EVALUATION OF BIOCHEMICAL (TROPONIN-I) AND ECHOCARDIOGRAPHIC OUTCOMES OF REMOTE ISCHAEMIC PRECONDITIONING IN PATIENTS UNDERGOING ELECTIVE PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

BACKGROUND

Percutaneous coronary interventions are associated with myocyte damage. The repetitive brief periods of ischaemia protect the myocardium from a subsequent longer ischaemic insult and has been reported to reduce infarct size, preserve vascular endothelial function, decrease neutrophil accumulation and reduce apoptosis. However, this hypothesis remains debatable. The studies done so far have yielded heterogeneous results.[1]

MATERIALS AND METHODS

This was a randomised controlled study. This study compared effect of remote ischaemic preconditioning on changes in cardiac biomarker and echocardiographic parameters in patients undergoing elective coronary intervention.

RESULTS

The study outcomes were comparable in the two groups with remote ischaemic preconditioning with no statistically significant differences.

CONCLUSION

The study concludes an insignificant impact of remote ischaemic preconditioning on these outcome parameters.

KEY WORDS

Percutaneous Coronary Interventions, Remote Ischaemic Preconditioning, Troponin-I, Echocardiographic Parameters.

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BACKGROUND

Elective percutaneous coronary intervention is associated with cardiac troponin release in more than one-third of cases. However, the clinical significance of these events and their management remain a matter of considerable controversy and uncertainty.[2]

Some researchers studied the predictors and prognostic value of myocardial injury following stent implantation and role of cardiac troponins. T Nageh et al (2004) found that cardiac troponin-I increased post-procedurally in one-third of the stable patient population undergoing elective percutaneous coronary intervention and was independently and significantly predictive of an increased risk of adverse events at 18 months, predominantly in the form of repeat percutaneous coronary intervention.[3]

In 1986, Murry et al first introduced the concept of ischaemic preconditioning, in which repetitive brief periods of ischaemia protected the myocardium from a subsequent longer ischaemic insult.[4] Pre-conditioning has been reported to reduce infarct size, preserve vascular endothelial function, decrease neutrophil accumulation and reduce apoptosis.[1]

This protection not only acts locally, but also can protect distant tissues, a phenomenon known as remote ischaemic preconditioning, protects humans against endothelial ischaemia/ reperfusion injury and the extent of MI after adult coronary bypass surgery, paediatric surgery and non-cardiac surgery including percutaneous coronary intervention.[5]

Therefore, Current study has been carried out to assess the ability of remote ischaemic preconditioning to attenuate cardiac troponin-I release and left ventricular dysfunction after elective percutaneous coronary intervention in patients admitted in Medicine Department of Pt. JNM MC and Dr. BRAM Hospital, Raipur for elective coronary angioplasty.

MATERIALS AND METHODS

The study was initiated after obtaining Institutional Ethics Committee approval of the protocol. This was a randomised controlled study conducted in the Department of Medicine, Pt. JNM Medical College and Dr. BRAM Hospital, Raipur among young age patients (<= 60 years age excluding premenopausal females) admitted for elective percutaneous coronary angioplasty and stenting. The subjects with the following conditions were excluded from participating in the study- 1) Patients undergoing Emergency Percutaneous coronary intervention, 2) Elevated cardiac troponin - I level (> 0.04 ng/dL) before percutaneous coronary intervention, 3) Patients taking drugs like nicorandil or glibenclamide and 4) Peripheral disease excluding application of the cuff.

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The patients were randomised into the two groups by flick of a coin- "Heads" were allocated to remote ischaemic preconditioning group (Interventional group) and "Tails" were assigned to the non-interventional group. In order to achieve a difference of mean with effect size of 0.8, α-error probability of 0.05 and power of 80% with allocation ratio of 1:1, a sample size of 21 patients in each group of study was derived by sample size software G*power.

The due care was ensured to prevent anginal episodes in the participants in the course of study. In the interventional group, after informed consents a blood pressure cuff was placed around their non-dominant upper arm. The cuff was inflated to 200 mmHg pressure for 5 minutes followed by 5 minutes of deflation to allow reperfusion for 3 cycles. The non-interventional group did not undergo this cycle. Echocardiography was done, and venous blood sample was withdrawn prior to first inflation and 24 hours after coronary angioplasty. The subjects in the two groups were studied for Quantitative Cardiac Troponin-I levels before and 24 hrs. after elective coronary angioplasty as primary variable for outcome. Ejection Fraction (2D Echocardiography) before and 24 hrs. after elective coronary angioplasty in the two group was studied as secondary outcome variable.

The following confounding variables could have played a role in influencing the outcome in the two groups: 1) BP Cuff-to-angioplasty balloon inflation time difference and 2) The angioplasty balloon occlusion time and area of myocardium affected during percutaneous coronary intervention.

Data was analysed using SPSS Version 16.0. Continuous variables were tested for significance using the unpaired t-test and p-value of < 0.05 was considered statistically significant. The statistical tests employed were unpaired t-test, chi-square test and extended Fisher's exact test. The intent was to predict the most affected parameter, remote ischaemic preconditioning procedure.

RESULTS

The baseline characteristics of the two groups were well matched with exception of dominance of male sex [Table 1].

In the 21 non-interventional group patients, the incidence of cardiac troponin-I at 24 hours rise was observed in 19 subjects with 8 (42%) having a troponin-I rise of less than 0.12 ng/mL, another 5 (26%) had troponin-I between 0.12-0.60 ng/mL defining peri-procedural myocardial infarction Type 4a. The troponin-I levels satisfying the WHO definition of myocardial infarction was seen in 6 (32%) of non-interventional subjects. The remote ischaemic preconditioning group had 9 (52%) in Troponin-I, less than 0.12 ng/mL rise group, 4 (24%) in peri-procedural myocardial infarction Type 4a troponin-I rise group and 4 (24%) in WHO defined myocardial infarction group respectively [Table 2].

Characteristic Total (%)	Non-Interventional Group (n= 21)	Interventional Groups (RIPC) (n= 21)	P value
Age			
31-40 Years	2 (9.5)	2 (9.5)	0.2 (NS)
41-50 Years	4 (19.0)	9 (42.9)	
51-60 Years	15 (71.40)	10 (47.6)	
Mean Age	53.19	49.90	0.13 (NS)
Sex			
Female 10 (23.8)	9 (42.9)	1 (4.8)	0.04
Male 32 (76.2)	12(57.1)	20(95.2)	
Diabetes Mellitus			
No 24 (57.1)	13 (61.9)	11 (52.4)	0.378 (NS)
Yes 18 (42.9)	8 (28.5)	10 (47.6)	
Hypertension			
No 27 (64.2)	15 (57.1)	12 (57.1)	0.5 (NS)
Yes 13 (30.9)	6 (0.28)	9 (42.8)	
Smoking/ Tobacco			
No 20 (47.6)	13 (61.9)	7 (33.3)	0.061 (NS)
Yes 22 (52.4)	8 (38.17)	14 (66.7)	
Alcohol			
No ()	17 (81.0)	10 (47.6)	0.026
Yes ()	4 (19.0)	11 (52.4)	
Creatinine	19	17	0.423 (NS)
Coronary Vessels			
SVD 9 (21.4)	3 (14.3)	6 (28.6)	0.2 (NS)
DVD 31 (73.8)	16 (76.2)	15 (71.4)	
TVD 2 (4.8)	2 (9.5)	0 (0)	

Table 1. Baseline Characteristics in the Two Groups

Variable	Non-Interventional Group (n= 21)	Remote Ischaemic Preconditioning (n= 21)	Total (n=42)
Post-PCI cardiac troponin-I (median), ng/mL	0.17 (0.00-9.04)	0.11 (0.03-8.03)	
Cardiac troponin-I < 0.04 ng/mL, n (%)	2	4	6
Incidence of MI, n	N= 19	N= 17	
No MI (< 0.12 ng/mL)	8 (42%)	9 (52%)	17 (47%)
MI4a (0.12 - 0.60)	5 (26%)	4 (24%)	9 (25%)
WHO defined MI (> 0.60 ng/mL)	6 (32%)	4 (24%)	10 (28%)

Table 2. Incidence of Ischaemic event post-PCI between Study Groups at 24 Hours

Biomarker Parameter	Group	No.	Median	Range	Z	P value
Troponin-I Pre-plasty						
	Non-Interventional	21	0.03	0.00-0.04	-0.724	0.57 (NS)
	RIPC	21	0.02	0.00-0.04		
Troponin-I Post-plasty						
	Non-Interventional	19	0.17	0.00-9.04	-0.793	0.36 (NS)
	RIPC	17				

Table 3. Comparison of Trop-I Post-PCI between Study Groups at 24 Hours (Paired T-Test)

Echo Parameter	Group	No.	Mean	SD	SE	T	P value
LVEF Pre-plasty							
	Non-interventional	21	47.86	8.88	1.94	0.09	0.93 (NS)
	RIPC	21	47.62	8.46	1.85		
LVEF Post-plasty							
	Non-interventional	19	46.32	8.95	2.05	-1.26	0.22 (NS)
	RIPC	17	50.00	8.48	2.06		

Table 4. Comparison of LV Function by Echocardiography Post-PCI between Study Groups at 24 Hours (Paired T-Test)

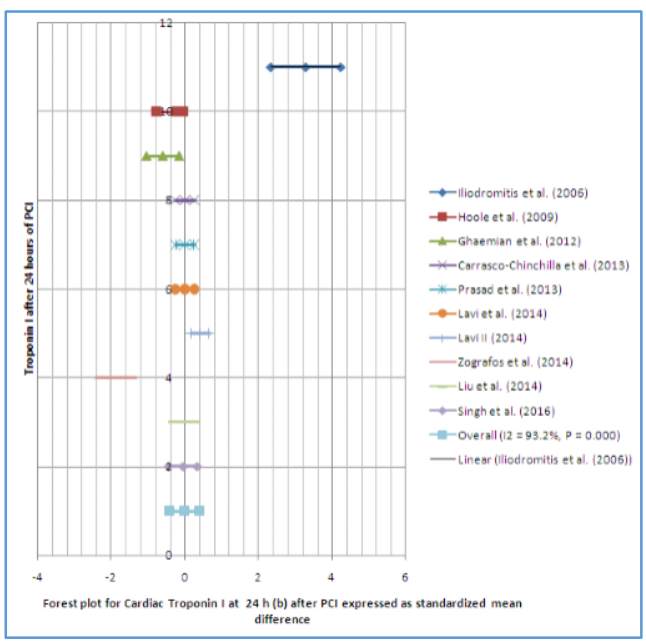

Figure 1. Forest Plot for Cardiac Troponin-I at 24 Hours in 10 Trials

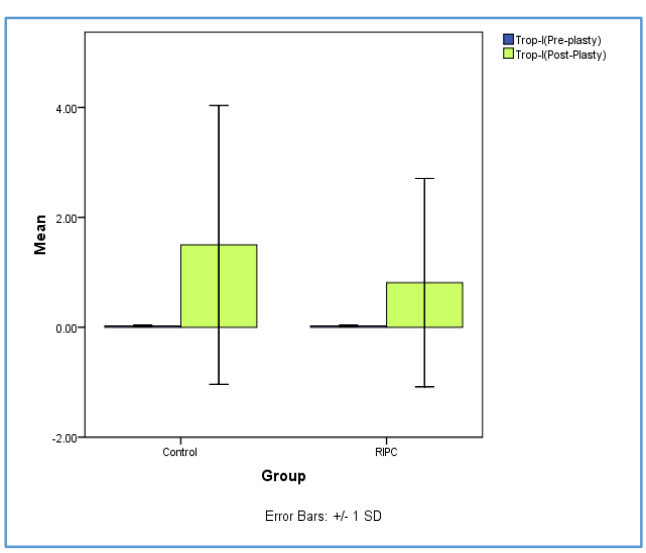

Figure 2. Comparison of Troponin-I Post-PCI between Study Groups at 24 Hours

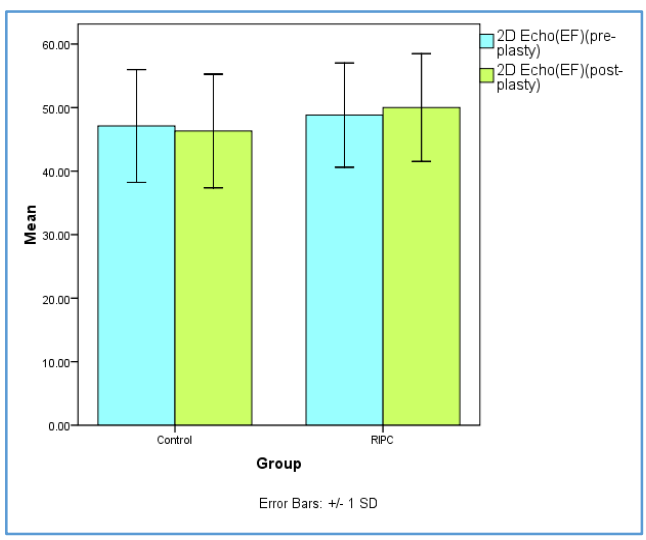

Figure 3. Comparison of Ejection Fraction on 2D Echocardiography between Study Groups at 24 Hours

DISCUSSION

This study of Evaluation of Biochemical (Troponin-I) and Echocardiographic outcomes of remote ischaemic preconditioning in patients undergoing Elective Coronary Angioplasty was conducted in Department of Medicine, Dr. BRAM Hospital, Raipur (CG) from March 2016 - Sept. 2017. A total of 42 patients (21 in remote ischaemic preconditioning group and 21 in non-interventional group each after randomisation) were enrolled in this study who were admitted in cardiac catheterisation laboratory for elective angioplasty. The two groups were matched for risk factors for age, incidence of diabetes, renal function, smoking and alcohol habituation, and the distribution of coronary artery disease.

In our study, out of 42 patients 6 (17%) patients had post-PCI Troponin-I < 0.04 ng/mL, 17 (47%) patients had post-PCI Troponin-I level < 0.12 ng/mL, while 19 (53%) patients had post-PCI Troponin-I level > 0.12 ng/mL (MI4a). Also, in non-interventional group 11 (57%) patients had peri-procedural MI, while in remote ischaemic preconditioning group 8 (47%) patients had peri-procedural MI [Table 2]. This observation shows that no significant difference was observed between two groups regarding troponin-I at pre-PCI or post-PCI interval, though the increase in Trop-I in non-interventional group was found to be higher in post plasty

individuals (z= -0.793 compared to z= -0.724 pre-plasty) [Table 3 and Figure 2].

There are 10 studies in a meta-analysis of 13 trials that reported the cardiac troponin-I levels at 24 hrs. after percutaneous coronary intervention to have no significant difference between the remote ischaemic preconditioning group and the non-interventional group (SMD−0.11; 95% CI: −0.48–0.27; = 0.585) with significant heterogeneity (<0.001, 2 = 92.6%)[2] [Figure 1].

A study was performed by Theodoros A Zografos (2014) to assess the ability of a brief remote ischaemic preconditioning protocol to attenuate cardiac troponin-I release after ad hoc percutaneous coronary intervention. 94 patients undergoing ad hoc percutaneous coronary intervention for stable coronary artery disease with undetectable pre-procedural cardiac troponin-I were recruited and randomised to receive remote ischaemic preconditioning (induced by one 5-minute inflation of a blood pressure cuff to 200 mmHg around the upper arm) or non-interventional group after the decision for percutaneous coronary intervention was made. The primary outcome was the difference between cardiac troponin-I levels 24 hours after percutaneous coronary intervention and cardiac troponin-I levels before coronary angiography (Cardiac troponin-I). Cardiac troponin-I in the remote ischaemic preconditioning group was significantly lower compared with the non-interventional group (0.04 ng/mL [interquartile range 0.01 to 0.14] vs 0.19 ng/mL [interquartile range 0.18 to 0.59], p < 0.001). The incidence of percutaneous coronary intervention-related myocardial infarction (MI) was greater in the non-interventional group (42.6% vs 19.1%) (p=0.014).[6]

In our study also, the incidence of percutaneous coronary intervention-related MI was greater in non-interventional group (57% vs 47%), but this was statistically insignificant. In conclusion, study's results suggest remote ischaemic preconditioning immediately before ad hoc percutaneous coronary intervention does not attenuate peri-procedural cardiac troponin-I release nor reduces the incidence of type 4a MI. In present study there was no significant difference in post-PCI troponin-I between two groups, but increase in troponin-I in non-interventional group was higher than remote ischaemic preconditioning group individuals (z=-0.793 compared to z=-0.724 pre-plasty).

Analysis of Ejection Fraction on 2D Echocardiography between Study Groups at different Time Interval

In the present study before angioplasty mean EF in non-interventional group was 47.86%, while in remote ischaemic preconditioning group it was 46.32%. The repeat left ventricular ejection fraction estimation after 24 hours angioplasty showed mean EF in non-interventional group of 46.32%, while in remote ischaemic preconditioning group it was 50%. This had no significant difference between two groups regarding 2D Echo EF, either pre-PCI or post-PCI, but increase in EF was higher in post-PCI remote ischaemic preconditioning subjects compared to pre-PCI (t= -1.26 compared to t= 0.09 pre-PCI) [Table 4 and Figure 3].

Stephen Hoole et al conducted study on 42 patents to study effect of remote ischaemic preconditioning on LV function on coronary occlusion and found that remote ischaemic preconditioning did not diminish the degree of ischaemic LV dysfunction during coronary balloon occlusion (59.2 (2.8) vs 62.8 (2.8), p= 0.15) and there was evidence of cumulative LV dysfunction despite remote ischaemic preconditioning [ejection fraction (EF) %: 54.3 (5.8) vs 44.9 (3.7), p= 0.03]. Remote ischaemic preconditioning did not improve contractile recovery during reperfusion (EF, %: 51.7 (3.6) vs 51.5 (5.7), p= 0.88 and 55.6 (2.8) vs. 56.0 (2.0), p=0.85).[7] In our study, there was no significant difference in post-PCI 2D echo EF in both groups, but increase in EF was higher in post-PCI remote ischaemic preconditioning subjects compared to pre-plasty (t= -1.26 compared to t= 0.09 pre-plasty).

Limitations of the Study

The study subjects are stable coronary patients undergoing elective percutaneous coronary intervention that may diminish difference in the rise of troponin, so prevent analysis of impact of remote ischaemic preconditioning. The use of high sensitive cardiac troponin might have proved useful in minute changes in these stable coronary patients.

CONCLUSION

The heterogeneity of measurable outcomes of remote ischaemic preconditioning seen in previous various studies was disfavoured by our study, which concluded that the remote ischaemic preconditioning yields no significant benefits in biochemical and echocardiographic outcomes in patients undergoing elective percutaneous interventions.

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