Remote ischemic preconditioning to reduce contrast-induced nephropathy.

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To demonstrate that remote ischemic preconditioning reduces contrast-induced nephropathy in patients ar high-rish of CIN (according CBO guidelines) next to the use of pre- and posthydration.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON37244

Source
ToetsingOnline

Brief title
RIPCIN study

Condition

- Nephropathies

Synonym
contrast-induced kidney injury, contrast-induced nephropathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,Cook medical, Aortic interventions

Intervention

Keyword: contrast-nephropathy, ischemic preconditioning

Outcome measures

Primary outcome

Change in serum creatinine levels from baseline (day prior to contrast

administration) to 48 hours after contrast administration.

Secondary outcome

-change in biomarkers (for kidney injury) levels in blood and urine from

baseline to 24 and/or 48 hours after contrast administration.

-incidence of CIN (>25% rise in serum creatinine)

-death, rehospitalization and/or hemodialysis within 6 weeks after

contrast-administration

Study description

Background summary

Iodine-containing contrast media are often used for diagnostic and therapeutic procedures. The number of procedures in which contrast meda are used is currently in the Netherlands approximately 1 million per year. It is expected that this number will rise considerablly in the near future. Despite the increasing use of low-osmolar instead of high-osmolar iodine-containing contrast media, the incidence of acute kidney injury due to contrast media is still significant. This so called contrast-induced nephropathy (CIN) is defined as a rise > 25% in serum creatinine within 72 hours after contrast administration without an alternative cause of kidney injury. CIN is associated with considerable morbidity and mortality.

Recently a CBO guideline on the use of iodine-containing contrast media is developed. All patienst who receive iodine-containing contrast should be screened for risk factors of CIN and also renal function should be measured (estimated glomerular filtration rate, based upon the MDRD formula). High risk patients should receive infusion with saline 8-20 hours prior to contrast

administration. Furthermore, 48-72 hours after contrast administration, renal function should be checked. Despite this treatment of high-risk patients the incidence of CIN is still 2-5% in this population.

Although the precise mechanims of CIN has not yet been elucidated, ischemia of the medulla seems to play an important role. The outer layer of the medulla is a high oxygen consuming area at a relatively far distance from the vasa recta (blood supply of the medulla). Contrast-induced vasoconstriction of the vasa recta attributes signifcantly to ischemia-reperfusion injury of the medulla which causes CIN. Furthermore, iodine-containing contrast media also have direct toxic effects on the tubular cells of the kidney, causing mitochondrial dysfunction and apoptosis.

Ischemic preconditioning is a phenomenon that was first discovered in 1986 by Murrey et al. Short ischemia of the myocardium reduces ischemia-repefusion injury due to a prolonged ischemic stimulus of the myocardium. Later, Pryzklenk et al. described that the protective effects of ischemic preconditioning also occurs if a short ischemic stimulus is applied to an organ at distance of the organ undergoing prolonged ischemia. Remote Ischemic PreConditioning (RIPC) with an extremity as remote organ is non-invasive, safe, low-cost and easy to implement into clinical practice. In great lines it is assumed that a humoral and/or neurogenic signal from the remote organ is transferred to the organ undergoing prolonged ischemia. In our experimental model of renal ischemia-reperfusion injury with hind limbs as remote organ, it appeared that the opiate-receptor plays a pivitol role in RIPC. Other possible humoral mediators are e.g. bradykinin, endocannabinoids and nitric oxide. In the target organ a intracellular signalling is initiated within seconds to minutes which reduces the mitochondrial permeability and this protects the cell for several hours against oxidative stress.

Recent preclinical research from our group showed that remote ischemic preconditioning using a hind limb as remote organ significantly reduces ischemia-reperfusion injury of the kidney. A recent retrospective cohort study by Whittaker et al. showed that multiple balloon inflations during coronary angioplasty (as remote stimulus) might reduce contrast-induced nephropathy. Furthermore, a recent randomized pilot study reported that in high-risk patients undergoing elective coronary angiography RIPC reduced CIN. However in this study a group of patients was included with a very high prevelance of CIN (40%). To question arises whether RIPC could also protect against contrast-induced kidney injury in a cohort of patients in which the prevelance of CIN is lower (approximately 5%). For this reason a study will be performed in which patients are included undergoing a diagnostic and/or therapeutic intervention with intravascular contrast at the departments of Surgery (division of Vascular- and Transplant Surgery) and Interventional Radiology of the Radboud University Nijmegen Medical Center.

Study objective

To demonstrate that remote ischemic preconditioning reduces contrast-induced nephropathy in patients ar high-rish of CIN (according CBO guidelines) next to the use of pre- and posthydration.

Study design

It concerns a single-center (RUNMC), blinded and randomized study. Inclusion will occur after informed consent by the treating physician of the department of Surgery. 76 sealed envelopes will be used to randomly divide consecutive patients with a 1:1 ratio between the control (sham preconditioning) and experimental (ischemic preconditioning) group.

Intervention

After informed consent, the researcher checks the scheduled time of the diagnostic and/or therapeutic procedure with iodine-containing contrast at the department of (interventional) radiology. The researcher is present at the angiography- or operation room or the CT-preparation room to perform the sham preconditioning or ischemic preconditioning procedure. RIPC will be applied by 4 cycles of 5 minutes inflation and 5 minutes deflation of a standard bloodpressure cuff around the upper arm at a pressure of the actual systolic bloodpressure plus 50 mmHg. Sham preconditioning will be applied in a similar fashion as the RIPC stimulus, but the blood pressure cuff is inflated to the actual diastolic blood pressure. The researcher carefully keeps the inflationpressure unvisible for both the patient and the (interventional) radiologist. The collection of patientcharacteristics, renal function data and the storage of urine samples will also be done by the researcher (not blinded).

Study burden and risks

Burden:
Patients are asked to fill in one questionnaire (10-15 minutes). Two additional blood samples are taken during the insertion or removal of the needle for infusion of the pré- and posthydration solution. The third blood sample at day 2 should be taken according to the CBO guideline and is therefore part of the standard treatment. The collection of two urine samples will occur one day prior to and after contrast administration. If a patient develops CIN (>25% rise in serum creatinine), the patient will be offered to pay a visit to the contrast outpatient clinic of the department of Nephrology (RUNMC) to check whether or not additional measures should be taken.

Risk:

A RIPC stimulus by short, repeated insufflations of a blood pressure cuff around the upper arm is generally considered as a safe technique. To our knowledge complications has not been described so far.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusioncriteria:
•Interventions with expected intravascular contrast volume > 100 mL:
-Thoracic Endovascular Aortic Repair (TEVAR)
-Endovascular Aortic Repair (EVAR)
-Digital Substraction Angiography (DSA)
-Percutaneous Transluminal Angioplasty (PTA)
-Percutaneous Intentional Endovascular Revascularisation (PIER)

-Carotic Artery Stenting (CAS)
-Percutaneous coiling/embolisation procedures
-Computed Tomographic Angiography

•High-risk of CIN (according CBO guideline):
- eGFR <45ml/min
- eGFR <60ml/min and diabetes
- eGFR <60ml/min ans 2 additional risk factors (peripheral artery disease, heart failure, >75 years, anaemia (Ht<0,39 for men and <0,36 for women), dehydration, use of diuretics and/or NSAID).;•Informed consent

Exclusion criteria

-Age < 18 years
-Hemo- and peritoneal dialysis
-Concomitant inclusion in another interventional study
-Percutaneous coiling/embolisation procedures of the kidney

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2012
Enrollment:	76
Type:	Actual

Ethics review

Approved WMO Date:	16-10-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL41890.091.12