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Remote ischemic conditioning for kidney protection: A meta-analysis

Ling Zhang, MD, PhD [a,c,1], Yongshu Diao, BN [a,1], Guangjun Chen, MD [b], Aiko Tanaka, MD [c], Glenn M. Eastwood, BN, BN, PhD [c,d], Rinaldo Bellomo, MBBS, MD, FRACP, FCICM, PG Dip Echo [c,d,*]

[a] Department of Nephrology, West China Hospital of Sichuan University, Sichuan, Chengdu, China
[b] Department of Anesthesiology, Austin Hospital, 145 Studley Road, Heidelberg, VIC 3084, Australia
[c] Department of Intensive Care Unit, Austin Hospital, 145 Studley Road, Heidelberg, VIC 3084, Australia
[d] Australian and New Zealand Intensive Care Research Centre, Melbourne, VIC, Australia

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ABSTRACT

Background: Results from randomized controlled trials (RCTs) concerning kidney effect of remote ischemic conditioning (RIC) are inconsistent.
Methods: We searched for relevant studies in Medline, Embase, the Cochrane Library, Google Scholar and Chinese database (SinoMed), as well as relevant references from their inception to November 2015. We performed a systematic review and meta-analysis of all eligible RCTs of RIC with kidney events.
Results: We included 37 RCTs from 2007 to 2015 involving 8168 patients. Pooled analyses of all RCTs showed RIC significantly reduced the incidence of investigator-defined acute kidney injury (AKI) compared with control groups (RR 0.84, 95% CI 0.73-0.96, $P = .009$) ($I^2 = 25\%$). However, the difference was not significant when only RIFLE (Risk, Injury, Failure, Loss, End Stage), AKIN (Acute Kidney Injury Network), or KDIGO (Kidney Disease Improving Global Outcomes) criteria were applied to the definition of AKI (RR 0.87, 95% CI 0.74-1.02, $P = .08$) ($I^2 = 22\%$). In subgroup analysis, RIC showed a significant benefit on reducing investigator-defined AKI in patients following percutaneous coronary intervention (RR 0.64, 95% CI 0.46-0.87), but not after cardiac surgery (RR 0.93, 95% CI 0.82-1.06). There was no difference for changes in the incidence of renal replacement therapy, estimated glomerular filtration rate or serum creatinine.
Conclusions: RIC might be beneficial for the prevention of investigator-defined AKI; however, the effect is likely small. Moreover, due to lack of an effect on use of renal replacement therapy, estimated glomerular filtration rate, RIFLE, AKIN, or KDIGO–defined AKI, and serum creatinine, the evidence for RIC is not robust. Finally, recent large-scale RCTs of RIC focusing on patient-centered outcomes do not support the wider application of RIC.

1. Background

Acute kidney injury (AKI) is a well-recognized complication of critical illness and is associated with high morbidity and mortality. Many different pharmacologic interventions have been used to prevent AKI in recent decades. However, the results have been disappointing [1–3].

Remote ischemic conditioning (RIC), also known as remote ischemic pre-conditioning, per-conditioning, or post-conditioning, involves the application of brief (minutes) reversible episodes of ischemia and reperfusion to an organ or tissue that is remote from the target organ or tissue [4]. Many researchers focused on the effect of RIC on cardiac protection, and found that RIC appeared to be an effective method for reducing ischemia/reperfusion myocardial injury, and it might reduce long-term clinical events in patients following cardiac surgery or percutaneous coronary intervention (PCI) [5].

However, whether RIC can reduce ischemia/reperfusion kidney injury is still an answered question and of great interest to nephrologists. Several clinical studies have reported that RIC might significantly reduce the incidence of AKI after cardiac and vascular surgery or PCI [6–8]. In addition, basic researchers have reported that the RIC stimulus releases mediators from the source tissue, which might prevent AKI by blocking free radical production and attenuating the inflammatory response [9]. Thus, the kidney may potentially benefit from the application of RIC. However, these findings have been challenged by recent randomized controlled trials (RCTs), which showed no effect of RIC on kidney protection [10,11].

Given the inconsistency of the existing RIC literature and the insufficient statistical power of primary studies, we conducted a meta-analysis of randomized controlled trials (RCTs) to summarize available evidence on the kidney protection achieved by RIC, including the incidence of AKI, need of renal replacement therapy (RRT), kidney biomarker levels and mortality.

* Corresponding author at: Department of Intensive Care Unit, Austin Health, 145 Studley Road, Heidelberg, VIC 3084, Australia. Tel.: +61 3 94965992.
E-mail address: rinaldo.bellomo@austin.org.au (R. Bellomo).
[1] Contribute equally to the study.

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2. Methods

We performed this systematic review using the guidelines proposed by the Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org). The protocol has been registered on PROSPERO (CRD42015024016) [12].

2.1. Study selection criteria

2.1.1. Participants

This review focused on patients with any intervention procedures who received RIC.

2.1.2. Interventions

For the purpose of the review, we used the term "RIC" to describe remote ischemic pre-conditioning, per-conditioning, or post-conditioning or any combination of above. The intervention of control group was no RIC or sham RIC.

2.1.3. Types of outcome measures

The primary outcome was investigator-defined AKI incidence, where AKI was defined by investigators in each study. Incidence of RRT, estimated glomerular filtration rate (eGFR), serum creatinine (Scr) and mortality were also analyzed.

2.1.4. Types of studies

We included all RCTs concerning the effect of RIC on kidney outcomes. We excluded non-randomized studies, studies published in abstracts, reviews, commentaries, and editorials.

2.2. Search methods for identification of studies

2.2.1. Study selection

We used the Cochrane risk of bias tool [13] to undertake, and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement methodology [14] to report, a systematic review and meta-analysis of RCTs. Two independent reviewers (LZ and GC) conducted a search in Medline, Embase, the Cochrane Library, Google Scholar, Chinese database (SinoMed) and relevant journals. Trials were considered without language or date restriction. We performed the last updated search on November 30, 2015. The following text words and corresponding heading terms were used as search terms: "remote preconditioning or remote post-conditioning or remote per-conditioning or remote conditioning or remote ischemic pre-conditioning or remote ischemic post-conditioning or remote ischemic per-conditioning or remote ischemic conditioning or remote ischaemic preconditioning or remote ischaemic postconditioning or remote ischaemic per-conditioning or remote ischaemic conditioning." Related articles and reference lists were manually searched to avoid omissions. After title screening, we evaluated abstracts for relevance and identified as included, excluded or requiring further assessment. At this stage, if a paper required further assessment, we contacted the study lead investigator by e-mail and/or telephone with a request for further information.

2.2.2. Data extraction

The inclusion criteria were as follows: (*a*) they were prospective RCTs concerning the effect of RIC on kidney outcomes; and (*b*) the intervention was any form of RIC as long as the only difference in the 2 arms was the performance of RIC; and (*c*) sufficient data available to calculate a relative risk (RR) or standardized mean difference (SMD) with 95% confidence interval (95% CI). The following exclusion criteria were used: (*a*) no relevant data of kidney outcomes; (*b*) nonhuman studies. For studies with the same or overlapping data by the same authors, the most suitable studies with the largest number of cases or latest publication dates were selected.

Two investigators (LZ and GC) assessed each study independently and recorded eligibility, quality and outcomes. Disagreements regarding eligibility arose with 6% of the articles ($\kappa = 0.88$), which were resolved by a third party through consensus. A third investigator (AT) provided arbitration in case of disagreement. We extracted the following study features: first author, publication year, country, study design, number of participant, protocol of RIC, incidence of AKI, incidence of RRT, estimate glomerular filtration rate (eGFR), serum creatinine (Scr) and mortality.

2.2.3. Quantitative data synthesis

Independently and in duplicate, reviewers assessed risk of bias using the Cochrane collaboration tool [13]. For each included study, a description, a comment, and a judgment as "high", "unclear", or "low" risk of bias was provided for each of the following domains: adequate random sequence generation; allocation sequence concealment; blinding for objective outcomes; incomplete outcome data; free of selective outcome reporting; and free of other bias. Studies with high risk of bias for any one or more key domains were considered as at high risk of bias. Studies with low risk of bias for all key domains were considered as at low risk of bias. Otherwise, they were considered as unclear risk of bias.

Before the analysis, data were standardized into equivalent units. For dichotomous variables such as incidence of AKI, the rates in the experimental (RIC) and control groups were expressed as RR and 95% CI. For continuous variable such as eGFR, SMD and 95% CI were calculated for each study. Heterogeneity was evaluated using the Cochrane Q test and the I^2 statistic to assess the degree of inter-study variation. I^2 values of 0% to 24.9%, 25% to 49.9%, 50% to 74.9%, and 75% to 100% were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity [15,16]. A random-effects model was performed to provide more conservative estimates of effect in the presence of known or unknown heterogeneity. Subgroup analyses were carried out by age, different intervention procedures, and different protocols of RIC. To reduce the risk of biased results of the meta-analysis, we also carried out a subgroup analysis restricted to blinding studies. We performed a sensitivity analysis that performed by pooling separately the most optimistic and pessimistic results from each included study. Publication bias was analyzed once sufficient RCTs were identified, by visual inspection of asymmetry in Begg's funnel plots as well as the Egger's test. [17] Data analysis was performed using Review Manager 5.2 (RevMan; The Cochrane Collaboration, Oxford, UK) and STATA 12.0 (StataCorp, College Station, TX).

3. Results

3.1. Eligible studies

The study selection process is presented in Fig. 1. The literature search yielded 812 potentially relevant records. By screening the titles, we removed 499 duplicate studies. After evaluating the abstract of each, 235 studies were excluded as they did not meet the inclusion criteria. Subsequently, we carefully read the full text of each of the remaining 78 studies and excluded 41 studies: no kidney data (n = 23), conference abstracts (n = 10), overlapping data (n = 4) and protocols (n = 4). Finally, 37 RCTs were included in the meta-analysis.

As shown in Table 1, the eligible studies were conducted from 2007 through to 2015 with a total number of 8168 patients, and sample-size ranged from 39 to 1612. There were 34 studies in adult [6,7,10,11,18–37,8,38–46] and 3 in children [47–49]. Among them, 15 studies were from Europe, 13 from Asia, 4 from North America and 2 from Oceania. A variety of outcomes were recorded in these studies, including incidence of AKI (n = 31; 84%) [6,7,10,11,19–25,27,29,30,32–36,8,38–46,48,49], incidence of RRT (n = 15; 41%) [6,10,11,24,28,29,31,34,35,8,38,43,44,47,49], eGFR (n = 7; 19%) [21,26,27,32,37,40,44], Scr (n = 13; 35%) [18,21,22,26,27,29–31,36,37,8,39,41] and mortality (n = 19; 51%)