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Prophylactic corticosteroids for paediatric heart surgery with cardiopulmonary bypass (Review)

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[Intervention Review]

Prophylactic corticosteroids for paediatric heart surgery with cardiopulmonary bypass

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ABSTRACT

Background

Corticosteroids are routinely given to children undergoing cardiac surgery with cardiopulmonary bypass (CPB) in an attempt to ameliorate the inflammatory response. Their use is still controversial and the decision to administer the intervention can vary by centre and/or by individual doctors within that centre.

Objectives

This review is designed to assess the benefits and harms of prophylactic corticosteroids in children between birth and 18 years of age undergoing cardiac surgery with CPB.

Search methods

We searched CENTRAL, MEDLINE, Embase and Conference Proceedings Citation Index-Science in June 2020. We also searched four clinical trials registers and conducted backward and forward citation searching of relevant articles.

Selection criteria

We included studies of prophylactic administration of corticosteroids, including single and multiple doses, and all types of corticosteroids administered via any route and at any time-point in the perioperative period. We excluded studies if steroids were administered therapeutically. We included individually randomised controlled trials (RCTs), with two or more groups (e.g. multi-drug or dose comparisons with a control group) but not 'head-to-head' trials without a placebo or a group that did not receive corticosteroids. We included studies in children, from birth up to 18 years of age, including preterm infants, undergoing cardiac surgery with the use of CPB. We also excluded studies in patients undergoing heart or lung transplantation, or both; studies in patients already receiving corticosteroids; in patients with abnormalities of the hypothalamic-pituitary-adrenal axis; and in patients given steroids at the time of cardiac surgery for indications other than cardiac surgery.

Data collection and analysis

We used the Covidence systematic review manager to extract and manage data for the review. Two review authors independently assessed studies for inclusion, extracted data, and assessed risks of bias. We resolved disagreements by consensus or by consultation with a third review author. We assessed the certainty of evidence with GRADE.

Main results

We found 3748 studies, of which 888 were duplicate records. Two studies had the same clinical trial registration number, but reported different populations and interventions. We therefore included them as separate studies. We screened titles and abstracts of 2868 records and reviewed full text reports for 84 studies to determine eligibility. We extracted data for 13 studies. Pooled analyses are based on eight studies. We reported the remaining five studies narratively due to zero events for both intervention and placebo in the outcomes of interest. Therefore, the final meta-analysis included eight studies with a combined population of 478 participants.

There was a low or unclear risk of bias across the domains. There was moderate certainty of evidence that corticosteroids do not change the risk of in-hospital mortality (five RCTs; 313 participants; risk ratio (RR) 0.83, 95% confidence interval (CI) 0.33 to 2.07) for children undergoing cardiac surgery with CPB. There was high certainty of evidence that corticosteroids reduce the duration of mechanical ventilation (six RCTs; 421 participants; mean difference (MD) 11.37 hours lower, 95% CI -20.29 to -2.45) after the surgery. There was high-certainty evidence that the intervention probably made little to no difference to the length of postoperative intensive care unit (ICU) stay (six RCTs; 421 participants; MD 0.28 days lower, 95% CI -0.79 to 0.24) and moderate-certainty evidence that the intervention probably made little to no difference to the length of the postoperative hospital stay (one RCT; 176 participants; mean length of stay 22 days; MD -0.70 days, 95% CI -2.62 to 1.22). There was moderate certainty of evidence for no effect of the intervention on all-cause mortality at the longest follow-up (five RCTs; 313 participants; RR 0.83, 95% CI 0.33 to 2.07) or cardiovascular mortality at the longest follow-up (three RCTs; 109 participants; RR 0.40, 95% CI 0.07 to 2.46). There was low certainty of evidence that corticosteroids probably make little to no difference to children separating from CPB (one RCT; 40 participants; RR 0.20, 95% CI 0.01 to 3.92). We were unable to report information regarding adverse events of the intervention due to the heterogeneity of reporting of outcomes.

We downgraded the certainty of evidence for several reasons, including imprecision due to small sample sizes, a single study providing data for an individual outcome, the inclusion of both appreciable benefit and harm in the confidence interval, and publication bias.

Authors' conclusions

Corticosteroids probably do not change the risk of mortality for children having heart surgery using CPB at any time point. They probably reduce the duration of postoperative ventilation in this context, but have little or no effect on the total length of postoperative ICU stay or total postoperative hospital stay. There was inconsistency in the adverse event outcomes reported which, consequently, could not be pooled. It is therefore impossible to provide any implications and policy-makers will be unable to make any recommendations for practice without evidence about adverse effects. The review highlighted the need for well-conducted RCTs powered for clinical outcomes to confirm or refute the effect of corticosteroids versus placebo in children having cardiac surgery with CPB. A core outcome set for adverse event reporting in the paediatric major surgery and intensive care setting is required.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of corticosteroids for preventing inflammation in children who undergo heart surgery involving a heart-lung machine?

Why is this question important?

Children who are born with a heart defect, or who develop heart disease after birth, may need heart surgery. To operate, surgeons often need to stop the heart and lungs temporarily. To keep the child alive, they use a heart-lung machine that takes over the work of the heart and lungs. The machine adds oxygen to the blood, removes carbon dioxide from it, and pumps the blood back into the child's body.

We know that heart surgery involving a heart-lung machine causes inflammation across the body. This can cause complications ranging from low blood pressure to major organ dysfunction. In some cases, patients may die.

Corticosteroids (a type of anti-inflammation medicine) have been widely used to prevent inflammation in children who undergo heart surgery that requires a heart-lung machine, but their benefits and risks are unclear. To find out whether they prevent inflammation, and whether they are associated with any unwanted effects (such as poor wound healing, increased risk of infection or increased risk of death), we reviewed the evidence from research studies.

How did we identify and evaluate the evidence?

First, we searched the medical literature for randomized controlled studies (studies in which people are randomly divided into different treatment groups), because these studies provide the most robust evidence about the effects of a treatment. We then compared the results and summarised the evidence from all the studies. Finally, we assessed how certain the evidence was. To do this, we considered factors

such as the way studies were conducted, study sizes, and consistency of findings across studies. Based on our assessments, we categorised the evidence as being of very low, low, moderate or high certainty.

What did we find?

We found 13 studies that involved a total of 1087 children. The studies lasted for between 14 months and 30 months (duration was not reported for seven studies). Three corticosteroids were investigated: methylprednisolone (five studies), hydrocortisone (two studies) and dexamethasone (six studies). The studies compared these corticosteroids against a placebo (medicine that is exactly the same apart from it does not have the active medicine in it).

The evidence shows that:

- corticosteroids probably make little or no difference to the number of children who die in hospital after surgery (five studies, 313 children (participating in the studies), moderate-certainty evidence);

- corticosteroids probably make little or no difference to the number of children who die from any cause (five studies, 313 children, moderate-certainty evidence) or from heart and circulation problems specifically (three studies, 109 children, moderate-certainty evidence) at the longest follow-up time after surgery;

- corticosteroids may make little or no difference to whether children are taken off the heart-lung machine after surgery (one study, 40 children, low-certainty evidence).

- corticosteroids reduce the number of hours for which children need a breathing machine (six studies, 421 children, high-certainty evidence);

- corticosteroids make little or no difference to the length of time children spend in the intensive care unit (six studies, 421 children, high-certainty evidence);

- corticosteroids probably make little or no difference to the total length of time children spend in hospital after surgery (one study, 176 children, moderate-certainty evidence).

It is unclear whether corticosteroids are associated with non-fatal unwanted effects because the studies did not report on unwanted effects consistently.

What does this mean?

Giving corticosteroids to children who have heart surgery that requires a heart lung-machine:

- probably makes little or no difference to the number who die after surgery at any point or from any cause;

- may make little to no difference to whether children are taken off the heart-lung machine after surgery;

- probably reduces the length of time spent on the breathing machine after surgery, but this does not lead to a shorter stay in the intensive care unit or hospital.

Future studies need to collect information on non-fatal unwanted effects in a standardised way, so that we can evaluate the risks of corticosteroids.

How-up-to date is this review?

The evidence in this Cochrane Review is current to June 2020.

Summary of findings 1. Glucocorticoid compared to placebo for paediatric heart surgery with cardiopulmonary bypass

Glucocorticoid compared to Placebo for paediatric heart surgery with cardiopulmonary bypass

Patient or population: Children having heart surgery with cardiopulmonary bypass
Setting: Hospitals
Intervention: Glucocorticoid
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with glucocorticoid				
In-hospital postoperative mortality	Study population		RR 0.83 (0.33 to 2.07)	313 (5 RCTs)	⊕⊕⊕⊖ MODERATE[1]	8 studies had zero events in both arms of the study. Note that these are the same studies as reported all-cause mortality at longest follow-up.
	68 per 1,000	48 per 1,000 (20 to 116)				
Duration of postoperative mechanical ventilation	The mean duration of postoperative mechanical ventilation was 78.2 Hours	MD 11.37 Hours lower (20.29 Hours lower to 2.45 Hours lower)	-	421 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Length of postoperative ICU stay	The mean length of postoperative ICU stay was 7.67 Days	MD 0.28 Days lower (0.79 lower to 0.24 higher)	-	421 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Length of postoperative hospital stay	The mean length of postoperative hospital stay was 22 Days	MD 0.7 Days lower (2.62 lower to 1.22 higher)	-	176 (1 RCT)	⊕⊕⊕⊖ MODERATE[2]	
All-cause mortality at longest follow-up (longest follow-up was "in-hospital")	68 per 1,000	48 per 1,000 (20 to 116)	RR 0.83 (0.33 to 2.07)	313 (5 RCTs)	⊕⊕⊕⊖ MODERATE[1]	8 studies had zero events in both arms of the study. Note that these are the same studies as reported in-hospital postoperative mortality.

Cardiovascular mortality at longest follow-up (longest follow-up was "in-hospital")	93 per 1,000	37 per 1,000 (6 to 228)	RR 0.40 (0.07 to 2.46)	109 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3]
Failure to separate from CPB	100 per 1,000	20 per 1,000 (1 to 392)	RR 0.20 (0.01 to 3.92)	40 (1 RCT)	⊕⊕⊖⊖ LOW [2, 4]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

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

1Downgraded by one level for imprecision due to small sample sizes.
2Downgraded by one level for imprecision due to small sample size and only one study.
3Downgraded by one level for imprecision due to inclusion of both appreciable benefit and harm in the confidence interval.
4Downgraded by one level for publication bias where other studies excluded these patients from their analysis.

BACKGROUND

Description of the condition

Paediatric heart surgery outcomes have improved markedly over time as a result of marginal gains in training, technology and safety systems (Brown 2015; Hoashi 2015; Jacobs 2016; NICOR 2016). This improvement has been particularly notable in the last 20 years: the publication of heart surgery outcomes after the Kennedy Inquiry in the UK has been associated with a large increase in survival for risk-adjusted surgery (Kennedy 2001; Grant 2013). This has been mirrored worldwide (Brown 2015; Hoashi 2015; Jacobs 2016). One area where there is still controversy is corticosteroid use. Paediatric heart surgery with the use of cardiopulmonary bypass (CBP) results in a systemic inflammatory response. Corticosteroids have been widely used to mitigate the potentially deleterious effects of this response. The surgical intervention for which corticosteroids are used includes a variety of surgeries performed on the heart and great vessels. In most cases, this procedure aims to correct congenital heart diseases (i.e. heart malformations with which the child is born). In most cases (78% in the UK) (NICOR 2016), surgery will take place with the use of CBP, also known as the 'heart-lung machine.' Cannulae are placed in the child's major blood vessels and blood is channeled out of the body, oxygen is added, carbon dioxide is removed and the blood is then pumped back to the child's body. This allows the heart to be stopped and emptied of blood, which allows the surgeon to operate in a bloodless field on a non-beating heart (Barry 2015). As a result, there is activation of white blood cells and platelets, as well as coagulation cascades (Tarnok 2001), with the end signalling due to cytokines. Endothelial permeability increases and parenchymal damage by free radicals occurs (Fudulu 2016; Pesonen 2016). Fluid leaks out of the circulation and into the tissues, blood vessels vasodilate, hypovolaemia occurs and thus blood pressure drops. Many of the complications of cardiac surgery, including multi-organ failure and death, result from these mechanisms (Huffmyer 2015). Nevertheless, the impact of prophylactic corticosteroids on clinical outcomes following heart surgery on children remains unclear (Pasquali 2010; Keski-Nisula 2013).

Description of the intervention

Corticosteroids are hormones produced by the adrenal glands of all mammals. In humans, the naturally-occurring corticosteroid is called cortisol (hydrocortisone) (Gibbison 2013). Corticosteroids, at a molecular level, are composed of a steroid backbone plus various modifications to side-chains which can change the activity of the molecule. These modified side-chains are exploited by drug manufacturers to modify the different properties of corticosteroids. Corticosteroids are fat-soluble and therefore can pass freely through cell walls to bind to their receptors, which are found inside the target cells. Once they bind to their receptor, they travel into the cell nucleus and act as a transcription factor, changing the expression of cellular proteins (Gibbison 2013). Synthetic and naturally-occurring corticosteroids can be given either before, during or after cardiac surgery to elicit the beneficial effects described in the next section (Toledo-Pereyra 1980; Pasquali 2010; Keski-Nisula 2015). In this context, they are usually given as intravenous drugs and may be given as a bolus dose or by infusion. A variety of different steroid drugs are given. Frequently given drugs include dexamethasone (Lerzo 2011), methylprednisolone (Pasquali 2012), and hydrocortisone (Robert 2015). The dose given in this context is often equivalent to 10 to 20 times the total daily amount produced by adrenal glands in normal health.

How the intervention might work

Corticosteroids have several properties that make them attractive to give during the cardiac surgical perioperative period, their anti-inflammatory potential being their most desired feature. Cardiac surgery, with or without the use of CPB, causes systemic inflammation by the earlier-described mechanisms. This leads to poor perfusion which, coupled with the effects of inflammatory mediators that impact directly on the organs, can lead to organ dysfunction and potentially death (Medzhitov 2008). To the clinician, the most obvious organ dysfunction is altered haemodynamics, which is usually treated with inotropes and vasopressors postoperatively. The lungs are also frequently affected: the fluid that moves out of the vessels and into the lung tissue and alveoli (air spaces) can have a negative impact on ventilation and oxygenation, thus increasing the need for mechanical ventilatory support. Many studies have shown that corticosteroids reduce the concentrations and activity of inflammatory mediators after cardiac surgery and increase the concentrations of anti-inflammatory mediators, both locally in the heart and systemically in the circulating plasma (Keski-Nisula 2013; Graham 2014; Dreher 2015; Amanullah 2016). Inducing a shift of the inflammatory balance towards the anti-inflammatory reaction is thought, by extrapolation, to reduce capillary leak, vasodilatation and organ dysfunction. Corticosteroids act directly to vasoconstrict arterioles, as well as increasing salt and water retention in the kidney. These properties can improve blood pressure and, potentially, organ perfusion in the short- and medium-term. They also increase blood glucose levels by breaking down fats, proteins and carbohydrates into their constituent building blocks, which can be used for cellular energy.

Why it is important to do this review

Many corticosteroid studies are powered for and assess surrogate outcomes, such as inflammatory mediator levels, rather than objective clinical outcomes. Corticosteroids have several deleterious effects, which are traded off against the potentially beneficial effects outlined above. An increase in blood glucose, beneficial with respect to cellular energy, is associated with less favourable outcomes after cardiac surgery (Pasquali 2010). In the critically ill, corticosteroids impair wound healing and cause immunosuppression, which may allow secondary infections to develop (Pasquali 2012). Several studies also suggest that giving high-dose corticosteroids to a child may impair long-term cognitive development (Gibson 1993; Shinwell 2000; Yeh 2004). The neonatal population represents a group of particular interest, as the evidence for corticosteroid use has been inconclusive, and has possible life-long harms. Despite the lack of certainty over its risks and benefits, its use is still common practice in many centres. There is no consensus about whether or not to give corticosteroids (Fudulu 2018), nor is there consensus about the type of corticosteroids, dose regimens or timing of when they may be beneficial, e.g. preoperatively versus intraoperatively versus postoperatively. There are no national or international guidelines pertaining to perioperative corticosteroid use in the paediatric cardiac surgery population. Practice varies both among and within institutions; patients in one hospital may or may not receive corticosteroids, depending on the treating clinician.

OBJECTIVES

To assess the benefits and harms of prophylactic corticosteroids in children between birth and 18 years of age undergoing cardiac surgery with CPB.

METHODS

Criteria for considering studies for this review

Types of studies

We included individually randomised controlled trials (RCTs), including trials with more than two groups (e.g. multi-drug or dose comparisons with a control group) but not 'head-to-head' trials without a placebo or group not receiving corticosteroids. We specified in our review protocol that if we found any cross-over randomised studies, we would include only the initial period in our analyses. This Cochrane Review examines the effect of prophylactic corticosteroids in the perioperative period. It would be extremely difficult or impossible to design a crossover study reporting clinical outcomes examining this intervention. As such, we did not expect to find these. We excluded cluster-randomised controlled trials (cRCTs). They would be subject to significant bias in this context because the perioperative protocols and workloads would differ greatly among centres. In cRCTs, participants' characteristics might appear to be well-matched between groups but other factors, e.g. surgical techniques and postoperative care, would not. We included studies irrespective of their publication status.

We considered including large, published registry studies as well as individually randomised RCTs, but there is likely to be a critical risk of confounding in these study groups. The factors that cause clinicians to prescribe steroids prophylactically are not captured due to the difficulty in defining and documenting those reasons. Also, publications arising from registries have reported the same outcomes as reported in RCTs (e.g. mortality and hospital length of stay). They would thus duplicate evidence for an outcome domain of interest, but the effect estimate would have lower certainty. There would be more justification in including such studies if they reported rare or long-term outcomes such as cognitive function, which would complement outcomes reported in RCTs in an important way (Reeves 2013).

Types of participants

We included RCTs that recruited populations of children, from birth up to 18 years of age, including preterm infants undergoing cardiac surgery with the use of CPB. We excluded studies that included any participants with any of the following co-morbidities or characteristics.

- Undergoing heart or lung transplantation, or both
- Already being treated with corticosteroids
- With abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis
- Given steroids at the time of cardiac surgery for indications other than cardiac surgery (e.g. allergy, bronchoconstriction)

If findings were reported for an eligible subset of the trial population, we included the findings for the eligible subset. If any study included a subset of eligible participants but did not report findings for the eligible subset, we contacted the study authors to obtain patient-level data or aggregated data for the eligible subset. If this was not possible, then we included a study if 80% or more of the participants satisfied our eligibility criteria. We set this threshold on the assumption that up to 20% of ineligible participants would not markedly bias the average estimate. We recognise that this rule represents an uncertain compromise. However, we believed at the outset that the number of potential studies (and therefore participants) was likely to be small. This approach trades off the risk of a slightly biased answer against an answer too imprecise to be useful.

Types of interventions

Corticosteroids had to be administered prophylactically, i.e. in anticipation of adverse effects of cardiac surgery, for an RCT to be eligible. The corticosteroids could have been administered at any point in the preoperative, intraoperative or postoperative period, but the time-point and regimen must have been prespecified and given to all eligible participants randomised to the intervention group (apart from protocol deviations). We included studies that administered single or multiple doses and any type of corticosteroids administered by any route. Corticosteroid drugs considered were: hydrocortisone, dexamethasone, prednisolone, prednisone, methylprednisolone plus any other existing drugs or those in development.

We excluded studies that evaluated the effectiveness of 'rescue' corticosteroids (i.e. given in response to a clinical deterioration rather than prophylactically). However, we included studies that evaluated prophylactic corticosteroids and that allowed for 'rescue' corticosteroids to be given to treat patients who deteriorated.

We included trials that compared any corticosteroid with placebo or usual care without the use of corticosteroids. We also included multi-group studies comparing multiple doses, drugs or regimen of corticosteroids against a placebo/no corticosteroids control.

Types of outcome measures

Reporting one or more of the outcomes of interest to the review was not an inclusion criterion for a trial to be included in the review. We decided study eligibility strictly according to the eligibility of the population studied and the intervention evaluated.

Primary outcomes

- In-hospital, postoperative mortality
- Duration of postoperative mechanical ventilation (days)

An initial scoping search identified relatively few RCTs with relatively small numbers of participants. There was the possibility that there would not be sufficient power when the data were pooled to detect or exclude a clinically important difference in postoperative mortality, due to the low baseline mortality rate. Therefore, we included a second, continuous primary outcome which, if reported for a similar number of participants, would have greater power. Postoperative mechanical ventilation is an important outcome due to the risk of complications it confers, both directly attributable due to the intervention itself and indirectly, because a patient who is mechanically ventilated must be in treatment on an intensive care unit (a proxy marker for critical illness).

Secondary outcomes

- Length of postoperative intensive care unit stay

- Length of postoperative hospital stay
- All-cause mortality at longest follow-up
- Cardiovascular mortality at longest follow-up
- Duration of postoperative inotropes/vasopressors
- Failure to separate from cardiopulmonary bypass
- Adverse events

There is little consistency about the adverse events attributed to steroid use that clinicians regard as important in terms of both type of adverse event and the definitions and thresholds for reporting. Therefore, the adverse events that are reported by clinical trials are not consistent. They include outcomes such as infection, hyperglycaemia and poor wound healing. Such outcomes have never been universally defined. We anticipated that it might not be possible to synthesise adverse event data across the RCTs or even to tabulate event frequencies consistently across trials. We did, however, collect all available data and reviewed them. Where appropriate (similar definitions across studies) we attempted to pool this and report it in the meta-analysis.

Search methods for identification of studies

Electronic searches

We identified potentially eligible trials by systematic searches of the following bibliographic databases on 11 June 2020:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library via CRS Web
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 9 June 2020)
- Embase (Ovid, 1974 to 10 June 2020)
- CPCI-S (Conference Proceedings Citation Index-Science) on the Web of Science (Clarivate Analytics, 1990 to 11 June 2020)

We adapted the preliminary search strategy for MEDLINE (Ovid) (Appendix 1) for use in the other databases. We applied the Cochrane sensitivity-maximising RCT filter to MEDLINE (Ovid) (Lefebvre 2011), and adaptations of it to the other databases, except CENTRAL.

We also conducted a search in January 2020 of ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/), ISRCTN Registry (www.isrctn.com) and the European Union Clinical Trials Register (www.clinicaltrialsregister.eu) for ongoing or unpublished trials.

We searched all databases from 2000 to the present without any restriction on language of publication or publication status. We excluded studies before 2000 because 30-day mortality has declined remarkably in paediatric cardiac surgery (by around one-quarter to one-half in the UK, the USA and Japan) (Brown 2015; Hoashi 2015; Jacobs 2016; NICOR 2016). Studies before 2000 would be weighted disproportionately because of the higher death rates. Changes in clinical practice also make older studies less relevant to current practice. See also Sensitivity analysis.
We did not perform a separate search for adverse effects of corticosteroid use in paediatric cardiac surgery. We expected the search strategy to capture studies reporting beneficial or detrimental outcomes with equal likelihood.

Searching other resources

We checked the reference lists of all included studies, and any relevant systematic reviews identified, for additional references to RCTs, and included them if eligible. We also examined any relevant retraction statements and errata that applied to included studies. We made every attempt to contact study authors for any missing data.

Data collection and analysis

Selection of studies

Two review authors (AWLS, KIAM) independently screened titles and abstracts retrieved by the literature searches to identify potentially eligible studies, and coded them as either ‘obtain full text' (eligible or potentially eligible/unclear) or ‘do not obtain full text.' If there were any disagreements, a third review author arbitrated (BCR). We retrieved the full-text study reports and two review authors (BG, JCVS) screened full-text articles to identify studies for inclusion. We listed all studies that were excluded after full-text assessment with reasons for their exclusion. We resolved any disagreement through discussion. We identified duplicate reports of studies and collated multiple reports of the same study so that each study was the unit of interest in the review.

Data extraction and management

We used the Covidence systematic review manager for study screening and data extraction (Covidence 2020). Two review authors (DPF, JCVL) independently extracted study characteristics from included studies. Any differences in data extraction were resolved by a third review author (BG). The original extraction files were retained and a third consensus file produced with discrepancies resolved. We extracted the following data.

- Methods: the total duration of the study, number of study centres and location, study setting, withdrawals and date of the study
- Participants: the number randomised, the number lost to follow-up/withdrawn, number analyzed, mean age, age range, sex, inclusion criteria and exclusion criteria. Where reported, we extracted the underlying cardiac pathology.
- Interventions: intervention(s) and comparator
- Outcomes: the primary and secondary outcomes of interest to the review, and time points at which they were reported

One review author (BG) transferred data into the Review Manager 5 (RevMan 5) file (RevMan 2014) and double-checked that the data was entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two review authors (DPF, JCVL) independently assessed the risk of bias for each included study using the ‘Risk of bias' (RoB) tool Version 1.0 as described in Cochrane methods for individually RCTs (Higgins 2016; see Types of studies). We resolved any disagreements by discussion or by involving another review author (BG, BCR). We assessed the risk of bias according to the following domains.

- Selection bias (random sequence allocation; allocation concealment)
- Reporting bias (selective outcome reporting)

- Performance bias (blinding of participants and personnel)
- Detection bias (blinding in outcome assessment)
- Attrition bias (incomplete outcome data)
- Other sources of bias

For each outcome, the review authors judged the studies against the criteria in the tool (supported by quotes from the study where possible) and classified the risk of bias in each domain as high, low or unclear. We summarised the risk of bias judgements across different studies for each of the domains and overall. We entered review authors' risk of bias judgements into Covidence, including free-text explanations.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

We planned to analyze dichotomous data as odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (CIs) and continuous data as mean difference (MD) or standardized mean difference (SMD) values with 95% CIs. During the review, we preferred RRs as we could calculate these from reported numerators and denominators. We used MD for all continuous outcomes.

One study (Graham 2019) appropriately reported continuous outcomes as medians and interquartile ranges. We transformed these into means and standard deviations to allow assimilation of numbers, using the method of Hozo, Djulbegovic and Hozo (Hozo 2005). Had the numbers of studies doing this correctly been higher, we would have implemented a sensitivity analysis, excluding studies reporting these as a median. As this affected only one study, we did not conduct a sensitivity analysis.

Unit of analysis issues

If any multi-arm studies met the inclusion criteria of this review, then we planned to merge studies where the participant had received the intervention of prophylactic corticosteroids (regardless of specific corticosteroid or dose). Data for the same outcome with similar follow-up times were merged.

Dealing with missing data

We applied standard statistical formulae to calculate missing parameter estimates, wherever possible (e.g. using the RevMan 5 calculator to compute the standard deviation of an estimate from other report information such as the CI or exact P values). We attempted to contact investigators to verify key study characteristics and obtain missing numerical outcome data (e.g. when a study was identified only as an abstract).

Assessment of heterogeneity

We planned to use the I^2 statistic to describe heterogeneity among the treatment effects included in each analysis. We followed the guidance outlined in Section 9.5.2 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017)

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity*
- 50% to 90%: may represent substantial heterogeneity*
- 75% to 100%: considerable heterogeneity

*The importance of the observed value of the I^2 statistic depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity. If our I^2 statistic value indicated that heterogeneity were a possibility and either the Tau^2 were greater than zero or the P value were low (less than 0.10), heterogeneity may be have been due to a factor other than chance.

If observed, we intended to report substantial heterogeneity and explore possible causes by prespecified subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

For all analyses in which treatment effects from 10 or more RCTs were synthesised, we planned to create and examine a funnel plot to explore possible small study biases for the primary outcomes.

Data synthesis

We performed meta-analyses only where this was meaningful i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

We used random-effects meta-analytic models. We were evaluating a drug treatment, the effects of which should, in principle, be homogeneous; and thus we could have used a fixed-effect model. However, given that we evaluated prophylactic corticosteroids, irrespective of specific drug, dose or timing, differences in treatment regimen could have plausibly introduced heterogeneity among reported treatment effects. A random-effects model tends to make a pooled estimate more uncertain.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analysis where there was sufficient data:

- Age: from birth to ≤ 30 days and from 30 days to 18 years
- Route of administration (intravenous or oral)
- Timing of administration (preoperative, intraoperative or postoperative).

Sensitivity analysis

We intended to carry out sensitivity analyses to assess the robustness of the results for the following categories:

- Only including studies with a low risk of bias using the domains from the RoB 1.0 tool.
- If we believed that there is large amount of missing data that would have lead to serious bias, then we planned to explore the impact of including such studies by a sensitivity analysis (Dealing with missing data).

As described above, the improvement in cardiac surgery mortality over the last two decades may have lead to a decrease in mortality for the control during the period specified by our search strategy (year 2000 to present, noting that surgery may have been done considerably earlier in a study published in 2000). If we observed this relationship, a further sensitivity analysis would have considered the impact of down-weighting older studies (e.g. 2000 to 2005 versus 2006 to present) according to the mortality in the control group. To ensure that this sensitivity analysis

had reasonable power, we would have needed to consider the distribution over time of participants in included RCTs as well as changes in mortality since 2000 to set a cut-off for down-weighting some studies. We considered that a demarcation between 2000 to 2005 and 2006 to present would be reasonable.

We did not carry out the planned sensitivity analyses because there was insufficient information to justify them. The further planned sensitivity analysis would have been based on down-weighting older studies, which again we judged not justifiable given the small number of studies, and the fact that two-thirds of studies (contributing over 80% of the weight in the primary analysis) were carried out in the last 10 years.

Reaching conclusions

We based our conclusions only on findings from the quantitative analyses of included studies and avoided making recommendations for practice. Similarly, implications for future research that we propose describe research questions based on the findings or absence of findings in relation to perceived clinical priorities. They also outline what the remaining uncertainties are in the area.

Summary of findings and assessment of the certainty of the evidence

We created a Summary of findings (SoF) table ('Summary of findings 1') using the following outcomes.

- In-hospital, postoperative mortality
- Duration of postoperative mechanical ventilation
- Length of postoperative intensive care unit stay
- Length of postoperative hospital stay
- All-cause mortality at longest follow-up
- Cardiovascular mortality at longest follow-up
- Duration of postoperative inotropes/vasopressors
- Failure to separate from cardiopulmonary bypass

The above list does not include an explicit primary harm outcome for the reasons described above (see Types of outcome measures). Nevertheless, important harms might be expected to be reflected in the outcomes that steroids are hypothesised to benefit.

We used the five GRADE considerations (study limitations, inconsistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence derived from studies contributing data to meta-analyses for our prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017) using GRADEpro software (GRADEpro 2015). There was only one comparison (corticosteroids versus placebo) for which we generated an SoF table ('Summary of findings 1'). We used footnotes to justify all decisions to downgrade the certainty of the evidence.

We extracted study data, formatted our comparisons in data tables and prepared our SoF table ('Summary of findings 1') before writing the results and conclusions of our review.

RESULTS

Description of studies

We have presented the details of studies included in this review in the Characteristics of included studies, and reasons for exclusion in the Characteristics of excluded studies. We have detailed the status of ongoing trials in the Characteristics of ongoing studies.

Results of the search

We completed the search in June 2020. We retrieved 3748 records, of which 888 were reports of studies described in other publications (protocol papers, published conference abstracts or alternative analyses of the same trial data). Two studies that were included (Keski-Nisula 2013 and Keski-Nisula 2015) had the same clinical trial registration number, but different populations and interventions. We therefore treated them as separate studies. This led to 2868 records being screened, of which we excluded 2771 on the basis of their titles or abstracts. We reviewed the full texts of 83 studies (in 97 references) for eligibility and deemed 68 of these ineligible (76 references).

We took forward 13 studies (in 19 published references) for data extraction and RoB assessment. Five studies had zero events in both groups for all outcomes of interest and these were excluded from the quantitative analysis, leaving eight studies in the final quantitative meta-analysis (See Characteristics of excluded studies).

Two studies (Bronicki 2000; Checchia 2003) 'overlapped' 11 participants (i.e. these participants were included in both studies). It was impossible to extract individual patient data from the studies. The corresponding author for both studies, although contacted, did not reply. Due to the small number of participants who were included in both studies and their likely small impact on the overall outcome, we treated each study as separate. We identified no studies that we could not classify as either included or excluded. The flowchart for the results of the search are presented in Figure 1.

Figure 1. PRISMA diagram

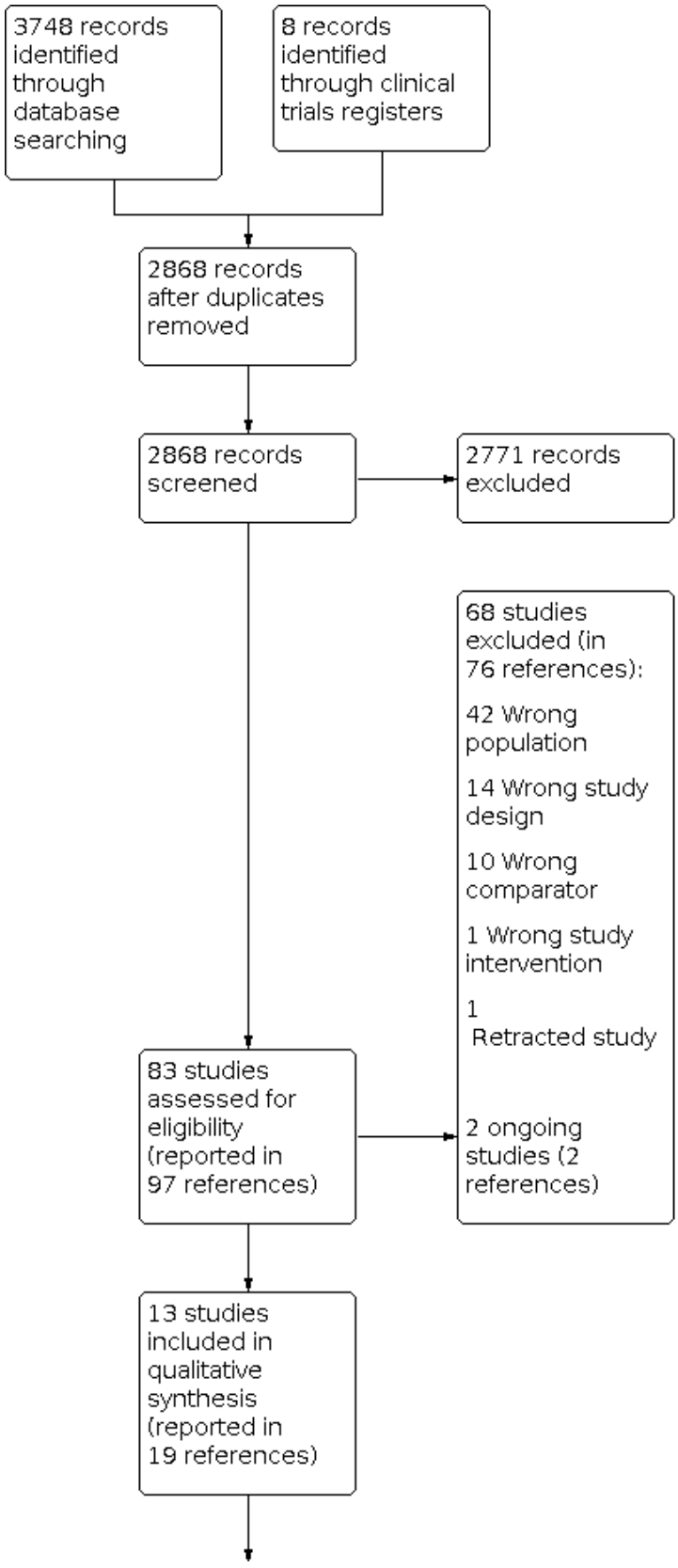
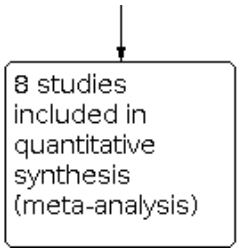


Figure 1. (Continued)



Included studies

We extracted data for 13 studies (comprising 1087 participants), although data for five studies (609 participants) were not included in the final quantitative meta-analysis due to zero event rates in both intervention and placebo groups for all the outcomes of interest. Therefore, the final meta-analysis included eight studies and a combined population of 478 participants. They covered all age ranges and where reported (in 11 studies) the mean ages were less than five years old. Similarly the sex of the participants was variably reported, at a lower frequency than age. All studies reported including male and female participants. The studies were all in secondary care (either in the operating room and/or the intensive care unit) from all areas of the world and included a range of surgical procedures (see Included studies for more detail). Most studies had small sample sizes (the largest overall had 246 participants; the largest in the meta-analysis had 190 participants; most other studies included fewer than 50 participants). Where reported, most studies were funded by non-commercial organisations. All studies gave the drug intravenously. Five studies used methylprednisolone, two used hydrocortisone and six studies used dexamethasone; all compared the drug with a placebo which, where specifically stated, was normal saline. Of the studies in the meta-analyses, four used methylprednisolone, two used hydrocortisone and two used dexamethasone. Studies administered the drug or placebo at various time-points in the perioperative process.

Excluded studies

Of the ineligible studies, 42 had the wrong population (In 40 studies, an adult population),14 had the wrong study design,10 had the wrong comparator, one had the wrong intervention and one study had been retracted. See Characteristics of excluded studies.

We identified two ongoing studies. One is recruiting participants under the age of one year undergoing cardiac surgery with CPB and receiving prophylactic methylprednisolone or placebo (STRESS 2021); this study has a target sample size of 1200. It is not scheduled to complete recruiting until early- or mid-2021.

Risk of bias in included studies

Figure 2 and Figure 3 summarise risk of bias in the included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

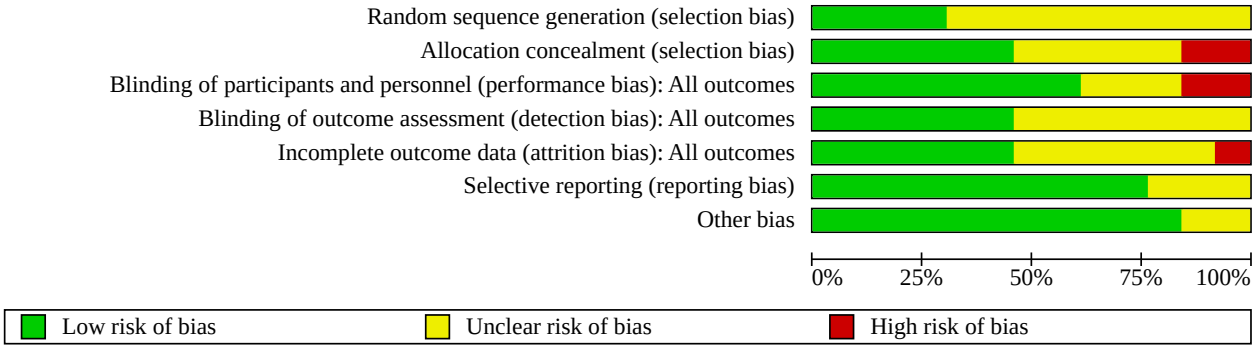
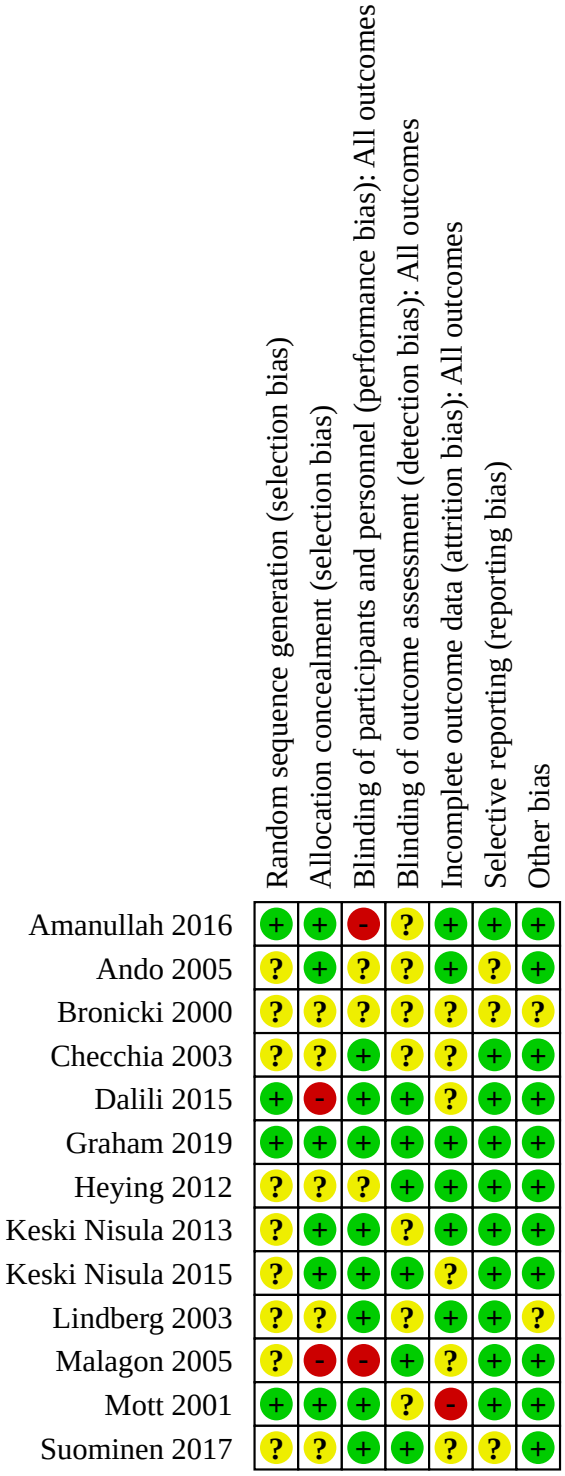


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Four of the 13 studies had a low risk of bias for random sequence generation; all others had unclear risk of bias in this domain. Six studies had a low risk of bias for allocation concealment; two studies were at high risk of bias for this domain. All others had unclear risk of bias in this domain.

Blinding

Malagon 2005 and Amanullah 2016 had a high risk of bias for blinding of participants and personnel. Eight other studies had a low risk of bias and three studies had an unclear risk of bias for this domain. We assessed six studies to be at low risk of bias for blinding of outcome assessment. The other eight studies had unclear risk of bias in this domain.

Incomplete outcome data

Mott 2001 had a high risk of bias for incomplete outcome reporting, in that participants who died after randomization or did not separate from CPB respectively were excluded. Six studies had an unclear risk of bias and six had a low risk of bias for this domain.

Selective reporting

Most of the included studies (10/13) had a low risk of bias for this domain. All others were at unclear risk of bias for this domain.

Other potential sources of bias

Eleven studies were assessed as low risk for other potential sources of bias and two were at unclear risk of bias for this domain.

Effects of interventions

See: **Summary of findings 1** Glucocorticoid compared to placebo for paediatric heart surgery with cardiopulmonary bypass

See Summary of findings 1 for the main outcomes. The small number of studies did not support use of the I^2 statistic (due to the statistic being biased under these conditions) and so this was not reported (von Hippel 2015). Although we pre-specified subgroups, we did not conduct analyses, again due to the small number of studies in each group (Higgins 2017).

In-hospital postoperative mortality

There was moderate certainty of evidence that perioperative corticosteroid changes the risk of in-hospital mortality (RR 0.83, 95% CI 0.33 to 2.07; 313 participants; five studies; moderate certainty of evidence; Analysis 1.1). We observed no visual heterogeneity in the forest plots. All studies reported this outcome, but there were zero events in both groups for eight studies, comprising 733 participants (Amanullah 2016, Ando 2005, Dalili 2015, Heying 2012, Keski Nisula 2015, Lindberg 2003; Malagon 2005; Mott 2001). Therefore, we did not include them in the meta-analysis. Five studies comprising 313 participants (Bronicki 2000, Checchia 2003, Graham 2019, Keski Nisula 2013 and Suominen 2017) were included for this outcome.

Duration of postoperative mechanical ventilation

Six studies (Ando 2005, Dalili 2015, Graham 2019, Keski Nisula 2013, Keski Nisula 2015 and Suominen 2017) were used for the meta-analysis for this outcome. There was high-certainty evidence that the intervention reduced the duration of mechanical ventilation (MD -11.37 hours, 95% CI -20.29 to -2.45; 421 participants; six studies; high certainty of evidence; Analysis 1.2). There was a small amount of observed heterogeneity in terms of the effect sizes for this outcome, but the direction of the effect was similar in all.

Length of postoperative ICU stay

There was high-certainty evidence that the intervention probably made little to no difference to the effect on the length of postoperative ICU stay (mean length of stay 7.67 days; MD -0.28 days; 95% CI -0.79 to 0.24; 421 participants; six studies; high certainty of evidence; Analysis 1.3). There was no visual heterogeneity observed on inspection of the forest plots. The studies included for this analysis were Ando 2005, Dalili 2015, Graham 2019, Keski Nisula 2013, Keski Nisula 2015 and Suominen 2017).

Length of postoperative hospital stay

Only one study (Graham 2019) examined the effect of the intervention on length of postoperative hospital stay. There was moderate certainty of evidence that the intervention had little to no effect on this outcome (mean length of stay 22 days; MD -0.7 days, 95%CI -2.62 to 1.22; 176 participants; one study; moderate certainty of evidence; Analysis 1.4).

All-cause mortality at longest follow-up

In eight studies with 733 participants there were zero events for this outcome in both groups (Amanullah 2016, Ando 2005, Dalili 2015, Heying 2012, Keski Nisula 2015, Lindberg 2003; Malagon 2005; Mott 2001). Therefore, we did not include them in the meta-analysis. Six studies comprising 353 participants (Bronicki 2000, Checchia 2003, Graham 2019, Keski Nisula 2013 and Suominen 2017) examined the effect of the intervention on all-cause mortality at the longest follow-up. There was moderate certainty of evidence that there was probably little to no difference in this outcome between intervention and the placebo (RR 0.83, 95% CI 0.33 to 2.07; 313 participants; five studies; moderate certainty of evidence; Analysis 1.5). There was no visual heterogeneity observed on inspection of the forest plots. The longest follow-up for all included studies was "in-hospital" and is therefore the same analysis as In-hospital post-operative mortality (Analysis 1.1

Cardiovascular mortality at longest follow-up

Three studies examined cardiovascular mortality (Bronicki 2000, Keski Nisula 2013 and Suominen 2017). There was moderate certainty of evidence that the intervention probably made little to no difference in the outcome between intervention and control groups (RR 0.40, 95% CI 0.07 to 2.46; 109 participants; three studies; moderate certainty of the evidence; Analysis 1.6). There was no visual heterogeneity observed on inspection of the forest plots. The longest follow-up for this outcome was "in-hospital".

Duration of inotropes

We were unable to examine this outcome due to the variety of outcome measures that were used for reporting inotrope use.

Failure to separate from CPB

Only one study (Keski Nisula 2013) specifically reported failure to separate from CPB after randomization, with events. There was a low certainty of evidence that the intervention probably made little to no difference to the effect in this outcome (RR 0.20, 95% CI

0.01 to 3.92; 40 participants; one study; low certainty of evidence; Analysis 1.7).

DISCUSSION

Summary of main results

We found a moderate certainty of evidence that corticosteroids have any effect on the in-hospital mortality in children having heart surgery with CPB. There was high-certainty evidence that corticosteroids reduce the duration of postoperative ventilation (on average, by about 11 hours) but probably make little to no difference to the effect on the total length of postoperative ICU stay. There was also moderate-certainty evidence that corticosteroids probably made little to no difference in the outcomes of total postoperative hospital stay, all-cause mortality or cardiovascular mortality at longest follow-up. There was low certainty of evidence that corticosteroids have any effect on failure to separate from CPB. See Summary of findings 1.

We were unable to collect information regarding adverse events of the intervention due to the heterogeneity of outcomes reporting this outcome domain. The two potential short-term adverse effects of corticosteroids in this setting are hyperglycaemia and infection. There was no standardized method of reporting these outcomes and thus they could not be combined. Methods of reporting inotrope and vasopressor use were also not standardized and for this reason, could not be pooled (or even reported in a useful way).

Overall completeness and applicability of evidence

The outcomes of the meta-analysis are broadly applicable to all settings of paediatric cardiac surgery with cardiopulmonary bypass – with the caveats of reduced certainty of evidence where stated. The studies as a whole were designed using a method that was relevant to the primary outcomes of the review (i.e. mortality and duration of mechanical ventilation) and the majority of studies included in the synthesis were mainly from the USA and Northern Europe, although there were included studies from the Middle East and Asia (Dalili 2015 and Amanullah 2016). Studies investigated different drugs: methylprednisolone, hydrocortisone and dexamethasone. Many of the separate studies share authors (e.g. Bronicki 2000 / Checchia 2003 and Keski Nisula 2013 / Keski Nisula 2015 and Suominen 2017). The fact that these studies were most likely to be included in the quantitative review will tend to reduce the external validity of the results. The studies included in the meta-analysis comprised a range of cardiac surgery procedures performed with CPB in all age ranges.

Quality of the evidence

We included 13 studies (1096 participants) in the synthesis, of which 8 studies (478 participants) contributed to the quantitative synthesis. Five studies (618 participants) were excluded from the quantitative synthesis because of zero event rates in both groups for dichotomous outcomes and did not report the continuous variable outcomes. This illustrates one of the issues with the studies contained within the review; most studies were small and even when pooled, the total number of participants may not be sufficient to demonstrate a difference in mortality due to the low event rate. This issue was predicted in our protocol and therefore we included a second primary outcome (postoperative mechanical ventilation) of a continuous nature that was more likely to give us the power to answer this question. We achieved this with high certainty.

Only one study (Graham 2019) was judged as at low risk of bias across all domains. The overall uncertain risk of bias in most studies, combined with the imprecision due to the small sample sizes of studies, resulted in our downgrading of evidence for most outcomes. The exceptions to this downgrading were duration of postoperative ventilation and length of postoperative ICU stay. Therefore, our overall judgement is that, apart from the latter two outcomes, the certainty of evidence is inadequate to draw firm conclusions. Furthermore, without pooled adverse event information, there is no information on which to make risk-benefit judgments.

Potential biases in the review process

The potential sources of bias in the process of conducting the review were small. We may not have identified studies that were not in the English language but the number of such studies is likely to be very small. We searched all major databases but were not able to formally examine publication bias due to the small number of studies. Given the inconsistency of the results, it would subjectively appear that there is no important publication bias for this intervention. All relevant data were obtained, and it is unlikely that the methods used by the authors could have introduced bias.

We converted published medians and ranges within studies to means and SDs, using the method of Hozo and colleagues (Hozo 2005). We did this to allow their inclusion in the meta-analysis, instead of being limited to a narrative summary. Only one study correctly used medians for length of stay and duration of mechanical ventilation. We combined data from this study with the others that did not use medians correctly. Whilst this is an approximation, we maintain that this remains relevant, since there was only one study for which this was done. Before doing so, we consulted the Cochrane Statistical Methods Group and received support for our approach.

Agreements and disagreements with other studies or reviews

One recent systematic review and meta-analysis concerns the same intervention (Scrascia 2014). As with our review, Scrascia 2014 showed no statistical effect of corticosteroids on mortality. They also found no effect on postoperative mechanical ventilation or intensive care stay. The change in our meta-analysis towards reduced postoperative mechanical ventilation is the result of including the study by Graham 2019. Without the inclusion of this study (as in Scrascia 2014) there would be no effect of corticosteroids on the outcome. This is due to the increased precision of a large study (i.e. reducing the confidence intervals), but the point estimates reported are consistent. Graham 2019 is the only study with a low risk of bias across all domains. The results of our meta-analysis also concur with very large retrospective analyses of national databases, such as the one reported by Pasquali 2012 This analysis reported no effect of corticosteroids on mortality or length of stay outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

It is impossible to provide any implications for practice without robust adverse event information to allow the risk trade-off between benefits and harms. We are unable to do this for

corticosteroids in the context of paediatric cardiac surgery with CPB.

Implications for research

The evidence synthesised by this review for the most important outcome of mortality is uncertain due to imprecision. However, the low and declining mortality rate (Kennedy 2001; Grant 2013; Brown 2015; Hoashi 2015; Jacobs 2016) of paediatric cardiac surgery makes this outcome less useful than some composite measure of postoperative morbidity, both in the short term and long term. Our review has highlighted the need for adequately powered and well-conducted RCTs to confirm or refute the effect of corticosteroids versus placebo in children having cardiac surgery with CPB. The studies should be large enough to separately analyze the outcomes of all children, as well as the neonatal and non-neonatal populations. The studies should be powered for clinical outcomes rather than biochemical markers and would also need to collect robust adverse event information (including long-term follow-up of cognitive and educational outcomes), using a core outcome set, to allow robust decisions about their use to be made. We anticipate that the STRESS study (STRESS 2021) will have a major impact on the evidence base for this topic. This trial is due to finish recruiting in June 2021, and will include almost twice as many participants (1200) as are in our meta-analysis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amanullah 2016

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** Parallel group **Total Duration of Study:** 2 years **Number of study centres and location:** 1 centre **Study setting:** PICU **Withdrawals:** None **Study Date:** April 2010 to April 2012

Participants	**Baseline Characteristics**
	
	Corticosteroid
	
	• Age range: not reported
	• Age (mean): not reported
	• Age (median IQR), months: 31 (62)
	• Number randomised: 76
	• Number lost to follow-up/withdrawn: 11
	• Number analysed: 65
	• Underlying cardiac pathology:
	  ○ Cyanotic 29
	  ○ Acyanotic 35
	  ○ TOF 22
	  ○ VSD or combined 20
	• Sex: male 43, female 21
	
	Placebo
	
	• Age range: not reported
	• Age (mean): not reported
	• Age (median IQR), months: 48 (78)
	• Number randomised: 76
	• Number lost to follow-up/withdrawn: 12
	• Number analysed: 64

Amanullah 2016 *(Continued)*

- Underlying cardiac pathology:
  - Cyanotic 29
  - Acyanotic 36
  - TOF 25
  - VSD or combined 24
- Sex: male 41, female 24

Overall

- Age range: not reported
- Age (mean): not reported
- Age (median IQR), months: not reported
- Number randomised: 152
- Number lost to follow-up/withdrawn: 23
- Number analysed: 129
- Underlying cardiac pathology:
  - Cyanotic 58
  - Acyanotic 71
  - TOF 47
  - VSD or combined 44
- Sex: male 84, female 45

Included criteria: children between the ages of 1 month and 18 years undergoing their first elective cardiac surgery with cardiopulmonary bypass

Exclusion criteria:

PREOPERATIVELY

Children with a history of premature birth (less than 28 weeks of gestation) Compromised immune system (known immunodeficiency or use of immunomodulatory therapy)

PERIOPERATIVELY

Those who perioperatively had two or more clinical or laboratory signs of active infection that were not attributable to any other cause:

- Fever more than 100°F
- Heart rate or respiratory rate more than the normal range for age
- White blood cell count more than 15% of the upper limit of normal
- Elevated C-reactive protein level

INTRAOPERATIVELY

Patients who required cardiopulmonary bypass for more than six hours or who required a second run of cardiopulmonary bypass during the same surgery. Patients who required medically appropriate steroid therapy during this time.Those who had to be taken back to the operating room for unforeseen complications.Those who expired before the completion of the 24 hour postoperative period.

Pretreatment: nil

Interventions	Corticosteroid • Drug name: dexamethasone • Route: IV • Dose: 1 mg/kg • Timing (preoperative, intraoperative, postoperative): preoperative, intraoperative and postoperative Placebo

Amanullah 2016 *(Continued)*

- Drug name: Normal saline
- Route: IV
- Dose: not specified
- Timing (preoperative, intraoperative, postoperative): preoperative, intraoperative and postoperative

Outcomes	Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome • **Unit of measure**: hours, IQR • **Direction**: Lower is better Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome • **Notes**: They have measured inotrope scores, not duration of inotropes Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome Adverse events • **Outcome type**: Dichotomous outcome • **Data value**: Change from baseline In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome • **Direction**: Lower is better Length of postoperative hospital stay • **Outcome type**: Continuous outcome • **Direction**: Lower is better
Identification	**Sponsorship source:** University Research Council. Aga Khan University **Country:** Pakistan **Setting:** PICU **Comments:** NA **Authors name:** Muhammad M Amanullah **Institution:** The Aga Khan University **Email:** muneer.amanullah@aku.edu **Address:** Department of Surgery, The Aga Khan University Hospital, Stadium Road, PO Box 3500, Karachi 74800, Pakistan.

Amanullah 2016 *(Continued)*

Year: 2015

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer generated randomization scheme
Allocation concealment (selection bias)	Low risk	"Randomisation was carried out by an independent statistician"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Anaesthesia resident prepared the syringes"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other bias

Ando 2005

Study characteristics

Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** February 2002 to June 2004 **Number of study centres:** 1 **Study setting:** PICU - Hospital **Withdrawals:** None reported **Study date:** 2005
Participants	**Baseline characteristics** Corticosteroid • Mean age: 12.3 +/- 3.8 days • Age range: not reported • Number lost to follow-up/withdrawn: 0 • Sex: not reported

Ando 2005 *(Continued)*

- Underlying cardiac pathology (if available):
  - VSD with interrupted aortic arch 3
  - VSD with coarctation of the aorta 1
  - TAPVD 4
  - TGA 2
- Age (median): not reported
- Number randomised: 10
- Number analysed: 10

Placebo

- Mean age: 9.4+/- 4.8, days
- Age range: not reported
- Number lost to follow-up/withdrawn: 0
- Sex: not reported
- Underlying cardiac pathology (if available):
  - VSD with interrupted aortic arch 3
  - VSD with coarctation of the aorta 1
  - TAPVD 3
  - TGA 3
- Age (median): not reported
- Number randomised: 10
- Number analysed: 10

Overall

- Mean age: not reported
- Age range: not reported
- Number lost to follow-up/withdrawn: 0
- Sex: not reported
- Underlying cardiac pathology (if available):
  - VSD with interrupted aortic arch 6
  - VSD with coarctation of the aorta 2
  - TAPVD 7
  - TGA 5
- Age (median): not reported
- Number randomised: 20
- Number analysed: 20

Included criteria: neonates within 28 days after birth undergoing complete biventricular repair

Exclusion criteria: mechanical ventilation, evidence of infection, receiving more than renal dose dopamine (5mcg/kg/min), and genetic disorder or chromosomal abnormality.

Pretreatment: no statistical differences

Interventions	Corticosteroid • Drug name: Hydrocortisone sodium succinate • Time: After discontinuation of cardiopulmonary bypass • Route: IV • Dose: 0.18 mg/kg/hr for 3 days, 0.09 mg/kg/hr for 2 days, and 0.045mg/kg/hr for 2 days • Timing (preoperative, intraoperative, postoperative): infusion after CPB for 2 days Placebo • Drug name: 5% glucose solution

Ando 2005 *(Continued)*

- Time: After discontinuation of cardiopulmonary bypass
- Route: IV
- Dose: not reported
- Timing (preoperative, intraoperative, postoperative): intraoperative

Outcomes

All-cause mortality at longest follow-up

- **Outcome type**: Dichotomous outcome
- **Reporting**: Fully reported
- **Data value**: Endpoint

Length of postoperative hospital stay

- **Outcome type**: Continuous outcome
- **Reporting**: Fully reported
- **Unit of measure**: Days
- **Direction**: Lower is better
- **Data value**: Endpoint
- **Notes**: Other

Length of postoperative intensive care unit stay

- **Outcome type**: Continuous outcome
- **Reporting**: Fully reported
- **Unit of measure**: Hours
- **Direction**: Lower is better
- **Data value**: Endpoint

Duration of postoperative inotropes/vasopressors

- **Outcome type**: Continuous outcome
- **Reporting**: Fully reported
- **Direction**: Lower is better
- **Data value**: Endpoint

Duration of postoperative mechanical ventilation

- **Outcome type**: Continuous outcome
- **Reporting**: Fully reported
- **Unit of measure**: Hours
- **Direction**: Lower is better
- **Data value**: Endpoint

Failure to separate from cardiopulmonary bypass

- **Outcome type**: Dichotomous outcome
- **Reporting**: Fully reported

In-hospital postoperative mortality

- **Outcome type**: Dichotomous outcome
- **Direction**: Lower is better

Cardiovascular mortality at longest follow-up

- **Outcome type**: Dichotomous outcome

Adverse events (Hypoglycaemia, Blood glucose level g/dL)

Ando 2005 *(Continued)*

- **Outcome type**: Continuous outcome

Identification	**Sponsorship source:** none reported **Country:** Japan **Setting:** PICU **Comments:** N/A **Authors name:** Makoto Ando **Institution:** Sakakibara Heart Institute, **Email:** maando@shi.heart.or.jp. **Address:** Department of Pediatric CardiacSurgery, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu-si, Tokyo,183-0003 Japan **Year:** 2005
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	"Allocation was concealed to all clinical participants and data interpreter"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Allocation was concealed to all clinical participants and data interpreter - clinical staff may have known"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Low risk	No other bias

Bronicki 2000

Study characteristics

Methods	**Study design:** RCT **Study grouping:** Parallel group

Bronicki 2000 *(Continued)*

Duration of Study: not specified

Number of study centres: 1

Study setting: PICU

Withdrawals: unclear

Study Date: 2000

Participants

Baseline characteristics

Corticosteroid

- Age range (months): 0.9 - 96.0
- Age (mean + SD): 28 +/- 33 months
- Age (median): not reported
- Number randomised: 15
- Number lost to follow-up/withdrawn: 0
- Number analysed: 15
- Underlying cardiac pathology:
  - VSD 5
  - Arterial Switch 1
  - VSD and RV-PA conduct 1
  - Subaortic resection 1
  - TOF 1
  - Aortic valvotomy 1
  - Subaortic resection and MVR 1
  - MVR 0
  - Atrioventricular canal defect 1
  - Hemitruncus repair 0
  - Fontan 0
  - Revision of CA 0
  - VSD and RV muscle resection 1
  - ASD and RV muscle resection 1
  - sinus venosus ASD 1
- Sex: not reported

Placebo

- Age range (months): not reported
- Age (mean +SD): not reported
- Age (median): not reported
- Number randomised: not reported
- Number lost to follow-up/withdrawn: not reported
- Number analysed: not reported

Bronicki 2000 *(Continued)*

- Underlying cardiac pathology:
  - VSD 3
  - Arterial Switch 3
  - VSD and RV-PA conduct 2
  - Subaortic resection 1
  - TOF 1
  - Aortic valvotomy 0
  - Subaortic resection and MVR 0
  - mitral valve replacement 1
  - AV canal 0
  - Hemitruncus repair 1
  - Fontan 1
  - Revision of coronary artery 1
  - VSD and RV muscle resection 0
  - ASD and RV muscle resection 0
  - Sinus venosus ASD 0
- Sex: not reported

Overall

- Age range (months): not reported
- Age (mean + SD): not reported
- Age (median): not reported
- Number randomised: 29
- Number lost to follow-up/withdrawn: 0
- Number analysed: 29
- Underlying cardiac pathology:
  - VSD 8
  - Arterial Switch 4
  - VSD and RV-PA conduct 3
  - Subaortic resection 2
  - TOF 2
  - Aortic valvotomy 1
  - Subaortic resection and MVR 1
  - Mitral valve replacement 1
  - AV canal 1,
  - Hemitruncus repair 1
  - Fontan 1
  - Revision of coronary artery 1
  - VSD and RV muscle resection 1
  - ASD and RV muscle resection 1
  - Sinus venosus ASD 1
- Sex: male 17, female 12

Included criteria: children undergoing open heart surgical procedures for congenital heart defects.

Exclusion criteria: preoperative use of corticosteroids or nonsteroid anti-inflammatory agents, isolated atrial septal defect, CPB time greater than 200 minutes, and aortic cross-clamp time greater than 120 minutes.

Pretreatment: similar at baseline

Interventions	Corticosteroid • Drug name: Dexamethasone

Bronicki 2000 *(Continued)*

- Route: IV
- Dose: 1 mg/kg
- Timing (preoperative, intraoperative, postoperative): preoperatively

Placebo

- Drug name: Normal saline
- Route: IV
- Dose: NA
- Timing (preoperative, intraoperative, postoperative): preoperative

Outcomes	Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome • **Direction**: Lower is better Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome Adverse events (Wound healing dehiscence) • **Outcome type**: Adverse event In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome • **Direction**: Lower is better Length of postoperative hospital stay • **Outcome type**: Continuous outcome
Identification	**Sponsorship source:** not Specified **Country:** USA **Setting:** PICU **Comments:** N/A **Authors name:** Ronald A. Bronicki **Institution:** Northwestern University Medical School, Children's Memorial Hospital **Email:** c-backer@nwu.edu **Address:** Children's Memorial Hospital, 2300 Children's Plaza, m/c 22, Chicago, IL 60614

Bronicki 2000 *(Continued)*

	Year: 2000
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Unclear risk	Unclear inclusion and exclusion criteria as well as how the participants were dealt with.

Checchia 2003

Study characteristics

Methods	**Study design:** RCT **Study grouping:** Parallel group **Total duration of study:** Not reported **Number of study centres:** 1 **Study setting:** Theatre/PICU **Withdrawals:** none reported **Study Date:** not reported
Participants	**Baseline characteristics** Corticosteroid • Age range: not reported • Age (mean +/- SD, months): 2.4 + / - 3.4 • Age (median): not reported

Checchia 2003 *(Continued)*

- Number randomised: 15
- Number lost to follow-up/withdrawn: 0
- Number analysed: 15
- Underlying cardiac pathology:
  - VSD 7,
  - Subaortic resection 2
  - TOF repair with ventriculotomy 2
  - Aortic valvotomy 1
  - Rastelli with ventriculotomy 1
  - CAVC repair 1
  - Arterial Switch 1
- Sex: male 10, female 5

Placebo

- Age range: not reported
- Age (mean +/- SD, months): 2.3 +/- 3.3
- Age (median): not reported
- Number randomised: 13
- Number lost to follow-up/withdrawn: 0
- Number analysed: 13
- Underlying cardiac pathology:
  - VSD 4
  - Rastelli with ventriculotomy 2
  - Arterial Switch 2
  - Fontan 1
  - MVR 1
  - Hemitruncus with ventriculotomy 1
  - Sub aortic resection 1
  - TOF repair with ventriculotomy 1
- Sex: male 9, female 4

Overall

- Age range: not reported
- Age (mean +/-SD, months): not reported
- Age (median): not reported
- Number randomised: 28
- Number lost to follow-up/withdrawn: 0
- Number analysed: 28
- Underlying cardiac pathology:
  - VSD 11
  - Rastelli with ventriculotomy 3
  - Arterial switch 3
  - Fontan 1
  - MVR 1
  - hemitruncus with ventriculotomy 1
  - subaortic resection 3
  - TOF repair with ventriculotomy 3
  - aortic valvotomy 1
  - CAVC repair 1
- Sex: male 19, female 9

Included criteria: children undergoing open-heart surgery for congenital heart disease.

Checchia 2003 *(Continued)*

	Exclusion criteria: patients undergoing repair of an isolated atrial septal defect, if there was a history of preoperative use of corticosteroid or nonsteroidal antiinflammatory agents, if they were febrile (38.5°C), or had an elevated white blood cell count (12,000 cells/mm3). **Pretreatment:** none
Interventions	Corticosteroid • Drug name: Dexamethasone • Dose: 1 mg/kg • Route: IV • Timing (preoperative, intraoperative, postoperative): intraoperative Placebo • Drug name: Normal saline • Dose: not reported • Route: IV • Timing (preoperative, intraoperative, postoperative): intraoperative
Outcomes	All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome • **Direction**: Lower is better Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome Length of postoperative hospital stay • **Outcome type**: Continuous outcome Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome Adverse effects • **Outcome type**: Dichotomous outcome
Identification	**Sponsorship source:** None reported **Country:** USA **Setting:** PICU **Comments:** NA

Checchia 2003 *(Continued)*

Authors name: Paul A. Checchia

Institution: Children's Memorial Hospital, Chicago, USA

Email: cbacker@childrensmemorial.org

Address: Children's Memorial Hospital, 2300 Children'sPlaza, m/c 22, Chicago, IL 60614

Year: 2003

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were sequentially randomised"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"all treating physicians were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other bias

Dalili 2015

Study characteristics

Methods

Study design: RCT

Study grouping: Parallel group

Total duration of study: not reported

Number of study centres: 1

Study setting: PICU

Withdrawals: not reported

Participants

Baseline characteristics

Corticosteroid

Dalili 2015 *(Continued)*

- Age range: not reported
- Age (mean+/-SD): 39.8 +/- 24.7 months
- Age (median): not reported
- Number randomised: 50
- Number lost to follow-up/withdrawn: 0
- Number analysed: 50
- Underlying cardiac pathology: not reported
- Sex: male 27, female 23

Placebo

- Age range: not reported
- Age (mean +/- SD): 38.2 +/- 19.8
- Age (median): not reported
- Number randomised: 50
- Number lost to follow-up/withdrawn: 0
- Number analysed: 50
- Underlying cardiac pathology: not reported
- Sex: male 27, female 23

Overall

- Age range: not reported
- Age (mean+/-SD): 39 +/- 22.3
- Age (median): not reported
- Number randomised: 100
- Number lost to follow-up/withdrawn: 0
- Number analysed: 100
- Underlying cardiac pathology: not reported
- Sex: male 54, female 46

Included criteria: children aged 0 to 15 years who underwent total repair of Fallot's Tetralogy

Exclusion criteria: not reported

Pretreatment: no significantly differences between groups

Interventions	Corticosteroid • Drug name: Methylprednisolone • Dose: 30 mg/kg • Route: IV • Timing (preoperative, intraoperative, postoperative): postoperative Placebo • Drug name: no drug • Dose: none • Route: IV • Timing (preoperative, intraoperative, postoperative): postoperative
Outcomes	All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome

Dalili 2015 *(Continued)*

Duration of postoperative inotropes/vasopressors

- **Outcome type**: Continuous outcome

Duration of postoperative mechanical ventilation

- **Outcome type**: Continuous outcome
- **Direction**: Lower is better

Cardiovascular mortality at longest follow-up

- **Outcome type**: Adverse event

Adverse effects (Infection)

- **Outcome type**: Dichotomous outcome

Failure to separate from cardiopulmonary bypass

- **Outcome type**: Dichotomous outcome

In-hospital postoperative mortality

- **Outcome type**: Dichotomous outcome

Length of postoperative hospital stay

- **Outcome type**: Continuous outcome

Identification	**Sponsorship source:** None reported **Country:** Iran **Setting:** PICU **Comments:** NA **Authors name:** Mohammad Dalili **Institution:** Rajale Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran. **Email:** drdalili@yahoo.com **Address:** Rajale Cardiovascular Medical and Research Center, Vali-asr St., Niayesh Blvd, Tehran, IR Iran. **Year:** 2014
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised into 2 groups. Computer generated randomization specified
Allocation concealment (selection bias)	High risk	A placebo could not be prepared
Blinding of participants and personnel (performance bias)	Low risk	"all treating physicians were blinded"

Dalili 2015 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Different staff
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Specified outcomes reported
Other bias	Low risk	No other bias

Graham 2019

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** 5 years **Number of study centres:** 2 **Study date:** June 2012 and ended in November 2017 **Study setting:** PICU **Withdrawals:** 14

Participants	**Baseline Characteristics**
	Corticosteroid
	• Mean age: 9.1 days
	• Age range: not reported
	• Number lost to follow-up/withdrawn: 10
	• Sex: female 35, male 46
	• Underlying cardiac pathology (if available):
	  ○ Corrective 50
	  ○ Palliative 31
	• Age (median): not reported
	• Number randomised: 91
	• Number analysed: 81
	Placebo
	• Mean age: 8.2 days
	• Age range: not reported
	• Number lost to follow-up/withdrawn: 4
	• Sex: female 35, male 60
	• Underlying cardiac pathology (if available):
	  ○ Corrective 60
	  ○ Palliative 35

Graham 2019 *(Continued)*

- Age (median): not reported
- Number randomised: 99
- Number analysed: 95

Overall

- Mean age: 8.6 days
- Age range: not reported
- Number lost to follow-up/withdrawn: 14
- Sex: female 70, male 106
- Underlying cardiac pathology (if available):
  - Corrective 110
  - Palliative 66
- Age (median): not reported
- Number randomised: 190
- Number analysed: 176

Included criteria: infants ≤ 1 month (31 days) of age scheduled to undergo cardiac surgery with CPB.

Exclusion criteria: prematurity (defined as < 37 weeks post gestational age) at the time of surgery, treatment with steroids in the 2 days prior to surgery, participation in research studies involving the evaluation of investigational drugs or vaccines within 30 days of randomization, suspected infection that would contraindicate steroid use (e.g. herpes), known hypersensitivity to methylprednisolone or other contraindication to steroid therapy (e.g. gastrointestinal bleeding), preoperative use of mechanical circulatory support or active resuscitation at the time of proposed randomization.

Pretreatment: nil

Interventions	Corticosteroid • Drug name: Methylprednisolone • Route: IV • Dose: 30 mg/kg • Timing (preoperative, intraoperative, postoperative): intraoperative Placebo • Drug name: not reported • Route: IV • Dose: not reported • Timing (preoperative, intraoperative, postoperative): intraoperative
Outcomes	All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Length of postoperative hospital stay • **Outcome type**: Continuous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome

Graham 2019 *(Continued)*

	Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome • **Direction**: Lower is better Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Adverse events • **Outcome type**: Adverse event
Identification	**Sponsorship source:** National Heart, Lung, and Blood Institute (NHLBI). **Country:** USA **Setting:** PICU **Comments:** none **Authors name:** Eric M. Graham **Institution:** Medical University of South Carolina **Email:** grahamem@musc.edu **Address:** Children's Heart Center, 165 Ashley Ave; MSC 915, Charleston, SC 29425 **Year:** 2019
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned by permuted block randomization within strata according to the planned procedure being palliative or corrective and by the surgeon."
Allocation concealment (selection bias)	Low risk	"All patients, caregivers, health-care providers, and investigation personnel were blinded to the treatment allocation until the close of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study drug was prepared and masked by the local investigational pharmacy and delivered to the operating room"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All patients, caregivers, health-care providers, and investigation personnel were blinded to the treatment allocation until the close of the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported

Graham 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other bias

Heying 2012

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** not stated **Number of study centres:** not reported **Study date:** not reported **Study setting:** PICU **Withdrawals:** none reported

Participants	**Baseline Characteristics**
	Corticosteroid
	• Mean age: not reported
	• Age range (days): 7-21
	• Number lost to follow-up/withdrawn: 0
	• Sex: not reported
	• Underlying cardiac pathology (if available):
	  ○ VSD 1
	  ○ Rashkind balloon dilatation 5
	• Age (median): 9
	• Number randomised: 9
	• Number analysed: 9
	Placebo
	• Mean age: not reported
	• Age range (days): 8-17
	• Number lost to follow-up/withdrawn: 0
	• Sex: not reported
	• Underlying cardiac pathology (if available):
	  ○ VSD 2
	  ○ Rashkind balloon dilatation 6
	• Age (median): 11
	• Number randomised: 11
	• Number analysed: 11
	Overall
	• Mean age: not reported
	• Age range (days): not reported
	• Number lost to follow-up/withdrawn: 0

Heying 2012 *(Continued)*

- Sex: not reported
- Underlying cardiac pathology (if available):
  - VSD 3
  - Rashkind balloon dilatation 11
- Age (median): not reported
- Number randomised: 20
- Number analysed: 20

Included criteria: neonates (age, 8 to 21 days) diagnosed with TGA with or without ventricular septum defect scheduled for arterial switch operation

Exclusion criteria: not reported

Pretreatment: no differences

Interventions	Corticosteroid • Drug name: Dexamethasone • Route: IV • Dose: 1 mg/kg • Timing (preoperative, intraoperative, postoperative): preoperative Placebo • Drug name: Sodium Chloride • Route: IV • Dose: 1 ml • Timing (preoperative, intraoperative, postoperative): preoperative
Outcomes	All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Length of postoperative hospital stay • **Outcome type**: Continuous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome • **Direction**: Lower is better Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Adverse events

Heying 2012 *(Continued)*

- **Outcome type**: Adverse event

Identification	**Sponsorship source:** Deutsche Forschungsgemeinschaft. Research Foundation Flanders (FWO, Klinische Doctoraatsbeurs), Belgium **Country:** Belgium and Germany **Setting:** PICU **Comments:** It is not clear if this is a single or multiple centre (Belgium and Germany) or single centre **Authors name:** Ruth Heying **Institution:** University Hospital Aachen, Aachen, Germany University Hospital Liège, Liège, Belgium German Heart Centre at the Technical University, Munich, Germany **Email:** ruth.heying@uzleuven.be **Address:** UZ Leuven,Herestraat 49, 3000 Leuven, Belgium **Year:** 2012
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"code was broken after data acquisition was completed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other bias

Keski Nisula 2013

Study characteristics

Methods	**Study design:** RCT **Study grouping:** Parallel group

Keski Nisula 2013 *(Continued)*

Duration of study: not reported

Number of study centres: not reported

Study date: not reported

Study setting: not reported

Withdrawals: not reported

Participants	**Baseline Characteristics**
	
	Corticosteroid
	
	• Mean age (days): 9.9 +/- 7.0
	• Age range: not reported
	• Number lost to follow-up/withdrawn: -
	• Sex: male 12, female 8
	• Underlying cardiac pathology (if available):
	  ○ Hypoplastic aortic arch 2
	  ○ Norwood 8
	  ○ TGA 7
	  ○ TAPVD 1
	  ○ Truncus 1
	  ○ Interrupted aortic arch 1
	• Age (median): not reported
	• Number randomised: 20
	• Number analysed: 20
	
	Placebo
	
	• Mean age (days): 11.0 +/-- 7.2
	• Age range: not reported
	• Number lost to follow-up/withdrawn: 0
	• Sex: male 11, female 9
	• Underlying cardiac pathology (if available):
	  ○ Hypoplastic aortic arch repair 8
	  ○ Norwood operation 4
	  ○ TGA repair 4
	  ○ Truncus arteriosus repair 2
	  ○ Interrupted aortic arch repair 0
	  ○ B-T shunt without ACC 1
	• Age (median): not reported
	• Number randomised: 20
	• Number analysed: 20
	
	Overall
	
	• Mean age: not reported
	• Age range: not reported
	• Number lost to follow-up/withdrawn: 0
	• Sex: male 23, female 17

Keski Nisula 2013 *(Continued)*

- Underlying cardiac pathology (if available):
  - Hypoplastic aorticarch repair=10
  - Norwood operation=10
  - TGA repair=11
  - Truncus arteriosus repair=3
  - Interrupted aortic arch repair=1
  - B-T shunt without ACC 1
- Age (median): not reported
- Number randomised: 40
- Number analysed: 40

Included criteria: neonates (age 28 days) undergoing open-heart surgery

Exclusion criteria: not reported

Pretreatment: nil

Interventions	Corticosteroid • Drug name: Methylprednisolone • Route: IV • Dose: 30 mg/kg • Timing (preoperative, intraoperative, postoperative): intraoperative Placebo • Drug name: Saline • Route: IV • Dose: NA • Timing (preoperative, intraoperative, postoperative): intraoperative
Outcomes	*A*ll-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Length of postoperative hospital stay • **Outcome type**: Continuous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome • **Direction**: Lower is better Cardiovascular mortality at longest follow-up

Keski Nisula 2013 *(Continued)*

- **Outcome type**: Dichotomous outcome

Adverse events (hypoglycaemia, glucose (mmol/L)

- **Outcome type**: Continuous outcome

Identification	**Sponsorship source:** The Foundation for Pediatric Research and Helsinki UniversityCentral Hospital **Country:** Finland **Setting:** PICU **Comments:** na **Authors name:** Juho Keski-Nisula **Institution:** Children's Hospital, Helsinki University Central Hospital. **Email:** juho.keski-nisula@hus.fi **Address:** Department of Anesthesiaand Intensive Care, Children's Hospital, Helsinki University Central-Hospital, P.O B. 281, Stenbackinkatu 11, FI-00029 HUS, Helsinki, Finland **Year:** 2013
Notes	This study has the same ISCRTN number as Keski-Nisula 2015 - but a different population and intervention. Treated as separate studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"In this randomised (sealed envelope), double-blind, placebo-controlled investigation,"
Allocation concealment (selection bias)	Low risk	"A pharmacist who was not involved in the care of the study patients prepared methylprednisolone and placebo solutions."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All the syringes were covered with nontransparent paper foil"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other bias

Keski Nisula 2015

Study characteristics

Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** not reported **Number of study centres:** 1 **Study date:** not reported **Study setting:** PICU **Withdrawals:** not reported

Participants	**Baseline Characteristics**
	
	Corticosteroid
	
	• Mean age (months) + SD: 5.5 + / - 3.14
	• Age range: not reported
	• Number lost to follow-up/withdrawn: -
	• Sex: not reported
	• Underlying cardiac pathology (if available):
	  ○ AVSD 9
	  ○ VSD 21
	• Age (median): not reported
	• Number randomised: 30
	• Number analysed: 30
	
	Placebo
	
	• Mean age (months) + SD: 4.9 + / - 3.3
	• Age range: not reported
	• Number lost to follow-up/withdrawn: not reported
	• Sex: not reported
	• Underlying cardiac pathology (if available):
	  ○ AVSD 7
	  ○ VSD 8
	• Age (median): not reported
	• Number randomised: 15
	• Number analysed: 15
	
	Overall
	
	• Mean age (months) + SD: not reported
	• Age range: not reported
	• Number lost to follow-up/withdrawn: -
	• Sex: not reported
	• Underlying cardiac pathology (if available):
	  ○ AVSD 16
	  ○ ASD 29
	• Age (median): not reported
	• Number randomised: 45
	• Number analysed: 45
	
	Included criteria: children between 1 and 18 months of age undergoing VSD or AVSD repair

Keski Nisula 2015 *(Continued)*

	Exclusion criteria: • Prematurity (defined as 36 weeks gestational age) • Steroid treatment before operation • preoperative mechanical ventilation • Preoperative need of inotropic agents or mechanical circulatory support **Pretreatment:** no significant difference
Interventions	**Intervention Characteristics** Glucocorticoid • Drug name: Methylprednisolone • Route: IV • Dose: 30mg/kg • Timing (preoperative, intraoperative, postoperative): intraoperative Placebo • Drug name: Normal saline • Route: IV • Dose: - • Timing (preoperative, intraoperative, postoperative): preoperative and intraoperative
Outcomes	All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Length of postoperative hospital stay • **Outcome type**: Continuous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome • **Direction**: Lower is better Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Adverse events (Infection) • **Outcome type**: Adverse event
Identification	**Sponsorship source:** Helsinki University Central Hospital

Keski Nisula 2015 *(Continued)*

	Country: Finland **Setting:** PICU **Comments:** NA **Authors name:** Juho Keski-Nisula **Institution:** Children's Hospital, Helsinki University Central Hospital; **Email:** juho.keski-nisula@hus.fi **Address:** Department of Anesthesiaand Intensive Care, Children's Hospital, Helsinki University Central-Hospital, PO Box 281, Stenbackinkatu 11, FI-00029 HUS, Helsinki, Finland; **Year:** 2015
Notes	This study has the same ISCRTN number as Keski-Nisula 2013 - but a different population and intervention. Treated as separate studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised by sealed envelope equally into three study groups."
Allocation concealment (selection bias)	Low risk	"A pharmacist not involved in the care of the study patients prepared two syringes, which contained either MP or placebo (corresponding volume of saline solution);"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"these were subsequently covered by nontransparent paper. All the patients received two study drug syringes regardless of treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All study and clinical personnel were blinded to the treatment allocation until the study period ended"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified outcomes
Selective reporting (reporting bias)	Low risk	Appears to have reported all outcomes
Other bias	Low risk	No other bias

Lindberg 2003

Study characteristics

Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** Not reported

Lindberg 2003 *(Continued)*

Number of study centres: 1

Study setting: PICU

Withdrawals: 1

Study Date: Not clear

Participants	**Baseline Characteristics**
	
	Corticosteroid
	
	• Age range (IQR): 1.2 - 9.8 years
	• Age (median): 4.3 years
	• Number randomised: 20
	• Number lost to follow-up/withdrawn: 1
	• Number analysed: 19
	• Underlying cardiac pathology:
	  ○ ASD 8
	  ○ ASD+MR 1
	  ○ TF repair 1
	  ○ Aortic atresia and hypoplastic ascending aorta 1
	  ○ AS 1
	  ○ Single ventricle 1
	  ○ Subvalvular pulmonary stenosis + VSD =1
	  ○ CA Fistula 1
	  ○ Circumflex artery from pulmonary artery 1
	  ○ Pulmonary atresia + VSD 1
	  ○ PAPVD 1
	  ○ Mitral regurgitation 1
	• Sex: not reported
	
	Placebo
	
	• Age range (IQR): 1.5 - 8.2 years
	• Age (median): 4.5 years
	• Number randomised: 20
	• Number lost to follow-up/withdrawn: 0
	• Number analysed: 20
	• Underlying cardiac pathology:
	  ○ ASD 10
	  ○ ASD+MR 2,
	  ○ VSD 3
	  ○ Supravalvular AS 1
	  ○ Single ventricle 1
	  ○ Pulmonary atresia + VSD 2
	  ○ Pulmonary atresia, intact ventricular septum 1
	• Sex: not reported
	
	Overall
	
	• Age range (IQR): not reported
	• Age (median): not reported
	• Number randomised: 40
	• Number lost to follow-up/withdrawn: 1
	• Number analysed: 39

Lindberg 2003 *(Continued)*

- Underlying cardiac pathology:
  - ASD 18
  - ASD and MR 3
  - VSD 3
  - ToF 1
  - Ao atresia and hypoplastic ascending aorta 1
  - AS 1
  - Suprvalvular AS 1
  - Single ventricle 2
  - PS and VSD 1
  - CA Fistula 1
  - Anomalous CA
  - Pulmonary Atresia and VSD 3
  - Pulmonary Atresia 1
  - PAPVD 1
  - MR 1
- Sex: not reported

Included criteria: children (>10 kg) about to have open heart surgery

Exclusion criteria: not reported

Pretreatment: no differences

Interventions	Corticosteroid • Drug name: Dexamethasone • Route (intravenous or oral): IV • Dose: 1mg / kg • Timing (preoperative, intraoperative, postoperative): intraoperative Placebo • Drug name: Sodium chloride 0.9% • Route (intravenous or oral): IV • Dose: not reported • Timing (preoperative, intraoperative, postoperative): intraoperative
Outcomes	Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Failure to separate from cardiopulmonary bypass

Lindberg 2003 *(Continued)*

- **Outcome type**: Dichotomous outcome

Adverse events

- **Outcome type**: Adverse event

In-hospital postoperative mortality

- **Outcome type**: Dichotomous outcome
- **Direction**: Lower is better

Length of postoperative hospital stay

- **Outcome type**: Continuous outcome

Identification	**Sponsorship source:** not reported **Country:** Sweden **Setting:** PICU **Comments:** none **Authors name:** L. Lindberg **Institution:** University Hospital, Lund, Sweden **Email:** larsolavlindberg@hotmail.com **Address:** Department of Pediatric Anesthesia and Intensive Care, University Hospital Lund,S-221 85 Lund, Swede **Year:** 2003
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The nature of the agent was masked."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Specified outcomes reported
Selective reporting (reporting bias)	Low risk	Specified outcomes reported

Lindberg 2003 *(Continued)*

Other bias	Unclear risk	No other bias

Malagon 2005

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** 14 months **Number of study centres:** 1 **Study date:** October 2003 and December 2004 **Study setting:** PICU **Withdrawals:** Not reported

Participants	**Baseline Characteristics**
	
	Corticosteroid
	
	• Mean age (95%, CI): 12.2 (6.7 - 17.8) months
	• Age range: not reported
	• Number lost to follow-up/withdrawn: not reported
	• Sex: male 43, female 27
	• Underlying cardiac pathology (if available)
	  ○ Aortic Stenosis 1
	  ○ Atrial septation 0
	  ○ AVSD 6, Fontan 2
	  ○ Glenn 10
	  ○ Homograft
	  ○ Interupted Aortic Arch 1
	  ○ MAPCA 1
	  ○ MVA 2
	  ○ MVR 0
	  ○ Norwood 5
	  ○ Pulmonary Stenosis 1
	  ○ Rastelli 1
	  ○ Switch 10
	  ○ TAPVD 3
	  ○ TOF 9
	  ○ Truncus 1
	  ○ TVA 1
	  ○ TVR 0
	  ○ VSD 14
	• Age (median): not reported
	• Number randomised: 70
	• Number analysed: 70
	
	Overall
	
	• Mean age (95%, CI): not reported

Malagon 2005 *(Continued)*

- Age range: not reported
- Number lost to follow-up/withdrawn: not reported
- Sex: male 76, female 64
- Underlying cardiac pathology (if available):
  - AS 4
  - Atrial septation 1
  - AVSD 13
  - Fontan 8
  - Glenn shunt 15
  - Homograft 4
  - Interrupted Aortic Arch 2
  - MAPCA 2
  - MVA 3
  - MVR 1
  - Norwood 9
  - Pulmonary Stenosis 2
  - Rastelli 2
  - Switch 20
  - TAPVD 5
  - TOF 18
  - Truncus repair 3
  - TVA 1
  - TVR 1
  - VSD 26
- Age (median): not reported
- Number randomised: 140
- Number analysed: 140

Included criteria: pediatric patients with CPB for cardiac surgical procedures.

Exclusion criteria: patients operated on without CPB.

Pretreatment: nil

Interventions	Corticosteroid • Drug name: Dexamethasone • Route: IV • Dose: 1 mg/kg • Timing (preoperative, intraoperative, postoperative): intraoperative
Outcomes	All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Length of postoperative hospital stay • **Outcome type**: Continuous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Duration of postoperative mechanical ventilation

Malagon 2005 *(Continued)*

- **Outcome type**: Continuous outcome

Failure to separate from cardiopulmonary bypass

- **Outcome type**: Dichotomous outcome

In-hospital postoperative mortality

- **Outcome type**: Dichotomous outcome
- **Direction**: Lower is better

Cardiovascular mortality at longest follow-up

- **Outcome type**: Dichotomous outcome

Adverse events

- **Outcome type**: Adverse event

Identification	**Sponsorship source:** not reported **Country:** Netherlands **Setting:** PICU **Comments:** None **Authors name:** Ignacio Malagon **Institution:** Leiden University Medical Center **Email:** jmalagon@lumc.nl **Address:** Leiden University Medical Center,Albinusdreef 2, P.O. Box 9600,2300 RC Leiden, The Netherlands **Year:** 2005
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised using standard randomization tables"
Allocation concealment (selection bias)	High risk	"The use of placebo is not allowed by our hospital ethics committee."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The use of placebo is not allowed by our hospital ethics committee."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"cTnT concentrations were measured by the hospital clinical chemistry laboratory, and the analysts were unaware of the conduct of this study."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified

Malagon 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	Appear to report all outcomes
Other bias	Low risk	No other bias

Mott 2001

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** 30 months **Number of study centres:** 1 **Study date:** March 1996 to June 1998 **Study setting:** operating theatre and PICU **Withdrawals:** 20 (6 due to death, 14 due to protocol deviation)

Participants	**Baseline Characteristics**
	Corticosteroid
	• Mean age: 36.6 months
	• Age range: not reported
	• Number lost to follow-up/withdrawn: not reported
	• Sex: not reported
	• Underlying cardiac pathology :
	  ○ AVR 4
	  ○ PVR 1
	  ○ ASD 16
	  ○ VSD 26
	  ○ AVSD 3
	  ○ MVR 2
	  ○ CAVC 7
	  ○ Aortic Arch Advancement 5
	  ○ Interrupted Aortic Arch and VSD Closure 1
	  ○ Glenn 8
	  ○ Fontan 4
	  ○ TOF 11
	  ○ Pulmonary arterioplasty 1
	  ○ RV resection and VSD 2
	  ○ PVR or AVR 1
	  ○ Subaortic stenosis+/- VSD 5
	  ○ HLHS Stage-1 3
	  ○ TGA + / - VSD 10
	  ○ Rastelli 3
	  ○ TAPVD 8
	• Age (median): not reported
	• Number randomised: not reported

Mott 2001 *(Continued)*

- Number analysed: 126

Placebo

- Mean age: 44 months
- Age (median): not reported
- Number randomised: not reported
- Number lost to follow-up/withdrawn: not reported
- Number analysed: 120
- Underlying cardiac pathology:
  - AVR 3
  - Ross 3
  - PVR 1
  - ASD 21
  - VSD 17
  - AVSD 3
  - TVR 2
  - MVR 9
  - CAVC 7
  - Aortic Arch Advancement 4
  - Interrupted Aortic Arch and VSD Closure 1
  - Glenn 12
  - Fontan 3
  - TOF 11
  - Pulmonary arterioplasty 2
  - RV resection and VSD 1
  - Pulmonary artery unifocalisation / VSD repair 1
  - PVR or AVR 1
  - Subaortic stenosis + /- VSD 3
  - HLHS Stage-1 5
  - TGA+/- VSD 16
  - Rastelli 2
  - Senning 1
  - TAPVD 4
- Sex: not reported

Overall

- Mean age: not reported
- Age (median): not reported
- Number randomised: 266
- Number lost to follow-up/withdrawn: 20
- Number analysed: 246

Mott 2001 *(Continued)*

- Underlying cardiac pathology:
  - AVR 7
  - Ross 3
  - PVR 2
  - ASD 37
  - VSD 45
  - AVSD 6
  - TVR 2
  - MVR 11
  - CAVC 14
  - Aortic Arch Advancement 9
  - Interrupted Aortic Arch and VSD Closure 2
  - Glenn 20
  - Fontan 7
  - TOF 22
  - Pulmonary arterioplasty 3
  - RV resection and VSD 3
  - Pulmonary artery unifocalisation / VSD repair 1
  - PVR or AVR 2
  - Subaortic stenosis + / - VSD 8, HLHS Stage-1 8
  - TGA+/- VSD 26
  - Rastelli 5
  - Senning 1
  - TAPVD 12
- Sex: not reported

Included criteria: paediatric patients with CPB for cardiac surgical procedures.

Exclusion criteria: Allergy to methylprednisolone, patients being treated with a steroid for chronic immune suppression, and patients with previously documented hematologic, hepatic or renal dysfunction.

Interventions	Corticosteroid • Drug name: Methylprednisolone • Route: IV • Dose: 1 mg/kg then 4 post-op doses 6 hour intervals • Timing (preoperative, intraoperative, postoperative): intraoperative and postoperative Placebo • Drug name: Sodium chloride 0.9% • Route (intravenous or oral): IV • Dose: same volume and dosing times • Timing (preoperative, intraoperative, postoperative): intraoperative and postoperative
Outcomes	
Identification	**Sponsorship source:** not reported **Country:** USA **Setting:** operating theatre and PICU **Comments:** none **Authors name:** Antonio Mott

Mott 2001 *(Continued)*

	Institution: Texas Childrens Hospital **Email:** AMott@bcm.tmc.edu **Address:** Section of Pediatric Cardiology, Texas Childrens Hospital, 6621 Fannin, MC#2-2280, Houston. Texas 77030 **Year:** 2005
Notes	No outcomes of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"each patient a study number from the randomisation table that was created by the study statistician."
Allocation concealment (selection bias)	Low risk	"Drugs delivered by pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Non-involved staff delivered drugs"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients who died were excluded after randomization
Selective reporting (reporting bias)	Low risk	Specified outcomes reported
Other bias	Low risk	No other bias

Suominen 2017

Study characteristics

Methods	**Study design:** RCT **Study grouping:** Parallel group **Duration of study:** 30 Months **Number of study centres:** 1 **Study date:** April 2012 and October 2014 **Study setting:** PICU **Withdrawals:** 0
Participants	**Baseline Characteristics**

Suominen 2017 *(Continued)*

Corticosteroid

- Mean age (intervention), SD: 8.1 +/- 2.6 days
- Age range: not reported
- Number lost to follow-up/withdrawn: 0
- Sex: male 15, female 5
- Underlying cardiac pathology (if available):
  - TGA repair 10
  - Hypoplastic aortic arch repair 3
  - Norwood 5
  - TAPVD repair 1
  - VSD repair 1
  - Truncus arteriosus repair 0
  - TOF repair 0
- Age (median): not reported
- Number randomised: 20
- Number analysed: 20

Placebo

- Mean age (Intervention), SD: 8.2 + / - 4.7
- Age range: not reported
- Number lost to follow-up/withdrawn: 0
- Sex: male 14, female 6
- Underlying cardiac pathology (if available):
  - TGA repair 8
  - Hypoplastic aortic arch repair 4
  - Norwood 3
  - TAPVD repair 2
  - VSD repair 1
  - Truncus arteriosus repair 1
  - TOF repair 1
- Age (median): not reported
- Number randomised: 20
- Number analysed: 20

Overall

- Mean age (Intervention), SD: not reported
- Age range: not reported
- Number lost to follow-up/withdrawn: 0
- Sex: male 29, female 11
- Underlying cardiac pathology (if available):
  - TGA repair 18
  - Hypoplastic aortic arch repair 7
  - Norwood 8
  - TAPVD repair 3
  - VSD repair 2
  - Truncus arteriosus repair 1
  - TOF repair 1
- Age (median): not reported
- Number randomised: 40
- Number analysed: 40

Suominen 2017 *(Continued)*

	Included criteria: neonates (age 28 days) who were undergoing non emergency cardiac operations with cardiopulmonary bypass (CPB). **Exclusion criteria:** Symptoms related to prematurity or birth before 36 weeks of gestational age, chromosomal abnormalities, administration of corticosteroids before the operation, and the need of preoperative inotropic support other than milrinone **Pretreatment:** none
Interventions	**Intervention Characteristics** Corticosteroid • Drug name: Hydrocortisone • Route: IV • Dose: 2 mg/kg methylprednisolone (after induction) then HCT infusion 0.2 mg/kg/h for 48 hours, 0.1 mg/kg/h for 48 hours, and 0.05 mg/kg/h for 24 hours • Timing (preoperative, intraoperative, postoperative): intraoperative and postoperative Placebo • Drug name: Saline • Route: IV • Dose: NA • Timing (preoperative, intraoperative, postoperative): postoperative
Outcomes	All-cause mortality at longest follow-up • **Outcome type**: Dichotomous outcome Length of postoperative hospital stay • **Outcome type**: Continuous outcome Length of postoperative intensive care unit stay • **Outcome type**: Continuous outcome Duration of postoperative inotropes/vasopressors • **Outcome type**: Continuous outcome Duration of postoperative mechanical ventilation • **Outcome type**: Continuous outcome Failure to separate from cardiopulmonary bypass • **Outcome type**: Dichotomous outcome In-hospital postoperative mortality • **Outcome type**: Dichotomous outcome Cardiovascular mortality at longest follow-up • **Outcome type**: Dichotomous outcome Adverse events (insulin administration) • **Outcome type**: Dichotomous outcome Adverse events (Wound infections) • **Outcome type**: Dichotomous outcome

Suominen 2017 *(Continued)*

	Adverse events (Septic blood culture-positive) • **Outcome type**: Dichotomous outcome
Identification	**Sponsorship source:** The Paulo Foundation (Tapani Tammiston rahasto 2012 to P.K.S) and the Foundation of Paediatric Research (130069 to P.K.S) **Country:** Finland **Setting:** PICU **Comments:** Nil **Authors name:** Pertti K. Suominen **Institution:** Children's Hospital, Helsinki University Hospital **Email:** pertti.suominen@hus.fi **Address:** Department of Anesthesia and Intensive Care, Children's Hospital, Helsinki University Hospital, University of Helsinki, Stenbackinkatu 11, FI-00029 HUS Helsinki, Finland **Year:** 2017
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised by sealed envelope into two groups."
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All study and clinical personnel were blinded to the treatment allocation until the study period ended"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All study and clinical personnel were blinded to the treatment allocation until the study period ended."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Low risk	No other bias

Abbreviations: ASD: Atrial-septal defect, VSD: Ventriculo-septal defect, AVSD: Atrio-ventriculo-septal defect, CAVC: Complete atrio-ventricular canal defect, TGA: Transposition of the great arteries, TAPVD: Total anomalous pulmonary venous drainage, PAPVD: Partial anomalous pulmonary venous drainage, MVR: Mitral valve repair/replacement, MVA: Mitral Valve Annuloplasty, TVR: Tricuspid valve replacement, TVA: Tricuspid valve annuloplasty, PS: Pulmonary stenosis, MAPCA: Major aorto-pulmonary collateral arteries, CA: Coronary artery, TOF: Tetralogy of Fallot, RV: Right ventricle, PA: Pulmonary artery, HLHS: Hypoplastic left heart syndrome

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AbbasiTashnizi 2013	Wrong comparator
AbdEl Hakeem 2003	Adult population
Alten 2011	Wrong study design
Anic 2004	Adult population
Brettner 2018	Adult population
Bronicki 2012	Wrong comparator
Bunge 2014	Adult population
Carrel 2017	Wrong study design
Celik 2004	Adult population
Chaney 2001	Adult population
Clarizia 2011	Wrong study design
Corbi 2001	Wrong study design
Crawford 2017	Wrong study design
delaMotte 2014	Adult population
Demir 2009	Adult population
Dhar 2012	Adult population
Dreher 2015	Wrong study design
Ebrahimi 2010	Adult population
Ebrahimi 2016	Adult population
Fernandez 2011	Wrong patient population
Fillinger 2002	Adult population
Fontela 2011	Wrong comparator
Garg 2014	Wrong study design
Gessler 2005	Wrong study design
Glumac 2017	Adult population
Graham 2011	Wrong comparator

Study	Reason for exclusion
Hauer 2012	Adult population
Heckmann 2002	Wrong study design
Juneja 2000	Adult population
Keski Nisula 2016	Wrong comparator
Keski-Nisula 2020	Wrong study design
Kilger 2003	Adult population
Kilger 2011	Wrong patient population
Liakopoulos 2007	Adult population
Liu 2007	Wrong comparator
Loef 2004	Adult population
Maeda 2016	Wrong study design
Malagon 2005a	Retracted Study
Mardani 2012	Adult population
McClure 2017	Adult population
Modan Moses 2010	Wrong study design
Murphy 2011	Adult population
Namdari 2011	Adult population
NCT00293592	Adult population
NCT00490828	Adult population
NCT00879931	Adult population
NCT01296074	Adult population
NCT03002259	Adult population
Oliver 2004	Adult population
Ottens 2013	Adult population
Paparella 2017	Adult population
Poyrazoglu 2016	Wrong study design
Rahman 2010	Wrong comparator
Robert 2015	Wrong study design

Study	Reason for exclusion
SanchezCanovas 2016	Adult population
Santarpino 2009	Adult population
Sauer 2013	Adult population
Schelling 2004	Adult population
Soltani 2013	Wrong comparator
Suezawa 2013	Adult population
Suominen 2005	Wrong intervention
Varan 2002	Wrong comparator
vonSpiegel 2002	Adult population
Weis 2006	Adult population
Whitlock 2006	Adult population
Withington 2014	Wrong comparator
Yared 2000	Adult population
YasserMohamed 2009	Adult population

Characteristics of ongoing studies *[ordered by study ID]*

NCT02615262

Study name	Intraoperative Dexamethasone in Pediatric Cardiac Surgery
Methods	Parallel RCT
Participants	Children up to 12 months
Interventions	Dexamethasone 1 mg per 1 kg of body weight intravenously immediately after induction of anaesthesia
Outcomes	Major complications [Time Frame: 30 days after surgery] Composite of all-cause death, myocardial infarction, need for extracorporeal membrane oxygenation implantation, cardiac arrest, acute renal failure (stage "injury" or higher according to pRIFLE scale), prolonged mechanical ventilation (> 24 hours), stroke, seizure, coma.
Starting date	December 2015
Contact information	Vladimir Lomivorotov, PhD Novosibirsk Research Institute of Circulation Pathology
Notes	

STRESS 2021

Study name	STeroids to REduce Systemic Inflammation After Infant Heart Surgery (STRESS)
Methods	RCT
Participants	Age < 1 year at the time of surgery Undergoing heart surgery with CPB as part of standard clinical care
Interventions	Methylprednisolone IV preoperative and intraoperative
Outcomes	Primary Outcome Measures : • A composite mortality, major morbidity and length of stay global rank endpoint with endpoints ranked according to severity. [Time Frame: Until hospital discharge. Length of stay up to 6 months] Secondary Outcome Measures : • Mortality including in-hospital mortality or mortality after hospital discharge but within 30 days of the last cardiac operation of the admission [Time Frame: up to 30 days] • Death or major complication as previously defined and reported by the STS-CHSD registry. [Time Frame: Until hospital discharge. Length of stay up to 6 months] • Postoperative hospital length of stay [Time Frame: Until hospital discharge. Length of stay up to 6 months] • Prevalence of prolonged (>7days) mechanical ventilation [Time Frame: Until hospital discharge. Length of stay up to 6 months] • Occurrence of postoperative low cardiac output syndrome. Based upon the STS-CHSD registry defined "cardiac dysfunction resulting in low cardiac output" complication variable [Time Frame: Until hospital discharge. Length of stay up to 6 months] • Occurence of any one or more of the following STS-CHSD-defined major postoperative infectious complications: Postprocedural infective endocarditis; Pneumonia; Sepsis; Deep wound infection; Mediastinitis [Time Frame: Until hospital discharge. Length of stay up to 6 months] • Any other postoperative complications from the start of study drug administration until hospital discharge. [Time Frame: Until hospital discharge. Length of stay up to 6 months] • PK/PD - Time to maximum concentration (Tmax) [Time Frame: Pre-2nd dose and minimum of 2 of any of the following 5 time points (0-30 minutes after the start of CPB, 0-30 minutes after MUF, 1-2 hours after completion of CPB, 4-6 hours after completion of CPB, or 16-24 hours after completion of CPB)] • PK/PD - Maximum concentration (Cmax) [Time Frame: Pre-2nd dose and minimum of 2 of any of the following 5 time points (0-30 minutes after the start of CPB, 0-30 minutes after MUF, 1-2 hours after completion of CPB, 4-6 hours after completion of CPB, or 16-24 hours after completion of CPB)] • PK/PD - Clearance (CL) [Time Frame: Pre-2nd dose and minimum of 2 of any of the following 5 time points (0-30 minutes after the start of CPB, 0-30 minutes after MUF, 1-2 hours after completion of CPB, 4-6 hours after completion of CPB, or 16-24 hours after completion of CPB)] • PK/PD - Volume of distribution (Vd) [Time Frame: Pre-2nd dose and minimum of 2 of any of the following 5 time points (0-30 minutes after the start of CPB, 0-30 minutes after MUF, 1-2 hours after completion of CPB, 4-6 hours after completion of CPB, or 16-24 hours after completion of CPB)] • Postoperative biomarkers of the inflammatory response to cardiopulmonary bypass including interleukins 6 and 8 [Time Frame: Pre-2nd dose; a minimum of 2 of any of the following 5 time points (0-30 min after the start of CPB, 0-30 min after MUF, 1-2 hrs after CPB end, 4-6 hrs after CPB end, or 16-24 hrs after CPB end); and 36-48 hrs after CPB end]
Starting date	October 2017
Contact information	

STRESS 2021 *(Continued)*

Notes

DATA AND ANALYSES

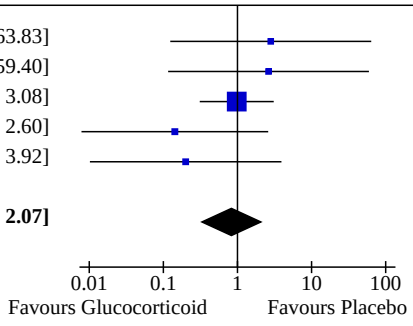
Comparison 1. Corticosteroid vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 In-hospital postoperative mortality	5	313	Risk Ratio (IV, Random, 95% CI)	0.83 [0.33, 2.07]
1.2 Duration of postoperative mechanical ventilation (hours)	6	421	Mean Difference (IV, Random, 95% CI)	-11.37 [-20.29, -2.45]
1.3 Length of postoperative ICU stay (days)	6	421	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.79, 0.24]
1.4 Length of postoperative hospital stay	1	176	Mean Difference (IV, Random, 95% CI)	-0.70 [-2.62, 1.22]
1.5 All-cause mortality at longest follow-up	5	313	Risk Ratio (IV, Random, 95% CI)	0.83 [0.33, 2.07]
1.6 Cardiovascular mortality at longest follow-up	3	109	Risk Ratio (IV, Random, 95% CI)	0.40 [0.07, 2.46]
1.7 Failure to separate from CPB	1	40	Risk Ratio (IV, Random, 95% CI)	0.20 [0.01, 3.92]

Analysis 1.1. Comparison 1: Corticosteroid vs Placebo, Outcome 1: In-hospital postoperative mortality

Study or Subgroup	Glucocorticoid Events	Glucocorticoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bronicki 2000	1	15	0	14	8.6%	2.81 [0.12 , 63.83]
Checchia 2003	1	15	0	13	8.6%	2.63 [0.12 , 59.40]
Graham 2019	5	81	6	95	63.4%	0.98 [0.31 , 3.08]
Keski Nisula 2013	0	20	3	20	10.0%	0.14 [0.01 , 2.60]
Suominen 2017	0	20	2	20	9.5%	0.20 [0.01 , 3.92]
Total (95% CI)		**151**		**162**	**100.0%**	**0.83 [0.33 , 2.07]**
Total events:	7		11			

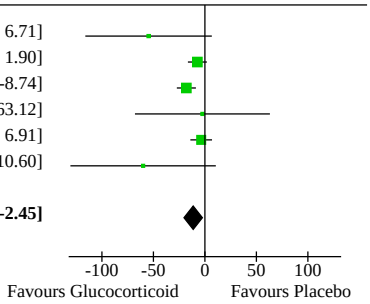
Heterogeneity: Tau² = 0.00; Chi² = 3.48, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Corticosteroid vs Placebo, Outcome 2: Duration of postoperative mechanical ventilation (hours)

Study or Subgroup	Glucocorticoid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ando 2005	83.5	42.1	10	138.2	89.7	10	2.0%	-54.70 [-116.11 , 6.71]
Dalili 2015	18.2	11.04	50	25.5	31.3	50	32.6%	-7.30 [-16.50 , 1.90]
Graham 2019	108	27.6	81	126	35	95	32.5%	-18.00 [-27.26 , -8.74]
Keski Nisula 2013	134.4	100.8	20	136.8	110.4	20	1.8%	-2.40 [-67.92 , 63.12]
Keski Nisula 2015	27.6	17.28	30	31.2	16.8	15	29.5%	-3.60 [-14.11 , 6.91]
Suominen 2017	124.8	67.2	20	184.8	146.4	20	1.5%	-60.00 [-130.60 , 10.60]
Total (95% CI)			**211**			**210**	**100.0%**	**-11.37 [-20.29 , -2.45]**

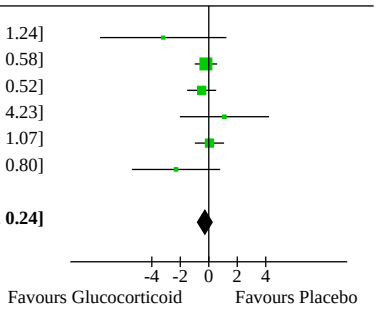
Heterogeneity: Tau² = 41.40; Chi² = 8.57, df = 5 (P = 0.13); I² = 42%
Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Corticosteroid vs Placebo, Outcome 3: Length of postoperative ICU stay (days)

Study or Subgroup	Glucocorticoid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ando 2005	10.2	3	10	13.4	6.5	10	1.3%	-3.20 [-7.64 , 1.24]
Dalili 2015	3.02	1.9	50	3.22	2.1	50	42.8%	-0.20 [-0.98 , 0.58]
Graham 2019	11.7	3.1	81	12.2	3.8	95	25.3%	-0.50 [-1.52 , 0.52]
Keski Nisula 2013	9.3	5.2	20	8.2	4.9	20	2.7%	1.10 [-2.03 , 4.23]
Keski Nisula 2015	2.55	1.75	30	2.5	1.6	15	25.1%	0.05 [-0.97 , 1.07]
Suominen 2017	7.8	3.4	20	10.1	6.2	20	2.7%	-2.30 [-5.40 , 0.80]
Total (95% CI)			**211**			**210**	**100.0%**	**-0.28 [-0.79 , 0.24]**

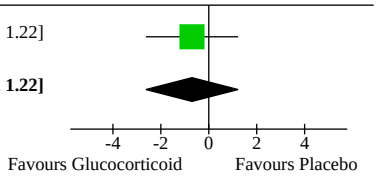
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 5 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Corticosteroid vs Placebo, Outcome 4: Length of postoperative hospital stay

Study or Subgroup	Favours Glucocorticoid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Graham 2019	22	6.36	81	22.7	6.64	95	100.0%	-0.70 [-2.62 , 1.22]
Total (95% CI)			**81**			**95**	**100.0%**	**-0.70 [-2.62 , 1.22]**

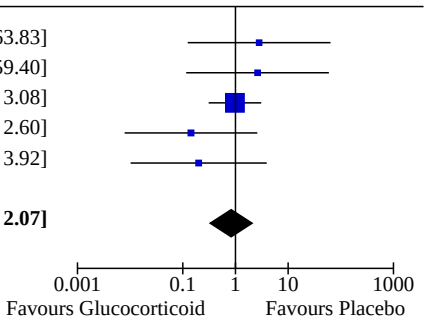
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Corticosteroid vs Placebo, Outcome 5: All-cause mortality at longest follow-up

Study or Subgroup	Glucocorticoid Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bronicki 2000	1	15	0	14	8.6%	2.81 [0.12 , 63.83]
Checchia 2003	1	15	0	13	8.6%	2.63 [0.12 , 59.40]
Graham 2019	5	81	6	95	63.4%	0.98 [0.31 , 3.08]
Keski Nisula 2013	0	20	3	20	10.0%	0.14 [0.01 , 2.60]
Suominen 2017	0	20	2	20	9.5%	0.20 [0.01 , 3.92]
Total (95% CI)		**151**		**162**	**100.0%**	**0.83 [0.33 , 2.07]**
Total events:	7		11			

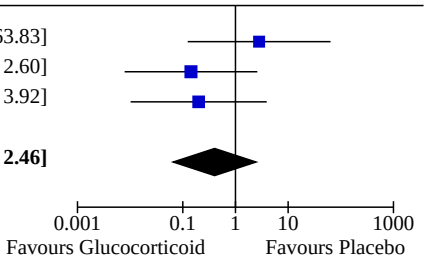
Heterogeneity: Tau² = 0.00; Chi² = 3.48, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Corticosteroid vs Placebo, Outcome 6: Cardiovascular mortality at longest follow-up

Study or Subgroup	Glucocorticoid Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bronicki 2000	1	15	0	14	30.9%	2.81 [0.12 , 63.83]
Keski Nisula 2013	0	20	3	20	35.3%	0.14 [0.01 , 2.60]
Suominen 2017	0	20	2	20	33.7%	0.20 [0.01 , 3.92]
Total (95% CI)		**55**		**54**	**100.0%**	**0.40 [0.07 , 2.46]**
Total events:	1		5			

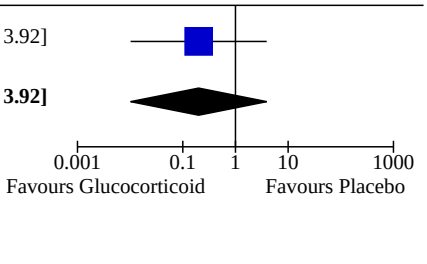
Heterogeneity: Tau² = 0.22; Chi² = 2.19, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Corticosteroid vs Placebo, Outcome 7: Failure to separate from CPB

Study or Subgroup	Glucocorticoid Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Keski Nisula 2013	0	20	2	20	100.0%	0.20 [0.01 , 3.92]
Total (95% CI)		**20**		**20**	**100.0%**	**0.20 [0.01 , 3.92]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MESH DESCRIPTOR Adrenal Cortex Hormones EXPLODE ALL AND CENTRAL:TARGET

#2 corticosteroid* AND CENTRAL:TARGET

#3 steroid* AND CENTRAL:TARGET

#4 corticoid* AND CENTRAL:TARGET

#5 MESH DESCRIPTOR Mineralocorticoids EXPLODE ALL AND CENTRAL:TARGET

#6 MESH DESCRIPTOR Glucocorticoids AND CENTRAL:TARGET

#7 glucocorticoid* AND CENTRAL:TARGET

#8 MESH DESCRIPTOR Hydrocortisone AND CENTRAL:TARGET

#9 hydrocortisone* AND CENTRAL:TARGET

#10 MESH DESCRIPTOR Dexamethasone AND CENTRAL:TARGET

#11 dexamethasone* AND CENTRAL:TARGET

#12 MESH DESCRIPTOR Methylprednisolone AND CENTRAL:TARGET

#13 methylprednisolone* AND CENTRAL:TARGET

#14 MESH DESCRIPTOR Prednisolone AND CENTRAL:TARGET

#15 prednisolone* AND CENTRAL:TARGET

#16 MESH DESCRIPTOR Prednisone AND CENTRAL:TARGET

#17 prednisone* AND CENTRAL:TARGET

#18 mineralocorticoid* AND CENTRAL:TARGET

#19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 MESH DESCRIPTOR Thoracic Surgery AND CENTRAL:TARGET

#21 MESH DESCRIPTOR Cardiovascular Surgical Procedures EXPLODE ALL AND CENTRAL:TARGET

#22 MESH DESCRIPTOR Cardiac Surgical Procedures EXPLODE ALL AND CENTRAL:TARGET

#23 ((cardiac or cardiol* or heart) NEAR2 (surgery or surgeries or surgical or procedure* or operat*)) AND CENTRAL:TARGET

#24 MESH DESCRIPTOR Cardiopulmonary Bypass AND CENTRAL:TARGET

#25 cardiopulmonary bypass AND CENTRAL:TARGET

#26 cpb AND CENTRAL:TARGET

#27 heart NEAR3 bypass AND CENTRAL:TARGET

#28 cardiac NEAR3 bypass AND CENTRAL:TARGET

#29 MESH DESCRIPTOR Heart Defects, Congenital AND CENTRAL:TARGET

#30 #29 OR #28 OR #27 OR #26 OR #25 OR #23 OR #24 OR #22 OR #21 OR #20

#31 #30 AND #19

#32 >1999:YR AND CENTRAL:TARGET

#33 #31 AND #32

MEDLINE Ovid

1. exp Adrenal Cortex Hormones/

2. (corticosteroid* or steroid*).tw.

3. corticoid*.tw.

4. exp Mineralocorticoids/

5. Mineralocorticoid*.tw.

6. Glucocorticoids/

7. Glucocorticoid*.tw.

8. Hydrocortisone/

9. Hydrocortisone*.tw.

10. Dexamethasone/

11. Dexamethasone*.tw.

12. Methylprednisolone/

13. Methylprednisolone*.tw.

14. Prednisolone/

15. Prednisolone*.tw.

16. Prednisone/

17. Prednisone*.tw.

18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. Thoracic surgery/

20. exp Cardiovascular Surgical Procedures/

21. exp cardiac surgical procedures/

22. ((cardiac or cardiol* or heart) adj2 (surgery or surgeries or surgical or procedure* or operat*)).tw.

23. Cardiopulmonary Bypass/

24. cardiopulmonary bypass.tw.

25. cpb.tw.

26. (heart adj3 bypass).tw.

27. (cardiac adj3 bypass).tw.

28. Heart Defects, Congenital/

29. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30. 18 and 29

31. randomized controlled trial.pt.

32. controlled clinical trial.pt.

33. randomized.ab.

34. placebo.ab.

35. drug therapy.fs.

36. randomly.ab.

37. trial.ab.

38. groups.ab.

39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40. exp animals/ not humans.sh.

41. 39 not 40

42. 30 and 41

43. limit 42 to yr="2000 -Current"

Embase Ovid

1. exp corticosteroid/

2. (corticosteroid* or steroid*).tw.

3. corticoid*.tw.

4. exp mineralocorticoid/

5. Mineralocorticoid*.tw.

6. glucocorticoid/

7. Glucocorticoid*.tw.

8. hydrocortisone/

9. Hydrocortisone*.tw.

10. dexamethasone/

11. Dexamethasone*.tw.

12. methylprednisolone/

13. Methylprednisolone*.tw.

14. prednisolone/

15. Prednisolone*.tw.

16. prednisone/

17. Prednisone*.tw.

18. or/1-17

19. thorax surgery/

20. exp cardiovascular surgery/

21. ((cardiac or cardiol* or heart) adj2 (surgery or surgeries or surgical or procedure* or operat*)).tw.

22. cardiopulmonary bypass/

23. cardiopulmonary bypass.tw.

24. cpb.tw.

25. (heart adj3 bypass).tw.

26. (cardiac adj3 bypass).tw.

27. congenital heart malformation/

28. or/19-27

29. 18 and 28

30. random$.tw.

31. factorial$.tw.

32. crossover$.tw.

33. cross over$.tw.

34. cross-over$.tw.

35. placebo$.tw.

36. (doubl$ adj blind$).tw.

37. (singl$ adj blind$).tw.

38. assign$.tw.

39. allocat$.tw.

40. volunteer$.tw.

41. crossover procedure/

42. double blind procedure/

43. randomized controlled trial/

44. single blind procedure/

45. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46. (animal/ or nonhuman/) not human/

47. 45 not 46

48. 29 and 47

49. limit 48 to yr="2000 -Current"

CPCI-S

13 #12 AND #11 Indexes=CPCI-S Timespan=2000-2020

12 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

11 #10 AND #5

10 #9 OR #8 OR #7 OR #6

9 TS=(cardiac NEAR/3 bypass)

8 TS=(heart NEAR/3 bypass)

7 TS=("cardiopulmonary bypass" OR cpb)

6 TS=((cardiac or cardiol* or heart) NEAR/2 (surgery or surgeries or surgical or procedure* or operat*))

5 #4 OR #3 OR #2 OR #1

4 TS=(Mineralocorticoid* OR Glucocorticoid* OR Hydrocortisone* OR Dexamethasone* OR Methylprednisolone* OR Prednisolone* OR Prednisone*)

3 TS=corticoid*

2 TS=steroid*

1 TS=corticosteroid*

Trials Registers

(cardiac OR heart)

(steroid OR prednisolone)

(surgery OR surgical OR procedure)

HISTORY

Protocol first published: Issue 8, 2018
Review first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

BG, JCVL, DPF, GPG, KIAM, BCR, AWLS and SLL wrote and edited the manuscript.

BG, JCVL, DPF, AWLS, and BCR assessed manuscripts for primary and secondary outcomes.

GPG, MAMA, SCS, GDA and SLL provided advice on outcomes.

DECLARATIONS OF INTEREST

BG: Dr Gibbison's institution is in receipt of project grants from the UK National Institute of Health Research and the British Heart Foundation to carry out research surrounding the topics of cardiac surgery, perioperative care and perioperative hypothalamic-pituitary-adrenal function including corticosteroids.

JCVL: none known.

KIAM: none known.

DPF: none known.

MAMA: none known.

GPG: none known.

AWLS: none known.

SCS: none known.

SLL: none known.

GDA: none known.

BCR: Prof Barnaby Reeves is funded (both part salary and research consumables) in part by the Cardiovascular theme of the NIHR Bristol Biomedical Research Centre.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK

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- UK NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

RoB 1 tool was used rather than RoB 2 as stated in the protocol due to RoB 2 not being implemented by the time it was required.

We did not search grey literature.

We used the Covidence systematic review manager. This changed the process required for many parts of the review. The system means that:

1. Data extraction and risk of bias assessment are done by the same people at the same time.
2. Only two people can do the processes of screening and data extraction at any one time
3. Only one person can resolve disputes

Therefore, only JCVL and BG undertook full text screening. We resolved disputes by consensus. JCVL and DPF extracted data and performed the assessment of risk of bias.

We transformed one study (Graham 2019) that had correctly used medians and range for length for continuous outcomes (e.g. length of stay). Other studies reported means and SD, even though they had non-normal distributions.

We did not perform sensitivity analyses for the reasons outlined in the text.

We did not perform I^2 statistical analysis due to the low number of studies and therefore the bias that this may cause under these conditions.

We did not perform subgroup analysis due to the low number of studies (< 10).

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects] [*therapeutic use]; Bias; Cardiac Surgical Procedures [*methods] [mortality]; Cardiopulmonary Bypass [*adverse effects] [mortality]; Cause of Death; Dexamethasone [therapeutic use]; Heart-Lung Machine [adverse effects]; Hospital Mortality; Hydrocortisone [therapeutic use]; Inflammation [etiology] [*prevention & control]; Intensive Care Units, Pediatric [statistics & numerical data]; Length of Stay; Methylprednisolone [therapeutic use]; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn