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Effect of remote ischemic Pre-conditioning on primary percutaneous coronary intervention outcomes: a randomized clinical trial

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Abstract

Background: Remote ischemic preconditioning (RIPC) is a simple non-invasive method by using cycles of ischemia and reperfusion on a remote organ.

Objective: To determine the effect of RIPC outcomes in patients with ST-segment-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

Methods: This double blind randomized clinical trial was conducted in two teaching and reference hospitals in Mashhad, Iran. Sixty patients with acute STEMI were enrolled from October 2018 to January 2019. The patients were allocated into two groups, by using sealed envelope randomization i.e., a study group of patients who had undergone RIPC intervention and a control group of patients who had not undergone RIPC. Half an hour before PPCI, a sphygmomanometer cuff was placed around the left upper arm and inflated up to 200mmHg for five minutes; then the cuff was deflated for another five minutes, and this cycle was repeated 3 times before or during PPCI. Corrected Thrombolysis in Myocardial Infarction (TIMI) frame count, ST-segment resolution, reperfusion arrhythmias and contrast induced nephropathy (CIN) were evaluated in both groups after PPCI. Study data was analyzed by SPSS version 16.

Results: A total number of 26 males and 14 females were studied in study groups (n=20 for each). Both groups were homogenous according to their baseline characteristics. Both TIMI grade and Corrected Thrombolysis in Myocardial Infarction Frame Count CTFC significantly improved after RIPC ($p=0.001$ and $p<0.0001$ respectively). Moreover, CIN and reperfusion arrhythmias were reduced in the intervention group ($p=0.028$ and $p=0.016$ respectively). Also, ST-segment resolution was significantly different among groups ($p=0.002$). After adjusting for baseline factors only a significant relationship was observed between performing intervention and final TIMI grade (OR=26.416, 95% CI for OR=1.063, 656.184, $p=0.046$).

Conclusion: RIPC can effectively reduce CIN and reperfusion arrhythmias in patients undergoing PPCI. Also, RIPC improved ST segment resolution and TIMI flow grade, and corrected TIMI frame count. Based on our results, RIPC may have a protective effect of on PPCI outcomes.

Trial registration: The trial was registered at the Iranian Clinical Trial Registry (IRCT) (http://www.irct.ir) with the IRCT identification number IRCT20150614022713N2.

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Abbreviations / Acronyms:
ACE: Angiotensin Converting Enzyme; **ARB:** Angiotensin Receptor Blockers; **AIVR:** Accelerated Idioventricular Rhythm; **ATP:** Adenosine Triphosphate; **CABG:** Coronary Artery Bypass Grafting; **CAD:** Coronary Artery Disease; **CCB:** Calcium Channel Blockers; **CI:** Confidence Interval; **CIN:** Contrast Induced Nephropathy; **CTFC:** Corrected Thrombolysis in Myocardial Infarction Frame Count; **HF:** Heart Failure; **IQR:** Interquartile Range; **LAD**: Left Anterior Descending Artery; **LCX:** Left Circumflex Artery; **LVEF:** Left Ventricular Ejection Fraction; **MDRD:** Modification of Diet in Renal Disease; **OR:** Odds Ratio; **PCI:** Percutaneous Coronary Intervention; **PPCI:** Primary PCI; **RCA:** Right Coronary Artery; **RIPC:** Remote Ischemic Pre-conditioning; **ROS:** Reactive Oxygen Species; **SBP:** systolic blood pressure; **STEMI:** ST Segment Elevation Myocardial Infarction; **TIMI:** Thrombolysis in Myocardial Infarction

1. Introduction

Appropriate perfusion of an organ is mandatory for its survival and any disruption in tissue perfusion may further result in organ dysfunction. Occlusion of coronary vessels during an atherosclerosis process or thromboembolism will result in cardiac tissue mal-perfusion and develop ischemia and infarction. The prevalence of myocardial infarction depends on age and rises from 0.06% in men younger than 45 to 12.8% in those who are older than 75 years old (1, 2). There are different strategies available for treating MI, which are applicable according to patient condition and the experience of the health care providers. These strategies include drugs therapies, thrombolytic therapy, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) (3). Primary PCI (PPCI) is a reperfusion therapy which is performed in patients who usually have ST segment elevation MI (STEMI) at early stages of cardiac symptom onset (4). The basic concept of reperfusion therapies is resolving hypoxia and hypo-perfusion of myocardium. However, the reperfusion is not always a harmless process (5). During an ischemic state, usually metabolic acidosis develops because of anaerobic metabolism and ischemia injury will occur. After re-establishment of blood supply, reactive oxygen species (ROS) production and local inflammation increases secondary injury. Ischemia reperfusion injury may end up in apoptosis, necrosis and autophagy in sever state while moderate injury may induce active recovery in order to survive and control ROS (5, 6). Various preventive strategies have been proposed for decreasing reperfusion injury. Remote ischemic pre-conditioning (RIPC) is a recently proposed non-pharmacological method for prevention of reperfusion injury and other complications of PPCI (7-9). During RIPC, short and consecutive cycles of ischemia and reperfusion are applied to the body organ. This procedure will result in releasing of different chemokines and hormones to the bloodstream (10, 11). Although various benefits, regardless of cardio-protection, including “renoprotective” effects have been reported for RIPC in patients undergoing elective PCI, the efficacy of RIPC in patients undergoing cardiac interventions including PPCI is controversial in the literature (10-13, 16). Some studies have reported that RIPC may not even be effective in reducing cardiac troponin and C-reactive protein while others have provided conflicting results (17-19). Regarding such controversial results and the lack of enough data regarding the use of RIPC in PPCI, the aim of this study was to evaluate the effect of RIPC intervention on PPCI outcome after ST elevation myocardial infarction (STEMI) patients undergoing PPCI.

2. Material and Methods

2.1. Study Design

This randomized clinical trial was carried out (from October 2018 to January 2019) on STEMI patients undergoing PPCI who were referred to the cardiology departments of Imam Reza Hospital and Ghaem hospital in Mashhad, Iran.

2.2. Sampling and blinding

Based on the previous study of CTFC and by considering the power of 80% and significance level of 95, the study sample size was calculated as 60 patients (8). The study population was divided by a blinded researcher into 2 groups according to sealed envelope randomization. Both the intervention and control group received PPCI while the intervention group also received the intervention described below.

2.3. Inclusion and exclusion criteria

STEMI patients who were older than 20 years old and whose symptoms began within 12 hours before admission were included in the present study. Patients with cardiogenic shock and kidney transplant or undergoing dialysis as well as patients who underwent imaging study with contrast agent within a week before admission were excluded from the study. Moreover, those patients who were not able to tolerate cuff inflation for 5 minutes were excluded from participating in the study. Other exclusion criteria included primary Thrombolysis in Myocardial Infarction (TIMI) flow 2 or 3, Rentrop grade greater than 1, left main coronary artery disease requiring coronary artery bypass graft, and cardiac arrest after PPCI. The last exclusion criteria in PPCI setting was No-Reflow. No-Reflow is a serious complication with potentially grave consequences. This Phenomenon and its treatment by Adenosine or sodium Nitroprusside is a major confounding factor on the endpoints such as final TIMI flow and CTFC. Therefore, STEMI patients with No-Reflow during PPCI were excluded.

2.4. Interventions

Since activation of PPCI team and approximately half an hour before PPCI, blood pressure cuff was fastened around the patient's arm. Application of RIPC was done by a Cath-lab nurse who was blinded and unaware of the RIPC procedure and study protocol. The cuff held about 200 mmHg for 5 minutes, and then the cuff was deflated for 5 minutes and this cycle was repeated four times. In some patients in order not to delay the PPCI procedure, intervention continued during the procedure. All patients received 300 mg of Aspirin and 600 mg of clopidogrel prior to PPCI. Angiography and angioplasty were done from femoral or radial approach. Each patient received 50-70 U/kg or 70-100 U/kg unfractionated heparin if integrilin was or was not used respectively. Integrilin or thrombosuction was used according to European Society of Cardiology 2017 guidelines (20). Each patient received 320 mg/ml Visipaque (GE Healthcare, Ireland). Serum creatinine of all patients was recorded at baseline, 24 and 48 hours after PPCI and glomerular filtration rate (GFR) was calculated by Modification of Diet in Renal Disease (MDRD) method (21). For all patients, the contrast agent Visipaque (TM 320mg/ml, GE Healthcare, Ireland) was used. No one received nephrotoxic drugs such as non-steroidal anti-inflammatory drugs and aminoglycosides before coronary angiography and/or angioplasty.

2.5. Baseline variables

Before the intervention, baseline patient information including age and gender was obtained. Then, the past medical history including diabetes mellitus, hypertension, dyslipidemia, heart disease and related health interventions as well as history of recently used medications including aspirin, clopidogrel, statin, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), as well as beta blockers and calcium channel blockers (CCB) were recorded. Hematological tests including measurement of hematocrit, hemoglobin, fasting blood sugar, hemoglobin A1c (HbA1c), total cholesterol, triglycerides (TGs), low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), serum creatinine and calculation of estimated glomerular filtration rate (eGFR) by MDRD Equation (Modification of Diet in Renal Disease) were performed. Anemia, diabetes mellitus and dyslipidemia were recorded by the same criteria as our previous study (22, 23). Each patient underwent transthoracic echocardiography before PPCI and Left Ventricular Ejection Fraction (LVEF) was recorded. The patients were then divided in to two groups and the amounts of contrast agent used in angiography were recorded for each patient.

2.6. Outcomes

Primary study outcomes were TIMI flow grading, CTFC, ST-segment resolution and reperfusion arrhythmias. The secondary outcome was Contrast induced nephropathy (CIN). Contrast induced nephropathy was defined as absolute increase in serum creatinine for 0.3 mg/dL within 2 days of exposure to contrast agent. As well as CIN, TIMI flow grading and corrected TIMI frame count (CTFC), ST segment resolution was also considered after procedure. In the present study, Corrected TIMI Frame Count (CTFC) was considered as dividing left anterior descending artery TIMI frame count by 1.7 (23). A baseline and post PCI 12-lead electrocardiogram was obtained from patients in order to determine ST segment resolution 30 minutes post-PCI. The percentage of ST-segment resolution was considered with regard to the lead with maximal ST segment elevation at baseline as less than 50 % resolution, 50 to 70% resolution and greater than 70 % resolution. Reperfusion arrhythmias (including ventricular fibrillation, sustained ventricular tachycardia, atrial fibrillation, sinus tachycardia, non-sustained ventricular tachycardia, accelerated idioventricular rhythm, sinus bradycardia, and high grade atrioventricular block) were recorded within 24 hours post-PCI.

2.7. Ethics of research

This study was approved by the ethics committee of Mashhad University of Medical Sciences (Ref: IR.MUMS.MEDICAK.REC.1397.340) and all patients were informed of the project content before entering the study. Informed consent was obtained from all participants and privacy and confidentiality of the patients' information were considered in the study. The study was registered at the Iranian Clinical Trial Registration Center (IRCT Code: IRCT20150614022713N2. The code can be validated on http://www.irct.ir).

2.8. Statistical analysis

Study data was analyzed using the statistical package for social sciences (SPSS) software version 16. The normality distribution of continuous variables was checked using the Shapiro-Wilk test. Normally distributed variables were presented as mean and standard deviation (SD) while non-normally distributed variables were presented using median and interquartile range (IQR). Independent t-test was used to compare normally distributed variables between groups while the Mann-Whitney test was used for comparison of non-normally distributed variables. Chi-square and Fisher's exact tests were used to compare distribution patter of categorical variables between groups. As the outcome measures were categorical, the binary logistic regression was performed to assess the relationship between outcome measures and the allocated group. Univariate logistic regression was first used to assess the relationship between type of intervention and outcome variables then multivariate logistic regression was performed to assess the relationship between type of intervention and outcome variables after adjusting for age, baseline heart rate and systolic blood pressure. The odds ratio (OR) and 95% confidence interval (CI) for OR were reported for logistic regression analyses. The level of significance was considered as $p<0.05$. The Cohen's d ranged from 0.2 (small effect) to 0.7 (medium effect) for the t-test while the effect size ranged from 0.07 (small effect size) to 0.30 (medium effect size) and ranged from 1.14 to 1.30 for univariate and 1.14 for multivariate logistic regression analysis, which all indicate small effect size.

3. Results

3.1. Baseline characteristics

Statement flow diagram is illustrated in Figure 1. During the study period, 100 patients with STEMI undergoing PPCI were considered in the present study. Among them, 60 subjects were considered eligible to enter the study according to the inclusion criteria and willingness of patients. Twenty patients were excluded according to the exclusion criteria (Figure 1). The patients who were excluded were referred to another treatment service and therefore their medical information was also transferred and was not accessible by the researchers and was not included in the present study. The mean (standard deviation) age of patients was 59.6 (10.7) years and most of the patients were male (65%). The patients' demographic data has been summarized in Table 1.

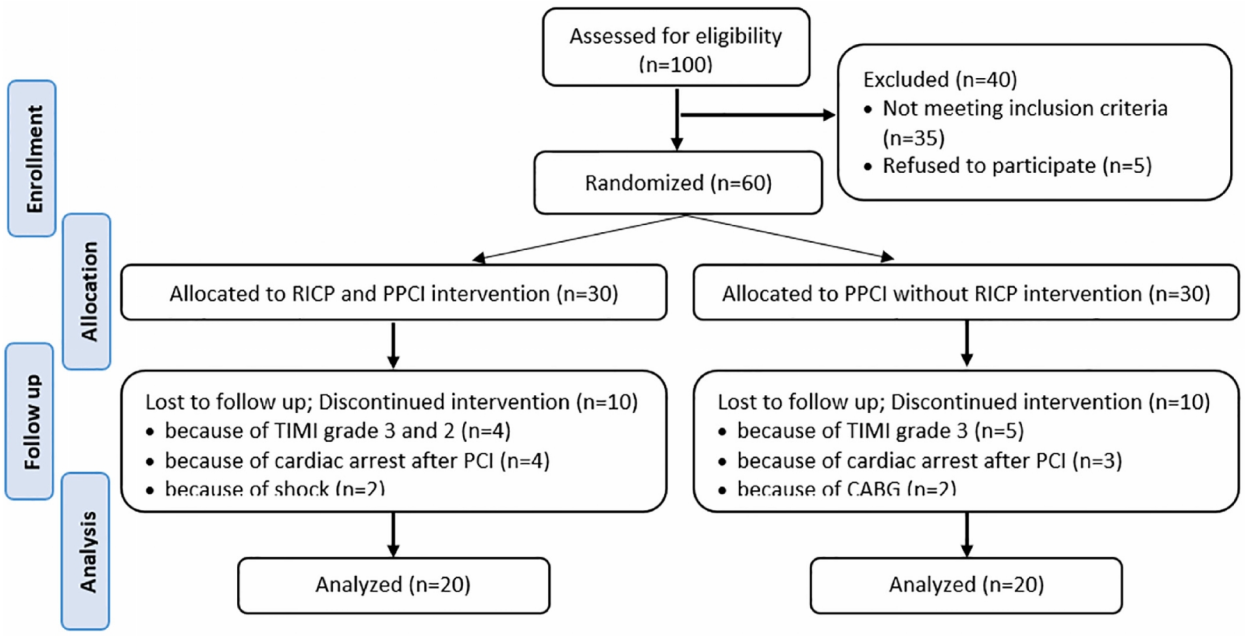

Figure 1. Study flow diagram (CONSORT 2010)

3.2. The outcomes that were studied

According to Chi-square test findings in the present study results, patients undergoing RIPC had a significantly lower CIN in contrast to those who had not received this intervention (χ^2 (df=1)= 4.80, p=0.028). Also, those patients who received RIPC showed lesser reperfusion arrhythmias (χ^2 (df=1) = 5.76, p=0.016). TIMI grade was not different among the study groups (Fisher's exact test, P=0, 50). The intervention group with RIPC experienced greater ST segment resolution (χ^2 (df=2) = 12.13, p=0.002). Reperfusion arrhythmia was more common in the control group compared to the RIPC group (χ^2 (df=3) = 5.75, p=0.016). The most common reperfusion arrhythmia was AIVR (13 patients, 32.5%) followed by non-sustained ventricular tachycardia in combination with AIVR (4, 10.0%). Although sinus bradycardia was only observed in the control group, there was no significant difference in the distribution pattern of reperfusion arrhythmias between groups (χ^2 (df=3) = 2.05, p=0.562).

Table 1. Baseline Demographic and Epidemiological and Clinical Data

Variable		Study groups			p-value
		PPCI (n=20)	PPCI (n=20)+ RIPC (n=20)	Total (n=40)	
		57.50 (14.000)	60.45±11.610	59.60±10.777	
Gender	Male n (%)	12 (60)	14 (70)	26 (65)	0.440[b]
	Female n (%)	8 (40)	6 (30)	14 (35)	
Baseline HR (bpm)		81.65±12.407	79.00±13.534	80.33±12.885	0.552[a]
Baseline SBP (mmHg)		141.25 (26.699)	146.50 (31.544)	143.88±28.967	0.620[C]
Hospitalization Time (days) (SD)		3.00 (1.000)	4.00 (1.000)	3.4±0.928	0.221[c]
Door to Balloon (min)		52.50 (33.000)	60.00 (30.000)	58.00 (28.00)	0.862[c]
Pain to Balloon Time (h) (%)	< 6 h	80	80	80	<1.000[b]
	6-12 h	20	20	20	
History of CAD, n (%)	No	16 (80)	17 (85)	33 (82.5)	0.173[b]
	Yes	4 (20)	3 (15)	7 (17.5)	
History of PCI, n (%)	No	15 (78.9)	17 (85)	32 (82.1)	0.242[b]
	Yes	4 (21.1)	3 (15)	7 (17.9)	
History of CABG, n (%)	No	20 (100)	20 (100)	40 (100)	<1.000[d]
	Yes	-	-	-	
History of MI, n (%)	No	19 (95)	20 (100)	39 (97.5)	<1.000[d]
	Yes	1 (5)	-	1 (2.5)	
Pre-Infarctional Angina, n (%)	No	13 (65)	12 (60)	25 (62.5)	0.107[b]
	Yes	7 (35)	8 (40)	15 (37.5)	
Family History of CAD, n (%)	No	16 (84.2)	18 (90)	34 (87.2)	0.661[d]
	Yes	3 (15.8)	2 (10)	5 (12.8)	
Hypertension, n (%)	No	9 (45)	9 (45)	18 (45)	<1.000[b]
	Yes	11 (55)	11 (55)	22 (55)	
Dyslipidemia, n (%)	No	13 (65)	13 (65)	26 (65)	<1.000[b]
	Yes	7 (35)	7 (35)	14 (35)	
Diabetes, n (%)	No	15 (75)	13 (65)	28 (70)	0.731[d]
	Yes	5 (25)	7 (35)	12 (30)	
Active Smoker, n (%)	No	20 (100)	17 (85.0)	33 (82.5)	<1.000[d]
	Yes	4 (20)	3 (15)	7 (17.5)	
Addiction, n (%)	No	17 (85)	18 (90)	35 (87.5)	<1.000[d]
	Yes	3 (15)	2 (10)	5 (12.5)	
Out of Hospital cardiac arrest	No	20 (100)	20 (100)	40 (100)	<1.000[d]
	Yes	-	-	-	
History of HF, n (%)	No	19 (100.0)	18 (94.7)	37 (97.4)	<1.000[d]
	Yes	0 (.0)	1 (5.3)	1 (2.50)	

a: t-test test, b: Chi-square test, c: Mann-Whitney U test; d: Fisher's exact test. PPCI: Primary percutaneous Coronary Intervention; RIPC: remote ischemic pre-conditioning; PCI: percutaneous coronary intervention; CAD: coronary artery disease; HR: Heart rate; SBP: systolic blood pressure; CABG: coronary artery bypass graft; HF: heart failure; MI: myocardial infarction

3.3. Comparison of variables between study groups

The two groups were comparable with each other in terms of gender, age, laboratory findings, past medical history, echocardiography findings. Receiving acetylsalicylic acid (χ^2 (df=2) = 2.67, p=0.102), clopidogrel (Fisher's exact test, p=0.500), ACE inhibitors (Fisher's exact test, p=1.000), ARB (Fisher's exact test, p=1.000), statins (Fisher's exact test, p=0.480), and beta blockers (Fisher's exact test, p=1.000). Calcium channel blocker (CCB) was not prescribed for patients in either group (data is not shown in Table 1). Among the study groups, after PPCI, only reperfusion arrhythmia (χ^2 (df=1) = 5.76, p=0.016), CIN (χ^2 (df=1) = 4.80, p=0.028) and ST segment resolution (χ^2 (df=2) = 12.13, p=0.002) were significantly different (Table 2).

Table 2. Clinical characteristics of study participants in study groups.

Variable		Total (n=40)	PPCI (n=20)+RIPC	PPCI (n=20)	χ^2/U	p-value
LVEF	Less than 30%, n (%)	13 (32.5)	5 (25)	8 (40)	1.052	0.591
	31 to 44%, n (%)	25 (62.5)	14 (70)	11 (55)		
	45 to 55%, n (%)	2 (5)	1 (5)	1 (5)		
Reperfusion Arrhythmias, n (%)	No	19 (48.7)	13 (68.4)	6 (30)	5.757	0.016
	Yes	20 (51.3)	6 (31.6)	14 (70)		
Types of reperfusion arrhythmia n (%)	AIVR	13 (32.5)	4 (66.7)	9 (64.3)	2.051	0.562
	Non sustained ventricular tachycardia	1 (2.5)	0 90.0)	1 (7.1)		
	Sinus bradycardia	2 (5.0)	0 (0.0)	2 (14.3)		
	Non sustained ventricular tachycardia and AIVR	4 (10.0)	2 (33.3)	2 (14.3)		
Access	Radial	18 (45)	10 (50)	8 (40)	0.404	0.525
	Femoral	22 (55)	10 (50)	12 (60)		
Infarcted related artery	LAD	26 (65)	14 (70)	12 (60)	1.154	0.327
	LCX	4 (10)	1 (5)	3 (15)		
	RCA	10 (25)	5 (25)	5 (25)		
MI location	Anterior	25 (62.5)	14 (70)	11 (55)	0.960	0.327
	Inferior-lateral	15 (37.5)	6 (30)	9 (45)		
Vessel disease	Single vessel disease	20 (50)	9 (45)	11 (55)	0.420	0.311
	Two vessel disease	13 (32.5)	7 (35)	6 (30)		
	three vessel disease	7 (17.5)	4 (20)	3 (15)		
Final TIMI flow	2	8 (20.0)	3 (15)	5 (25)	12.379	0.001[a]
	3	32 (80.0)	17 (85)	15 (75)		
Integrillin use	No	12 (30)	6 (30)	6 (30)	<0.0001	1.00
	Yes	28 (70)	14 (70)	14 (70)		
CIN, n (%)	No	30 (75)	18 (90)	12 (60)	4.800	0.028[a]
	Yes	10 (25)	2 (10)	8 (40)		
Mean CTFC (SD)		15.27±6.699	11.20±4.324	19.35±6.201	4.821	<0.0001[b]
Mean contrast volume		156.00 (58.000)	185.00 (94.000)	168.00±47.969	153.000	0.211 [c]
ST segment resolution, n (%)	<50%	17 (42.5)	4 (20)	13 (65)	12.133	0.002
	50-70%	4 (10)	1 (5)	3 (15)		
	>70%	19 (47.5)	15 (75)	4 (20)		

a: Fisher exact test; b: independent-samples t-test; c: Mann-Withney U test; LVEF: left ventricular ejection fraction; AIVR: Accelerated Idioventricular Rhythm; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; MI: myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction; CIN: contrast induced nephropathy; CTFC: corrected Thrombolysis in Myocardial Infarction frame count

3.4. Relationship between type of intervention and outcome measures

The univariate regression analysis revealed a significant relationship between the intervention group and final TIMI grade (OR=20.408, 95% CI for OR= 1.028, 405.023, p=0.048) and reperfusion arrhythmias (OR=0.072, 95% CI for OR= 0.006, 0.934, p=0.044). The multivariate regression adjusted for age, baseline heart rate and systolic blood pressure revealed only a significant relationship between the intervention group and final TIMI grade (OR=26.416, 95% CI for OR=1.063, 656.184, p=0.046). Performing RIPC was associated with higher final TIMI grades (p=0.046); however, reperfusion arrhythmia was not associated with intervention (p=0.077) (Table 3).

Table 3. Relation between the intervention group and outcome variables before and after adjusting for age, baseline heart rate and systolic blood pressure

Variable	Univariate analysis				Multivariate analysis			
	p-value	OR	95% CI for OR		p-value	OR	95% CI for OR	
			Lower	Upper			Lower	Upper
Initial TIMI grade	0.460	0.436	0.049	3.916	0.783	0.706	0.060	8.358
Final TIMI grade	0.048	20.408	1.028	405.023	0.046	26.416	1.063	656.184
ST resolution								
<50%	0.613	0.379	0.009	16.233	0.458	0.236	0.005	10.663
50-70%	0.107	6.391	0.672	60.809	0.096	9.358	0.671	130.542
Reperfusion arrhythmias	0.044	0.072	0.006	0.934	0.077	0.091	0.006	1.294
CIN	0.853	0.795	0.071	8.912	0.691	0.584	0.041	8.248

OR: Odds ratio; ST resolution >70% was considered as reference variable; TIMI: Thrombolysis in Myocardial Infarction; CIN: contrast induced nephropathy

4. Discussion

To the best of our knowledge, the present pilot study is the first of its kind that has been conducted in our country. The present clinical trial was performed to investigate the effect of RIPC intervention on reperfusion injury among patients with STEMI undergoing PPCI. We have demonstrated that performing RIPC for STEMI patients undergoing PPCI will reduce CIN, arrhythmia as well as ST segment resolution. Although the effect sizes of our study were small and medium, we can expand our results to a more general population, but still further larger clinical trials are needed. In our previous study, we have demonstrated the relation between RIPC and risk of CIN in patients undergoing angiography or angioplasty (23). The reperfusion injury can be categorized into 4 groups which are reperfusion arrhythmias, myocardial stunning, lethal myocardial injury and microvascular damage (24). At the time of reflow, many cells will sustain irreversible damage because of metabolic and ion disturbances (24). Cardiac arrhythmia is the best indicator of reperfusion injury while it is easy and inexpensive to measure. It has been demonstrated that reperfusion arrhythmia and injury are not different among PPCI and thrombolytic therapy (25). Thrombolytic therapy has a significantly higher rate of Accelerated Idioventricular Rhythm (AIVR) and atrial fibrillation in contrast to PPCI, while the prevalence of other arrhythmias did not differ significantly (25). The most common cause of reperfusion arrhythmia is Delayed afterdepolarization (DAD) (26). The calcium overload within the cardiac cell, because of calcium inflow or release by endoplasmic reticulum, is responsible for DAD in cardiac tissue. The self-sustaining rhythmic activity of the heart will occur when the threshold reaches depolarization and a spontaneous action potential occurs. These oscillations of cardiac cells membrane potentials appear after repolarization, which will further result in arrhythmias, especially AIVR. Furthermore, reduction in Adenosine triphosphate (ATP) which is a result of excessive intracellular calcium is also responsible for further arrhythmias because of closure of potassium ATP dependent channels and shortened action potentials (26). There are numerous cardio-protective approaches available to prevent reperfusion injury, which can be categorized into post-conditioning and peri-conditioning. The post-conditioning, which has not been evaluated in the present research, will be performed by use of pharmaceutical agents or angioplasty (27). The peri-conditioning, which has been evaluated in the present research, is usually applied by performing cyclic ischemia and reperfusion in remote organs (28). Decrease in intracellular calcium and oxidative stress as well as delaying in restoration of neutral PH and preventing neutrophil accommodation are possible explanations for the effect of peri-conditioning on the human heart (29). Recent clinical trials evaluated the effect of RIPC on patients undergoing PPCI. White et al. reported that RIC prior to PPCI can reduce MI size and myocardial edema. Our study did not evaluate infarction size by cardiac magnetic resonance imaging, as similar to White et al.'s study. Although as similar to our study, they have used RIPC in upper extremities, their sample size was much greater than our study (9). Also, RIPC in the lower extremities has been considered effective in reducing enzymatic infarct size as well as improvement of ST resolution

in patients with STEMI undergoing PPCI (8). Furthermore, performing RIPC in STEMI patients undergoing PPCI has been reported to be effective in improving long-term clinical outcomes. Sloth et al. conducted the first trial about the long-term effect of RIPC on patients undergoing PPCI. They have demonstrated that major adverse cardiac and cerebrovascular events could be affected by RIPC after STEMI (7). Rentoukas et al. have performed a similar trial on patients undergoing PPCI. In agreement with our results but with greater sample size, they have demonstrated that morphine along with RIPC during PPCI can prevent reperfusion injury (30). Along with the additive effect of morphine on RIPC, and similar to our study, this study has demonstrated that RIPC can also provide better ST segment resolution. Also, a recent meta-analysis has reported that RIPC can be effective in reducing biomarker release and provide better ST segment resolution (31). This meta-analysis has evaluated post, pre and peri-conditioning while our study was conducted by preconditioning. This meta-analysis confirmed our findings regarding the positive effect of ischemic conditioning on ST segment resolution in STEMI patients. Our present study also demonstrated that patients undergoing RIPC may have reduced arrhythmias. The effect of RIPC on arrhythmias in STEMI patients undergoing PPCI was not widely discussed in the literature. Another study which was conducted by Healy et al. on patients undergoing major vascular surgery demonstrated that preconditioning would not significantly affect post procedure arrhythmias (32).

Regardless of the positive effect of RIPC on reperfusion arrhythmias and ST segment resolution, we have also found that CIN can be affected by RIPC. According to our results, the CIN can be significantly affected by performing RIPC before PPCI. Previously, we reported the incidence of CIN as 17.6% while in the present study 40% of our control population undergoing PPCI have developed CIN (23). The exact mechanism behind the renal protection of RIPC is not clearly understood. However, it has been reported that RIPC can develop its effect on kidneys in two different ways; generating nitric oxide/nitrate and release of damage associate proteins, and inducing cell cycle arrest in kidneys (33). Nitric oxide generation and vasodilatation can prevent renal vasoconstriction, while damaged associate proteins will further prevent cell death and therefore prevent renal injury (33). Moreover, recent meta-analyses about the efficacy of RIPC has demonstrated that this intervention can reduce the incidence of AKI and MI in patients undergoing PCI (34, 35). Bei et al. have evaluated 10 randomized clinical trials which have evaluated the effect of RIPC in patients undergoing PCI or coronary angiography (36). They have revealed that RIPC is effective for reducing contrast-induced acute kidney injury. Also, the RIPC of the upper limb was significantly more effective in reducing contrast-induced acute kidney injury in contrast to RIPC of lower limb (36). Our study has confirmed this result. Some studies such as Igarashi et al. demonstrated that serum creatinine and eGFR as well as nephropathy biomarkers before and after the intervention are not different when applying RIPC (13). A possible explanation of variations in study results about the effect of RIPC on CIN could be the definition of CIN in different studies. Fikret (37) as well as Igarashi (13) calculated the CIN during the first 48 hours after angiography, while some studies considered CIN 30 days after angiography (35). Also, using different management strategies can affect the CIN as mentioned before (23). Appropriate hydration by normal saline is one of these effective factors (23). However, the effect of other medications before PPCI such as administration of analgesics should be addressed. In the present study, we have tried to minimize such effects by adjusting these factors among our study groups.

Despite the mentioned studies regarding the role of RIPC, still some issues have to be addressed. The application and timing of RICP is one of these issues, which can affect the intervention outcome. While, as the same as in our previous study, RIPC can be applied based on the predictable manner in patients who are candidate for angiography, in emergency settings such as PPCI, the perfect timing prior to application is not possible (23). During PPCI, time saving for providing the best coronary intervention is the most important issue and performing RIPC should not delay the management. So, performing RIPC could be prolonged even during PPCI. According to these facts, we have considered the least possible timing of performing RIPC in our patients in order not to interfere with the PPCI. Our protocol may successfully demonstrate the protective effect of RIPC during this time period on CIN. Some researchers have even suggested that RIPC can be considered even during air transportation of STEMI patients (38). Regarding the study limitations, a possible limitation of the present clinical trial could be the limited sample size. Also, performing long-term follow up, as well as investigating other biomarkers for detection of CIN could be beneficial for future studies.

5. Conclusions

According the study results, patients with STEMI who underwent PPCI along with RIPC intervention may have lower CIN, arrhythmias and favorable TIMI grade, CTFC and ST segment resolution. Using RIPC may be an inexpensive and effective intervention in reducing PPCI outcomes including arrhythmias and nephropathy.

However, our study had some limitations including sample size, which requires further clinical trials for confirmation.

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Trial registration:
The trial was registered at the Iranian Clinical Trial Registry (http://www.irct.ir) with the IRCT identification number IRCT20150614022713N2.

Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
AG and SMS designed the work. All authors contributed to data acquisition and drafting the manuscript. SMS performed the data analysis and revising the manuscript. All authors are accountable for all aspects of the work

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