INPLASY PROTOCOL

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The funder will have no role in the this study. The authors alone are responsible for the writing and content of this article. The authors have no conflicts of interest to disclose.

Can high-dose corticosteroids in cardiopulmonary bypass bring more benefits?

Chai, T[1]; Qiu, Z[2]; He, J[3]; Zheng, H[4]; Xu, F[5]; Hu Y[6]; Zhou, H[7]; Li, Y[8]; Chen, L[9].

Review question / Objective: **Although corticosteroid prophylaxis in adult cardiac surgery has been studied extensively for 40 years, its role remains controversial, and the optimal dose remains uncertain.**
Condition being studied: **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.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 June 2020 and was last updated on 21 June 2020 (registration number INPLASY202060080).

INTRODUCTION

Review question / Objective: **Although corticosteroid prophylaxis in adult cardiac surgery has been studied extensively for 40 years, its role remains controversial, and the optimal dose remains uncertain.**

Rationale: **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.

Condition being studied: 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.

METHODS

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.

Participant or population: 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.

Intervention: 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.

Comparator: Comparing corticosteroid with placebo or equal volume of normal saline, initiated either before or at the time of cardiopulmonary bypass.

Study designs to be included: Randomized controlled trials (RCTs) of interest which meet inclusion criteria published or unpublished will be included.

Eligibility criteria: 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.

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

Main outcome(s): All-cause mortality (in-hospital); occurrence of atrial fifibrillation (in the postoperative period); fatal and non-fatal myocardial infarction (defifined as: ECG changes, echocardiological changes, disproportionate elevation of troponines); pulmonary complications (including pulmonary edema and/or infection); acute kidney injury (renal failure, acute renal failure, acute kidney disease, renal complications).

Additional outcome(s): Postoperative infection, postoperative insulin use, gastro-intestinal bleeding, re-thoracotomy, neurological complications, inotropic use, blood transfusion, mechanical ventilation time, re-intubation, length of ICU stay, CRP/IL-6/IL-8 concentrations at 24 hours after cardiopulmonary bypass, vaso-active medication.

Data 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 fifibrillation; myocardial infarction; pulmonary complications; acute kidney injury;

postoperative infection; postoperative insulin use; gastro-intestinal bleeding; re-thoracotomy; neurological complications; inotropic use; blood transfusion; mechanical ventilation time; re-intubation; 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.

Quality assessment / Risk of bias analysis: The Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias of each trial included. The two 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 as high, low, or uncertain and the results of the evaluation will be shown on the risk of bias graph.

Strategy of data synthesis: 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 (p50%), we will use the DerSimonian and Laird random effect model to analyze the extracted data. Because of the high heterogeneity may be caused by the different types of tumors, different stages of tumors diagnosed by pathology and different means of adjuvant therapy after operation, we will make a subgroup analysis of the types of tumors (esophageal squamous cell carcinoma, esophageal adenocarcinoma), the pathological stages of tumors, and the means of adjuvant therapy after operation (types of chemotherapeutic drugs, whether or not radiotherapy is accepted). 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).

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, we will conduct a subgroup analysis of the literature published before and after 2005 by time.

Sensibility 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.

Language: without any language restrictions.

Country(ies) involved: China.

Keywords: Cardiac surgery, cardiopulmonary bypass, steroid, inflammation, Meta-analysis.

Dissemination plans: The results of the study will be published in a peer-reviewed journal.

Contributions of each author:
Author 1 - Tianci Chai - drafted the manuscript.
Author 2 - Zhihuang Qiu - drafted the manuscript.

Author 3 - Jian He - provided statistical expertise.
Author 4 - Hui Zheng - provided statistical expertise.
Author 5 - Fan Xu - provided statistical expertise.
Author 6 - Yunnan Hu - provided statistical expertise.
Author 7 - Hao Zhou - provided statistical expertise.
Author 8 - Yumei Li - contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 9 - Liangwan Chen - The author read, provided feedback and approved the final manuscript.