



Myocardial protective and anti-inflammatory effects of dexmedetomidine in patients undergoing cardiovascular surgery with cardiopulmonary bypass: a systematic review and meta-analysis

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Abstract

Cardiopulmonary bypass (CPB) technology provides potential for cardiac surgery, but it is followed by myocardial injury and inflammation related to ischemia–reperfusion. This meta-analysis aimed to systematically evaluate the cardioprotective effect of dexmedetomidine on cardiac surgery under CPB and its effect on accompanied inflammation. PubMed, Cochrane Library, EMBASE and Web of Science databases were comprehensively searched for all randomized controlled trials (RCTs) published before April 1st, 2021 that explored the application of dexmedetomidine in cardiac surgery. Compared with the control group (group C), the concentrations of CK-MB in the perioperative period and cTn-I at 12 h and 24 h after operation in dexmedetomidine group (group D) were significantly decreased ($P < 0.05$). In addition, in group D, the levels of interleukin-6 at 24 h after operation, tumor necrosis factor- α at the 12 h and 24 h after operation were significantly decreased ($P < 0.05$). At the same time, the length of Intensive Care Unit stay in group D was significantly shorter than group C ($P < 0.05$). However, there was no significant difference in interleukin-10 level, C reactive protein level, the time on ventilator and length of hospital stay between the two groups ($P > 0.05$). The application of dexmedetomidine in cardiac surgery with CPB can reduce CK-MB and cTn-I concentration and interleukin-6, tumor necrosis factor- α levels to a certain extent and shorten the length of Intensive Care Unit stay, but it has no significant effect on IL-10 level, C reactive protein level, the time on ventilator and length of hospital stay.

Keywords Dexmedetomidine · Myocardial protective · Anti-inflammatory effects · Cardiac surgery · Cardiopulmonary bypass

Introduction

Cardiopulmonary bypass (CPB) provides blood and oxygen to the body's organs and tissues when the heart stops working, allowing open-heart surgery to be performed successfully and maintaining the body's metabolism [1]. However, owing to the lack of blood supply to the heart during CPB,

perioperative myocardial protection, which directly affects the recovery of cardiac function post-surgery, is very important [2]. Myocardial protection strategy refers to a variety of perioperative techniques used to reduce ischemia–reperfusion injury and prevent postoperative cardiac dysfunction [3, 4]. The main method is to reduce myocardial oxygen demand, such as inducing lower body temperature and non-beating heart. Besides, some drugs that provide myocardial protective effects are included too [5].

In addition to myocardial injury, the inflammatory response related to CPB is also one of the issues worthy of our concern in open-heart surgery. During CPB, the contact of patients' blood with tube system will produce a large number of inflammatory mediators, that can cause tissue and organ damage [6].

As a highly selective α_2 -adrenergic receptor agonist, dexmedetomidine can reduce the release of cytokines, inhibit

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inflammation response and alleviate ischemia–reperfusion injury, thus exerting its organ-protective effects [7, 8].

Some clinical studies have been implemented to explore whether there is a similar effect in cardiac surgery under CPB. Most of them have reported that the addition of dexmedetomidine can inhibit inflammation and provide myocardial protection [9, 10]; however, the study by Tosun reported that myocardial damage was not reduced by the administration of dexmedetomidine [2]. In addition, there is a meta-analysis [11] that studied the myocardial protective effect of dexmedetomidine during cardiac surgery. However, it makes a comprehensive analysis of all types of cardiac surgery, fails to distinguish between CPB and non-CPB. Moreover, it is only limited to the changes of hemodynamics, and does not involve the detection of myocardial injury markers and inflammatory factors.

To solve these problems, this meta-analysis aimed to clarify whether dexmedetomidine can inhibit the inflammatory response, provide myocardial protection, and promote the recovery of patients by analyzing randomized controlled trials.

Methods

We conduct this meta-analysis according to the rules of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses which can be used as a basis for reporting systematic reviews of different types of research.

Literature search

The PubMed, Cochrane Library, EMBASE and Web of Science databases were comprehensively searched for randomized controlled clinical trials (RCTs) published before April 2021 that investigated the application of dexmedetomidine in CPB or cardiac surgery. Additionally, the reference lists of all included studies were checked for any potential additional publications. The key words included dexmedetomidine, cardiopulmonary bypass, thoracic surgery, and cardiac surgical procedures. The detailed search strategies were presented in the Supplemental materials (Supplementary Table 1 Details about the search strategies).

Inclusion and exclusion criteria

The inclusion criteria for the studies were as follows:

(1) it was a randomized controlled trial; (2) the target population comprised patients undergoing cardiovascular surgery with CPB; (3) it compared dexmedetomidine with normal saline; (4) outcomes were related with cardiac

function indicator(s), myocardial injury marker(s), inflammatory factor(s), and the length of hospital stay; and (5) the full text was available.

The exclusion criteria were as follows:

(1) it was a duplicate publication, review, editorial, abstract, comment, case report, animal study, or expert consensus/guidance; (2) surgery was not performed with CPB; and (3) research about pediatric cases.

Data extraction

Two reviewers independently screened the papers from their titles and abstracts and selected relevant studies met the eligibility criteria. Data were extracted and collated independently by the same two reviewers independently with any disagreement settled by a third reviewer. We sent e-mails to the original investigators when requisite data were lacking in the publications.

The following items were extracted: (1) basic information: name of the first author, publication date, sample size, demographic data of participants; (2) techniques: type of surgery, anesthesia method, perioperative medication, dose and administration rate of dexmedetomidine; (3) primary outcomes: the concentrations of creatine kinase-MB (CK-MB) and cardiac troponin I (cTn-I) at different time points; (4) secondary outcomes: the levels of interleukin-6 (IL-6), IL-10, tumor necrosis factor- α (TNF- α) and C reactive protein (CRP) at different time points, the time on ventilator, the length of Intensive Care Unit (ICU) stay and length of hospital stay.

Statistical analysis

The meta-analysis was conducted using Review Manager Software (Revman 5.4, Cochrane Collaboration, Oxford, United Kingdom). Continuous data was expressed by weighted mean difference (WMD) and 95% confidence interval (CI). If the mean was too different or the unit of measurement was inconsistent, the data was expressed by standard Mean Difference (SMD) and 95% CI. Cochran's Q test and Higgins' I^2 statistical test were used to assess the statistical heterogeneity. The results showed low level of heterogeneity when $I^2 < 50\%$, and a fixed-effects model would be used. The results showed significant heterogeneity when $I^2 \geq 50\%$, in which case a sensitivity analysis and subgroup analyses would be conducted to identify the source of heterogeneity. If the heterogeneity could not be eliminated, a random-effects model that estimated the uncertainty of results with sampling error and studies variance would be used. Descriptive analysis was used for data that cannot be merged.

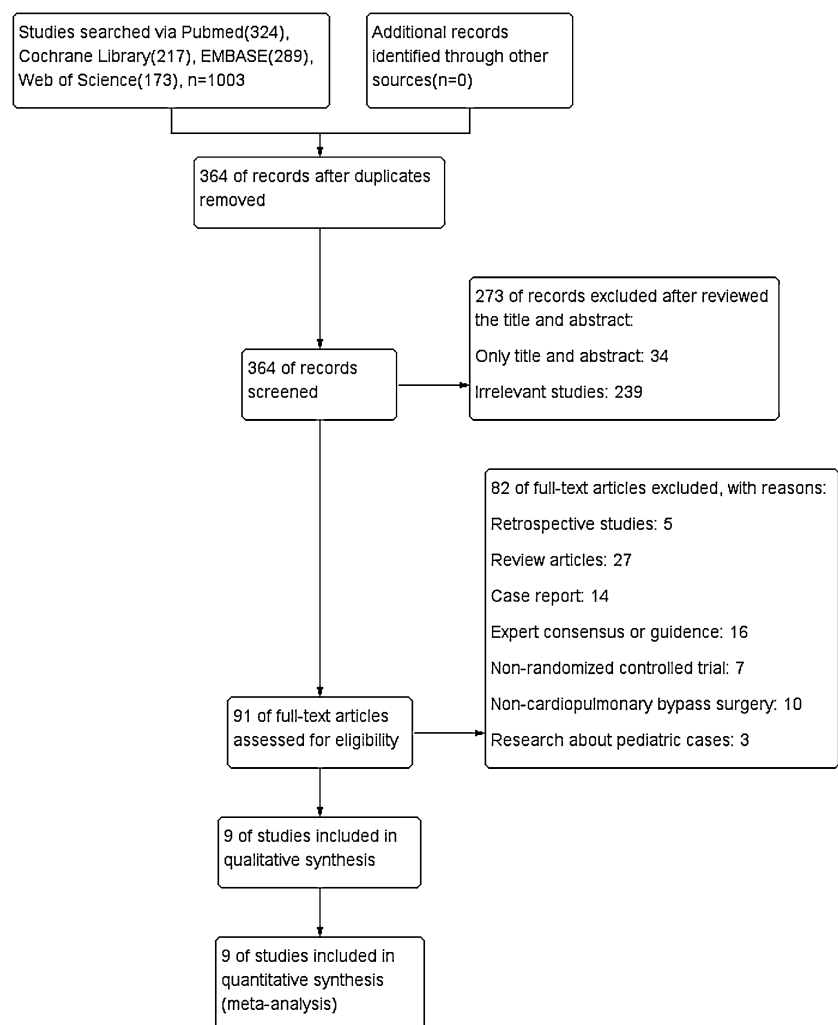
Risk of bias assessment was done using Cochrane Collaboration tool (Cochrane, London, UK). Finally, a funnel plot was used to visually assess the potential publication bias.

Results

Search results and study characteristics

A total of 1003 articles were retrieved, and 364 of them remained after excluding duplicate articles. Based on the title and abstract, 273 articles were excluded, leaving 91 articles. 82 articles were discarded for various reasons (retrospective study, review article, case report, expert consensus or guidance and so on) when the full text was browsed for further screening, and 9 studies [2, 7, 9, 10, 13–17] finally met the inclusion criteria (Fig. 1 Flow chart of study selection). The characteristics of the 9 studies involved 418 participants were summarized in Table 1 Characteristics of the included studies.

Fig. 1 Flow chart of study selection



Primary outcomes

CK-MB concentration

The pooling results showed that the concentration of CK-MB between the two groups has no significant difference at these several time points individually, including 15 min after declamping the aorta, the end of operation, 24 h and 48 h after operation. However, the comprehensive results showed that the concentration of CK-MB in dexmedetomidine group (group D) was significantly lower than that of the control group (group C) (SMD 0.70; 95% CI 0.16–1.25; $P < 0.05$; $I^2 = 91\%$), which suggested a certain clinical significance. The meta-analysis results at the above time points showed heterogeneity. The sensitivity analysis and subgroup analysis failed to identify the source of heterogeneity, and a random-effects model was used for further analysis. (Fig. 2 CK-MB concentration).

Table 1 Characteristics of the included studies

Study	Sample size (C/D group)	Type of surgery	Age (C/D group)	Sex (male/female) (C/D group)	Induction of anesthesia	Maintenance of anesthesia	Dose of dexmedetomidine
Ammar 2017	25/25	NM (cardiac surgery)	59.1 ± 6.2/55.4 ± 7.1	18/7 20/5	Propofol 1.5–2 mg/kg Fentanyl 3–5 µg/kg Cisatracurium 0.1 mg/kg	Isoflurane Fentanyl 3–5 µg/kg/h Cisatracurium 2 µg/kg/min	5 min before CPB (a loading dose of 1 µg/kg over 15 min, followed by 0.5 µg/kg/h) until 6 h after surgery 0.3 µg/kg/h during the entire surgery
Bulow 2016	11/12	CABG	65 ± 8/60 ± 6	7/4 8/4	Propofol 4 µg/ml (TCI) Sufentanil 0.5–1 µg/kg Pancuronium 0.1 mg/kg	Propofol 4 µg/ml (TCI) Sufentanil 0.5–1 µg/kg/h Pancuronium 1/3 dose of anesthesia Induction	
Chen 2015	32/32	CABG	62.9 ± 7.2/61.8 ± 7.8	24/8 20/12	Propofol 2 mg/kg Sufentanil 0.5–1 µg/kg Cisatracurium 0.15 mg/kg	Sevoflurane 1.5–2.5% Cisatracurium 0.1 mg/kg/h Propofol 1 mg/kg/h	A loading dose of 0.5 µg/kg for 10 min, followed by 0.5 µg/kg/h until the completion of the surgery 0.4 µg/kg/h
Elgebaly 2020	30/30	CABG	57.8 ± 8.3/58.5 ± 7.9	17/13 16/14	Propofol 0.5–2 mg/kg Fentanyl 5 µg/kg Cisatracurium 0.5 mg/kg	Propofol 2 mg/kg/h Isoflurane Cisatracurium 10 µg/kg/min Fentanyl 0.5–1 µg/kg	
Tosun 2013	20/18	CABG	63.60 ± 8.33/60.36 ± 11.12	14/6 13/5	Fentanyl 2–5 µg/kg Etomidate 0.2–0.3 mg/kg Rocuronium 1 mg/kg	Fentanyl 5 µg/kg/h Sevoflurane 0.5–2% Rocuronium	A loading dose of 1 µg/kg over 10 min followed by 0.5 µg/kg/h, until the end of surgery
TÜRKTANI 2017	30/30	CABG	53.90 ± 15.43/59.83 ± 14.22	21/9 17/13	Propofol 1 mg/kg Fentanyl 1 µg/kg Vecuronium 0.1 mg/kg	Sevoflurane 0.5–1.5% loading dose	0.3–0.9 µg/kg/h infusion after a 0.5 µg/kg 10 min loading dose
Ueki 2014	19/18	Valve repair/replacement 31 CABG 6	69.0 ± 11.7/70.5 ± 9.5	8/11 8/10	Midazolam 3–5 mg Fentanyl 1 µg/kg Rocuronium 0.6 mg/kg	Sevoflurane 0.8–2.0% (before CPB) Propofol 4–6 mg/kg/h (after CPB) NM	1 µg/kg for 10 min after aortic cross-clamping, and 0.5 µg/kg/h intraoperatively Continuously infused at the rate of 0.5 µg/kg/h until the end of operation
Wang 2020	30/30	CABG 17 Mitral valve replacement 10 Aortic dissection 11 Aortic valve replacement 10 Thoracic aortic aneurysm 12	44.25 ± 5.82/42.77 ± 5.91	19:11 17:13	NM	NM	

Table 1 (continued)

Study	Sample size (C/D group)	Type of surgery	Age (C/D group)	Sex (male/female) (C/D group)	Induction of anesthesia	Maintenance of anesthesia	Dose of dexmedetomidine
Zhou 2019	13/13	valve replacement	58.6 ± 8.9/57.4 ± 9.3	4:10 Lost to follow-up (n = 1)	Midazolam 0.1–0.2 mg/kg Etomidate 0.2–0.3 mg/kg Sufentanil 0.2–0.3 µg/kg Rocuronium 0.6–0.9 mg/kg	Sevoflurane Propofol Sufentanil	Started with a 0.5 µg/kg loading dose for 10 min followed by a 0.5 µg/kg/h maintenance dose

C group Control group, D group Dexmedetomidine group, CPB Cardiopulmonary bypass, CABG coronary artery bypass graft, NM not mentioned

cTn-I concentration

Compared with the group C, cTn-I concentration in group D was significantly decreased at 12 h (SMD 3.62; 95% CI 3.00–4.24; $P < 0.05$; $I^2 = 0\%$) and 24 h (SMD 3.49; 95% CI 0.41–6.58; $P < 0.05$; $I^2 = 98\%$) after operation. However, no significant difference was found between the two groups at the time points of CPB in progress, 15 min after declamping the aorta, the end of operation and 48 h after operation. The sensitivity analysis and subgroup analysis failed to eliminate the heterogeneity, and a random-effects model was used for further analysis. (Fig. 3 cTn-I concentration).

Secondary outcomes

IL-6 levels

The level of IL-6 at several time points including CPB in progress, 12 h and 24 h after operation was analyzed. The result showed the level of IL-6 in group D was lower than group C at 24 h (MD 37.47; 95% CI 11.13–63.81; $P < 0.05$; $I^2 = 99\%$) after operation. No difference was found at other time points. A random-effect model was used to complete the analysis as the heterogeneity cannot be eliminated by sensitivity analysis and subgroup analysis. (Fig. 4 IL-6 levels).

IL-10 levels

The synthesized data showed that there was no significant difference between the two groups when it came to the level of IL-10 at 24 h after operation. (Fig. 5 IL-10 levels).

TNF-α levels

As shown in the result, the level of TNF-α in group D was lower at 12 h (SMD 2.92; 95% CI 0.35–5.48; $P < 0.05$; $I^2 = 96\%$) and 24 h (SMD 4.13; 95% CI 2.91–5.35; $P < 0.05$; $I^2 = 71\%$) after operation when compared with group C. Sensitivity analysis and subgroup analysis failed to eliminate the heterogeneity, so a random-effect model was used. There was no obvious difference between the two groups at the time point of CPB in progress. (Fig. 6 TNF-α levels).

CRP levels

In terms of CRP, there was no significant difference between the two groups. A random-effect model was used as the

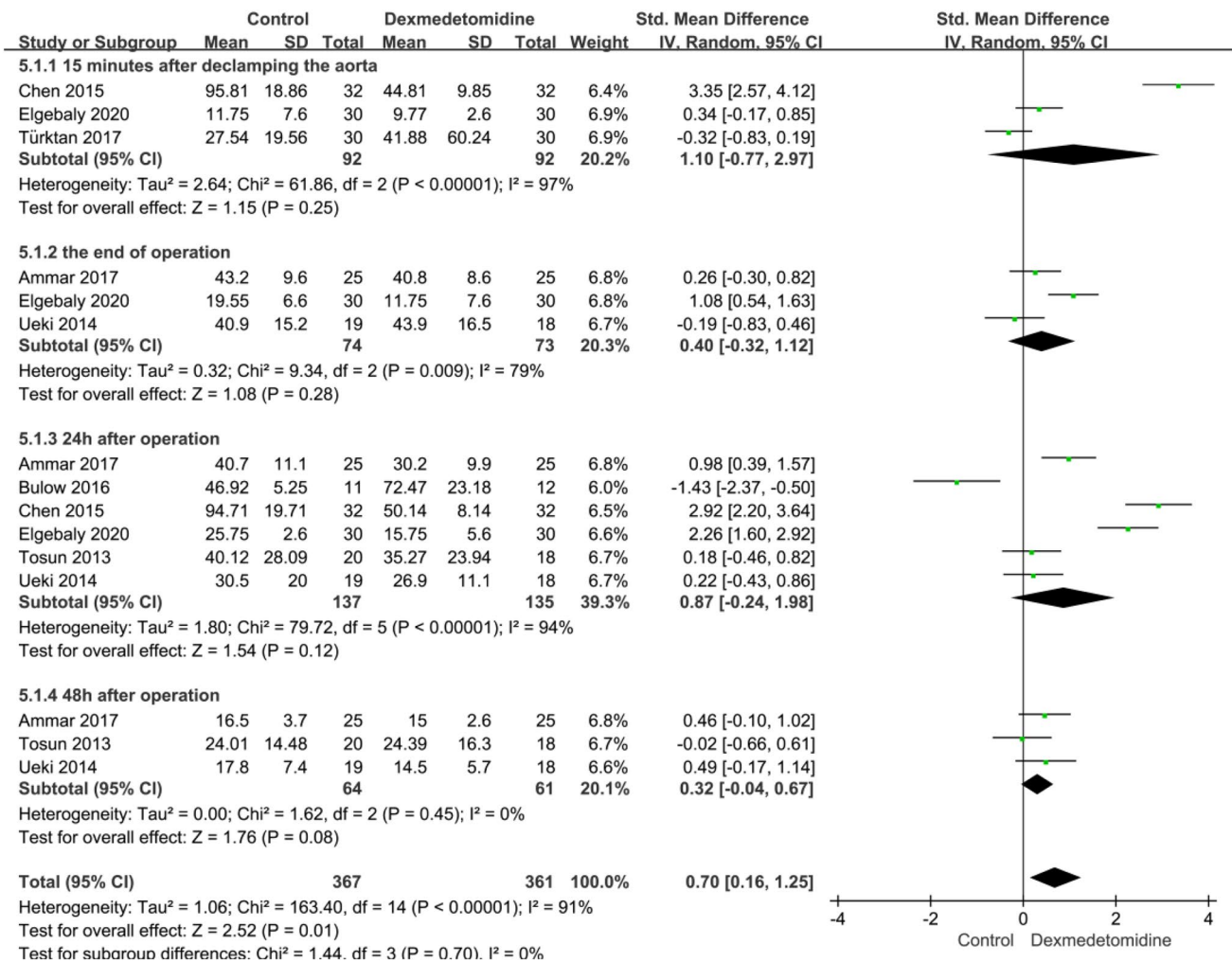


Fig. 2 CK-MB concentration

heterogeneity cannot be eliminated by sensitivity analysis and subgroup analysis. (Fig. 7 CRP levels).

Time on ventilator, length of ICU stay, and hospital stay

A total of 5 studies, 231 cases involved the time on ventilator. The results showed that the use of dexmedetomidine in the operation cannot shorten the time of patients on ventilator (MD 1.91; 95% CI -0.14 to 3.95; P > 0.05; I² = 78%). (Fig. 8 The time on ventilator).

The length of ICU stay, was shown in 5 studies, involving 231 cases, and better outcome was shown in group D (MD 0.66; 95% CI 0.55–0.77; P < 0.05; I² = 0%). (Fig. 9 The length of ICU stay).

The length of hospital stay was recorded in 3 studies including 133 patients. The results showed that there was no significant difference between the two groups (MD -0.20; 95% CI: -2.46 to 2.05; P > 0.05; I² = 86%). (Fig. 10 The length of hospital stay).

Bias assessment

We can learn from the risk of bias graph (Fig. 11 Risk of bias graph), one study [17] had high risk for attrition bias, while other studies have not found any high risk items. As for the publication bias, slight asymmetry can be found in the funnel plot, so we concluded that there was possibility of publication bias. (Fig. 12 Funnel plot).

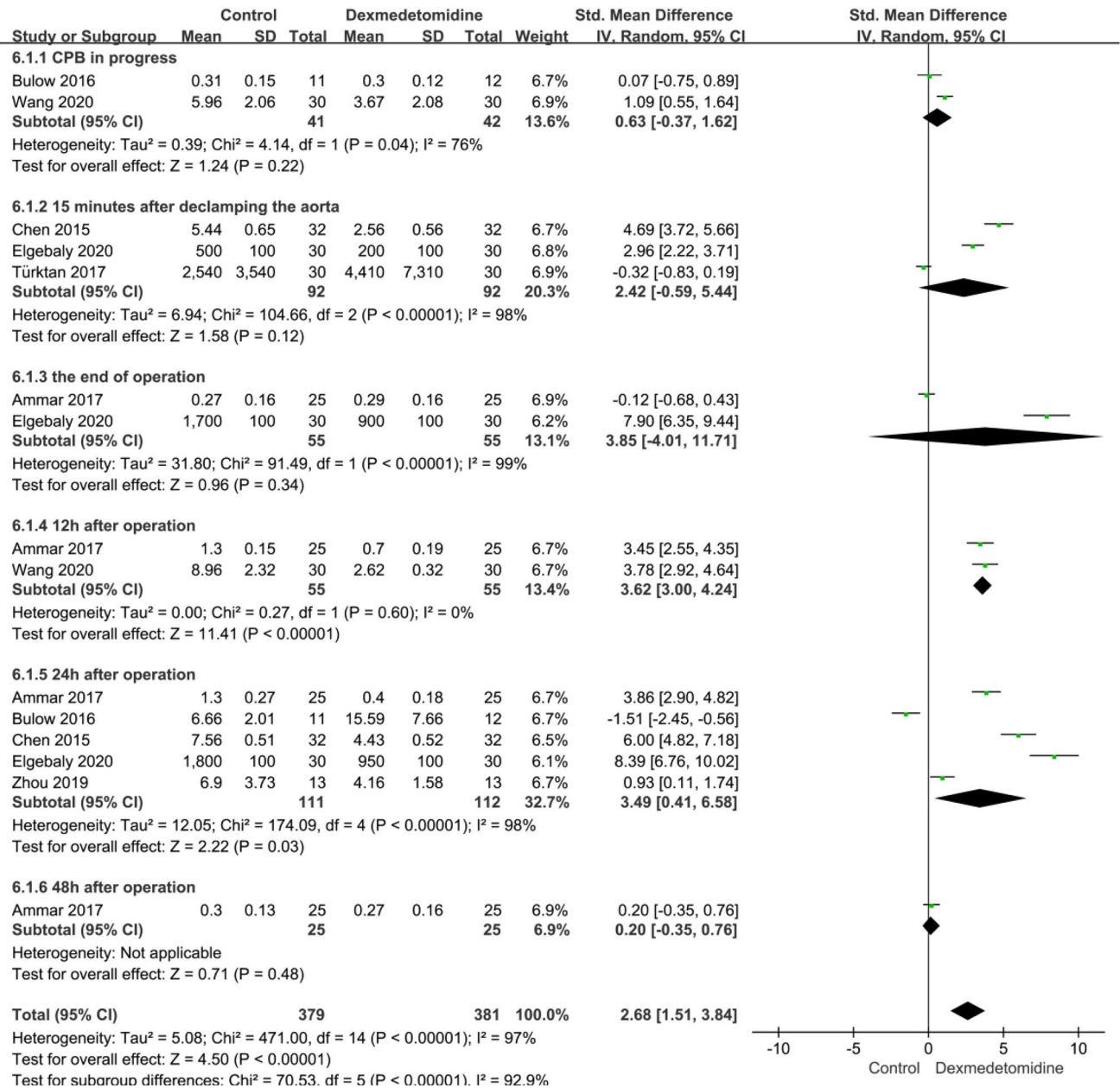


Fig. 3 cTn-I concentration

Discussion

Cardiac surgery with the CPB procedure is associated with ischemia/reperfusion injury, which is closely related to reversible postischemic cardiac dysfunction and irreversible myocardial cell death [18]. Therefore, CPB

surgery requires a series of measures to provide myocardial protection, aimed at reducing oxygen consumption of myocardial cells so as to adapt cardiomyocytes to transient ischemia. *Inflammatory response results from tissue reperfusion injury, and is also the primary cause of ischemia–reperfusion injury* [19]. Dexmedetomidine

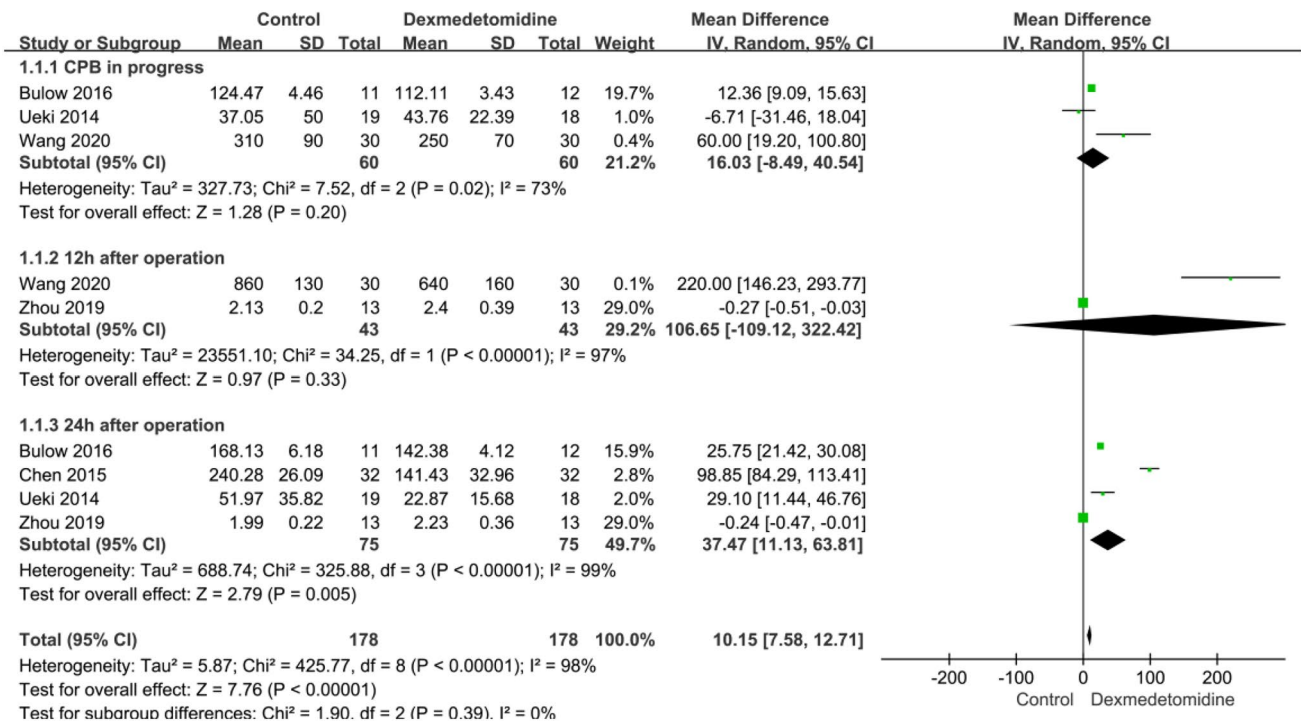


Fig. 4 IL-6 levels

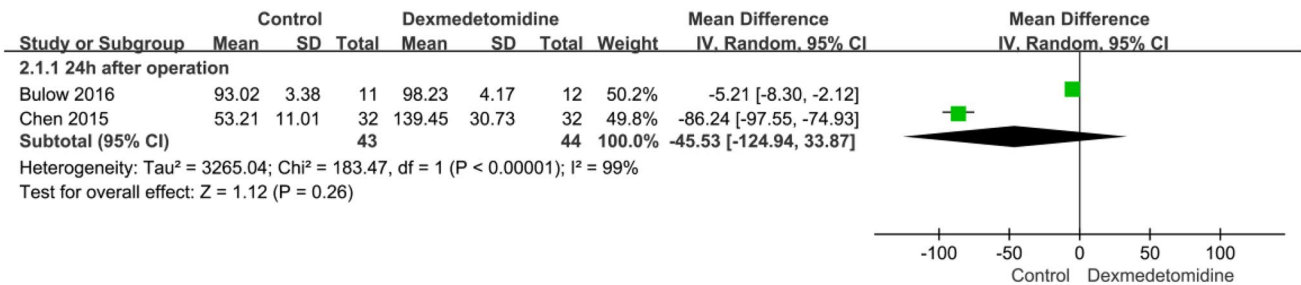


Fig. 5 IL-10 levels

has been investigated in many studies because it can reduce the release of cytokines, inhibit the inflammatory response, reduce ischemia–reperfusion injury, and thereby contribute to organ protection [20–22]. In the related research involved in this meta-analysis, a loading dose of 0.5–1.0 µg/kg for 10–15 min, followed by the maintenance dose of 0.3–0.5 µg/kg/h until the completion of the surgery was the main dosage and timing of administration of dexmedetomidine.

The level of CK-MB and cTn-I can be used to judge the condition of myocardial injury, and its dynamic changes often provide a more meaningful reference [23, 24]. The

result of this meta-analysis showed that the addition of dexmedetomidine can significantly reduce the levels of CK-MB and cTn-I, but the level of cTn-I on the 48 h after operation was comparable between the two groups, which suggested that dexmedetomidine may have a certain myocardial protective effect in the early postoperative period.

In addition to the effect on markers of myocardial injury, dexmedetomidine also inhibited the intensity of inflammatory response. The results showed that dexmedetomidine decreased the levels of pro-inflammatory cytokines IL-6 and TNF-α during CPB procedure, but there was no significant

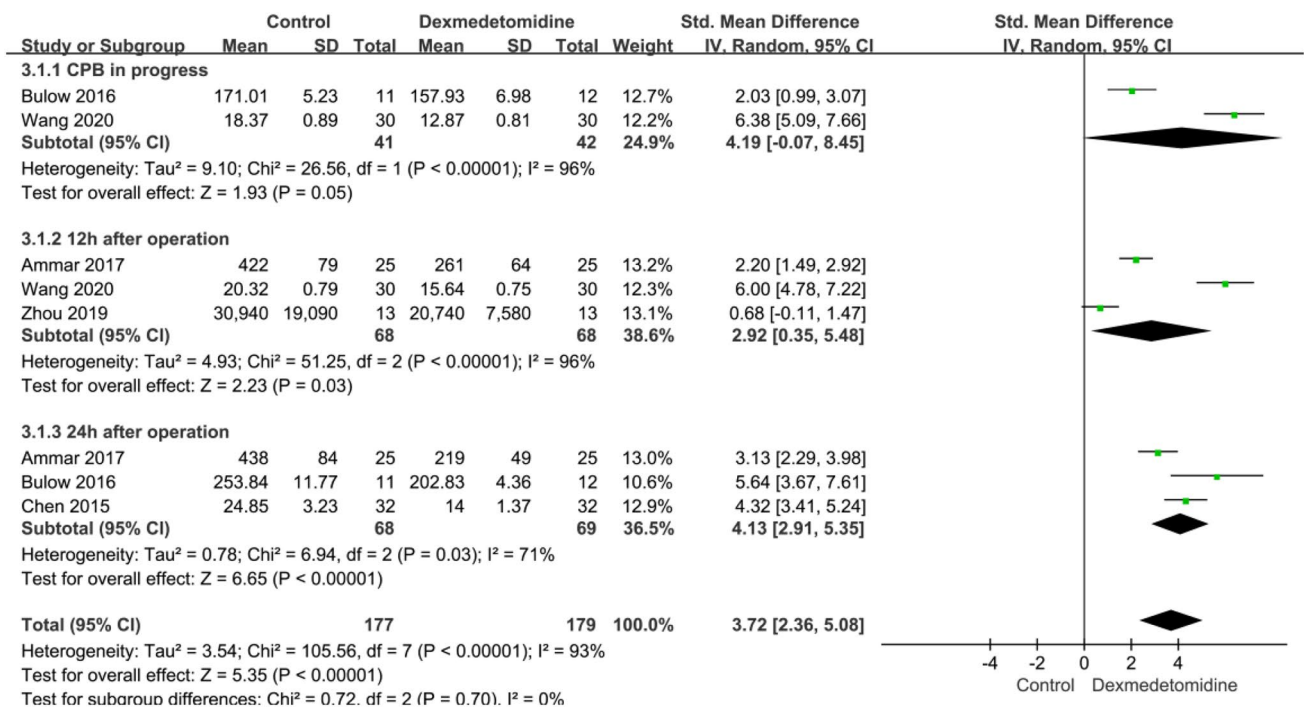


Fig. 6 TNF-α levels

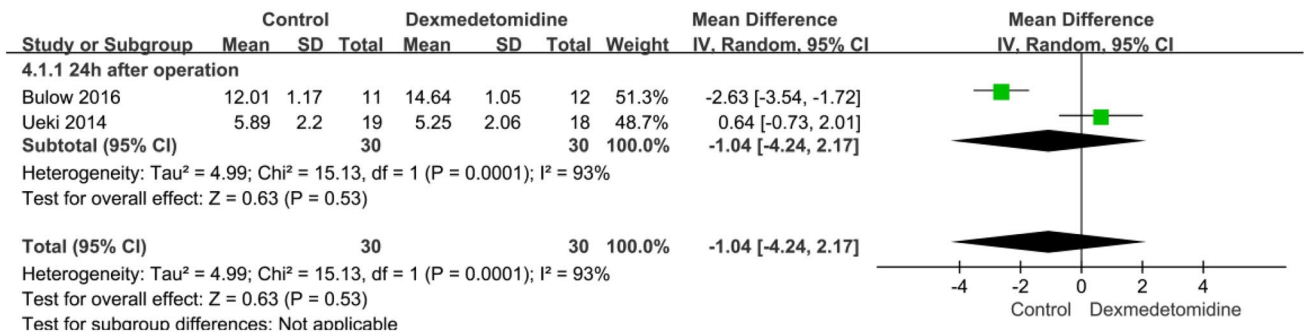


Fig. 7 CRP levels

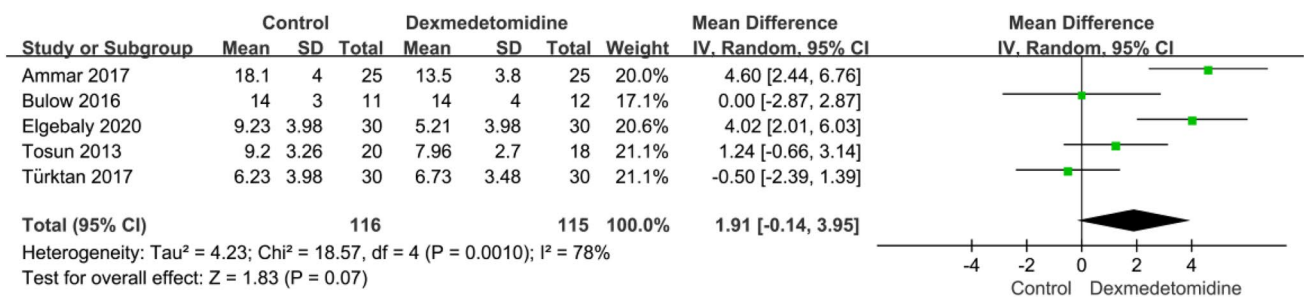


Fig. 8 The time on ventilator

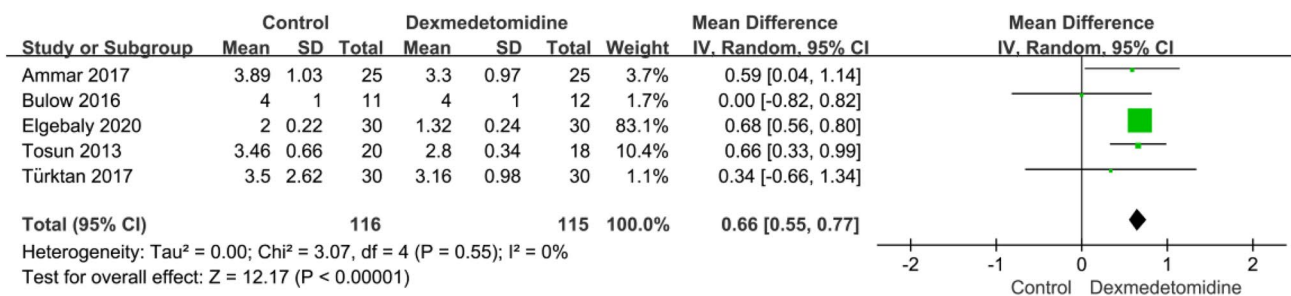


Fig. 9 The length of ICU stay

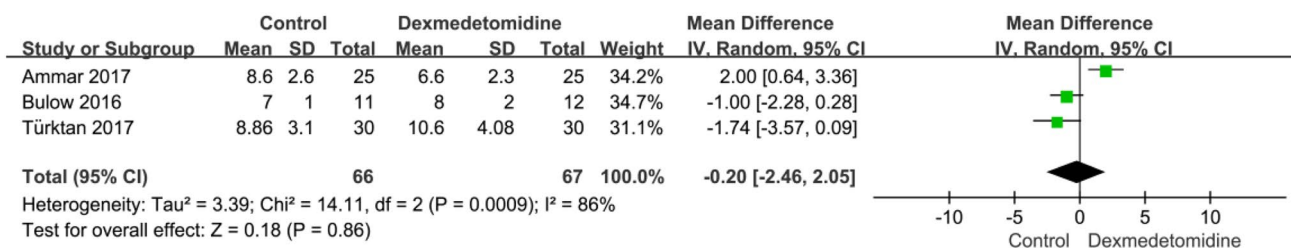
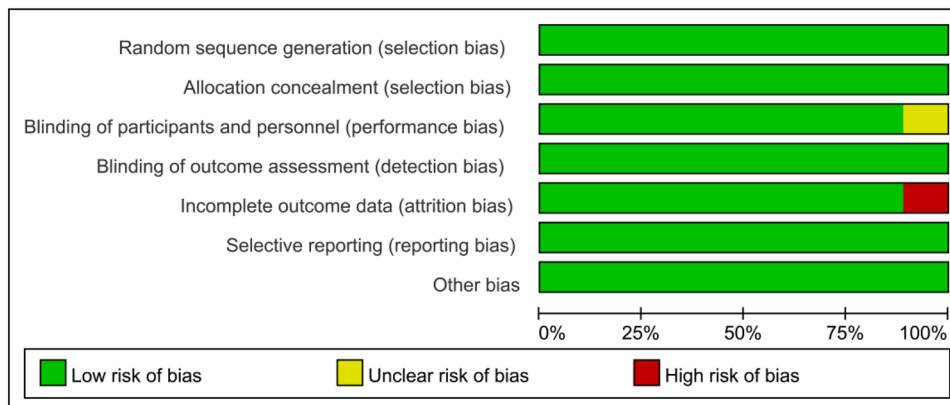


Fig. 10 The length of hospital stay

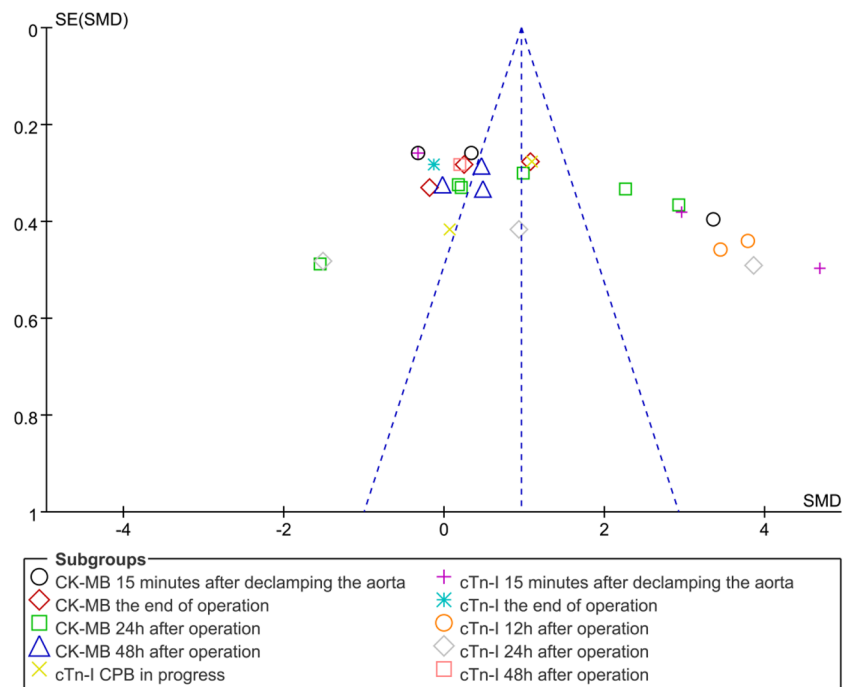
Fig. 11 Risk of bias graph



difference in anti-inflammatory cytokine IL-10 between the two groups. In addition, related meta-analysis has previously shown that dexmedetomidine can also significantly reduce the levels of IL-6, IL-8 and TNF- α during routine general anesthesia [25]. The mechanism of dexmedetomidine in reducing inflammation may be closely related to the inhibition of NF- κ B pathway and Toll-like receptor [15, 26–29]. Reducing the degree of inflammation may be beneficial to the rehabilitation of patients, because some studies have shown that the occurrence of inflammation is associated with adverse cardiac outcomes [30, 31].

Dexmedetomidine shortened the length of ICU stay, which suggested that dexmedetomidine perhaps can promote the rapid recovery of cardiac function in patients. However, no significant difference was found in the length of hospital stay between two groups, which may indicate that the long-term rehabilitation promoting effect of dexmedetomidine on patients undergoing CPB surgery is not clear.

Fig. 12 Funnel plot



Conclusion

The administration of dexmedetomidine during CPB can provide myocardial protection by inhibiting inflammation, which may be beneficial to the rapid recovery of patients. However, further studies are needed to explore the effect of dexmedetomidine on the long-term prognosis of patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00540-021-02982-0>.

Author contributions MLC and XL contributed to the articles screening, data synthesis and data collection. GM contributed to the study design and preparation of the primary manuscript. MLC contributed to the edited of this article.

Declarations

All authors declaring that they have read and accept the “Terms and Conditions for Anaesthesia and Intensive Care Submissions”.

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