Prophylactic steroids for pediatric open heart surgery (Review)

Robertson-Malt S, Afrane B, Elbarbary M
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Prophylactic steroids for pediatric open heart surgery

Suzi Robertson-Malt¹, Barry Afrane², Mahmoud Elbarbary³

¹Nursing Affairs, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia. ²King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. ³King Abdulaziz Cardiac Center, Riyadh, Saudi Arabia

Contact address: Suzi Robertson-Malt, Nursing Affairs, King Faisal Specialist Hospital & Research Centre, MBC 01, PO BOX 3354, Riyadh, 11211, Saudi Arabia. santoshasuzi@yahoo.com. srobertson@kfshrc.edu.sa.

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ABSTRACT

Background
The immune response to cardiopulmonary bypass in infants and children can lead to a series of postoperative morbidities and mortality i.e. hemodynamic instability, increased infection and tachyarrhythmias. Administration of prophylactic doses of corticosteroids is sometimes used to try and ameliorate this pro-inflammatory response. However, the clinical benefits and harms of this type of intervention in the pediatric patient remains unclear.

Objectives
To systematically review the beneficial and harmful effects of the prophylactic administration of corticosteroids, compared with placebo, in pediatric open heart surgery.

Search methods
The trials registry of the Cochrane Heart Group, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Issue 4, 2006), MEDLINE (1966 to January 2007), EMBASE (1980 to January 2007) were searched. An additional handsearch of the EMRO database for Arabic literature was performed. Grey literature was searched and experts in the field were contacted for any unpublished material. No language restrictions were applied.

Selection criteria
All randomized and quasi-randomized controlled trials of open heart surgery in the pediatric population that received corticosteroids pre-, peri- or post-operatively, with reported clinical outcomes in terms of morbidity and mortality.

Data collection and analysis
Eligible studies were abstracted and evaluated by two independent reviewers. All meta-analyses were completed using RevMan4.2.8. Weighted mean difference (WMD) was the primary summary statistic with data pooled using a random-effects model.

Main results
All cause mortality could not be assessed as the data reports were incomplete. There was weak evidence in favor of prophylactic corticosteroid administration for reducing intensive care unit stay, peak core temperature and duration of ventilation [WMD (95% CI) -0.50 hours (-1.41 to 0.41); -0.20°C (-1.16 to 0.77) and -0.63 hours (-4.02 to 2.75), respectively].
**Authors’ conclusions**

The use of prophylactic steroids in pediatric patients to reduce postoperative complications commonly experienced following cardiopulmonary bypass surgery is not supported by the existing evidence. Further well designed and adequately powered randomized controlled trials are needed to more accurately estimate the benefit and harm of this intervention.

**PLAIN LANGUAGE SUMMARY**

Prophylactic steroids for pediatric open heart surgery

After open heart surgery in children complications can occur such as rapid heart rate, breathlessness, low blood pressure, poor circulation, fever, and reduced urine output. These complications are caused by disturbances to the body’s metabolism which, in turn, may be due to an immune reaction made by the body’s defence systems in response to the surgery. These complications can be life-threatening if left untreated. Corticosteroids are anti-inflammatory drugs that are sometimes used to treat this immune response. However the clinical benefits and harms of corticosteroids in open heart surgery remain unclear. The objective of this study was to review systematically the existing research to determine the effects of corticosteroids in these circumstances. All trials where patients received corticosteroids before, during or after operation were considered. Of the trials found, only four involving 127 children were eligible for inclusion. Unfortunately the most important outcome, death, could not be assessed because of incomplete reports. There was only weak evidence in favor of the use of corticosteroids, with duration of ventilatory support and stay in intensive care being reduced by about half a day compared with control groups. Due to the poor quality of the trials, the use of corticosteroids to reduce the inflammatory response following surgery is of uncertain benefit.

**BACKGROUND**

**Description of the condition and intervention**

Systemic inflammatory response syndrome (SIRS) that ensues after cardiopulmonary bypass can be a major cause of morbidity and mortality. The physiological pathway that leads to this syndrome is complex and multifaceted. When left uncontrolled, it has been implicated in the clinical deterioration of numerous body systems such as the neurological, cardiac, renal, pulmonary, vascular and haematological systems (El Barbary 2002). The reported incidence of overall complications ranges from 4% to 44% (Johnson 1999; Kimmel 1991). In the pediatric patient, major neurological complications have been reported as high as 6%. Age has been shown to be a significant determinant of the level of immunological response (Duval 1999). The younger the patient, the greater the immune response to cardiopulmonary bypass (Duval 1999). In particular, the level of circulating cytokine has been shown to be affected by age. For this reason, conscientious effort on the clinician’s behalf needs to be made to intervene in this downward cascade of events, including the use of various pharmacological agents such as steroids aimed at improving the postoperative care and survival of the pediatric cardiac surgical patient.

SIRS is a pro-inflammatory state that can cause tachycardia, tachypnea/hyperpnea, hypotension, hypoperfusion, oliguria, leukocytosis/leukopenia, pyrexia/hypothermia, and the need for volume infusion. Metabolic acidosis is a frequent companion to SIRS, and is driven principally from lactate production (Budette 2004). The pathophysiology of SIRS in the setting of cardiopulmonary bypass is complex but essentially involves the body’s reaction to the contact of the cardiopulmonary bypass apparatus, resulting in the activation of endothelial cells, leukocytes, platelets and visceral proteins plus the activation of complements and the subsequent initiation of coagulation, fibrinolytic and kallikrein cascades (Casey 1993; Drusin 1965; Budette 2004; Tarnok 2001). In addition, circulating endotoxins and cytokines may be elevated resulting in increasing endothelial cell permeability (Casey 1993; Niazi 1979). White blood cells migrate across the ‘leaky’ blood vessel walls into other tissues and various serum proteases and neutrophil elastase are released that in turn exaggerate both vascular and cellular damage (Tarnok 2001). It is known that neonate, infant and adult myocardium each have a distinct systemic response to cardiopulmonary bypass (Friedrich 2003; Lequier 2000; Schroeder 2003). The type of operation performed in the child with congenital heart disease coupled with the preoperative oxidative stress of the congenital anomaly all present fundamental physiological differences that cannot be extrapolated to the adult population. Compared with the adult patient, the child with a congenital heart defect is seen to be at an increase risk for...
endotoxemia pre- and peri-operatively due to the low perfusion of the intestine and bowel or due to the relatively abnormal intestinal perfusion with cyanotic arterial blood (Lequier 2000). Of greatest concern related to the prophylactic use of corticosteroids in a complex surgical setting is the influence that steroids have on insulin/glycemic control. Hyperglycemia is not uncommon with the use of systemic corticosteroids. Landmark research by Van den Berghe and colleagues demonstrated the substantial impact that uncontrolled hyperglycemia, in both diabetics and non-diabetics, can play on postoperative morbidities and mortality (Van den Berghe 2001).

Why it is important to do this review

The clinical benefits and harms of corticosteroid treatment following cardiopulmonary bypass in pediatric patients are not clear (Mayumi 1997; Morton 1976; Seghaye 1993). While much has been written about the favorable use of steroids, other studies refute this claim on the basis that steroids alone may not be adequate to arrest the multi-faceted, complex and dynamic nature of SIRS (Maharaj 2004). Additionally, inconsistency exists in the choice of agent (glucocorticoid or mineralocorticoid), preferred dosage regimen and complications associated with its administration (Clapp 1998; Niazi 1979; Wakabayashi 1993; Wilson 1994). It is therefore prudent to systematically review the existing research to assist the clinician in their decision making toward minimizing the deleterious effects of cardiopulmonary bypass in pediatric patients.

OBJECTIVES

To assess the short-term beneficial and harmful effects, in relation to hospital morbidity and mortality, of the administration of corticosteroids during either the pre-, peri- or postoperative period of cardiopulmonary bypass in pediatric open heart surgery.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized and quasi-randomized clinical trials were included irrespective of blinding, publication status, or language.

Types of participants

Male or female patients, aged between 31 days and 18 years from any ethnic origin, undergoing open heart surgery with cardiopulmonary bypass for a congenital cardiac anomaly. All trials where they defined their population/sample as pediatric were included. Neonates and patients under going heart transplantation were excluded.

Types of interventions

All studies including one or more of the following, plus standard therapy, were considered for inclusion in this review:

- Any type of corticosteroid, at any dose or administration regime.
- Corticosteroids compared with no intervention, placebo, supportive therapy, or conventional therapy.
- Trials of corticosteroids plus supportive therapy versus supportive therapy alone were included. Co-interventions were allowed as long as all arms of the randomized allocation received the same co-interventions.

Types of outcome measures

Primary outcome measures (at the end of treatment and at maximal follow-up after the end of treatment):

- All-cause mortality (0-30 days post operative); and
- Morbidity (0-72 hours post operative).

Secondary outcome measures (all other complications within the first 72 hours post surgery):

- Temperature >38°C or <36°C;
- Heart rate for age limit;
- Respiratory rate > 40 breaths/min;
- Acidosis (elevated lactate levels or reduced pH);
- Sepsis: WBC > 12,000 cells/mm³, > 4000 cells/mm³ or, > 10% immature (band) forms;
- Prolonged length of stay;
- Hemodynamic instability; and
- Inotrope requirements > 10 ucg/kg/min for longer than 48 hours.

Adverse events were classified into two principle groups. (1) Serious: death; life-threatening; required hospitalization or prolongation of hospitalization; or resulted in persistent or significant disability. (2) Non-serious: any event that may jeopardise the patient and require intervention to prevent one of the former serious adverse events from occurring.

Search methods for identification of studies

Electronic searches

The trials registry of the Cochrane Heart Group, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Issue 4, 2006), MEDLINE (1966 to January 2007) and EMBASE (1980 to January 2007) were searched. In addition to the terms below, filters were used to identify randomized controlled trials on MEDLINE and EMBASE using the Cochrane Collaboration’s recommended ‘highly sensitive search strategies’. Studies in all languages were sought.
The search strategy for CENTRAL on The Cochrane Library is listed below. Strategies for other databases are detailed in additional tables Table 1; Table 2; Table 3. Terms in capitals are exploded MeSH terms and those in lower case are text word searches.

#1 CARDIAC SURGICAL PROCEDURES
#2 (cardiac next surger*)
#3 (heart next surger*)
#4 cardiosurgery
#5 CARDIOPULMONARY BYPASS
#6 EXTRACORPOREAL CIRCULATION
#7 (cardiopulmonary next bypass*)
#8 (#1 or #2 or #3 or #4 or #5 OR #6 or #7)
#9 ANTI-INFLAMMATORY AGENTS
#10 IMMUNOSUPPRESSIVE AGENTS
#11 ADRENAL CORTEX HORMONES
#12 steroid*
#13 corticoster*
#14 immunosuppress*
#15 GLUCOCORTICOIDs
#16 MINERALOCORTICOIDS
#17 predniso*
#18 dexamethasone*
#19 hydrocortiso*
#20 methylpredniso*
#21 budesonide*
#22 cortiso*
#23 fludrocortiso*
#24 betamethasone
#25 (#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)
#26 (#18 or #19 or #20 or #21 or #22 or #23 or #24)
#27 (#25 or #26)
#28 (#8 and #27)
#29 child*
#30 adolessenc*
#31 pediatric*
#32 paediatric*
#33 infant*
#34 (#29 or #30 or #31 or #32 or #33)
#35 (#28 and #34)

Handsearches
No relevant Arabic publications were identified from the middle eastern region that were not already included on MEDLINE or the EMRO (Eastern Mediterranean Regional Office) database of WHO. No additional trials were located from the handsearched reference lists of included trials.

Additional searches
Ongoing trials were searched through the National Research Register and the web site (www.controlled-trials.com) and grey literature through the database of SIGLE (System for Information on Grey Literature in Europe). Conference Papers Index was used to search for eligible trials, with no additional abstracts located. Authors and experts in this field were contacted to ask if they knew of any other research either being conducted or completed but unpublished. No additional trials were identified from these personnel communications.

Data collection and analysis

Selection of trials for inclusion
Two reviewers (Robertson-Malt and Afrane) independently selected the trials by reading titles and abstracts of all identified citations. All potentially eligible studies were retrieved for further assessment according to the protocol’s pre-specified criteria. Any disagreement was resolved by discussion with a third party (El Barbary).

Data extraction
Data extraction was carried out independently by the same reviewers, using standard data extraction forms (Table 4). The methodological rigour and clinical significance of each trial was assessed independently by each reviewer using the established standards of the Cochrane Collaboration. The quality assessment process was not blinded to authorship or journal of publication and paid particular attention to the randomization procedure (especially allocation concealment), with studies being rated one of the following.

1. Allocation concealment
A (adequate): randomization method described would not allow investigator/participant to know or influence intervention group before eligible participant entered the study.
B (unclear): randomization stated but no information on method used available.
C (inadequate): method of randomization used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group.

2. Blinding
Investigators: Yes/no/not stated.
Participants: Yes/no/not stated.
Outcome assessor: Yes/no/not stated.
Data analysis: Yes/no/not stated.

3. Intention-to-treat analysis
Yes: specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
No: not specifically reported but confirmed on study assessment.
Unclear: unable to determine or confirm with authors.

4. Completeness to follow-up
Percentage of patients lost to follow-up.
If the above data was not available in the trial reports, further information was sought by correspondence with the principal investigator(s). A total of six authors were contacted. Two responded with no additional information to give. Differences in data extraction was resolved by discussion.

Data synthesis
Of the included studies, continuous scales of measurement were used to assess the effects of treatment (length of stay). The weighted mean difference (WMD) was used if trials used similar scales of measurement whilst the standard mean difference was used when different scales of measurement were used. Data was pooled using the random-effects model. Heterogeneity was analysed using a chi-square test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance, and also by $I^2$, which is calculated from Cochran Q and describes the percentage of total variation across studies that is due to heterogeneity (Higgins 2003). A value of 0 indicates no observed heterogeneity and larger values indicate increasing heterogeneity.

The data is displayed in forest plots. Adverse effects are tabulated and assessed with descriptive techniques, as they are different for the various agents used.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.

Of the 626 titles and abstracts found, 17 studies were identified as potentially suitable (Figure 1). A total of 11 potential trials were excluded. Five excluded studies did not fulfil the methodological criteria: one descriptive study (Chew 2001); one multisite survey (Checchia 2005); one prospective controlled study (Gessler 2005); one retrospective design (Shore 2001); and one non-randomised study (Wilson 1994). Three studies were excluded due to unclear outcome measures (Duval 1999; Malagon 2005a; Mott 2001) and three studies were excluded because participants did not meet inclusion criteria (Eguchi 1969; Malagon 2005b; Toledo-Pereyra 1980). A breakdown of each of the excluded studies addressing the specifics of their study design and outcomes can be seen/found in the excluded studies table. One trial (Huber 1992) is awaiting further assessment following translation.
Figure 1. QUOROM statement

Potentially relevant publications identified and screened for retrieval: 626

Papers excluded on the basis of title and abstract (generally due to lack of suitability of study design or intervention): 609

Papers retrieved for more detailed evaluation: 17

Excluded:
- Methodological criteria - 5
- Unclear outcomes - 3
- Participant criteria - 3
- Total - 11

Awaiting assessment - 1

Papers included: 5 reports of 4 studies

RCTs with outcome data useful in the systematic review: 4

By outcome:
- Mortality - 1
- Length of stay in ICU - 3
- Duration of ventilation - 3
- Peak core temp - 3

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The remaining five reports of four studies were identified by full text review to be RCTs or quasi-RCTs, providing a total of 127 participants. There was no disagreement between reviewers regarding inclusion of trials.

Risk of bias in included studies

Study quality was essentially poor. All the trials were small and did not discuss sample size determination or whether the study was adequately powered to demonstrate significance. Only one of the four included studies had adequate allocation concealment (Bronicki 2000). All authors were contacted for further methodological detail but no additional information was provided. Intention-to-treat analysis was not openly discussed by any author. All four studies were ruled ‘adequate’ for inclusion from study assessment.

Effects of interventions

Summary of the four included trials

1. Bronicki 2000
A randomized prospective, double blinded study of 29 children with a mean age of 28 months. Fifteen children received 1mg/kg of intravenous (iv) dexamethasone and 14 received iv saline solution 1 hour prior to cardiodiopulmonary bypass. Dexamethasone caused an eightfold decrease in interleukin-6 levels and a greater than threefold decrease in tumour necrosis factor-a levels after cardiodiopulmonary bypass (P < 0.05). Complement component C3a and absolute neutrophil count were not affected by dexamethasone. The mean rectal temperature for the first 24 hours postoperatively was significantly lower in the group given dexamethasone than in the controls (37.2° +/- 0.4°C versus 37.7 +/- 0.4°C; P = 0.007). Dexamethasone-treated patients required less supplemental fluid during the first 48 hours (22 +/- 28 mL/kg versus 47 +/- 34 mL/kg; P = 0.04). Compared with controls, dexamethasone-treated children had significantly lower alveolar-arterial oxygen gradients during the first 24 hours (144 +/- 108 mmHg versus 214 +/- 118 mmHg; P = 0.02) and required less mechanical ventilation (median duration, 3 days versus 5 days; P = 0.02).

2. Lindberg 2003
A randomized prospective study of 40 children with weight > 10 kg and a mean age of 52 months. Dexamethasone 1mg/kg or saline placebo, prior to cardiopulmonary bypass. Dexamethasone decreased C-reactive protein concentration on the first postoperative day (P < 0.05), but did not affect the release of vWF:Ag or S100B. There was no significant difference in oxygenation, body temperature, fluid balance, leukocyte and platelet counts, days in the intensive care unit (ICU) or days on mechanical ventilation between the placebo and dexamethasone-treated groups.

3. Schroeder 2003
A randomized, prospective study of 29 children with a mean age of 4 months, to receive preoperative and intraoperative methylprednisone (30 mg/kg 4 hours before bypass and in bypass prime, n = 14) or intraoperative methylprednisone only (30 mg/kg, n = 15). Postoperative outcome was assessed by intubation time, CICU length of stay, fluid balance, arterio-venous O2 difference and inotrope requirements. Compared with intraoperative methylprednisone alone, combined preoperative and intraoperative methylprednisone was associated with reduced myocardial mRNA expression for IL-6, MCP-1, and ICAM-1 both before and after bypass (P < 0.05). Patients who received combined steroids had lower serum IL-6 and increased IL-10 at end-bypass (P < 0.05), although differences were negligible by 24 hours. Combined methylprednisolone treatment was associated with reduced fluid requirements, lower body temperature, and lower arterio-venous O2 difference for the first 24 hours after surgery (P < 0.05), along with trends toward improvement in other clinical outcomes.

4. Varan 2002
A randomized, prospective trial of 30 children with a mean age of 48 months, to receive 30 mg/kg of iv methylprednisolone (n = 15) compared with 2mg/kg iv methylprednisolone (n = 15) prior to cardiodiopulmonary bypass. Postoperative core temperature, duration of mechanical ventilation, period of stay in intensive care unit and oxygenation indices did not significantly differ in the two groups.

Primary outcomes

Mortality
Only one trial reported morbidity: Bronicki 2000 reported one death. The child was assigned to the treatment group (n = 1/15).

Secondary outcomes

Only two of the anticipated secondary outcomes could be reported as a pooled analysis: length of stay in ICU and peak core temperature. Data were available for duration of ventilation and are presented here. No adverse events related to the use of corticosteroids were reported in any of the studies.

Length of stay in ICU
All of the included studies reported length of stay in ICU (Bronicki 2000; Lindberg 2003; Schroeder 2003; Varan 2002). However only three of the studies could be pooled as Bronicki’s report did not provide the necessary data (means and standard deviations) to be included in the pooled comparison. The pooled data of the three studies, which equates to a total of 98 participants, failed to demonstrate benefit with the use of iv steroids to reduce the postoperative length of stay in ICU (WMD -0.50 hours, 95% CI -1.41 to 0.41).

Peak core temperature
Three out of four of the included studies reported peak core temperature (Bronicki 2000; Schroeder 2003; Varan 2002). The pooled data of the three studies, which equates to a total of 89 participants, failed to demonstrate benefit with the use of iv steroids to reduce the peak core temperature experienced during the post-
operative period (WMD -0.20°C, 95% CI -1.16 to 0.77).

**Duration of ventilation**

All of the included studies reported duration of ventilation (Bronicki 2000; Lindberg 2003; Schroeder 2003; Varan 2002). However, only three of the studies could be pooled as, Bronicki’s report did not provide the necessary data (means and standard deviations) to be included in the pooled comparison. The pooled data of the three studies, which equates to a total of 98 participants, failed to demonstrate benefit with the use of iv steroids to reduce the duration of ventilation (WMD -0.63 hours, 95% CI -4.01 to 2.76).

**DISCUSSION**

Each of the four included studies demonstrates that treating the pediatric patient with intravenous steroids may play a role in the attenuation of the inflammatory response in the post-operative period as evident by the trend in reduced length of stay in ICU, duration of ventilation and fever. The pooled comparisons however fail to demonstrate any benefit. This meta-analysis has several potential problems because of the limitations of the primary data. Overall the quality of the studies is poor with only one of the four trials demonstrating adequate allocation concealment. Trials with inadequate allocation concealment can exaggerate the efficacy of the experimental treatment by 30-40% (Schultz 1995) and meta-analyses of low quality trials may overestimate the benefit of therapy (Moher 1998). This observation makes the need for adequately powered, well designed and reported trials necessary. The effects of publication bias could not be formally assessed because of the small number of studies. Key investigators in this field, who were contacted, did not reveal any unpublished data.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

This systematic review and meta-analysis of RCTs demonstrates that the prophylactic use of intravenous steroids in the pediatric patient does not significantly reduce post-operative complications as measured by length of stay in ICU, peak core temperature and duration of ventilation. There is insufficient reporting of the adverse effects of steroids (mainly sepsis and bleeding). The decision to use steroids prophylactically to attenuate the inflammatory response in the post-operative period is not supported by available evidence.

**Implications for research**

Further well designed and adequately powered RCTs are needed to adequately estimate the benefit and harm of this intervention.

**ACKNOWLEDGEMENTS**

We thank Theresa Moore, Katherine Wornell and Margaret Burke of the Cochrane Heart Group for their help and assistance with the protocol. We thank all participants who were in the clinical trials themselves to contribute knowledge of corticosteroids for prophylaxis in pediatric open heart surgery. Also warm appreciation is given to the excellent support provided by the National Gulf Centre for Evidence-Based Medicine through their educational support and systematic review workshops.

**REFERENCES**

**References to studies included in this review**

Bronicki 2000 [published data only]

Lindberg 2003 [published data only]

Schroeder 2003 [published data only]

Varan 2002 [published data only]

**References to studies excluded from this review**
Chew 2001 [published data only]

Duval 1999 [published data only]

Eguchi 1969 [published data only]

Gessler 2005 [published data only]

Malagon 2005a [published data only]

Malagon 2005b [published data only]

Mott 2001 [published data only]

Shore 2001 [published data only]

Toledo-Pereyra 1980 [published data only]

Wilson 1994 [published data only]

References to studies awaiting assessment

Huber 1992 [published data only]

Additional references

Budette 2004

Casey 1993

Clapp 1998

Drusin 1965

El Barbary 2002

Friedrich 2003

Higgins 2003

Johnson 1999
Kimmel 1991

Lequier 2000

Maharaj 2004

Mayumi 1997

Moher 1998

Morton 1976

Niazi 1979

Schultz 1995

Seghaye 1993

Tarnok 2001

Van den Berghe 2001

Wakabayashi 1993

* Indicates the major publication for the study
### Characteristics of included studies [ordered by study ID]

#### Bronicki 2000

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<th>RCT (randomized by pharmacy)</th>
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<td>Participants</td>
<td>29 (17M/12F)</td>
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<td></td>
<td>Mean age: intervention = 28 months; control = 25 months</td>
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<tr>
<td>Interventions</td>
<td>Intervention group: 15 = dexamethasone 1 mg/kg (maximum dose 10 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Control group: 14 = placebo of N/Saline</td>
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<tr>
<td>Outcomes</td>
<td>Core temp: intervention = 37.2; control = 37.7</td>
</tr>
<tr>
<td></td>
<td>Supplemental fluids: intervention = 22.1 mL/kg; control = 46.7 mL/kg</td>
</tr>
<tr>
<td></td>
<td>Length of stay in ICU: intervention = 4 days; control = 7 days</td>
</tr>
<tr>
<td></td>
<td>Duration of ventilation: intervention = 3 days; control = 5 days</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine levels: intervention = 7%; control = 50%</td>
</tr>
<tr>
<td></td>
<td>Morbidity: intervention = 1; control = 0</td>
</tr>
<tr>
<td></td>
<td>Wound infection: intervention = 0; control = 0</td>
</tr>
<tr>
<td>Notes</td>
<td>Exclusion criteria: preoperative glucocorticoids or NSAI, ASD, CPB time &gt; 200 min; Aortic xclamp &gt; 120 min</td>
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<td></td>
<td>Blinding: 3/4</td>
</tr>
<tr>
<td></td>
<td>Intention to treat: yes</td>
</tr>
<tr>
<td></td>
<td>Complete follow up: 0%</td>
</tr>
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</table>

#### Lindberg 2003

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT (pharmacy coding - clinicians blinded to treatment)</th>
</tr>
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<tbody>
<tr>
<td>Participants</td>
<td>39</td>
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<tr>
<td></td>
<td>Mean age: intervention = 4.3 years; control = 4.5 years</td>
</tr>
<tr>
<td>Interventions</td>
<td>Intervention group: 19 = dexamethasone 1 mg/kg prior to CPB</td>
</tr>
<tr>
<td></td>
<td>Control group: 20 = placebo of N/Saline</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Duration of ventilation: intervention = 3.3 hours; control = 3.7 hours</td>
</tr>
<tr>
<td></td>
<td>Length of stay in ICU: intervention = 2 days; control = 2 days</td>
</tr>
<tr>
<td></td>
<td>Fluid balance: intervention = 37 mL; control = 102 mL</td>
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#### Risk of bias

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<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
**Lindberg 2003**  
(Continued)

| Notes | Blinding: 4/4  
|       | Intention to treat: yes  
|       | Complete follow up: 0% |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

**Schroeder 2003**

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT (double blind)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>29 (18M/12F)</td>
</tr>
<tr>
<td></td>
<td>Mean age: intervention = 4.4 months; control = 2.1 months</td>
</tr>
</tbody>
</table>
| Interventions          | Intervention group: 14 = methylprednisone 4 hours pre- and intra-operatively 30 mg/kg  
|                        | Control group: 15 = methyl 30 mg/kg intra-operatively only |
| Outcomes               | Core temp: intervention = 36.4; control = 37.1  
|                        | Supplemental fluids: intervention = 111 mL/kg; control = 134 mL/kg  
|                        | Length of stay in ICU: intervention = 4.4 days; control = 6.1 days  
|                        | Duration of ventilation: intervention = 74 hours; control = 85 hours |
| Notes                  | Exclusion criteria: sepsis, chronic or acute lung disease, immunodeficiency, gastrointestinal bleeding  
|                        | Blinding: 3/4  
|                        | Intention to treat: yes  
|                        | Complete follow up: 0% |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

**Varan 2002**

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT (random assignment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Mean age: intervention = 3.4 years; control = 4.5 years</td>
</tr>
</tbody>
</table>
| Interventions          | Intervention group: 15 = methylprednisone 30 mg/kg for 30 min  
|                        | Control group: 15 = 2 mg/kg methyl prior to cardiopulmonary bypass |
Outcomes

- Core temp: intervention = 39; control = 38.6
- Blood loss: intervention = 15.8 mL/kg/day; control = 18.1 mL/kg/day
- Urine volume: intervention = 2.6 mL/kg/hour; control = 2.1 mL/kg/hour
- Length of stay in ICU: intervention = 65.9 hours; control = 62.2 hours
- Duration of ventilation: intervention = 9 hours; control = 10 hours
- Serum creatinine levels: intervention = 0.6 mg/dL; control = 0.5mg/dL
- Inotropic support: intervention = 193 mg/kg; control = 190 mg/kg

Notes

- Blinding: 1/4
- Intention to treat: yes
- Complete follow up: 0%

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

NSAI = non steroidal anti-inflammatory; ASD = atrial septal defect; CPB = cardiopulmonary bypass.

Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checchia 2005</td>
<td>Multisite survey</td>
</tr>
<tr>
<td>Chew 2001</td>
<td>Descriptive study</td>
</tr>
<tr>
<td>Duval 1999</td>
<td>Randomized trial - primary outcome of circulating cytokines</td>
</tr>
<tr>
<td>Eguchi 1969</td>
<td>Adults undergoing coronary bypass surgery</td>
</tr>
<tr>
<td>Gessler 2005</td>
<td>Prospective control study</td>
</tr>
<tr>
<td>Malagon 2005a</td>
<td>Randomized controlled trial - primary outcome intestinal permeability measures. Did include some similar outcome measures: Duration of Ventilation; Core temp - however data was incomplete - no recording of SD</td>
</tr>
<tr>
<td>Malagon 2005b</td>
<td>Included neonates</td>
</tr>
<tr>
<td>Mott 2001</td>
<td>Double blind randomized control trial - primary outcome postpericarditomy syndrome</td>
</tr>
<tr>
<td>Shore 2001</td>
<td>Retrospective audit to assess steroids effect on level of epinephrine requirements</td>
</tr>
</tbody>
</table>
(Continued)

<table>
<thead>
<tr>
<th>Toledo-Pereyra 1980</th>
<th>Adult coronary artery bypass surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson 1994</td>
<td>Prospective controlled trial</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. Length of Stay ICU

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Total length of time in ICU post CPB</td>
<td>3</td>
<td>98</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.50 [-1.41, 0.41]</td>
</tr>
</tbody>
</table>

### Comparison 2. Duration of Ventilation

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Total number of hours ventilated post CPB</td>
<td>3</td>
<td>98</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.63 [-4.01, 2.76]</td>
</tr>
</tbody>
</table>

### Comparison 3. Peak Core Temperature

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Peak Core Temperature in the first 24 hrs post CPB</td>
<td>3</td>
<td>89</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.20 [-1.16, 0.77]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Length of Stay ICU, Outcome 1 Total length of time in ICU post CPB.

**Review:** Prophylactic steroids for pediatric open heart surgery

**Comparison:** 1 Length of Stay ICU

**Outcome:** 1 Total length of time in ICU post CPB

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Glucocorticosteroid</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroeder 2003</td>
<td>14</td>
<td>15</td>
<td>-1.70 [-3.37, -0.03]</td>
<td>22.2 %</td>
<td></td>
</tr>
<tr>
<td>Lindberg 2003</td>
<td>19</td>
<td>20</td>
<td>-0.40 [-1.34, 0.54]</td>
<td>45.9 %</td>
<td></td>
</tr>
<tr>
<td>Varan 2002</td>
<td>15</td>
<td>15</td>
<td>0.20 [-1.10, 1.50]</td>
<td>31.8 %</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 48 50 100.0 % -0.50 [-1.41, 0.41]

Heterogeneity: Tau² = 0.24; Chi² = 3.12, df = 2 (P = 0.21); I² = 36%

Test for overall effect: Z = 1.08 (P = 0.28)

### Analysis 2.1. Comparison 2 Duration of Ventilation, Outcome 1 Total number of hours ventilated post CPB.

**Review:** Prophylactic steroids for pediatric open heart surgery

**Comparison:** 2 Duration of Ventilation

**Outcome:** 1 Total number of hours ventilated post CPB

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Glucocorticosteroid</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroeder 2003</td>
<td>14</td>
<td>15</td>
<td>-11.00 [-56.09, 34.09]</td>
<td>0.6 %</td>
<td></td>
</tr>
<tr>
<td>Varan 2002</td>
<td>15</td>
<td>15</td>
<td>-1.00 [-7.39, 5.39]</td>
<td>28.1 %</td>
<td></td>
</tr>
<tr>
<td>Lindberg 2003</td>
<td>19</td>
<td>20</td>
<td>-0.40 [-4.41, 3.61]</td>
<td>71.3 %</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 48 50 100.0 % -0.63 [-4.01, 2.76]

Heterogeneity: Tau² = 0.0; Chi² = 0.23, df = 2 (P = 0.89); I² = 0.0%

Test for overall effect: Z = 0.36 (P = 0.72)
Analysis 3.1. Comparison 3 Peak Core Temperature, Outcome 1 Peak Core Temperature in the first 24 hrs post CPB.

Review: Prophylactic steroids for pediatric open heart surgery

Comparison: 3 Peak Core Temperature

Outcome: 1 Peak Core Temperature in the first 24 hrs post CPB.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Glucocorticosteroids</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronicki 2000</td>
<td>15 37.3 (0.4)</td>
<td>14 37.7 (4)</td>
<td>14.3 % -0.40 [ -2.51, 1.71 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schroeder 2003</td>
<td>14 36.4 (0.1)</td>
<td>15 37.1 (0.3)</td>
<td>43.9 % -0.70 [ -0.86, -0.54 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varan 2002</td>
<td>15 39 (0.6)</td>
<td>16 38.6 (0.4)</td>
<td>41.8 % 0.40 [ 0.04, 0.76 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>44</td>
<td>45</td>
<td>100.0 % -0.20 [ -1.16, 0.77 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.55; Chi² = 29.73, df = 2 (P<0.00001); I² =93%

Test for overall effect: Z = 0.40 (P = 0.69)

ADDITIONAL TABLES

Table 1. Search methods for MEDLINE on Ovid

1 exp Cardiac Surgical Procedures/
2 Cardiopulmonary Bypass/
3 cardiac surger$.tw.
4 heart surger$.tw.
5 cardiosurgery.tw.
6 cardiopulmonary bypass$.tw.
7 or/1-6
8 exp Anti-Inflammatory Agents/
9 exp Adrenal Cortex Hormones/
10 Mineralocorticoids/
11 steroid$.tw.
12 corticosteroid$.tw.
13 immunosuppress$.tw.
14 predniso$.tw.
15 dexamethason$.tw.
16 methylprednison$.tw.
17 hydrocortiso$.tw.
18 budesonide$.tw.
19 cortiso$.tw.
### Table 1. Search methods for MEDLINE on Ovid  (Continued)

<table>
<thead>
<tr>
<th>Step</th>
<th>Search Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>fludrocortiso$.tw.</td>
</tr>
<tr>
<td>21</td>
<td>or/8-20</td>
</tr>
<tr>
<td>22</td>
<td>7 and 21</td>
</tr>
<tr>
<td>23</td>
<td>limit 22 to “all child (0 to 18 years)”</td>
</tr>
<tr>
<td>24</td>
<td>randomized controlled trial.pt.</td>
</tr>
<tr>
<td>25</td>
<td>controlled clinical trial.pt.</td>
</tr>
<tr>
<td>26</td>
<td>Randomized controlled trials/</td>
</tr>
<tr>
<td>27</td>
<td>random allocation.sh.</td>
</tr>
<tr>
<td>28</td>
<td>double blind method.sh.</td>
</tr>
<tr>
<td>29</td>
<td>single-blind method.sh.</td>
</tr>
<tr>
<td>30</td>
<td>or/24-29</td>
</tr>
<tr>
<td>31</td>
<td>exp animals/ not human/</td>
</tr>
<tr>
<td>32</td>
<td>30 not 31</td>
</tr>
<tr>
<td>33</td>
<td>clinical trial.pt.</td>
</tr>
<tr>
<td>34</td>
<td>exp Clinical trials/</td>
</tr>
<tr>
<td>35</td>
<td>(clin$ adj25 trial$).ti,ab.</td>
</tr>
<tr>
<td>36</td>
<td>((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.</td>
</tr>
<tr>
<td>37</td>
<td>placebos.sh.</td>
</tr>
<tr>
<td>38</td>
<td>placebo$.ti,ab.</td>
</tr>
<tr>
<td>39</td>
<td>random$.ti,ab.</td>
</tr>
<tr>
<td>40</td>
<td>research design.sh.</td>
</tr>
<tr>
<td>41</td>
<td>or/33-40</td>
</tr>
<tr>
<td>42</td>
<td>41 not 31</td>
</tr>
<tr>
<td>43</td>
<td>32 or 42</td>
</tr>
<tr>
<td>44</td>
<td>43 and 23</td>
</tr>
</tbody>
</table>

### Table 2. Search methods for EMBASE on Ovid

<table>
<thead>
<tr>
<th>Step</th>
<th>Search Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp heart surgery/</td>
</tr>
<tr>
<td>2</td>
<td>Cardiopulmonary Bypass/</td>
</tr>
<tr>
<td>3</td>
<td>cardiac surger$.tw.</td>
</tr>
<tr>
<td>4</td>
<td>heart surger$.tw.</td>
</tr>
<tr>
<td>5</td>
<td>cardiosurgery.tw.</td>
</tr>
<tr>
<td>6</td>
<td>cardiopulmonary bypass$.tw.</td>
</tr>
<tr>
<td>7</td>
<td>or/1-6</td>
</tr>
<tr>
<td>8</td>
<td>exp Antiinflammatory Agent/</td>
</tr>
<tr>
<td>9</td>
<td>exp Corticosteroid/</td>
</tr>
<tr>
<td>10</td>
<td>steroid$.tw.</td>
</tr>
<tr>
<td>11</td>
<td>corticosteroid$.tw.</td>
</tr>
<tr>
<td>12</td>
<td>immunosuppress$.tw.</td>
</tr>
<tr>
<td>13</td>
<td>predniso$.tw.</td>
</tr>
<tr>
<td>14</td>
<td>dexamethason$.tw.</td>
</tr>
<tr>
<td>15</td>
<td>methylprednison$.tw.</td>
</tr>
<tr>
<td>16</td>
<td>hydrocortiso$.tw.</td>
</tr>
<tr>
<td>17</td>
<td>budesonide$.tw.</td>
</tr>
<tr>
<td>18</td>
<td>cortiso$.tw.</td>
</tr>
</tbody>
</table>
Table 2. Search methods for EMBASE on Ovid (Continued)

19 fludrocortisone.tw.
20 or/8-19
21 7 and 20
22 clinical trial/
23 randomized controlled trial/
25 trial$tw.
26 follow-up.tw.
27 double blind procedure/
28 placebo$tw.
29 placebo/
30 factorial$.ti,ab.
31 (crossover$ or cross-over$).ti,ab.
32 (double$ adj blind$).ti,ab.
33 (singl$ adj blind$).ti,ab.
34 assign$.ti,ab.
35 allocat$.ti,ab.
36 volunteer$.ti,ab.
37 Crossover Procedure/
38 Single Blind Procedure/
39 or/22-38
40 (exp animal/ or exp animal experiment/ or exp nonhuman/) not exp human/
41 39 not 40
42 21 and 41
43 limit 42 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)

Table 3. Search methods for SIGLE

19 #7 and #18
#18 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#17 budesonide*
#16 fludrocortisone*
#15 hydrocortison*
#14 betamethasone
#13 cortison*
#12 methylprednison*
#11 predniso*
#10 dexamethason*
#9 corticosteroide*
#8 steroid*
#7 #1 or #2 or #3 or #4 or #5 or #6
#6 septal defect*
#5 congenital heart
#4 cardiopulmonary bypass
#3 cardiac surgery
Table 3. Search methods for SIGLE  (Continued)

| #2 heart surgery |
| #1 cardiosurgery |

Table 4. Data extraction form

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td></td>
</tr>
<tr>
<td>PUBLICATION ID</td>
<td></td>
</tr>
<tr>
<td>YEAR OF PUBLICATION</td>
<td></td>
</tr>
<tr>
<td>LANGUAGE</td>
<td></td>
</tr>
<tr>
<td>TYPE OF STUDY</td>
<td></td>
</tr>
<tr>
<td>COMMENTS ON STUDY DESIGN</td>
<td></td>
</tr>
<tr>
<td>Allocation was concealed and drawn consecutively</td>
<td></td>
</tr>
<tr>
<td>Disclosure of Allocation was Possible</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment was not stated or was unclear</td>
<td></td>
</tr>
<tr>
<td>Allocation was not concealed (e.g quasi -randomisation)</td>
<td></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria were clearly defined in the text?</td>
<td></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria were not clearly defined in the text?</td>
<td></td>
</tr>
<tr>
<td>Outcomes of patients who withdrew or were excluded from after allocation were either detailed separately or included in an intention to treat analysis or the text stated that there were no withdrawals.</td>
<td></td>
</tr>
<tr>
<td>Outcome of patients who withdrew or were excluded after allocation were NEITHER detailed separately nor included in an intention to treat analysis</td>
<td></td>
</tr>
<tr>
<td>Treatment and control groups were adequately described at entry (a minimum of 4 admission details were described (age,sex,weight, allergies)</td>
<td></td>
</tr>
<tr>
<td>Treatment and control groups were NOT adequately described at entry</td>
<td></td>
</tr>
</tbody>
</table>
The text stated that the care programmes other than the trial options were identical
The text stated that the care programmes other than the trial options were NOT identical

Outcome measures were clearly defined in the text
Outcome measures were NOT clearly defined in the text

Outcome assessors were blind to the allocation of patients
Outcome assessors were NOT blind to the allocation of patients

The timing of outcome measures was appropriate
The timing of outcome measures was NOT appropriate

METHODS:
Physician- Blinded
Outcome assessor blinded

PARTICIPANTS:
Number of eligible participants
Number enrolled in study
Number Males : Females
Age range
Type of surgery

Were groups similar at entry

INTERVENTION
Steroid type
Dose
Withdrawals : total number
Drop outs: total number
Included in analysis:

COMMENT ON TREATMENT

OUTCOMES: (mean values for continuous data)

Reported treatment group SD
Reported control group SD
Mortality %
Duration of ventilation (hours:mins)
Need for renal dysfunction %
Length of Stay ICU (days)
Capillary Leak %
Temperature %
Inotrope therapy (> 3 agents ) %
Table 4. Data extraction form (Continued)

<table>
<thead>
<tr>
<th>Authors contacted regarding unreported outcome data</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date contacted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response received</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COMMENTS ON OUTCOMES

WHAT'S NEW

Last assessed as up-to-date: 29 July 2007.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 September 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 4, 2007

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 July 2007</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

Suzi Robertson-Malt: prepared and designed the protocol; completed the database searches; participated in writing the review; for purposes of dual data collection, screened papers for inclusion or exclusion; extracted data from included papers.

Mahmoud Barbary: conceived the review and helped prepare and design the protocol; participated in writing the review; provided the methodological and clinical perspective on the data; for purposes of data collection, made final decision when consensus was not achieved.

Barry Afrane: participated in preparing the protocol; provided pharmacological perspective; for purposes of dual data collection, screened papers for inclusion or exclusion; extracted data from included papers.
DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- King Faisal Heart Institute, Saudi Arabia.
- National Guard Hospital, Saudi Arabia.

External sources

- National Gulf Centre for Evidence Based Medicine, Saudi Arabia.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Cardiac Surgical Procedures [*adverse effects]; Infant, Newborn; Injections, Intravenous; Intensive Care Units, Pediatric; Length of Stay; Postoperative Complications [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Infant; Male