



Original Article

Remote ischemic preconditioning for prevention of contrast induced nephropathy—Insights from an Indian study



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ABSTRACT

Objectives: To study if four cycles of remote ischemic preconditioning (RIPC) could offer protection against contrast induced nephropathy (CIN) and post procedural renal dysfunction in high risk patients undergoing percutaneous coronary intervention (PCI).

Methods: This was a prospective single blind randomized sham controlled trial where patients undergoing coronary angioplasty with stage III chronic kidney disease were randomized into sham preconditioning and remote ischemic preconditioning. The primary outcome was the reduction in the incidence of CIN. The secondary outcomes were the maximum improvement in eGFR, maximum reduction in serum creatinine and composite of requirement of hemodialysis, death and rehospitalization for heart failure up to 6 weeks after PCI.

Results: Eleven out of fifty patients in the study group developed CIN (22%) compared to eighteen out of the fifty control patients (36%) ($p = 0.123$). There was a statistically significant improvement in the post procedure creatinine values at 24 h ($p = 0.013$), 48 h ($p = 0.015$), 2 weeks ($p = 0.003$), 6 weeks ($p = 0.003$) and post procedure glomerular filtration rate (eGFR) values at 24 h ($p = 0.026$), 48 h ($p = 0.044$), 2 weeks ($p = 0.015$) and 6 weeks ($p = 0.011$) in study group compared to control group. The secondary outcome composite of requirement of hemodialysis, death and rehospitalization for heart failure was not statistically significant ($p = 0.646$).

Conclusion: RIPC does not result in significant reduction of CIN. However RIPC helps in the prevention of post procedural worsening in eGFR and serum creatinine even up to 6 weeks.

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1. Introduction

Contrast induced nephropathy (CIN) is the acute worsening of renal function after parenteral administration of iodinated contrast media in the absence of other causes. CIN by the European Society of Urogenital Radiology (ESUR) criteria has been defined as an increase in serum creatinine of 0.5 mg/dL (44 mol/L) or an increase by at least 25% above baseline within 48 h after contrast administration.¹ Current techniques to prevent contrast induced nephropathy include pre-procedural hydration with isotonic saline, usage of iso-osmolar non-ionic contrast media, pre-medicating with N-acetyl cysteine, and withdrawal of nephrotoxic drugs.^{2–4} However despite the best of precautions, nearly 20–30% of patients with underlying risk factors for CIN undergoing coronary angiography go on to develop contrast induced nephropathy.⁵ Remote ischemic preconditioning (RIPC) was first demonstrated by Birnbaum et al in 1996.⁶ It is a novel

Abbreviations: CIN, contrast induced nephropathy; RIPC, remote ischemic preconditioning; RenPro, renal protection; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; MRS, Mehran risk score; ERICCA, effect of remote ischemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass graft surgery; RIP HEART, remote ischemic preconditioning for heart surgery; CABG, coronary artery bypasses graft; STAT-5, signal transduction and activation of transcription –5; RIPCIN, remote ischemic preconditioning to reduce contrast-induced nephropathy; ERIC-CIN, effect of remote ischemic conditioning on contrast-induced nephropathy in patients undergoing elective coronary angiography; CTRL, clinical trial registry –India.

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technique of conferring protection to an organ at risk of sustained ischemia by subjecting another organ, distant from the target organ site to repetitive episodes of transient ischemia followed by reperfusion. RIPC is associated with cardioprotection and renoprotection. Traditionally, the RIPC protocol consists of giving 4 cycles of inflation by a blood pressure cuff for 5 min each, followed by deflation for 5 min after each inflation to one of the upper limbs.

Intravascular use of iodinated contrast causes direct damage to the renal tubules. More importantly, it is associated with decreased prostaglandin synthesis, diminished nitric oxide mediated vasodilatation and increase in renal adenosine concentration. This tilts the balance in favor of vasoconstrictors in the renal medulla.^{7,8} Postulating the role of contrast mediated renal vasoconstriction, subsequent medullary ischaemia and ischemic reperfusion injury in the pathogenesis of CIN, Fikret et al devised the pilot Renal protection (RenPro) trial which showed an overwhelming benefit of RIPC in reducing the incidence of CIN in high risk patients.⁹ The present study attempts to prove if 4 cycles of RIPC could offer a means of protection against CIN and post PCI renal worsening in high risk patients undergoing PCI. Though CIN traditionally occurs up to 48 to 72 h after PCI, studies have shown that minor derangements in eGFR which do not fall into the gamut of CIN continue to accrue in patients even after hospital discharge.^{10,11} It was with this objective that we decided to study if RIPC positively influenced the renal parameters of the study patients at 24 h, 48 h, 2 weeks and 6 weeks.

2. Materials and methods

2.1. Study design

This was a prospective single blind randomized control trial conducted at the Department of Cardiology, Government Medical College Trivandrum, India for a period of 15 months from April 2015. This study complies with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board (IRB)/Human ethics committee Medical College Thiruvananthapuram, India on 6th March 2015 (IEC no: 03/39/2015/MCT). The patient recruitment began on 1st April 2015 and was completed on July 31st 2016. The trial is registered in the Clinical Trial registry –India (CTRI) (www.ctri.nic.in). The CTRI registration number is CTRI/2017/10/010210. A written informed consent was taken from all the patients prior to enrollment.

2.2. Study protocol

The study population included patients with coronary artery disease at high risk of CIN. An eGFR less than 60 ml/mt/m² is an important risk factor for CIN. This has been well validated in the landmark study by Mehran et al and in an Indian study.^{12,13}

2.2.1. The inclusion criteria

Patients aged above 18 years who underwent elective PCI in the Dept of Cardiology, Government Medical College Thiruvananthapuram were included in the study. All patients had stage III chronic kidney disease as defined by eGFR between 30 and 60 ml/min/m² calculated by the Cockcroft-Gault formula.

2.2.2. The exclusion criteria

Patient undergoing routine hemodialysis or peritoneal dialysis and patients in whom RIPC could not be performed due to pathology of both arms (for example, dystrophy, recent trauma, chronic upper limb amputation for any reason, chronic wounds) were excluded from the study. Patients undergoing PCI with a contrast load of less than 100ml were excluded from the final

analysis. As it has been postulated that RIPC acts through favorable opening up of the ATP sensitive potassium channels in the effector organ, patients on T. Glibenclamide (which is a potent Potassium ATP channel blocker) or T. Nicorandil (which is an ATP sensitive potassium channel opener) were excluded from the study.¹⁴

2.3. Sample size

As we had planned to include patients at very high risk of CIN with strict inclusion criteria, the expected incidence of CIN was assumed to be between 20 and 30%. Based on the previous pilot trial by Fikret et al, it was known that RIPC could induce a risk reduction of 30% in the incidence of CIN in the study group compared to the sham group.⁹ Using a study power of 0.8 and a 2 sided significance level of 0.05, it was calculated that 50 patients would be required in each arm of the study.

2.4. Methodology

We used a computer generated block randomization technique to randomly assign patients posted for elective PCI. Once the patient satisfied the inclusion criteria, they were randomized to receive one of two treatments: sham preconditioning (control group) or RIPC before cardiac catheterization through intermittent upper-arm ischemia (study group).

All patients received standard prophylactic measures for prevention of CIN namely, continuous intravenous saline infusion (0.9%) 12 h before to 24 h after PCI (1 ml per kilogram of body weight per hour), oral N-acetylcysteine 600 mg twice orally, the day before and on the day of PCI and withdrawal of nephrotoxic drugs.

RIPC was accomplished by performing 4 cycles of alternating 5 min inflations and 5 min deflations using a standard upper-arm blood pressure cuff to a level 50 mm Hg above the individual's systolic blood pressure to induce transient arm ischemia followed by reperfusion. RIPC was started immediately before cardiac catheterization. The time between the last inflation cycle and the start of procedure was <45 min. If more than 45 min had elapsed after the last preconditioning cycle, the patient was subjected to 4 additional cycles of RIPC. A pulse-oximeter was applied to the preconditioned limb during cuff inflation to confirm ischemia. Ischemia was assumed with the loss of the pulsatile signal on the monitor.

Sham conditioning was done by inflating the blood pressure cuff to 30 mm of Hg for 5 min followed by deflation for 5 min for a total of 4 cycles. The patient was not informed whether they were a study patient or a sham patient.

The preconditioning was done in the waiting room adjacent to the cardiac catheterization lab by an independent technician who was blinded to the study.

Cardiac catheterization was performed according to standard clinical practice. PCI was performed as per standard guidelines. In all patients iodixanol; a non-ionic low-osmolar contrast medium was used. If less than 100 ml of contrast medium was used for an individual patient, he or she was excluded from the study.

The post-procedural period was divided into the acute phase during hospitalization (24, 48 h) and follow-up phase (2 weeks and 6 weeks after PCI). Samples in the acute phase were obtained from all subjects during hospitalization. Data for the 2 week and 6-week follow-up time points were acquired through out-patient visits

2.5. Outcomes

The primary outcome was the incidence of CIN, which was defined as an increment of serum creatinine by 0.5 mg/dL or a

relative increase of serum creatinine of at least 25% over the baseline value within a period of 24 to 48 h after contrast medium administration. The secondary outcomes were the following: maximum elevation of serum creatinine, maximum improvement of eGFR, composite of death, re-hospitalization for heart failure and requirement of hemodialysis.

These variables were looked for in all patients prospectively at 24 h, 48 h, 2 weeks and 6 weeks.

2.6. Statistical analysis

Descriptive statistics such as mean, standard deviation and percentages were calculated in order to describe the sample. Categorical variables were analysed by the Chi square test. Normally distributed continuous variables were analysed by a Student *t*-test. The serum creatinine and eGFR of the study group at 24 h, 48 h, 2 weeks and 6 weeks were analysed in comparison to the control group by the Mann–Whitney *U* test, as these variables violated the assumption of normality. The variables were then log transformed to adjust for skewness and then repeated measure

ANOVA was implemented to look for differences in the serum creatinine and eGFR over time within each group and the interaction of this change over time between the two groups. The statistical analyses were performed with SPSS software (version 17.0). A 2-sided probability value of 0.05 was considered to indicate statistical significance.

3. Results

Over the study period of 15 months, 1260 patients underwent elective PCI at our center, after exclusion 108 patients were randomized on the basis of a computer generated block randomization algorithm in to the control and study group. Eight patients who underwent PCI with a contrast load of less than 100 ml were excluded from the final analysis (four from the case group and four from the control group each). The details of the patients' recruitment are shown in Fig. 1.

The two groups were matched with respect to all baseline characteristics including mean age, ejection fraction, hemoglobin, baseline eGFR, and Mehran risk score (MRS).¹²

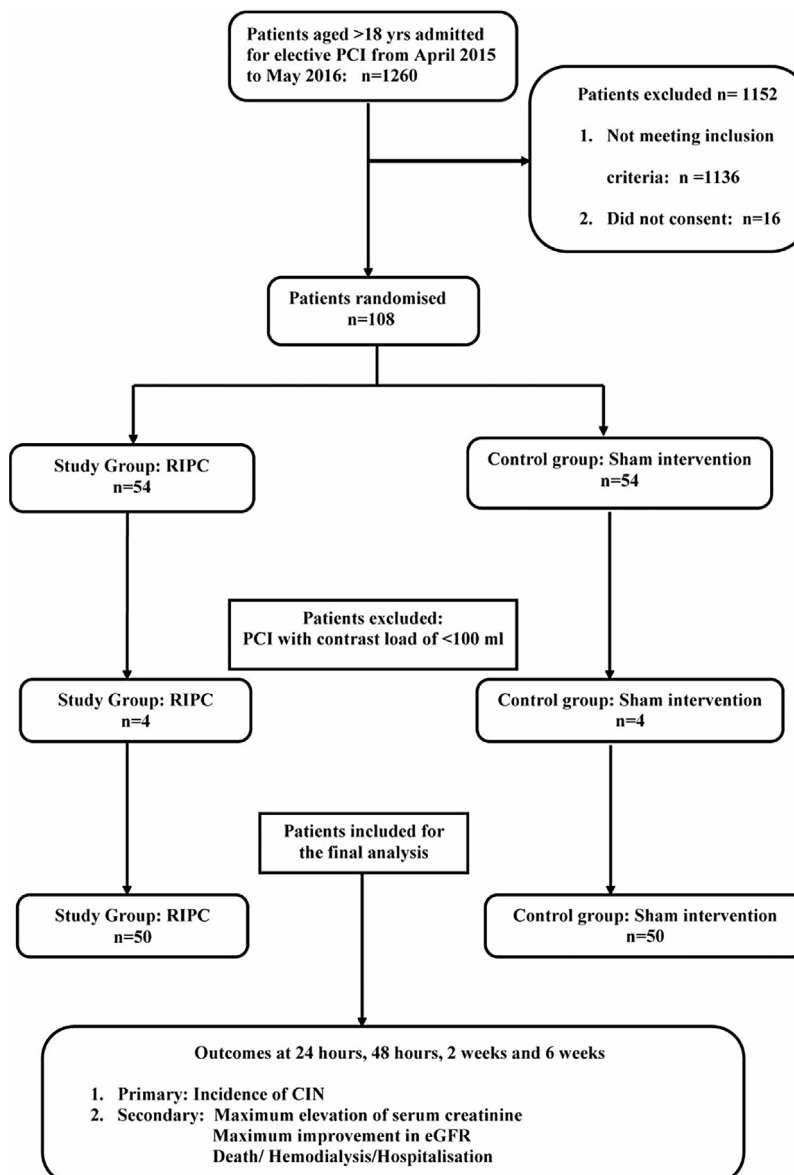


Fig. 1. Flowchart showing recruitment of patients.

Table 1
Baseline Demographic and Clinical Characteristics.

	Case n = 50 mean	Control n = 50 mean	p
Mean Age,y	62.8 ± 9.1	60.5 ± 8.5	0.203
Male Sex n, (%)	43 (86)	40 (80)	0.875
Mean LV EF,%	54.1	54.4	0.913
Anemia n, (%)	26 (52)	24 (48)	0.689
Diabetes Mellitus n, (%)	27 (54)	30 (60)	0.545
Hypertension n, (%)	30 (60)	34 (68)	0.405
Peripheral artery disease n, (%)	13 (26)	14 (28)	0.822
Heart Failure n, (%)	9 (18)	9 (18)	0.950
Dyslipidemia n, (%)	13 (26)	14 (28)	0.822
Periprocedural hypotension n, (%)	3 (6)	3 (6)	0.856
Smoker n, (%)	30 (60)	34 (68)	0.405
eGFR, ml/min	46.1	46.9	0.644
Volume of Dye used, ml	218.6	198.4	0.120
Mean Mehran Risk Score	10.4	10.5	0.802
Mehran Risk Score n, (%)			
Low risk ≤5	2 (4)	1 (2)	0.782
Intermediate risk 6–10	27 (54)	28 (56)	0.852
High risk 11–15	17 (34)	19 (38)	0.821
Very high risk >15	4 (8)	2 (4)	0.877
Baseline cardiovascular drugs n, (%)			
Beta blocker	46 (92)	45 (90)	0.583
Angiotensin converting enzyme inhibitor	19 (38)	15 (30)	0.482
Angiotensin receptor blocker	5 (10)	3 (6)	0.519
Calcium channel blocker	6 (12)	4 (8)	0.574
Loop diuretic	9 (18)	9 (18)	0.920
Aldosterone Antagonist	2 (4)	3 (6)	0.611

LVEF: Left ventricular ejection fraction, eGFR: Estimated glomerular filtration rate.

On analysing the risk factors for CIN it is seen that the prevalence of systemic hypertension, diabetes mellitus, periprocedural hypotension, heart failure and anemia among the randomized patients was similar in both groups. The details of the baseline risk factors and demographics in both groups of patients are shown in Table 1.

The mean MRS was 10.4 (±3.5) and 10.5 (±3) in the study and control group respectively. The baseline eGFR calculated by the Cockcroft-Gault formula was 46.1 (± 8.9) ml/mt and vs 46.9 (±7.9) ml/mt in the study group and control group, respectively. In spite of the randomization the contrast volume used in the treatment arm was slightly higher than the control arm. Analysing the pre-procedural risk of CIN, it was observed that based on the MRS, the distribution of patients was even in the study group compared to the control group. At baseline the cardiovascular drugs given in both groups were similar.

3.1. Primary outcomes

Eleven out of 50 patients in the study group developed CIN (22%) compared to 18 out of the 50 control patients (36%).

Though the patients in the RIPC group had a lower incidence of CIN compared to the control group, it did not reach statistical significance (p = 0.123). The details of CIN in both groups are shown in Table 2.

Table 2
Table showing the details of CIN in cases and controls.

CIN	Case		Control		χ^2	p
	N	%	N	%		
Yes	11	22	18	36	2.380	0.123
No	39	78	32	64		
Total	50	100	50	100		

CIN: Contrast induced nephropathy.

3.2. Secondary outcomes

3.2.1. The trend of serum creatinine elevations

From a mean baseline serum creatinine of 1.52 mg/dl (±0.22) and 1.53 mg/dl (±0.21) in the control and study groups respectively, there was a statistically significant reduction in the serum creatinine at 24 h (p = 0.013), 48 h (p = 0.015), 2 weeks (p = 0.003), 6 weeks (p = 0.003) in the study group compared to the sham group. The details are given in Table 3 and Fig. 2.

3.2.2. The trend of reduction in eGFR

There was a statistically significant improvement in the post procedure eGFR in the preconditioned group compared to the sham at 24 h (p = 0.026), 48 h (p = 0.044), 2 weeks (p = 0.015) and 6 weeks (p = 0.011). The details are shown in Table 3 and Fig. 3.

The results of repeated measure ANOVA which was implemented to look for differences in the serum creatinine and eGFR over time within each group were p < 0.001 and p < 0.001 respectively. The interaction of this change over time between the two groups were p = 0.020 and p < 0.001 respectively.

3.2.3. Secondary outcome composite of the need for hemodialysis, death and re-hospitalization for heart failure

Similarly the secondary outcome composite of the need for hemodialysis, death and re-hospitalization for heart failure were not significantly different (p = 0.646). Only 1 patient in either group needed to undergo hemodialysis and the remaining CIN patients were managed conservatively. In the control group 2 patients died while in the study group only 1 patient died (p = 0.558). One patient each in the study and the control group had out of hospital sudden cardiac death (probably arrhythmic death). The other death in the control group was subacute probable stent thrombosis. All 3 deaths occurred in patients who had developed CIN. There were a total of 3 heart failure admissions, 2 in the control versus 1 in the study group (p = 0.558). The details are shown in Table 4. This suggests that though a total of 29 of the 100 randomized patients developed CIN only 10.3% were re-admitted with heart failure.

3.3. Complications after RIPC

No complications were noted with RIPC. Eight percent of patients (n = 4) had transient paresthesia.

4. Discussion

CIN is a scourge in the era of interventional cardiology. Since this complication is associated with an increased risk of sudden death, this is vigorously treated and attempts have been made to prevent this potentially fatal complication. In addition to the traditional preventive concepts such as limiting contrast load, premedicating with N-acetyl cysteine and periprocedural hydration; novel strategies like use of trimetazidine, the Renal guard system (a urine output based hydration system for achievement of high urinary flow rates) and remote ischemic preconditioning have evolved.^{15,16} In the limited armamentarium against CIN, RIPC is yet to make its headway.

4.1. RIPC and CIN: the birth of a novel concept

The first study which looked at RIPC in terms of protection from CIN was the Ren Pro trial, where 100 high risk patients undergoing coronary angiogram were randomized into 2 groups of 50 each; one group was given RIPC and the other sham conditioning with the aim of reducing the incidence of CIN. The study demonstrated a

Table 3
Table showing the change in serum creatinine and eGFR over time in study and control groups.

	Case (N = 50)		Control (N = 50)		Mann-Whitney U test	
	Median	Inter quartile range	Median	Inter quartile range	z	p
Serum Creatinine						
Baseline	1.50	1.30–1.70	1.40	1.40–1.60	-0.235	0.814
24 h	1.40	1.20–1.83	1.60	1.40–2.00	-2.497	0.013
48 h	1.45	1.28–1.80	1.60	1.40–1.83	-2.433	0.015
2 week	1.40	1.30–1.63	1.60	1.40–1.78	-2.935	0.003
6 week	1.40	1.20–1.63	1.50	1.40–1.80	-2.977	0.003
eGFR						
Baseline	44.3	39.7–49.7	46.3	40.2–53.1	-0.603	0.546
24 h	46.8	36.1–56.5	40.5	34.1–49.9	-2.220	0.026
48 h	45.5	37.3–56.3	42.0	34.4–48.4	-2.013	0.044
2 week	47.4	39.3–53.4	41.7	33.8–48.3	-2.434	0.015
6 week	46.5	37.8–56.2	42.7	31.9–49.1	-2.551	0.011

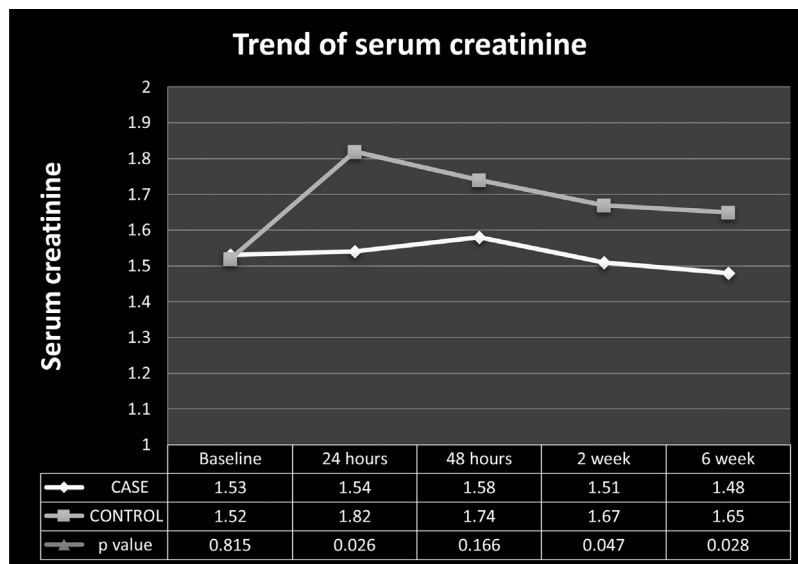


Fig. 2. Graph showing the trend of serum creatinine.

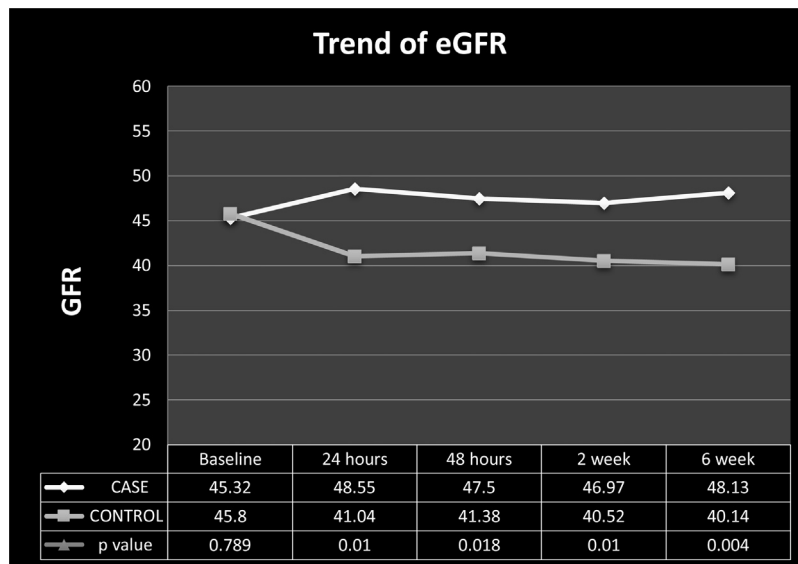


Fig. 3. Graph showing the trend of eGFR.

Table 4

Table showing secondary outcome composite of death/rehospitalization/ hemodialysis.

Composite of Death/ Rehospitalization/Hemodialysis	Category				Total	p	
	Case		Control				
	N	%	N	%	N	%	
Yes	2	4.0	3	6.0	5	5.0	0.646
No	48	96.0	47	94.0	95	95.0	
Total	50	100.0	50	100.0	100	100.0	

significant reduction in the incidence of CIN in the study versus the control group (40% vs 12%). In addition RIPC significantly decreased the incidence of the composite end point of death, hospitalization or hemodialysis at 6 weeks. A point of contention has always been the relatively high risk of CIN in the study. Another conspicuous difference was that a 12% higher number of patients underwent PCI in the study group than the control group (34% vs 22%).⁹ In 2013 Deftereos et al published an interesting study which showed that serial intermittent balloon inflation and deflation during PCI was found to confer protection against CIN.¹⁷ Reflecting on these observations it could be possible that the higher number of interventions in the study group in the RenPro trial could have some bearing in the overwhelming reduction of CIN in the study versus the control group.

As RIPC has been found most useful in reducing the risk of CIN in patients at the highest possible risk, we included only those patients with a similar risk profile. The mean MRS was 10.4 (± 3.5) and 10.5 (± 3) in the study and control group respectively with the predicted risk of CIN calculated to be 26%. In our study all patients in both the study and control group underwent PCI, so any additional benefit of balloon dilatation in reducing CIN incidence was balanced in both cohorts, and to an extent negated. Patients who had only coronary angiography were excluded. Similarly patients who underwent PCI with a total contrast volume of less than 100 ml were also excluded. This was done to reinforce the elevated baseline risk of CIN of the patient population.

The current study did not show a significant difference in the incidence of CIN in the preconditioned group compared to the sham group. However a statistically significant reduction in the post procedure serum creatinine at 24 h ($p = 0.013$), 48 h ($p = 0.015$), 2 weeks ($p = 0.003$), 6 weeks ($p = 0.003$) in the RIPC group compared to control group was observed. The difference in serum creatinine values was evident as early as 24 h and persisted till 6 weeks.

The improvements in eGFR values were equally impressive. There was a statistically significant improvement in the post procedure eGFR values in the preconditioned group compared to the sham group at 24 h ($p = 0.026$), 48 h ($p = 0.044$), 2 weeks ($p = 0.015$) and 6 weeks ($p = 0.011$). The eGFR and the serum creatinine values in the study group improved beyond the baseline value as early as 24 h and this effect remained sustained over 6 weeks in comparison to the control group.

The positive trend of a lesser rise in the baseline serum creatinine and a final dip at 6 week post procedure in the study group did not translate into a statistically significant decrease in the incidence of contrast induced nephropathy in the study group compared to the control group (22% vs 36%, $p = 0.123$).

Surprisingly despite the relatively high incidence of CIN in both the study and control group, the incidence for death, hemodialysis and re-hospitalization for heart failure symptoms were low in both the groups.

4.2. Paradoxical outcomes of RIPC in cardiac surgery trials

Interestingly the recently published multicenter Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients undergoing Coronary Artery Bypass Graft surgery (ERICCA) and Remote Ischemic Preconditioning for Heart Surgery (RIP HEART) trials showed that upper limb RIPC performed among patients undergoing cardiac surgery did not confer a benefit in either cardiovascular (death/MI/rehospitalization) or renal (prevention of acute kidney injury) outcomes. The RIPHEART trial was a prospective, double-blind, multicenter, randomized, and controlled trial involving 1403 patients who were scheduled for elective cardiac surgery requiring cardiopulmonary bypass under total anesthesia with intravenous propofol. The trial compared upper-limb RIPC with a sham intervention.¹⁸ The ERICCA trial conducted at 30 cardiac surgery centers in the United Kingdom enrolled a total of 1612 patients (811 in the sham group and 801 in the ischemic-preconditioning group) who were undergoing on-pump CABG, with or without valve surgery. It is pertinent to note that 92.5% patients in the sham group and 93.9% of patients in the RIPC group had induction with propofol.¹⁹ In the light of these two multicenter trials it should be stressed that the seemingly positive studies done in RIPC and prevention of CIN should be repeated in different populations with larger numbers.

However the proponents of RIPC suggest that, in both trials randomization was done after anesthesia induction with propofol and before surgical incision. Propofol has been noted to blunt the cardioprotective effects of RIPC by interference with the Signal Transduction and Activation of Transcription-5 (STAT-5) activation in a previous randomized control trial, albeit a small one involving only 24 patients.²⁰ However the unforeseen failure of these two multicenter trials could not possibly be attributed to the attenuation of beneficial effects of RIPC by propofol alone. It is imperative to consider the differences in the pathophysiology of renal injury in patients undergoing cardiac surgery and CIN. Though the transient hypoperfusion associated with cardiopulmonary bypass may cause renal injury, post CABG renal failure is predominantly attributed to atheroembolism where RIPC may not have a tangible role. In contradistinction, intra-arterial administration of contrast during PCI causes contrast induced vasospasm to occur in a stuttering manner. The contrast can immediately enter the renal arteries from the aorta followed by a delayed phase, when the contrast gets reabsorbed through the coronary venous system. Iodinated contrast tilts the balance in favor of vasoconstrictors in the renal medullary vasa recta by free radical mediated injury and direct tubulotoxicity. There is profound reperfusion injury to the metabolically active renal medulla in response the contrast induced vasospasm.^{7,8} RIPC can thus protect the highly ischaemia sensitive renal medulla and alleviate CIN. This hypothesis was again tested in the Remote Ischemic Preconditioning to reduce Contrast-Induced Nephropathy (RIPCIN) trial which was a multicenter, single blinded, randomized controlled trial in which 76 patients at risk of CIN received standard hydration combined with RIPC or hydration with sham preconditioning.²¹ Though there was no difference in the incidence of CIN between the preconditioned and the sham group (2 patients each), a pre-defined subgroup analysis of patients with a MRS > 11, showed a significantly reduced change in serum creatinine from baseline to 48 to 72 h in patients allocated to the RIPC group (Δ creatinine – 3.3 ± 9.8 mmol/L) compared with the sham group (Δ creatinine + 17.8 ± 20.1 mmol/L) ($p = 0.048$). A metaanalysis of ten randomized control trials with 1389 patients showed that upper limb RIPC significantly reduced the incidence of CIN in patients undergoing PCI/CAG (OR = 0.52, 95% CI = 0.34–0.77, $p = 0.001$).²²

4.3. RIPC in the Asian scenario

A Korean study which randomized 102 diabetic patients undergoing PCI into the RIPC group and sham group with the aim of reducing the incidence CIN was conspicuous for its negative result.²³ However the RIPC was done for a total of 3 cycles rather than the standard 4 cycles. In a recent trial from Denmark it has been demonstrated that the ideal RIPC stimulus should include 4–6 cycles lasting two to five minutes of cuff inflation followed by deflation.²⁴ The inadequate preconditioning stimuli could have probably contributed to the failure of the study.

5. Limitations

The current study was a single center study. Other biomarkers to measure renal injury like NGAL, KIM-1 and Cystatin-c were not used. Further it was only a short term study which evaluated outcomes upto 6 weeks.

6. Conclusions

To the best of our knowledge the present study is the first study to observe the effect of RIPC in reducing the incidence of CIN in high risk patients undergoing elective PCI in the Indian scenario. The current study is notable for the fact that the serum creatinine and eGFR values were studied up to a 2 week and 6 week period post PCI which give interesting insights regarding the trend of renal injury in these high risk patients.

It is imperative to note that the current study failed to meet its stringent primary end point, which is the reduction in the incidence of CIN as defined by the ESUR criteria. However it remains to be seen if the numerically higher reduction in the CIN incidence in the preconditioned group compared to the sham group would have achieved statistical significance had additional patients been enrolled. The present study has also conclusively shown that the initial reduction in serum creatinine and the improvement in eGFR in the study group noted at 24 h have persisted till the end of 6 weeks. Strikingly, the decline in the eGFR values in the sham group reached the nadir at the end of 6 weeks indicating the lingering nature of contrast induced kidney injury.

The need of the hour is a multicenter sham controlled trial enrolling high risk patients undergoing PCI. The Effect of remote ischemic conditioning on contrast-induced nephropathy in patients undergoing elective coronary angiography (ERIC-CIN) trial is one such trial which has planned to recruit 362 patients at high risk of CIN and study the effect of RIPC in reducing the incidence of CIN.²⁵ We hope that the ERIC-CIN trial will give us the much needed clarity regarding the true status of remote ischemic preconditioning in the fight against CIN.

What is known: RIPC is a non invasive manoeuvre which has been shown to reduce the incidence of CIN in patients undergoing cardiac catheterization.

What this study adds: The current study shows that though there is a statistically significant improvement in eGFR and serum creatinine at 24 h, 48 h, 2 weeks and 6 weeks in the preconditioned group compared to the control group; it did not translate into a statistically significant reduction in the incidence of CIN between the two groups.

Conflict of interest statement

None of the authors have any potential conflict of interest in the current study.

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