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General Medicine

STUDY OF EFFECT OF REMOTE ISCHEMIC POST-CONDITIONING IN ST ELEVATION MYOCARDIAL INFARCT PATIENTS

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ABSTRACT

Background: Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide.Patients with CHD suffer significant morbidity and mortality and Infarct size is a key determinant of prognosis.

Aims and Objectives: To evaluate whether remote ischemic Post-conditioning (RIPC) could safely reduce enzymatic infarct size in patients with ST-elevation myocardial infarction (STEMI). To evaluated ECG changes & Echocardiographic in patients who underwent RIPC.

Materials and methods: This institutional study consists of total 52 subjects (n=26 in the case group and n=26 in control group), aged between 18-50 year, with ST-elevation myocardial infarction (STEMI)..

Results: Our study findings show that the maximum no. of patients were present in 41-51 years of age group (n=37, 71.15%), Most of the subjects were male (n=45, 86%). The frequencyof Smoking & Tobacco was the highest (26.92 % & 19.23 % respectively).Significant difference present between Trop T (Quantitative) levels in RIPC (case) group and control group at various time intervals with a sequential decline in trop T levels with time (P<0.0001*). RIPC (cases) group having significantly lower TROP T at all three-time interval (P<0.0001*) as compared to control group. There was a significant difference was present between ST resolutions in RIPC (case) group at various time intervals. A significant difference in ST resolution was observed between study groups at day 1 (P=0.013*) and highly significant at day 3 (P=0.004*).Maximum area under the ROC curve was shown at day 3 with a significance of P<0.0001*.

Conclusion: RIPC definitely reduces infarct size and has a great impact on ST Segment resolution in ECG. RIPC helps early recovery & better reperfusion as compared

KEYWORDS : Remote ischemic post-conditioning; Coronary heart disease; Trop-T levels; ST-elevation; myocardial infarction

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of morbidity and mortality worldwide.[1] In India according to the World Health Organization (WHO) CHD accounted for 24% of all deaths in 2008.[2] In 2015 WHO reported the age-standardized CAD mortality rates among males and females in India (per 100,000) at 363-443 and 181-281, respectively. Cardiovascular disease (CVD) deaths accounts for 30.8% of all deaths by 2010 and estimated to be 32.5% of all deaths by 2030 globally.[3]

Patients with CHD still suffer significant morbidity and mortality & ST-elevation myocardial infarction (STEMI) is a leading cause. Infarct size is a key determinant of prognosis. Murry et al[4] first described the phenomenon of ischemic preconditioning (IPC) in which the application of brief cycles of non-lethal ischemia and reperfusion to the heart reduced subsequent myocardial infarct size in the canine heart.

In pre-clinical studies, the impact of myocardial reperfusion injury accounts up to 50% of the final infarct size, in this regard, the phenomenon of ischemic conditioning may provide an endogenous strategy for protecting the heart against ischemia-reperfusion injury (IRI). Among strategies aimed at limiting reperfusion injury, myocardial ischemic preconditioning, obtained by exposing the ischemic myocardium to brief periods of ischemia/reperfusion immediately after reperfusion, showed promising results in both animal and small clinical studies. However, the relevance of this intervention in the clinical setting remains unclear [5]

Botker et al (2010)[6] experimentally proved that the cardioprotective effect of myocardial conditioning, wherein myocardial reperfusion is interrupted by several short-lived episodes of ischemia, overcomes this problem, and can be applied at the onset of myocardial reperfusion in patients presenting with an acute MI. However, IPC requires an intervention to be applied to the heart directly which may not be feasible in all clinical settings. In this regard, remote ischemic conditioning (RIC) may provide a non-invasive endogenous therapeutic strategy for protecting the heart against acute IRI.[7,8,9,10] RIC describes the cardioprotective effect elicited from applying one or more cycles of non-lethal ischemia-reperfusion to an organ or tissue remote from the heart.

This study aims to evaluate whether remote ischemic Post-conditioning (RIPC) could safely reduce enzymatic infarct size in patients with STEMI. We also evaluated ECG & echocardiography changes in patients who underwent RIPC.

MATERIAL AND METHODS

Study design and setting:

This is a hospital-based cross-sectional study conducted between June 2016 to October 2017 in the Department of Medicine, Dr. B.R.A.M. Hospital Raipur among 52 STEMI patients admitted to ICCU ward of Medicine Department.

Sample size and Study subjects:

The present study included two groups, first group (termed “case” in further discussion) included patients who consented for RIPC; and the other group (termed “control”) who refuse for same. Total 52 subjects (n=26 case and n=26 control) were included in the study. Patient aged between 18-50 year, with STEMI (defined as chest pain for more than 30 minutes with new ST elevation in two contiguous leads in ECG with the cut points ≥ 0.2 mV, >2 mm), willing and capable to provide informed consent were included in our study. Patients with history of cardiogenic shock, post-cardiac arrest status, need for mechanical ventilation, known peripheral artery disease or evidence of lower limb ischemia, previous anterior STEMI and all NSTEMI were excluded from our study.

Data collection:

Ethical clearance from concerned college committee and written informed consent from all study participants was obtained. 26 patients with STEMI who gave consent for RIPC included in the case group were assigned for pre-conditioning. Patients (n=26) who did not consented for RIPC and willing to participate in study, were assigned to Control group. Venous blood was withdrawn for trop-T, ECG and Echo done on day 0, 1 & 3 for each of the patient in both the groups.

The primary endpoint was infarct size, assessed by the area under the curve of trop-T level. Secondary endpoint included resolution of ST-

Segment in ECG and improvement of ejection fraction (EF) in echocardiography.

Statistical analysis:

The data and results are interpreted in actual figures and percentages and appropriate test being applied. Statistical analysis was done by using description and inferential statistics. All the data were expressed in mean ± standard deviation (SD). The analysis was performed by using Student's t-test for the difference between means and Chi-square test was used to analyze the significance of the difference between frequency distribution of the data. Comparison of time interval done by Friedman test and comparison of various time interval performed by Mann-Whitney U test, Wilcoxon test,and Z test. A P value <0.05 was considered as statistically significant.

RESULTS

The present study was conducted in the Department of medicine Dr. B.R.A.M. Hospital, Raipur among 52 STEMI patients (26 cases and 26 controls).

Maximum numberof patients were in 41-51 years of age group (71.15%) (n=37) of which 15(57.7%) were cases and 22(84.6%) control. Most of the subjects were male (n=45, 86%) (Table 1).

Table 1: Analysis of age and sex distribution of patients

		CASE		CONTROL	
Age (years)	N=26	%	N =26	%	
	<30	5	19.2	0	0
	31-40	6	23.1	4	15.4
	41-50	15	57.7	22	84.6
Gender	Female	4	15.4	3	11
	Male	22	84.6	23	89

25 patients had no addiction related risk factor, 14 were chronic smoker, 10 were chronic tobacco chewer 03 gave history of ganja addiction.

Table 2: Comparison of Trop-T in case & control groups at various time intervals

		N	Mean	SD	min	max	p Value
Case	Day 0	26	3469.0	1041.5	400.0	5487.0	<0.0001*
	Day 1	26	3069.1	1127.8	9.5	5214.0	
	Day 3	26	2617.3	1210.2	6.9	5010.0	
Control	Day 0	26	5875.2	1256.59	3558.00	7774.00	<0.0001*
	Day 1	26	5594.8	1222.86	3321.00	7478.00	
	Day 3	26	5287.3	1177.06	3221.00	7101.00	

There was a significant difference present between Trop T (Quantitative) levels in both RIPC (case) and control group at various time intervals with a sequential decline in trop T levels with time (P<0.0001*) (Table 2).

Table 3: Comparison of TROP T at various intervals between study groups

Trop T	Group	N	Mean	SD	SEM	Z	P Value
Day 0	Case	26	3469.0	1041.46	204.25	-5.344	<0.0001*
	Control	26	5875.2	1256.59	246.44		
Day 1	Case	26	3069.1	1127.79	221.18	-5.408	<0.0001*
	Control	26	5594.8	1222.86	239.82		
Day 3	Case	26	2617.3	1210.19	237.34	-5.646	<0.0001*
	Control	26	5287.3	9650.85	1892.69		

RIPC (cases) group was found to have significantly lower TROP T at all three-time interval (P<0.0001*) as compared to control group, but the difference in trop T level was found to be highest on day 3 (z=-5.64) compared to z=-5.40 on day 1 and z=-5.344 at day 0. (Table 3).

Significant difference was present between ST resolutions in RIPC (case) group at various time intervals; mean 4.12±1.70 on day 0, 3.15±1.22 on day 1 & 2.77±1.14 on day 3 with a sequential decline in ST level on ECG levels with time. (P<0.0001*) (Table 4). A significant difference was present between ST resolution in ECG in control group at a various time interval (p<0.0001). Mean 4.29±1.36 on day 0, 4.06 ± 1.30 on day 2 & 3.75± 1.18 on day 3, there was a sequential decline in ST-elevation levels with time but the difference was not as marked as in RIPC group (Table 4).

Table 4: Comparison of ST resolution in RIPC (case) group at various time intervals

	Parameter	Duration	N	Mean+S.D.	Min	Max	P Value
Case	ST elevation (mm)	Day 0	26	4.12+1.70	2	8	<0.0001*
		Day 1	26	3.15+1.22	1	6	
		Day 3	26	2.77+1.14	1	6	
Control	ST elevation (mm)	Day 0	26	4.29+1.36	2	7	<0.0001*
		Day 1	26	4.06+1.30	2	7	
		Day 3	26	3.75+1.18	2	6	

ROC curve for Trop T between RIPC (case) and control group was plotted. Maximum area under the curve was shown at day 3 with a significance of P<0.0001* (Table 5 and Fig 1)

Table 5: ROC curve for Trop T between case (RIPC) and control group

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Day 0	.932	.033	.000*	.867	.997
Day 1	.937	.031	.000*	.875	.999
Day 3	.956	.024	.000*	.909	1.004

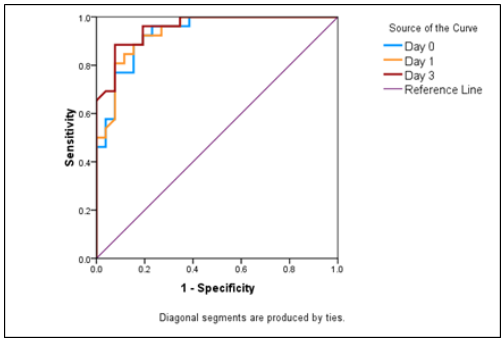

Fig 1: ROC curve for Trop T between RIPC and control group

There was no significant difference in ST resolution was observed between study groups at day 0, the difference was found to be significant at day 1 (P=0.013*) and highly significant at day 3 (P=0.004*) (Table 6).

Table 6: Comparison of ST-segment resolution at various intervals between study groups

ST elevation(mm)	Group	N	Mean+SD	SEM	t	P Value
Day 0	Case	26	4.12+1.70	0.33	-.405	.687
	Control	26	4.29+1.36	0.27		
Day 1	Case	26	3.15+1.22	0.24	-2.584	.013*
	Control	26	4.06+1.30	0.25		
Day 3	Case	26	2.77+1.14	0.22	-3.049	.004*
	Control	26	3.75+1.18	0.23		

Comparison of Ejection fraction at various intervals between study groups shows no significant difference between two groups at any given time interval (table 7).

Table 7: Comparison of Ejection fraction at various intervals between study groups

EF (%)	Group	N	Mean+SD	SEM	t	P-Value
Day 0	Case	26	43.46+8.34	1.64	-.779	.440
	Control	26	45.19+7.68	1.51		
Day 1	Case	26	43.46+8.34	1.64	-.779	.440
	Control	26	45.19+7.68	1.51		
Day 3	Case	26	43.46+8.34	1.64	-.779	.440
	Control	26	45.19+7.68	1.51		

DISCUSSION

CHD is the leading cause of morbidity and mortality worldwide.[1] In our study majority of the subjects were male and in the age group of 41 to 50 years. In study by Khan et al[11] , they found 88% of subjects were in the age group of >40 years and 77% were male. Studies by Razzaq et al [12] and Hong et al [13] also concluded the similar results.

In our study, smoking as risk factor had the highest frequency followed by tobacco while the majority did not have any addiction. Studies by Kaul et al[14]and Joshi et al[15] concluded smoking (76.2%), hypercholesterolemia (36.3%), hypertension (32.5%), positive family history (28.7%), and diabetes mellitus (5%) as risk factor for CAD.

In our study, we measured quantitative trop-T for enzymatic infarct size. In both these groups, there was a sequential decrease in the level of trop T (quantitative) with time. Trop T was the important cardiac marker for estimation of infracts size. It increases in the first 12-24 hrs and then it gradually declines over next 4-5 days. Similarly, Tian et al[16] found that the peak hs-cTnT at 3–4 hrs post-exercise was substantially higher ($P < 0.05$) in adolescents [median (range): 211.0 (11.2–794.5) ng/l] compared with adults [median (range): 19.1 (9.7–305.6) ng/l]. Peak hs-cTnT was followed by a rapid decrease in both groups, although adolescent data had not returned to baseline at 24 h.

The study showed a significant reduction in the levels of trop T in RIPC (case) group compared to control in all three-time interval (day 0,1 &3). The difference in trop T level was found to be highest on day 3. Ahmed et al[17] also found that the mean cTnT at 16 hours after PCI was lower in the RIPC group compared with the control group. Andreka et al[18] in their study found that the total serum creatine kinase release during the first 72 h of reperfusion was significantly reduced in the post-conditioned group than in the control group; this represents 26% reduction in the infarct size (P=0.01). Uçar et al[19] also found that 16th-hour cTn-I was insignificantly lower in the preconditioning arm (0.026 µg/l vs. 0.045 µg/l, p = 0.186). The incidence of cTn-I elevation which is 5-fold above the upper reference limit (URL) (> 0.115 µg/l) in Myocardial infarction patients; was found to be lower in the preconditioning group.

There was a significant decrease/ resolution of ST-Segment in ECG on day 0, 1 and 3. Control group also had an ST-Segment resolution but was not as marked as in case group. When compared, both groups (cases & control) had no significant ST resolution on day 0, the difference was found to be significant on day 1 and highly significant on day 3. The results were comparable with study by Zhang et al[20]. In this randomize control trial (RCT) they found that ST-segment resolution favored RIC group than the control group (RR 1.39; 95% CI 1.03–1.86; P=0.03). Crimi et al[21] and Wang et al[22] also found the significant difference in ST-segment resolution between RIPC and control subjects (P-value = 0.015 & 0.04 respectively).

In our study echocardiography was performed on day 0, 1, and 3 and no significant difference was found in E.F. of cases and control. Similarly, Munk et al[23] in their RCT found no significant difference in LV function on day 1 (EF-2D, 0.510.10 versus 0.490.10; P=0.22) and after 30 days (EF-2D, 0.540.08 versus 0.530.10) between the rIC and the pPCI-alone groups. Freixa et al[24] concluded that left ventricular diameters and volumes, as well as LVEF, were similar in both groups at 1 week and 6 months as assessed by ce-CMR and echocardiography. In contrast with post conditioning, control patients presented a significant LVEF improvement between the first week and the sixth month after MI 46.71+8.6% at 1 week vs. 50.32+9.8% at 6 months; P = 0.01). However, this difference became non-significant when measuring the absolute change in LVEF (2.25+6.1% in the post conditioning group vs. 4.08+8.3% in the control group; P = 0.35).

In our study mean area under the curve of a cardiac enzyme of RIPC group was 25.75 % less than the control group. Maximum area under the curve for enzymatic infarct size was found on day 3 compared to day 0. Crimi et al[21] found that the median area under the curve of the cardiac enzyme was 8,814 arbitrary units in the RIPC group and 10,065 arbitrary units in control subjects (P= 0.043), which was similar to our study. White et al[25] found that RIPC reduced MI size by 27%, when compared with control subjects (P= 0.009). At 24 hrs, high-sensitivity trop-T was lower with RIPC (P = 0.037).

SUMMARY AND CONCLUSION

RIPC definitely reduces infarct size as measured by Quantitative Top T in myocardial infarct patients (ST Segment Elevation). It also has great impact on ST Segment resolution in ECG. RIPC helps early recovery & better reperfusion as compared to control. There was no improvement found in echocardiography with respect of EF (Ejection Fraction) in the study subjects. However, this is a small study which needs further evaluation in a large study. RIPC is a non-invasive simple procedure which could help recover patient faster. It also reduces hospital stay, morbidity and mortality.

CONFLICT OF INTEREST - The authors declare no conflicts of interest in this work

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