REMOTE ISCHEMIC PRECONDITIONING, A NOVEL RENOPROTECTIVE STRATEGY AGAINST CONTRAST INDUCED ACUTE KIDNEY INJURY

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Contribution
IG, AHL, JMT conceived the idea. IG, AA & ASM planned the study, did the data collection. IG, AHL, KAK drafted the manuscript. All the author contributed significantly in manuscript submission.

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ABSTRACT

Objective: To compare contrast induced Acute Kidney Injury amongst patients with stable angina, unstable angina and Non ST elevation myocardial infarction undergoing elective Coronary angiography and or percutaneous coronary intervention with versus without applying Remote Ischemia Preconditioning.

Methodology: It is a randomized control trial conducted at The Aga Khan University Hospital, Karachi, from January, 2015 till June, 2015. Patients aged ≥30 years, having baseline serum creatinine level ≥ 1.4mg/dl with the above mentioned conditions who were to undergo coronary angiography and or percutaneous coronary intervention were randomly assigned to one of either intervention group or control group. All patients received standard care followed by application of RIPC to the intervention arm only. Baseline characteristics of all patients were recorded and they were followed for 48 hours. The data was analyzed using STATA version 12.0.

Results: Out of 103 patients, 53 were in Intervention arm and 50 in Control arm with an average age 65 and 66 years respectively. Majority were male in both the groups. The primary outcome (Contrast Induced Nephropathy) was significantly lower in the intervention arm vs control arm (3.7% vs 14%). Multivariable logistic regression analysis suggested a protective effect of the intervention (RIPC) with adjusted Odd Ratio of 0.07 (95% CI: 0.007-0.72, p-value: 0.026). Patients with prior MI were at higher risk for CI-AKI.

Conclusion: Remote Ischemic Preconditioning has a significantly higher renal protective role against Contrast Induced Nephropathy.

Key Words: Remote ischemic preconditioning; Contrast induced acute kidney injury; Coronary angiography; Percutaneous coronary intervention; Acute renal failure; Biochemical messengers, Oxidative stress
INTRODUCTION

Contrast induced acute kidney injury (CI-AKI) is one of the major complications of percutaneous coronary intervention (PCI), contributing to considerable morbidity and mortality. It is estimated that CI-AKI is responsible for about 12% of in-hospital acute renal failure (ARF) and is considered to be the third leading cause of hospital acquired ARF. It is not uncommon in South Asian population as is evident from the studies in India where the incidence of CI-AKI in elderly is 10.5%. The incidence of CI-AKI after PCI in Pakistan is 9.6%, ranging from as low as 4.4% in those with serum creatinine level of less than 2.0mg/dl to as high as 42.9% in those with serum creatinine more than 4.1mg/dl.

Although the exact mechanism of CI-AKI is unknown, the proposed mechanism is renal ischemia resulting in the release of toxic free radicals which lead to tubular epithelial cell injury and direct toxic effect of the contrast material.

There is a wide spectrum of risk factors associated with CI-AKI, but pre-existing renal dysfunction is considered to be the leading risk factor. Other factors include diabetes mellitus (DM), hypertension (HTN), hypotension, hypovolemia, nephrotoxic drugs and the type and amount of contrast material administered. The chances and severity of CI-AKI are even higher in those undergoing coronary interventions because of underlying multiple comorbidities and greater contrast volume.

Several strategies have been proposed and adopted for the prevention of CI-AKI including administration of acetylcysteine, intravenous hydration with normal saline, bicarbonate and prostaglandins but has no or limited benefits.

Due to the limited benefits of the above mentioned strategies, other novel strategies are intensively required in order to prevent or treat CI-AKI. In this respect, remote ischemia preconditioning seems to be a viable option.

The concept of ischemic preconditioning was first introduced by Murry and his colleagues, in 1986 who demonstrated experimentally that one or more cycles of non-lethal ischemia and reperfusion prior to coronary artery occlusion reduces infarct size. In 1990, Przyklenk et al. extended this concept to remote ischemic preconditioning (RIPC) when they demonstrated, while experimenting on dogs, that brief, non-lethal ischemia and reperfusion in circumflex (LCX) coronary artery territory led to reduction in the infarct size in left anterior descending (LAD) artery territory. It was further projected that repeated episodes of ischemia and reperfusion in a remote organ like kidney or small intestine had a cardio-protective role.

The application of this concept to human volunteers and then to patients was done by MacAllister and his co-workers, who used upper limb to induce ischemia and studied its beneficial effects on the heart. The exact mechanism of RIPC is still unknown but the proposed mechanism is that transient non-lethal ischemia and reperfusion in one organ or tissue has a protective effect on a remote organ or tissue by releasing biochemical messengers that act against oxidative stress.

As CI-AKI is a major contributor to morbidity and mortality in patients undergoing coronary interventions and the existing strategies for the prevention of CI-AKI have limited benefits, novel strategies should be tested to prevent or overcome its occurrence. RIPC strategy is a simple, non-pharmacological and easy to apply method without side effects and requires less expertise. It may be beneficial for a large number of patients undergoing elective coronary interventions. A pilot randomized control trial conducted by Fickert et al. in Germany showed that the incidence of CI-AKI was 40% in control group (conventional modalities) versus 12% in the intervention group (RIPC). To the best of our knowledge, no randomized trial has been conducted on this topic in our part of the world. Thus the current study aims to explore the effect of RIPC as compared to standard conventional measures in reducing the incidence of CI-AKI post coronary intervention.

METHODOLOGY

It is a single center randomized control trial, conducted at The Aga Khan University Hospital Karachi, Pakistan from January 19, 2015 to July 18, 2015. The study was approved by Ethical Review Committee of the Aga Khan University Hospital Karachi (ERC No:3164-MED-ERC-14) and was conducted according to the Good Clinical Practice Guidelines. Written informed consent was obtained from all eligible participants prior to randomization into groups.

We recruited adult patients aged 30 years and above, having baseline serum creatinine level of 1.4mg/dl or higher with the diagnosis of Stable Angina (SA), Unstable Angina (UA) and Non ST elevation myocardial infarction (NSTEMI) who were to undergo a planned procedure of coronary angiography (CA) with tentative PCI. Patients with end stage renal disease (ESRD) requiring hemodialysis, ST elevation myocardial infarction (STEMI) and cardiogenic shock were excluded from the study. We also excluded patients who were taking or had taken nephrotoxic drugs within seven days before the procedure. Study participants were followed up to 48 hours after the procedure. After 48 hours, serum creatinine level of all the study participants was measured. The authors designed the study and collected, analyzed and interpreted the data. All the authors contributed to the writing of the manuscript, made the decision to submit it for publication and vouch for accuracy and completeness of the data and analysis. There is no role of funding sources in the study.

The trial has two arms; the intervention arm and the control arm. Patients were randomly assigned in 1:1 ratio to one of the two groups, Group A consisted of intervention arm in...
which RIPC protocol was applied whereas Group B was a control arm in which RIPC protocol was not applied. The allocation of patients to each arm was concealed, by sealed opaque envelope method.

After obtaining written informed consent and randomization, all the study participants, received standard care in the form of intravenous saline (0.9%) at a rate of 1 ml/kg, 6 hours before and 6 hours after the procedure and limitation of contrast medium administration to less than \{(5 \times \text{body weight kg}) \times (\text{serum creatinine}[\text{mg/dl}])^{-1}\}\) according to the practiced clinical guidelines. In all patients Ultravist® 300 (Iopromide; 370 mg I /ml; osmolarity 496 mOsm/L H2O at 37°C), a nonionic low-osmolar contrast medium was used. Data was collected on a paper based questionnaire. Serum creatinine level was checked for all study participants at baseline and at 48 hours after contrast exposure. For participants in the intervention arm, RIPC was performed in addition to the standard of care as discussed above. RIPC was done by 4 cycles of alternate 5 minutes inflation and 5 minutes deflation of a standard blood pressure cuff applied around the patient's upper arm at 50 mmHg higher than systolic blood pressure of that particular patient. This was done one hour before the start of the procedure. Coronary angiography and percutaneous coronary intervention was later performed by a certified cardiologist according to the clinical standards.

The primary endpoint was the occurrence of CI-AKI after 48 hours in both the control and intervention arms. The secondary end points were the occurrence of pulmonary edema, loss of radial pulse, need for hemodialysis and in hospital mortality due to cardiovascular causes during the course of hospitalization.

CI-AKI was defined as a rise in the serum creatinine of Y 0.5mg/dl from baseline within 48 hours of exposure to the contrast medium. SA was defined as exertional chest pain or discomfort radiating to left arm, neck, jaw or back which relieved with rest, which was stable over Ý4 weeks, with normal ECG and troponin-I level. UA was defined as new onset chest pain or resting chest pain or chest pain lasting more than 20 minutes with or without ST depressions in ECG but with normal troponin-I level. NSTEMI was defined as new onset chest pain or resting chest pain or chest pain lasting more than 20 minutes with or without ST depressions in ECG but with elevated troponin-I level. HTN was defined as BP of more than 140/90 for more than 20 minutes with or without ST depressions in ECG on onset chest pain or resting chest pain or chest pain lasting more than 20 minutes with or without ST depressions in ECG.

For continuous variables, we first examined the distribution of the observations. Normally distributed continuous variables were reported as means with standard deviations (SD), whereas non-normally distributed continuous variables were reported as median with interquartile range (IQR). For categorical variables, frequency and percentages was calculated and these were also calculated for the outcome variable (CI-AKI). Binary logistic regression was applied to the data as the outcome variable was dichotomous. Analysis was done based on intention to treat principle and was carried out using STATA version 12.0. All p-value less than 0.05 was considered to be significant.

RESULTS

A total of 1000 patients were screened for the study during the study period. Of these, 888 patients were excluded based on the exclusion criteria and 9 patients did not give informed consent. Thus 103 patients were randomized of which 53 patients were in group A (Intervention arm) in which RIPC protocol was applied, and 50 patients in group B (Control arm) in which RIPC protocol was not applied. Figure 1.

The average age of participants in the intervention group was 65 years and that in the control group was 66 years. Majority were male in both the groups. The study groups were balanced with respect to baseline characteristics especially the comorbidities, cardiovascular medications and other risk factors for CI-AKI, with the exception of family history and smoking though the proportion of patients for these parameters were very low Table 1. CA plus minus PCI were successfully completed in all the study participants according to the protocol and all were followed up at 48 hours.

The primary outcome (occurrence of CI-AKI post procedure) was significantly lower in the intervention arm as compared to the control arm(3.7% and 14%). Multivariable logistic regression suggested a protective effect of the intervention (RIPC)with adjusted Odd Ratio of 0.07 (95% CI: 0.007-0.72, p-value: 0.026) when adjusted for all other variables Table 2.

All study participants were successfully discharged home and no secondary outcome was reported in our study, hence we were unable to gauge their effect with the intervention.

Patients with prior MI were at higher risk of developing CI-AKI as compared to those with no history of prior MI (Adjusted OR:5.54, 95% CI: 1.08-27.44), however female gender, smoking, age and amount of contrast were not associated with the occurrence of CI-AKI Table 2.
Figure 1: Study Flow Chart

Table 1: Baseline Characteristics of Study Participants (n=103)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (RIPC applied) n=53</th>
<th>Group 2 (RIPC not applied) n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>65.0±10.3</td>
<td>66.0±7.9</td>
</tr>
<tr>
<td>Hemoglobin level (g/dl)</td>
<td>12.1±1.6</td>
<td>11.7±2.1</td>
</tr>
<tr>
<td>Amount of contrast (ml)</td>
<td>102.8±74.2</td>
<td>101.9±57.3</td>
</tr>
<tr>
<td>Baseline creatinine(mg/dl)</td>
<td>1.6±0.3</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>Male n(%)</td>
<td>41(77.3)</td>
<td>37(74.0)</td>
</tr>
<tr>
<td>HTN n(%)</td>
<td>49(92.4)</td>
<td>42(84.0)</td>
</tr>
<tr>
<td>Dyslipidemia n(%)</td>
<td>31(58.5)</td>
<td>30(60.0)</td>
</tr>
<tr>
<td>DM n(%)</td>
<td>43(81.1)</td>
<td>36(72)</td>
</tr>
<tr>
<td>Family history n(%)</td>
<td>3(5.6)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Smoking n(%)</td>
<td>7(13.2)</td>
<td>2(4.0)</td>
</tr>
<tr>
<td>Prior PCI n(%)</td>
<td>9(16.9)</td>
<td>7(14.0)</td>
</tr>
<tr>
<td>Prior CABG n(%)</td>
<td>13(24.5)</td>
<td>11(22)</td>
</tr>
<tr>
<td>IAPB Insertion n(%)</td>
<td>2(3.7)</td>
<td>1(2.0)</td>
</tr>
</tbody>
</table>
DISCUSSION

CI-AKI is a serious complication of contrast medium administration in patients undergoing PCI. Keeping in view the scarcity of available preventive strategies, renewed forms of strategies are intensely required to prevent this dreaded complication of such procedures. In this respect, our study, which is a randomized control trial, is the first of its kind from our country studying the effects of RIPC on the development of CI-AKI. We report a significant reduction in the incidence of serum creatinine based CI-AKI in RIPC group as compared to the control group, in patients with pre-existing renal dysfunction (serum creatinine of >1.4 mg/dl), undergoing CA and or PCI.

Multivariable analysis after adjusting for all other co-variables such as DM, HTN, age, gender, amount of contrast and baseline creatinine showed potential benefits of RIPC in the prevention of CI-AKI as RIPC independently has a strong reno-protective role.

The pathogenic mechanism responsible for CI-AKI is multifactorial and thus a strategy focusing on single aspect of the pathogenesis would not be sufficient. RIPC has protective effect in various ways. As for example ischemic preconditioning helps in keeping the vessel patent after thrombolytic therapy, the renoprotective effect of RIPC is present even on remote vessels, IPC keeps fibrin architecture active in thrombus, and IPC attenuates platelet activation-aggregation.

Our findings are in coherence with the previously conducted studies. The protective role of RIPC on renal function and myocardium salvage has been demonstrated in prior studies, using various ways of induction of ischemia and in different clinical settings.

Recently a meta-analysis and trial sequential analysis of 16 randomized control trials from China demonstrated the protective role of RIPC in the prevention of CI-AKI. It suggested that IPC was more effective in those patients who received pre or post procedure hydration explaining synergistic effect of the two strategies. This is clinically important as the two strategies can both be applied to draw the maximum benefits in favor of patients.

The overall incidence of CI-AKI in our study is lower than that in some other studies. The low incidence of CI-AKI is because of different reasons. Firstly we took great care to provide adequate intravenous hydration, before and after the procedure, which is the sole effective preventive strategy at the moment. Secondly the average amount of contrast medium in our study was less than that in some other studies (102 vs 186-190 ml). Thirdly, we used serum creatinine level for the diagnosis of CI-AKI which is less sensitive than other biomarker such as L-FABP as were used by others. Thus some of the cases of CI-AKI might have been missed using serum creatinine level. However, using this same biomarker for both the intervention and control groups, the comparison of the two groups was not affected.

Our study is different from some other studies, with respect to the protocol of induction of ischemia. Our RIPC protocol is more precise and reliable than others because of induction of ischemia in the whole upper limb, which is a larger tissue for the release of biochemical messengers as opposed to small segment of myocardium in case of intracoronary balloon inflation as used by others. RIPC application to upper limb is safer as limbs tolerate ischemia far better than myocardium. Moreover, the four cycle protocol that we used in our study instead of three cycle protocol as used by some others and the use of upper limb for the RIPC protocol both have been shown to be more effective for the induction of ischemia and thus the release of biochemical messengers.

Igarashi et al used similar protocol for RIPC showing its effectiveness in the prevention of CI-AKI.

Table 2: Effect of RIPC on the Occurrence of CI-AKI among Patients Undergoing CA and or PCI (n=103)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>RIPC (N=53)</th>
<th>Control (N=50)</th>
<th>Adjusted OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast induced nephropathy</td>
<td>2 (3.78)</td>
<td>7 (14)</td>
<td>0.07 (0.007-0.72)</td>
<td>0.026</td>
</tr>
<tr>
<td>Prior MI</td>
<td>18 (34)</td>
<td>7 (14)</td>
<td>5.45 (1.08-27.44)</td>
<td>0.040</td>
</tr>
<tr>
<td>Female</td>
<td>13 (26)</td>
<td>12 (24)</td>
<td>0.39 (0.038-3.90)</td>
<td>0.422</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (13.2)</td>
<td>2 (4)</td>
<td>8.16 (0.40-163.80)</td>
<td>0.170</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>65.0±10.3</td>
<td>66.0±7.9</td>
<td>0.10 (0.96-1.02)</td>
<td>0.695</td>
</tr>
<tr>
<td>Amount of Contrast (ml)*</td>
<td>102.8±74.2</td>
<td>101.9±57.3</td>
<td>1.0 (0.99-1.01)</td>
<td>0.880</td>
</tr>
</tbody>
</table>

*Mean ± SD
benefits on the occurrence of CI-AKI using L-FABP as opposed to serum creatinine in our study. However, majority of the studies investigating the effect of contrast on renal function have used serum creatinine as a marker of CI-AKI. Serum creatinine is more easily available, cheaper than L-FABP with reasonable accuracy to identify CI-AKI at 48 hours and thus most suited for developing regions like ours.

In our study we did not find any association of CI-AKI with other risk factors like DM, HTN, amount of contrast material and baseline serum creatinine level whereas other studies have shown this differently as discussed above. In this respect, the amount of contrast has immense importance because it has been previously associated with the occurrence of CI-AKI. However, recent meta-analysis failed to demonstrate the dose-effect relationship of the contrast medium, thus supporting the results of our study.

LIMITATIONS

It is a single center, non-blinded randomized control trial with a limited number of patients. Results can be generalized to the population similar to that in the trial. Large pragmatic studies are suggested to explore the applicability of this intervention in other population settings. We used serum creatinine as a marker for CI-AKI which starts to rise after 24 hours as opposed to serum cystatin C and neutrophil gelatinase associated lipocalin (NGAL) which are more sensitive markers of CI-AKI and start to rise in the first 6 hours after contrast exposure. However we conducted these test after 48 hours giving enough time for serum creatinine level to rise (if it has to rise) and based our measurement accordingly minimizing the chance of measurement bias.

CONCLUSION

RIPC is a simple, inexpensive, well tolerated and non-pharmacological strategy with a significantly high renal protective role against CI-AKI. In future, multicenter studies must be conducted to study the effect of RIPC at a large population scale. Also we recommend that being a feasible, in-expensive and non-pharmacological strategy, RIPC may be adopted as a preventive tool along with other existing strategies for the prevention of CI-AKI, keeping in view, the grave nature and high incidence of CIN.

REFERENCES

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