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Original Article

Remote ischemic preconditioning for prevention of contrast-induced nephropathy – A randomized control trial☆

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ABSTRACT

Background: There is a lack of sufficient data regarding the protective effects of remote ischemic preconditioning (RIPC) in patients at risk of developing contrast-induced nephropathy (CIN). Thus, this study was conducted to determine whether RIPC as an adjunct to standard therapy prevents CIN in high-risk patients undergoing coronary intervention.

Methods: In a single-center, double-blinded, randomized controlled trial, 162 patients who were at risk of CIN received standard hydration combined with RIPC or hydration with sham preconditioning. RIPC was accomplished by four cycles of 5 min ischemia and 5 min reperfusion of the forearm. The primary endpoint was a rise in serum creatinine (>0.5 mg/dL or >25%) from baseline to serum creatinine 48–72 h after contrast administration.

Results: Of the 162 patients, 81 were randomly allocated to receive sham preconditioning and 81 to receive RIPC. Significantly reduced serum creatinine levels were observed in patients with a Mehran moderate risk allocated to sham group compared to the RIPC group (0.070 ± 0.16 mg/dL vs. 0.107 ± 0.13 mg/dL, p = 0.001). With regards to the primary endpoint, a significantly higher change in serum creatinine from baseline to 48–72 h was observed in the sham group compared to the RIPC group (0.023 ± 0.2 μmol/L vs −0.064 ± 0.1 μmol/L, p < 0.001).

Conclusion: RIPC as an alternative to standard therapy, improved serum creatinine levels after contrast administration in patients at risk of CIN. However, present data indicate that RIPC might have beneficial effects in patients with a moderate or high risk of CIN.

1. Introduction

Coronary angiography (CA) and percutaneous coronary intervention (PCI) are routinely performed in patients with coronary artery disease. In the past few years, with the development of clinical diagnosis and interventional therapy, the use of iodine-containing contrast media in PCI is increasing and can lead to contrast-induced nephropathy (CIN).[1,2] Consequently, CIN has become a common complication of PCI and has become the third leading cause of acute renal failure in hospital.[3,4] Ongoing techniques to prevent CIN include pre-procedural hydration with isotonic saline, utilization of iso-osmolar non-ionic contrast media, pre-medicating with N-acetyl cysteine, and removal of nephrotoxic drugs.[5,6] Unfortunately and resoundingly successful prevention options are lacking because nearly 20–30% of patients with underlying risk factors for CIN undergoing CA go on to develop CIN.[7] However, new treatment strategies are warranted to decrease incidence of CIN in patients undergoing CA.

In this respect, remote ischemic preconditioning (RIPC) was demonstrated in 1996.[8] It is a novel, non-pharmacological prevention strategy inducing transient episodes of ischemia by the occlusion of blood flow in non-target tissue such as a limb before a subsequent ischemia-reperfusion injury occurs in a more distant organ.[9] RIPC has been shown to have protective effects on the remote organs such as the heart, brain, lung, kidney, intestine or skeletal muscle via an adaptational response that protects against the ischemia and reperfusion insult.[9,10] Recently, RIPC has been evaluated to prevent CIN.[11,12] Even though RIPC showed protective effects on urinary liver-type fatty acid-binding protein levels in

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patients with CIN, the serum creatinine levels in the RIPC and control groups did not show significant differences.[13] Since, there has been a lack of sufficient data regarding the protective effects of RIPC in patients at risk of developing CIN, a randomized controlled trial was conducted to determine whether RIPC as an adjunct to standard therapy prevents CIN in high-risk patients undergoing coronary intervention.

2. Methods

2.1. Study design and study population

A single-center, double-blinded, randomized controlled trial was performed at a tertiary-care center in India. A total of 162 patients were included within 12 months duration after approval from the institutional ethics committee. Patients with age ≥18 years, serum creatinine levels of >1.0 mg/dL with ≥2 high risk factors based on Mehran risk factors or patients with estimated glomerular filtration rate (eGFR) levels of <60 mL/min/1.73 m^2 and patients undergoing selective coronary intervention either by coronary angiography or by percutaneous trans luminous coronary angiography (PTCA) were included in the study. Patients who refused to sign the inform consent form, patients undergoing routine haemodialysis or peritoneal dialysis and patients in whom RIPC could not be performed due to pathology of both the arms (for example, dystrophy, recent trauma and chronic wounds) were excluded from the study. Signed informed consent forms were obtained from all the patients in the study.

2.2. Study procedure

The present study was initially planned in two-steps. The present first-step was designed to prove the concept that RIPC might be beneficial in patients at high-risk for CIN. Based upon the results of the present study a second extended study may be designed to test the effects of RIPC on cardiovascular mortality and morbidity. According to the standard guidelines, all participating patients received the standard hydration schedule consisting of intravenous infusion with saline 0.9% solution of 1 ml/kg/h for 6 h before and 12 h after the contrast administration. Nephrotoxic drugs (e.g. aminoglycosides, non-steroidal anti-inflammatory drugs, and calcineurin inhibitors), and metformin were discontinued. RIPC was accomplished by performing four cycles of ischemia and reperfusion of the forearm by inflating a blood pressure cuff around the upper arm at 50 mmHg above the actual systolic pressure for 5 min, followed by 5 min of reperfusion. Ischemic preconditioning was started immediately within 3 h before patients undergoing selective coronary intervention. The sham preconditioning was performed in the same way as the RIPC, except inflating the blood pressure cuff to 10 mmHg below the actual diastolic pressure during 5 min, followed by 5 min of reperfusion. The cycle of inflation and deflation avoids bias in the Shams group. Also, inflation only till the diastolic blood pressure cannot compromise blood pressure to muscles or induce ischemia. Hence, Shams protocol serves both purposes of avoiding bias without inducing ischemia. The time between the last inflation cycle and the start of the intervention was planned to be within 45 min. In the interest of blinding, the investigator confirmed that the inflation pressure was not visible to either the patient or the interventional cardiologist.

2.3. Endpoints and definitions

The primary endpoint was a rise in serum creatinine (>0.5 mg/dL or >25%) from baseline to serum creatinine 48–72 h after contrast administration. The secondary endpoints were the incidence of contrast-induced nephropathy (CIN) requiring rehospitalization, haemodialysis, and mortality within 6 weeks of contrast administration. CIN is defined as an absolute rise of 0.5 mg/dL or a relative increase of 25% in serum creatinine over baseline within 48–72 h of contrast administration. The eGFR level was calculated by using the Modification of Diet in Renal Disease (MDRD) equation.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared using the student's *t*-test or Mann–Whitney *U* test. Categorical variables were expressed as frequencies and percentages and compared using the Pearson chi-square test or Fischer's exact test. A p-value < 0.05 was considered as statistically significant. The analysis was performed using Statistical Package for Social Sciences (SPSS) software version 15.0 (SPSS Inc., Chicago, Illinois, USA).

3 .Results

3.1. Baseline characteristics

A total of 162 patients were included in the study. Of these, 81 were randomly allocated to receive sham preconditioning and 81 to receive RIPC. None of the patients were excluded after randomization. The two groups were matched with respect to all baseline characteristics including mean age, gender, risk factors, New York Heart Association classification, ejection fraction and type of coronary intervention. There were no statistical differences in these baseline characteristics between the sham group and RIPC group. On analyzing the risk factors for CIN it is seen that the prevalence of hypertension, diabetes, anaemia, peripheral vascular disease, prior coronary artery disease and prior myocardial infarction was similar in both the groups. On admission, the mean values of haemoglobin, volume of contrast, baseline serum creatinine and eGFR values were similar with no statistical difference between both the groups. After 48–72 h, the serum creatinine (1.44 ± 0.21 μmol/L vs. 1.35 ± 0.21 μmol/L, p = 0.007) was found to be significantly higher in the sham group than in the RIPC group. The details of the baseline characteristics are shown in Table 1.

3.2. Mehran risk score and outcome measures

In this study, Mehran low risk score [43 (53.1%) vs. 54 (66.7%)] was significantly higher in both the groups followed by moderate-risk [18 (22.2%) vs. 19 (23.5%)], high risk [18 (22.2%) vs. 6 (7.4%)] and mild risk [2 (2.5%) vs. 2 (2.5%)], respectively ($p = 0.064$). Among the patients who were classified according to their Mehran risk score, significantly reduced serum creatinine levels were observed in patients with a Mehran moderate risk allocated to the sham group than the RIPC group (0.070 ± 0.16 mg/dl vs. 0.107 ± 0.13 mg/dl, p = 0.001). The changes in serum creatinine per group divided by Mehran risk score are displayed in Table 2. With regards to the primary endpoint, a significantly higher change in serum creatinine from baseline to 48–72 h was observed in the sham group compared to the RIPC group (0.023 ± 0.2 μmol/L vs −0.064 ± 0.1 μmol/L, p < 0.001). The clinical outcome measures of this study are delineated in Table 3.

4. Discussion

According to the Dutch guidelines, the current study indicates that RIPC induced by intermittent upper arm ischemia before diagnostic and therapeutic coronary procedures demonstrated a

Table 1
Baseline characteristics.

Variable	Sham Group ($n = 81$)	RIPC Group ($n = 81$)	p value
Age, (Mean ± SD, years)	57.8 ± 8.0	55.9 ± 8.3	0.164
Male, *n* (%)	51 (63.0%)	53 (65.4%)	0.743
Risk factors			
Hypertension, *n* (%)	58 (71.6%)	55 (67.9%)	0.608
Diabetes Mellitus, *n* (%)	45 (55.1%)	51 (63.0%)	0.337
Anaemia, *n* (%)	3 (3.7%)	8 (9.9%)	0.118
PVD, *n* (%)	3 (3.7%)	1 (1.2%)	0.311
Prior CAD, *n* (%)	10 (12.4%)	11 (13.6%)	0.815
Prior MI, *n* (%)	12 (14.8%)	13 (16.1%)	0.828
Congestive heart failure (NYHA Class)			
NYHA Class 1, *n* (%)	45 (55.6%)	43 (53.1%)	0.331
NYHA Class 2, *n* (%)	26 (32.1%)	31 (38.3%)	
NYHA Class 3, *n* (%)	8 (9.9%)	3 (3.7%)	
NYHA Class 4, *n* (%)	2 (2.5%)	4 (5.0%)	
Left ventricular ejection fraction (LVEF)			
30–44%, *n* (%)	13 (16.1%)	11 (13.6%)	0.808
45–59%, *n* (%)	44 (54.3%)	48 (59.3%)	
>60%, *n* (%)	24 (29.6%)	22 (27.2%)	
Type of intervention			
CAG, *n* (%)	77 (95.1%)	77 (95.1%)	1.000
PTCA, *n* (%)	4 (4.9%)	4 (4.9%)	
Haemoglobin, (Mean ± SD, g/dL)	12.3 ± 1.1	12.2 ± 1.3	0.967
Volume of contrast, (Mean ± SD, mL)	51.5 ± 9.1	52.6 ± 13.0	0.736
Baseline serum creatinine, (Mean ± SD, μmol/L)	1.41 ± 0.18	1.42 ± 0.18	0.631
Serum creatinine (48–72 h), (Mean ± SD, μmol/L)	1.44 ± 0.21	1.35 ± 0.21	0.007[a]
eGFR, (Mean ± SD, mL/min)	50.71 ± 7.65	51.76 ± 7.08	0.526
eGFR (48–72 h), (Mean ± SD, mL/min)	50.17 ± 11.38	51.92 ± 10.56	0.114
Mehran risk score			
Low risk, *n* (%)	43 (53.1%)	54 (66.7%)	0.064*
Moderate risk, *n* (%)	2 (2.5%)	2 (2.5%)	
High risk, *n* (%)	18 (22.2%)	19 (23.5%)	
Very high risk, *n* (%)	18 (22.2%)	6 (7.4%)	

PVD – Peripheral vascular disease; CAD – Coronary artery disease; MI – Myocardial infarction; NYHA – New York Heart Association; CAG – Coronary angiography; PTCA – Percutaneous transluminal coronary angiography; eGFR – Estimated glomerular filtration rate
[a] Significant.

protective effect to reduce contrast-induced kidney injury in patients who are at risk of developing CIN.[14] This protective effect appeared to be independent of all other factors such as contrast medium amount and comorbidities of the patients.

In 2004, Mehran et al[15] developed a risk classification system to predict risk for CIN in patients undergoing CA. The most comprehensive and best-validated risk stratification scores include both clinical and procedural variables and is divided into four risk classes of developing contrast-induced acute kidney injury (CI-AKI): Low (risk score ≤ 5), moderate (risk score 6–12), high (risk score 11–15) and very high (risk score ≥ 16). In a study, Er et al. investigated the effects of RIPC in 60% of patients with a high or very high risk of developing CI-AKI, whereas Igarashi et al. included only 6% of very high-risk patients.[13,16] In this study, 44.4% of patients were at high or very high risk of developing CIN. In line with these findings, based on the reported Mehran risk score, Er et al. noted that incidence of CIN should lie between 26 and 30% rather than 40% in the control group.[17] Although the authors explained this discrepancy due to the high prevalence of heart failure and diabetes in their cohort.

Indeed, serum creatinine is not an adequate marker for CI-AKI but excretion of creatinine in urine is the result of glomerular filtration and tubular secretion.[18,19] Furthermore, serum creatinine does not accurately depict kidney function until a steady-state has been reached because the levels of serum creatinine also depend on non-renal factors such as muscle mass and hydration status.[20,21] Our study results are in contrast to those of previous randomized trials involving RIPC to prevent CIN. First of all, in contrast to Menting et al.[14] and Igarashi et al.[13] this study showed that RIPC significantly affects the change in serum creatinine 48–72 h after

Table 2
Change in serum creatinine per group divided by Mehran risk score.

Mehran Risk	N	Group	Change in serum creatinine mg/dl (Mean ± SD)	p value
Low Risk	97	Sham ($n = 43$)	0.006 ± 0.25	0.124
		RIPC ($n = 54$)	−0.0615 ± 0.15	
Moderate Risk	4	Sham ($n = 2$)	0.200 ± 0.00	0.333
		RIPC ($n = 2$)	0.000 ± 0.00	
High Risk	37	Sham ($n = 18$)	0.070 ± 0.16	0.001[a]
		RIPC ($n = 19$)	0.107 ± 0.13	
Very high Risk	24	Sham ($n = 18$)	−0.002 ± 0.19	0.923
		RIPC ($n = 6$)	0.027 ± 0.06	

[a] Significant.

Table 3
Clinical outcomes.

	Sham Group ($n = 81$)	RIPS Group ($n = 81$)	p value
Primary endpoint			
Change in serum creatinine from baseline to 48–72 h, (Mean ± SD, μmol/L)	0.023 ± 0.2	−0.064 ± 0.1	<0.001[a]
Secondary endpoint			
Re-hospitalization within 6 week, *n* (%)	–	–	–
Dialysis within 6 week, *n* (%)	–	–	–
Mortality within 6 week, *n* (%)	–	–	–

[a] Significant.

contrast medium exposure. However, in contrast to this study, Menting et al.[14] found that creatinine change in patients at high to very high risk of developing CIN was significantly lower in the RIPC group compared with those in the sham group. Unfortunately, this study did not report the incidence of serum cystatin C level. The rates of re-hospitalization, death or haemodialysis did not affect the study which is similar to a study done by Er et al.[16] Nevertheless, the results of the present study support the hypothesis that RIPC reduces the incidence of creatinine based CIN in patients who are at risk of developing CIN. Thus, RIPC mediated counter-regulatory pathways may eventually offer additional clinical benefit and contribute to better clinical outcomes.

This study has some strengths. Firstly, it was performed in a tertiary-care center, and the patients were initially included in the study based on their renal dysfunction, so the protocol represents the routine daily practice in our hospital. This is why the majority of the study population had a low or moderate risk of developing CIN. Secondly, this randomized controlled trial included more patients than previous similar studies did. Lastly, this study was completely double-blinded to reduce the risk of bias. Nonetheless, the present study has a few limitations. The investigation of the beneficial effects of RIPC on renal function is a single-center trial with limited sample size. Serum creatinine levels generally raise between 48 and 72 h after contrast administration, it would have been ideal to measure creatinine levels at both 48 and 72 h.

5. Conclusion

The results from this randomized controlled trial demonstrated that the simple and well-tolerated application of RIPC in patients at risk of renal dysfunction undergoing CA reduced the incidence of procedure-related CIN. Thus, the use of RIPC may be a feasible therapeutic procedure and a large study on high-risk patients should be performed to assess the effect of RIPC as an alternate to hydration to provide additional protection in these high-risk patients.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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