RESEARCH ARTICLE

Assessment of cardiac parameters after the administration of nicorandil before primary percutaneous coronary intervention

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Abstract

Objective: To assess cardiac troponin I and creatine kinase-myocardial band levels, electrocardiogram changes and major adverse cardiac events after treatment with nicorandil before primary percutaneous coronary intervention.

Methods: The comparative, analytical study was conducted from October to November 2022 at the Pharmacology Department of Army Medical College, National University of Medical Sciences, Rawalpindi, Pakistan, in collaboration with the Rawalpindi Institute of Cardiology, Rawalpindi. The sample comprised ST-elevated myocardial infarction patients of either gender aged at least 30 years with an ejection fraction of at least 35% undergoing primary percutaneous coronary intervention. Participants were selected based on the above-mentioned inclusion and informed consent was taken before their enrolment in this research study. The sample was randomised into control group A receiving conventional acute coronary syndrome treatment, and intervention group B receiving nicorandil in addition to the conventional treatment. Cardiac troponin I and creatine kinase-myocardial band levels, electrocardiogram changes, and major adverse cardiac events noted and compared. Data was analysed using SPSS 26.

Results: Of the 140 patients, 70(50%) were in each of the 2 groups. In group B, 60(85.7%) patients achieved a completely settled ST segment on electrocardiogram compared to 25(35.7%) in group A (p=0.001). There was a significant inter-group difference with respect to cardiac troponin I value 6 hours after percutaneous coronary intervention and major adverse cardiac events (p<0.05), but creatine kinase-myocardial band level was no significantly different between the groups (p=0.761).

Conclusion: Prophylactic use of nicorandil in ST-elevated myocardial infarction patients decreased the incidence of reperfusion injury.

Keywords: Nicorandil, Percutaneous coronary intervention, Ischaemic reperfusion injury. (JPMA 74: 917; 2024)

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Introduction

The major proportion of deaths in Pakistan are due to cardiovascular diseases (CVDs) that cause approximately 18 million deaths annually, and this number is expected to rise because of various modifiable and non-modifiable factors. The national health system is forced to bear the expenses of cardiac patients who are hospitalized because of CVDs, including both ST-elevated myocardial infarction (STEMI) and non-ST-elevated myocardial infarction (NSTEMI). Coronary artery disease (CAD) affects almost 126 million people in the world, leading to 9 million deaths around the globe. Even with the availability of novel preventive and therapeutic techniques, CVDs continue to cause mortality. Non-communicable diseases (NCDs) caused 16 million deaths in 2017, and 82% of them were in low- and middle-income countries (LMICs), and 37% occurred due to CVDs.[1]

In the modern era, conventional pharmacological treatment modalities have been replaced with interventional procedures to restore the perfusion of ischaemic myocardium, especially in STEMI cases. This route must be approached within 90 minutes as this is the maximum time in which this technique can save cardiac cells from apoptosis and permanent cell death.[2] However, 8-40% of STEMI patients come to the hospital after 12 hours of the onset of symptoms. These cases are commonly labelled as late presenters.[3]

Paradoxically, this procedure causes more harm than benefit by causing ischaemic reperfusion injury (IRI). Various mechanisms are involved at the molecular and cellular levels in causing IRI, including calcium overload, micro-embolisation, proteolysis, mitochondrial permeability transition pore (MPTP) opening, and mitochondrial collapse leading to stunned myocardium and no-reflow phenomenon (NRP).[4]

The late presenters are divided into two major groups; unstable patients with signs and symptoms of ongoing ischaemic changes, and stable asymptomatic cases. It is

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advised to consider primary percutaneous coronary intervention (PCI) even in unstable late presenters, and routine PCI must only be reserved for stable STEMI patients presenting within 12-48 hours following the start of symptoms.[2] Imaging studies have proved that primary PCI has beneficial outcomes in STEMI, especially those cases presenting within 72 hours of fibrinolysis treatment after the initiation of symptoms.[5]

The incidence of myocardial infarction (MI) is increasing in the world. To diagnose this fatal condition, various significant clinical investigations are used, like electrocardiogram (ECG), echocardiography (Echo), cardiac biomarkers, and coronary angiography.[6]

The cardiac biomarkers representing an acute MI attack are mainly segregated into three major categories. The first category is that of biomarkers released from injured cardiac tissue and dispersed into the blood circulatory system, such as lactate dehydrogenase (LDH), creatine kinase (CK), myoglobin, cardiac troponin I (cTnI), cTnT, heart-type fatty acid-binding protein (H-FABP) and myosin-binding protein c (CMYc). The second category is of biomarkers raised as a result of reactionary changes occurring in various organs and systems after MI, like interleukins (ILs), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). The third category comprises biomarkers that have abnormal concentration levels in the serum before MI, such as glucose, aspartate aminotransferase (AST), ribonucleic acids (RNAs) and serum albumin-to-creatinine ratio (sACR).[6]

In addition to MI diagnosis, these biomarkers also add to atherosclerosis progression, evaluation and prognosis of cardiac tissue function.[7,8]

Cardiac biomarkers' concentrations alter with the period post-MI (Table 1).

Among the cardiac biomarkers, cTnI is more sensitive and specific, and is widely used clinically.[9,10]

In the emergency department (ED), acute MI is diagnosed by ECG changes; mainly, ST-segment elevation. ECG characteristically follows the progression of abnormal changes beginning with acute T waves and moving towards ST-segment elevation. Sometimes pathologic Q waves can appear early or late in this process. The progression of ECG through these changes can occur rapidly after the occlusion of coronary vessels.[11]

Major adverse cardiac events (MACE) include reperfusion arrhythmias, reperfusion angina, heart failure (HF) and death. These events happen after PCI in hospitalised patients, and indicate failure of the procedure, and suggest that perfusion of myocardial tissue has not been achieved even in the absence of any physical coronary obstruction. This leads to poor prognosis after primary PCI in STEMI patients.[12]

To cater to this paradoxical IRI phenomenon, one of the anti-anginal drugs act via stimulating guanylyl cyclase and potassium adenosine triphosphate (ATP) channel-opener, causing hyperpolarisation and, thus, dilating coronary vasculature by both mechanisms. It has one novel mechanism of ischaemic preconditioning (IP) by which it stabilises the inner mitochondrial membrane, thereby preventing its rupture and preventing IRI.[13,14]

The current study was planned to assess cTnI and creatine kinase-myocardial band (CK-MB) levels, ECG changes and MACEs after treatment with nicorandil before primary PCI.

Patients and Methods

The comparative, analytical study was conducted from October to November 2022 at the Pharmacology Department of Army Medical College (AMC), National University of Medical Sciences (NUMS), Rawalpindi, Pakistan, in collaboration with the Rawalpindi Institute of Cardiology (RIC), Rawalpindi. After approval from the ethics review boards of respective institutions, the sample size was calculated using the World Health Organisation (WHO) calculator.[15] The sample was raised using non-probability convenience sampling technique. Those included were STEMI patients of either gender aged at least 30 years with an ejection fraction (EF) on Echo of at least 35% undergoing primary PCI. Patients taking glibenclamide and glimepiride, and those who had received streptokinase before reaching the hospital were excluded.

The sample was randomised using the envelope method into control group A receiving conventional acute coronary syndrome (ACE) treatment, and intervention group B receiving nicorandil in addition to the conventional ACE treatment. The conventional treatment comprised tablet nitroglycerin 0.5mg sublingually stat, tablet aspirin 300mg orally stat, tablet clopidogrel 300mg orally stat, and injection heparin 5,000 units intravenous (IV). Baseline levels of cTnI, CK-MB, and ECG were recorded before PCI initiation. This was followed by the interventional procedure in the cardiac catheterisation laboratory. The second reading of cTnI and CK-MB was taken 6 hours after PCI, and an ECG reading was also noted 12 hours after the procedure. MACE was documented after 2 hours (reperfusion arrhythmia), 24 hours (reperfusion angina) and 48 hours (heart failure and death).

Data was analysed using SPSS 26. Data was presented as frequencies and percentages. Chi-square test and

independent t-test were used to analyse changes, as appropriate. P<0.05 was considered significant.

Results

Of the 140 patients, 70(50%) were in each of the 2 groups. Demographic details of the patients are mentioned in (Table 2) below. In group B, 60(85.7%) patients achieved a completely settled ST segment on ECG compared to 25(35.7%) in group A. STEMI had partially settled in 9(12.09%) participants in group B and 34(48.6%) in group A. No improvement was seen in 1(1.04%) patient in group B, and 11(15.7%) patients in group A. There was a significant difference in the recovery of ST-segment elevation post-PCI between the groups (p=0.001) (Table 3).

There was no significant differences in cTnI and CK-MB values at baseline between the groups (p>0.05). There was a significant inter-group difference with respect to cTnI value 6 hours post-PCI, but CK-MB level was no significantly different (Table 4).

Table-1: Cardiac biomarkers' variation phases.

Markers	Detectable	Peak Level	Return To Normal
AST	12 to 24 hours	24 to 48 hours	10 to 14 days
Troponin-T	4 to 8 hours	12 to 48 hours	7 to 10 days
Troponin- I	4 to 6 hours	12 hours	3 to 10 days
CK-MB	4 to 9 hours	12 to 24 hours	48 to 72 hours

AST: aspartate aminotransferase, CK-MB: Creatine kinase-myocardial band.

Table-2: Demographic details of the study groups.

Study Variables	Study Groups	Nicorandil (n=70)	Control (n=70)	*p*-value
Age group(years)	40 to 50	25 (35.07%)	18 (25.7%)	0.272
	51 to 60	45 (64.03%)	52 (74.3%)	
Mean age (years)		54.05±6.13	53.27±6.72	
Gender	Male	58 (82.09%)	65 (92.9%)	0.119
	Female	12 (17.01%)	5 (7.1%)	

Table-3: ECG post PCI in the study groups.

ECG 12 hours after PCI	Study Groups		
	Nicorandil	Control	*p*-value
Completely settled	60(85.07%)	25(35.7%)	0.001
Partially settled	9(12.09%)	34(48.6%)	
Not settled	1(1.04%)	11(15.7%)	

ECG: Electrocardiogram, PCI: Percutaneous coronary intervention.

Table-4: Mean distribution of cardiac biomarkers in the study groups.

Cardiac Biomarkers	Study groups				*p*-value
	Nicorandil		Control		
	Male	Female	Male	Female	
Cardiac Troponin 1					
Baseline	3.87±2.38	4.53±2.14	3.85±3.39	2.83±2.35	0.876
6 hours after PCI	1.74±3.21	1.63±2.48	5.3±4.66	3.4±1.44	0.002
CK-MB					
Baseline	32.50±93.80	24.67±11.95	17.65±90.703	10.59±15.68	0.891
6 hours after PCI	11.89±9.43	13.52±9.92	22.67±9.46	25.01±8.16	0.761

CK-MB: Creatine kinase-myocardial band levels, PCI: Percutaneous coronary intervention.

Table-5: Major adverse cardiac events (MACE) in the study groups.

		Study groups [n (%)]		
		Nicorandil	Control	*p*-value
Reperfusion arrhythmias after 2 hours of PCI	Yes	1(1.4)	8(11.04)	0.016
	No	69(98.6)	62(88.06)	
Reperfusion angina after 24 h of PCI	Yes	5(7.1)	22(31.04)	0.001
	No	65(92.9)	48(68.06)	
Heart failure after 48 hours of PCI	Yes	0.0(0.0)	3(4.03)	0.08
	No	70(100)	67(95.07)	
Death after 48 hours of PCI	Yes	0.0(0.0)	0.0(0.0)	
	No	70(10)	70(100)	
Any significant ECHO changes after PCI	Yes	0.0(0.0)	0.0(0.0)	
	No	70(100)	70(100)	

PCI: Percutaneous coronary intervention.

Reperfusion arrhythmia occurred in 1(1.4%) patient in group B compared to 8(11.04%) in group A 2 hours post-PCI (p=0.016). Reperfusion angina occurred in 5(7.1%) group B patients compared to 22(31.04%) in group A (p=0.001). There was no HF case in group B 48 hours post-PCI compared to 3(4.03%) in group A (p=0.08). There was no mortality or significant Echo changes at 48 hours post-PCI in any of the 2 groups (Table 5).

Discussion

CAD has a major share in both morbidity and mortality of cardiac patients globally. The treatment revolves around either pharmacological or interventional procedures. Prompt reperfusion by primary PCI in STEMI improves the prognosis of the disease and has long-term favourable effects. This intervention ironically deteriorates cardiac function in some patients owing to IRI, and leads to myocardial stunning and decreased cardiac function. To prevent IRI, numerous medications are being explored and used. They can be administered through multiple routes, including oral, intracoronary, or IV.[16] In the current study, nicorandil was used orally before PCI to prevent IRI.

The findings of ECG after 12 hours showed that STEMI was completely settled in a significantly larger number of patients in the nicorandil group compared to the control group. The finding was in agreement with Kostic et al., Wang et al.[17] and Yang et al.[18]

In the current study, cTnI level was significantly reduced 6 hours post-PCI in males and females in the nicorandil group, suggesting reduced myocardial injury with nicorandil, while no significant difference was seen in CK-MB values. Wang et al. also showed higher sensitivity of cTnI than CK-MB in predicting and reducing the infarct size.[17] Several other studies have observed that CK-MB levels 4-12 hours post-PCI serves as a good predictor for the size of the ischaemic area.[19,20]

Nicorandil's cardio-protective effect was confirmed by a

randomised placebo-controlled trial involving 5,126 cases of stable angina with an average follow-up of 1.6 years.[21]

MACEs in the current study included reperfusion arrhythmias after 2 hours, reperfusion angina after 24 hours, and HF and death after 48 hours. Reperfusion arrhythmias are thought to be indicators of successful reperfusion. However, these arrhythmias have also been suggested to occur possibly due to ongoing myocardial cell damage and ischaemia if it remains persistent.[22,23] In the current study's nicorandil group, reperfusion arrhythmias occurred in only 1.4% patients compared to 11.04% in the control group, proving that nicorandil successfully restored blood flow to ischaemic myocardium by limiting the infarct size. Studies have suggested that reperfusion arrhythmias are non-invasive indicators of myocardial cell damage.[24]

In the current study, no patient died and no significant changes were seen in Echo 48 hours post-PCI, but nicorandil showed overall better outcomes compared to the control group, which was in line with Zhang et al.[25]

The current results agreed with the findings of a randomised trial that had a 5-year follow-up in which nicorandil was given 20-30 minutes before PCI as an IV infusion of 12mg in 100ml of saline. The study found that a single dose of nicorandil improved not only early but also late clinical events, including cardiovascular death or hospital admission due to worsening congestive heart failure (CHF).[26]

The current study has its limitations. It was done at a single centre with a small sample size and without much ethnic variation. Multicentre studies should be conducted with larger and more diverse samples.

Conclusion

Prophylactic use of nicorandil in STEMI patients decreased IRI incidence. The administration of nicorandil was beneficial for cardiac patients without any evident adverse effects. Its use may be promoted in PCI patients.

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Author Contribution:

MI: Design, collected and assembles the data, statistical analysis, interpretation and writing.
MN: Supervision, concept and revision.
SH: Supervision, clinical setting and revision.
KF, SA, MW: Reviewing, final approval and ensuring accuracy and integrity of entire data.