

## REVIEW ARTICLE

# Steroids in cardiac surgery: a systematic review and meta-analysis

N. Dvirnik<sup>1,2</sup>, E. P. Belley-Cote<sup>1</sup>, H. Hanif<sup>2</sup>, P. J. Devereaux<sup>1,3,4</sup>, A. Lamy<sup>1,2,4</sup>, J. M. Dieleman<sup>5,6</sup>, J. Vincent<sup>4</sup> and R. P. Whitlock<sup>1,2,4,\*</sup>

<sup>1</sup>Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada, <sup>2</sup>Division of Cardiac Surgery, McMaster University, Hamilton, Ontario, Canada, <sup>3</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada, <sup>4</sup>Population Health Research Institute, Hamilton, Ontario, Canada, <sup>5</sup>Division of Anaesthesiology, Intensive Care, and Emergency Medicine, University Medical Center Utrecht, The Netherlands and <sup>6</sup>Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia

\*Corresponding author. E-mail: [Richard.Whitlock@phri.ca](mailto:Richard.Whitlock@phri.ca).

## Abstract

**Background:** Cardiopulmonary bypass (CPB) induces a systemic inflammatory reaction that may contribute to post-operative complications. Preventing this reaction with steroids may improve outcomes. We performed a systematic review to evaluate the impact of prophylactic steroids on clinical outcomes in patients undergoing on-pump cardiac surgery.

**Methods:** We searched MEDLINE, EMBASE, and Cochrane CENTRAL for randomised controlled trials (RCTs) comparing perioperative corticosteroid administration with a control group in adults undergoing CPB. Outcomes of interest included mortality, myocardial infarction, and new onset atrial fibrillation. We assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach.

**Results:** Fifty-six RCTs published between 1977 and 2015 were included in this meta-analysis. Mortality was not significantly different between groups [3.0% (215/7258 patients) in the steroid group and 3.5% (252/7202 patients) in the placebo group; relative risk (RR), 0.85; 95% confidence interval (CI), 0.71–1.01;  $P=0.07$ ;  $I^2=0\%$ ]. Myocardial injury was more frequent in the steroid group [8.0% (560/6989 patients), compared with 6.9% (476/6929 patients); RR, 1.17, 95% CI, 1.04–1.31;  $P=0.008$ ;  $I^2=0\%$ ]. New onset atrial fibrillation was lower in the steroid group [25.7% (1792/6984 patients) compared with 28.3% (1969/6964 patients), RR, 0.91, 95% CI, 0.86–0.96,  $P=0.0005$ ,  $I^2=43\%$ ]; this beneficial effect was limited to small trials ( $P$  for interaction  $<0.00001$ ).

**Conclusions:** After randomising 16 013 patients, steroid administration at the time of cardiac surgery had an unclear impact on mortality, increased the risk of myocardial injury, and the impact on atrial fibrillation should be viewed with caution given that large trials showed no effect.

**Keywords:** cardiac surgical procedures; cardiopulmonary bypass; cardiovascular diseases; postoperative complications; steroids

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**Editor's key points**

- The authors performed a systematic review/meta-analysis to examine the possibility that steroids might reduce systemic inflammation after cardiac surgery, and improve outcome.
- The pooled data were derived from more than 16 000 patients, and showed an unclear effect on mortality, while increasing some risks.

Cardiopulmonary bypass (CPB) induces a systemic inflammatory reaction by exposing the blood to foreign surfaces, non-physiologic flow, and hypothermia. This is exacerbated by the ischemia-reperfusion injury when weaning from CPB.<sup>1–3</sup> This complex inflammatory reaction may contribute to post-operative complications such as ventricular dysfunction and organ failure.<sup>3,4</sup> Preventing this reaction may improve outcomes after on-pump cardiac surgery.

In 2008, a systematic review and meta-analysis of randomised controlled trials (RCTs) evaluated the efficacy and safety of prophylactic steroids in patients undergoing CPB.<sup>5</sup> Even though it included 44 trials (3205 patients), the meta-analysis lacked power for outcomes with lower incidence rates such as mortality [16 trials, 2038 patients, 65 events, relative risk (RR), 0.73; 95% confidence interval (CI), 0.45–1.18]. However, the meta-analysis reached optimal information size (OIS) for atrial fibrillation (RR, 0.71, 95% CI, 0.59–0.87,  $P=0.001$ ,  $I^2=21%$ ) in favour of steroid use, and the duration of intensive care unit (ICU) and hospital stay were shorter with steroids [weighted mean difference (WMD) –0.23 days, 95% CI, –0.40 to –0.07], WMD –0.59 days, 95% CI, –1.17 to –0.02, respectively].

Two large RCTs have been published since that meta-analysis. The Steroids In caRdiac Surgery (SIRS) trial comprising 7507 patients demonstrated no significant difference in 30-day mortality (RR, 0.88; 95% CI, 0.71–1.09).<sup>6</sup> The reduction in atrial fibrillation suggested in the meta-analysis was not seen in the SIRS trial (RR, 0.97; 95% CI, 0.89–1.06). The results of the Dexamethasone in Cardiac Surgery (DECS) study ( $n=4494$ ) were similar, with no benefit on mortality (RR, 0.92; 95% CI, 0.57–1.49) or atrial fibrillation (RR, 0.94; 95% CI, 0.87–1.02).<sup>7</sup>

Although literature has reported that meta-analyses are at risk of overestimating intervention effects, a simulation study performed by Mills and colleagues<sup>8</sup> suggested that once the OIS is reached in a meta-analysis, overestimation is less likely. The primary objective of this systematic review and meta-analysis was to answer the following research question: In patients undergoing on-pump cardiac surgery, is the prophylactic administration of steroids safe and effective in reducing morbidity and mortality?

**Methods****Eligibility criteria**

We searched for published RCTs comparing perioperative corticosteroid administration with a control group (placebo or standard care) in adults undergoing CPB. Eligible trials had to report at least one of the predetermined outcomes of interest listed below. Eligible RCTs were included regardless of their primary objective or language of publication. Our methods were consistent with the previous steroid meta-analysis<sup>5</sup> and

all 44 trials from that systematic review were included in our analysis.

**Trial identification**

We searched MEDLINE, EMBASE, and Cochrane CENTRAL using the pre-tested SIGN filters (<http://www.sign.ac.uk>) for RCTs. Our search terms included: cardiac surgery, cardiac surgical procedure, open-heart surgery, coronary artery bypass, mitral valve, aortic valve, heart valve, CPB, extracorporeal circulation, preoperative, and prophylactic, in combination with generic and trade names of steroid preparations. Finally, we reviewed the references of included studies for other potentially relevant studies and asked experts at our centre if they were aware of other relevant trials. See [Supplementary Material B](#) for the search strategy.

**Trial selection**

All references retrieved from the electronic search were uploaded into RefWorks (RefWorks-COS-2.0), and duplicates were removed. Remaining titles and abstracts were screened in duplicate by two independent reviewers and full text reports for all references deemed possibly relevant by any reviewer were retrieved and reviewed in duplicate to determine full eligibility criteria. Any disagreements were discussed; in all cases one person recognised an error. Reviewers' agreement for full text eligibility was assessed using Kappa statistic and was very good ( $\kappa=0.95$ ).<sup>9</sup>

**Data extraction and quality assessment**

We collected descriptive data (e.g. patient population, surgery type, intervention, comparator) and markers of validity (e.g. blinding) from all selected trials. Outcomes of interest were mortality, myocardial infarction or injury (MI), neurological events (stroke/transient ischaemic attack), new onset atrial fibrillation, ICU stay, wound and infectious complications, and hospital length of stay. We accepted the authors' definitions for clinical outcomes. Two reviewers using pre-designed data collection forms independently extracted the data. Consensus was sought for discordant data and authors were contacted for missing data relevant to our study. The quality of individual trials was assessed based on methodological completeness, focusing on appropriate randomisation, double blinding, and adequate follow up (Jadad and colleagues<sup>10</sup>). The 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) approach was used to rate the overall quality of evidence for individual clinical outcome effects by two reviewers.<sup>11</sup> The criteria potentially leading to downgrading of RCT evidence in the GRADE approach are study limitations, imprecision, indirectness, inconsistency, and potential publication bias.<sup>12</sup>

**Statistical analysis**

Clinical outcome data were extracted from each trial comparing patients receiving steroid therapy with the control group. Binary outcomes (i.e. death, MI, neurological events, renal failure, new atrial fibrillation, wound and infectious complications) were reported as RRs with 95% CI. Continuous variables (hospital and ICU lengths of stay) were reported as mean difference (MD) with 95% CI. The effect estimates of the

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