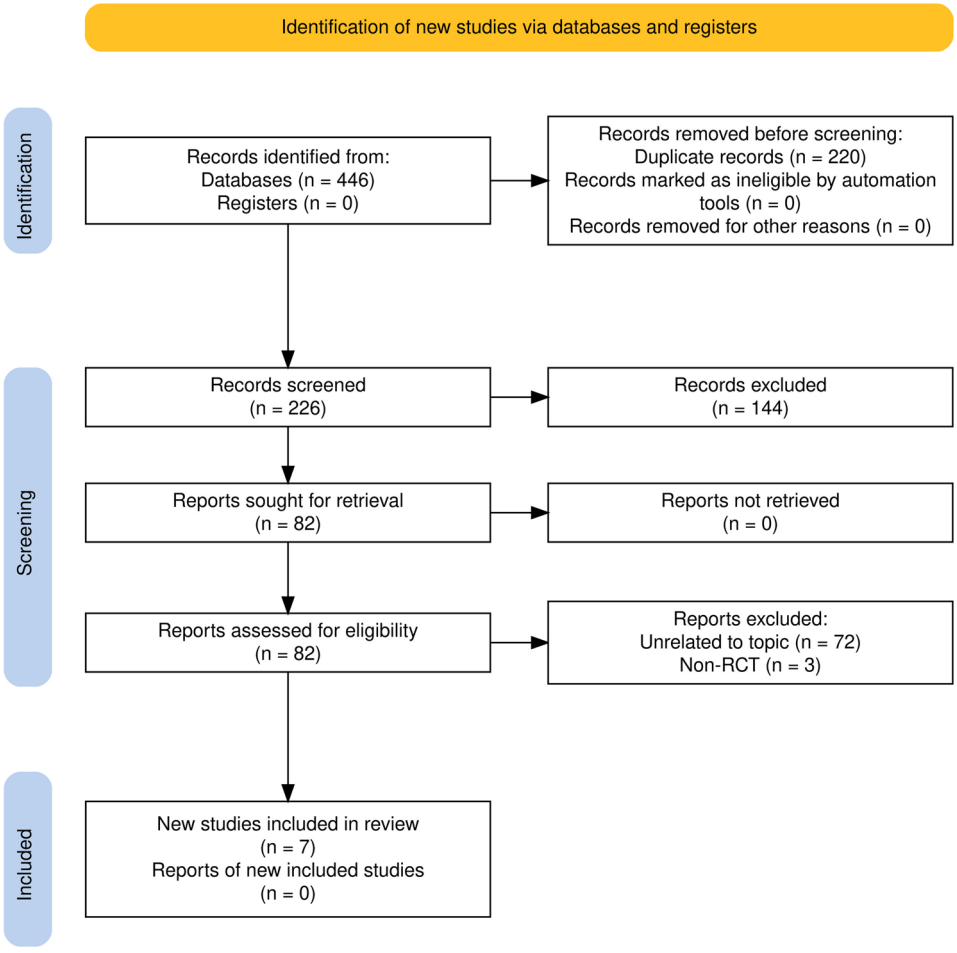

Fig. 1 The flow chart of the search and study selection process

Table 1 Design and outcomes of the studies included in the meta-analysis

Num	Author/ Year	Design	Intervention assignments		Participants				Cardiac surgery
			Dexmedetomidine(Time)	Control	Sample size, *n*	Mean age, years(D/C)	Male%, (D/C)	Delirium observation time	
1	Li/2017	RCT, MC	Anesthesia and early postoperative	Placebo	285	66/68	67/71	First five days after surgery	CABG Valve replacement
2	Turan/2020	RCT, MC	Maintenance before operation and after operation	Placebo	794	63/62	67/73	First five days after surgery	Cardiac surgery with cardiopulmonary bypass
3	Likhvantsev/2021	RCT, SC	Maintenance before operation and after operation	Placebo	169	63/62	74/71	First five days after surgery	Cardiac surgery with cardiopulmonary bypass
4	Priye/2015	RCT, SC	Intravenous pumping was maintained for 12 h after operation	Placebo	64	45/41	53/50	During the ICU stay	CABG, valve surgery, and atrial septal defect closure
5	Qu/2023	RCT, SC	Every night throughout the ICU stay for up 3 days postoperatively	Placebo	394	68/70	77/70	First three days after surgery	Cardiac surgery with cardiopulmonary bypass
6	Wang/2023	RCT, SC	Anesthesia until the end of the operation	Placebo	652	54/54	49/51	First seven postoperative days	Cardiac valve surgery with bypass
7	Huet/2024	RCT, MC	Every night for a maximum of 7 days after surgery	Placebo	331	73/73	78/74	First seven postoperative days	Cardiac surgery with or without cardiopulmonary bypass.

CABG = Coronary Artery Bypass Grafting; D/C = Dexmedetomidine group/ control group; ICU = Intensive care unit; SC = Single center; MC = Multi-center; Placebo = Placebo or normal saline; RCT = Randomized clinical trial

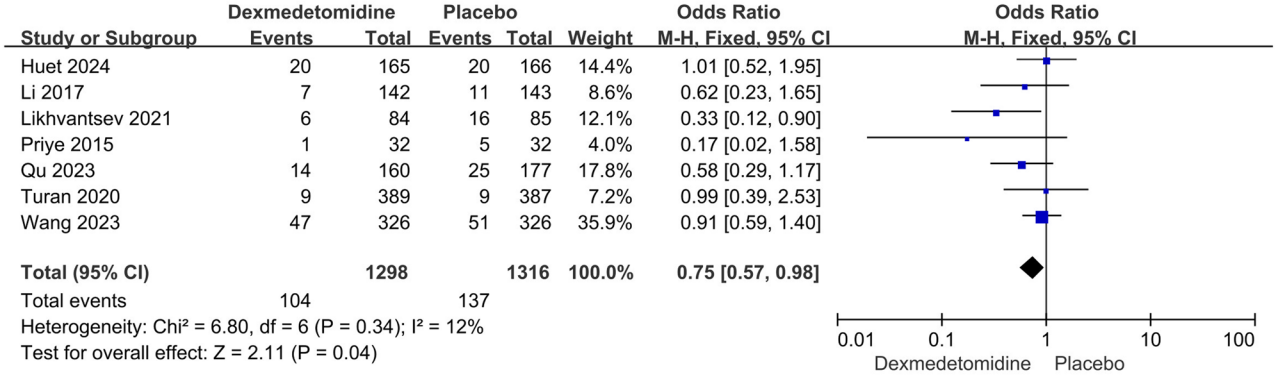

Fig. 2 Forest plot of postoperative delirium between dexmedetomidine and placebo

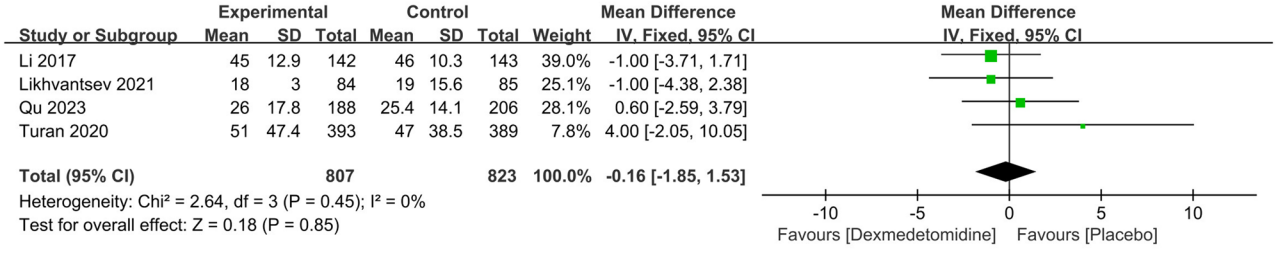

Fig. 3 Forest plot of length of ICU stay between dexmedetomidine and placebo

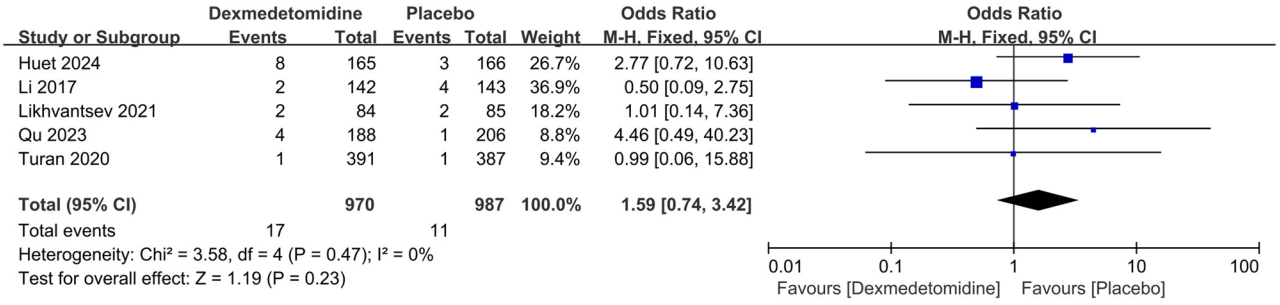

Fig. 4 Forest plot of mortality between dexmedetomidine and placebo

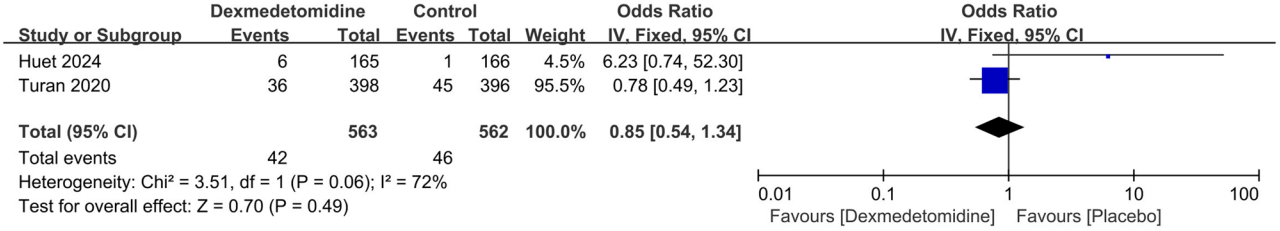

Fig. 5 Forest plot of bradycardia between dexmedetomidine and placebo

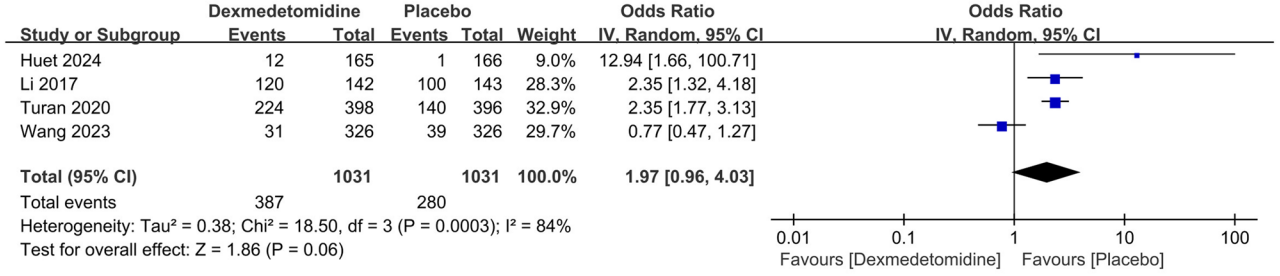

Fig. 6 Forest plot of hypotension between dexmedetomidine and placebo

hypotension (Fig. 6)(OR 1.97, 95%CI 0.96–4.03, $I^2 = 84\%$, $P = 0.06$).

We used Revman to investigate the impact of a single study on the overall pooled estimate of each predefined outcome. The results of the bias risk assessment for these trials were summarized in the Supplementary File. The quality of the included studies was medium to high, two of which received full marks. Some of them had some risk of bias derived from detection bias, attrition bias and reporting bias.

Discussion

In the present meta-analysis, which includes a total of seven medium to high quality randomized controlled trials from the last decade, the results suggest that dexmedetomidine has some effectiveness in reducing the incidence of delirium after cardiac surgery. In addition, a comprehensive analysis of safety endpoints for the use of dexmedetomidine was performed, which included variables such as length of intensive care unit stay, mortality, occurrence of hypotension, and occurrence of bradycardia. Although there were some differences in the length of follow-up for mortality across studies, the results were generally consistent. The occurrence of adverse events showed no significant difference between the two groups.

Postoperative delirium often occurs after surgical procedures performed under general anesthesia. Despite extensive research, the underlying pathophysiology of postoperative delirium remains unclear. Most cases manifest within the first 2–3 days after surgery and manifest as impaired attention, disoriented behavior, impaired cognitive function and, in severe cases, delirium. Without preventive measures and intervention strategies for postoperative delirium, a lengthy progression and course of the disease can be expected. It has been shown that this can lead to long-term cognitive impairment, potentially leading to complications such as brain atrophy and dementia, significantly increasing the risk of postoperative mortality [20]. The etiology of postoperative delirium remains to be elucidated, although several possible mechanisms have been postulated, including neurotransmitter

theory, neuroinflammatory mechanisms, stress mechanisms, cerebral blood supply, and metabolic disorders. Risk factors for development include trauma, stress, postoperative pain, renal dysfunction, diabetes, and sleep cycle disorders [21–22]. Patients who have had heart surgery are more likely to experience delirium. This is mainly related to the surgical approach, the duration of the procedure, cardiopulmonary bypass, cardiac function, internal environment disorders and postoperative hypoxemia. In the context of postoperative delirium in the intensive care unit, current research suggests that a variety of interventions are required that go beyond mere drug treatment [23]. A comprehensive treatment approach that integrates various therapeutic modalities is likely to become a future research direction.

Early diagnosis and treatment of delirium can effectively reduce the duration of the condition, its serious consequences and adverse effects, and facilitate the recovery of patients. The Confusion Assessment Method-CAM (CAM) is a well-established diagnostic tool that adheres to the diagnostic criteria outlined in DSM-III-R for delirium. It has demonstrated good reliability and validity, and its research findings have been extensively cited in the academic literature. The CAM-ICU scale was developed by Ely, building on the foundations laid out by CAM. It is particularly well-suited to patients who are intubated and unable to communicate verbally, such as those admitted to the ICU following cardiac surgery. These patients often require systematic monitoring and treatment, with the use of auxiliary ventilation being a common occurrence. The CAM-ICU scale is a suitable tool for the assessment of delirium in such patients. The study incorporated two types of clinical trials, which are widely utilised to facilitate prompt and precise patient evaluation by medical professionals [24–25]. The sedative effect of dexmetopidine is not dependent on the cerebral cortex, meaning that patients in the anesthetic state during the non-rapid eye movement (NREM) subphase of natural sleep are not susceptible to respiratory depression. This characteristic confers a unique clinical advantage. The specific pharmacological mechanism may be [26–27]: (1) improvement of sleep; (2) interaction with related neurotransmitters to regulate inflammatory factors; (3) increased the uptake rate of cerebral glucose and the expression of brain-derived neurotrophic factor; (4) activation of associated attachment kinase and protein kinase to reduce postoperative stress and produce neuroprotective effects. Consequently, dexmedetomidine exerts significant clinical effects in the prevention and treatment of postoperative delirium, thereby enhancing the quality of life of patients and potentially reducing clinical costs [28]. The drug has been shown to inhibit sympathetic nerve activity by activating postsynaptic membrane receptors, which may have implications for blood pressure and heart rate regulation [29]. However, these effects appear to be minimal in the present study. This may be attributable to the exclusion of individuals with bradycardia from the study during the enrolment phase, resulting in a relatively modest sample size. Furthermore, it is acknowledged that numerous factors have the capacity to influence heart rate and blood pressure. Consequently, larger samples and more consistent studies are required in the future to elucidate the impact of analgesia, agitation and other factors on heart rate and blood pressure [30–31].

Dexmedetomidine is a central, highly selective, short-acting alpha-2 adrenoreceptor agonist with anti-anxiety, anti-sympathetic and sedative effects [32]. Recent studies have shown that dexmedetomidine has potential benefits in alleviating surgical stress and can be used as a co-analgesic to reduce inflammatory states [33–34] and help restore postoperative sleep structure [35]. All of these theoretically beneficial effects could potentially improve perioperative care for patients undergoing heart surgery through ERAS (Enhanced Recovery After surgery) program [34]. In addition, the application of dexmedetomidine in many clinical studies, in addition to observing the clinical manifestations of delirium, lack of certain EEG monitoring, using EEG to guide the evaluation of analgesia and sedation should also become a way in the future [36–37]. There is also a correlation between delirium and stroke [38], and the correlation between postoperative delirium and previous stroke in cardiac patients is also a direction worth exploring in the future.

Finally, it is important to acknowledge the limitations of the study. The heterogeneity of the study can be increased primarily by administering different drug doses, different time windows and different follow-up periods. In addition, the number of randomized controlled trials is currently limited and the sample size of some experiments is small. Therefore, it is necessary to conduct more extensive research in the future. The results of our meta-analysis suggest that future studies should further verify the preventive effect of dexmedetomidine on preoperative delirium in patients undergoing cardiac surgery. In recent years, preoperative use of dexmedetomidine has been suggested as a future research direction [39]. Finally, we recommend exploring different administration time windows and including nursing interventions and other comprehensive treatment modalities in the analysis. The present study found that dexmedetomidine was used in combination with dexmedetomidine during and after surgery.

Conclusions

Dexmedetomidine is safe for cardiac surgery patients and to some extent reduces the incidence of delirium in cardiac surgery patients, which is more important in preoperative use.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-025-03360-7.

Supplementary Material 1

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Author contributions
CM, DW and YZ searched the scientific literature and drafted the manuscript. JS and G-B M contributed to data abstract. L-JC, YB and PL contributed to conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. The authors read and approved the final manuscript.

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Data availability
Data sets are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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