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Original Article

Remote ischemic preconditioning for prevention of contrast-medium-induced nephropathy: (*RenoProtection*-trial)

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ABSTRACT

Background: Contrast-medium-induced acute kidney injury is associated with substantial morbidity and mortality. The underlying mechanism has been partially attributed to ischemic kidney injury. The aim of this randomized, double-blind, sham-controlled trial was to assess the impact of remote ischemic preconditioning on contrast-medium-induced acute kidney injury.

Methods: Patients with impaired renal function (serum creatinine >1.4 mg/dL and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2) undergoing elective coronary angiography were randomized in a 1:1 ratio to standard care with (n = 50) or without ischemic preconditioning (n = 50; intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff). Overall, both study groups were at high risk to develop contrast-medium-induced acute kidney injury using Mehran risk score. The primary endpoint was the incidence of contrast-medium-induced kidney injury, defined as an increase of serum creatinine ≥25% and/or ≥0.5 mg/dL above baseline at 48 h after contrast-medium exposure.

Results: Contrast-medium-induced acute kidney injury occurred in 26 patients (26%), 20 (40%) in the control group and 6 (12%) in the remote ischemic preconditioning group (OR 0.21; 95% CI 0.07–0.57; P = 0.002). No major adverse events were related to remote ischemic preconditioning.

Conclusions: Remote ischemic preconditioning before contrast-medium use prevents contrast medium-induced acute kidney injury in high risk patients. Our findings merit a larger trial to establish remote ischemic preconditioning on clinical outcomes.

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1. Introduction

Contrast-medium-induced acute kidney injury (CI-AKI) is a serious complication of coronary angiography (CA). CI-AKI is one of the most leading causes of hospital-acquired acute renal failure, accounting for 12% of all cases, and is associated with considerable morbidity and mortality.[1,2] With increasing use of contrast-medium in diagnostic and interventional procedures, the prevalence of CI-AKI is expected to rise in the next decades. Pre-existing renal dysfunction with estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 is the main predictor of CI-AKI, and its severity directly correlates with the incidence of CI-AKI.[3–5] Other risk factors for CI-AKI include diabetes mellitus, major cardiovascular comorbidities, hypovolaemia, administration of high doses of contrast medium, and concomitant use of drugs that interfere with the regulation of renal perfusion.[5] Patients undergoing CA are generally at high risk to develop CI-AKI due to existing comorbidities. In this respect, remote ischemic preconditioning (IPC) may offer a novel, non pharmacological prevention strategy for lowering CI-AKI incidence in patients undergoing CA. It is assumed that IPC procures protective effects on tissue or organ by multiple brief cycles of ischemia and reperfusion applied to another remote tissue or organ. This simple technique can be used in all medical centers worldwide. The role of IPC to reduce the incidence of CI-AKI is unknown. In this prospective, randomized, sham-controlled pilot study we hypothesized that IPC applied prior to CA may be beneficial in the prevention of CI-AKI in patients at high risk. Unfortunately, up to date resoundingly successful prevention options are missing. Novel prevention and treatment strategies are required to decrease CI-AKI incidence and to preserve kidney function in patients undergoing CA.

2. Methods

2.1. Study population

Eligible patients were aged 18 years or older; presented with stable angina pectoris and were admitted to the Cardiology Department of the Nizams Institute of Medical Sciences, Hyderabad for elective CA. Renal function test displayed impaired renal function with elevated serum creatinine of >1.4 mg/dL or reduced eGFR <60 mL/min/1.73 m^2 calculated by the MDRD formula ((mL/min/1.73 m2) = 186 × (serum creatinine [mg/L]) −1.154 × (age [years]) −0.203 × (0.742 if female) × (1.210 if of African descent)).[6] No patient had end-stage renal failure with the need for hemodialysis. This prospective, randomized, blinded sham-controlled pilot single-center trial was done from January 2013 until June 2014 at Nizams Institute of Medical Sciences, Hyderabad. All patients gave their written informed consent.

2.2. Study protocol

Sealed envelopes were used to randomly assign consecutive patients in a 1:1 ratio to receive one of the two treatments: standard CA with Sham preconditioning prior to CA (control-group), or emote ischemic preconditioning prior to standard CA through intermittent upper arm Ischemia. In accordance to the internal department guidelines all patients received standard care for patients with impaired renal function undergoing CA: oral *N*-Acetylcysteine 600 mg twice orally, the day before and at the day of CA, and continuous intravenous saline infusion (0.9%) 12 h before to 12 h after CA (1 mL per kilogram body weight per hour); withdrawal of nephrotoxic drugs (e.g., aminoglycosides, non-steroidal anti-inflammatory drugs, calcineurin inhibitors, metformin, and others); limitation of contrast medium application < 5 × body weight [kg] × (serum creatinine [mg/dL]) −1.[7] The primary outcome was the incidence of CI-AKI, which was defined as an increment of serum creatinine greater than 0.5 mg/dL, or by a relative increase of at least 25% over the baseline value within a period of 48-h after contrast medium administration. The secondary outcomes were the maximum elevation of serum creatinine, cystatin C, and urinary neutrophil gelatinase-associated lipocalin (NGAL) in a 48-h time-frame after contrast-medium exposure. The composite cardiovascular endpoint included death, rehospitalization or hemodialysis during 6-weeks follow-up.

2.3. Procedures

IPC was done by performing four cycles of alternating 5-min inflation and 5-min deflation of a standard upper-arm blood-pressure cuff to individuals' systolic blood pressure plus 50 mmHg to induce transient and repetitive arm ischemia and reperfusion. IPC was started immediately before CA. The time between last inflation cycle and CA start was less than 45 min. Sham preconditioning was performed by the same way as IPC, inflating an upper arm blood-pressure cuff to diastolic pressure levels and then deflating the cuff for 10 mmHg to maintain non-ischemic upper arm compression for blinding purposes of the patients. For blinding purposes of the physicians, investigators performing the preconditioning procedure (AMN, HD and KMD) were not involved in all other data acquisition and statistical analysis. CA was performed according to standard clinical practice. Percutaneous intervention was performed at physicians' decision. In all patients Accupaque 300® (Iohexol; osmolarity 0.64 Osm/kg H_2O at 37 °C), a nonionic low-osmolar contrast medium, was used. Post-procedural period was divided in acute phase during hospitalization (48 h and more) and follow-up, 6 weeks after coronary angiography. Samples in the acute phase were obtained from all subjects during hospitalization. Data for the 6-weeks follow-up time-point were acquired during the visits of patients in our outpatient clinic.

2.4. Study oversight

The study protocol was approved by the local ethics committee and was designed in accordance with the Helsinki II declaration. The trial was conducted in accordance with the trial protocol. The advisory board recommended reporting the present preliminary results due to the observed clear beneficial effects of IPC.