Impact of Nicorandil to Prevent Reperfusion Injury in Patients With Acute Myocardial Infarction

— Sigmart Multicenter Angioplasty Revascularization Trial (SMART) —

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Background Nicorandil in conjunction with percutaneous coronary intervention (PCI) has been reported to reduce reperfusion injury events and improve cardiac function in patients with acute myocardial infarction (AMI). This multicenter study was undertaken to determine the effectiveness and optimal administration of nicorandil in AMI patients.

Methods and Results Ninety-two patients with first AMI were randomly assigned to 1 of 3 groups: intracoronary administration of nicorandil (Group A), combined intravenous and intracoronary administration of nicorandil (Group B), and no nicorandil administration (Group C). The primary endpoint was a composite of the incidence of reperfusion-induced arrhythmia, chest pain, and no-reflow/slow-reflow. The secondary endpoint was the combined rate of improvement in the Thrombolysis in Myocardial Infarction frame count (cTFC) and ST resolution (STR). A significant difference was observed in the primary endpoint for Group B as compared with Group C (p=0.05). In the meantime, a significant improvement was shown in the secondary endpoint for Group B compared with Group C (p=0.04 and 0.006 for cTFC and STR, respectively).

Conclusions Combined intravenous and intracoronary administration of nicorandil reduces reperfusion injury during PCI and improves the cTFC and STR in AMI, and appears to be preferable to intracoronary administration alone. (Circ J 2006; 70: 1099–1104)

Key Words: K+ channel opener; Percutaneous coronary intervention; Reperfusion injury; ST resolution; TIMI frame count

Significant improvement in the prognosis of myocardial infarction (MI) has been achieved with reperfusion therapy, which produces immediate recanalization and thus reduces infarction size and mortality rate. However, experimental and clinical studies have demonstrated that myocardial impairment, known as reperfusion injury, may occur as a result of reperfusion. Even after recanalization is achieved, reperfusion injury often occurs, including no-reflow or slow-reflow, in which sufficient myocardial blood flow cannot be obtained, resulting in a poor outcome of cardiac function in the long term. Ito et al. investigated the association between the no-reflow phenomenon and left ventricular (LV) function and reported that the phenotype is associated with a decrease in wall motion score, LV ejection fraction, and regional wall motion. In addition, a very poor outcome often occurs in routine clinical practice when reperfusion-induced arrhythmia or chest pain is observed during the reperfusion procedure. Therefore, prevention of reperfusion injuries, such as no-reflow, reperfusion-induced arrhythmia and chest pain, will contribute to improvement of the long-term prognosis for chronic cardiac function in patients with acute MI (AMI).

Nicorandil is an antianginal agent with a dual mechanism of action: nitrate and K+ATP channel opener. The nitrate action causes vasodilation of systemic veins and epicardial coronary arteries, while the ATP-sensitive potassium channel opener action causes vasodilation of peripheral and coronary resistance arterioles. Nicorandil not only decreases preload and afterload, but also increases coronary blood flow. Nicorandil has a safety record equivalent to those of oral nitrates, β-blockers, and calcium antagonists.

Recent reports have determined that the no-reflow phenomenon is improved by intracoronary administration of verapamil or nicorandil or adenosine in conjunction with coronary angioplasty. Sakata et al. reported that a single intracoronary administration of nicorandil improved myocardial blood flow and chronic wall motion after reperfusion in patients with AMI. Ito et al. reported that intravenous bolus administration followed by continuous infusion of nicorandil improved reperfusion injury and wall function.
Those studies were, however, performed in a single center, and there has not been a report concerning the effectiveness of nicorandil according to the method of administration to patients with AMI. Therefore, the present study was designed to investigate the effectiveness of nicorandil for reperfusion injury and to determine the optimal administration method for AMI patients undergoing reperfusion therapy in a multicenter trial.

This study was a randomized pilot trial comparing 3 types of nicorandil administration: intracoronary, combined intracoronary and intravenous (an intravenous bolus injection and continuous infusion were given in addition to intracoronary administration) and non-administration.

**Methods**

**Subjects**

The subjects were 92 patients who had been hospitalized for a first AMI from May 2000 through December 2002 with grade 0 or 1 Thrombolysis in Myocardial Infarction (TIMI) during initial coronary angioplasty within 6 h of the onset of symptoms. Two patients who had lesions involving multiple arteries and were switched to treatment with coronary artery bypass grafting were excluded from analysis. This report is based upon the data obtained from the remaining 90 patients.

AMI was diagnosed on the basis of chest pain of ≥30 min duration, ST segment elevation or depression in 2 contiguous leads of the 12-lead electrocardiogram (ECG) and >3-fold elevation of creatine kinase (CK) above the maximum level in the normal range.

The exclusion criteria were a history of coronary artery bypass grafting, previous MI, and cardiogenic shock. The physicians obtained written informed consent from each patient, and the study was approved by the hospital ethics committee.

**Study Design**

Immediately after AMI was diagnosed, the patients were allocated to 1 of 3 groups by the envelope method: intracoronary administration of nicorandil group (Group A), combined intravenous and intracoronary administration of nicorandil group (Group B), and no nicorandil administration (Group C).

In Group A, 0.5 mg per dose (1–2 mg in total in principle) of nicorandil was intracoronarily administered 1–2 times before and after percutaneous coronary intervention (PCI) balloon inflation.

In group B, 96 mg nicorandil injection was dissolved in 100 ml physiological saline or transfusion fluid to make its concentration approximately 1 mg/ml. Then 4 ml (≈4 mg) was intravenously injected, followed by a continuous drip infusion of 6 ml/h (≈6 mg/h). In addition, nicorandil was administered intracoronarily as in Group A. Heparin was injected over a period of 48 h after coronary angioplasty, and aspirin was administered to all patients.

The primary composite endpoint consisted of reperfusion-induced arrhythmia, chest pain, and no-reflow/slow-reflow, conditions that allowed evaluation of the degree to which reperfusion injury was inhibited. The secondary endpoint was the combined outcome of TIMI frame count (cTFC) and ST resolution (STR).

**No-Reflow/Slow-Reflow**

No-reflow and slow-reflow were diagnosed when the TIMI and thrombolysis flow grades were 2 or lower, despite a successful PCI such as balloon angioplasty or stent insertion. The diagnosis of the no-reflow and slow-reflow phenomena was based on cineradiographs sent to Yamada Red Cross Hospital and examined by an experienced technician without knowledge of the patient group allocation.

**Reperfusion-Induced Arrhythmia**

The incidence of ventricular arrhythmia was evaluated by monitoring the ECG in the catheter room and coronary care unit. Reperfusion-induced arrhythmia was diagnosed when ventricular tachycardia (>100 pulses/min over a minimum period of 3 heart beats) or fibrillation was observed within 24 h of angioplasty.

**Chest Pain**

The number of episodes of chest pain was recorded for patients who complained of chest pain that lasted for at least 30 min within the 24 h following onset of MI.

**cTFC**

The cTFC was measured according to the method of Gibson et al.20 to determine blood flow at the time of coronary angiography. The cine frame counts derived from the injection of contrast medium to the peripheral landmark were measured on the coronary angiogram. The frame rate was measured at 30 frames/s. Coronary angiography was performed at a 30° right anterior oblique/caudal projection angle for the left anterior descending and left circumflex arteries and a 60° or 30° left anterior oblique/cranial projection angle for the right coronary artery. The cTFC was measured by a physician without knowledge of the patient group allocation.

**STR**

In order to evaluate STR, the total sum of the ST segments elevation from the J point to the point reached 20 ms later was calculated from the 12-lead ECG recorded before the start of reperfusion, and 90 min (range: 80–120 min) after the completion of reperfusion. Evaluation of anterior infarction was based on the total sum of the ST elevation in leads V1–6, I and aV L, and the total sum of the ST depression in leads II, III and aV F. Evaluation of non-anterior infarction was based on the total sum of the ST elevation in leads II, III and aV R (including I, aV L, V5, and V6, if present), and the total sum of the ST depression in V1–4. STR was measured by a physician without knowledge of the patient group allocation. The rate of improvement in ST elevation was classified as “complete resolution” (70% or more improvement) and “no resolution” (<70%).

**Statistical Analysis**

Data were presented as mean ± SD or mean ± SE. For continuous variables, Kruskal-Wallis’s test or 1-way analysis of variance was used to assess the differences among the 3 groups in the univariate analysis. Tukey’s test was used for multiple comparisons of individual groups. A discrete quantity analyzed using the χ²-test. The stepwise method was used with a variable of p<0.2 as the explanatory variable in multiple logistic analysis. A value of p<0.05 was considered to be statistically significant.

**Results**

Ninety patients from 5 centers allocated to Groups A, B,
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and C as 32, 31 and 27 patients, respectively, were eligible for analysis.

There were no differences among the 3 groups in background factors such as age, sex, time from the onset of symptoms to reperfusion, stent placement rate, coronary risk factors, or culprit lesions (Table 1). None of the patients showed severe hemodynamic impairment or cardiogenic shock (hypotension with systolic blood pressure <90mmHg and tachycardia >100 beats/min not caused by hypovolemia) before or after the administration of nicorandil, although we do not have real-valued hemodynamic parameters.

Primary Composite Endpoint (Inhibition of Reperfusion Injury)

Reperfusion-induced arrhythmia, chest pain, and the no-reflow/slow-reflow phenomena were defined as the primary composite endpoint. These events were observed in 4 of 32 patients (13%) in Group A, 3 of 31 patients (10%) in Group B and 9 of 27 patients (33%) in Group C, showing a difference between Groups B and C in the incidence of the primary composite endpoint (Fig 1: p<0.05). The incidence of no-reflow/slow-reflow was low in Groups A and B (1 of 32 patients (3%) and 1 of 31 patients (3%), respectively) compared with 5 of 27 patients (19%) in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and Lesion Characteristics of the 3 Groups of AMI Patients</th>
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<tbody>
<tr>
<td></td>
<td>Group A</td>
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<tr>
<td>N</td>
<td>32</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.5±10.0</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>27/5</td>
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<tr>
<td>Diabetes mellitus</td>
<td>9 (28%)</td>
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<tr>
<td>Hypertension</td>
<td>13 (41%)</td>
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<tr>
<td>Obesity</td>
<td>6 (19%)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>17 (53%)</td>
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<tr>
<td>Smoking</td>
<td>17 (53%)</td>
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<tr>
<td>Time to reperfusion from onset, h</td>
<td>3.98±1.51</td>
</tr>
<tr>
<td>TIMI grade (0/1,2,3)</td>
<td>18/14</td>
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<tr>
<td>No. of diseased vessels (1/2/3)</td>
<td>25/6/10</td>
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<td>LAD/LCX/RCA</td>
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Results are mean±SD or number of patients (%).

Group A, intracoronary administration of nicorandil; Group B, combined intravenous and intracoronary administration of nicorandil; Group C, no nicorandil administration.

AMI, acute myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, Thrombolysis in Myocardinal Infarction; DS, diameter stenosis.

Fig 1. Primary endpoint. Group A, intracoronary administration of nicorandil; Group B, combined intravenous and intracoronary administration of nicorandil; Group C, no nicorandil administration. There was a significant difference by χ² test in the rate of occurrence of the composite endpoint in Groups B and C. VT/Vf, ventricular tachycardia/ventricular fibrillation; NR/SR, no-reflow/slow-reflow. *p<0.05.
Group C; however, there was no significant difference among the 3 groups. A similar result was obtained for the incidence of reperfusion-induced arrhythmia. As for chest pain, Group B showed a significantly low incidence in comparison with Group C (p<0.05).

Factors contributing to the occurrence of the composite endpoint were assessed using multiple logistic analysis. Explanatory variables were: allocation (Group A, B or C), age (<60 years vs ≥60 years), CK (<2,400 IU/L vs ≥2,400 IU/L), diabetes mellitus, hypertension, hyperlipidemia, smoking, time from the onset of symptoms to reperfusion (within 3 h vs 3–6 h), and the TIMI flow grade before recanalization (0 vs 1+2+3). The odds ratio for the occurrence of the composite endpoint in Group B was 0.155, showing a significant reduction compared with Group C (Table 2: p=0.016). The odds ratio for the same endpoint in Group A was 0.249, showing no significant reduction compared with Group C (Table 2: p=0.052).

**cTFC**

The cTFC was 19.13±6.92 in Group A, 18.78±7.39 in Group B, and 25.65±12.44 in Group C, showing a significant difference among the 3 groups (Fig 2: p=0.027). Multiple comparison using Tukey’s test revealed a significant improvement in cTFC in Group B compared with Group C (p=0.041), but did not show a significant improvement in Group A compared with Group C (p=0.991).

**STR**

The ECG data from before and within 90 min of PCI were available for 54 of the 90 patients. There were no significant differences among the 3 groups in age, sex, time from the onset of symptoms to reperfusion, coronary risk factors, or culprit lesions (data not shown). “Complete resolution” occurred in 17% (3/18) in Group C, vs 50% (9/18) in Group A, and 67% (12/18) in Group B. Group B achieved complete resolution at a significantly higher rate than Group C (Fig 3: p=0.006).

Factors contributing to “complete resolution” (improvement of 70% or more) were assessed using multiple logistic analysis and the results indicated that both “intracoronary administration” and “combined intravenous and intracoronary administration” were significant factors compared to treatment without nicorandil (Table 3: p=0.0138 and 0.0016, odds ratio =12.3 and 30.5, respectively). Age less than 60 years and TIMI flow grade ≥1 before reperfusion were also found to be significant factors in “complete resolution”.

**Discussion**

**Nicorandil Administration Method and Composite Endpoint**

It has recently been shown that the no-reflow phenomenon occurs in approximately one-third of patients treated...
successfully with coronary angioplasty for AMI. Because the no-reflow phenomenon is attributable to coronary microvascular obstruction, recanalization of the coronary blood vessels may not always reflect restoration of blood flow of the myocardium at the microcirculation level. It is clinically very important to prevent the no-reflow phenomenon because the clinical course and LV function in the chronic phase are poor in patients who develop this phenomenon. Sakata et al reported that myocardial blood flow and wall motion in the chronic phase are improved by intracoronary administration of 2 mg nicorandil following coronary angioplasty after reperfusion. Watanabe et al also reported that the intravenous administration of nicorandil in the rat ischemic reperfusion model significantly prevented the incidence of no-reflow and reduced the occurrence of morphological abnormalities of myocardial blood capillaries and the decrease in blood capillary capacity. Ito et al and Sugimoto et al reported that no-reflow was reduced, with a lower incidence of complications during hospitalization period, and the outcome during the chronic phase was improved by intravenous administration of 4 mg nicorandil and continuous infusion of 6 mg/h nicorandil prior to coronary angioplasty. Although no significant preventive effect of no-reflow and slow-reflow was observed in our study, the incidence of the composite endpoint, including reperfusion-induced arrhythmia and chest pain, was significantly low with combined intracoronary and intravenous administration of nicorandil.

In the present study nicorandil administration was initiated after confirmation of the diagnosis of AMI. It has been reported that the size of the no-reflow lesion is extremely small at the time of coronary reperfusion, but increases within 15 min of reperfusion2 suggesting that there is myocardial blood flow in the no-reflow lesion immediately after reperfusion. Therefore, nicorandil can act on the coronary microvessels via blood circulation during reperfusion. The possible mechanisms by which nicorandil prevents reperfusion injury and improves myocardial blood flow are as follows. First, nicorandil dilates small vessels by opening K+ATP channels thus improving the microcirculation by dilating resistance vessels. Second, nicorandil reduces the migration of leukocytes and suppresses the production of excess free radicals. Thus, nicorandil may reduce the injury to coronary microvessels by leukocytes and improve myocardial blood flow. In addition, it has been reported that the incidence of reperfusion-induced arrhythmia is significantly high because the area of myocardial injury becomes broad in cases of the no-reflow phenomenon. Although significant prevention of reperfusion-induced arrhythmia was not observed in the present study, it is possible in principle to inhibit reperfusion-induced arrhythmia by preventing the no-reflow phenomenon. Furthermore, most patients who have chest pain within 24 h of AMI onset experience a poor clinical prognosis. It is considered that nicorandil prevents the occurrence of chest pain after onset of AMI by its vasodilatory action, improvement of microcirculation and increase of coronary blood flow. These effects seem to persist with continuous intravenous administration of nicorandil after PCI and therefore the occurrence of chest pain was significantly reduced in this study.

**Nicorandil Administration and cTFC/STR**

A significant difference was observed in the cTFC in the group that received intracoronary and intravenous administration of nicorandil compared with the non-nicorandil administration group. Because cTFC is considered to reflect the condition of the peripheral coronary arteries it appears that intravenous administration of nicorandil improved the blood flow there by opening the K+ channels.

STR, which measures how much the ST elevation is relieved after recanalization, is a simple and useful index of coronary microcirculation following recanalization. Van't Hof et al compared the long-term outcome in 3 groups: “complete resolution” with at least 70% improvement of STR, “partial resolution” with 30–70% improvement, and “no resolution” with less than 30% improvement 1 h after recanalization. They reported that the long-term outcome was more favorable in the “complete resolution” group than in the other 2 groups. Our present examination has shown that the ratio of the patient who experienced 70% and more improvement in STR was higher in the group receiving intravenous nicorandil in addition to intracoronary injection than in the nicorandil non-administration group.

In addition, nicorandil administration was shown to be a significant factor for obtaining “complete resolution”, as analyzed by multiple logistic analysis. Therefore, nicorandil administration prior to and throughout reperfusion appears to be effective from the viewpoint of STR.

**Study Limitation**

This was a pilot study aimed at examining the effects of nicorandil for reperfusion injury and the optimum dosages for intracoronary administration alone or in addition to intracoronary injection. Because there has not been a similar study performed to date, further investigations of the effectiveness of nicorandil in comparison with the placebo and in more cases are needed. The present study was designed to evaluate the acute phase of MI and sufficient evaluation of the chronic phase, using such indexes as wall motion, LV ejection rate and LV telediastolic-volume-index, was not done. Because systematic analysis of patients in the chronic phase of MI was not performed, it cannot be concluded whether or not nicorandil improves cardiac function in the chronic phase and thereby improves the prognosis. However, in this study, prevention of reperfusion injury and improvement of cTFC and STR were observed for continuous intravenous administration of nicorandil in addition to intracoronary injection, and because it has been reported that improvement in reperfusion injury, cTFC and STR contribute to improved, cardiac function and wall motion in the later stages, the beneficial effects of continuous intravenous additional administration of nicorandil on the chronic phase can be well predicted. A study using “improvement of outcome in the chronic phase” as a primary endpoint is needed.

**Optimal Nicorandil Administration Method**

One of this study’s goals was to determine the optimal method of nicorandil administration by comparing intracoronary administration group (Group A), combined intravenous and intracoronary administration group (Group B), and no nicorandil administration group (Group C). Because significant differences in the composite endpoint, cTFC and STR, were observed in Group B in comparison with Group C, continuous and intravenous nicorandil administration in addition to intracoronary injection seems to be useful. Group A showed a tendency toward improvement in comparison with Group C, but it was not significant. One of the reasons for the effectiveness of additional intra-
venous administration is considered to be useful. By continuous infusion of nicorandil after reperfusion is considered to be useful.

Although nicorandil-induced arrhythmia did not occur in the present study, there is a risk of inducing arrhythmia by intracoronary administration of nicorandil which makes intravenous administration a safer choice. Intravenous administration needs to be further examined from the viewpoint of safety.

References