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Useful Clinical Effects of Short Term Consumption of Nicorandil on Early Outcome in Patients with Acute Coronary Syndrome

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Abstract: Nicorandil is a cardioprotective agent that improves anginal symptoms through dilatation of the coronary arteries as well as reduction of coronary vascular resistance. To assess the protective effects of short-term use of nicorandil on in-hospital outcome of patients with acute coronary syndrome. In a randomized double-blinded controlled trial, 240 patients suffered from typical chest pain and hospitalized with the final diagnosis of acute coronary syndrome infarction (NSTEMI) were included. The participants were randomly assigned to the intervention group receiving routine anti-thrombotic and anti-platelet drugs plus nicorandil 20 mg^{-1} bidorally 120 patients or control group receiving only routine cardiovascular drugs (120 patients). The severity of chest pain gradually reduced within 4 days of the study in both interventional and control groups but the decreasing trend in pain score was significantly more downward in former group. The prevalence rate of cardiac arrhythmias was 14.4% within a day after intervention that was significantly lower in intervention group than in control group (19.5 vs. 9.5%, $p = 0.031$). The occurrence rate of increase cardiac enzyme in the intervention and control groups was 9.9 and 29.7%, respectively with a significant difference ($p<0.001$). Also, the means level of cardiac enzymes including CK-MB and troponin T were initially lower in intervention group within the first day of assessment but remained similar in the next days. Regarding echocardiography indices, end-diastolic diameter was significantly lower in intervention group than in control group (47.4 vs. 49.7 mm, $p = 0.034$). Also, mitral insufficiency was significantly less prevalent in the former group (44.0 vs. 72.0%, $p<0.001$). No differences were observed in length of hospital stay or number of involved coronary arteries.

Key words: Acute coronary syndrome, nicorandil, outcome, resistance, enzymes

INTRODUCTION

Nicorandilis a vasodilatory anti-anginal medication commonlyused to improve anginal symptoms. It acts through different mechanisms including dilatation of the coronary arteries at low plasma concentrations as well as reduction of coronary vascular resistance at higher plasma concentrations (Kukovetz *et al*., 1992). The main molecular mechanisms regarding therapeutic effects of nicorandil include increased K^+ATP channel opening through which nicorandil inactivates voltage-gated calcium channels and therefore, reduces free intracellular Ca (Nakae *et al*., 2000). It can also increase Rho-kinase activity that leads to inhibition of myosin phosphatase activity and decrease in calcium sensitivity and hypercontraction (Takemoto *et al*., 2002; Kandabashi *et al*., 2000).

It has been suggested that in comparison with isolated reperfusion therapy adjunction of nicorandil results in better functional outcome following acute

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Myocardial Infarction (MI) (Sakata *et al*., 1997). It has been reported that intravenous infusion of nicorandil could improve tissue perfusion enhance recovery of cardiac function, and reduce early complications in patients with anterior acute MI (Ito *et al*., 1999). Moreover, nicorandil has also been shown to have a cardioprotective effect in ischemic regions demonstrated by reduced myocardial necrosis and improvement of myocardial stunning following coronary artery reperfusion and thus mimics ischemic preconditioning (Horinaka, 2011; Grover, 1997; Ohno *et al*., 1997; Schultz *et al*., 1997; Iwakura *et al*., 2009; Lee *et al*., 2008). In this regard, it seems that routine use of intravenous infusion of nicorandil can result in appropriate management of angina pectoris, providing long-term cardioprotection, and also improving the prognosis of ischemic heart disease. In contrast to the above mentioned findings, there are reports which are against beneficial effects of nicorandil. In a study performed on MI patients, it was reporte that intravenous nicorandil did not affect left ventricular ejection fraction after MI (Kitakaze *et al*., 2007).

The present study aimed to assess the protective effects of short-term consumption of nicorandi l on in-hospital outcome of patients with Non-ST segment Elevation Myocardial Infarction (NSTEMI).

MATERIALS AND METHODS

In a randomized double-blinded controlled trial, 240 patients who presented to our hospital with typical ischemic chest pain and did not show ST-segment elevations were with the diagnosis of acute coronary syndrome were included. The diagnosis of acute coronary syndrome was made on the basis of chest pain of >30 min duration and >3-fold increase in serum Creatine Kinase (CK) activity without ST segment elevation>2 mm in Contiguous Electrocardiographic (ECG) leads. The exclusion criteria were age <18 year or >80 years, cardiogenic shock or an underlying condition in which hypotension may be poorly tolerated for nicorandil infusion.

The participants were randomly assigned to the intervention group or control group. Both groups received routine treatments applied in our center for acute coronary syndrome patients including anti-thrombotic and anti-platelet drugs. The intervention group received nicorandil (20 mg twice daily orally) in addition to routine treatments. All patients were followed during hospitalization chest pain (according to The Canadian Cardiovascular Society Angina Grading Scale) (Kaul *et al*., 2009), functional class (according to the guidelines of New York heart Association, NYHA), arrhythmia, echocardiographic findings and cardiac enzymes were documented. Two-dimensional echocardiography was performed with a commercially available electrical sector scanner during 48 h of hospitalization and systolic and diastolic functional parameters as well as valvular heart abnormalities were assessed (cardiac enzyme was assessed twice in first day and 3 times arter 1st day).

The study endpoint was to assess reduce in chest pain, change in cardiac necrosis indices, changes in echocardiography parameters, appearing cardiac arrhythmias, progression of infarction to STEMI type and also in-hospital death.

Results are reported as mean Standard Deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the students t-test for the continuous variables and the chi-square test (or Fishers exact test if required) for the categorical variables. Trend of the changes in severity of chest pain was assessed using the Friedman test. The p values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). All subjects gave the informed consent for this study protocol and the study protocol was approved by the institutional research and research committees of our university.

RESULTS

In total, 240 patients (120 in intervention group and 120 in control group) were included into the study. The two groups were matched for gender, age and some cardio vascular risk factors including diabetes mellitus, hypertension, serum LDL level and previous cardiac interventions. However, current smoking was more observed in the interventional group and instead, serum triglyceride level was higher in the controls (Table 1).

Functional class: Table 2 presents functional class of the studied groups during hospitalization. As shown, in all days patients who received nicorandil had better functional class compared to control group.

Chest pain: Regarding improvement in chest pain score, the severity of chest pain gra dually reduced within four days of the study in both interventional and control groups but the decreasing trend in pain score was significantly more downward in intervention group (Fig. 1 and 2).

Arrhythmia: In total, the prevalence rate of cardiac arrhythmias was 14.4% within the first day of admission

Table 1: Baseline characteristics and clinical data of the study population

Characteristics	Nicorandil group (N= 120)	Control group (N= 120)	p-values
Male	55 (45.8%)	50 (41.7%)	0.886
Age, year			
Diabetes mellitus	30 (25.4%)	38 (31.7%)	0.286
Hypertension	69 (59.0%)	60 (50.0%)	0.104
Hyperlipidemia	68 (57.6%)	49 (41.0%)	0.010
Triglyceride >250 mg dL^{-1}	33 (28.2%)	20 (17.0%)	0.033
Serum LDL >100 mg dL^{-1}	48 (41.0%)	45 (37.5%)	0.615
Current smoking	18 (15.3%)	39 (32.5%)	0.002
Previous PCI	4 (3.4%)	4 (3.4%)	0.999
Previous CABG	16 (13.6%)	10 (8.3%)	0.196
Previous MI	10 (8.5%)	16 (13.3%)	0.230

PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Grafting; MI = Myocardial Infarction

Table 2: Frequency (percentage) of patients according to NYHA classification in 4 days after admission among patients with NSTEMI

	NYHA				
Characteristics	I	II	III	IV	p-values
First day					
Intervention	114 (95.0)	4 (3.3)	0	0	<0.001
Control	95 (79.2)	25 (20.8)	0	0	
Second day					
Intervention	28 (23.3)	28 (23.3)	0	0	<0.001
Control	30 (25.4)	65 (55.1)	20 (16.9)	0	
Third day					
Intervention	6 (5.0)	19 (15.8)	3 (2.5)	0	<0.001
Control	4 (3.6)	49 (43.8)	44 (39.3)	1 (0.9)	
Fourth day					
Intervention	0.0	10 (11.5)	5 (5.7)	0	<0.001
Control	0 .0	20 (23.8)	35 (41.7)1	(1.2)	

Table 3: Comparison of serum cardiac enzyme levels between interventionand control groups

Enzyme	Intervention group (N= 120)	Control group (N= 120)	p-values
CK-MB			
First time	19.83	117.31	<0.001
Second time	53.33	81.89	0.060
Third time	56.50	53.91	0.824
Fourth time	38.67	44.95	0.598
Troponin group			
First time	1.74	3.30	0.050
Second time	3.46	4.25	0.676
Third time	2.25	2.44	0.875
Fourth time	--	0.97	---

which was significantly lower in intervention group than in control group (19.5 vs. 9.5%, p = 0.031). This difference was mainly revealed in the occurrence of ventricular tachycardia (0 vs. 4.2%, p = 0.023).

Cardiac enzymes: The frequency of acute coronary syndrome in the intervention and control groups was 9.9 and 29.7%, respectively (p<0.001). Also, the means level of cardiac enzymes including CK-MB and troponin t were initially lower in intervention group within the first day of assessme but remained similar in the next days (Table 3).

Echocardiographic indices: End-diastolic diameter was significantly lower in intervention group than in control group (47.4 vs. 49.7 mm, p = 0.034). Also, mitral insufficiency was significantly less prevalent in

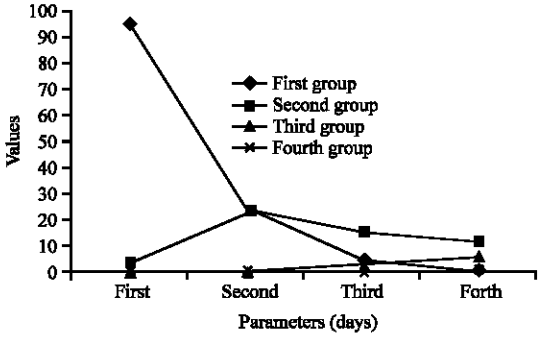

Fig. 1: Trend of the changes in pain score in intervention group

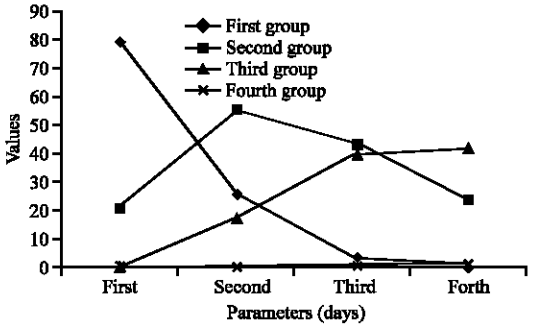

Fig. 2: Trend of the changes in pain score in control group

intervention group (44.0 vs. 72.0%, p<0.001). No differences were revealed in other echocardiography parameters between the two groups.

Hospitalization duration: The length of hospital stay in intervention and control groups were statistically similar (3.96 vs. 4.16 days, p = 0.327). Also, the mean number of involved coronary vessels was similar on angiography report between the two groups (2.33 vs. 1.60, p = 0.144).

DISCUSSION

Short-term consumption of nicorandil in patients with acute coronary syndrome has been introduced as a potential therapeutic agent with multiple beneficial effects on early cardiovascular functional indices including anginal pain severity, preventing cardiac arrhythmias especially ventricular tachycardia, ischemic events indicated by lowering CK-MB and troponin t levels and also improving some echocardiography parameters such as end-diastolic diameter and severity of mitral insufficiency that can be finally result in improvement of in-hospital mortality and morbidity (Ono *et al*., 2004). similarly, showed that nicorandil administered as 4 mg as bolus injection followed by constant infusion at 8 mg h^{-1}

for 24 h could lead to higher left ventricular ejection fraction and cardiac index as well as to lower plasma brain natriuretic peptide level, lower in-hospital cardiac events and also lower rate of re-hospitalization (Ono *et al*., 2004). In a recent randomized trial, a significant improvement was found in outcome due to a reduction in major coronary events including death, non-fatal myocardial infarction or unplanned hospital admission for cardiac chest pain by anti-anginal therapy with nicorandil in patients with stable angina (IONA, 2002). In another study by Horinaka *et al*. (2010) death from all causes was significantly lower by 35% in the nicorandil group than in the control group. There were also significant reductions in secondary endpoints including cardiac death (56%), fatal myocardial infarction (56%), cerebral or vascular death (71%) and congestive heart failure (33%) in then icorandil group. The clinical benefits of nicorandil have been shown to be mediated by its role in reducing the area of ischamin lesion and myocardial necrosis as well as reducing the expression levels of endoplasmic reticulum stress markers leading prevention of anginal attacks as well as the increase in exercise tolerance (Izumiya *et al*., 2011; Malysheva, *et al*., 2011). Nicorandil as a K-ATP channel opener and nitric oxide releaser not only can inhibit myocardial stunning but also can suppress myocardial necrosis in is chemic reperfusion (Grover, 1997; Ohno *et al*., 1997; Schultz *et al*., 1997). It can be also protect endothelial function in the coronary arteries from ischemic reperfusion injury via activation of mitochondrial K-ATP channels (Maczewski and Bercewicz, 1998; Ren *et al*., 2001) and therefore, these mechanisms can explain beneficial clinical and echocardiographic indices in acute coronary syndrome patients. As we pointed in the present study, the use of nicorandil resulted in prevention of ventricular tachycardia. It has been previously reported that nicorandil reduces lethal ventricular arrhythmia in the initial phase after acute coronary syndrome (Patel *et al*., 1999) that this mechanism might also play a role in reducing fatal cardiac events.

In this study, the dose of nicorandil 40 mg day was similar to used in IONA study (40 mg day) (IONA, 2002) and higher that that used in JCAD study (Horinaka, 2011). The recommended dose of this drug in Europe and Oceania is 10-40 mg twice daily and 7.5-30 mg three times daily in Asia (Simpson and Wellington, 2004). These findings, thus, suggest that although our employed dosages caused favorable effects on cardiovascular parameters in acute coronary syndrome patients, lower doses such as 15 mg day of nicorandil might be adequate to activate K-ATP channels. However, the optimal dosage of nicorandil remains to be determined. In summary, short-term use of nicorandil can improve in hospital outcome with regard to chest pain severity, occurrence of cardiac arrhythmias, ischemic events and echo cardiography parameters in patients with acute coronary syndrome.

CONCLUSION

Short-term use of nicorandil can improve in-hospital outcome with regard to chest pain severity, occurrence of cardiac arrhythmias, is chemic events and echocardiography parameters in patients with acute coronary syndrome.

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