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Dexmedetomidine as a myocardial protector in pediatric heart surgery using cardiopulmonary bypass: a systematic review

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Background: In recent years, dexmedetomidine has been studied as a cardioprotective agent. However, studies on its application in pediatric heart surgery using cardiopulmonary bypass (CPB) remain limited. This systematic review aimed to provide information on the cardioprotective effect of dexmedetomidine in children undergoing heart surgery using CPB.

Methods: The authors searched several databases (MEDLINE, Embase, Cochrane Library, etc.) to identify all trials comparing the levels of myocardial injury via biomarkers, including pediatric patients undergoing heart surgery using CPB who received dexmedetomidine versus placebo or other anesthetic agents. Literatures from non-primary studies were excluded. Two reviewers independently screened studies for eligibility and extracted data. The Cochrane Risk-of-Bias tool was implemented to evaluate any potential biases. Information from eligible studies was summarized and correspondingly reviewed based on any quantitative outcomes.

Results: We identified six trials composed of 419 participants, three of which ($n = 241$) showed significantly reduced interleukin-6 (IL-6) levels in the dexmedetomidine group, while one study ($n = 40$) showed no IL-6 difference between groups. Cardiac troponin I (cTnI) and creatinine kinase-myocardial band (CK-MB), as myocardial injury biomarkers, were found to be lower in two trials ($n = 180$). Despite several limitations hindering this review from pooling the data objectively, the majority of published studies indicated that dexmedetomidine is a seemingly efficacious agent protecting against cardiac injury during bypass.

Conclusions: These studies suggest that dexmedetomidine has cardioprotective effects through the lowering of cardiac injury biomarkers while improving its clinical outcomes after heart surgery using bypass.

Keywords: biomarkers, cardiac surgical procedure, cardiopulmonary bypass, child, dexmedetomidine, heart injury

Introduction

Since the earliest days of modern cardiac surgery, the risk of perioperative myocardial dysfunction, with associated morbidity and mortality, has been reported. Important factors that contribute to myocardial injury include not only the metabolic consequences of oxygen deprivation but also the premorbid condition of the myocardium, reperfusion injury, acute alterations in signal transduction systems, and the effects of circulating inflammatory mediators[1]. The use of cardiopulmonary bypass (CPB), is known to cause a systemic inflammatory response and myocardial injury due to ischemia-reperfusion injury, endotoxemia, and contact of blood with the foreign surface of the CPB circuit[1].

There are some differences between pediatric and adult hearts, most notably in terms of size and contractibility. Smaller amounts of contractile elements and higher proportions of water and collagen content partially explain the poor contractile response of the immature heart to inotropes, their poor preload reserve, and their poor tolerance to afterload. There is also a relative abundance of polyunsaturated fatty acids in the membranes of cellular and subcellular organelles, increasing the risk of oxidative damage and resulting in the immature cyanotic heart being more

HIGHLIGHTS

- Cardiopulmonary bypass (CPB) can cause a systemic inflammatory response and myocardial injury.
- Ischemic–reperfusion injury, endotoxemia, and contact of blood with the foreign surface of the CPB circuit.
- Dexmedetomidine can attenuate inflammatory response and myocardial injury after CPB in pediatric cardiac surgery.
- An agreed core outcome set of clinically important, standardized, validated endpoints for assessing myocardial protection in children should be developed.

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vulnerable to oxidative insult[2]. Suboptimal myocardial protection remains the main cause of high morbidity and mortality in congenital heart surgery[3].

Myocardial protection describes techniques to protect the function of the myocardial tissue by reducing metabolic needs to prevent ischemia and decrease the consequences of ischemia-reperfusion injury and inflammatory responses. There are two main methods to protect the myocardium: cardioplegia by direct administration to cardiac surgery to temporarily arrest the heart and non-cardioplegia techniques, such as temperature, intermittent fibrillation, and the use of anesthetic agents, etc[1,4]. The use of anesthetic agents has been increasing in recent years to conduct myocardial protection procedures. One of the most promising agents is dexmedetomidine, which has yielded good cardioprotective properties not only in preclinical studies but also in recent open-heart surgeries[5–7].

Dexmedetomidine is a novel α-2 agonist with sedative, hypnotic, analgesic, and sympatholytic properties[8,9]. Owing to its effect in reducing inflammatory responses, dexmedetomidine may have a protective role in myocardial ischemic–reperfusion and has a high potential for use in clinical anesthesia[8]. The use of dexmedetomidine as a cardioprotector can be applied during preconditioning, intraconditioning, and postconditioning periods of cardiac surgery. Administering dexmedetomidine at any of these stages can prevent myocardial necrosis and apoptosis caused by the use of the CPB machine[4,8].

Recent practice has shown variations in the use of dexmedetomidine for myocardial protection in pediatric cardiac surgery worldwide. The loading dose, infusion dose, and time of administration of dexmedetomidine during pediatric cardiac surgery varied among the studies[9–14]. Moreover, the biomarker used to determine the myocardial protective effect of dexmedetomidine in pediatric cardiac surgery was also inconsistent[9–14]. Thus, this phenomenon has raised the question of whether dexmedetomidine is truly suitable for myocardial protection in pediatric cardiac surgery. Therefore, through a comprehensive literature review, we conducted a systematic review to evaluate whether dexmedetomidine has a myocardial protective effect in pediatric cardiac surgery using a CPB machine.

Material and methods

The Cochrane Handbook for Systematic Reviews of Interventions was used to conduct this review[15]. The review is also reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and criteria[16]. All eligibility criteria, search terms, and data items were defined in advance, and the review has been submitted and registered to PROSPERO (the International Prospective Register of Systematic Reviews) and the Research Registry[17,18]. To ensure high-quality review, this study was also self-assessed using the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) critical appraisal tool for systematic reviews[19].

Trial eligibility

All randomized clinical trials (RCTs) comparing the levels of myocardial injury or inflammation biomarkers between pediatric patients undergoing heart surgery using CPB who received dexmedetomidine versus placebo or other anesthetic agents were screened for eligibility criteria. The inclusion criteria were as follows: studies with subjects from 0 to 18 years of age; studies in which dexmedetomidine was used as an anesthesia adjuvant during cardiac surgery, or a component of CPB priming solution, an infusion during CPB time, or an adjuvant for postoperative (within a 24-h period) sedation and analgesia; and studies with one of the following outcomes: levels of biomarkers associated with myocardial injury or inflammation with or without any type of hemodynamic profile or any type of clinical outcome or mortality. Literature from books, book chapters, conference proceedings or abstracts, editorials, commentaries, and non-primary studies, as well as studies that were not published in English, were excluded from further analysis.

Search strategy

A systematic literature search for all RCTs was conducted using seven databases, such as MEDLINE, Embase, Cochrane Library, ScienceDirect, Scopus, EBSCOhost, and Sage Journal. The search was conducted using Boolean operators "AND" and "OR". The search terms were ("dexmedetomidine" OR "precedex") AND ("cardiac surgery" OR "heart surgery") AND ("cardiopulmonary bypass") AND ("pediatric" OR "pediatrics" OR "paediatric" OR "paediatrics" OR "child" OR "children" OR "infant" OR "infants") with a slight modification of keywords in each database. Moreover, an advanced search strategy was used whenever appropriate to narrow the search results. The full search queries and strategies used in each database can be found in Table 1. Additionally, the full search strategy could be visualized according to PRISMA 2020 criteria and flowchart in the following Figure 1[16].

Study selection

The citations from the electronic data search were uploaded into Mendeley software (*Mendeley-Desktop-1.19.8-OSX-Universal*). Duplicates were automatically identified using Mendeley's duplication removal tool. All articles were screened by two reviewers, and any disagreement was resolved by other reviewers for consensus. Then, the selection process was conducted by manual deduplication, followed by title screening and abstract screening consecutively for relevant studies based on the information provided. Full-text screening and review were then conducted to screen the studies against the eligibility criteria. Studies with irrelevant outcomes or methods in detailed reviews were excluded. Reference lists of publications gained following full-text review were evaluated to identify further possible studies not found in database searches and treated using a similar screening approach as stated above.

Data extraction

The data were independently extracted by two reviewers. The first reviewer extracted the following information using a customized data extraction form: authors' names, year of publication, study design, total number of participants included in the study, type of heart surgery, anesthesia agents used, and description of primary outcomes. The extracted data were then organized into a table for a summary and characteristics of each study. The second reviewer read each article and evaluated the data extraction forms to ensure the accuracy of data extraction. The obtained data were tabulated and compared against the initially required data found in the customized form. Missing data and unclear

Table 1

Search queries of each scientific databases

Scientific databases	Search queries (complete search strategy)	Hit	Access date
MEDLINE	((((dexmedetomidine[Title/Abstract]) OR (dexmedetomidine[MeSH Terms]) AND (randomizedcontrolledtrial[Filter])) AND ((((((cardiac surger*[Title/Abstract]) OR (heart surger*[Title/Abstract])) AND (cardiopulmonary bypass[Title/Abstract])) OR (cardiac surgery[MeSH Terms])) OR (heart surgery[MeSH Terms])) AND (cardiopulmonary bypass[MeSH Terms]) AND (randomizedcontrolledtrial[Filter]))) AND ((((((pediatric*[Title/Abstract]) OR (paediatric*[Title/Abstract])) OR (child*[Title/Abstract])) OR (infant*[Title/Abstract])) OR (children [MeSH Terms])) OR (infants[MeSH Terms]) AND (randomizedcontrolledtrial[Filter]))) AND (randomized controlled trial[Publication Type])	5	16 July 2022
Cochrane Central	#1 MeSH descriptor: [Dexmedetomidine] explode all trees #2 (dexmedetomidine):ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Thoracic Surgery] explode all trees 177 #4 ((cardiac or heart) NEXT surger*):ti,ab,kw AND (cardiopulmonary NEXT bypass):ti,ab,kw (Word variations have been searched) #5 #1 OR #2 #6 #3 OR #4 #7 MeSH descriptor: [Child] explode all trees #8 MeSH descriptor: [Infant] explode all trees #9 (pediatric):ti,ab,kw OR (infant*):ti,ab,kw OR (child*):ti,ab,kw (Word variations have been searched) #10 #7 OR #8 OR #9 #11 #5 AND #6 AND #10	33	17 July 2022
ScienceDirect	(dexmedetomidine OR precedex) AND (“caldiopulmonary bypass”) AND (“cardiac surgery” OR “heart surgery”) AND (“pediatric” OR “child” OR “infant”) AND (“randomized controlled trial”)	41	17 July 2022
Scopus	TITLE-ABS (dexmedetomidine) OR TITLE-ABS (preceded) AND TITLE-ABS (“heart surgery”) OR TITLE-ABS (“cardiac surgery”) AND TITLE-ABS (“cardiopulmonary bypass”) AND TITLE-ABS (pediatric) OR TITLE-ABS (child) OR TITLE-ABS (infant) AND (LIMIT-TO (SRCTYPE , “j”)) AND (LIMIT-TO (DOCTYPE , “ar”))	27	19 July 2022
SAGE Journal	[[All dexmedetomidine] OR [All precedex]] AND [[All “cardiac surgery”] OR [All “heart surgery”]] AND [All “cardiopulmonary bypass”] AND [[All pediatric] OR [All child] OR [All infant]]	45	29 July 2022
Embase	#1 AND #2 AND #3 AND #4 #4. pediatric:ab,ti OR child:ab,ti OR infant:ab,ti OR ‘child’/exp OR ‘infant’/exp #3. (cardiac OR heart) AND surger*:ab,ti #2. cardiopulmonary AND bypass:ab,ti #1. dexmedetomidine:ab,ti OR ‘dexmedetomidine’/exp OR ‘dexmedetomidine’ OR precedex:ab,ti OR ‘precedex’/exp OR ‘precedex’	69	29 July 2022

reporting were managed by emailing the investigator to request raw data and trial registrations or protocols.

Outcome definition

The primary outcome was the effect of dexmedetomidine on the levels of biomarkers associated with myocardial injury or inflammation. Inflammatory biomarkers consist of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ), and nuclear factor kappa B (NF-κB). While the myocardial injury biomarkers are cardiac troponin I (cTnI), creatine kinase-myocardial band (CK-MB), and heart-type fatty acid binding protein (H-FABP). Additionally, any other biomarker of inflammation or myocardial injury may also be included if available. The measurement time points were not predetermined. The secondary outcomes consisted of morbidity (length of intensive care and duration of mechanical ventilation support) and the inotropic score. In addition, other variables for which data are sought include the number of participants, type of heart surgery, anesthesia agents used, etc., which have been aforementioned in the previous subsection.

Quality assessment

The quality of each study was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB2). Each RCT was evaluated for its random sequence generation, allocation concealment, outcome assessment blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The result of each factor could be ‘High’, ‘Low’, or ‘Some Concerns’ risk of bias. Each trial’s overall risk of bias was classified as low (low risk in all domains), high (high risk of bias in one or more domains), or unclear (none of the above). It was assessed independently by two reviewers, and disagreements were resolved by two other reviewers for consensus.

Results

In total, 228 articles were identified using an electronic search strategy. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. After removing duplicate articles, 159 were included. After screening the titles and abstracts, we excluded 152 studies because they did not meet the inclusion criteria. We retrieved the full papers of the remaining seven studies for further evaluation of the full text. Of these, one study was excluded because no relevant primary outcomes were reported[20]. Ultimately, six selected publications were included in this systematic review.

A total of 419 participants were retrieved from the six trials or studies included. The design characteristics of the included studies are summarized in Table 2. All studies were RCTs, originating from four countries, with China being the most frequent (3, 50%) and only one (16.7%) originating from Egypt, the United States

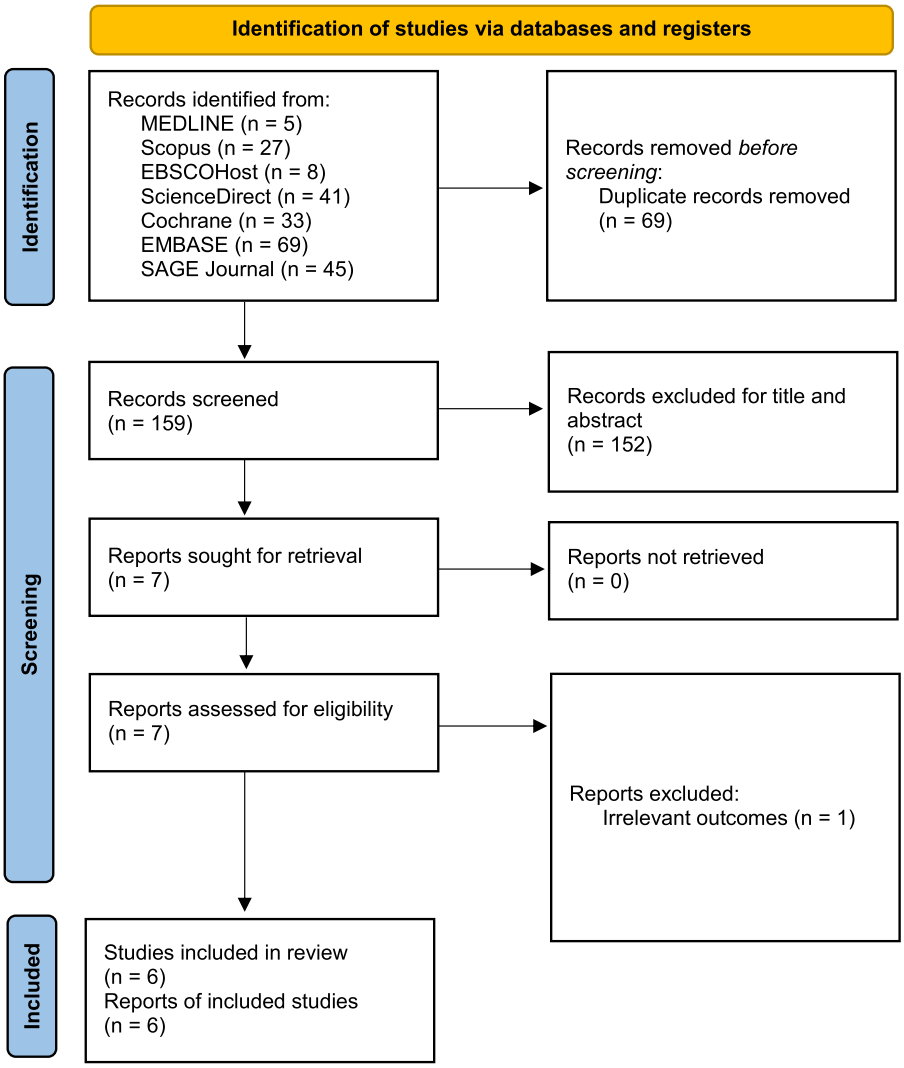

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection.

of America, and Iran. All the studies were published in English, as mentioned in the eligibility criteria.

Each randomized trial included 40–90 children, with a median of 75.5 (IQR 46–90). Patient age ranged from 1 month to 13 years, with a median of 44.9 months (IQR 30–62.4 months). The types of congenital heart diseases (CHDs) were reported in five of the six articles. Therefore, of the 419 total patients in six articles, there was only information about the types of CHD in 379 patients. Most surgical procedures were performed for ventricular septal defect (VSD), with 189 procedures (45.1%). In addition, procedures were low-risk, with a total of 378 (90.2%) children undergoing operations with a Risk-Adjusted classification for Congenital Heart Surgery (RACHS-1) score below 3 and one (0.2%) child with a RACHS-1 score of 3. The reported CPB time and aortic cross-clamp time data were extracted from five studies because we found that one study reported unclear data. The mean CPB time across the studies was 66.5 min, and the mean aortic cross-clamp time across the studies was 39.3 mins. The most frequent comparator in the non-intervention group was normal saline in 5 (83.3%), followed by low-dose and high-dose fentanyl in 1 (16.7%) trial (Table 2).

Outcome measures

All six trials (100%) had a defined primary endpoint. The required outcome measures were biomarkers of myocardial injury or systemic inflammation followed by duration of mechanical ventilation (4, 66.7%), hemodynamics (3, 50%), and postoperative complications (3, 50%) as the most common outcomes measured (Table 3).

Related to the outcome metrics as seen in Table 4, inflammatory response after CPB in pediatric cardiac surgery was measured with inflammatory markers interleukin-6 (IL-6) in five studies (83.3%), tumor necrosis factor alpha (TNF-α) in four studies (66.7%), C-reactive protein (CRP) in two studies (33.3%), nuclear factor kappa B (NF-κB) in one study (16.7%), and interferon-gamma (IFN-γ) in one study (16.7%). Thus, there were 329 participants measured for IL-6, 268 participants measured for TNF-α, 130 participants measured for CRP, 90 participants measured for NF-κB, and 61 participants measured for IFN-γ. All studies have shown that dexmedetomidine can attenuate the inflammatory response after CPB in pediatric cardiac surgery. On the measurement of IL-6, Totonchi*et al.* reported a lower value

Table 2

Characteristics of included trials

Characteristics	*n* (%)
Cardiopulmonary bypass	6 (100)
Country of origin	
Egypt	1 (16.7)
USA	1 (16.7)
Iran	1 (16.7)
China	3 (50)
Language of publication	
English	6 (100)
Number of arms	
2	2 (33.3)
3	4 (66.7)
Design	
Parallel groups	6 (100)
Intervention comparison	
Normal saline	5 (83.3)
Low-dose and high-dose fentanyl	1 (16.7)

in the dexmedetomidine, despite not significantly (8.112 ± 1.47 vs. 8.45 ± 1.45)[14]. Abdelrahman *et al.*[11] and Qiu *et al.*[13] also reported a similar trend, with levels of IL-6, IFN-γ, TNF-α, and NF-κB marked significantly lower in the dexmedetomidine group compared to the control at all operative and postoperative measurements,. Zhang *et al.*[8] reported similar trend (891.04 ± 90.81 vs. 1291.38 ± 145.05 pg/ml, 28 h postsurgery).

Two (33.3%) studies with a total of 180 participants evaluated the effect of dexmedetomidine in alleviating myocardial injury in pediatric cardiac surgery. Serum biomarker assays for myocardial injury, cTnI, CK-MB, and H-FABP were lower in the dexmedetomidine group than in the non-intervention group. Zhang *et al.*[9] reported a significantly lower value of CK-MB in the dexmedetomidine group as compared to the placebo group (40.02 ± 8.11 vs. 45.05 ± 7.88 U/l) 28 h after the surgery, while the cTnI is significantly lower 20 h after the CPB procedure (0.945 ± 0.139 vs. 1.045 ± 0.137). Unfortunately, Ming *et al.*[10] did not quantify the results in their reports; however, the use of dexmedetomidine has significantly lowered the value of CK-MB, cTnI, and H-FABP at the end of the surgery, 6-h postsurgery, and 24-h postsurgery. Even lower in higher doses of dexmedetomidine (0.2 vs. 0.1 μg/kg). These measures were inconsistently reported as concentrations at time points from before surgery to 48 h postsurgery; scheduling of sample collection was variable and timed from reperfusion, end of CPB, end of surgery, or arrival in the intensive care unit (ICU). The heterogeneity of patients, interventions, and reported outcome measures prevented meta-analysis. Only the short-term results up to the point of discharge were recorded.

Table 3

Defined outcome measures most frequently reported in included trials

Outcome measures	*n* (%)
Clinical	
Duration of mechanical ventilation	4 (66.7)
Hemodynamics	3 (50)
Postoperative complication	3 (50)
Inotropic support	2 (33.3)
Length of ICU stay	2 (33.3)
Length of hospital stay	1 (16.7)
Emergence agitation score	1 (16.7)
Postoperative pain score	1 (16.7)
Blood products usage in ICU	1 (16.7)
Nonclinical	
Biomarkers of myocardial injury	2 (33.3)
Biomarkers of systemic inflammation	6 (100)
Arterial lactate	3 (50)

ICU, intensive care unit.

Quality of trials

Figure 2 depicts the risk-of-bias assessment for each of the five domains as well as the overall bias. The overall risk of bias was a concern in two (33.3%) trials and low in four (66.7%) trials. Concerns arose as a result of inadequate reporting of randomization and masking processes, as well as an inability to exclude selective reporting due to the lack of trial registration or a published protocol.

Discussion

RCTs represent the gold standard for evaluating healthcare interventions because of their thorough testing of predetermined protocols and bias minimization. In this systematic review of the published literature, we identified only six RCTs that measured the effect of dexmedetomidine on myocardial protection in pediatric cardiac surgery using cardiac bypass. Risk of bias in the included studies was assessed using the RoB2 tool, and from six included studies, four studies had a low risk of overall bias, and two studies had some concerns for bias. The two studies were concerned because there was no information about the concealment of subject allocation, potentially leading to bias in the randomization process[9,10].

Heart surgery with the CPB method is associated with ischemia-reperfusion injury, which is linked to reversible post-ischemic cardiac dysfunction and irreversible myocardial cell death[6]. The levels of CK-MB and cTnI can be utilized to assess the severity of myocardial injury, and their dynamic variations can often provide a useful reference[21]. There were only two studies using cTnI and CK-MB as myocardial injury biomarkers as the primary endpoint: the two RCTs were conducted by Ming *et al.*, 2021[10] and Zhang *et al.*, 2018[22]. Although both RCTs have some limitations, including the risk of bias in the study population and randomization process, the overall critical appraisal was good. We noted that the long-suspected beneficial effects of dexmedetomidine are true in children undergoing cardiac surgery. While dexmedetomidine likely improves cardiac function in children, it also prevents myocardial infarcts marked by lower myocardial biomarkers, suggesting that dexmedetomidine may have a myocardial protective effect in the early postoperative period. These two trials included one or more serum cardiac cTnI, CK-MB, and H-FABP levels, measured at varying time points up to 48 h, and variably reported as measured concentrations or peak levels. The overall results showed that the dexmedetomidine group had significantly lower levels of cTnI, CK-MB, and H-FABP when administered dexmedetomidine as part of a priming solution, as well as infusion at varying time points, especially from the end of surgery to 48 h postoperation[9,10]. However, the fact that most of the studies

Table 4

Outcome metrics reported in included trials

Number	Author (year)	Number of patients included; sex distribution (male/female)	Type of CHD	DEX administration	CPB duration (min), mean (SD)	Ischemic/ cross-clamp time (min), mean (SD)	Relevant primary endpoints	Recording time of primary endpoint	Endpoint outcome		Results	
									Primary	Secondary	Primary	Secondary
1	Abdelrahman *et al.* (2020)[11]	61 (1–8 years); 33/28	ASD, VSD, subaotic membrane, pulmonal stenosis, partial AV canal defect, aorta stenosis	IV bolus of 0.5 μg/kg, followed by infusion of 0.5 μg/kg/h continued till the end of CPB	77.7 (22.1)	50.9 (18.5)	1. IL-6 2. INF-γ	1. During bypass 2. 6 h after surgery 3. 24 h after surgery	The level of inflammatory mediators (IL-6 and INF-γ)	1. Inotropic support 2. Duration of mechanical ventilation 3. Length of ICU stay 4. Length of hospital stay	Lower IL-6 and INF-γ	Mechanical ventilation duration, ICU duration, and inotropic score were lower in DEX group than control group
2	Ming *et al.* (2021)[10]	90 (1–6 years); 52/38	ASD, VSD, ASD + VSD	Infusion of 0.2 μg/kg/h for group D1 and 0.4 μg/kg/h for group D2 from the start of anesthesia to the end of the operation	D1 group: 76.40 (14.55) D2 group: 71.55 (15.63)	D1 group: 37.75 (13.86) D2 group: 36.50 (13.04)	1. CK-MB 2. cTnI 3. H-FABP 4. Lactic acid 5. CRP 6. NGAL 7. Scr 8. BUN 9. NSE 10. S100β 11. Ca-jvO2	1. Before surgery 2. End of surgery 3. 6 h after surgery 4. 24 h after surgery 5. 48 h after surgery	Inflammatory markers and myocardial injury markers levels Kidney injury parameter	1. Tracheal extubation time	Group D2: Lower CK-MB at 24 and 48 h postoperation Lower cTnI at 6, 24, and 48 h postoperation Lower H-FABP at end of surgery, 6 h postoperation Lower lactic acid and CRP	Tracheal intubation time in group D1 and group D2 were shorter than in group C
3	Naguib *et al.* (2013)[12]	48 (30 days to 3 years); 32/16	ASD, AVSD, ToF	Low-dose fentanyl 10 μg/kg (LDF) + DEX 1 μg/kg loading dose, followed by infusion 0.5 μg/kg/h until separation from CPB	113 (74–225)	82 (41–128)	1. ACTH 2. Plasma cortisol 3. Epinephrine 4. Norepinephrine 5. Lactate 6. Glucose level 7. IL-6 8. IL-8 9. IL-10 10. TNF-α	1. At baseline 2. After sternotomy 3. CPB start 4. End of the procedure 5. 24 h postoperative	Metabolic, hormonal, cytokine	1. Postoperative inotropic score day 1 2. Inotropic at ICU admission 3. Duration of mechanical ventilation 4. Length of ICU stay 5. Length of CTICU stay 6. Time on ventilator	Lower ratio of IL-6 with IL-10 at 24 h after surgery Lower plasma lactate levels	LDF + DEX group had a significantly lower inotropic score on postoperative day 1
4	Qiu *et al.* (2020)[13]	90 (6–12 years); 43/47	ASD, VSD	Group 1: 1 μg/kg/h IV bolus, followed by a 0.2 μg/kg/h	Group 1: 44 (13) Group 2: 45 (11)	Group 1: 23 (6) Group 2: 25 (7)	1. TNF-α 2. NF-κB 3. IL-6	1. Before the surgery 2. At the end of CPB	Expression of inflammatory factor	None	Lower NF-κB, TNF-α, and IL-6 at the end of	None

				infusion Group 2: 0.5 μg/kg IV bolus, followed by a 0.1 μg/kg/h infusion				3. 2 h after CPB 4. 6 h after CPB 5. 24 h after CPB			CPB, 2, 6, and 24 h after CPB	
5	Totonchi et al (2017)[14]	40 (6 months to 6 years); 16/14	Congenital heart disease	After central venous and arterial catheter insertion, initial loading dose of 0.5 μg/kg during 10 min was administered, followed by a continuous infusion of 0.5 μg/kg	1.93 (5.247)	4.27 (4.60)	1. Lactate 2. TNF-α 3. IL-6 4. CRP	1. Before DEX administration 2. After separation of pump 3. 24 h after ICU admission	Stress response (inflammatory and neuroendocrine responses)	1. Duration of mechanical ventilation	No significant difference in lactate, IL-6, TNF, and CRP concentrations	No significant difference in duration of mechanical ventilation
6	Zhang et al (2018)[22]	90 (1 month to 13 years); 48/42	VSD, ASD, pulmonary stenosis	Group B: 1 μg/kg as a part of priming solution. Group C: 1 μg/kg IV infusion immediately after anesthesia induction, and the infusion was completed within 15 min	Group B: 51.78 (12.18) Group C: 53.25 (12.17)	Group B: 29.05 (7.23) Group C: 30.17 (8.21)	1. CK-MB 2. TNF-α 3. IL-6 4. cTnI 5. LDH	1. Before anesthesia induction 2. 30 min after CPB 3. 6 h after CPB 4. 20 h after CPB 5. 28 h after CPB	Myocardial injury marker and inflammatory marker	None	Group B: Lower level of cTnI at 20 h after bypass, lower CK-MB at 28 h after CPB Group C: Lower level of cTnI at 20 h after bypass, lower CK-MB at 28 h after CPB Lower LDH, TNF-α, IL-6 at 20 and 28 h after CPB	None

ACTH, adrenocorticotropic hormone; ASD, atrial septal defect; AV, atrioventricular; BUN, blood urea nitrogen; CHD, congenital heart disease; CK-MB, creatinine kinase-myocardial band; CPB, cardiopulmonary bypass; CRP, C-reactive protein; CTICU, cardiothoracic intensive care unit; cTnI, cardiac troponin I; H-FABP, heart-type fatty acid binding protein; ICU, intensive care unit; IL, interleukin; INF, interferon; IV, intravenous; LDF, low-dose fentanyl; LDH, lactate dehydrogenase; NF-κB, nuclear factor kappa B; NGAL, neutrophil gelatinase-associated lipocalin; NSE, neuron-specific enolase; Scr, serum creatinine; SD, standard deviation; TNF-α, tumor necrosis factor alpha; VSD, ventricle septal defect.

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Abdelrahman et al.	Dexmedetomidine	Normal Saline	NA	1						
Ming et al	Dexmedetomidine	Normal Saline	NA	1						
Naguib et al	LDF + Dexmedetomidine	LDF, HDF	NA	1						
Qiu et al	Dexmedetomidine	Saline	NA	1						
Tontochi et al	Dexmedetomidine	Normal Saline	NA	1						
Zhang et al	Dexmedetomidine	Normal Saline	NA	1						

Note: Green, low risk; yellow, some concerns; red; high risk.
D1 – Randomization process
D2 – Deviations of the intended interventions
D3 – Missing outcome data
D4 – Measurement of the outcome
D5 – Selection of the reported result

Figure 2. Cochrane risk-of-bias scores for included trials.

used different biomarkers highlights the lack of a systematic approach for reporting biomarker release following ischemia-reperfusion in children.

Dexmedetomidine decreases the severity of the inflammatory response, in addition to its effect on indicators of myocardial injury. Five trials used IL-6 as an inflammatory marker[9,11–14], but all six trials used other inflammatory markers as the main outcomes, resulting from different pathways producing proinflammatory markers. Dexmedetomidine was found to reduce the levels of proinflammatory cytokines, including IL-6, INF-γ, NF-κB, TNF-α, and LDH (lactate dehydrogenase) measured at various time points starting at the end of CPB to 28 h post-CPB procedure[9,11–14]. One study also reported CRP as an inflammatory marker, and the level was significantly lower in the dexmedetomidine groups[10]. In contrast, one trial reported that no significant difference in IL-6, TNF-α, and CRP concentrations was detected[14]. This finding could be caused by some previously mentioned limitations of the study that may alter the effect of dexmedetomidine on stress responses, including a small sample size and a study population of pediatric patients who had to start dexmedetomidine after the induction of anesthesia and insertion of arterial lines. As a result, surgery stress responses may have started to an unavoidable degree by the time of dexmedetomidine administration. The mechanism by which dexmedetomidine reduces inflammation may be closely related to the inhibition of NF-κB pathways and Toll-like receptors[23–26]. Reducing the degree of inflammation may be beneficial in reducing morbidity because some studies have shown that the occurrence of inflammation is associated with adverse cardiac outcomes and increased myocardial injury biomarkers[25].

An increased level of IL-6 and IL-8 was associated with the length of use of the CPB machine[27,28]. The use of CPB machines in open-heart surgery reduces the oxygen supply to the myocardium and increases the glycolysis process, decreases adenosine triphosphate synthesis, and induces mitochondrial edema, which causes the process of necrosis in the myocardial[29]. The increase in IL-8 is also related to the duration of aortic cross-clamping and the duration of circulatory arrest[27]. When the aortic cross-clamp is opened, reperfusion injury can occur due to oxidative stress caused by the return of circulatory function[30].

Elevated levels of IL-6 and IL-8 24 h after removal of the CPB machine were associated with increased duration of mechanical ventilation and longer ICU stay[27]. Two studies reported that the dexmedetomidine group had lower mechanical ventilation duration[10,11], while the other two studies showed no significant difference in mechanical ventilation time[12,14]. Other outcome measures differed in terms of definition, time, and measurement as well. Two studies evaluated dexmedetomidine in relation to the inotropic score. In 2020, Abdelrahman *et al.*[11] showed that the dexmedetomidine group had a lower inotropic score than the control group ($P = 0.009$), while Naguib *et al.*[12] in 2013 reported that there were no statistically significant differences between the three groups relative to the inotropic score on arrival to the ICU or on postoperative day 1,. High inotropic scores are associated with a long duration of intensive care, a long duration of mechanical ventilation, and fluid imbalance[31].

Myocardial protection in open-heart surgery aims to avoid myocardial injury due to extracorporeal circulation, aortic cross clamps, and reperfusion injuries caused by detached aortic cross clamps[32]. Adequate myocardial protection during open-heart surgery in pediatric patients is an important factor in determining the outcome of surgery[2]. There, few studies have investigated the effect of dexmedetomidine on myocardial protection in pediatric cardiac surgery using CPB. The range of dexmedetomidine loading doses in this study was 0.5 μg/kg and the infusion rate was between 0.1 and 0.5 μg/kg/h. Many methods have been used to administer dexmedetomidine during pediatric cardiac surgery. Several studies have reported dexmedetomidine as a loading dose and as a continuous infusion during pediatric cardiac surgery[11–13]. Dexmedetomidine itself can be useful as a neuroprotective and cardioprotective agent during preconditioning, intraconditioning, and postconditioning by reducing necrosis of the cells and inhibiting oxidative stress, especially during the preconditioning period[4]. Preconditioning dexmedetomidine can attenuate myocardial reperfusion injury by downregulating the HMGB1–TLR4–MyD88–NF-κB pathway[33]. In the postconditioning period, dexmedetomidine inhibits the release of proinflammatory factors by reducing the expression of necroptosis mediators, inhibiting the release of inflammatory factors, and reducing the pyroptosis process by reducing the release of HMBG1[9,19]. Dexmedetomidine also reduced the formation of proinflammatory factors through AMPK/PI3K/Akt/eNOS pathways in the preconditioning period. As a result, the myocardial infarct area decreased and the release of proinflammatory cytokines such as TNF-α and IL-6[33]. Dexmedetomidine also activated the anti-inflammation process by activating the α7nAChR

receptors, which increased acetylcholine regulation and endogenous antioxidant enzyme[34,35].

Our study found that the range of ages in these six trials was between 30 days and 13 years, and the youngest population was studied in China. None of the studies included neonatal populations. A study showed that the plasma concentration of dexmedetomidine in neonatal populations would be dramatically changed by the CPB machine; it would increase during the early phase of CPB and gradually decrease until the end of CPB[36]. The inflammation caused by reperfusion injury may cause apoptosis and necrosis. Apoptotic cells produce proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α. This process can lead to systemic inflammatory response syndrome (SIRS), which rarely occurs in neonatal patients because of their immature immune response[34,37].

The heterogeneity of patients, interventions, and reported outcome measures among studies prevented the findings from being pooled for meta-analysis. Our findings are consistent with those of a prior, more limited meta-analysis conducted in 2015 on the effect of dexmedetomidine on myocardial protection in pediatric congenital heart surgery, which included five RCTs and nine observational studies involving 2229 patients. The assessed outcomes of the meta-analysis included hemodynamics, duration of ventilation, ICU and hospital stays, blood glucose levels, postoperative care requirements, and postoperative delirium. However, in this study, the biomarker levels of myocardial injury and inflammation were not evaluated as outcomes. This meta-analysis reported that the perioperative use of dexmedetomidine is associated with better outcomes in pediatric patients with CHD, including more stable intraoperative hemodynamics, shorter length of postoperative mechanical ventilation, reduced stress responses, postoperative analgesia requirements, and postoperative delirium[37,38].

Limitations

This study has several limitations. First, only a few studies have presented findings with comparable outcomes, preventing us from performing meta-analyses to advise clinical practice. The different measurements and biomarkers used in the included studies hindered us from pooling the data objectively for further quantitative analysis. Despite several biomarkers being assessed in different studies, we believe that the data were not sufficient for pooled analysis.

Recommendations for future research

We suggest that a consensus core outcome set of clinically significant, standardized, and validated endpoints for evaluating myocardial protection in children should be designed to allow future high-quality trials and meta-analyses of pooled data. Further studies to implement these are needed for a more impactful study of dexmedetomidine or any other agents in cardiac surgery.

Clinical implications for health managers and policymakers

This study is beneficial for further studies on myocardial protection procedures in pediatric cardiac surgery, particularly for congenital heart surgery procedures. Further discussion is needed to properly discuss the advantages and disadvantages of dexmedetomidine for myocardial protection; however, this systematic review might add further value to this discussion.

Conclusions

In conclusion, our systematic review suggests that dexmedetomidine has a myocardial protective effect in pediatric heart surgery using CPB. Marked variations in biomarkers and correlated clinical outcomes demonstrate the need for a high-quality, homogenous-sample study to determine the effect of cardioprotective strategies more accurately. Despite the limitations of this systematic review, the results indicated that dexmedetomidine is an efficacious cardioprotective drug in children undergoing cardiac surgery with CPB.

Ethical approval

Due to the design of this study is systematic review, the need for ethical approval was waived.

Consent

Due to the design of our study, the need for informed consent was waived.

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Author contribution

D.K. (first author): conception and design of the study, data analysis and data collection, and the creation of the manuscript draft; Y.W. (co-author, corresponding author): conducted the study design, data collection, data analysis, and manuscript revision and finalization; C.E.B. (co-author) and L.K.D. (co-author): helped conceptualize the study design, data collection, manuscript revision, and finalization.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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Guarantor

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Data availability statement

Datasets generated during the current study are available upon reasonable request.

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