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Research review

The role of remote ischemic preconditioning in organ protection after cardiac surgery: a meta-analysis

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) appears to protect distant organs from ischemia–reperfusion injury. We undertook meta-analysis of clinical studies to evaluate the effects of RIPC on organ protection and clinical outcomes in patients undergoing cardiac surgery.
Methods: A review of evidence for cardiac, renal, and pulmonary protection after RIPC was performed. We also did meta-regressions on RIPC variables, such as duration of ischemia, cuff pressure, and timing of application of preconditioning. Secondary outcomes included length of hospital and intensive care unit stay, duration of mechanical ventilation, and mortality at 30 days.
Results: Randomized control trials ($n = 25$) were included in the study for quantitative analysis of cardiac ($n = 16$), renal ($n = 6$), and pulmonary ($n = 3$) protection. RIPC provided statistically significant cardiac protection (standardized mean difference [SMD], −0.77; 95% confidence interval [CI], −1.15, −0.39; $Z = 3.98$; $P < 0.0001$) and on subgroup analysis, the protective effect remained consistent for all types of cardiac surgical procedures. However, there was no evidence of renal protection (SMD, 0.74; 95% CI, 0.53, 1.02; $Z = 1.81$; $P = 0.07$) or pulmonary protection (SMD, −0.03; 95% CI, −0.56, 0.50; $Z = 0.12$; $P = 0.91$). There was no statistical difference in the short-term clinical outcomes between the RIPC and control groups.
Conclusions: RIPC provides cardiac protection, but there is no evidence of renal or pulmonary protection in patients undergoing cardiac surgery using cardiopulmonary bypass. Larger multicenter trials are required to define the role of RIPC in surgical practice.

1. Introduction

Remote ischemic preconditioning (RIPC) is a method whereby brief intermittent periods of ischemia and reperfusion (IR) of tissues provide protection to distant organs from subsequent periods of prolonged IR injury [1]. RIPC in patients undergoing cardiac surgery has been performed with repeated cycles of IR using a blood pressure cuff on a patient's limb. A number of

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randomized control trials have been conducted with quite variable outcomes, and we were interested in finding out which population will gain the most benefit. We also investigated, if there is a need for varying the protocol for RIPC for different patient groups, and whether the improvements in surrogate markers actually translate into better clinical outcomes. Most of the meta-analyses published to date report on cardiac protection based on time-point measurement, such as at 12 h postintervention, whereas we believe that area under the curve (AUC) reduction in cardiac biomarkers provides better evidence of cardioprotection. We conducted a meta-analysis where cardiac protection was assessed using AUC. Additionally, we also present meta-analyses to assess the effectiveness of RIPC on protection to other organs in patients undergoing cardiac surgery.

2. Materials and methods

We conducted a review and meta-analysis. This research was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [2]. The study protocol is registered with (International Prospective Register of Systematic Reviews) PROSPERO with a registration number of CRD42012003174 [3].

2.1. Search strategy

Literature search was done on the following databases: MEDLINE, EMBASE, SCOPUS, Web of Knowledge, Cochrane, and Global Health library. The last day of the literature search was on February 5, 2013. The Medical Subject Heading (MeSH) terms or keywords searched were "ischemic preconditioning," "myocardial ischemic preconditioning," "remote ischaemic preconditioning," "remote ischemic preconditioning", "limb ischemic preconditioning," "cardiovascular surgical procedures," "cardiac surgical procedures," "thoracic surgery," "coronary artery bypass," "heart valve prosthesis implantation," "ventricular septal defects," "atrial septal defects," and "cardiopulmonary bypass."

2.2. Inclusion and exclusion criteria

Human randomized control trials of RIPC involving adult or pediatric cardiac surgical patients were included. Inclusion of the studies and extraction of data were done by one of the researchers. We included studies that assessed cardiac, renal, or pulmonary protection. Inclusion of a study for meta-analysis required reporting of myocardial injury biomarkers over at least 24 h postoperatively, with AUC values, incidence of postoperative acute kidney injury, or postoperative dynamic lung compliance. Postoperative myocardial injury biomarkers included troponin I, troponin T, and creatinine kinase (CK)–MB. The incidence of acute kidney injury was used to reflect renal protection. Acute Kidney Injury Network and Risk, Injury, Failure, Loss, and End-stage kidney disease criteria were used to define acute kidney injury [4,5]. Postoperative pulmonary function was assessed using dynamic lung compliance. Postoperative mortality, length of intensive care unit (ICU) and hospital stays, and ventilation period were also analyzed from the included studies. Studies published in non-English languages were excluded.

2.3. Data extraction

The outcome measures as defined previously were extracted during the data analysis. Authors were contacted if any additional data were needed. If not reported directly, AUC was calculated from the tabulated data or from graphs. When both were available, troponin results were chosen over CK-MB because of higher sensitivity and specificity for myocardial injury [6–8]. CK-MB was also included, if it was the only cardiac biomarker reported in the study.

Included studies were appraised and their risk of bias assessed using the Cochrane risk of a bias tool [9]. A subgroup analysis of the included studies was performed for three different surgical populations: coronary artery bypass surgery (CABG), valve replacement surgery, and pediatric cardiac surgery.

2.4. Statistical methods

Data analysis was carried out using Review Manager 5.2 (The Cochrane Collaboration, Copenhagen). Standardized mean difference (SMD) and the corresponding 95% confidence interval (CI) were calculated for continuous outcome data using a random effects model. In the case of dichotomous outcome data, risk ratios and their corresponding 95% CIs were calculated and analyzed using a random effects model. The X^2 test and I^2 were used to evaluate statistical heterogeneity.

Meta-regression analysis (using Stata v12 [StataCorp LP, Texas]) was carried out to assess if there was a correlation between the duration of ischemia, cuff pressure, timing of intervention, limb used (upper *versus* lower limb), and the treatment effect. Duration of ischemia was calculated by multiplying the duration of ischemia per cycle by the number of cycles. Cuff pressure was defined as the pressure to which the blood pressure cuff was inflated. Only studies that provide exact cuff pressures were assessed. Timing of intervention was classified as to either before or after anesthetic induction, that is, "early phase" and "late phase" RIPC or both. The treatment effect was a reduction in the release of cardiac injury biomarker as reflected by the SMD. We did sensitivity analysis, if there were any studies that showed extreme positive or negative results compared with other studies.

3. Results and discussion

3.1. Literature search

Using the MeSH terms and keywords mentioned earlier, we retrieved 252 articles from MEDLINE, 249 articles from EMBASE, 639 articles from SCOPUS, 624 articles from Web of Knowledge, 2 from Cochrane, and 63 from Global Health Library giving a total of 1829 articles. After removing duplicates, we were left with 1429 articles. The abstract of these articles was read, and of these, only 32 articles were found to be relevant. They were all randomized controlled trials conducted on patients who underwent cardiac surgery, where at