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Original article

The effect on periprocedural myocardial infarction of intra-coronary nicorandil prior to percutaneous coronary intervention in stable and unstable angina

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ABSTRACT

Background: Intravenous nicorandil infusion dilates the coronary artery and reduces inflammation, coronary spasm, and arrhythmia. Periprocedural myocardial infarction (PMI) is a frequent and prognostically important complication of percutaneous coronary intervention (PCI). This prospective randomized study was designed to evaluate the efficacy of intracoronary nicorandil on PMI after elective PCI.
Methods and results: Eighty-one patients with stable or unstable angina undergoing PCIs of the left anterior descending artery were randomly assigned to the nicorandil group ($n = 41$) or the control group ($n = 40$). In the nicorandil group, 4 mg of intracoronary nicorandil was infused prior to PCI. Post-PCI, peak levels of creatine kinase (CK)-MB and troponin I were measured and angiographic findings were analyzed. Side branch status was also assessed. All PCIs were successful. One cerebrovascular infarction and one acute ST segment elevation myocardial infarction with acute stent thrombosis occurred in the nicorandil group. No deaths occurred, and no other major cardiac adverse events were observed in either group over 6 months follow-up. The post-PCI peak CK-MB and troponin I levels were not significantly different between the two groups. There were no significant differences between the nicorandil and control subjects in side branch occlusion or flow reduction, or in the jail index.
Conclusions: Intra-coronary nicorandil infusion had no significant effect on PMI and cardiac enzymes after PCI in patients with stable or unstable angina.

Introduction

Periprocedural myocardial infarction (PMI) is a common complication of percutaneous coronary intervention (PCI). PMI is related to myocardial damage after PCI and is associated with worse subsequent cardiac outcomes [1]. It occurs most commonly due to distal embolization, side-branch occlusion, coronary dissection, and altered collateral flow [2]. Given its undesirability, a number of therapeutic modalities to reduce PMI have been considered, but no practical and useful method has yet been clearly demonstrated. Nicorandil is an antianginal agent with a dual mechanism of action; it induces nitrate- and ATP-sensitive potassium channels to open. The action of nicorandil on nitrate-mediated channels causes vasodilation of systemic veins and epicardial coronary arteries. The opening of ATP-sensitive potassium channels in response to nicorandil causes vasodilation of peripheral and coronary resistance arterioles, dilating resistance vessels [3]. Nicorandil also reduces inflammation, arrhythmia, and spasm. Intravenous and intracoronary nicorandil in acute ST segment elevation myocardial infarction (STEMI) reduced no reflow, slow flow, and infarct area [3,4]. Murakami et al. reported that intravenous nicorandil infusion reduced the incidence of minor cardiac marker elevation in patients undergoing elective PCI [5]. However, data on the influence of intracoronary nicorandil on the prevention of PMI are limited. We therefore conducted a prospective, randomized, single-center study that was designed to evaluate the efficacy of intra-coronary nicorandil on PMI prevention.

Methods

Subjects

The study group comprised 81 patients who visited the Cardiology Department of Pusan National University Hospital for chest pain between March 2010 and June 2011. All subjects were

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diagnosed with stable or unstable angina pectoris, without baseline elevation of cardiac enzymes. Exclusion criteria were acute STEMI, non-ST segment elevation myocardial infarction (NSTEMI), liver and kidney dysfunction, age > 80 years, cardiogenic shock, temporary pacemakers or intra-aortic balloon pumps, and use of nitrate, nicorandil, or calcium channel blockers before PCI. The patients were scheduled to undergo PCI at the left anterior descending (LAD) artery. For evaluating side branch occlusion, cases in which stent insertion into side branches was required were also excluded. Subjects were assigned to a nicorandil group ($n = 41$) or a control group ($n = 40$). In the nicorandil group, 4 mg of intra-coronary nicorandil was infused prior to PCI (2 mg before ballooning and 2 mg before stenting). The control group was treated without nicorandil. The study protocol was approved by the ethical committee of Pusan National University Hospital and written informed consent was obtained from each patient.

Procedures

Diagnostic coronary angiographies were performed via the right or left femoral artery and via the radial artery using the Seldinger method. All patients received antiplatelet agents (aspirin, clopidgrel) and heparin. The guidewire was passed into the culprit lesion. Patients in the nicorandil group were then administered 2 mg intracoronary nicorandil prior to percutaneous transluminal coronary angioplasty. An additional dose of 2 mg intracoronary nicorandil was given before stent implantation. A minimum interval of 3 min was observed between the first and second doses of nicorandil, to reduce adverse effects. In the control group, conventional PCI was performed without nicorandil administration. In the nicorandil recipients and the control subjects, one or more drug-eluting stents (DES) were implanted for the treatment of LAD artery lesions. Success of the procedure was defined as >50% increase in internal luminal diameter, <30% residual stenosis, and a thrombolysis in myocardial infarction (TIMI) flow grade 3.

Cardiac enzymes

Blood was collected just before PCI and 6, 12, 24, 48, and 72 h after successful PCI for measuring the concentrations of creatine kinase myocardial band (CK-MB) and cardiac troponin I (cTnI). CK-MB and cTnI were measured by immunoassay (UniCel DxI 800 system, Beckman Coulter, Fullerton, CA, USA). The normal reference values for CK-MB, and cTnI were <5 μg/L, and 0.05 ng/mL, respectively.

Analysis of coronary angiography

Angiograms were taken after stent implantation in all study patients, and no-reflow phenomenon (transient or final), slow flow, dissection, and distal embolization were recorded. One of the main causes of PMI is side branch occlusion. Side branches of more than 1 mm and less than 2 mm in diameter were therefore analyzed, including septal branches and diagonal branches. Side branch status was described in terms of branch occlusion, narrowing, and TIMI flow reduction. The side branch was considered narrowed when there was a >50% stenosis after stent placement and reduction of TIMI flow by more than one grade at any time after stent placement was defined as "TIMI flow reduction". As described above, "jail index" was defined and used. The jail index was calculated as the number of occluded side branches, or side branches with a reduced TIMI flow after PCI, divided by the total number of side branches of the LAD covered by the stents. Jail index was expressed as a percentage.

Clinical outcomes

Clinical outcomes were evaluated by recording major adverse cardiac events (MACEs) during the hospitalization period and over 6 months of follow-up. MACEs were defined as death, STEMI, NSTEMI, target lesion revascularization (TLR), and target vessel revascularization (TVR). TLR was defined as a repeat revascularization within the stent or within segments 5-mm distal or proximal to the stent. TVR was defined as a revascularization of any lesion located in the same previously treated epicardial vessel.

Statistical analysis

Data are presented as mean ± SD or mean ± SE. For continuous variables, Student's t test was used to assess the differences between groups. Nominal variables were analyzed with the chi-squared test. A value of $p < 0.05$ was considered to be statistically significant.

Results

Patient characteristics

Of 81 patients eligible for this study, 41 were assigned to the nicorandil group and 40 to the control group. There were no differences between the nicorandil group and the control group in background factors including age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, previous history of myocardial infarction (MI) or coronary angioplasty, and family history of ischemic heart disease. In addition, there were no significant differences between the two groups in laboratory findings such as lipid profile, C-reactive protein (CRP), and creatinine (Table 1).

Coronary angiographic and procedural characteristics

There were no differences between the nicorandil and control groups in lesion type according to the American College of Cardiology/American Heart Association lesion classification [nicorandil group: type B2 2/41 (4.9%), type C 39/41 (95.1%); control group: type B2 1/40 (2.5%), type C 37/40 (92.5%), $p = 0.305$]. There were also no differences between the groups in the occurrence of three vessel disease (nicorandil group, 17/41 (41.5%); control group, 17/40 (42.5%), $p = 0.265$) (Table 2). Mean LAD artery lesion diameters were 2.4 ± 0.51 mm in the nicorandil group and 2.43 ± 0.51 mm in the control group. LAD artery lesion lengths were 27.4 ± 3.9 mm in the

Table 1
Baseline clinical characteristics.

N (90)	Nicorandil group (*N* = 41)	Control group (*N* = 40)	*p*
Disease			
Stable angina	21 (51.2%)	23 (57.5%)	0.657
Unstable angina	20 (48.8%)	17 (42.5%)	
Age (years)	66.2 ± 9	65.3 ± 10	0.654
Male	20 (48.8%)	25 (62.5%)	0.266
Hypertension	27 (65.9%)	27 (67.5%)	0.531
Diabetes mellitus	15 (36.6%)	14 (35.0%)	0.533
Smoking	14 (34.1%)	14 (35.0%)	0.561
Family history of MI	7 (17.1%)	5 (12.5%)	0.753
Previous angioplasty	3 (7.3%)	0 (0%)	0.241
Dyslipidemia	9 (22.0%)	8 (20.0%)	0.523
Total cholesterol (mg/dL)	182.5 ± 31.8	193.9 ± 35.9	0.118
LDL (mg/dL)	118.18 ± 26.3	119.67 ± 34.9	0.835
HDL (mg/dL)	41.15 ± 9.5	43.4 ± 11.64	0.347
Creatinine (mg/dL)	1.02 ± 0.53	1.04 ± 0.23	0.8
hsCRP (mg/dL)	0.788 ± 2.0	0.448 ± 0.5	0.287

MI, myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.