Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials

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CRD summary
This generally well-conducted review found some evidence of reductions in new-onset atrial fibrillation, post-operative bleeding and durations of intensive care unit and hospital stays for patients who underwent cardiopulmonary bypass surgery. On the basis of the results of the trials included in the review, the authors' conclusions reflected the evidence presented and are likely to be reliable.

Authors' objectives
To assess the safety and efficacy of perioperative prophylactic steroids in patients who underwent cardiopulmonary bypass surgery.

Searching
EMBASE, MEDLINE, The Cochrane Library and CINAHL were searched. Search terms were reported. Reference lists from retrieved articles were searched. PubMed was searched for related key publications to those already retrieved. There were no language restrictions. Articles published only as abstracts were not included.

Study selection
Randomised controlled trials (RCTs) in adults who underwent cardiopulmonary bypass were eligible for inclusion if perioperative treatment with prophylactic steroids was compared to standard care or placebo. An additional inclusion criterion was that studies reported at least one of the outcomes: mortality; myocardial infarction; neurological events; new onset atrial fibrillation; transfusion requirements; post-operative bleeding; duration of ventilation; duration of intensive care unit (ICU) and hospital stay; and complications that related to infections, wound healing or the gastrointestinal tract.

The enrolled populations were patients who underwent surgery for isolated coronary artery bypass grafts (CABG), all cardiopulmonary bypass and valvular surgery. Steroid treatment included dexamethasone, methylprednisolone, hydrocortisone and prednisolone in varying dosages and formulations.

Two reviewers applied the inclusion criteria independently and resolved any differences by discussion.

Assessment of study quality
Two reviewers independently read the included studies and assessed methodological quality using the five-point Jadad scale, which assessed randomisation, blinding, withdrawals and dropouts. Any trial that attained a score of greater than or 3 points on the scale was judged to have been of high quality.

Data extraction
Data was extracted on the outcomes stated above as reported in each trial. Relative risks were calculated for binary outcomes and weighted mean differences were calculated for continuous variables; corresponding 95% confidence intervals (CI) for both were calculated for each trial. The reviewers contacted the corresponding authors from trials to obtain missing data. Two independent reviewers extracted data and resolved differences by discussion.

Methods of synthesis
The DerSimonian and Laird random-effects model was used to calculate pooled estimates of effect for each outcome.

Statistical heterogeneity for each pooled outcome was assessed using the $I^2$ test. A value of 25% or less was considered to represent low heterogeneity. Sources of heterogeneity were determined a priori and examined in further analyses. These included blinding status, surgery type, and dose and type of steroid. Sensitivity analyses were undertaken to examine the effects of the use of imputed data and the inclusion of high quality studies. Publication bias was
investigated using a funnel plot.

**Results of the review**

Forty-four RCTs (n=3,205) with a median trial size of 51 patients were included in the review. Twenty-six studies (59%) scored three or more points on the Jadad scale. Twenty nine trials used double-blinding.

**New-onset atrial fibrillation:** There was a statistically significant decrease observed in the numbers of patients who developed new-onset atrial fibrillation. There was an observed trend towards a statistically significant reduction in new-onset atrial fibrillation after treatment with prophylactic steroids (relative risk 0.71, 95% CI 0.59 to 0.87, p=0.001).

**Post-operative bleeding:** Treatment with steroids was associated with a small but significant decrease in post-operative bleeding (weighted mean difference -100mL, 95% CI -149.82 to -49.29, p<0.0001). There were no differences between steroid and comparator groups in transfusion requirements.

**Duration of intensive care unit and hospital stay:** Statistically significant reductions in intensive care unit stay (weighted mean difference -0.23, 95% CI -0.40 to -0.07, p=0.006) and hospital stay (weighted mean difference -0.59, 95% CI -1.17 to -0.02, p=0.04) were observed in patients who received steroid treatment compared to patients who received standard care or placebo.

**Other outcomes:** There were no statistically significant differences observed between the steroid group and the comparators for myocardial infarctions, neurological events and duration of mechanical ventilation. There was a trend towards statistically significant benefit for steroid-treated patients compared to placebo or standard care for overall mortality (relative risk 0.73, 95% CI 0.45 to 1.18). Few studies reported on post-operative wounds and gastrointestinal and infectious complications; there were no significant differences reported in the pooled analyses of these outcomes.

**Heterogeneity:** Results for length of intensive care unit and hospital stays, duration of mechanical ventilation, post-operative bleeding and transfusion requirements were statistically heterogeneous. In the studies of coronary artery bypass graft patients, steroid treatment was not found to significantly decrease the duration of mechanical ventilation (n=13, 95% CI -0.21 to 2.51 hours); a statistically significant benefit was found for the other surgery studies in which this outcome was evaluated (n=10, 95% CI -1.28 to -0.40 hours).

Sensitivity analyses showed similar results except for the outcome of duration of hospital stay, for which the difference between the steroid and comparator groups was no longer statistically significant. Funnel plots of outcomes with a sufficient number of trials showed no evidence of publication bias.

**Authors’ conclusions**

Perioperative steroid treatment conferred clinical benefits in a decrease in new-onset atrial fibrillation in patients who underwent cardiopulmonary bypass and may have reduced post-operative bleeding and the duration of both intensive care unit and hospital stays. There was a trend towards a reduction in mortality with steroid treatment, although the meta-analysis was not sufficiently powered for this outcome. A sufficiently powered trial was necessary to explore the safety of steroids in this population.

**CRD commentary**

The review addressed a clear question and had clearly stated inclusion criteria with respect to study design, participants, treatments and outcomes. The authors searched relevant databases for published articles and articles published in languages other than English were available for inclusion. There was no apparent attempt to locate unpublished material, which meant that relevant studies may have been missed. Steps were taken to minimise reviewer bias and errors in all parts of the review. Some clinical heterogeneity was reported between the included trials with respect to steroids used and protocols. Most included patients had lower-risk isolated coronary artery bypass graft, which the authors stated was not representative of populations treated by cardiovascular surgery. This raised questions about the applicability of the findings of this research to patients at higher risk when undergoing cardiopulmonary bypass surgery. This was generally a well-conducted review and the authors’ conclusions seem reliable based on the evidence presented.

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

Research: The authors stated that a sufficiently powered trial was required to establish the clinical effect of perioperative steroids on cardiopulmonary bypass patients. Optimal protocols for steroid treatment needed to be ascertained. The available data from the literature was insufficient to draw conclusions about the safety of steroid treatment in this population.

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