Original Research Article

A study to find out the effect of remote ischemic post conditioning of lower limb in patients of acute myocardial infarction undergoing primary percutaneous coronary intervention

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ABSTRACT

Background: Reperfusion therapy of affected myocardium is among the most successful method for infarct size reduction and achieving the better outcome in patients with ST-segment elevation myocardial infarction (STEMI). Primary percutaneous coronary intervention (pPCI) is among best procedures for successful reperfusion therapy which has effect in reduction of size of infarct, maintaining ventricular function for better outcome. In this study, authors were aimed to assess whether remote ischemic post-conditioning (RIPC) of lower limb could reduce enzymatic infarct size in patients with acute STEMI undergoing pPCI.

Methods: A case control, cross sectional, hospital based randomized study was carried out in Institute of Cardiovascular Sciences, IPGMER, Kolkata, from February 2014 to October 2015. Total 40 patients (20 cases and 20 controls) who were undergoing primary PCI for acute myocardial infarction were taken for study. In the active treatment group, the protocol was started with thrombectomy. The lower limb was exposed to 3 cycles of ischemia/reperfusion, each obtained by 5 min cuff inflation at 200mmHg, followed by 5 min complete deflation. End point of the study will be enzymatic infarct size assessed by the area under the curve of creatine kinase-myocardial band (CK-MB) release.

Results: The AUC of serum CK release during the first 72 hours of reperfusion was significantly reduced (p=0.0341) in the post-conditioned group compared with the control group, averaging 9632 units in postconditioned compared with 13493 units in control group which represented 26% of reduction of infarct size.

Conclusions: Remote ischemic post conditioning of lower limb significantly improves blush grading and enzymatic infarct size reduction with a trend towards significant reduction of mean ST segment deviation.

Keywords: Acute myocardial infarction, pPCI, RIPC, STEMI

INTRODUCTION

Among the major causes of worldwide mortality and morbidity, ST-segment elevation myocardial infarction (STEMI) remains the foremost and size of infarct could be a key element for diagnosis.[1] Primary percutaneous coronary intervention (pPCI) is one of the best procedures for successful reperfusion which has effect in reduction of size of infarct, maintaining ventricular function for better outcome.[2] Immediate restoration of blood flow could limit such intervention advantage due to lethal injury of myocardial cells. Previous reports reveal the influence of myocardial reperfusion injury affects up to half of the final infarct size.[1,3]

Reperfusion therapy of affected myocardium is among the finest method for infarct size reduction and achieving the better outcome in patients with STEMI. The regain of coronary blood flow will prompt further damage in myocardium. Several factors including oxidative stress, intracellular calcium accumulation, rapid restoration of pH, inflammation and opening of the so-called mitochondrial permeability transition pore intermediates reperfusion injury. Clinically identified features include arrhythmias or myocardial stunning, myocardial infarction or microvascular obstruction.

Researchers reported ischemic preconditioning i.e. implementation of brief episodes of ischemia-reperfusion just before a prolonged coronary artery obstruction limit infarct size in experimental preparations, but is not possible in clinical practice as the coronary artery is obstructed at the time of hospital admission. Then Zhao et al reported a phenomenon known as postconditioning which is induced by a sequence of reversible ischemia-reperfusion but is just after the prolonged ischemic insult.[4] Protection afforded by postconditioning is equivalent to preconditioning. Although ischemic preconditioning has consistently proven to be cardioprotective, its clinical application is clearly limited.

In the present study, authors were interested to evaluate whether remote ischemic post-conditioning (RIPC) of lower limb could reduce enzymatic infarct size in patients with acute STEMI undergoing primary percutaneous coronary intervention (pPCI).

METHODS

A case control, cross sectional, hospital based study conducted during February 2014 to October 2015. Study was conducted at the Institute of Cardiovascular Sciences Kolkata, IPGME and R. With the study population total 40 patients (20 cases and 20 controls) were taken for study.

Inclusion criteria

Male and female patients between 18 to 80 years, diagnosis of STEMI according to ACC/AHA ECG criteria and who are candidates for primary angioplasty were included. The culprit coronary artery had to be occluded at the time of admission (TIMI 0 flow grade), and had to be adequately re-perfused (TIMI 2 to 3 flow grade) after PTCA.

Exclusion criteria

Previous STEMI or non STEMI within 6 months, patients in Killip class IV, Evidence of retrograde filling by collaterals at coronary angiography, severe multi-vessel coronary artery disease likely to require further interventions.

The study was approved by ethical committee of institute.

Study tools and techniques

Various epidemiological, clinical, hematological and biochemical parameters were recorded in these patients, as described below.

Clinical parameters included detailed cardiovascular system examination and clinical history. Laboratory data of patients included hemoglobin, total leukocyte count, differential count, platelet count, blood sugar, serum sodium, potassium, liver function tests, renal function tests, CPK-MB level, electrocardiography, 2D echocardiography.

Coronary angioplasty

All patients were pre-medicated with loading doses of Ecosprin (325 mg) and clopidogrel (600 mg) and atorvastatin (80 mg). Coronary angiography was performed using a standard Seldinger technique. Iohexol (Omnipaque) was used as contrast agent for coronary angiography. Coronary angiography allowed identification of the culprit coronary artery and checked that reperfusion had not occurred before PTCA (TIMI 0 flow grade) and that no collateral filling from homolateral or contralateral coronary vessels was present.

After diagnostic angiography, eligible patients were randomized 1:1 to pPCI and RIPC or conventional pPCI. All selected patients were prepared with a thigh-sized limb cuff before arterial puncture (contralateral in case of femoral access). In the active treatment group, the protocol was started with thrombectomy. The lower limb was exposed to 3 cycles of ischemia/reperfusion, each obtained by 5 min cuff inflation at 200 mmHg, followed by 5 min complete deflation. End point of the study was enzymatic infarct size assessed by the area under the curve of creatine kinase-myocardial band (CK-MB) release.

In the end, coronary angiography was performed in both groups to assess coronary patency and to estimate the myocardial perfusion index using the blush grade evaluation. The angioplasty procedure was then completed according to physician judgment with respect to patient status.

Standard 12-lead ECGs were recorded at admission and 48 hours later. Maximal ST-segment change was measured by a cardiologist unaware of the patient's group. At all-time points, ST-segment shift was measured 80 ms after the J point.

Blood samples were taken at admission, after 4 hours of opening of the artery, then after 8, 24, 48 and 72 hours. Area under the curve (AUC; arbitrary units) of serum creatine kinase CK release (Beckman Kit, expressed in IU/L) was measured in each patient by computerized planimetry and used as a surrogate marker of infarct size.

RESULTS

The baseline characteristics and clinical data of the patients are depicted in Table 1. In the post-conditioned group, the mean age was 56.7±10.62 years. In the control group, the mean age was 55.08±9.1 years. Among cases 12 patients were male and 8 patients were female respectively. Among control group 13 patients were male and 7 patients were female respectively. In the post-conditioned group, the mean BMI was 30.53±5.4. In the control group, the mean BMI was 31.19±5.67.

Out of 20 patients in cases 10 patients were hypertensive and in the control group 11 patients were hypertensive. Out of 20 patients in cases 8 patients (40%) were smokers and in the control group 10 patients (50%) were smokers.11 patients (55%) out of 20 patients were dyslipidemic and in the control group 10 patients (50%) were dyslipidemic. Out of 20 patients in cases 5 patients (25%) were diabetic and in the control group 4 patients (20%) were diabetic. There is no statistical significant difference of between two groups (P=0.69).

Among cases 10(50%) patients had LAD, 4 (20%) patients had LCX and 6 (30%) patients had RCA as their culprit vessel respectively. Among control group 9 (45%) patients had LAD, 3 (15%) patients had LCX and 8 (35%) patients had RCA as their culprit vessel respectively.

Table 1: Baseline characteristics and clinical data.

Characteristics	Cases (%)	Control (%)	P value
Age (years)	56.7±10.62	55.08±9.1	0.529
Sex			0.98
Male	12 (60)	13 (65)	
Female	8 (40)	7 (35)	
Body mass index (kg/m^2)	30.53±5.4	31.19±9.1	0.639
Hypertension	10 (50)	11 (55)	0.92
Smoker	8 (40)	10 (50)	0.75
Dyslipidaemia	11 (55)	10 (50)	0.99
Diabetes	5 (25)	4 (20)	0.91
EF%	45.7±6	46.2±7	0.69
LAD/LCX/RCA	10/4/6	9/3/8	0.71
Mean ST segment deviation at 0 hr	4.35±0.8	4.2±0.79	0.08
Mean ST deviation at 48 hr	0.87±0.66	1.45±0.91	0.06

Figure 1 presents blush grading after primary PCI among the two groups. Among cases 11 patients (55%) had blush grade 3, 6 patients (30%) had blush grade 3 and 2 patients (15%) had blush grade 1 respectively after primary PCI. Among control group 4 patients (20%) had blush grade 3, 8 patients (40%) had blush grade 2 and 8 patients (40%) had blush grade 1 respectively after primary PCI. There was no statistical significance between the two groups.

	GRADE 1	GRADE 2	GRADE 3
cases	3	6	11
controls	8	8	4
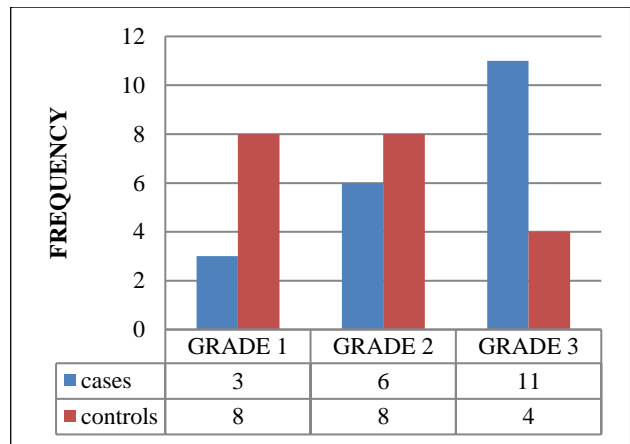
Figure 1: Blush grading after primary PCI.
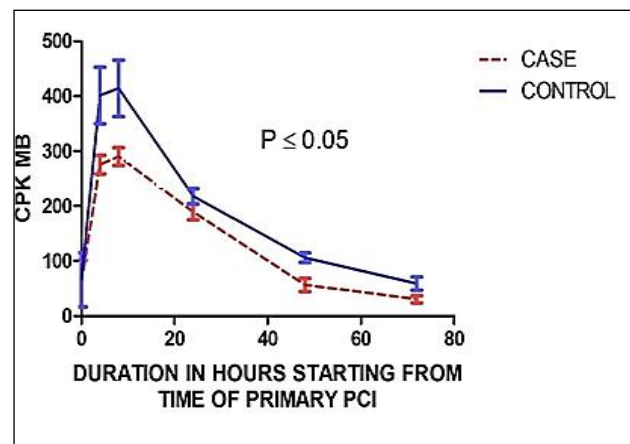
Figure 2: Area under curve (AUC) of CPK MB release during first 72 hours.

The AUC of serum CK release during the first 72 hours of reperfusion was significantly reduced (p=0.041) in the post-conditioned group compared with the control group (Figure 2).

DISCUSSION

In the control group and post conditioned group, the mean age was 55.08±9.1 years and 56.7±10.62 years. There was no statistical difference between the two groups (p=0.529). Among the total cases, 12 patients (60%) were male and 8 patients (40%) were female respectively. Among control group 13 patients (65%) were male and 7 patients (35%) were female respectively. There was no statistical significant difference of sex distribution between two groups. The seemingly greater number of males could be explained by the fact that women patients often neglect their initial symptoms and seek medical advice late due to personal and family pressure. Thus, in a hospital-based study, women patients form a minority.

In the control group, the mean BMI was 31.19±9.1. In the post-conditioned group, the mean BMI was 30.53±5.4.

There was no statistical significant difference of BMI between two groups (p=0.639). Thus, most of the patients in both case and control groups were overweight. Previous studies also support that obesity and overweight are risk factors for acute myocardial infarction (AMI).[5]

Out of 20 patients in cases, 10 patients (50%) and in the control group 11 patients (55%) were hypertensive respectively. There was no statistical significant difference of between two groups. Out of 20 patients in case group 11 patients (55%) and in the control group 10 patients (50%) were dyslipidaemic respectively. This high prevalence of hypertension and dyslipidaemia in the study group are in accordance with the risk factors of AMI.

Out of 20 patients in cases, 8 patients (40%) and in the control group 10 patients (50%) were smokers respectively. There was no statistical significant difference of between two groups (p=0.75). In Indian subcontinent percentage of smokers are quite high and this has been reflected in our data. Similarly, 5 patients (25%) in cases and in the control group 4 patients (20%) were diabetic. The prevalence of diabetes has increased in India in last two decades and high prevalence of diabetes in study group indicates its strong correlation with AMI.[6]

There was no statistical significant difference of ejection fraction between case (45.7±6.0) and control (46.2±7) groups (p=0.69). 10 (50%) patients in case group had LAD, 4 (20%) patients had LCX and 6(30%) patients had RCA as their culprit vessel respectively. In control group 9 (45%) patients had LAD, 3 (15%) patients had LCX and 8 (40%) patients had RCA as their culprit vessel respectively.

Mean ST segment deviation at 0 hour between cases and control group were 4.35±0.8 mm and 4.2±0.79 mm respectively. There was no statistical significant difference of between two groups (p=0.08).

Among the cases 11 patients (55%) had blush grade 3, 6 patients (30%) had blush grade 2 and 3 patients (15%) had blush grade 1 respectively after primary PCI. Among control group 4 patients (20%) had blush grade 3, 8 patients (40%) had blush grade 2 and 8 patients (40%) had blush grade 1 respectively after primary PCI. There was significant statistical significant difference of between two groups.

Abnormalities associated with increasing myocardial perfusion, as assessed by the myocardial blush grade (MBG) correlate with unfavorable ventricular remodeling and risk for mortality even after adjusting for the presence of TIMI grade 3 flow or a normal TIMI frame count.[7,8] They are better indicator for microvascular integrity. In this study, short term or long term clinical outcomes were not assessed, instead of that laboratory and Cath lab markers were assessed for successful reperfusion and cardiac injury. Myocardial blush grading is one of the markers for successful reperfusion at microvascular level. In our study in the post conditioned group there was significant improvement of myocardial blush grading indicating favorable result with post conditioning. Though previous studies on post conditioning showed similar effect, recently a large study conducted by Joo-Yong Hahn didn't not find any significant difference of MBG between post conditioned and control group.[9] In their study postconditioning was not performed per protocol in around 10% of patients and balloon occlusion for ischemic postconditioning was performed before stenting so there may be a possibility of incomplete establishment of flow before postconditioning violating the basic principle of post conditioning. Moreover, they used pre-dilatation balloon and thrombosuction catheter for establishment of flow in most of the patients. In our study, we have used thrombosuction catheter in most of the patients. The reason behind that was by use of pre-dilatation balloon we are actually allowing more thrombus to migrate towards distal microcirculation causing more damage to microcirculation which is against the principle of direct stenting which should be a preferred strategy for management of STEMI. We have used thrombosuction catheter in almost all patients for establishing flow. The reason behind this strategy was that most of the patients in the study group had initial TIMI 0 flow. Now before putting stents we have to see the distal segments. Thrombosuction catheter has advantage over pre-dilatation balloon that chances of distal thrombus migration are less in case of thrombosuction catheter. In our institution, we use pre-dilatation balloon for establishing flow as a bail out strategy. To this regard it was postulated that cardioprotective effects of postconditioning may also be attenuated by thrombus aspiration because thrombus aspiration was reported to improve myocardial reperfusion.[10]

The AUC of serum CK release during the first 72 hours of reperfusion was significantly reduced (p=0.0341) in the post-conditioned group compared with the control group, averaging 9632 units in post-conditioned compared with 13493 units in control group which represented 26% of reduction of infarct size. The peak of CPK MB release was also markedly lower in the post-conditioned (291±16.23 IU/L) than in the control (415.2±51.31 IU/L) group (p≤0.0001). The major finding of this study is that postconditioning reduced infarct size by 26%. The reduced enzymatic infarct size observed here closely resembles that reported in the preconditioned human heart by Kloner et alCK release is a surrogate end point that has been validated with respect to SPECT imaging in several studies and represents a useful and easily available technique to evaluate irreversible myocardial injury in clinical practice.[11]

Overall, our data strongly suggest that enzymatic infarct size reduction was not due to a difference in either major determinant of infarct size but actually reflects a protective effect of post conditioning because we have

already demonstrated that baseline variables were similar in two groups. Although CK release was assessed over a 72-hour reperfusion period, further studies are needed to confirm, e.g., with techniques like SPECT or MRI performed weeks to months after AMI, that infarct size reduction is permanent.

This study shows that remote ischemic post conditioning of the lower limb at the time of primary PCI can reduce enzymatic infarct size by 26% in patients with STEMI undergoing primary PCI within 6 hours of symptoms onset. Most of the clinical studies that explored the effect of myocardial post-conditioning in humans, applied brief cycles of ischemia/reperfusion to the culprit artery after stenting. The protective effect of local post conditioning in STEMI patients remain unclear and recently prompted safety concerns related to possible thrombus micro embolization occurring during repeated balloon inflations to the infarct-related artery.

Coronary arteries without evidence of retrograde filling to avoid potential confounders due to spontaneous reperfusion and/ or collateral protection. RIPC consisted of 3 cycles of leg ischemia/reperfusion started at the time of reperfusion. We believe that timing could have potentially relevant implications beyond classification.

RIPC significantly improved ST resolution. ST resolution has been proposed as a marker of efficient microvascular reperfusion, and it yields prognostic information beyond that provided by coronary TIMI flow grade. Several studies have shown a consistent relationship between STR and subsequent mortality.[12]

RIPC was also associated with improvement in myocardial blush grading(MBG). MBG has been proposed as a more efficient marker of successful microvascular reperfusion than TIMI flow grade and TIMI frame count and has been positively associated with long-term mortality in STEMI patients.[13]

From this study, we can conclude that remote post conditioning of lower limb significantly improves blush grading and enzymatic infarct size reduction with a trend towards significant reduction of mean ST segment deviation. Obtaining such a beneficial effect by simple manipulation of reperfusion is of major potential clinical interest. Whether ischemic postconditioning has to be performed as such in daily clinical practice is an unanswered question. Obviously, it represents a feasible, safe, and efficient cardioprotective intervention. Additional studies are needed to address its effect on post-ischemic functional recovery, no reflow, and even cardiovascular morbidity within the months after AMI. Unfortunately, all patients with AMI will not be able to benefit from such a treatment, including those who are not selected to receive PTCA. Important research must be done to understand the molecular mechanism of this protection to develop new drugs to apply pharmacological postconditioning to all patients with AMI.

Limitations of this present study sample size was small and subgroup analysis was not done. The study was not double-blinded. We used CPK MB release over 72 hours as a surrogate marker for myocardial injury. Though there are studies which show good correlation between CPK MB release and myocardial injury demonstrated by SPECT study, recently MRI scan emerged as a reliable tool for estimation of myocardial edema and infarct size, though standard protocol is still lacking. Had the study been conducted by MRI or SPECT, it would have had more impact on final outcome than only relying on surrogate marker i.e AUC estimation of CPK MB over 72 hours. But cost constraint is always a factor in conducting a study using MRI or SPECT to each patient. The study was conducted in a state medical college and hospital and maximum patients of our institute are from low socioeconomic background.

We used thrombosuction catheter in maximum patients. The cardioprotective effects of postconditioning may be attenuated by thrombus aspiration because thrombus aspiration was reported to improve myocardial reperfusion. In clinical setting during primary PCI many a times we have to use pre-dilatation balloon to establish reflow, because without visualizing distal segment we can't put a stent. Thrombosuction often establishes reflow; if it fails we have no way except use of pre-dilatation balloon. Now problem using balloon is it will aggravate distal thrombus migration which will in turn harm distal micro circulation and lead to myocardial injury.

It was not a longitudinal study. Parameters such that all-cause mortality, hospital admission with heart failure, improves in ejection fraction were not included in this study so the benefit of enzymatic reduction of infarct size whether it is translating into clinical benefit is not known from the study.

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