Journal of Anesthesia (2025) 39:577–589
https://doi.org/10.1007/s00540-025-03506-w

ORIGINAL ARTICLE

Prophylactic corticosteroids in neonatal cardiac surgeries using cardiopulmonary bypass: a systematic review and meta-analysis

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Received: 11 November 2024 / Accepted: 15 April 2025 / Published online: 15 May 2025

Abstract

Purpose Neonates undergoing cardiopulmonary bypass (CPB) are at a high risk of a systemic inflammatory response leading to cardiac, respiratory, and renal dysfunction due to their small body size and insufficient adrenal stress response. We hypothesized that corticosteroids reduce systemic inflammatory response and improve clinical outcomes in neonates undergoing cardiac surgery with CPB.

Methods A systematic search was conducted on six databases including MEDLINE from their inceptions to August 20, 2024. Inclusion criteria were randomized controlled trials (RCTs) comparing corticosteroids and placebo in neonates undergoing cardiac surgery with CPB. The primary outcomes were IL-6 and IL-10 serum levels. The secondary outcomes were postoperative clinical outcomes such as length of intensive care unit (ICU) stay, mortality, and incidence of acute kidney injury. Pooled risk ratios or mean differences (MDs) and 95% confidence intervals (CIs) were calculated using random-effects meta-analysis. Certainty of evidence were assessed following GRADE. This study was registered in PROSPERO (CRD42024548217).

Results Seven RCTs met all inclusion criteria, consisting of 316 patients. Administration of corticosteroids significantly decreased plasma IL-6 on POD1 (MD -64.21 pg/mL, 95% CI -118.26 to -10.16) and plasma IL-10 on POD1 (MD − 4.60 pg/mL, 95% CI − 8.07 to − 1.12). We confirmed corticosteroids administration did not improve clinical outcomes.

Conclusion Corticosteroids significantly reduced inflammatory cytokines on POD1. Routine prophylactic use of corticosteroids is not recommended even in neonatal cardiac surgery, however, because of high incidence of adrenal insufficiency in neonates after cardiac surgery with CPB, neonates with clinically suspected adrenal insufficiency could benefit from perioperative corticosteroids administration.

Keywords Cardiac surgical procedures · Cardiopulmonary bypass · Inflammation · Newborn · Steroids

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Introduction

Congenital heart defects are the most common birth anomalies, with moderate-to-severe variants occurring in approximately 6 per 1000 live births. From 2010 to 2016, approximately 70% of neonatal cardiac operations in North America were performed under cardiopulmonary bypass (CPB) [1, 2].

CPB is known to cause a systemic inflammatory response due to the contact of blood with the extracorporeal circuit and organ reperfusion injury with bypass discontinuation [3]. Cytokines and interleukins play important regulatory roles in the inflammatory response, particularly interleukin-6 (IL-6) and interleukin-8 (IL-8), both of which are elevated following CPB [3–8] and are associated with postoperative cardiac dysfunction, AKI, and lung injury [3]. Interleukin-10 (IL-10) also increases following CPB, but results in downregulation of proinflammatory cytokines (IL-6, IL-8) during and after CPB, therefore suggesting a protective role [4].

Compared to older populations, CPB in neonates presents unique challenges due to their smaller body size, which creates a relatively larger blood-circuit interface, and the need for higher pump flow rates to meet their elevated metabolic demands. These factors lead to increased exposure of blood to the foreign surfaces of the bypass circuit, resulting in heightened inflammation [9–11]. This may result in an increased risk of postoperative morbidity. For example, neonates are known to have the highest risk for cardiac surgery-related acute kidney injury (AKI) of all populations [12] a significant predictor of in-hospital mortality [13].

Corticosteroid administration has been used to minimize systemic inflammation during and after CPB. Compared to older populations, neonates may benefit most from corticosteroid supplementation in conditions of high systemic inflammation since they have immature (depressed) hypothalamic–pituitary–adrenal axis activity, resulting in insufficient cortisol production in the face of critical injury/illness [14]. In practice, there is wide variability in administrating of prophylactic corticosteroids for pediatric cardiac surgery. According to the surveys conducted in 2005 and 2018, up to 70% of centers or anesthesiologists selectively use prophylactic corticosteroids depending on cases [15, 16]. Although there is no consensus on which patient group prophylactic corticosteroids should be directed at, their usage appears to be higher in neonatal cardiac surgeries [15, 16]. A previous systematic review reported that corticosteroid administration in neonates undergoing cardiac surgery with CPB did not impact in-hospital mortality [17]. However, it is not known in neonates undergoing cardiac surgery with CPB if corticosteroids reduce the systemic inflammatory response, which may impact length of ICU stay and the incidence of comorbidities such as cardiac dysfunction requiring higher inotropic support, lung injury requiring prolonged mechanical ventilation, and AKI.

In the current review, we hypothesized that the prophylactic administration of corticosteroids during CPB in neonates would reduce the levels of biochemical markers of systemic inflammation, such as IL-6. We further hypothesized that this reduction would lead to a shorter ICU stay and a lower incidence of postoperative morbidities in neonates undergoing cardiac surgery with CPB.

Methods

The protocol for the current review was registered at PROSPERO (CRD42024548217). The study is reported following Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [18].

Systematic literature search

A systematic literature search of Ovid Medline, Medline In-Process/ePubs, Ovid Embase Classic + Embase, Cochrane Central Register of Controlled Trials, Clarivate Web of Science, and Elsevier SCOPUS was conducted on December 1, 2023 and updated on August 20, 2024 with the help of a librarian (JC). Search terms included steroid/corticosteroid AND CPB AND neonate. To increase the sensitivity of the search strategy, terms related to the study design were not used. The detailed systematic literature search strategy is presented in Supplementary File 1.

Study selection

Title screening, abstract screening, and full text assessment were conducted independently by two investigators (KK and NN) using DistillerSR™ (Evidence Partners Inc., Ottawa, ON, Canada). Disagreements were resolved by discussion with a third reviewer (MS).

Inclusion and exclusion criteria

Inclusion criteria were: (1) neonates (≤ 28 days old) undergoing cardiac surgery with CPB; (2) pre-, intra-, and/or postoperative administration of corticosteroids compared to normal saline control; (3) reported results for any of the predefined primary or secondary study outcomes; (4) randomized controlled trial (RCT) study design; and (5) full-text publication.

Exclusion criteria were: (1) age of patients ≥ 29 days; (2) patients undergoing cardiac surgery without CPB; (3)

administration of corticosteroids in the control group; (4) control intervention other than normal saline; (5) no reported results for any primary or secondary outcomes; (6) publication types other than full-text article RCTs; and (7) duplicate studies.

Primary and secondary outcomes

The primary outcome was the serum levels of Il-6, IL-8, or IL-10 during and after surgery until postoperative day 6 (POD6). The secondary outcomes were length of ICU stay, in-hospital mortality after surgery, length of mechanical ventilation until first extubation after surgery, incidence of AKI (defined as a 50% increase in plasma creatinine levels after surgery compared with preoperative levels [19], vasoactive inotropic score (VIS; defined as the sum of the dose of inotropes used postoperatively [20], and postoperative serum lactate levels from arrival in ICU to POD6.

Data extraction

Data were extracted from all eligible trials independently by two investigators (KK and NN) using a standardized data collection form. Study characteristics extracted were identification data (first author's last name, year of publication, journal name, country), study setting (single or multicenter, country of enrollment, years of study enrollment), and whether studies reported following the Consolidated Standard of Reporting Trials (CONSORT) statement or not [21]. Demographic data extracted were patient age (in days), sex, weight (in kilograms), ASA score, and Risk Adjustment for Surgery for Congenital Heart Surgery (RACHS-1) score. Corticosteroid treatment data extracted were steroid used (dexamethasone, methylprednisolone, hydrocortisone), timing (preoperative, intraoperative), method (bolus, infusion), and dose (in mg/kg and dexamethasone was converted to equipotent dose of methylprednisolone) [22, 23]. Intraoperative characteristics extracted were procedure type, anesthetic agent, fluid volume, blood loss, transfusion requirement, hemoglobin/hematocrit, duration of anesthesia, duration of CPB, duration of aortic cross clamp, and duration of hypothermia. Primary outcomes (levels of and timing of serum IL-6, IL-8, and IL-10 measurements, in pg/mL) and secondary outcome data (length of ICU stay in days, in-hospital mortality, length of mechanical ventilation/time until first extubation in days, incidence of AKI, VIS, postoperative serum lactate in mmol/dL) were extracted. When outcomes were reported in figures only, Engauge Digitizer version 12.1 was used to digitize and extract the data [24].

Data synthesis: meta-analysis, subgroup analyses, and sensitivity analyses

Pairwise random-effects meta-analysis models were employed to compute mean differences (MD) with 95% confidence intervals (CI) of intravenous corticosteroids in comparison to normal saline for IL-6, IL-8 and IL-10 levels, length of ICU stay, length of mechanical ventilation, VIS, and lactate levels. Pairwise random-effects meta-analysis models were also used to compute risk ratios (RRs) with 95% CI for mortality and incidence of AKI. Meta-analyses were performed for all outcomes (and if applicable, timepoints) reported by at least two studies. For each model, statistical heterogeneity was assessed using the I^2 statistic, with $I^2 = 50–74\%$ reflecting moderate heterogeneity and $I^2 \geq 75\%$ reflecting high heterogeneity.

A subgroup analysis to examine the effect of postoperative serum lactate level (≥ 4.8 mmol/L vs. < 4.8 mmol/L) on incidence of AKI, VIS, length of mechanical ventilation, and length of ICU stay was planned [25]. Subgroup analyses for incidence of AKI were also planned based on serum IL-6 (> 100 pg/mL vs. ≤ 100 pg/mL) and serum IL-10 levels (> 30 pg/mL vs. ≤ 30 pg/mL) [26]. For incidence of AKI, VIS, length of mechanical ventilation, length of ICU stay, and mortality outcomes, subgroup analysis by RACHS-1 score was also planned (≥ 4 vs. < 4) [23, 27, 28].

Sensitivity analyses for all outcomes were conducted by excluding trials with high risk of bias.

All statistical analyses were conducted using R version 4.3.0 and Review Manager by Cochrane (RevMan) version 5.4.1.

Quality assessments

Critical appraisal for each individual study was performed independently by two investigators (KK and NN) using the Cochrane Risk of Bias 2 (RoB 2) tool assessment for parallel trials [29]. Disagreements were resolved with discussion with a third reviewer (MS). The RoB 2 tool consists of five domains: randomization process, assignment to intervention, missing outcome data, measurement of the outcome, and selection of the reported result. Studies were classified as having overall low risk, some concerns, or high risk of bias according to the findings for these five domains.

The certainty of evidence was assessed through the Grading of Recommendation Assessment, Development and Evaluation (GRADE) certainty framework which consists of the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [30, 31]. The certainty of the evidence was classified as high, moderate, low or very low [32].

Publication bias was planned to be assessed using a funnel plot and Egger's regression test if more than ten articles were included [33].

Results

Systematic literature search

The literature search yielded 720 records. After removing duplicates, title and abstract screening, and full text assessment, eight publications met all inclusion criteria. The PRISMA flow diagram is shown in Fig. 1. The result of the search strategy is shown in Supplementary File 1.

Characteristics of eigible studies

The characteristics of the seven included publications are presented in Table 1, [34–41]. These papers represented five unique RCTs, with two being post-hoc analyses of other included papers. The studies were published between 2005 and 2021. The total number of participants was 316. Steroids used were preoperative bolus of methylprednisolone or dexamethasone, and postoperative continuous infusion of hydrocortisone. Out of the included seven studies, four reported plasma IL-6, one reported plasma IL-8, four reported plasma IL-10, three reported plasma lactate, three reported VIS, two reported AKI, and four reported lengths of ICU stay, mortality and length of mechanical ventilation. All extracted outcome data are presented in Supplementary Files 2 and 3.

Plasma IL-6, IL-8, IL-10

The summary of findings for the primary outcomes are presented in Table 2. For plasma IL-6, the only specific timepoint that could be synthesized was POD1 which was reported by two RCTs. In the control group, mean plasma IL-6 on POD1 was 250.15 pg/mL. Administration of corticosteroids significantly decreased plasma IL-6 on POD1 compared with the administration of placebo (MD − 64.21 pg/mL, 95% CI − 118.26 to − 10.16, low certainty of evidence). There was no evidence of heterogeneity ($I^2 = 0\%$) (Fig 2). Only one RCT reported plasma IL-8 and meta-analysis was not conducted. Plasma IL-10 on

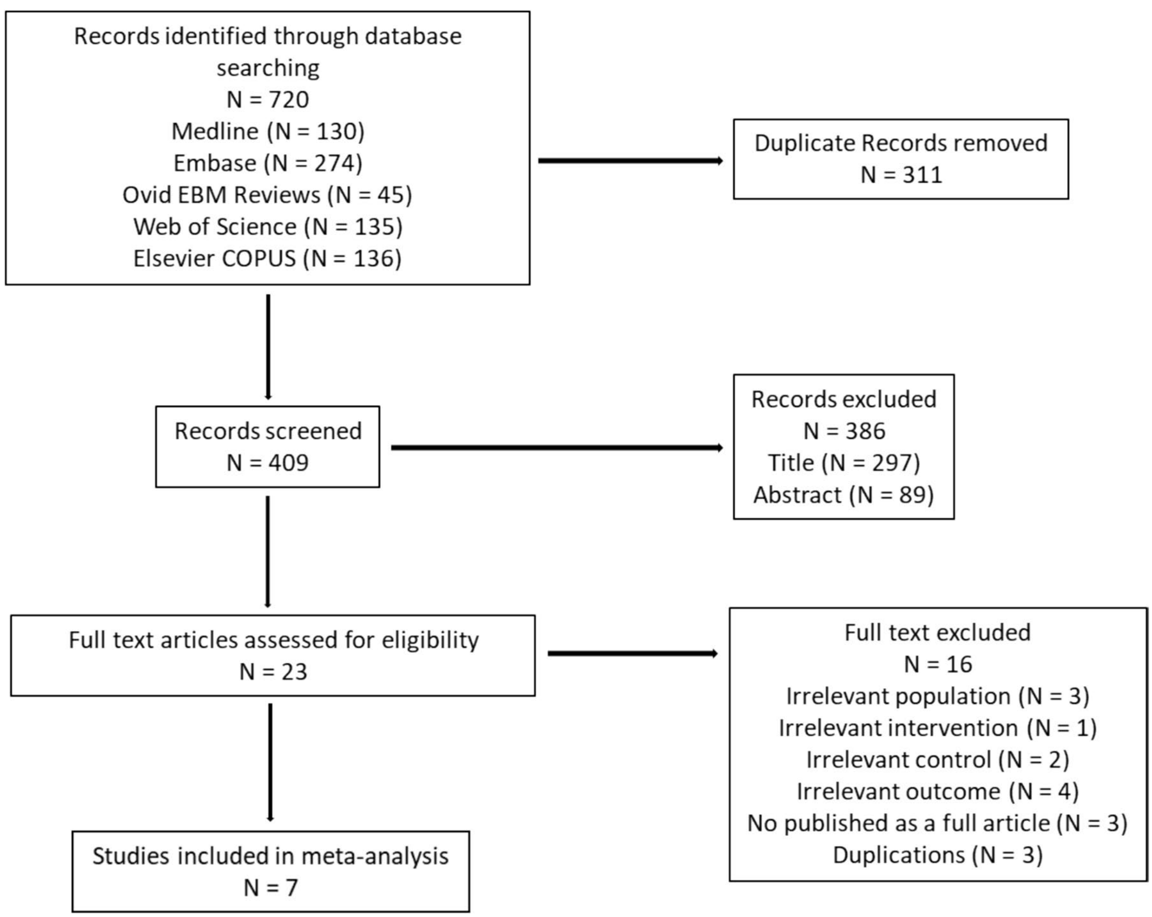

Fig. 1 PRISMA Flow Diagram. *PRISMA* Preferred reporting items for systematic review and meta-analysis

Table 1 Study characteristics of eight eligible trials

Author study year	Type of study	No. of participants		Steroid used (bolus dose)	Outcomes reported						
		Intervention	Control		Interleukin	Lactate	AKI	VIS	Length of ICU stay	Length of mechanical ventilation	Mortality[a]
Kaskinen et al. 2021	Single center double-blind	20	20	Methylprednisolone (2 mg/kg) hydrocortisone[e]	No	No	No	No	Yes	Yes	Yes
Graham et al. 2019	Multicentre double-blind	81	95	Methylprednisolone (30 mg/kg)	No	Yes	Yes	Yes	Yes	Yes	Yes
Jahnukainen et al.[b] 2018	Single center double-blind	20	20	Methylprednisolone (2 mg/kg) hydrocortisone[f]	Yes	No	No[h]	No	No	No	No
Suominen et al. 2017	Single center double-blind	20	20	Methylprednisolone (2 mg/kg) hydrocortisone[g]	Yes	Yes	No	Yes	Yes	Yes	Yes
Pesonen et al.[c] 2016	Single center double-blind	20	20	Methylprednisolone (30 mg/kg)	No	No	Yes	No	No	No	No
Keski-Nisula et al. 2013	Single center double-blind	20	20	Methylprednisolone (30 mg/kg)	Yes	Yes	No	Yes	Yes	Yes	Yes
Heying et al.[d] 2012	Multicentre double-blind	9	11	Dexamethasone (1 mg/kg)	Yes	No	No	No	No	No	No

AKI Acute kidney injury, *ICU* intensive care unit, *VIS* vasoactive inotropic score

[a]Mortality definition: Kaskinen 2021 and Suominen 2017, death in ICU; Graham 2019, death occurred after operation but before hospital discharge; Keski-Nisula 2013, death occurred within 30 days after operation

[b]Study is post-hoc analysis of Suominen's study

[c]Study is post-hoc analysis of Keski-Nisula's study

[d]All participants are neonates undergoing arterial switch operation

[e]Hydrocortisone was administered 6 h after CPB with tapering doses for 5 days: 0.2 mg/kg/h for 48 h, 0.1 mg/kg/h for 48 h, 0.05 mg/kg/h for 24 h

[f]Hydrocortisone was administered 6 h after the operation with tapering doses for 5 days: 0.2 mg/kg/h for 48 h, 0.1 mg/kg/h for 48 h, 0.05 mg/kg/h for 24 h

[g]Hydrocortisone was administered 6 h after the operation with tapering doses for 5 days: 0.2 mg/kg/h for 48 h, 0.1 mg/kg/h for 48 h, 0.05 mg/kg/h for 24 h

[h]Incidence of AKI was not reported separately in intervention and control groups

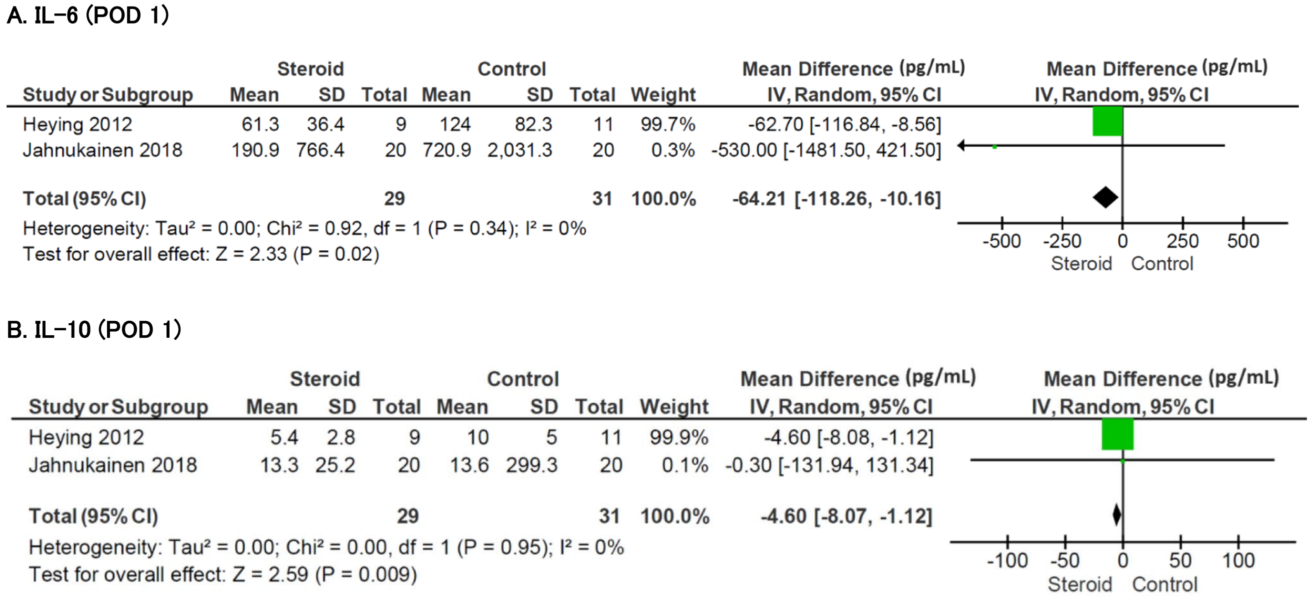

Fig. 2 The Effect of Steroid for Interleukin-6 and Interleukin-10. A. The effect of steroid for the value of Interleukin-6 at POD 1. B. The effect of steroid for the value of Interleukin-10 at POD 1. *CI* confidence interval, *IL* interleukin, *IV* inverse variance, *POD* postoperative day, *SD* standard deviation

Table 2 Summary of findings for interleukin-6 and interleukin-10

Outcomes	Anticipated absolute effects* (95% CI)		№ of particip nts (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with corticosteroid		
IL-6 (POD 1)	The mean IL-6 was 250.15 pg/mL	MD 64.21 pg/mL lower (118.26 lower to 10.16 lower)	60 (2 RCTs)	⨁⨁◯◯ Low[a,b,c,d]
IL- 10 (POD 1)	The mean IL-10 was 10.0 pg/mL	MD 4.6 pg/mL lower (8.07 lower to 1.12 lower)	60 (2 RCTs)	⨁⨁◯◯ Low[a,c,d]

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

CI confidence interval, *GRADE* grading of recommendation assessment development and evaluation, *IL* interleukin, *MD* mean difference, *RCT* randomized controlled trial

*The risk in the intervention group (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[a]One study was high risk of bias (Heying 2012)

[b]One study (Jahnukainen 2018) had a wide CI with an extreme point estimate

[c]One study (Jahnukainen 2018) had a wide CI and different point estimate than the other study

[d]Only two studies could be included, so we are potentially unable to assess the effect and heterogeneity

POD1 was reported by two RCTs. In the control group, mean plasma IL-10 on POD1 was 10.0 pg/mL. Administration of corticosteroids significantly decreased plasma IL-10 on POD1 compared with the administration of placebo (MD − 4.60 pg/mL, 95% CI − 8.07 to − 1.12, low certainty of evidence). There was no evidence of heterogeneity ($I^2 = 0\%$) (Fig. 2).

Plasma lactate, VIS, length of ICU stay, length of mechanical ventilation, incidence of AKI, mortality

The summary of findings for the secondary outcomes are presented in Table 3. Plasma lactate at the time of ICU arrival and on POD1 were analyzed (reported by two RCTs). Administration of corticosteroids significantly increased plasma lactate compared to the administration of placebo, at the time of ICU arrival (MD 1.41 mmol/L, 95% CI 0.57 to 2.26, low certainty of evidence) or on POD1 (MD 0.57 mmol/L, 95% CI 0.10 to 1.04, low certainty of evidence) (Supplementary File 4). Administration of corticosteroids did not significantly decrease VIS on POD1 (MD − 1.39, 95% CI − 4.53 to 1.75, low certainty of evidence), length of ICU stay (MD − 0.90 days, 95% CI − 2.39 to 0.59, moderate certainty of evidence), length of mechanical ventilation (MD − 0.36 days, 95% CI − 1.24 to 0.53, low certainty of evidence), incidence of AKI (RR 1.01, 95% CI 0.74 to 1.38, low certainty of evidence), or mortality (RR 0.57, 95% CI 0.22 to 1.49, low certainty of evidence).

GRADE and rsk of bias assessment

The components of the certainty of evidence assessment using GRADE criteria are presented in Supplementary Files

Table 3 Summary of findings for lactate, vasoactive inotropic score, length of intensive care unit stay, length of mechanical ventilation, incidence of acute kidney injury, and mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with steroid			
Lactate (ICU arrival)	The mean Lactate at ICU arrival was 3.76 mmol/L	MD 1.41 mmol/L higher (0.57 lower to 2.26 higher)	NA	80 (2 RCTs)	⊕⊕◯◯ Low[a,b,g]
Lactate (POD 1)	The mean Lactate POD 1 was 2.01 mmol/L	MD 0.57 mmol/L higher (0.1 lower to 1.04 higher)	NA	80 (2 RCTs)	⊕⊕◯◯ Low[a,b,g]
VIS (POD 1)	The mean VIS POD 1 was 17.61	MD 1.39 lower (4.53 lower to 1.75 higher)	NA	256 (3 RCTs)	⊕⊕◯◯ Low[a,c,d]
Length of ICU stay	The mean length of ICU stay was 9.57 days	MD 0.9 days lower (2.39 lower to 0.59 higher)	NA	296 (4 RCTs)	⊕⊕⊕◯ Moderate[a]
Length of mechanical ventilation	The mean length of mechanical ventilation was 5.51 days	MD 0.36 days lower (1.24 lower to 0.53 higher)	NA	296 (4 RCTs)	⊕⊕◯◯ Low[a,e]
Incidence of AKI	423 per 1,000	428 per 1000 (313 to 584)	RR 1.01 (0.74–1.38)	212 (2 RCTs)	⊕⊕◯◯ Low[f,g]
Mortality	84 per 1,000	48 per 1000 (18 to 125)	RR 0.57 (0.22–1.49)	296 (4 RCTs)	⊕⊕◯◯ Low[a,h]

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

AKI acute kidney injury, *CI* confidence interval, *GRADE* grading of recommendation assessment development and evaluation, *ICU* intensive care unit, *MD* mean difference, *NA* not applicable, *POD* postoperative day, *RCT* randomized controlled trial, *RR* risk ratio, *VIS* vasoactive inotropic score

[*]The risk in the intervention group (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[a]One study (Keski-Nisula 2013) was high risk of bias

[b]The magnitude of effect is small, the CI does not suggest a significant benefit or harm

[c]VIS data were graphically represented for: Keski-Nisula 2013, Graham 2019, and Suominen 2017. Data extraction using a digitizer software potentially misinformed and the data points could be inaccurate

[d]Two studies (Keski-Nisula 2013, Suominen 2017) have wide CIs and include the possibility of a small or no effect

[e]Three studies (Kaskinen 2021, Keski-Nisula 2013, Suominen 2017) had wide CIs and include the possibility of a small or no effect

[f]One study was high risk of bias (Pesonen 2016)

[g]Two studies only be included. It is potentially unable to assess the effect and heterogeneity

[h]Three studies (Kaskinen 2021, Keski-Nisula 2013, Suominen 2017) had wide CIs. The CIs include the possibility of a small or no effect

5 and 6. While the result for length of ICU stay had moderate certainty, all other outcomes had low certainty of evidence. The components of the risk of bias assessment are presented in Supplementary File 7. There were 3 RCTs identified with high risk of bias using Cochrane RoB 2 criteria.

Subgroup analysis and sensitivity analysis

The pre-planned subgroup analyses could not be performed as the included RCTs presented insufficient data of serum lactate level, IL-6 level, IL-10 level, and RACHS-1.

The results of the sensitivity analysis excluding trials with high risk of bias are presented in Supplementary File 8. Since the primary IL-6 and IL-10 analyses involved only two studies, this sensitivity analysis could not be performed, but one of the two studies was identified as high risk of bias due to deviations from the intended intervention (Heying 2012) [41]. Sensitivity analysis was conducted on VIS, length of ICU stay, length of mechanical ventilation, and mortality. There were no significant results for all outcomes.

Discussion

In the current review, perioperative administration of corticosteroids was found to significantly reduce IL-6 and IL-10 on POD1 in neonates undergoing cardiac surgery with CPB. However, the certainty of evidence of these outcomes were low. There was no significant difference in the clinical outcomes except for higher plasma lactate on ICU arrival and POD1 in the corticosteroids administered group.

Our findings and existing literature

In previous studies of adult cardiac surgeries with CPB, corticosteroids suppressed IL-6 and IL-8, while IL-10 increased [42, 43]. Our IL-6 findings support the findings from these studies in the neonatal population. In both the adult studies, IL-6 was measured on POD1, consistent with the timepoint synthesized in our study. However, contrary to the adult studies, our study found that corticosteroids suppressed IL-10. In the adult studies, the timepoints where plasma IL-10 were significantly higher in the corticosteroid group were all prior to POD1: after aortic declamp at the end of CPB in the study by Azab et al. [43] and 60 min after aortic declamp and 60 min after CPB in the study by Fillinger et al.[42] These studies also did not find significant differences in plasma IL-10 at POD1. In our study, plasma IL-6 and IL-10 were pooled only on POD1 due to lack of data at other timepoints. This discrepancy in the analyzed timepoints may explain the contrasting results of corticosteroid effect on plasma IL-10. Overall, in our study, a reduction in the biochemical markers of post-CPB inflammatory reaction could be confirmed, but with low certainty.

Clinical outcomes

In previous studies, the effect of corticosteroid administration on clinical outcomes for pediatric patients undergoing cardiac surgery with CPB was inconclusive. In our study, corticosteroid administration did not change clinical outcomes. Our null findings regarding mortality are supported by numerous previous meta-analyses of the pediatric population [17, 44, 45]. However, our finding regarding mechanical ventilation differs from these studies. A Cochrane Review on the pediatric population undergoing cardiac surgery with CPB demonstrated that corticosteroid administration did not change length of ICU stay, length of hospital stay, or mortality [44]. Likewise, a meta-analysis by Takeshita et al. of pediatric cardiac surgeries with CPB demonstrated that corticosteroids did not change mortality, length of ICU stay, and length of hospital stay; however, the duration of mechanical ventilation (MD − 5.54 h, 95% CI − 9.75 to − 1.34) and incidence of low cardiac output syndrome (RR 0.75, 95% CI 0.59 to 0.96) were both decreased [17]. In their subgroup analysis on the neonatal population, they also demonstrated that corticosteroids administration did not change mortality, which is consistent with our findings. A meta-analysis by Cheema et al. of pediatric patients undergoing cardiac surgery with CPB demonstrated that corticosteroids were associated with a lower duration of mechanical ventilation (MD − 0.63 days, 95% CI − 1.16 to − 0.09 days), reduced incidence of postoperative low cardiac output syndrome (RR 0.76, 95% CI 0.60 to 0.96), and reduced reoperations (RR 0.37 95% CI 0.19 to 0.74), but, again, there was no significant reduction in mortality, length of ICU stay and length of hospital stay [45].

The most recent meta-analysis by Losiggio et al. of 17 RCTs and 6598 cardiac surgery patients with CPB included all patients < 65 years old, including pediatric and neonatal populations. The study demonstrated that corticosteroids reduced mortality (RR 0.69 95% CI 0.52 to 0.92) and highest postoperative VIS (MD − 2.07, 95% CI − 3.69 to − 0.45), but no statistically significant difference was found in occurrence of AKI, myocardial infarction, and infections [46]. In their subgroup analysis of the neonatal population, no significant difference in mortality was found, supporting our findings [46].

Implications of the results for practice

In our study, a reduced inflammatory reaction due to corticosteroid administration could be concluded looking at IL-6 on POD1. The inflammatory reaction is a complicated cascade involving many cytokines interacting with each other, including cytokines which were not examined in our study, such as tumor necrosis factor-a (TNF-a) and IL-8. Furthermore, the change in levels for each cytokine varies in magnitude, direction, and timing in response to stimulation [47, 48]. Plasma IL-6 level peaks at 4 h after CPB, whereas plasma IL-10 level peaks at the end of CPB, and both decrease thereafter. The decrease trend is also different between plasma IL-6 and plasma IL-10, with plasma IL-6 decreasing over a couple of days following CPB whereas plasma IL-10 decreases rather rapidly in several hours after CPB [47–49]. Therefore, it is difficult to assess the degree to which corticosteroids affected the inflammatory response using plasma IL-6 and IL-10 at only one timepoint.

IL-10 is typically considered to reduce inflammation but its pathways of action are beneficial in some regards and maladaptive in others [50]. In fact, several studies have suggested that high plasma IL-10 levels could result in immune hyporesponsiveness, leading to a higher risk of postoperative complications [51]. A single center prospective study of 126 patients undergoing CABG with CPB demonstrated that high plasma IL-10 levels 24 h after CPB are related to increased clinical complications [47]. We need to consider the pleiotropic nature of cytokines complicating when to measure to show benefits vs. maladaptation.

The RCTs included in our study have considerable variabilities in the type of corticosteroids administered, the timing of administration, and the dosage. In six out of seven RCTs, methylprednisolone was given at induction of anesthesia and in 1 RCT dexamethasone was given 4 h prior to CPB initiation. Dexamethasone is a long-acting glucocorticoid with a half-life of 36 to 54 h, and methylprednisolone is an intermediate-acting with a half-life of 18 to 36 h [22, 52, 53]. The difference in the timing of administration of dexamethasone and methylprednisolone in these studies is assumed to be a few hours. Therefore, it is considered to have a minimal impact on the outcomes, at least up to POD1 [54]. Regarding the dosage, methylprednisolone was used at either 2 mg/kg or 30 mg/kg and dexamethasone at 1 mg/kg, equivalent to 5.4 mg/kg of methylprednisolone [22, 52, 53]. In 3 RCTs, hydrocortisone infusion was administered in addition to methylprednisolone and dexamethasone. However, its dose of the hydrocortisone infusion was equal to or less than 0.2 mg/kg/h which is almost negligible compared to bolus doses of methylprednisolone and dexamethasone. In the previous studies comparing high-dose methylprednisolone (30 mg/kg) with low dose (2 mg/kg or 5 mg/kg) in pediatric cardiac surgery using CPB, there was no significant difference in inflammatory response, including plasma IL-6 and IL-10 levels [55, 56]. Based on these facts, the influence of variabilities of corticosteroids administration on our primary outcome is not considered to be high.

The incidence of relative adrenal insufficiency in neonates after cardiac surgery with CPB is reported to be 32.5% [57]. This may imply that the use of corticosteroids could be considered for those patients at highest risk of insufficient adrenal stress response such as neonates. Current EACTS/EACTA/EBCP guidelines of adult cardiac surgery do not recommend routine prophylactic use of corticosteroids during cardiac surgery [58], but there are no specific guidelines regarding corticosteroid use during pediatric and neonate cardiac surgery. Based on our study findings, even for neonates undergoing cardiac surgery with CPB, routine prophylactic administration of corticosteroids may not be beneficial. However, administration of corticosteroids attenuate inflammation caused by CPB and there could be some population in neonates who benefit from corticosteroid administration such as those with clinically suspected or confirmed adrenal insufficiency. Studies with larger sample size and specific target population with clinically suspected or confirmed adrenal insufficiency are required for definitive conclusion.

Future research

Future research comparing additional cytokines, such as TFN-a and IL-8, alongside IL-6 and IL-10, at multiple timepoints is needed in order to better understand the trends and interactions among these cytokines. This will result in a better understanding of the overall effect of corticosteroids on intraoperative inflammation and allow for correlation with subsequent clinical outcomes.

In terms of clinical outcomes, it is necessary to study adverse effects of corticosteroids to evaluate relative benefit of its administration.

In addition, research to identify which patient populations are at highest risk of relative adrenal insufficiency and who might benefit most from corticosteroid administration is required.

Limitations and strengths

This study has some limitations. First, despite the use of a broad search strategy and inclusion criteria there were still a small number of studies included in the various analyses. For example, only two studies could be included for the analysis of IL-10 at POD1, and the results were largely driven by the study by Heying et al.[41] Subgroup analyses were planned for the incidence of AKI, inotropic score, mechanical ventilation, length of ICU stay and mortality, but could not be conducted due to a lack of data. Second, we were able to analyze plasma IL-6 and IL-10 levels at only one timepoint, despite extracting data for all available timepoints from the included studies. Some studies only showed figures without explicitly reporting the exact value for plasma IL-6 and plasma IL-10 concentrations. For those studies we digitized the figures to extract data as accurately as possible, leading to potential error. We analyzed only plasma IL-6 and plasma IL-10 levels as there was insufficient data to conduct a meta-analysis on IL-8.

Third, modified ultrafiltration (MUF) is known to remove mediators that could result in inflammatory response and improve clinical outcomes [59]; the use of MUF can significantly impact on the outcomes investigated in our study. However, 6 out of 7 eligible studies in our study did not specify its use. Future RCTs should report MUF use.

Fourth, we did not plan to conduct a meta-analysis on the adverse effects of corticosteroid administration. Of the seven eligible studies, three reported on blood glucose level and insulin administration, and two reported on infection. In the existing literature, it is shown that there is a significant association of methylprednisolone with infection in the lower surgical risk group of neonates undergoing cardiac surgery with CPB [60] and a significant increase in insulin treatment. [61] We could not elaborate on higher lactate levels on POD1 in the context of these adverse effects.

The current review also has several strengths. Ours is the first to collect and analyze the effect of corticosteroids on the levels of inflammatory cytokines in neonates undergoing cardiac surgery with CPB. Although there are several systematic reviews and meta-analyses of corticosteroids administration to pediatric cardiac surgeries with CPB, our study is the first focused on neonatal cardiac surgery with CPB looking at morbidity and clinical outcomes. Compared to previous systematic reviews which included only three or four studies in their analyses, the current review captures the largest number of studies of the neonatal population (five unique studies and two post-hoc analyses) [17, 45, 46].

Conclusions

Based on our study findings, even for neonates undergoing cardiac surgery with CPB, routine prophylactic administration of corticosteroids may not be beneficial. However, administration of corticosteroids attenuate inflammation caused by CPB and there could be some population in neonates who benefit from corticosteroid administration such as those with clinically suspected or confirmed adrenal insufficiency. Studies with larger sample size and specific target population with clinically suspected or confirmed adrenal insufficiency are required for definitive conclusion.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-025-03506-w.

Acknowledgements Jason T Maynes and Kazuyoshi Aoyama acknowledges the Department of Anesthesiology and Pain Medicine, University of Toronto, and the Hospital for Sick Children, for secured academic time to conduct the current work as a recipient of a Merit Award 2023-2025.

Author contributions Kumi Kataoka and Kazuyoshi Aoyama conceived this paper. Kumi Kataoka, Makoto Sumie, and Kazuyoshi Aoyama developed the protocol. Jessie Cunningham performed the systematic literature searches, managed database results and documentation. Kumi Kataoka, Naoko Niimi, and Makoto Sumie performed the systematic review. Kumi Kataoka, Ruxandra-Ioana Adam, and Makoto Sumie performed data extraction. Kumi Kataoka, Makoto Sumie, and Alan Yang performed the analysis on the result of the literature search and extracted data. Kumi Kataoka, Sierra Cheng, Makoto Sumie, Ruxandra-Ioana Adam, Alan Yang, and Kazuyoshi Aoyama interpreted data. Kumi Kataoka and Sierra Cheng wrote the initial draft of the manuscript. Makoto Sumie, Ruxandra-Ioana Adam, Naoko Niimi, Jessie Cunningham, Alan Yang, William C.K. Ng, Jason Hayes, Jason T Maynes, and Kazuyoshi Aoyama helped draft the final version, which was approved by all authors.

Funding This work was supported by POS Summer Studentship Program, Hospital for Sick Children 2024 (Sierra Cheng, Ruxandra-Ioana Adam, Jason Hayes, Kazuyoshi Aoyama), Canadian Anesthesiologists' Society Research Award 2022–2024 (Kazuyoshi Aoyama), Canadian Anesthesiologists' Society Career Scientist Award in Anesthesia 2024–2026 (Kazuyoshi Aoyama) and Project Grants (PJX179857, PJT183603) 2022–2024, Canadian Institutes of Health Research (Kazuyoshi Aoyama). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data availability All relevant data are available within the article and supplementary materials.

Declarations

Conflict of interest All authors declare no conflict of interests.

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