Reviewer’s report

Title: Remote ischemic preconditioning to reduce contrast-induced nephropathy

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Reviewer: Josée Bouchard

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Dr. Sterenborg and colleagues will perform a randomized controlled trial including 76 patients to determine whether standard hydration combined with remote ischemic preconditioning (RIPC) versus hydration with sham preconditioning during contrast administration have an effect on serum creatinine levels 48 to 72 hours after contrast administration.

Strengths: The study is a two-center randomized controlled single-blinded study with adequate allocation concealment (sealed envelopes) including patients at high risk for contrast-induced nephropathy (CIN), as defined by international guidelines (guidelines should be referenced).

Major Revisions

1. The authors have planned to conduct this RCT with a relatively small number of patients. This small n affects the definition of the primary outcome, as the standard definition of CIN could not be applied, i.e. an increase in creatinine levels by 25% or 0.5 mg/dl within 48-72 hours. This is a significant limitation of the study which needs to be clearly stated.

2. The authors have defined the primary outcome as a change in serum creatinine levels from baseline to 48 to 72 hours. The sample size is calculated on the assumption that fluid administration decreases creatinine levels and that RIPC can further decrease creatinine levels. The concept that fluid administration decreases creatinine levels needs to be clarified. This concept has been detailed in some references such as Moran and Myers, Kidney Int 1985; Pickering Crit Care 2013.

   It is counterintuitive to have a decrease in creatinine levels as the primary outcome in a study on CIN. A larger recent randomized controlled study (225 patients) on the same subject including patients undergoing urgent percutaneous coronary intervention found that serum creatinine increased by 14% in the control group and by 7% in the RIPC group, which is not concordant with the power calculation presented in this study (Deftereos JACC 2013). Although the authors referenced Er et al in their power calculation, this group also found similar results, i.e. an increase in serum creatinine levels in both groups at 48 hours (Er et al, Circulation 2012).

3. In their power calculation, the authors mentioned that the expected rate of loss to follow-up is 8%. However this does not seem to be taken into account in the final calculation (38 patients in the experimental and control arms, numbers that
are not increased by 8%).

4. Why did the authors choose to ask patients to fill up a questionnaire for comorbidities and medications? Will they use chart review?

5. Did the authors ensure 1) to withhold nephrotoxic drugs 48 hours before and after the procedure in both groups and 2) to have a similar rate of utilization of N-acetylcysteine between groups (although its efficacy is controversial)?

Minor issues not for publication

6. The authors should include references to justify the cut-off of >100 mL intravascular contrast (McCullough PA, Am J Med 1997, Manske, Am J Med, 1990)

7. There are many typos in the text which should be corrected, such as:
   a. Page 3. pathofysiology
   b. Page 3. Te instead of the
   c. Page 5. during 5 minutes followed by 5 minutes of reperfusion T (no period at the end of the sentence)

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.