Efficacy and safety of corticosteroids prophylaxis in cardiac surgery

A protocol for systematic review and meta-analysis

Jian He, MS\textsuperscript{a}, Yuling Zhang, MS\textsuperscript{a}, Zhihuang Qiu, PhD\textsuperscript{a}, Tianci Chai, PhD\textsuperscript{a}, Guanhua Fang, PhD\textsuperscript{a}, Yunnan Hu, PhD\textsuperscript{b}, Fan Xu, PhD\textsuperscript{b}, Qiyu Huang, MS\textsuperscript{a}, Hui Zheng, PhD\textsuperscript{a}, Hao Zhou, PhD\textsuperscript{a}, Mengyue Tian, BS\textsuperscript{b}, Liang Wan Chen, PhD\textsuperscript{a,*}

Abstract

Background: Although corticosteroid prophylaxis in adult cardiac surgery has been studied extensively for 40 years, its role remains controversial, and the optimal dose remains uncertain. The objective of this meta-analysis was to estimate the clinical benefits and risks of corticosteroid use in cardiopulmonary bypass.

Methods: We will search Pubmed, Web of Science, Embase, Clinical Trials, and Cochrane Central Register of Controlled Trials for relevant clinical trials published in any language before August 1, 2020. Randomized controlled trials (RCTs) of interest which meet inclusion criteria published or unpublished will be included. We will divide the included studies into child and adult groups for analysis. If sufficient data are available, the included trials will be divided into 4 subgroups: ≤20 mg/kg (low dose), 20–40 mg/kg (slightly high dose), 40–100 mg/kg (high dose), and >100 mg/kg (ultra high dose) based on the equivalent hydrocortisone dose. INPLASY registration number: INPLASY20201000044.

Results: The results of this study will be published in a peer-reviewed journal.

Conclusion: This study will compare the efficacy of prophylactic corticosteroids for adults and children undergoing cardiac surgery with CPB. Due to the nature of the disease and intervention methods, randomized controlled trials may be inadequate, and we will carefully consider inclusion in high-quality, non-randomized controlled trials, but this may result in high heterogeneity and affect the reliability of the results.

Abbreviations: CPB = cardiopulmonary bypass, GRADE = Grading of Recommendations, Assessment, Development and Evaluation, Hi-Q = high quality, ICU = intensive care unit, MeSH = Medical Subject Heading, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, CI = confidence interval, RR = relative risk, RCTs = randomized controlled trials, SIRS = systemic inflammatory response syndrome, SMD = standardized mean difference.

Keywords: cardiac surgery, cardiopulmonary bypass, inflammation, meta-analysis, steroid

1. Introduction

Most cardiac operations are performed under cardiopulmonary bypass, however, it is well known that cardiopulmonary bypass often causes systemic inflammatory response syndrome (SIRS).\textsuperscript{1,2} SIRS related to complement, platelets, neutrophils, monocytes, macrophages activation and cascade (coagulation, fibrinolytic, stimulating peptide enzyme), leading to endothelial permeability increase, blood vessels and organ parenchyma cell injury, and

This study was supported by Fujian Key Laboratory of Cardio-Thoracic Surgery (Fujian Medical University), National Natural Science Foundation of China (NO. 81670438 and 81700418), Fujian Province Major Science and Technology Program (NO. 2018YJ001-1), and the Project for Fostering Key Middle-aged and Young Talents Supported by Health Commission Foundation of Fujian Province (NO. 2019-ZQN-50). The funder will have no role in this study. The authors alone are responsible for the writing and content of this article.

Because this study will be based on published or unpublished records and studies, there is no need for ethics approval. The results of the study will be published in a peer-reviewed journal.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

* Correspondence: Liang Wan Chen, Department of Cardiac Surgery, Fujian Medical University Union Hospital, No. 29 New Power Road, Fuzhou 350004, China (e-mail: chenliangwan@fjmu.edu.cn).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: He J, Zhang Y, Qiu Z, Chai T, Fang G, Hu Y, Xu F, Huang Q, Zheng H, Zhou H, Tian M, Chen LW. Efficacy and safety of corticosteroids prophylaxis in cardiac surgery: a protocol for systematic review and meta analysis. Medicine 2020;99:50(e23240).

Received: 15 October 2020 / Accepted: 19 October 2020

http://dx.doi.org/10.1097/MD.0000000000023240
liver, kidney, nervous system dysfunction, myocardium injury and infarction, respiratory failure, multiple organ dysfunction, and death are closely related.\(^\text{[2–7]}\)

Corticosteroids is a low-cost drug that can effectively inhibit inflammation, limit systemic capillary leakage syndrome and reduce organ damage, thus providing a theoretical basis for its clinical application.\(^\text{[8–10]}\) However, corticosteroids may have their own side effects, causing hyperglycemia, which is associated with immunosuppression and poor wound healing. In addition, high doses of corticosteroids were associated with an increased risk of gastrointestinal bleeding and myocardial infarction.\(^\text{[11–12]}\)

The beneficial effects of glucocorticoids on adults and children undergoing heart surgery remain controversial.\(^\text{[13–15]}\)

Three meta-analysis of small RCTs showed that prophylactic corticosteroids can reduce the risk of atrial fibrillation after cardiac surgery in adults, reduce the duration of mechanical ventilation and hospital stay, but can cause some potential side effects.\(^\text{[15–7]}\) None of the 3 studies analyzed pediatric studies, and there was a lack of high-quality, large-sample randomized controlled trials. The clinical results of the analysis were not comprehensive and the evidence obtained was not robust. Subsequently, 2 large multicentre randomized controlled trials showed that corticosteroid treatment had no benefit in adult patients undergoing heart surgery and increased the risk of myocardial infarction.\(^\text{[13–14]}\) However, guidelines for adult cardiac surgery do not recommend routine prophylactic use of corticosteroids to reduce complications. Therefore, the purpose of this study was to systematically review and meta-analyze the dose-dependent benefits and risks of prophylactic glucocorticoids in adults and children undergoing cardiopulmonary bypass.

2. Objective

We will conduct a systematic review and meta-analysis to estimate the clinical benefits and risks of corticosteroid use in cardiopulmonary bypass.

3. Methods

This protocol is performed adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement. The results of this systematic review and meta-analysis will be published with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyze (PRISMA) guidelines.

3.1. Patient and public involvement

This study will be based on published or unpublished studies and records and will not involve patients or the public directly.

3.2. Eligibility criteria

**3.2.1. Types of studies.** Only randomized controlled clinical trials comparing corticosteroid with placebo or equal volume of normal saline, initiated either before or at the time of cardiopulmonary bypass were included. Studies that used unequal concurrent medical therapies or studies that evaluated corticosteroid in off-pump cardiac surgery were excluded.

**3.2.2. Types of participants.** Patients with heart, valve, or aortic disease are treated surgically under extracorporeal circulation and there will be no restrictions on sex, ethnicity, economic status, and education.

**3.2.3. Types of interventions.** Cardiac surgery with cardiopulmonary bypass with or without prophylactic corticosteroid administration. For comparator study arms, trials with concomitant study arms on other interventions were not excluded, as long as patients in the comparator arm received the same treatment as the corticosteroid arm except for corticosteroid administration.

**3.2.4. Types of outcome measures**

**3.2.4.1. Primary outcomes.** Composite end-point, consisting of the following:

- all-cause mortality (in-hospital);
- occurrence of atrial fibrillation (in the postoperative period);
- fatal and non-fatal myocardial infarction (defined as: ECG changes, echocardiological changes, disproportionate elevation of troponines, specific biological marker);
- pulmonary complications (including pulmonary edema and/or infection);
- kidney injury (renal failure, acute renal failure, acute kidney disease, renal complications).

**3.2.4.2. Secondary outcomes.**

- postoperative infection
- neurological complications
- gastro-intestinal bleeding
- postoperative insulin use
- mechanical ventilation time
- Delirium
- length of ICU stay
- LOS hospital
- Duration of CPB
- vaso-active medication
- re-thoracotomy
- inotropic score
- blood transfusion
- re-intubation
- CRP/IL-6/IL-8 concentrations at 24 hours after cardiopulmonary bypass

3.3. Information sources

Two reviewers (CTC, QZH) will search Pubmed, Web of Science, Embase, and Clinical Trials, and Cochrane Central Register of Controlled Trials for relevant clinical trials published before August 1, 2020 without any language restrictions.

3.4. Search strategy

The subject terms and keywords corresponding to Medical Subject Heading (MeSH) terms will be used to search for eligible trials in the databases as mentioned above with no language restrictions. Search strategies in PubMed are shown in Table 1.

3.5. Data collection and analysis

We will adopt the methods described in the Cochrane Handbook for Systematic Reviews of Interventions to pool the evidence.

**3.5.1. Study selection.** Two authors (CTC, QZH) will screen independently each title and abstract of all the papers searched and the trials do not meet the inclusion criteria described in this
protocol will be excluded. Full text of all the possible eligible trials will be screened independently and in duplicate by the 2 authors. Trials which are irrelevant or do not meet the inclusion criteria will be excluded. Trials that meet the inclusion criteria and excluded studies with the reasons for their exclusion will be documented by 2 authors (CTC, QZH). If there is a disagreement between the 2 authors, we will resolve the disagreement by discussing with the third author (LYM). If necessary, we will consult the fourth author (CLW) to resolve the disagreement.

Selectin process will be shown in PRISMA flow chart in details.

3.5.2. Data extraction and management. We will extract the following data from the trials included.

- Study characteristics: author, publication date, country, study design, randomization, periods of data collection, follow-up duration, withdrawals, and overall duration of study.
- Population characteristics: age, sex, BMI, operation, blood pressure, history of diabetes, performance status, ethnicity, history of smoking, and inclusion criteria.
- Interventions: The types, doses, time and routes of corticosteroids used in extracorporeal circulation.
- Outcomes: mortality; occurrence of atrial fibrillation; myocardial infarction; pulmonary complications; acute kidney injury; postoperative infection; postoperative insulin use; gastrointestinal bleeding; re-thoracotomy; neurological complications; inotropic use; blood transfusion; mechanical ventilation time; reintubation; length of ICU stay; CRP/IL-6/IL-8 concentrations at 24 hours after cardiopulmonary bypass; vaso-active medication.

We will use the pre-designed table to record the data extracted from the included trials. If relevant data of the trials is lost or unclear, we will consult the author via email before determining whether the study is included.

3.6. Assessment of risk of bias

The Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias of each trial included. The 2 authors (CTC, QZH) will evaluate the risk of bias based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other bias. The risk of bias in each domain will be assessed as high, low, or uncertain and the results of the evaluation will be shown on the risk of bias graph.

3.7. Data analysis

We will use Review Manager and Stata software to synthesise the data extracted. If the data extracted from the included studies are evaluated as highly homogeneous, we will conduct meta-analysis on them for the purpose of obtaining a clinically meaningful result. In order to carry out a standard meta-analysis, we will use the Chi² and I² statistic test to evaluate statistical heterogeneity among the studies. If there is high heterogeneity (P<.1 or I² statistic >50%), we will use the DerSimoinian and Laird random effect model to analyze the extracted data. Otherwise, we will adopt fixed-effect model to analyze the data. We will adopt the Mantel-Haenszel method to pool the binary data and the results will be reported in the form of relative risk (RR) with the 95% confidence interval (CI). Inverse variance analysis method will be used to pool the continuous data and the results will be reported in the form of standardized mean difference (SMD) with 95% confidence interval (CI).

3.7.1. Subgroup analysis. If there is substantial heterogeneity and the available data are sufficient, we will perform subgroup analysis for searching potential origins of heterogeneity. If sufficient data are available, the included trials will be divided into 4 subgroups: ≤20 mg/kg (low dose), 20–40 mg/kg (slightly high dose), 40–100 mg/kg (high dose), and >100 mg/kg (ultra high dose) based on the equivalent hydrocortisone dose.

3.7.2. Sensitivity analysis. We will conduct sensitivity analysis to evaluate the robustness and the reliability of aggregation results by eliminating trials with high bias risk.
If reporting bias exists, we will use the methods of fill and trim to analyze publication bias.

3.8. Publication bias
Funnel charts and Eggers test will be adopted to assess publication bias if there are no less than 10 eligible trials. If reporting bias is suspected in a trial, we will contact the corresponding author via email to find out whether there are additional outcome data which were not reported.

3.9. Evidence evaluation
We will classify the quality of all evidence into 4 levels (high, medium, low, and very low) in accordance with the criteria of GRADE (study limitations, imprecision, publication bias, indirectness bias, and effect consistency). [1,27]

4. Discussion
Systemic inflammatory response in the incidence of complications after heart surgery plays a crucial role in elevated levels of proinflammatory cytokines and complement activation leads to the occurrence of capillary leak syndrome, [1] thereby worsening organ function. [2,7] Corticosteroids can effectively inhibit systemic inflammation and reduce the level of inflammatory factors, providing a theoretical basis for prophylactic administration in cardiac surgery under CPB. [3–10]

A large number of randomized controlled trials showed that the prophylactic use of corticosteroids in patients with heart operation under CPB did not bring any benefits, but increased the risk of myocardial infarction, prolonged the time of mechanical ventilation. [8–10] Adult cardiac surgery guidelines and clinical routine cardiac surgery in adults and children are not used in preventive corticosteroids. However, the clinical effects of corticosteroids are dose-dependent. The strength of its anti-inflammatory effects and clinical side effects are closely related to corticosteroids dosage. [3,4,7] We assumed that there is an appropriate dosage range that can effectively inhibit systemic inflammation and trigger protective function of corticosteroids. Corticosteroids have the least side effect, protecting rather than destroying cardiomyocytes. Therefore, we are going to conduct a systematic review and meta-analysis of dose-dependent benefits and risks of corticosteroid prevention in cardiopulmonary surgery.

Author contributions
Liang Wan Chen and Zhihuan Qiu are the guarantor of the article. Jian He and Yuling Zhang conceived and designed the study. Zhihuan Qiu, Tianci Chai, Guanhua Fang, Yunnan Hu, Fan Xu, Quyu Huang, and Fei Luo drafted this protocol. Peipei Zhang, Tianci Chai, Hui Zheng, Hui Zheng, Hao Zhou, and Mengyue Tian, will perform the search, screening and extraction. Liang Wan Chen and Zhihuan Qiu have strictly reviewed this protocol and approved of publication.

Conceptualization: Jian He, Yuling Zhang, Guanhua Fang.
Data curation: Jian He, Yuling Zhang, Guanhua Fang, Yunnan Hu.
Formal analysis: Jian He, Yuling Zhang, Hao Zhou.
Funding acquisition: Mengyue Tian, Liangwan Chen.
Investigation: Jian He, Fan Xu.

Methodology: Jian He.
Project administration: Tianci Chai, Quyu Huang.
Resources: Jian He, Tianci Chai, Hui Zheng.
Software: Jian He.
Supervision: Zhihuan Qiu.
Validation: Jian He, Zhihuan Qiu.
Visualization: Jian He, Zhihuan Qiu.
Writing – original draft: Jian He, Zhihuan Qiu.
Writing – review & editing: Jian He.

References
[1] D’Agostino RS, Jacobs JP, Badhwar V, et al. The society of thoracic surgeons adult cardiac surgery database: 2018 update on outcomes and quality. Ann Thorac Surg 2019;107:24–32.
[2] Kirklin JK, Westaby S, Blackstone EH, et al. Complement and damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 1983;86:845–57.
[3] McGuinness J, Boucher-Hayes D, Redmond JM. Understanding the inflammatory response to cardiac surgery. Surgeon 2008;6:162–71.
[4] Loef BG, Henning RH, Epema AH, et al. Effect of dexamethasone on perioperative renal function impairment during cardiac surgery with cardiopulmonary bypass. Br J Anaesth 2004;93:793–8.
[5] Whitlock RP, Chan S, Devereaux PJ, et al. Clinical benefit of steroids use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials. Eur Heart J 2008;29:2592–600.
[6] Ho KM, Tan JA. Benefits and risks of corticosteroids prophylaxis in adult cardiac surgery; a dose-response meta-analysis. Circulation 2009;119:1853–66.
[7] Ng KT, Van Paassen J, Langan C, et al. The efficacy and safety of prophylactic corticosteroids for the prevention of adverse outcomes in patients undergoing heart surgery using cardiopulmonary bypass: a systematic review and meta-analysis of randomized controlled trials. Eur J Cardiothoracic Surg 2020;doi:10.1093/jetc/ezz325.
[8] Pesonen E, Keski-Nisula J, Andersson S, et al. High-dose methylprednisolone and endothelial glycolayx in paediatric heart surgery. Acta Anaesthesiol Scand 2016;60:1386–94.
[9] Heyng R, Webage E, Schumacher K, et al. Dexamethasone pretreatment provides antiinflammatory and myocardial protection in neonatal arterial switch operation. Ann Thorac Surg 2012;93:869–76.
[10] Bronski RA, Backer CL, Baden HF, et al. Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg 2000;69:1490–5.
[11] Chaney MA. Corticosteroids and cardiopulmonary bypass: a review of clinical investigations. Chest 2002;121:921–31.
[12] Mayumi H, Zhang QW, Nakashima A, et al. Synergistic immunosuppression caused by high-dose methylprednisolone and cardiopulmonary bypass. Ann Thorac Surg 1997;63:129–37.
[13] Dieleman JM, Nierich AP, Rosseel PM, et al. Dexamethasone for Cardiac Surgery (DECS) Study Group: is a high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 2012;308:1761–7.
[14] Whitlock RP, Devereaux PJ, Teoh KH, et al. SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386:1243–53.
[15] Keski-Nisula J, Pesonen E, Olkkola KT, et al. Methylprednisolone in neonatal cardiac surgery: reduced inflammation without improved clinical outcome. Ann Thorac Surg 2013;95:2126–32.
[16] Kunst G, Mihovenc M, Boer C, et al. Authors/Task Force Members; EACTS/EACTA/EBCP Committee Reviewers. 2019EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. Br J Anaesthet 2019;123:713–57.
[17] Higgin JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[18] Lomivorotov V, Koroliv I, Boboshko V, et al. Effect of intraoperative dexamethasone on major complications and mortality among infants undergoing cardiac surgery: The DECISION Randomized Clinical Trial. JAMA 2020;323:2485–92.