Perioperative prophylactic corticosteroids for cardiac surgery in children: A systematic review and meta-analysis

Huzaifa Ahmad Cheema[a,b,#], Arsalan Ali Khan[c,#], Awab Hussain Ahmad[c,#], Abdullah Ali Khan[c], Amna Khalid[b], Abia Shahid[a,b], Alaa Hamza Hermis[d], Ali Syed[e], Neha Bansal[f], Koichi Yuki[g,h], Sunil J. Ghelani[i,j], and Sourbha S. Dani[k] *Lahore, Pakistan; Babylon, Iraq; WI, USA; NY, USA; MA, USA;*

Abstract

Objective Perioperative corticosteroids have been used for pediatric cardiac surgery for decades, but the underlying evidence is conflicting. We aimed to investigate the efficacy and safety of perioperative prophylactic corticosteroids in pediatric heart surgeries.

Methods We searched electronic databases until March 2023 to retrieve all randomized controlled trials (RCTs) that administered perioperative prophylactic corticosteroids to children undergoing heart surgery. We used RevMan 5.4 to pool risk ratios (RRs) and mean differences (MDs).

Results A total of 12 RCTs (2,209 patients) were included in our review. Corticosteroids administration was associated with a nonsignificant reduction in all-cause mortality (RR 0.62; 95% CI: 0.37-1.02, $I^2 = 0\%$; moderate certainty); however, it was associated with a lower duration of mechanical ventilation (MV) (MD −0.63 days; 95% CI: −1.16 to −0.09 days, $I^2 = 41\%$; high certainty). Corticosteroids did not affect the length of ICU and hospital stay but significantly reduced the incidence of postoperative low cardiac output syndrome (LCOS) (RR 0.76; 95% CI: 0.60-0.96, $I^2 = 0\%$; moderate certainty) and reoperation (RR 0.37; 95% CI: 0.19-0.74, $I^2 = 0\%$; moderate certainty). There was no increase in adverse events except a higher risk of hyperglycemia and postoperative insulin use.

Conclusions The use of perioperative corticosteroids in pediatric heart surgeries is associated with a trend toward reduced all-cause mortality without attaining statistical significance. Corticosteroids reduced MV duration, and probably decrease the incidence of LCOS, and reoperations. The choice of corticosteroid agent and dose is highly variable and further larger studies may help determine the ideal agent, dose, and patient population for this prophylactic therapy. (Am Heart J 2023;266:159–167.)

Background

Approximately 40,000 children are born with a congenital heart defect each year in the US, and a significant proportion requires surgeries with cardiopulmonary bypass (CPB).[1-3] Although these surgical procedures significantly improve outcomes, these patients are at risk for postoperative complications due to CPB-related systemic inflammatory response syndrome, negatively impacting recovery and increasing the duration of mechanical ventilation (MV) and hospital stay.[4-6] To address this, corticosteroids have been used perioperatively for decades because of their favorable anti-inflammatory properties, but the underlying evidence to support their use is conflicting. The previous meta-analyses on this topic have reported inconsistent results in terms of mortality, duration of MV, and length of ICU and hospital stay.[7-10] However, these reviews have been limited by the small

From the [a]Department of Cardiology, King Edward Medical University, Lahore, Pakistan, [b]Department of Medicine, King Edward Medical University, Lahore, Pakistan, [c]Department of Surgery, King Edward Medical University, Lahore, Pakistan, [d]Al-Mustaqbal University College, Hillah, Babylon, Iraq, [e]Medical College of Wisconsin, Milwaukee, WI, [f]Division of Pediatric Cardiology, Mount Sinai Kravis Children's Hospital, New York, NY, [g]Cardiac Anesthesia Division, Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Boston, MA, [h]Department of Anaesthesia and Immunology, Harvard Medical School, Boston, MA, [i]Department of Cardiology, Boston Children's Hospital, Boston, MA, [j]Department of Pediatrics, Harvard Medical School, Boston, MA, [k]Division of Cardiovascular Medicine, Beth Israel Lahey Health, Lahey Hospital and Medical Center, Burlington, MA

[#]Contributed equally as joint first authors.

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Reprint requests: Huzaifa Ahmad Cheema, MBBS Department of Cardiology, King Edward Medical University, Nila Gumbad Chowk, Lahore, Punjab 54000, Pakistan.

E-mail address: huzaifacheema@kemu.edu.pk.

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sample sizes of included randomized controlled trials (RCTs); the most recent included only 1,349 pediatric patients and hence, was underpowered to detect any difference in important clinical outcomes.[9]

The largest RCT to date, the Steroids to Reduce Systemic Inflammation after Infant Heart Surgery (STRESS) trial, has recently been published, enrolling 1,263 infants, almost equivalent to the cumulative sample sizes of all previous RCTs.[11] Therefore, we conducted this updated meta-analysis to investigate the efficacy and safety of perioperative corticosteroids in pediatric cardiac surgeries with greater certainty and power.

Methods

This meta-analysis was registered with PROSPERO (CRD42023401004) and undertaken following the *Cochrane Handbook for Systematic Reviews of Interventions* and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[12,13]

Data sources and searches

We searched the following databases and trial registers from inception till March 2023: the Cochrane Central Register of Controlled Trials (CENTRAL, via The Cochrane Library), MEDLINE (PubMed), Embase, and ClinicalTrials.gov using a search strategy consisting of relevant keywords and Medical Subject Headings (MeSH). Additionally, we conducted a partial grey literature search in Google Scholar and backward citation tracking using reference lists of relevant articles. The detailed search strategy is presented in Supplementary Table 1.

Eligibility criteria

We included all studies that fulfilled the following criteria: (1) study design: RCTs; (2) population: pediatric patients (less than or equal to 18 years) undergoing cardiac surgery with CPB; (3) intervention: prophylactic perioperative corticosteroids regardless of dosing regimen; (4) comparator: placebo or no use of corticosteroids; and (5) outcomes: reporting at least 1 outcome of interest. Studies that used corticosteroids nonprophylactically were excluded.

Study selection and data extraction

We imported all the literature retrieved from our searches into Mendeley Desktop 1.19.8 and removed any duplicates. Two reviewers independently completed the title and abstract screening, followed by full-text screening. Any disagreement was settled through discussion and by consulting a third author.

Data regarding study characteristics (including authors and study location), patient population (including age and gender), corticosteroids (including type, dosage, and duration and timing of drug administration), and primary and secondary outcomes were extracted into a prepiloted excel sheet.

Outcomes

Our primary outcomes were all-cause mortality and duration of MV. Our secondary outcomes included length of ICU and hospital stay, the incidence of postoperative low cardiac output syndrome (LCOS) and reoperation for bleeding, any adverse events, and specific adverse events of interest.

Risk of bias assessment

To assess the internal validity of included RCTs, 2 authors independently applied the revised Cochrane "Risk of Bias" tool (RoB 2.0).[14] RoB 2.0 assesses the risk of bias in 5 domains: randomization process, blinding, and deviations from protocol, missing outcome data, measurement of outcome, and selective outcome reporting. The studies were assigned a rating of low risk of bias, some concerns, and a high risk of bias.

Data synthesis

The meta-analysis was carried out using review manager (RevMan, Version 5.4; The Cochrane Collaboration, Copenhagen, Denmark) under a random-effects model utilizing risk ratio (RR) and mean difference (MD) with corresponding 95% confidence intervals (CIs) as the effect measures. The I^2 statistic was used to quantify our syntheses' statistical heterogeneity. In addition, subgroup analyses based on the type of corticosteroid used and the age of the patients (neonates vs infants vs children) were conducted for our primary outcomes. Finally, in syntheses with at least 10 studies, publication bias was checked using a funnel plot and Egger's test for funnel plot asymmetry in Stata 17.0 (StataCorp LLC, College Station, TX, USA).

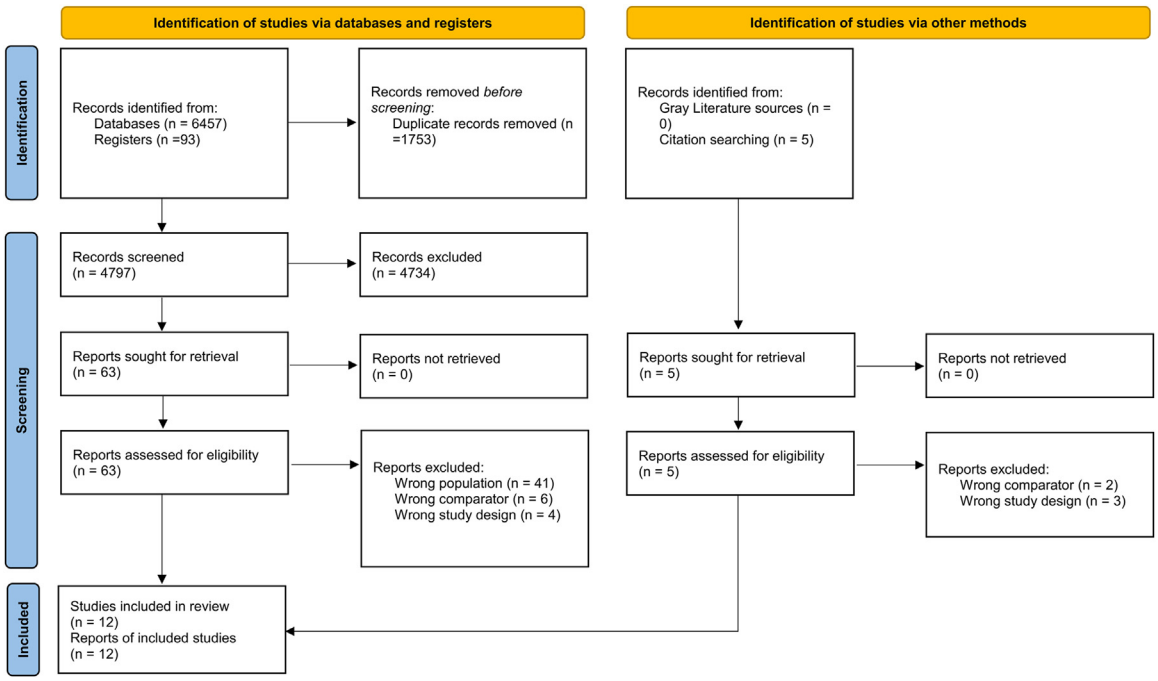
Certainty of evidence assessment

We evaluated the certainty of the evidence for each outcome using the five Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. A very low, low, moderate, and high certainty rating was given for each body of evidence.[15,16] We judged pooled estimates to be imprecise if the optimal information size (OIS) threshold was not met or the associated 95% CIs included the null effect and appreciable benefit or harm.[17] The OIS is the sample size required to detect a 25% relative risk reduction based on the median control group risk for dichotomous outcomes and a clinically significant difference for continuous outcomes.

Results

We included 12 RCTs reporting data from 2,209 patients in our meta-analysis.[11,18,27,28,19-26] The detailed

Figure 1



PRISMA 2020 flowchart.

study selection process is illustrated in Figure 1. One RCT was multinational, while the rest were conducted in one country each. Three RCTs were conducted in neonates, 5 in infants, and the rest in children. Methylprednisolone was used in 8 RCTs, while dexamethasone and hydrocortisone were utilized in two RCTs each. The timing of drug administration and dosing regiments were variable. The detailed study characteristics of each trial are presented in Table 1.

Risk of bias in included studies

Six of the included studies had a low risk of bias,[11,21,23,25-27] while the remaining six had some concerns of bias primarily due to issues in the domain of selective outcome reporting.[18-20,22,24,28] The risk of bias assessment is summarized in Supplementary Figure 1.

Results of the meta-analysis

Primary outcomes

All-cause mortality

The pooled analysis showed that corticosteroid administration was associated with a nonsignificant reduction in all-cause mortality in children undergoing heart surgery (RR 0.62; 95% CI: 0.37-1.02, $I^2 = 0\%$; Figure 2). The quality of evidence was rated as moderate due to concerns about imprecision (Table 2). There was no evidence of publication bias on the inspection of funnel plot asymmetry (Egger's *P*-value = .540).

Subgroup analyses based on the type of corticosteroid used (*Pinteraction* = 0.63) and the age of patients (*Pinteraction* = 0.72) were consistent with the primary analysis (Supplementary Figures 2 and 3).

Duration of mechanical ventilation

Corticosteroids reduced the duration of MV (MD −0.63 days; 95% CI: −1.16 to −0.09 days, I^2=41%; Figure 3). The certainty of evidence was rated as high due to the absence of any concerns in the GRADE domains (Table 2).

In the subgroup analysis by corticosteroid type, only hydrocortisone was found to reduce the duration of MV (MD −1.84 days; 95% CI: −3.58 to −0.09 days, $I^2 = 0\%$) as compared to dexamethasone and methylprednisolone. However, this difference was not significant in the test for subgroup differences (*Pinteraction* = 0.35; Supplementary Figure 4). On stratifying by age, the benefit of corticosteroids was restricted to neonates only (MD −2.39 days; 95% CI: −4.31 to −0.46 days, $I^2 = 0\%$; *Pinteraction* = 0.04) and was not seen in infants or children (Supplementary Figure 5).

Secondary outcomes

Efficacy outcomes

There was no significant difference in the length of ICU stay (MD −0.42 days; 95% CI: −0.91 to 0.08 days,

Table 1. Characteristics on included trials

Study ID	Location	Sample size	Age*	Male, n (%)	Study population	Intervention	Dosing regimen
Ando 2005	Japan	20 (10 vs 10)	12.3 ± 3.8 vs 9.4 ± 4.8 (d)	-	Neonates	Hydrocortisone	IV, 0.81 mg/kg/hr, 7 days, postoperatively
Bronicki 2000	USA	29 (15 vs 14)	28 ± 33 vs 25 ± 35 (mo)	17 (58.6)	Children	Dexamethasone	IV, 1 mg/kg, preoperatively
Dalili 2015	Iran	100 (50 vs 50)	39.8 ± 24.7 vs 38.2 ± 19.8 (mo)	27 (54) vs 27 (54)	Children (0-15 years)	Methylprednisolone	IV, 30 mg/kg of body weight, postoperatively
Graham 2019	USA	176 (81 vs 95)	9.1 ± 5.4 vs 8.2 ± 5.6 (wk)	46 (56.7) vs 60 (63.1)	Infants	Methylprednisolone	IV, 30 mg/kg, intraoperatively
Hill 2022	USA	1200 (599 vs 601)	126.0 (14.0-191.0) vs 124.0 (14.0-182.0) (d)	320 (53.4) .vs 334 (55.7)	Infants	Methylprednisolone	IV, 30 mg/kg of body weight
Keski-Nisula 2013	Finland	40 (20 vs 20)	9.9 ± 7.0 vs 11.0 ± 7.2 (d)	12(60) vs 11(55)	Neonates	Methylprednisolone	IV, 30 mg/kg, perioperatively
Keski-Nisula 2015	Finland	45 (15 vs 15 vs 15)	5.9 ± 3.8 vs 5.1 ± 2.3 vs 4.9 ± 3.3 (mo)	-	Children (1-18 months)	Methylprednisolone	IV, 30 mg/kg at anesthesia induction and 30 mg/kg through the CPB circuit
Keski-Nisula 2020	Finland	30 (15 vs 15)	6.0 (4.8-8.3) vs 6.7 (5.6-8.1) (mo)	10 (66) vs 7(50)	Infants	Methylprednisolone	IV, 30 mg/kg, at anesthesia induction
Lomivorotov 2020	Russia, Brazil, China	394 (194 vs 200)	6.5 (4.0-9.3) vs 5.7 (3.8-9.3) (mo)	93 (47.9)	Infants	Dexamethasone	IV 1 mg/kg after anesthesia induction
Robert 2015	USA	40 (19 vs 21)	5 (4-7) vs 6 (5-11) (d)	-	Infants	Hydrocortisone	IV, 50 mg/m2/d after removal of CPB
Suominen 2017	Finland	40 (20 vs 20)	0.27 ± 0.086 (d)	15 (75)	Neonates	Methylprednisolone and hydrocortisone	IV methylprednisolone 2 mg/kg after anesthesia induction followed by IV hydrocortisone 0.2mg/kg/h (with tapering dose) over 5 days
Toledo-Pereyra 1980	USA	95 (47 vs 48)	-	-	Children	Methylprednisolone	IV, 30mg/kg

CPB, cardiopulmonary bypass; IV, intravenous.
* Data reported as mean SD or median (IQR).

Table 2. Grading of recommendations assessment, development, and evaluation (GRADE) summary of findings

Outcome	No. of participants (studies)	Effect estimate (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence (GRADE)
All-cause mortality	2,209 (12)	RR 0.62 (0.37, 1.02)	Not serious	Not serious	Not serious	Serious*	Undetected†	⊕⊕⊕⊖ MODERATE
Duration of mechanical ventilation (days)	884 (9)	MD -0.63 (−1.16 to −0.09)	Not serious	Not serious	Not serious	Not serious	NA	⊕⊕⊕⊕ HIGH
Length of ICU stay (days)	914 (10)	MD −0.42 (−0.91 to 0.08)	Not serious	Not serious	Not serious	Serious‡	Undetected§	⊕⊕⊕⊖ MODERATE
Length of hospital stay (days)	1,830 (5)	MD -0.61 (−1.32 to 0.11)	Not serious	Not serious	Not serious	Serious‡	NA	⊕⊕⊕⊖ MODERATE
Postoperative low cardiac output syndrome	1,556 (5)	RR 0.76 (0.60-0.96)	Not serious	Not serious	Not serious	Serious‡	NA	⊕⊕⊕⊖ MODERATE
Reoperation for bleeding	1,623 (3)	RR 0.37 (0.19, 0.74)	Not serious	Not serious	Not serious	Serious‡	NA	⊕⊕⊕⊖ MODERATE
Adverse events	1,739 (4)	RR 0.93 (0.85, 1.02)	Not serious	Not serious	Not serious	Serious*	NA	⊕⊕⊕⊖ MODERATE
Infection	2,065 (8)	RR 1.03 (0.72, 1.47)	Not serious	Not serious	Not serious	Serious*	NA	⊕⊕⊕⊖ MODERATE
Acute kidney injury	1,939 (6)	RR 0.92 (0.65, 1.29)	Not serious	Not serious	Not serious	Serious‡	NA	⊕⊕⊕⊖ MODERATE
Neurologic events	1,594 (2)	RR 0.75 (0.37, 1.53)	Not serious	Serious‖	Not serious	Serious‡	NA	⊕⊕⊖⊖ LOW
Arrhythmia	1,734 (4)	RR 0.94 (0.79, 1.12)	Not serious	Not serious	Not serious	Serious*	NA	⊕⊕⊕⊖ MODERATE
Postoperative glucose levels	1,985 (9)	MD 19.83 (5.24 to 34.43)	Not serious	Serious¶	Not serious	Not serious	NA	⊕⊕⊕⊖ MODERATE
Need for postoperative insulin	1,568 (7)	RR 2.60 (1.80, 3.76)	Not serious	Not serious	Not serious	Serious‡	NA	⊕⊕⊕⊖ MODERATE

CI, confidence interval; MD, mean difference; NA, not applicable; RR, risk ratio.

* The 95% CI fails to exclude important benefit or harm.

† No evidence of funnel plot asymmetry (Egger's p-value = 0.540)

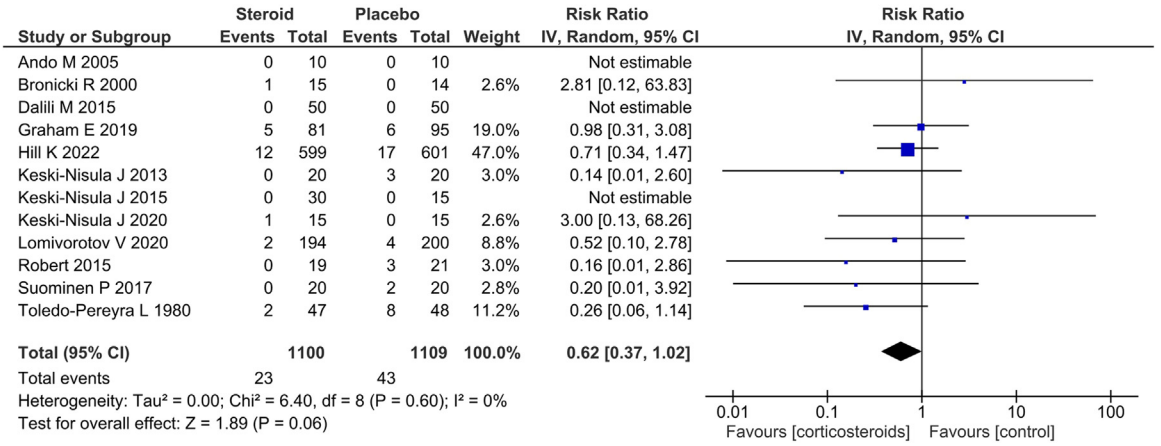
‡ The optimal information size (OIS) is not met.

§ No evidence of funnel plot asymmetry (Egger's *P*-value = .296)

‖ Moderate heterogeneity (I^2 = 38%) with little overlap between 95% CIs.

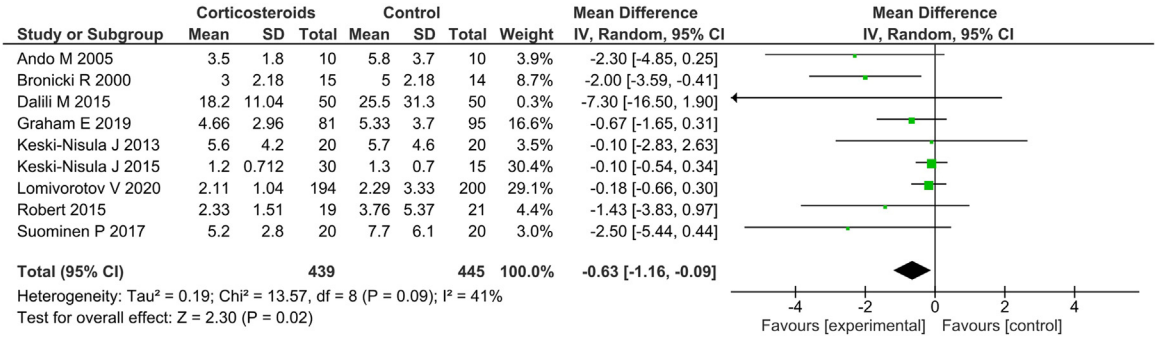
¶ High heterogeneity (I^2 = 96%).

Figure 2



Effect of perioperative corticosteroids on all-cause mortality in children undergoing heart surgery.

Figure 3



Effect of perioperative corticosteroids on the duration of mechanical ventilation in children undergoing heart surgery.

I^2 = 20%; moderate certainty; Supplementary Figure 6) and hospital stay (MD −0.61 days; 95% CI: −1.32 to 0.11 days, I^2 = 0%; moderate certainty; Supplementary Figure 7) between the corticosteroid and control groups. There was no evidence of publication bias in the length of ICU stay (Egger's *P*-value = .296).

Corticosteroids significantly reduced the incidence of LCOS (RR 0.76; 95% CI: 0.60-0.96, I^2 = 0%; moderate certainty; Supplementary Figure 8) and reoperation for bleeding (RR 0.37; 95% CI: 0.19-0.74, I^2 = 0%; moderate certainty; Supplementary Figure 9).

Adverse events

The rate of any adverse events (RR 0.93; 95% CI: 0.85-1.02, I^2 = 0%; moderate certainty; Supplementary Figure 10), any infection (RR 1.03; 95% CI: 0.72-1.47, I^2 = 0%; moderate certainty; Supplementary Figure 11), acute kidney injury (AKI) (RR 0.92; 95% CI: 0.65-1.29, I^2 = 10%; moderate certainty; Supplementary Figure 12), neurological events (RR 0.75; 95% CI: 0.37-1.53, I^2 = 38%; low certainty; Supplementary Figure 13), and arrhythmia (RR 0.94; 95% CI: 0.79-1.12, I^2 = 0%; moderate certainty; Supplementary Figure 14) did not differ significantly between the 2 groups. Corticosteroids increased postoperative glucose levels (MD 19.83 mg/dL; 95% CI: 5.24-34.43 mg/dL; I^2 = 96%; moderate certainty; Supplementary Figure 15) and the need for postoperative insulin (RR 2.60; 95% CI: 1.80-3.76, I^2 = 6%; moderate certainty; Supplementary Figure 16).

Discussion

This meta-analysis of 12 RCTs with 2,209 pediatric patients is the largest to date on this topic. Our findings showed, with moderate certainty of evidence, that there was a trend towards reduced all-cause mortality with perioperative use of corticosteroids in pediatric cardiac

surgery; however, this did not attain statistical significance. Corticosteroids reduced the duration of MV with a higher benefit observed with hydrocortisone and in neonates but did not affect the length of ICU and hospital stay. Furthermore, corticosteroids probably reduce the incidence of postoperative LCOS and reoperation for bleeding.

The lack of a statistically significant mortality benefit in our meta-analysis, although consistent with prior meta-analyses,[7-10] should be interpreted in the context of several factors. Though not attaining statistical significance, there was a trend toward a reduction in mortality with corticosteroids. This may be due to insufficient power, as our estimates still suffered from substantial imprecision despite pooling the largest number of patients to date. This is reflected by a failure to reach the threshold for the OIS in our GRADE assessment. Therefore, a benefit in mortality may become apparent with the addition of more RCTs in the future. In contrast to the STRESS trial that concluded that prophylactic methylprednisolone had no benefit in infants undergoing surgery with CPB, this meta-analysis shows a shorter duration of MV, a lower incidence of LCOS, and a lower rate of reoperation for bleeding.[11] These findings also contrast with the results of prior meta-analyses that found no effect of corticosteroids on the duration of MV or risk of LCOS.[9,10] However, these reviews were limited by the small sample sizes of older RCTs and lacked the power to detect any differences in clinical outcomes. A Cochrane meta-analysis from 2020 could not provide any implications for practice and highlighted the need for well-powered RCTs to provide more reliable results.[8] Accordingly, with the addition of 2 large multicenter RCTs,[11,25] our review provided more robust evidence to support the use of perioperative corticosteroid therapy in pediatric cardiac surgery.

Postoperative LCOS is a frequent complication following congenital cardiac surgery, with a reported incidence of 25% to 60%.[29] It is associated with significant morbidity and mortality.[30,31] In this context, our finding of a reduced risk of LCOS with corticosteroid therapy is promising and has not been observed in any meta-analysis or individual RCT before.[10,11,20,26] Furthermore, a higher incidence of reoperations in the control group is likely also linked to the higher incidence of LCOS in this group prompting the need to undertake reparative re-exploration in such cases.

Postoperative LCOS is a frequent complication following congenital cardiac surgery, with a reported incidence of 25% to 60%.[29] It is associated with significant morbidity and mortality as well as a significant risk for reoperation due to the need to undertake surgical exploration for bleeding sources or reparative re-exploration.[30,31] Our study found a significantly lower risk of LCOS and reoperation for bleeding with corticosteroid therapy, which has not been observed in prior meta-analyses or individual RCTs.[10,11,20,26] Given the close interaction and association of the 2, the low risk of reoperation may go hand-in-hand with the low incidence of LCOS.

Regarding safety, corticosteroid use resulted in higher postoperative glucose levels leading to an increased requirement for insulin. This is consistent with known side effects of corticosteroids and can be appropriately managed with close monitoring and insulin therapy as needed. There was no increase in other adverse events, including infection, AKI, neurologic events, and arrhythmia.

It is important to consider the limitations of our analysis. The disproportionate postoperative use of corticosteroids in the control group in trials could impede the overall validity of our results.[32] Moreover, despite pooling a large cumulative sample size, our meta-analysis was still underpowered for most clinical outcomes assessed as indicated in our GRADE assessment. Furthermore, the RCTs on this topic have exhibited considerable variabilities in the trial protocol, such as differences in the ages of patients, the type of corticosteroid administered, the timing of administration, dosage utilized, duration of CPB, and center-based perioperative practices that contributed to heterogeneity in our meta-analysis. We mitigated this by conducting subgroup analyses suggesting that corticosteroids' benefits may be restricted to hydrocortisone and the neonatal population. However, these findings should be interpreted cautiously as subgroup comparisons are observational. In addition, some subgroups were limited due to small sample sizes, as only a few trials met the eligibility criteria for those subgroups. Therefore, further large-scale well-powered RCTs are required to establish definitive benefits of corticosteroid therapy and investigate subpopulations of interest.

In conclusion, while our meta-analysis did not achieve statistical significance for reduced mortality with corticosteroid use in pediatric cardiac surgery, the shorter MV duration, reduced incidence of postoperative LCOS, and reoperation for bleeding all suggest substantial clinical benefits of their use. These findings are important, especially given the challenges of conducting large trials in this patient population. However, further large-scale RCTs with strict trial protocols to mitigate the influence of institutional perioperative practices are still needed to confirm these findings and determine the optimal agent, dosing, and patient selection for corticosteroid therapy in pediatric cardiac surgery.

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Patient consent for publication

Not required.

Ethics approval

Not applicable.

Disclosures

The authors report no relationships that could be construed as a conflict of interest.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Huzaifa Ahmad Cheema: Conceptualization, Writing – original draft, Project administration, Methodology, Formal analysis. **Arsalan Ali Khan:** Methodology, Data curation, Formal analysis, Writing – original draft. **Awab Hussain Ahmad:** Methodology, Data curation, Formal analysis, Writing – original draft. **Abdullah Ali Khan:** Methodology, Data curation, Writing – original draft. **Amna Khalid:** Writing – original draft, Formal analysis. **Abia Shahid:** Conceptualization, Methodology, Validation. **Alaa Hamza Hermis:** Validation, Writing – review & editing. **Ali Syed:** Validation, Writing – review & editing. **Neha Bansal:** Validation, Writing – review & editing. **Koichi Yuki:** Validation, Writing – review & editing. **Sunil J. Ghelani:** Validation, Writing – review & editing, Supervision. **Sourbha S. Dani:** Writing – review & editing, Supervision, Methodology, Project administration.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.09.006.

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