Myocardial Protective Effects of Nicorandil During Percutaneous Coronary Intervention in Patients With Unstable Angina

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Background The purpose of the study was to prospectively evaluate the protective effect of nicorandil during percutaneous coronary intervention (PCI) in patients with unstable angina (UAP).

Methods and Results Two hundred patients (61±10 year-old, male 143) diagnosed with UAP at an emergency medical center were randomly assigned to 2 groups: intravenous isosorbide dinitrate, Group I (n=100), or intravenous nicorandil, Group II (n=100). PCI was performed 12–48 h after infusion of each agent. Serum concentrations of creatine kinase-MB (CK-MB), cardiac troponin T (cTnT), and I (cTnI) were measured before and 6, 12, 24 h after PCI. Patients with non-coronary chest pain, requiring emergency coronary angiogram, temporary pacemaker or glycoprotein IIb/IIIa receptor blocker were excluded. PCI was successfully performed in 96 patients (Group I=54, 61.7±8.2 years, 32 males; Group II=42, 60.4±11.7 years, 27 males). No significant differences in clinical or coronary angiographic characteristics were observed between the 2 groups. The concentration of CK-MB was elevated in 9 patients (17%) of Group I and 6 (14%) of Group II, cTnT in 16 (30%), 6 (14%) and cTnI in 25 (46%), 9 (21%) after PCI. Elevation of any troponin was less frequent in Group II [28/54 (52%) vs 10/42 (24%) patients, $p=0.01$]. Major adverse coronary events during the 6-month clinical follow-up occurred in 9 (17%) of Group I and 5 patients of Group II (12%, $p=NS$). Follow-up echocardiography revealed lower left ventricular ejection fraction in Group I than in Group II ($65.4\pm7.2\%$ vs $71.0\pm6.7\%$, $p=0.03$).

Conclusion Nicorandil has a myocardial protective effect during PCI in patients with UAP. (Circ J 2005; 69: 306–310)

Key Words: Angioplasty; Nicorandil; Percutaneous coronary intervention; Unstable angina

Myocardial injury commonly occurs during percutaneous coronary intervention (PCI) and can be easily monitored by measuring myocardial enzymes.^{1–4} Nicorandil is the opener of the adenosine triphosphate (ATP)-sensitive K⁺ channel and is known to have an antiarrhythmic effect, through shortening of the action potential, and myocardial protective functions, such as the reduction of the resistance of micro-coronary artery flow by relaxing the smooth muscles of blood vessel and preconditioning.^{5–8} Investigating the myocardial protective effect of nicorandil, the IONA study (Impact of Nicorandil in Angina), a large-scale research on stable angina, reported that oral administration of nicorandil reduced death from coronary artery disease and unexpected hospitalization for non-fatal myocardial infarction or chest pains.⁹ There have been several studies evaluating the myocardial

protective effect of nicorandil for unstable angina (UAP) or acute myocardial infarction patients, but no large-scale research has been carried out yet!^{10–12}

The purpose of this study was to prospectively examine the myocardial protective effect of nicorandil by evaluating the myocardial enzymes of the patients with UAP who underwent successful PCI 12–48 h after the injection of nicorandil.

Methods

Subjects

The subjects were 200 patients who visited the Emergency Medical Center of Chonnam National University Hospital for chest pain during the period March to December 2002 and who were clinically diagnosed as UAP, but definitely ruled out from having myocardial infarction. This study excluded those who had a history of myocardial infarction within the past 3 months, valvular heart disease or a myocardial disease, musculoskeletal disease, bundle-branch block or atrioventricular block, pacemaker, uncontrollable diabetes or oral ulcer. Patients with systolic blood pressure below 100 mmHg, or who were currently taking sulfonyleurea or had been for more than 5 years in the past were also excluded.

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Fig 1. Schematic diagram of the study patients. ISDN, isosorbide dinitrate; IHD, ischemic heart disease; CAG, coronary angiogram; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Study Groups and Treatment

All patients were treated according to the diagnosis of UAP, and they were randomly divided into 2 groups in order of admission to the hospital. Patients in Group I (n=100) were treated with isosorbide dinitrate injection and those in Group II (n=100) with nicorandil. The injection of isosorbide dinitrate began at 2 mg/h and was gradually increased to 4 mg/h, with a further increase up to 8 mg/h or decrease depending on the patients' symptoms. The initial nicorandil treatment was a 4 mg injection, and then infusion at a rate of 4 mg/h, up to 6 mg/h or less depending on symptoms. Both treatments were given for 12–48 h before PCI and for 48 h after PCI, then replaced with oral medication of 80–160 mg/day ISDN in group I and 10–15 mg/day nicorandil in group II for the next 6 months. Patients who required urgent PCI within 12 h of the treatment initiation were excluded from the analysis (Fig 1).

Coronary Angiography and PCI

Coronary angiography was mainly carried out via the radial artery or femoral artery using a 5 or 6 French coronary artery introducer (Judkins or Amplatz). Lesions were classified according to the American College of Cardiology/American Heart Association (ACC/AHA)¹³ and coronary artery blood flow was evaluated as Thrombolysis In Myocardial Infarction (TIMI) flow.¹⁴

Depending on the angiography results and the patient's condition, treatment was PCI, coronary artery bypass graft (CABG) or medication. Patients allocated to PCI were given aspirin and ticlopidine or clopidogrel before the procedure, and PCI was performed through either the radial or femoral artery using a 6–8 French introducer (Judkins or Amplatz). Before starting the procedure, 7,500–10,000 units of heparin were given iv and the activated clotting time was maintained at >300 s. Once the guide wire passed through the culprit lesion, balloon dilatation or a stent placement was performed using a Phillips H5000 or Allura digital cardiac imaging system. The treatment was regarded as successful when the luminal diameter of the target artery

increased by at least by 50%, residual stenosis was less than 30% and TIMI flow was grade 3. If platelet glycoprotein IIb/IIIa inhibitor was used before PCI, or a temporary pacemaker was inserted, the case was excluded from analysis.

Cardiac Enzymes

In 96 successful PCI patients, blood was collected just before PCI and 6, 12 and 24 h from PCI, for measurement of the concentrations of creatine kinase (CK), CK-MB, cardiac troponins T (cTnT) and I (cTnI). CK and CK-MB was measured by immune inhibition method (Synchron CX9, Beckman Coulter, USA), cTnT and cTnI by immunoassay (Elecys 1020, Boehringer Mannheim Diagnostics, Germany and Opus, Dade Behring Inc, USA, respectively). The normal reference values for CK-MB, cTnT and cTnI were <8 mg/dl, 0.05 ng/ml, and 0.01 ng/ml, respectively. In each test, the value just before PCI was compared with the highest of those obtained after PCI to examine the myocardial protective effect of each drug. Elevation of CK-MB was defined as maximal value of CK-MB >16 mg/dl and elevated more than 5% of the value before PCI. Elevation of cTnT was defined as maximal value >0.2 ng/ml and elevated more than >0.1 ng/ml before PCI. Elevation of cTnI was defined as maximal value >0.1 ng/ml and elevated more than >0.05 ng/ml before PCI.

Clinical Follow-up

Throughout the 6-month follow-up, the 2 groups were compared in terms of major adverse cardiac events (MACE), such as cardiac death, myocardial infarction accompanied by increased CK-MB, or revascularization such as PCI or CABG. Echocardiography was carried out on both the admission day and at the 6th month, by different physicians unaware of which group the patients were from. The left ventricular ejection fraction (LVEF) was measured by the area–length method on both the admission day and at the 6th month, and the results of both examinations were compared between the 2 groups.

Table 1 Clinical and Angiographic Characteristics of the Study Groups

	Group I (n=54)	Group II (n=42)	p value
Age (years)	61.7±8.2	60.4±11.7	0.54
Male (%)	32 (59)	27 (64)	0.68
Risk factor (%)			
Smoking	25 (46)	119 (45)	0.59
Hypertension	32 (59)	29 (69)	0.60
Diabetes mellitus	6 (11)	5 (12)	0.62
Family history	2 (4)	1 (2)	0.52
Hyperlipidemia	21 (39)	17 (41)	0.64
Angiographic findings (%)			
1-vessel disease	32 (59)	27 (64)	0.59
2-vessel disease	15 (28)	8 (19)	
3-vessel disease	7 (13)	7 (17)	
Target artery (%)			
LAD	31 (57)	23 (55)	0.61
LCX	13 (24)	10 (24)	
RCA	10 (19)	19 (21)	
ACC/AHA Type (%)			
A	1 (2)	0 (0)	0.07
B ₁	34 (63)	20 (48)	
B ₂	7 (13)	15 (36)	
C	12 (22)	7 (17)	
TIMI flow (%)			
0	5 (9)	1 (2)	0.41
I	5 (9)	2 (5)	
II	11 (20)	11 (26)	
III	33 (61)	28 (67)	
Procedure (%)			
Ballooning	7 (13)	11 (26)	0.12
Stenting	47 (87)	31 (74)	
Intervention (%)			
Single vessel	44 (82)	35 (83)	0.82
Multiple vessel	10 (18)	7 (17)	

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction.

Table 2 Incidence of Elevated Cardiac Enzymes During Percutaneous Coronary Intervention

	Group I (n=54)	Group II (n=42)	p value
CK-MB	9 (17%)	6 (14%)	0.67
Troponin T	16 (30%)	6 (14%)	0.06
Troponin I	25 (46%)	9 (21%)	0.03
Elevated troponin	28 (52%)	10 (24%)	0.01

CK-MB, creatine kinase isoenzyme-MB.

Statistical Analysis

All measurements are represented as mean value±standard deviation. Student's t-test, ANOVA and Fisher's exact test were conducted using SPSS (Chicago, IL, USA), and statistical significance was admitted when $p<0.05$.

Results

Of the 200 patients, 36 were excluded because their chest pain was caused by other than ischemic heart disease, 9 required urgent coronary angiography within 12h of drug administration because their chest pain was uncontrollable, and another 155 underwent elective coronary angiography between 12 and 48h of drug administration. No significant coronary stenosis was observed in 39 of those 155 cases, and CABG or medical treatment was carried out in 13 cases because PCI was not indicated. As a result, 103 patients

underwent PCI and 6 needed IIb/IIIa inhibitor as planned or for rescue because of no-reflow or side branch occlusion and 1 case needed a temporary pacemaker for rescue because of complete heart block. PCI was successful in 96 cases: 54 in Group I and 42 in Group II (Fig 1).

The comparative results for the 96 cases of successful PCI only are as follows. There were 25 smokers (46%) in Group I and 19 (45%) in Group II, there were 32 (59%) and 29 (69%) patients with hypertension, respectively, 6 (11%) and 5 (12%) with diabetes, 2 (4%) and 1 (2%) with a family history of ischemic heart disease, and 21 (39%) and 17 (41%) with hyperlipidemia. There was no significant difference between the group for coronary risk factors.

According to the coronary angiography results, there were 32 cases of single-vessel disease (59%), 15 cases of 2-vessel disease (28%) and 7 cases of 3-vessel disease (13%) in Group I and 27 (64%), 8 (19%) and 7 (17%), respectively, in Group II. No significant difference was observed between the groups. The target lesion was in the left anterior descending artery in 31 (57%) and 23 (55%) cases in Group I and Group II, respectively, in the left circumflex artery in 13 (24%) and 10 (24%) and in the right coronary artery in 10 (19%) and 9 (21%). No significant difference was observed between the groups. As for the type of lesion, there were 2 cases of Type A was (2%), 34 of Type B₁ (63%), 7 of Type B₂ (13%) and 12 of Type C (22%) in Group I, and 0 (0%), 20 (48%), 15 (36%) and 7 (17%), respectively, in Group II. As for TIMI flow, there were 5 cases of TIMI 0 was (9%), 5 of TIMI I (9%), 11 of TIMI II (20%) and 33 of TIMI III (61%) in Group I, and 1 (2%), 2 (5%), 11 (26%) and 28 (67%), respectively, in Group II. No significant difference was observed between the groups (Table 1).

As for PCI, 7 cases (13%) had balloon dilatation only and 47 (87%) had balloon dilatation and then stenting in Group I, and there were 11 cases (26%) and 31 (74%), respectively, in Group II. Multivessel PCI was performed in 10 cases (18%) in Group I and 7 cases (17%) in Group II, and no significant difference was observed between the groups.

CK-MB, cTnT and cTnI concentrations in Group I were 10.7 ± 6.3 mg/dl, 0.02 ± 0.05 ng/ml and 0.31 ± 0.68 ng/ml, respectively, and 9.6 ± 4.9 mg/dl, 0.04 ± 0.10 ng/ml and 0.35 ± 1.38 ng/ml in Group II. Maximum concentrations after PCI were 9.1 ± 7.0 mg/dl, 0.03 ± 0.05 ng/ml and 0.69 ± 1.24 ng/ml, respectively, in Group I, and 8.5 ± 6.2 mg/dl, 0.03 ± 0.06 ng/ml and 0.36 ± 0.68 ng/ml in Group II. Delta values defined as maximum value minus the value before PCI, were 1.2 ± 3.5 mg/dl, 0.01 ± 0.02 ng/ml and 0.33 ± 1.32 ng/ml, respectively, in Group I, and 1.1 ± 2.6 mg/dl, 0.01 ± 0.01 ng/ml and 0.14 ± 0.39 ng/ml in Group II. After PCI, CK-MB was increased in 9 cases (17%) in Group I and 6 (14%) in Group II, cTnT was increased in 16 cases (30%) in Group I and 6 (14%) in Group II, and cTnI was increased in 25 cases (46%) in Group I and 9 (21%) in group II, and for all troponins, the concentration was increased in 28 cases (52%) in Group I and 10 (24%) in Group II. The incidence of increased enzyme concentrations was significantly lower in Group II than in Group I ($p=0.01$).

During the 6-month follow-up period, there were 2 cases (4%) of myocardial infarction in Group I and 1 (2%) in Group II, and 1 (17%) and 4 (10%) of reperfusion such as PCI or CABG. Nine cases (17%) of MACE occurred in Group I and 5 (12%) in Group II, but without significant

difference between the 2 groups ($p=0.57$).

The LVEF measured by echocardiography was $66.5 \pm 7.8\%$ in Group I and $64.7 \pm 9.0\%$ in Group II on admission and no significant difference was observed between the 2 groups, but 6 months later it was $65.4 \pm 7.2\%$ in Group I and $71.0 \pm 6.7\%$ in Group II, which was significantly higher than Group I ($p=0.03$, Fig 2).

Discussion

Increased myocardial troponin concentration is commonly observed during PCI in patients with coronary artery disease and is known to be caused by damage to the myocardial cells during PCI. However, the myocardial troponin concentration has not been used properly to monitor the damage to myocardial cells after successful PCI.^{4,15–18} Myocardial troponin is a protein controlling myocardial contraction and is not detected in the blood under normal conditions. Because it is cardiac specific, it can be used as an indicator of myocardial damage and is more sensitive and specific to myocardial cell damage than CK-MB.^{19–20} The authors have previously reported that the release of myocardial troponin after PCI is common in patients with successful PCI, particularly TnI, which is a sensitive indicator of minor myocardial damage.⁴

It has been found that the higher the concentration of myocardial troponin on admission for acute coronary artery syndrome the higher the incidence of myocardial infarction and death, so the myocardial troponin concentration is used in the evaluation of acute coronary artery syndrome patients for establishing the treatment strategies and evaluating prognosis.^{23–25}

Nicorandil is a compound of a nicotinamide derivative and nitrate moiety, which works like a nitrate drugs and at the same time opens ATP-sensitive K^+ channels. similar to the nitrate drugs it increases blood flow in the coronary artery and decreases both preload and afterload. These drugs also have an anti-arrhythmic effect by shortening the action potential through opening of the K^+ channel, and myocardial protective functions such as reducing the resistance of micro-coronary artery flow through relaxation of the smooth muscles of the blood vessels, and preconditioning.^{5–8} Ischemic preconditioning, which is understood to reduce the size of the infarct by protecting the myocardium from severe ischemia following one or more episodes of myocardial ischemia–reperfusion, is known to occur as the K^+ channel is opened. Nicorandil has a function similar to ischemic preconditioning and is known to reduce the size of the infarct and promote the recovery of systolic function after infarction.^{26–30}

The Impact of Nicorandil in Angina research, which was a large-scale study of the myocardial protective effect of nicorandil in the high-risk group of patients with stable angina, reported that 13.1% of patients who had oral nicorandil died from coronary artery disease or were admitted unexpectedly for non-fatal myocardial infarction or chest pains, which was significantly lower than the 15.5% of patients who given placebo, so nicorandil could improve prognosis in stable angina.⁹ In one study of patients with UAP, Patel et al reported that the frequencies of transient myocardial ischemia, ventricular tachycardia and supra-ventricular tachycardia were reduced in patients who had oral nicorandil.¹⁰ Another study of patients with myocardial infarction who had PCI reported that those who had an injection of nicorandil showed significant improvement in

Fig 2. Comparative left ventricular ejection fraction (LVEF) measured by echocardiography on admission and at 6 months follow-up in the isosorbide dinitrate (ISDN) and nicorandil (NICO) infusion groups.

LV function, wall motion score index and regional wall motion, as well as less frequent complications in hospital and less frequent no-reflow phenomenon on contrast echocardiography.^{11,31–33} Investigations of the myocardial protective effect of nicorandil during PCI reported that ST-segment sum and QT dispersion during PCI decreased in chronic stable angina patients after oral nicorandil was administered for 1 week.^{12,34} Ikeda et al compared the degree of ST-segment elevation in acute myocardial infarction patients who required primary coronary artery intervention in those injected with nicorandil and those with isosorbide dinitrate.³⁵

The present study investigated UAP patients treated with nicorandil for 12–48 h prior to PCI, and examined the myocardial protective effect of nicorandil based on the rate of increase of myocardial troponin. The low rate of increase in such patients suggests a myocardial protective effect, which can be explained by nicorandil inhibiting myocardial damage during PCI. The effect is considered to originate from ischemic preconditioning, but long-term large-scale research on how such a transient myocardial protective effect influences long-term prognosis is needed.

Study Limitation

The present study has a potential limitation because we investigated the myocardial protective effects of nicorandil prospectively and although the treatment regimen was allocated randomly, it was open labeled.

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