Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis

Ho KM, Tan JA

CRD summary
This well-conducted review assessed whether the benefits and risks of corticosteroid use were dose dependent in adult cardiac surgery. The authors reliably concluded that low-dose corticosteroid was as effective as high-dose corticosteroid in reducing the risk of atrial fibrillation and duration of mechanical ventilation but with fewer potential side-effects in adult cardiac surgery.

Authors' objectives
To assess whether the benefits and risks of corticosteroid use are dose dependent in adult cardiac surgery.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL) (2008, Issue 1), EMBASE (January 1988 to August 2008) and MEDLINE (1966 to August 2008) were searched without language restrictions. Search filters for clinical trials and randomised controlled trials (RCTs) were used. Search terms were reported. Reference lists of editorials, reviews and original articles were searched. Websites of the International Network of Agencies of Health Technology Assessment and International Society of Technology Assessment in Health Care were searched.

Study selection
RCTs of adults (over 18 years old) who underwent cardiac surgery were eligible for inclusion if they compared corticosteroid with placebo or equal volume of normal saline before or at the time of cardiopulmonary bypass. Studies that used unequal concurrent medical therapies or that investigated corticosteroid in off-pump cardiac surgery were excluded. The main outcome of interest was the proportion of patients with new-onset fibrillation in the postoperative period. Other outcomes assessed included proportion of patients that developed infection after cardiac surgery, hyperglycaemia that required insulin infusion, hospital mortality, CRP/IL-6/IL-8 (C-reactive protein/interleukin-6/interleukin-8) concentrations at 24 hours after cardiopulmonary bypass or surgery, duration of mechanical ventilation and length of intensive care unit and hospital stay.

The total dose of corticosteroid used varied from 214mg to 72,000mg hydrocortisone in the included studies (where other steroids were used this was converted to hydrocortisone equivalents). Steroids used were hydrocortisone, prednisolone, methylprednisolone and dexamethasone. Participants ranged from 35 to 72 years old. Inclusion criteria of the primary studies varied; most were patients who underwent elective coronary artery bypass grafting (CABG).

Studies were selected independently by two reviewers.

Assessment of study quality
Methodological aspects such as allocation concealment, randomisation method, blinding of treatment and inclusion and exclusion criteria were assessed. Allocation concealment grading was based on the Cochrane approach and classified as adequate, uncertain or clearly inadequate. Validity appeared to be assessed by two reviewers.

Data extraction
Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for categorical outcomes. Means and standard deviations were calculated for continuous outcomes.

Data were extracted independently by two reviewers.

Methods of synthesis
Relative risks or means were pooled in a random-effects model to calculate pooled relative risks or weighted mean
differences (WMDs). Number needed to treat (NNT) was reported for some analyses.

The dose response of corticosteroid was examined using two methods. Using the first method, trials were stratified into low dose (<1000mg hydrocortisone or equivalent), medium dose (between 1000mg and 10,000mg hydrocortisone or equivalent) or high dose (>10,000mg hydrocortisone or equivalent). Individual studies were then listed sequentially according to the total dose of corticosteroid used in all studies. Forest plots were used to interpret subtle dose-response patterns. The interactions among the three dose strata were tested using the ratio of relative risks for categorical variables and mean difference for continuous variables.

For the second method, the dose of corticosteroid was used as a continuous predictor of whether dose affected relative risks of atrial fibrillation between studies. Statistical heterogeneity was assessed using the X² test and I² statistic (I² >40% represented significant heterogeneity).

Sensitivity analyses were performed by separate analysis of the following: double blinded trials; trials published after 1997; trials that did not use postoperative β-blockers; and those that included only coronary artery bypass graft surgery. A funnel plot was used to assess publication bias (risk of atrial fibrillation was used as the end-point). The trim and fill method was used to adjust for any potential publication bias.

### Results of the review

Fifty RCTs were included in the review (n=3,323). Seventeen RCTs had adequate allocation concealment, 26 had double or triple blinding and 14 had adequate allocation concealment and double blinding.

Corticosteroid prophylaxis was associated with a significant reduction in CRP concentration (WMD -44.2mg/L, 95% CI -15.4 to -72.9, p<0.01) and IL-6 concentrations (WMD -148pg/mL, 95% CI -114.8 to -181.1, p<0.01), although these were associated with significant heterogeneity (I²=90.7% for CRP and 98.1% for IL-6). There was a non-significant trend towards reduction of IL-8 after corticosteroid use, also with significant heterogeneity (I²=97.0%).

Corticosteroid prophylaxis was associated with a significant reduction in the risk of atrial fibrillation (RR 0.74, 95% CI 0.63 to 0.86, p<0.01, NNT 10; n=1,509) and hyperglycaemia that required insulin (RR 1.49, 95% CI 1.11 to 2.01, p<0.01; n=503). Corticosteroid prophylaxis did not have a significant effect on the risk of all-cause infection or mortality. No significant heterogeneity was found for these analyses.

Corticosteroid prophylaxis was associated with a significant reduction in duration of mechanical ventilation (WMD -0.68 hours, 95% CI -1.33 to -0.03, p=0.04; n=1,789). This outcome varied according to dose strata. High dose strata were associated with increased duration of mechanical ventilation (WMD 2.1 hours, 95% CI 1.76 to 2.52, p<0.01; n=276). The high dose corticosteroid effect was significantly different from low dose (p=0.03) or medium dose (p<0.01) effect. No significant difference was found between low and medium dose effects. No significant heterogeneity was found for these outcomes.

Corticosteroid prophylaxis was associated with a reduction in the length of intensive care unit stay (WMD -0.37 days, 95% CI -0.52 to -0.21, p<0.01) and hospital stay (WMD -0.66, 95% CI reported as -0.77 to -1.25, p=0.03). Both analyses were associated with significant heterogeneity (I²=89.1% for intensive care unit stay and 77.2% for hospital stay).

No significant difference between the three dose strata was found for the outcomes CRP, IL-6 and IL-8 concentrations, atrial fibrillation, hyperglycaemia that required insulin and length of intensive care unit or hospital stay.

Sensitivity analyses showed similar results. The funnel plot suggested publication bias. The adjusted effect of corticosteroid on atrial fibrillation (using the trim and fill method) remained significant (RR 0.75, 95% CI 0.63 to 0.89, p<0.01).

### Authors’ conclusions

Low-dose corticosteroid was as effective as high-dose corticosteroid in reducing the risk of atrial fibrillation and reducing the duration of mechanical ventilation but with fewer potential side-effects in adult cardiac surgery.
CRD commentary
The research question was supported by inclusion criteria for participants, intervention and study design. Several relevant electronic sources were searched for studies in all languages, which reduced the possibility of language bias. The authors did not report any attempts to find unpublished studies, which increased the risk of publication bias. Publication bias was indicated by the funnel plot; the authors attempted to adjust for this by using the trim and fill method. Study validity was assessed using appropriate criteria and taken into consideration in the analysis. Study selection, validity assessment and data extraction were performed in duplicate, which reduced possible reviewer bias and error. Meta-analysis appeared appropriate. Possible sources of heterogeneity were investigated. This review appeared generally well-conducted and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that large RCTs were needed to confirm the cost-effectiveness of low-dose corticosteroid prophylaxis in adult cardiac surgery.

Funding
Department of Intensive Care Medicine, Royal Hospital, Perth.

Bibliographic details

PubMedID
19332460

DOI
10.1161/CIRCULATIONAHA.108.848218

Original Paper URL
http://circ.ahajournals.org/cgi/content/abstract/119/14/1853

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenal Cortex Hormones /adverse effects /therapeutic use; Adult; Atrial Fibrillation /epidemiology /prevention & control; Cardiac Surgical Procedures /adverse effects /methods /mortality; Cardiopulmonary Bypass /adverse effects /methods /mortality; Humans; Inflammation /prevention & control; Intraoperative Complications /prevention & control; Length of Stay; Patient Selection; Postoperative Complications /epidemiology /prevention & control; Randomized Controlled Trials as Topic; Reperfusion Injury /prevention & control; Risk Assessment; Survival Analysis; Survivors; Treatment Outcome

AccessionNumber
12009105490

Date bibliographic record published
05/08/2009

Date abstract record published
03/02/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.