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Original Investigation

Remote Ischemic Preconditioning for Prevention of Acute Kidney Injury: A Meta-analysis of Randomized Controlled Trials

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Background: Remote ischemic preconditioning (RIPC) to prevent acute kidney injury (AKI) following cardiac and vascular interventions is a controversial practice.

Study Design: We conducted a systematic review and meta-analysis using the MEDLINE database (1966 through November 2013), EMBASE (1988 through November 2013), and Cochrane Library database.

Setting & Population: Patients undergoing cardiac and vascular interventions.

Selection Criteria for Studies: Randomized controlled trials comparing patient outcome with or without RIPC for prevention of AKI following cardiac and vascular interventions.

Intervention: RIPC using an inflatable tourniquet around the limb or cross-clamping the iliac arteries versus non-RIPC.

Outcomes: AKI, need for renal replacement therapy, postoperative kidney biomarkers, in-hospital mortality, and length of intensive care unit and hospital stay.

Results: 13 trials (1,334 participants) were included. RIPC decreased the risk of AKI for patients undergoing cardiac and vascular interventions compared with the control group (11 trials; 1,216 participants; risk ratio [RR], 0.70; 95% CI, 0.48-1.02; $P = 0.06$; $I^2 = 45\%$) with marginal statistical significance. There were no differences in levels of postoperative kidney biomarkers (serum creatinine and glomerular filtration rate), incidence of renal replacement therapy, in-hospital mortality, hospital stay, or intensive care unit stay between the 2 groups. Metaregression analysis indicated that contrast intervention was not a covariate contributing significantly to heterogeneity on the risk estimate for AKI incidence; also, there was no dose effect of RIPC using tourniquet cuff around the limb on AKI prevention based on different ischemia duration.

Limitations: Different AKI definitions adopted in the trials included.

Conclusions: RIPC might be beneficial for the prevention of AKI following cardiac and vascular interventions, but the current evidence is not robust enough to make a recommendation. Adequately powered trials are needed to provide more evidence in the future.

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INDEX WORDS: Remote ischemic preconditioning (RIPC); cardiac and vascular interventions; acute kidney injury (AKI); acute renal failure; renal impairment; meta-analysis.

Acute kidney injury (AKI) is a global health issue associated with substantial morbidity and mortality.[1,2] Even a small increase in serum creatinine level is associated with worse outcomes and higher mortality in both short- and long-term follow-up.[3] Cardiovascular intervention is one of the most frequent causes of AKI worldwide.[4,5] Also, AKI after cardiac and vascular interventions is associated independently with increased morbidity and mortality, as well as prolonged intensive care unit (ICU) and hospital stays.[6,7]

As Coleman et al[8] state, approaches to the prevention of AKI following cardiovascular intervention might include precise risk stratification of patients, allowing sufficient recovery after previous AKI, consideration of less costly surgical procedures, avoidance of cardiopulmonary bypass, minimizing injury from radiocontrast dyes or other nephrotoxic agents, and optimizing cardiovascular function and oxygen delivery. Unfortunately, most interventions now used to attenuate AKI after cardiovascular intervention are not supported definitively by evidence, and some have even proved harmful.[9-11]

In remote ischemic preconditioning (RIPC), application of mild nonlethal ischemia and reperfusion to one organ or tissue protects a different organ or tissue from a subsequent episode of lethal ischemia and reperfusion.[12] The RIPC stimulus reaches the target after humoral, neurogenic, and systemic inflammatory mediators transmit it from the source tissue.[13] In this respect, although the kidneys are not exposed directly

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to ischemia-reperfusion injury, RIPC might prevent kidney injury by its systemic effect of attenuating the consequent activation of inflammatory cascade and production of oxygen free radicals. Thus, RIPC offers the potential of a novel nonpharmacologic prevention strategy for decreasing AKI incidence in patients undergoing cardiac and vascular interventions.

To date, several clinical trials have been published that analyzed the role of RIPC in the prevention of kidney injury following cardiac and vascular interventions. However, published data are still limited and drawing conclusions from them remains controversial. Our primary objective was to systematically review the evidence of effects of RIPC on the prevention of postoperative kidney injury in patients who are undergoing cardiac and vascular interventions. As secondary objectives, we also assessed differences in the need for renal replacement therapy, postoperative kidney biomarker levels, in-hospital mortality, and length of ICU and hospital stays with the use of RIPC in these trials.

METHODS

Study Selection and Outcome Measures

Eligible studies had the following characteristics: (1) they were randomized controlled trials of any duration for prevention of AKI following cardiac and vascular interventions, (2) the intervention was RIPC as long as the only difference in the 2 arms was the use of RIPC, (3) trial participants (with or without preexisting kidney disease) underwent any cardiac and vascular interventions that were either elective or emergent, and (4) the studies reported the incidence of the outcome of interest, that is, AKI events following cardiovascular intervention (including zero events) in both arms.

The primary outcome measure was the development of AKI. Secondary outcome measures included initiation of renal replacement therapy, postoperative kidney biomarker levels, in-hospital mortality, and length of ICU and hospital stays.

Search Strategy

Electronic searches were performed using MEDLINE (1966 through November 2013), EMBASE (1988 through November 2013), and Cochrane Library databases. The following Medical Subject Headings terms and text words were used: ischemic preconditioning, cardiovascular surgical procedures, randomized controlled trial (RCT), controlled clinical trial, and remote ischemic preconditioning. Abstracts presented at the American Society of Nephrology, National Kidney Foundation, European Dialysis and Transplant Association, and World Congress of Nephrology meetings from 2009 through 2013 (if available online) were searched for additional unpublished data. References of recent review articles and the included studies also were searched for additional studies. There were no language restrictions. Titles and abstracts of the articles from these searches were independently analyzed by 2 of the authors (P.Z. and R.L.) to ascertain inclusion criteria conformity. The full text of an article was reviewed carefully if screening of its title and abstract was unclear with regard to its admissibility.

Study Validity Assessment

Studies included in the meta-analysis were evaluated for methodological quality using the criteria of the Jadad composite scale (randomization, blinding and withdrawals, and drop outs).[14] Allocation concealment and intention-to-treat analysis also were assessed.

Data Extraction

Two reviewers (P.Z. and R.L.) extracted data after assessing and reaching consensus for eligible studies by using a standardized data extraction form. Any discrepancies between the 2 reviewers were resolved by discussion with an arbitrator (Y.Y.). The same reviewers independently assessed each trial and extracted data about demographic characteristics of patients, type of surgical procedure, protocol for RIPC, incidence of AKI, incidence of renal replacement therapy, mortality, ICU and hospital stays, serum or plasma creatinine levels before and after surgery, and glomerular filtration rates (GFRs) before and after surgery. Any additional information required from the original investigators was requested by written correspondence, and 4 of the 13 authors responded to the queries; if relevant information was obtained in this manner, this was included in the review.

Data Analysis and Synthesis

We calculated risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and mean difference with 95% CI for continuous outcomes. To determine the robustness of our pooled effects, we compared our primary analysis with random-effects models by the Knapp-Hartung method,[15] except for rare events analyzed with fixed-effects models. We assessed statistical heterogeneity using χ^2 tests and determined the percentage of total variation across studies using Higgins I^2 statistic. I^2 values $>$ 25%, 50%, and 75% were considered evidence of low, moderate, and severe statistical heterogeneity, respectively.[16] Metaregression analyses were conducted to explore associations between potential covariates, including contrast intervention, different RIPC types and ischemia duration, and the risk estimate for AKI incidence in different subgroups, for which the response variable was the natural log–transformed hazard ratio and the explanatory variable was the effect of the potential covariate. This was investigated across trials by using random-effects metaregression models with inverse variance weighting. Analyses were carried out with the "metareg" command in Stata, version 12.0 (StataCorp LP). All statistical analyses were performed using R statistical software, version 2.15.0 (R Foundation for Statistical Computing) for the meta-analysis, except for the metaregression analysis using Stata, version 12.0.

RESULTS

Search Results and Study Characteristics

The search strategy generated identified 539 articles, of which 472 were excluded because they were either nonrandomized studies or evaluated interventions or outcomes that were not relevant to this review. Full-text assessment of 67 potentially relevant articles identified 13 eligible trials (Fig 1)[17-29]; all 13 were full-length articles.

A total of 1,334 participants were enrolled in the 13 studies, including 3 studies in patients undergoing vascular surgery,[17,18,22] 3 studies involving percutaneous coronary intervention,[19,25,29] and 7 studies involving cardiac surgery.[20,21,23,24,26-28] The RIPC method varied among studies: 11 studies used an inflatable tourniquet around the upper or lower limbs,[18-21,23-28,29] and 2 studies used cross-clamping of the iliac arteries.[17,22] The patients in 4 studies