Heart Surgery Forum 2024; 27(12): E1475–E1482
doi: 10.59958/hsf.7993

Systematic Review

Effects of Sedation Medications on Postoperative Delirium and Cognitive Dysfunction in Cardiac Surgery Patients with Cardiopulmonary Bypass: A Network Meta-Analysis

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Submitted: 22 August 2024 Revised: 19 September 2024 Accepted: 23 September 2024 Published: 25 December 2024

Abstract

Background: Neuropsychological deficits, such as delirium and cognitive dysfunction, are common consequences of cardiac surgery. The effectiveness of sedative drugs remains controversial. The purpose of this study was to collect and summarize the current evidence on the application of sedatives in randomized trials to prevent delirium and cognitive dysfunction in adult patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). **Methods**: We searched for relevant studies in the databases from inception to September 1, 2024. Randomized controlled trials (RCTs) investigating the effects of sedatives and comparators on postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) in adults undergoing cardiac surgery with CPB were included in this research. Frequentist network meta-analysis (NMA) was utilized for comparing various interventions. **Results**: Forty-five RCTs were included in the analysis. For POD, there were statistically significant differences between the dexmedetomidine group and the control group (odds ratio [OR]: 0.70; 95% CI: 0.50, 0.98; $p = 0.038$), which was mainly dependent on the effect of the postoperative application. Ketamine (92%) and esketamine (91%) also showed higher surface under the cumulative ranking curve (SUCRA) ranks, and trial sequential analysis also indicated their potential effectiveness. For the Mini-Mental State Examination (MMSE) outcome, the results indicated that dexmedetomidine (standardized mean difference [SMD]: 3.14; 95% CI: 1.12, 5.16; $p = 0.002$) and remifentanil (SMD: 4.24; 95% CI: 0.28, 8.20; $p = 0.036$) resulted in significantly higher MMSE scores than the control group. **Conclusions**: Postoperative dexmedetomidine significantly outperformed the control in terms of POD risk and MMSE score. Esketamine/ketamine also demonstrated potential efficacy in preventing POD. Further research is required to validate these findings.

Keywords

cardiopulmonary bypass; cognitive dysfunction; deep sedation; delirium; meta-analysis

Introduction

Postoperative delirium (POD) is an acute brain disorder in which patients experience a series of alterations in consciousness, attention, cognition, and perception following surgical procedures [1]. Postoperative cognitive dysfunction (POCD) is also a frequent complication of general anesthesia and is the most prevalent postoperative issue impacting the central nervous system. The field of cardiac surgery has advanced due to the evolution of cardiopulmonary bypass (CPB). Over 2 million cardiac surgeries are conducted globally annually, with the prevalence of POD in major cardiac surgery patients varying between 3% and 47%. The pathophysiology of POD is believed to involve disruptions in neurotransmitter signaling and neuroinflammation. CPB can lead to elevated systemic inflammatory levels, resulting in blood-brain barrier leakage, neuroinflammation, and oxidative stress. Further pathophysiological changes, such as microemboli formation in the brain, cerebral hypoperfusion, and reduced cerebral oxygen saturation, lead to ischemia and neuronal apoptosis [2]. Sedation medications exhibit anti-inflammatory, antioxidant, and anti-cell death effects, thereby providing neuroprotection after CPB [3]. Systematic reviews have provided evidence supporting the efficacy of sedative medications in mitigating the risk of delirium following cardiac surgery [4–11]. However, there is some controversy and conflicting results surrounding this topic [12,13].

This study utilized comprehensive analyses of the effects of various sedative drugs on POD and POCD in patients who underwent cardiac surgery with CPB via the network meta-analysis (NMA). In addition, subgroup analyses were conducted based on different stages of drug administration.

Methods

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (**Supplementary File 1**).

Search Strategy

Relevant databases, including PubMed, EmBase, and the Cochrane Library, were systematically searched from their inception to September 1, 2024, without any language restrictions. One author conducted the search using the following specified search string: (dexmedetomidine OR propofol OR sevoflurane OR midazolam OR clonazepam OR diazepam OR thiopental OR etomidate OR ketamine OR butorphanol OR remimazolam OR sedation OR sedative OR "Hypnotics and Sedatives"[Mesh] OR "Barbiturates"[Mesh] OR "Tranquilizing Agents"[Mesh] OR "Nitrazepam"[Mesh] OR "5-Methoxytryptamine"[Mesh] OR "Methaqualone"[Mesh] OR "Flurazepam"[Mesh] OR "Chlormethiazole"[Mesh]) AND ("valve replacement" OR "cardiac" OR "heart" OR "replantation"[MeSH Terms] OR "Heart"[Mesh]) AND (surger* OR surgical* OR interven* OR operation OR operative OR "Thoracic Surgery"[Mesh]) AND (brain OR cognitive OR delirium OR neurological OR cerebral OR "Cognitive Dysfunction"[Mesh] OR "Postoperative Cognitive Complications"[Mesh] OR "Delirium"[Mesh] OR "Neurocognitive Disorders"[Mesh]) AND (randomized clinical trials OR randomized trial OR random* OR "Randomized Controlled Trials as Topic"[Mesh]).

Study Selection

Inclusion and Exclusion Criteria

The inclusion criteria for the studies were as follows: (1) the study involved adult patients who underwent cardiac surgery with CPB; (2) randomized controlled trial (RCT) comparing one sedative drug against another sedative drug, blank, or placebo; and (3) the study reported dichotomous outcomes such as the incidence of POD or POCD or continuous score results such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA).

The exclusion criteria included: (1) the reported groups in the study presented significantly different intervention modalities (such as ischemic preconditioning and electrotherapy) in addition to the sedative drug of interest; (2) a retracted study; (3) reviews, editorials, conference articles, letters, protocols, nonhuman studies, and pediatric studies were also excluded. Two authors independently assessed study eligibility based on titles, abstracts, and full texts. Disagreements between the two authors regarding the inclusion of a study were resolved by discussion.

Data Extraction and Study Quality Assessment

The extracted data included the name of the first author, publication year, study location, study registration information, sample size, intervention, control intervention, follow-up duration, and outcomes related to delirium and cognitive function. The main outcomes were POD and POCD, while the secondary outcomes included the MMSE score and MoCA score. In an attempt to include as many research results as possible, for results reported only as histograms and box plots, the resulting information was obtained from the figures for the analysis. The quality and risk of bias of the included studies were assessed using Cochrane tools.

Statistical Analysis

For dichotomous data, the effect size was determined using the odds ratio (OR) along with the 95% confidence interval (CI). For continuous outcomes, the standardized mean difference (SMD) and its corresponding 95% CI were computed by extracting the mean and standard deviation (SD) values. In instances where the mean and SD were not provided, a geometric mean transformation or an approximation of the median and interquartile range using the mean $\pm$ SD was used for the analysis. Frequentist NMA was utilized to compare various intervention modalities for direct and indirect RCT comparisons. The results (OR or SMD) from all studies were combined using a random effects model to address the clinical and methodological diversity among studies.

Network plots were used to connect all sedative pharmacological interventions. Nodes represented the drugs under comparison, and edges indicated direct comparisons between pharmacological agents. Nodes and edges were weighted based on the NMA weights and the inverse of the standard error of the effect. Surface under the cumulative ranking curve (SUCRA) values were utilized to demonstrate the hierarchy of pharmacological interventions. Subgroup analyses were conducted based on various stages of drug administration, including intraoperative, postoperative, and perioperative. Additionally, trial sequential analysis (TSA), a methodology that combines an information size calculation for a meta-analysis with the threshold of statistical significance, was utilized to assess the reliability of the statistical data. All p values were analyzed using a two-sided approach, with statistical significance set at a threshold of less than 0.05. Data analysis was conducted using R (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria) and RevMan (version 5.4, The Cochrane Collaboration, London, United Kingdom).

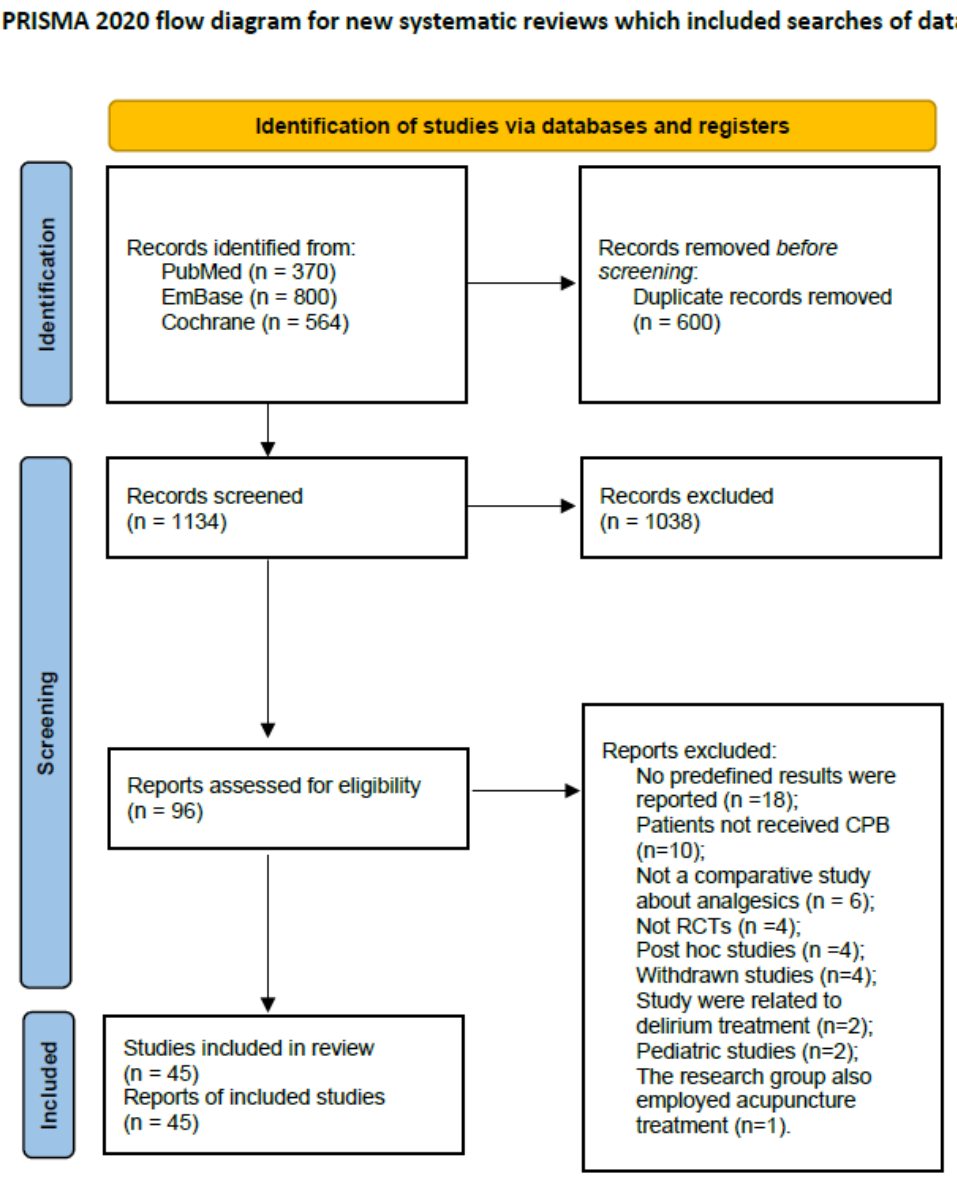

Fig. 1. Flowchart illustrating the literature search and selection process. CPB, cardiopulmonary bypass.

Results

The initial search yielded 2019 potential items, and after removing duplicates, 1267 unique items were obtained. After preliminary screening of abstracts and titles, 1165 articles were excluded based on the predefined inclusion and exclusion criteria. The full texts of the remaining 102 articles were collected. After careful inspection, 57 studies were excluded for the following reasons: no predefined results were reported (n = 22); patients did not receive CPB (n = 12); they were not comparative studies about analgesics (n = 6); they were not RCTs (n = 4); they were post hoc studies (n = 4); they were withdrawn studies (n = 4); they were related to delirium treatment (n = 2); they were pediatric studies (n = 2); and the research group also employed acupuncture treatment (n = 1). Finally, a total of 45 studies published between 1986 and 2024 were included, involving a total of 8016 patients. The detailed process of screening and selecting the final studies for analysis is illustrated in Fig. 1.

Among the included studies, 17 were published after 2020. Twelve studies were conducted in China, and ten were conducted in the United States. Twenty-three studies provided clinical registration information. One study was included in the analysis because more than 95% of participants received CPB [14] (**Supplementary Table 1**). Among the control interventions in the included studies, except for the blank intervention used as control in four studies [15–18], the remaining controls all refer to placebo (nor-

mal saline) (**Supplementary Table 1**). Therefore, the control group was not exclusively characterized as a placebo or blank group, so the term "control" was used to encompass both blank and placebo interventions.

All included studies were RCTs, and 33 studies employed blind masking. Nineteen studies utilized double-blind masking. Consequently, the design quality of the included studies was deemed high (Fig. 2).

Fig. 2. The risk of bias of the included studies.

For the dichotomous outcome of delirium, a total of 12 interventions, including the control, were analyzed (Fig. 3A). The results indicated that there were statistically significant differences between the dexmedetomidine and control groups (OR: 0.70; 95% CI: 0.50, 0.98; $p = 0.038$), with dexmedetomidine demonstrating a high SUCRA rank (79%). Among the other interventions, ketamine (92%) and esketamine (91%) had the highest SUCRA rankings (Fig. 3B). Additionally, significant differences were observed in the comparisons of dexmedetomidine *vs*. propofol; esketamine *vs*. midazolam, propofol, and remifentanil; and ketamine *vs*. midazolam, propofol, remifentanil, and sevoflurane (**Supplementary Table 2**).

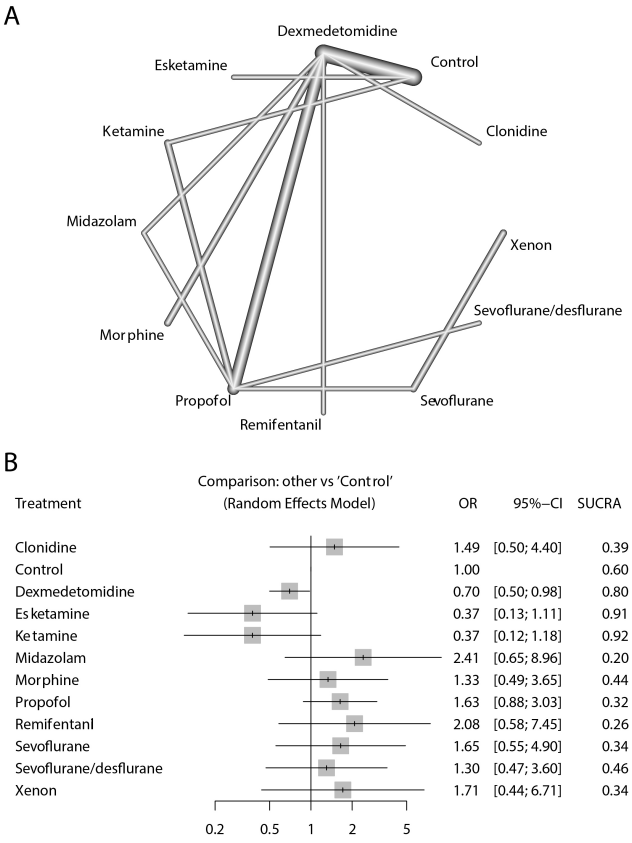

Fig. 3. Network and forest plots of the effect of analgesic drugs on postoperative delirium in patients who underwent cardiopulmonary bypass cardiac surgery in this meta-analysis. (A) Network plot. (B) Forest plot. SUCRA, surface under the cumulative ranking curve.

Esketamine, an isomer of ketamine, exhibited comparable SUCRA rankings in this study. The TSA method was employed to assess the reliability of the findings. The analysis of the random effects model revealed a close proximity between the Z-curve (blue line) and the Lan-DeMets bounds (red dashed line) (Fig. 4A). With an I^2 value of 43.19%, the outcomes derived from the fixed effects model indicated an intersection of the two line segments (Fig. 4B).

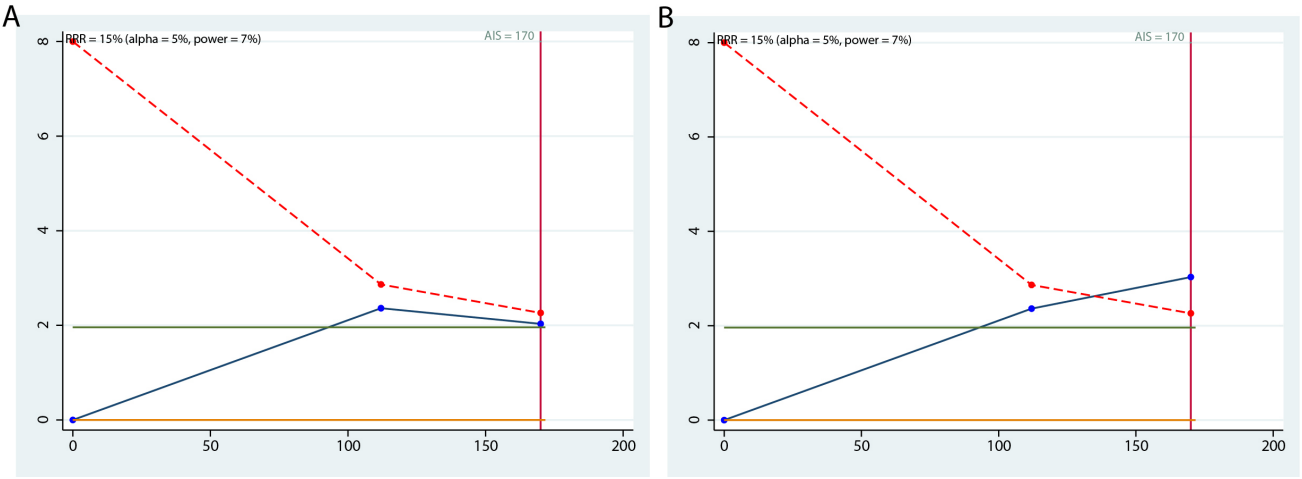

Fig. 4. TSA analysis results of the impact of esketamine/ketamine on the risk of postoperative delirium compared with the control group according to the random effects model (A) and fixed effects model (B). TSA, trial sequential analysis.

Hence, there is a need for further investigation into the efficacy of esketamine and ketamine, in contrast with the control, for mitigating delirium among cardiac surgery patients undergoing CPB.

In the subgroup analysis concerning stages of drug administration, eight drugs were administered intraoperatively (**Supplementary Fig. 1A**). The network analysis results indicated that no intervention method exhibited significant differences from the control. Ketamine, esketamine, and dexmedetomidine continued to demonstrate relative advantages (**Supplementary Fig. 1B**). Among the postoperative subgroups, seven drugs were analyzed (**Supplementary Fig. 1C**). Dexmedetomidine was the only agent that had an advantage over the control group, yet the difference was not significant (OR: 0.77; 95% CI: 0.49, 1.20; $p = 0.253$; SUCRA: 94%) (**Supplementary Fig. 1D**). In the perioperative subgroup, only the comparisons between the dexmedetomidine group and the control group were considered. The results of the random effect models showed no statistically significant differences (OR: 0.54; 95% CI: 0.24, 1.22; $p = 0.137$) (**Supplementary Fig. 1E**).

In terms of POCD outcomes, all interventions were administered intraoperatively. Eight interventions were assessed (Fig. 5A). The results revealed no statistically significant differences among the comparisons (**Supplementary Table 3**). Dexmedetomidine (76%), ketamine (67%), and thiopental (65%) exhibited relative advantages (Fig. 5B).

Thirteen interventions were assessed for MMSE scores (Fig. 5C). Dexmedetomidine (SMD: 3.14; 95% CI: 1.12, 5.16; $p = 0.002$; SUCRA: 82%) and remifentanil (SMD: 4.24; 95% CI: 0.28, 8.20; $p = 0.036$; SUCRA: 86%) resulted in significantly greater MMSE scores than the control group (Fig. 5D). No significant differences were observed in the remaining pairwise comparisons (**Supplementary Table 4**). According to the intraoperative subgroup analysis, dexmedetomidine significantly improved the patients' MMSE scores compared to those in the control group (SMD: 4.92; 95% CI: 0.65, 9.20; $p = 0.024$; SUCRA: 76%) (**Supplementary Fig. 2**).

In the analysis of the MoCA results, only three strategies were examined (Fig. 5E). Dexmedetomidine and remifentanil did not significantly differ from the control group (Fig. 5F, **Supplementary Table 5**). Subgroup analysis of intraoperative administration did not yield any statistically significant results (**Supplementary Fig. 3**).

Discussion

Cardiac surgery patients who undergo CBP are at an elevated risk of experiencing POD and POCD. This study employed a NMA approach to assess the comparative efficacy of various sedative drugs in mitigating the occurrence of POD and POCD. After conducting a thorough analysis of 45 studies, it was determined that dexmedetomidine has obvious advantages in reducing the risk of POD, and that esketamine/ketamine has also demonstrated the potential to mitigate the risk of delirium. Alternatively, medications such as propofol may increase the risk of POD.

Following CPB, the systemic inflammatory response affects the nervous system, thereby increasing the risk of POD. This study's findings indicate that dexmedetomidine significantly reduces the risk of POD following CPB. As a central α-2 adrenergic receptor agonist, dexmedetomidine possesses anxiolytic, sedative, analgesic, and anti-inflammatory properties. The proposed mechanism of action suggests that dexmedetomidine's neuroprotective effects are mediated through the inhibition of inflammatory responses, reduction of cell apoptosis and autophagy, maintenance of the blood-brain barrier (BBB) integrity, and stabilization of cellular structures [14]. Dexmedetomidine inhibits inflammatory responses by suppressing the activation

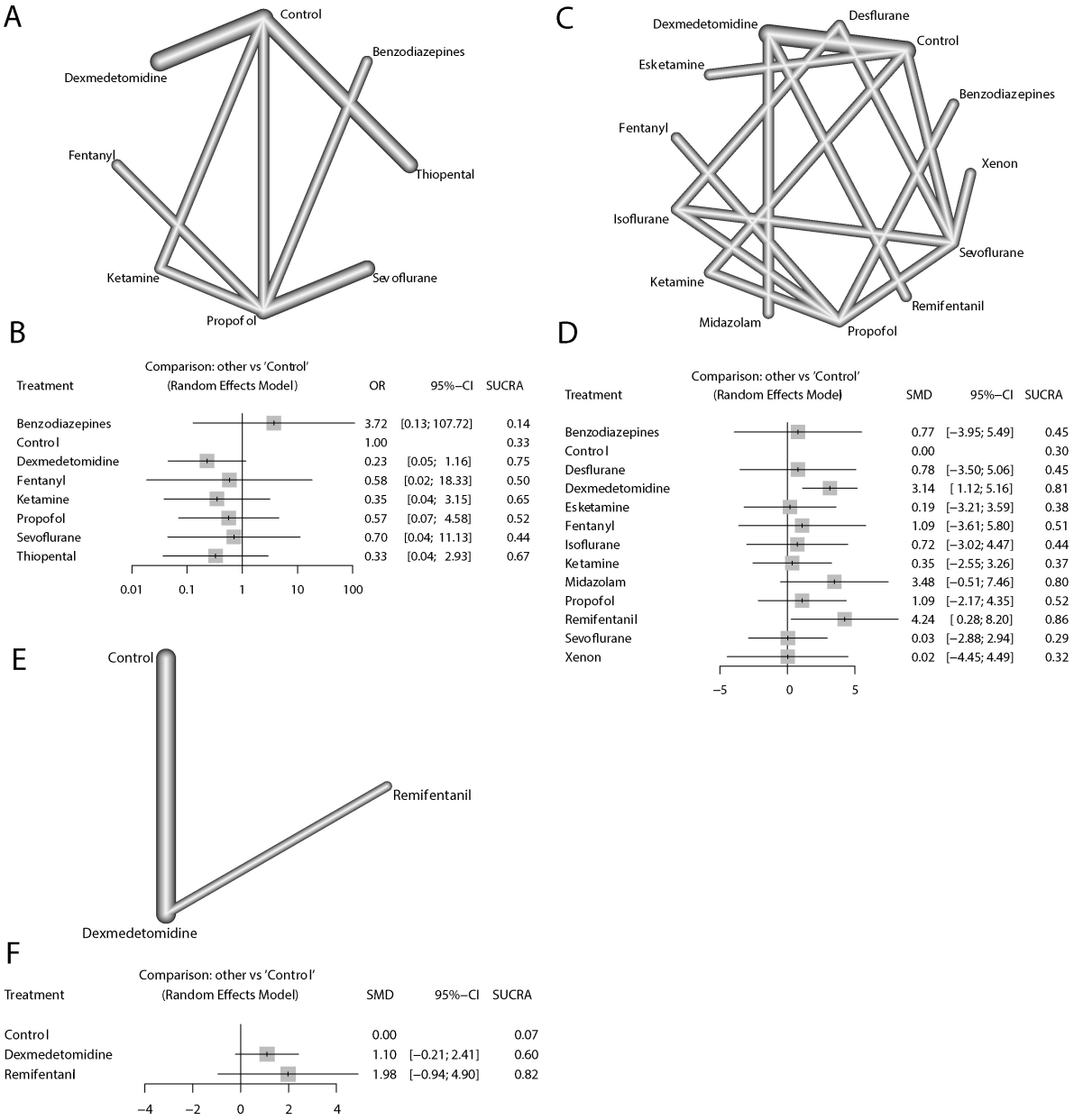

Fig. 5. Network and forest plots of the effect of analgesic drugs in patients who underwent cardiopulmonary bypass cardiac surgery in this meta-analysis. (A) Network plot for postoperative cognitive dysfunction (POCD) results. (B) Forest plot for POCD results. (C) Network plot for Mini-Mental State Examination (MMSE) scores results. (D) Forest plot for MMSE scores results. (E) Network plot for the Montreal Cognitive Assessment (MoCA) score results. (F) Forest plot for the MoCA score results. SMD, standardized mean difference.

of nuclear factor kappa-B (NF-κB) and the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasomes, and downregulates levels of inflammatory cytokines including Interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) [15,16]. Dexmedetomidine also inhibits brain endothelial cell inflammation and microvascular permeability by activating the Sigma-1R receptor [17]. Furthermore, it mitigates blood-brain barrier disorders and neuroinflammation by modulating Th1/Th2/Th17 polarization [18]. Additionally, it induces the expression of hypoxia inducible factor-1, inhibits neuronal autophagy, and exerts neuroprotective effects [19].

In this study, esketamine/ketamine also showed potential to mitigate the risk of delirium. Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, mediates neuroprotective effects by inhibiting NMDA receptor activation and stimulus pulse transmission. The NMDA receptor is a calcium (Ca^{2+}) permeable ion channel that plays a key role in synaptic function, plasticity, learning, and memory, as well as excitotoxicity and ner-

vous system injury and disease. In major surgery, ketamine has demonstrated neuroprotective effects, including anti-excitotoxicity, anti-neuronal apoptosis, anti-neuronal inflammation, and oxidative stress, as well as inhibition of microthrombosis. Ketamine can also regulate inflammation by inhibiting the production of TNF-α, IL-6, and IL-8 via the NF-κB, nuclear factor of activated T cells 4 (NFATc4), and NLRP3 inflammasomes [20,21]. Ketamine reduces neuronal apoptosis by decreasing cleaved caspase-3 levels, maintaining cAMP-response element binding protein (CREB) phosphorylation, and upregulating brain-derived neurotrophic factor (BDNF) [22]. It decreases intracellular calcium accumulation, and reduces platelet aggregation and microthrombosis, thereby improving microthrombosis during CPB surgery [22]. However, ketamine exhibits both neurotoxic and neuroprotective properties [23], which may be dose-dependent.

Two prior NMAs assessed the impact of dexmedetomidine on POD following CPB [10,13]. However, these studies provided conflicting findings on dexmedetomidine's ability to mitigate the risk of POD. This discrepancy may stem from the timing of drug administration, as our study indicates that dexmedetomidine, when administered postoperatively rather than intraoperatively, significantly reduces the risk of POD. Furthermore, Meco *et al.* [13] found that preoperative subanesthetic ketamine doses can significantly decrease the incidence of POD. This finding is consistent with our study's results. Notably, our study focused exclusively on cardiac surgery and CPB patients, who are potentially at a higher risk for delirium compared to those undergoing catheter-based interventions.

This study has several limitations. The primary outcomes of interest included POD and POCD. However, other significant clinical outcomes, such as mortality, were not included in the analysis. Recently, meta-analyses have assessed whether perioperative dexmedetomidine can reduce mortality in cardiac surgery patients. Dexmedetomidine did not significantly reduce the risk of death compared with that of controls (OR: 0.55; 95% CI: 0.27–1.13) [7,12]. These studies, however, lack an analysis of controlled intervention strategies, and a more comprehensive analysis warrants further investigation.

Conclusions

After conducting a comprehensive analysis of 45 studies, postoperative dexmedetomidine significantly outperformed the control group in terms of the risk of POD and the MMSE score. Esketamine/ketamine also demonstrated potential efficacy in preventing POD. Further research is required to validate these findings.

Availability of Data and Materials

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

Author Contributions

YZ and YL contributed to conception and design of the study. YL and FH organized the database. JW and HP performed the statistical analysis. YZ and YL wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.7993.

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