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Effects of Nicorandil on the Clinical and Laboratory Outcomes of Unstable Angina Patients after Coronary Angioplasty

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ABSTRACT

Introduction: Ischemic preconditioning mediated by potassium channels is a physiological protective mechanism. It is hypothesized that Nicorandil, which is a potassium channel activator, could protect the heart via preconditioning.
Materials and Methods: This clinical trial was conducted on 162 patients undergoing percutaneous coronary intervention (PCI) in Quem hospital, from January 2013 to January 2014,patients divided into two groups. The first group received standard treatment plus Nicorandil (10 mg, twice daily) for three days before and after angioplasty. The second group received standard treatment after PCI.
Results: Cardiac enzyme levels were significantly lower in the Nicorandil group at 6 and 12 hours after angioplasty,(p value =0.001) while no significant differences were observed in the symptoms and four-month prognosis of the study groups(p value=0.8).
Conclusion: It is recommended that a randomized clinical trial be conducted for the close evaluation of the effects of Nicorandil on unstable angina patients.

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Introduction

Mortality, myocardial infarction (MI) and readmission are among the known complications of unstable angina. Selection of invasive or conservative management strategies depends on the clinical and laboratory conditions of these patients. Therapeutic agents such as aspirin, heparin, beta-blockers, and statins are the cornerstone of medical treatment for unstable angina patients, while invasive strategies are commonly considered for high-risk patients.

Despite the advances in interventional procedures, coronary interventions are still associated with various complications, such as MI (1-3). Furthermore, asymptomatic elevation of cardiac enzyme levels after coronary interventions is another prominent complication, and controversies in this regard revolve around the detrimental effect of enzyme rise on the prognosis of unstable angina patients. MI associated with percutaneous coronary intervention (PCI) is defined as the increase of biomarkers above 3×99th percentile upper the reference limit.

Recurrent episodes of reversible ischemia increase cardiac resistance against ischemia. This ischemic preconditioning, which is mediated by potassium channels, is a physiological protective mechanism, Nicorandil is a potassium channel activator, which is considered an effective agent in the treatment of angina pectoris and hypertension. Lack of drug tolerance has been proposed as a unique feature of Nicorandil.

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According to the literature, if Nicorandil is administered after MI in high-risk patients, the associated cardioprotective effects could be mediated through the preconditioning phenomenon. This study aimed to evaluate the effects of Nicorandil on the clinical outcomes of unstable angina patients after invasive procedures (4-6) compare with control group.

Materials and Methods

This randomized clinical trial, double-blind study was conducted on 162 patients with unstable angina after obtaining written consent. Inclusion criteria were successful PCI treatment on admission (cardiac catheterization via the femoral approach, >50% final diameter stenosis, final TIMI grade flow of >3, final dissection of <grade D, and no urgent target vessel revascularization within 24 hours) and survival discharge.

Selected patients were randomly divided into two groups. The first group received standard treatment, consisting of a regimen of Aspirin, Clopidogrel, oral Nitrates, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and Nicorandil (10 mg) twice daily for three days before and after angioplasty. Patients in the second group only received standard treatment after the coronary intervention.

Cardiac enzymes (troponin-I and creatine phosphokinase-MB) were measured before and 6 and 12 hours after the procedure. In addition, electrocardiography and echocardiography were performed before and after the procedure.

Statistical Analysis

Continuous variables were presented as mean and standard deviation, and qualitative data were expressed as numbers and percentages. Moreover, differences in the nominal and qualitative variables between study groups were assessed using the Fisher's exact test. Data analysis was performed using PASW Statistics V.18.0 (SPSS Inc., Chicago, IL), and *P value* of less than 0.05 was considered statistically significant.

Patients were followed-up for the occurrence of complications until discharge from the hospital. Data were recorded on the in-hospital events of the patients and during a four-month period after discharge (all-cause mortality, re-infarction, and readmission).

Results

Demographic data of the studied patients are presented in Table 1. Mean age of patients is 58.8±10.6 y, 29% of patients are diabetic, 35% are hypertensive, 24% hyperlipidemic and 19% are smoker.

Drug-eluting stents were deployed in 98.8% of the patients with mean diameter of 2.86±0.3 (*P*=0.747) and mean length of 22.4±7.57 mm (*P*=0.535) in both groups.

Table1. Demographic data of patients

Age	58.8±10.6
M/F	2.7/1
Diabetes Melitus	47(29%)
Hypertension	57(35%)
Hyperlipidemia	39(24%)
Smoking	31(19%)

According to our findings, cardiac enzyme levels were significantly lower in the Nicorandil group at 6 and 12 hours after angioplasty (Table 2) *P*=0.001, while no significant difference was observed in the symptoms and four-month prognosis of the two groups (Table 3). Moreover, during the four-month follow-up, no major cardiovascular events and mortality were reported.

Table 2. Enzyme level after coronary angioplasty

Enzyme			Minimum	Maximum	Average	SD	
CK-MB Creatine Kinase-MB (CK-MB) test	6 hours	Case	2.0	20.0	10.4	2.8	t-test=4.84 *P-Value*=0.0001
		Control	4.0	43.0	14.8	7.5	
	12 hours	Case	5.0	30.0	12.5	4.5	t-test=3.92 *P-Value*=0.0001
		Control	5.0	58.0	16.8	8.8	
troponin I (TnI)	6 hours	Case	.01	.40	.08	.07	t-test=5.02 *P-Value*=0.0001
		Control	.01	.52	.15	.11	
	12 hours	Case	.02	.60	.13	12	t-test=3.43 *P-Value*=0.001
		Control	.01	.74	.20	.13	

Table 3. Symptoms difference between two groups

Group complain	Case		Control	
	Number	Percent	Number	Percent
Chest pain	79	97.5%	74	91.4%
Dyspnea	2	2.5%	7	8.6%
Total	81	100.0%	81	100.0%

Fisher's Exact Test *P-Value*=0.167

Discussion

To date, several studies have evaluated the effect of cardiac enzyme elevation and myocardial salvage after coronary interventions on prognosis and mortality (6, 7). Low elevation of creatine phosphokinase (CPK)-MB after

coronary stenting is a common phenomenon associated with infrequent occurrence of MI.

In this regard, a review article denoted that low-to-moderate elevation of CPK-MB could not predict the outcomes after coronary interventions in patients with normal left-ventricular (LV) function, while it could predict the outcomes of patients with baseline LV dysfunction or in patients who underwent interventions on degenerative saphe-nous grafts (8).

No relevant evidence supports the effectiveness of Nicorandil for stable angina patients (10). However, if these patients undergo PCI, Nicorandil could prevent microvascular dysfunction (11). In the present study, patients administered with Nicorandil had reduced cardiac enzyme levels after the intervention, while no significant difference was observed in the short-term clinical outcomes of the two groups. Moreover, no significant difference was observed in cardiac enzyme elevation of the patients with baseline LV dysfunction.

The mechanism of cardiac enzyme reduction remains unclear; however, some of the pharmacological properties of Nicorandil have been suggested to be involved in this mechanism. Nicorandil dilates coronary arteries and relieves microvascular spasm. Furthermore, it has been shown to affect microvascular function and reduce the infiltration of neutrophils into the ischemic myocardium (11). These effects may play a role in improving the function of stunned myocardium. Our findings may demonstrate the cause of reduced mortality in (the Impact of Nicorandil in Angina) IONA)study (12).

Vessels smaller than 100 μm are more sensitive to the effect of Nicorandil, and since women have smaller coronary arteries, they are likely to benefit more from this drug. However, findings of the present study were indicative of no significant difference between men and women in terms of study endpoints (11).

Conclusion

In conclusion, our findings did not show the benefits of Nicorandil for mortality and morbidity instable angina patients undergoing PCI despite the reduction in cardiac enzyme levels. This could be due to the relatively short-term follow-up of the patients, as well as the dosage and route of drug administration (13). Therefore, it is recommended that a randomized clinical trial be conducted for the further assessment of the effects of Nicorandil on unstable angina patients.

Conflict of Interest

The authors declare no conflict of interest.

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