Original Article

Remote Ischemic Preconditioning for Prevention of Contrast-Induced Acute Kidney Injury in Patients of CKD Stage III and IV Undergoing Elective Coronary Angiography: A Randomized Controlled Trial

Abstract

Introduction: Contrast-induced acute kidney injury (CI-AKI) is a serious complication of coronary angiography (CA). The aim of this randomized, parallel group, single blind, sham-controlled trial was to assess the safety and efficacy of the remote ischemic preconditioning on the prevention of CI-AKI. **Methods:** Patients of 18–80 years of age with CKD 3 and 4, who were admitted for elective coronary angiography in a tertiary care hospital in eastern India were randomized in a 1:1 ratio to standard care with ischemic preconditioning (n = 45; intermittent arm ischemia through 4 cycles of 5-min inflation and 5-min deflation of a blood pressure cuff) or with standard care and sham ischemic preconditioning (n = 42). Overall, both study groups were at moderate risk of developing CI-AKI according to the Mehran risk score. The primary endpoint was the incidence of CI-AKI, defined as an increase in serum creatinine ≥25% or ≥0.5 mg/dL above baseline at 48 h after contrast medium exposure. **Results:** CI-AKI occurred in 8 patients (19.04%) in the control group and 2 (4.4%) in the remote ischemic preconditioning group (odds ratio, 0.198, 95% confidence interval, 0.087 to 0.452; P = 0.04). No major adverse events were related to remote ischemic preconditioning. **Conclusions:** This study indicates that remote ischemic preconditioning is a simple and well-tolerated procedure, which reduces the incidence of CI-AKI in CKD 3 and 4 patients undergoing coronary angiography.

Keywords: *Chronic kidney disease, contrast-induced AKI, coronary angiography, remote ischemic preconditioning*

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Introduction

Contrast-induced acute kidney injury (CI-AKI) is an important cause of in-hospital acquired AKI, surpassed only by diseases that cause renal hypoperfusion and the use of nephrotoxic drugs.[1] CI-AKI accounting for 12% of all hospital-acquired AKI cases, and is associated with considerable morbidity and mortality.[2,3] CI-AKI is caused by a combined effect of renal ischemia and direct toxicity of the contrast agent on the tubular epithelial cell, and has a high incidence in patients with preexisting renal disease, diabetes mellitus, and congestive cardiac failure.[4] Strategies to prevent CI-AKI have not been universally successful. Novel prevention and treatment strategies are required to decrease the incidence of CI-AKI and to preserve kidney function in patients undergoing elective coronary angiography (CA). In this respect, remote ischemic preconditioning (rIPC) may offer a novel, nonpharmacological prevention strategy for decreasing CI-AKI incidence in patients undergoing CA. Remote ischemic preconditioning (IPC) is a method by which the deliberate induction of transient nonlethal ischemia of an organ protects against subsequent ischemic injury of another organ. In this context, rIPC has been shown to ameliorate myocardial injury during cardiac surgery with cold blood cardioplegia.[5]

The role of remote ischemic preconditioning in reducing the incidence of CI-AKI has been studied previously and has been shown to be effective in the setting of coronary angiography.[6] Application of standard practices in hydration has decreased the incidence of CI-AKI.[7] Whether the incidence of CI-AKI improves with rIPC even after application of current standard of care, including hydration, N-Acetyl Cysteine, and limiting the dose of contrast

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is not known. In this study, we tested the hypothesis that rIPC is safe and effective in decreasing the incidence of CI-AKI with CA compared to a sham procedure, after applying standard of care.

Methods

Study population

This prospective, parallel group, randomized, single blind, sham-controlled single center study was carried out from March 2016 to September 2017 at a tertiary care center in Eastern India. The duration of follow-up was 6 weeks. Patients with age ≥18 to 80 years, who were diagnosed cases of CKD stage III and IV and admitted for elective angiography, were included in the study. The patients were recruited among those selected for coronary angiography in the outpatients of the Cardiology and Nephrology departments of the hospital. The patients were allocated in the ratio of 1:1 in the study and control groups. Included patients had 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 Modification of Diet in Renal Disease formula:

186 × (serum creatinine [mg/l])$^{-1.154}$ × (age [years])$^{-0.203}$ × (0.742 if female) × (1.210 if of African descent).[8] Patients who had an end-stage renal failure with the need for hemodialysis or reduced eGFR <15 mL/min/1.73 m^2, were excluded. All patients gave their written informed consent. The study was cleared by the institutional ethics committee (dated 08/03/2016). Study was registered in clinical trial registry (CTRI No CTRI/2017/12/011049).

Study protocol

A total of 87 patients were recruited for the study and randomized as per a computer-generated Random number table into two groups (by R.S.). One group received hydration, N-acetylcysteine, and sham preconditioning (Control Group) and the other group received hydration, N-acetylcysteine, and remote ischemic preconditioning (IPC Group). The patients were blinded to the intervention used. In accordance with internal departmental guidelines, all patients received standard care for patients with impaired renal function undergoing CA: Oral *N*-acetylcysteine (NAC) 600 mg twice orally, the day before and on the day of CA, and continuous intravenous saline infusion (0.9%) 12 h before to 12 h after CA (1 mL/Kg/hour); withdrawal of nephrotoxic drugs (e.g., aminoglycosides, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, metformin, and others) for two weeks prior to the procedure. The patients did not receive any sedatives or central nervous system depressants prior to angiography. The patients were on standard treatment for ischemic heart disease prior to the procedure. Volume of contrast used was limited to <5 × body weight [kg] × (serum creatinine [mg/dL])$^{-1}$.[9]

The primary outcome was to assess the effect of remote ischemic preconditioning on the incidence of CI-AKI, defined as an increment of serum creatinine ≥0.5 mg/dl or a relative increase of ≥25% over the baseline value within a period of 48 h after contrast medium administration. Secondary outcomes' measures included maximum elevation of serum creatinine in a 48-h period and 6 weeks after contrast medium exposure, hemodialysis during 6-week follow-up. The composite cardiovascular endpoint included death and rehospitalization.

Procedures

Ischemic preconditioning (IPC) was accomplished by performing 4 cycles of alternating 5-min inflation and 5-min deflation of a standard upper-arm blood pressure cuff to the individual's systolic blood pressure plus 50 mmHg to induce transient and repetitive arm ischemia and reperfusion. IPC was started immediately before CA. The time interval between the last inflation cycle and the start of CA was <45 min. Sham preconditioning was performed in the same way as IPC, by inflating an upper-arm blood pressure cuff to diastolic pressure levels and then deflating the cuff for 10 mmHg to maintain nonischemic upper-arm compression for blinding purposes with regard to the patients.

CA was performed according to standard clinical practice. In all patients, Accupaque 300 (iohexol; osmolarity 0.64 Osm/kg H_2O at 37°C), a nonionic low-osmolar contrast medium, was used. The post-procedural period was divided into the acute phase during hospitalization (≥48 h) and follow-up (6 weeks after CA). Samples in the acute phase were obtained from all subjects during hospitalization. Data for the 6-weeks follow-up time point was acquired during patient visits in our outpatient clinic. A detailed history and routine examination of all the patients was done. Their written informed consent was taken. All patients underwent subjective and objective analysis which included: complete blood counts, renal function test and electrolytes, liver function test, lipid and sugar profile, echocardiography, ECG, USG abdomen, urine routine and microscopy, and urine culture and sensitivity.

Statistical analysis

We considered the probable incidence of CI-AKI in the control group to be of that in a high-risk category of 30% and with intervention, it should decrease to that in a low-risk group, which is 8%.[10] Accordingly, to achieve a two-sided significance level of 5% and a power of 80%, a sample size of 44 patients in each group was necessary. We used Chi-square test and Fischer's exact test to compare categorical variables. Continuous variables were compared with the t-test. The Odds Ratio and the difference in relative risk were calculated. The patients were analyzed on a per-protocol basis. Statistical analyses were performed with SPSS 20.0. A 2-sided probability value of <0.05 was considered to indicate statistical significance.

Results

Figure 1 shows the study flow diagram. A total of 147 patients were assessed for eligibility, but 36 did not fulfill the inclusion criteria, and 24 did not agree to the protocol. A total of 87 patients were included. Of these patients, 42 were randomly allocated to receive standard therapy (control group) and 45 to receive standard therapy plus IPC (IPC group). 7 patients in control group and 5 patients in the study group were lost to follow up;

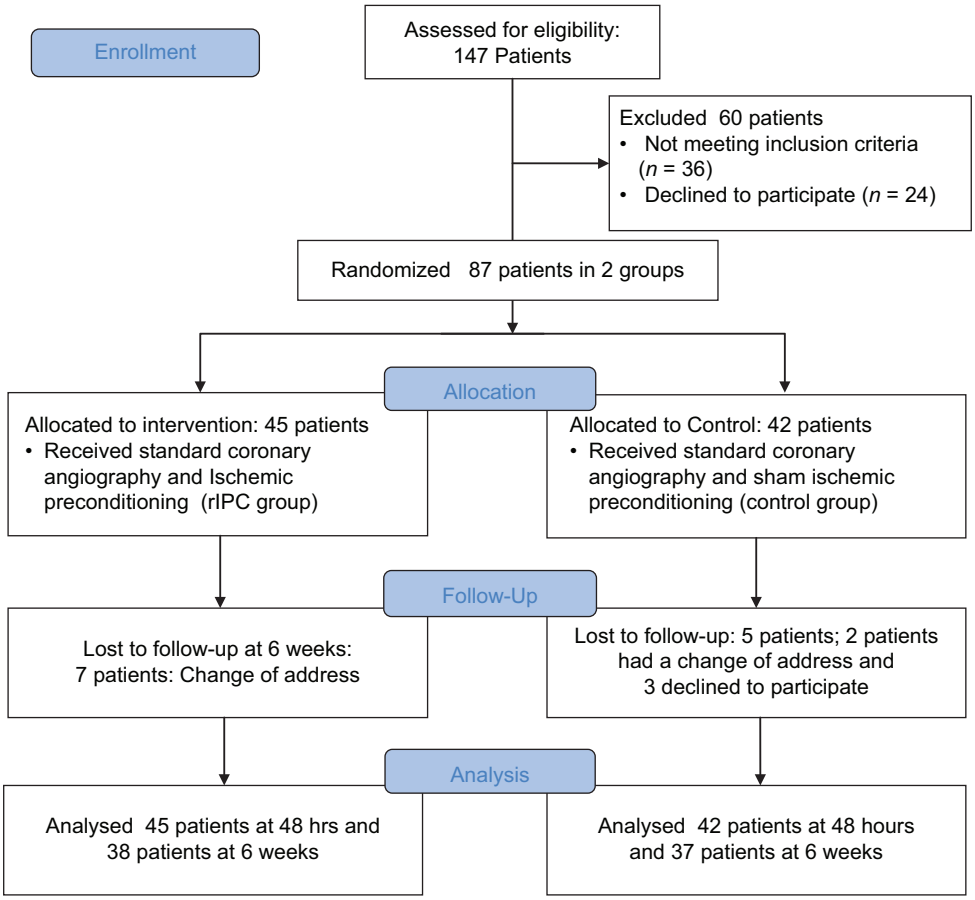

Figure 1: Flow diagram

Table 1: Baseline characteristics of patients

Age Group	Control Group (*n*=42)	IPC Group (*n*=45)
Mean Age±SD	55.35±10.76 years	57.76±7.8 years
Male	30 (71.42%)	38 (84.4%)
Hypertension	38 (90.4%)	41 (91.1%)
Smoker	19 (45.2%)	25 (55.5%)
Diabetes mellitus	26 (61.9%)	29 (64.4%)
Insulin therapy	9 (21.42%)	12 (26.6%)
Insulin therapy + OHA	7 (16.6%)	6 (13.3%)
OHA	10 (23.8%)	11 (24.4%)
Peripheral artery disease	2 (4.7%)	1 (2.2%)
Hemoglobin (g/dl)	11.25±1.6	11.46±1.5
Baseline eGFR (MDRD) ml/min/1.73 m^2	33.24±7.25	34.0±8.19
Baseline Creatinine (mg/dl)	2.14±0.44	2.16±0.46
Average volume of contrast medium (ml) (per patient)	37.04±6.04	40.02±7.61
Average duration between last cycle of sham/IPC and start of coronary angiography (min)	20.42±3.40	19.06±5.27
Heart failure: NYHA Class II	15 (35.7%)	11 (24.4%)
NYHA Class III	27 (64.3%)	33 (73.3%)
NYHA Class IV	0	1 (2.2%)

two shifted to another center and the rest could not be contacted.

The baseline characteristics are given in Table 1. Majority of patients were between 41 and 70 years of age in both groups. None of the baseline investigations showed any significant difference between the control group and IPC group. The Mehran risk scores are given in Table 2. Majority of the patients fall under moderate risk category as per this scoring system in both the groups. The calculated risk score suggests an equal probability of developing CI-AKI in both groups.[11]

Table 3 depicts antihypertensive medication use was similar in the 2 groups. Loop diuretics were withdrawn peri-procedurally and started again the day after CA. In 2 subjects (4.7%) in the control group and 1 (2.2%) in the IPC group, loop diuretics were given peri-procedurally to control heart failure. Table 4 depicts the primary study endpoint, CI-AKI, which occurred in 8 patients (19.04%) in the control group and 2 (4.4%) in the IPC group (odds ratio, 0.198, 95% confidence interval, 0.087 to 0.452; P = 0.045). Serum creatinine levels were done at baseline and after 48 h of angiography. Baseline serum creatinine was similar in both the groups (control group 2.14 ± 0.44, IPC group 2.16 ± 0.46 mg/dl) but increased significantly after 48 h in control group (control group 2.36 ± 0.75 mg/dl) compared to patients in IPC Group (IPC group 2.01 ± 0.54 mg/dl) (P = 0.016). In no patients did the urine output decrease to less than 0.5 ml/kg/hour to meet the urine output criteria for AKI. At 6 weeks, there was no significant difference in the creatinine levels between the groups (control group: 2.25 ± 0.51 vs. IPC group 2.21 ± 0.47; P = 0.75). One patient in the IPC group required hospitalization and died during follow-up (cause of death was myocardial infarction). None of the patients required dialysis during 6-week follow-up. The number needed to treat to prevent one episode of CI-AKI was 6.84 (~7).

With regards to diabetes, 5 patients out of the 26 diabetic patients in the control group had AKI compared to 3 out of 16 in the nondiabetic controls. In the IPC group, both the events occurred in diabetic patients; nondiabetic patients did not experience any AKI. The presence of diabetes does not influence the outcome ($P < 0.05$).

Table 2: Mehran contrast nephropathy risk scores in the study and control groups

CI-AKI risk score (score points)	Control Group (*n*=42)	IPC Group (*n*=45)	*P*
≤5	6 (14.2%)	4 (8.88%)	
6-10	35 (83.3%)	40 (88.8%)	
11-15	1 (2.3%)	1 (2.2%)	
≥16	0	0	
Average score	8.33±2.30	8.22±1.94	*P*=0.808

Table 3: Baseline antihypertensive use

Medicines	Control Group (*n*=42)	IPC Group (*n*=45)
β-blocker	33 (78.5%)	41 (91.1%)
Angiotensin-converting enzyme inhibitor	2 (4.7%)	5 (11.1%)
Angiotensin II receptor antagonist	5 (11.9%)	11 (24.4%)
Calcium channel blocker	39 (92.8%)	32 (71.1%)
Thiazide diuretics	0	0
Loop diuretics	39 (92.8%)	38 (84.4%)
Loop diuretics (periprocedural)	2 (4.7%)	1 (2.2%)
Spironolactone	2 (4.7%)	4 (8.8%)

Adverse effect

No major adverse events occurred during sham-control preconditioning and IPC. In 3 patients with IPC, 3 instead of 4 cycles of upper-arm ischemia were performed because of patients' discomfort. One patient with IPC developed mild reversible petechial spots distal to the blood pressure cuff.

Discussion

CI-AKI has been shown to be an independent predictor of 1-year mortality in patients with coronary artery disease. The incidence of CI-AKI varies substantially among several studies because of the lack of a uniform definition of CI-AKI.[4,12] Rates of CI-AKI may be as high as >50%, depending on the presence of risk factors such as chronic renal insufficiency, diabetes mellitus or heart failure.[11-14] To date, there is no effective prophylactic regimen to prevent CI-AKI. Dopamine, fenoldopam, furosemide, mannitol, aminophylline, atrial natriuretic peptide, captopril, calcium channel blockers, and alprostadil were not effective in reducing the incidence of CI-AKI.[7,15-17] Initial studies

Table 4: Primary and secondary outcomes

Outcomes	Control (*n*=42)	RIPC (*n*=45)	Odds ratio (95% CI)	Risk difference (95% CI)	*P*
Primary					
Occurrence of AKI	8 (19)	2 (4.4)	0.198 (0.087-0.452)	-0.146 (-0.279 to -0.013)	0.045
Creatinine (mg/dl)	**Mean±SD**		**Mean Difference (95% CI)**		***P***
Secondary					
Baseline	2.14±0.44	2.16±0.46	-0.02 (-0.21 to 0.17)		0.837
48 h	2.36±0.75	2.01±0.54	0.35 (0.06 to 0.63)		0.016
6 weeks	2.25±0.51	2.21±0.47	0.03 (-0.18 to 0.24)		0.756

assessing the ability of NAC to prevent CI-AKI were encouraging; however, the role of NAC in the prevention of CI-AKI has been questioned, because subsequent larger trials failed to demonstrate an NAC-associated benefit.[18,19]

Our hypothesis that IPC may be nephroprotective was largely based on earlier reports showing the beneficial action of IPC in several clinical settings. IPC has been reported to decrease the incidence of perioperative myocardial injury during cardiac surgery in adults[5,20,21] and children[22] and to diminish both myocardial and renal injury incidence during surgery for endovascular[23] and open surgical[24] repair of abdominal aortic aneurysm. Very recently, IPC before hospital admission has been shown to increase myocardial salvage by attenuation of reperfusion injury in patients with evolving myocardial infarction.[25]

It has been postulated that a remote organ releases humoral factors such as adenosine or bradykinin into the systemic circulation, which subsequently protects the remote region or organ. Other underlying mechanisms may include erythropoietin, activation of the KATP channel, nitric oxide, delta 1-opioid, and free radicals.[26] Some studies have also suggested that the protective effect of IPC may be caused by its beneficial anti-inflammatory or antioxidant effects and decreased extracellular levels of noxious metabolites, such as protons and lactate.[26,27] In addition, some other studies have favored a neurogenic pathway.[28] In a review by Dugbartey *et al*., it was discussed that neural and humoral pathways were activated in RIPC. "Reperfusion injury salvage kinase" (RISK) is a group of pro-survival kinases, which are an important target of RIPC. Endogenous antioxidant systems are also activated. Inhibition the opening of mitochondrial permeability transition pores is a cellular mechanism in RIPC.[29]

It is well known that reperfusion injury involves several pathways, including alterations in cellular metabolism, endothelial dysfunction, inflammation, hypercontracture, and necrosis/apoptosis.[30] Thus, IPC-mediated counter-regulatory protective pathways may eventually offer an additional clinical benefit and contribute to better clinical outcomes.

In 2004, Mehran *et al*.[11] developed a risk classification system to predict the risk for contrast medium-induced nephropathy in patients undergoing CA. This score includes clinical and procedural variables and is divided into 4 classes of risk of developing CI-AKI: Low (risk score <5), moderate (risk score 6–10), high (risk score 11–15), and very high (risk score ≥16). The calculated mean integer score for both groups in the present study was 8.33 ± 2.3 and 8.22 ± 1.94 $P = 0.808$ [Table 2], thus determining the present study population as a group at moderate risk of developing CI-AKI (>80% of the subjects were at moderate risk). In our study, the incidence of CIAKI is 19.04% in the control group, which is within the reported range and corresponds to the serum creatinine-based CI-AKI incidence predicted by Mehran *et al*.[11]

Results similar to our study were obtained by Er *et al*. (2012) RenPro trial.[6] Their study included 100 adults (mean age 73.2 years) with impaired renal function (serum creatinine 1.4 mg/dL and/or eGFR, 60 ml/min per 1.73 m2; mean Mehran score 13) who underwent elective coronary angiography. CI- AKI occurred in significantly fewer patients in the rIPC group than in the control group (12% versus 40%; $P = 0.002$). No major adverse events related to the procedure were reported. Overall, there was a substantial decrease in the number of patients developing CI-AKI in individuals who received rIPC before coronary angiography, suggesting that rIPC was particularly renoprotective in high-risk patients.

RIPC-mediated effects on the kidney have been extensively investigated in the setting of adult cardiac or vascular surgery. RIPC-induced cardioprotection and renoprotection were evaluated in 82 adults undergoing abdominal aortic aneurysm repair.[31] RIPC, induced by two cycles of intermittent cross-clamping of the common iliac artery, was associated with a 23% decrease in AKI (30% versus 7%; $P = 0.01$). In addition, rIPC significantly reduced the incidence of myocardial infarction. A separate study in the same clinical scenario, but with fewer patients ($N = 51$) and a different type of rIPC stimulus (common iliac artery clamping), did not find statistically significant differences in renal outcome indices.[23]

In another randomized clinical trial, the same authors aimed to determine whether rIPC can reduce renal injury in a smaller number of patients ($N = 40$) after endovascular aneurysm repair.[32] rIPC was induced by sequential lower limb ischemia. Although there were no significant differences in the rates of renal impairment, rIPC reduced renal injury during the procedure, as demonstrated by a reduction in postoperative urinary biomarker levels.

In a prospective randomized placebo-controlled trial ($N = 162$), Rahman *et al*. tested whether rIPC improves myocardial or other end-organ protection after on-pump coronary surgery.[33] Renal outcomes were among the secondary endpoints. The results showed that in patients undergoing multi-vessel coronary artery bypass graft (CABG) surgery, the incidence of AKI in those who received rIPC was similar to that of controls. However, this study was performed in anesthetized and, thus, patients were pain-free. On the other hand, there is evidence from several experimental studies that pain may be a strong trigger of preconditioning,[34] and rIPC is dependent on intact local neural pathways.[35] In this context, cautious interpretation of these results is needed, warranting further rIPC efficacy studies in anesthetized versus nonanesthetized subgroups.

In 2010, another retrospective study of nondiabetic patients undergoing elective CABG surgery found that rIPC using

transient ischemia of the forearm decreased the incidence of AKI.[36] A total of 78 consented patients were randomly assigned to either rIPC (N = 38) or control (N = 40) groups before CABG surgery. Of 40 patients in the control group, 10 (25%) developed stage 1 AKI and none developed stage 2 or 3 AKI. In contrast, only 1 of 38 patients (3%) in the rIPC group developed stage 1 AKI, although 3 patients developed stage 2 AKI. The overall difference in AKI between the two groups was statistically significant (P = 0.01).

Similar results were obtained in another study of lower limb preconditioning in patients undergoing elective CABG.[37] Sixty patients were randomized to rIPC or control groups. Significantly fewer patients in the rIPC group developed AKI within 48 h after surgery compared with the control group (20% versus 47%, P = 0.004), reflecting an absolute risk reduction of 0.27 (95% confidence interval, 0.24–0.76) and a significantly reduced relative risk due to preconditioning of 0.43 (95% confidence interval, 0.10–0.42).

Deftereos *et al*. recently provided additional evidence that remote ischemic post-conditioning may also be effective in preventing acute kidney damage in intermediate-risk patients (mean Mehran risk score).[11,38] The authors evaluated the renoprotective effect of remote ischemic postconditioning in patients with a non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (N = 225). The CI-AKI rate in the rIPC group was significantly lower than in the control group (12.4% versus 29.5%, P = 0.002). Furthermore, the 30-day rate of death or rehospitalization for any cause was 22.3% in the control group versus 12.4% in rIPC patients (P = 0.05).

There have been several studies on the effects of the remote ischemic preconditioning in the setting of coronary angiography over the last decade. A study done measuring urinary Liver-type Fatty Acid Binding Protein suggested that smaller elevations were present in the rIPC group.[39]

Results similar to our study have been reported in several trials[40,41] including the EUROCRIPS Cardiogroup 1 study[42]; in the latter, a benefit was found in the nondiabetic cohort but not in the diabetics. A meta-analysis of published trials suggested that rIPC can improve myocardial salvage index and myocardial infarct size post-MI.[43]

However, a study done in southern India demonstrated no improvement in incident AKI after rIPC in a cohort undergoing angiography, but there was an improvement in the post-procedure creatinine values.[44] The numerical incidence of AKI was less in the study group (11/50 vs. 18/50) but the difference did not reach statistical significance. This study had a slightly higher volume of contrast used in the treatment arm. In the RIPHEART study, RIPC was done on patients undergoing cardiopulmonary bypass, and it showed no benefit of the procedure. However, the patients underwent anesthesia by propofol, which may have ameliorated the benefits of RIPC in these patients.[45]

Overall, particularly in view of the latest published reports, and our study, it seems that rIPC is beneficial in reducing the incidence of CI-AKI in moderate-risk patients. However, further studies are necessary to establish the therapeutic value of rIPC in the clinical setting.

This study is limited by being a single center with a relatively few number of patients, and the fact that it was single blinded. The study population was also limited to the population from eastern India; hence, its applicability to other races and populations is not certain. In addition, we were not able to test for urinary biomarkers before or after the procedure.

Conclusions

The data derived from the study indicates that remote ischemic preconditioning is a simple and well-tolerated procedure which significantly reduces the incidence of contrast medium-induced acute kidney injury in patients of chronic kidney disease stage III and IV. Thus, the use of rIPC may be a feasible and highly attractive therapeutic procedure.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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