REMOTE ISCHEMIC PRECONDITIONING TO REDUCE CONTRAST-INDUCED NEPHROPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Nijmegen, the Netherlands
March, 2016
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KEYWORDS
Remote ischemic preconditioning, contrast media, contrast-induced nephropathy, acute kidney injury, humans, randomized controlled trial, meta-analysis, review
INTRODUCTION

Contrast media used for diagnostic and therapeutic procedures is the leading cause of hospital-acquired acute kidney injury (1). The incidence of contrast-induced acute kidney injury (CI-AKI) is still significant despite the increasing use of low-osmolar instead of high-osmolar iodine-containing contrast media and hydration protocols (2, 3). This so called contrast-induced nephropathy (CIN) is defined as an absolute rise of ≥0.5 mg/dL and/or a relative increase of ≥25% in serum creatinine compared to baseline within 48 to 72 hours after contrast administration without an alternative cause of kidney injury (4). In patients with CIN, 0.04-12.6% requires dialysis treatment and 1.9-31.2% had an one-year mortality (5). Contrast media are used in cardiac and vascular interventions and radiological diagnostics.

The pathogenesis of CIN is complex and not fully understood. Contrast media may have direct toxic effects on tubular cells but may also cause vasoconstriction of the vasa recta leading to tubular ischemia. Increased viscosity may also contribute to decreased oxygen delivery of the vasa recta (6). The episode of tubular cell ischemia is followed by reperfusion which may cause ischemia-reperfusion injury of the kidney after contrast administration.

Remote ischemic preconditioning (RIPC) is a short and harmless discontinuation of blood supply to an organ or tissue, followed by reperfusion that is applied before the onset of prolonged ischemia to a distant organ or tissue (7, 8). Although the precise mechanism of RIPC remains unknown, two major pathways may play a role: the humoral and neurogenic pathways (9). The protective effects of RIPC on renal ischemia-reperfusion injury has been shown in many animal studies (10, 11). Human trials also indicate that remote ischemic preconditioning may offer a novel, nonpharmacological prevention strategy to reduce CI-AKI (12, 13).

To determine whether evidence to date supports the use of RIPC, as a non-invasive, safe, and low-cost method, to reduce contrast mediated kidney injury, a systematic review with meta-analysis is required.

OBJECTIVE

A systematic review with separate meta-analyses for randomized controlled clinical trials following The Cochrane Collaboration methodology will be conducted (14). The main objective is to evaluate the effect of RIPC in the prevention of contrast-induced nephropathy in patients with preexisting kidney disease who undergo a diagnostic or therapeutic intervention for which intravascular contrast is used.
METHODS

CRITERIA FOR CONSIDERING TRIALS FOR THIS SYSTEMATIC REVIEW

STUDIES
All randomized controlled clinical trials irrespective of language, blinding or publication status will be considered for inclusion.

Inclusion criteria:
• All studies evaluating the effect of remote ischemic preconditioning in patients at risk of contrast-induced AKI.

PATIENTS
All adult patients (≥18 years) in high risk for CIN defined as eGFR <60 ml/min/1.73m² with or without additional risk factors, who undergo a diagnostic or therapeutic intervention with the use of contrast media. Risk factors are listed in table 1 (2, 5, 15, 16).

EXPERIMENTAL INTERVENTION
Patients in the experimental group of the study will receive intermittent RIPC of ischemia and reperfusion by inflating a blood pressure cuff around the upper extremity, the lower extremity or both.

CONTROL INTERVENTION
Patients in the control group receive sham preconditioning or no preconditioning.

OUTCOMES
Primary outcome: Incidence of contrast-induced nephropathy (absolute rise of ≥0.5 mg/dL and/or a relative increase of ≥25% in serum creatinine compared to baseline within 48 to 72 hours after contrast administration)

Secondary outcomes:
• Change in serum creatinine from baseline to day 2-3 after contrast administration.
• Other biomarkers (e.g. Cystatin C, NGAL, KIM-1, L-FABP) (17)
• Mortality during index hospitalization or within 30 days
• Dialysis during index hospitalization or within 30 days
- Rehospitalization during index hospitalization or within 30 days

**SEARCH METHODS FOR IDENTIFICATIONS OF STUDIES**
The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, PubMed/MEDLINE, EMBASE and Web of Science will be searched. The references of the identified trials and cross references will be searched to identify any further relevant randomized clinical trials. All randomized controlled clinical trials irrespective of language, blinding or publication status will be considered for inclusion.

**TRIAL REGISTRIES**

**TRIAL SELECTION AND EXTRACTION OF DATA**
Two authors (TS and ME) will independently identify trials and studies for inclusion. The authors will make a list of excluded studies with reasons for exclusion. The authors will extract:

- year and language of publication
- year of conduction of the trial
- patient demographics (e.g. number of patients, mean age, gender, medication used, risk factors for CIN, MDRD in ml/min)
- standard preventive measures (e.g. hydration protocol, discount of medication)
- RIPC protocol (number of inflations, extremity used for preconditioning)
- amount of contrast media administered
- outcome measures (see OUTCOMES, page 4/5.)

The PRISMA checklist and PRISMA flow diagram for systematic reviews will be used (18). In case of discrepancies, consensus will be reached by discussion or consultation of an independent researcher (MW). If there is unclear or missing data the corresponding authors of the individual trials will be contacted.

**ASSESSMENT OF BIAS RISK**
The two authors (TS and ME) will assess the risk of bias, without masking for trial names, according to the Cochrane Handbook for Systematic Reviews of Interventions (14).

Sequence generation

- low risk of bias (a random component in sequence generation process is described)
• uncertain risk of bias (insufficient information to assess whether the method used is likely to introduce confounders)

• high risk of bias (the method is improper and likely to introduce confounding, e.g. performed by date of admission)

Allocation concealment

• low risk of bias (if the unit of allocation was by institution, team or professional; allocation was performed on all units at the start of the study and there was some form of centralized randomization)

• uncertain risk of bias (insufficient information to assess whether the method used is likely to induce bias on the estimate of effect)

• high risk of bias (the method used is likely to induce bias on the final observed effect)

Blinding of participants, personnel (e.g. surgeon, radiologist) and outcome assessors

• low risk of bias (blinding was performed adequately or outcome measurement is not likely to be influenced by lack of blinding)

• uncertain risk of bias (there is insufficient information to assess whether the type of blinding used is likely to induce bias on the outcome measurement)

• high risk of bias (no blinding or incomplete blinding, and the outcome or the outcome measurement is likely to be influenced by lack of blinding)

Incomplete outcome data

• low risk of bias (the underlying reasons for missing data are unlikely to influence treatment effects or proper methods have been employed to handle missing data)

• uncertain risk of bias (there is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias on the outcomes)

• high risk of bias (the outcomes will likely be biased due to missing data and methods to handle missing data are unsatisfactory)

Selective outcome reporting

• low risk of bias (the trial protocol is available and all of the trial’s pre-specified outcomes that are of interest have been reported or similar)
uncertain risk of bias (there is insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting)

• high risk of bias (not all of the primary outcomes in this review have been reported and not all of the trial’s pre-specified outcome that are of interest in the review have been reported)

Source of funding

• low risk of bias (the trial’s source(s) of funding did not come from any parties that might have conflicting interest (e.g. the trial was funded by independent organizations)

• uncertain risk of bias (the source of funding was not clear)

• high risk of bias (the trial was funded by parties that may have conflicting interests)

Trials classified as low risk of bias in sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, source of funding and other potentials of bias will be considered as trial with a low risk of bias. Trials with one or more of these mentioned risk of bias domains scored as unclear or high risk of bias will be considered as trial with high risk of bias. To assess all the possible bias components, review manager version 5.2 will be used (19).

STATISTICAL METHODS

In case of low heterogeneity a meta-analysis will be performed. Random effects meta-analysis will be performed according to the Cochrane Handbook for Systematic Reviews and Interventions (15). The software package Review Manager 5.2 will be used (16). For dichotomous variables, the risk ratio (RR) with 95% confidence interval (CI) will be calculated. For continuous variables, the mean difference (MD) or the standard mean difference (SMD) with 95% CI will be calculated. If applicable, reasons for heterogeneity will be explored.

SENSITIVITY ANALYSIS

Trials with low risk of bias (all bias components scored as low risk) will be compared to trials with high risk of bias (one or more of bias components scored as unclear or high risk).

BIAS EXPLORATION

A funnel plot to explore small trial bias and use it’s asymmetry in funnel plot of trial size against treatment effect will be performed to asses this bias. Begg’s and Egger’s tests will be used to test for asymmetry in funnel plots.
SUBGROUP ANALYSIS

Comparing patient groups
- Low/moderate risk versus high risk in developing CIN
- Cardiac intervention versus other interventions

Comparing the different protocols
- One limb versus two limbs
- Upper extremity versus lower extremity
- Number of cycles
- Duration of ischemia
- Interval between RIPC and contrast administration

CONCLUSION

The objective is to perform a systematic review using the Cochrane Collaboration-methodology with meta-analyses evaluating the effect of RIPC in preventing of CIN in patients with preexisting kidney disease who had undergo an endovascular intervention with the use of intravascular contrast media. This protocol will be online available prior to the start of the review process at the PROSPERO website.
REFERENCES


ABBREVIATIONS USED IN THIS SYSTEMATIC REVIEW

AKI      acute kidney injury
CI       confidence interval
CI-AKI   contrast-induced acute kidney injury
CIN      contrast-induced nephropathy
KIM-1    kidney injury molecule-1
L-FABP   liver fatty acid binding protein
MD       mean difference
MDRD     mean glomerular filtration rate
NGAL     neutrophil gelatinase-associated lipocalin
RIPC     remote ischemic preconditioning
SDM      standard mean difference
Table 1. Risk factors for CIN.

<table>
<thead>
<tr>
<th>Risk factors for CIN</th>
<th>Patient-related factors</th>
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<tbody>
<tr>
<td></td>
<td>Age &gt; 75 y</td>
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<tr>
<td></td>
<td>Pre-existing kidney disease (eGFR &lt; 60 mL/min/1.73 m²)</td>
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<tr>
<td></td>
<td>Diabetes and impaired glucose tolerance</td>
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<td></td>
<td>Decreased effective blood volume (heart failure, dehydration)</td>
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<td></td>
<td>Hypoalbuminemia (&lt; 35 g/L)</td>
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<td></td>
<td>Anemia</td>
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<td></td>
<td>Baseline hematocrit value &lt;39% for men and &lt;36% for women</td>
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<td></td>
<td>Peripheral vascular disease</td>
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<td>Nephrotoxic medication (e.g. NSAIDs, high-dose diuretic agents)</td>
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<tr>
<td></td>
<td>Hyperuricemia</td>
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<td></td>
<td>Metabolic syndrome</td>
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<td></td>
<td>Prior stroke</td>
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<td>Hypertension</td>
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<td>Renal transplant</td>
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<tr>
<td></td>
<td>Procedure-related factors</td>
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<td>High volume of contrast media</td>
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<td></td>
<td>Osmolality and ionicity of contrast media</td>
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<td></td>
<td>Intra-arterial contrast media injection</td>
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<td></td>
<td>Multiple contrast media exposures in &lt; 72 h</td>
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<tr>
<td></td>
<td>Intra-aortic balloon pump</td>
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</tbody>
</table>

y: years; eGFR: estimated glomerular filtration rate; CIN: contrast-induced nephropathy; NSAIDs: non-steroidal anti-inflammatory drugs; h: hours.