Author's response to reviews

Title: The role of remote ischemic preconditioning on postoperative kidney injury in patients undergoing cardiac and vascular interventions: a meta-analysis

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Version: 2 Date: 16 February 2013

Author's response to reviews: see over
Dear editors,

Thank you for your letter on January 24 concerning our manuscript “The role of remote ischemic preconditioning on postoperative kidney injury in patients undergoing cardiac and vascular interventions: a meta-analysis” (MS: 1946942288794269), together with the comments from reviewers.

We have revised the manuscript in accordance with the reviewers’ comments, and carefully proofread the manuscript to minimize grammatical and spelling errors.

Here below are our responses to the reviewers’ comments, along with the indication of the location of the revision.

Thank you and all the reviewers for the kind advice. We hope that the revised manuscript can meet requirement for publication in Journal of Cardiothoracic Surgery.

Best Regard,

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Version: 2 Date: 11 February 2013

Author's response to reviews: see over
Reviewer's report

Title: The role of remote ischemic preconditioning on postoperative kidney injury in patients undergoing cardiac and vascular interventions: a meta-analysis

Version: 1 Date: 5 November 2012

Reviewer: FRANCESCO SEDDIO

Minor Essential revisions

Comment 1: The limit of the present study is the small number of studies. Of course this is a difficult set of patients and the authors tried to reduce the heterogeneity inside the groups, however I encourage the authors to find, if possible, a larger number of studies to analyse. In fact they have only 3 studies for patients undergoing vascular surgery.

Respond: We identified the published RCTs from the PubMed, EMBASE and Cochrane Library databases. In addition, we scanned the bibliographies of all relevant studies and recent review articles for further potential references. We also searched for unpublished and ongoing trials in clinicaltrials.gov and controlled-trials.com. However, in addition to the present studies, we could not find other trials which were eligible for this meta-analysis. In near future plan, we will perform an updated meta-analysis of RCTs of RIPC for renal protection if a number of additional RCTs are published.

Comment 2: In your manuscript you reported a subgroup analysis for patients undergoing cardiac surgery. Please could you tell us more about the role of RIPC on renal protection in this subgroup?

Respond: The reviewer’s comments are very helpful and important. The relevant changes have been made in the “Discussion” section (page 12, paragraph 2) accordingly: “Due to the limited number of trials included, only the group of studies in patients undergoing cardiac surgery was large enough to permit a subgroup analysis. We found that RIPC did not reduce the incidence of AKI in patients undergoing cardiac surgery. The hemodialysis requirement and mortality did not differ between
the RIPC and control group. The present analysis does not support the hypothesis that RIPC provides kidney protection in patients undergoing cardiac surgery.”

Comment 3: The authors conclude that there is no evidence that RIPC provides renal protection. Could the author comment this sentence?

Respond: The reviewer’s comments are very helpful and important. The explanation is stated as follows: This sentence means that RIPC has no beneficial effect on the postoperative occurrence of AKI, renal biomarkers, hemodialysis requirement, mortality, or hospital and ICU stays during cardiovascular interventions. However, in view of the size and quality of currently published studies, and the inherent limitations of meta-analysis extracted from these studies, our data should be regarded as exploratory with further studies needed in patients undergoing cardiac and vascular interventions.

According to this explanation, the relevant changes have been made in the “Discussion” section (page 13, paragraph 2).
Reviewer's report

Title: The role of remote ischemic preconditioning on postoperative kidney injury in patients undergoing cardiac and vascular interventions: a meta-analysis

Version: 1 Date: 25 September 2012

Reviewer: Scott A. LeMaire

Reviewer's report:

Major Compulsory Revisions

Comment 1: Although the authors have discussed their results in the context of some of the other meta-analyses evaluating the impact of RIPC on renal outcomes, this discussion should be expanded to include two other recent meta-analyses (Desai M, et al. Remote ischaemic preconditioning versus no remote ischaemic preconditioning for vascular and endovascular surgical procedures. Cochrane Database Syst Rev 2011;12:CD008472. – and – D'Ascenzo F, et al. Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis. Heart 2012; 98:1267-71.). A key issue is whether the current report adds knowledge or perspective beyond that provided by the other existing meta-analyses.

Respond: The reviewer’s comments are very helpful and important. We have addressed this comment in the “Discussion” section (page 10, paragraph 2) as followed: “To date, whether RIPC can protect kidney function in patients undergoing cardiac and vascular interventions is still a controversial issue. The meta-analyses by D’Ascenzo et al. and Brevoord et al. which evaluated the effect of RIPC in the patients undergoing cardiac and vascular interventions concluded that serum creatinine levels were both not reduced by RIPC. Recently Desai et al. published a meta-analysis including four RCTs of 115 patients undergoing vascular surgery, which showed no difference in the incidence of renal impairment between RIPC and controls. However, the meta-analysis by Alreja et al. showed that RIPC significantly reduced the levels of serum creatinine in the first few days after cardiac and vascular interventions. These apparent inconsistencies may be due to limitations in few
numbers of trials, small sample size and low to moderate methodological quality. Therefore, a further update of meta-analysis assessing the role of RIPC on renal protection in patients undergoing cardiac and vascular interventions should be performed. Compared with previous meta-analyses, our paper included the studies across a broader population over a longer time frame. Concerning renal end points, previous meta-analyses extracted either serum creatinine or incidence of AKI, whereas we tried to extract all renal outcomes from the included trials.”

**Minor Essential Revisions**

**Comment 1:** The authors should report whether the two investigators were in agreement in their selection of studies and their assessment of study validity/quality.

**Respond:** As suggested by the reviewer, the relevant changes have been made as followed:

“Literature search” section (page 5, paragraph 1): “There was complete consensus among two investigators on the final results.”

“Data extraction” section (page 5, paragraph 2): “Disagreements were resolved by contacting authors or reaching a consensus.”

**Comment 2:** The authors should clarify whether all of the studies used an intent-to-treat analysis.

**Respond:** In accordance with the reviewer’s suggestion, we have determined whether the intention-to-treat analysis was implemented in each trial (see Table 2).

**Comment 3:** The authors should consider reporting the results of the primary analysis after excluding the two low-quality studies.

**Respond:** Following the reviewer’s comment, a sensitivity analysis after excluding the two low-quality studies has been done in the “Results” section (page 10, paragraph 1) accordingly: “We performed a meta-analysis of high quality trials to evaluate the efficacy of RIPC for renal protection. There was no significant difference between two groups for incidence of AKI, renal biomarkers, hemodialysis requirement, or mortality after excluding the trials with low quality.”
Comment 4: The authors note that the studies employed different definitions for renal impairment, which is the primary outcome of interest. It would be useful to the reader to have the various definitions listed.

Respond: We have listed the various definitions for AKI in the “Results” section (page 7, paragraph 3) as followed: “The definitions included AKIN criterion [21, 23], RIFLE criterion [25], peak serum creatinine level > 2mg/dl [16], a postoperative decline in eGFR > 20% [18, 19], and a postoperative rise in serum creatinine > 0.5 mg/dL [20].”

Comment 5: Several minor grammatical errors need correction (“did not found” on page 11, “no enough” on page 12, “envelop” on page 21, etc.).

Respond: We have realized our mistake and carefully proofread the manuscript to minimize grammatical and spelling errors.

Discretionary Revisions

Comment 1: The authors discuss the degree of heterogeneity among studies in considerable detail. Of note, there is substantial mechanistic heterogeneity as well. The causes of kidney injury will differ in open aneurysm repair (embolic, hypovolemia/bleeding, transfusion), endovascular aneurysm repair (nephrotoxic contrast, embolic), and cardiac surgery (non-pulsatile flow during CPB, embolic, transfusion). This adds to the complexity of trying to determine whether RIPC is beneficial. Clearly, multiple studies will be needed to determine the impact of RIPC in these different clinical situations entailing different (but overlapping) mechanisms of kidney injury.

Respond: The reviewer’s comments are very helpful and important. Due to the small number of trials we only performed a subgroup analysis for the patients undergoing cardiac surgery. In near future plan, we will perform an updated meta-analysis to evaluate the effect of RIPC by operation type.