INPLASY PROTOCOL

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None declared.

The effect of Nitric oxide delivered via cardiopulmonary bypass on postoperative outcomes in patients who underwent cardiac surgery: a systematic review and meta-analysis

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Review question / Objective: **The aims of this study was to conduct a systematic review and meta-analysis to determine the efficacy of NO administration during CPB in cardiac surgeries.**
Eligibility criteria: **We included RCTs that compared NO administration via CPB with placebo or standard CPB on the clinical outcomes after cardiac surgeries, regardless of the age of the included patients. To reduce the heterogeneity, studies that adopted inhaled nitric oxide (iNO) or NO donors in perioperative period as interventions were excluded.**
Information sources: **We conducted a systematic search in PUBMED, Web of Science, and EMBASE.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 December 2022 and was last updated on 01 December 2022 (registration number INPLASY2022120002).

INTRODUCTION

Review question / Objective: **The aims of this study was to conduct a systematic review and meta-analysis to determine the efficacy of NO administration during CPB in cardiac surgeries.**

Condition being studied: **Cardiopulmonary bypass (CPB) is a common used technique that temporarily takes over the function of the heart and lungs during cardiac surgery. However, it may triggers a widespread endothelial injury, inflammatory response, and coagulation system dysfunction due to the exposure of blood to artificial surfaces. In addition, the trauma of cardiac surgery**

itself and ischemia-reperfusion injury can also aggravate systemic inflammatory response (SIR) and eventually lead to low cardiac output syndrome which is associated with higher mortality, prolonged mechanical ventilation, and unfavorable long-term outcomes.

Nitric oxide (NO) was reported to have a protective effect on inflammatory response and ischemia/reperfusion injury1,2. Moreover, NO also appears to determine the correlated role between impaired endothelial function and inflammation3. In recent years, NO delivered via CPB has been widely investigated in cardiac surgery with inconsistent results. Some clinical studies suggested that NO delivery during CPB exerted a cardioprotective effect4-6, reduced the incidence of acute kidney injury and low cardiac output syndrome7,8, shorten duration of invasive mechanical ventilation, length of ICU6. However, clinical studies showed various opinions on the postoperative outcomes. Several trails supported the effect of NO on myocardial protection, but no significant effect on other clinical outcomes4,5,8. Meanwhile, Niebler et al suggested no benefit of the use of NO via CPB on clinical outcomes9. A recent multi-center, large-sample study further supported the conclusion that the administration of NO via CPB did not significantly reduced the number of ventilator-free days or other clinical outcomes including incidence of low cardiac output syndrome, length of ICU or hospital stay10. A previous systematic review explored the effect of NO during CPB in cardiac surgery11. However, there are only 3 pilot randomized control trials (RCTs) included in that study. In consideration of the emerging studies and the inconsistent results published in recent years, it is necessary to update the systematic review and meta-analysis on this issue.

METHODS

Search strategy: We conducted a systematic search in PUBMED, Web of Science, and EMBASE using “Nitric oxide” and “Cardiopulmonary bypass” as subject terms from inception to inception to Nov 1, 2022.

Participant or population: Patients who received NO via CPB during cardiac surgery.

Intervention: NO administration via CPB.

Comparator: placebo or standard CPB.

Study designs to be included: Randomized control trials.

Eligibility criteria: We included RCTs that compared NO administration via CPB with placebo or standard CPB on the clinical outcomes after cardiac surgeries, regardless of the age of the included patients. To reduce the heterogeneity, studies that adopted inhaled nitric oxide (iNO) or NO donors in perioperative period as interventions were excluded.

Information sources: We conducted a systematic search in PUBMED, Web of Science, and EMBASE.

Main outcome(s): The primary outcomes included the mortality at longest follow-up and duration of postoperative invasive mechanicalventilation.

Additional outcome(s): The secondary outcomes included postoperative levels of interleukin [IL]-6, IL-8, tumor necrosis factor- α (TNFα), and cardiac troponin I (cTnI), the incidences of low cardiac output syndrome and acute kidney injure (AKI), need for extracorporeal life support, peritoneal dialysis or renal replacement therapy, length of stay (LOS) in hospital and intensive care unit (ICU).

Quality assessment / Risk of bias analysis: The Cochrane risk of bias tool recommended by the Cochrane Collaboration was used in this study for risk of bias assessment 14. There are seven domains in the Cochrane risk of bias tool, including the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome

data, selective reporting and other bias. The judgment of each domain is presented as "low risk", "high risk" or "unclear risk" based on the instruction of Cochrane Collaboration.

Strategy of data synthesis: Data analysis was performed by the Review Manager software (RevMan, version 5.3.5; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The DerSimonian and Laird random effects model was adopted to pool the weighted effect of estimates across all studies15. The inverse variance method was adopted to estimate study weights for dichotomous data and the Mantel–Haenszel method was used for continuous data. The risk ratios (RRs) and mean differences (MDs) were calculated for dichotomous data and continuous data respectively, with corresponding 95% confidence interval (95% CI). We estimated the means and standard deviations (SDs) from median, range and/or interquartile range by using the calculator with a compiled formula recommended by Luo and colleagues when means and SDs were not available in some studies.

Subgroup analysis: Statistical heterogeneity was evaluated using the I2 statistic. If the I2 statistic was greater than 50%, the heterogeneity was considered to be been significant. Significant heterogeneity was investigate by predefined subgroup analyses. We planned a subgroup analysis according to the population of included patients (children VS. adult).

Sensitivity analysis: A sensitivity analysis restricted to studies with low risk of bias was performed to assess the effect of risk of bias on the stability of calculated results.

Language restriction: None.

Country(ies) involved: China.

Other relevant information: The funnel plot was used to assess publication bias if more than ten studies were included. We performed trial sequential analysis (TSA) to determine if the required sample size to reach the threshold for statistical significance was met for some important outcomes.

Keywords: cardiac surgery, Cardiopulmonary bypass, Nitric oxide.

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