Comparison Between Nicorandil and Magnesium as an Adjunct Cardioprotective Agent to Percutaneous Coronary Intervention in Acute Anterior Myocardial Infarction

Mizuo Nameki, MD*; Iwao Ishibashi, MD; Yoshiya Miyazaki, MD; Yoshiaki Sakai, MD; Susumu Namikawa, MD*; Nehiro Kuriyama, MD*; Nobuyuki Komiyama, MD*; Kouichi Tsunoda, MD; Yoshiaki Masuda, MD*; Issei Komuro, MD*

Background It has been reported that both nicorandil and magnesium have a cardioprotective effect in experimental ischemia–reperfusion models. In the present study, the cardioprotective effects of nicorandil and magnesium as an adjunct to reperfusion therapy in patients with acute myocardial infarction (AMI) were compared.

Methods and Results Forty consecutive patients with AMI caused by occlusion of anterior descending coronary artery were randomized into 3 groups: (1) Group N: nicorandil was given as 4 mg iv and 4 mg ic before reperfusion, followed by continuous infusion at 4 mg/h for 24 h; (2) Group M: magnesium was administered at 10 mmol iv before reperfusion, followed by continuous infusion at 0.4 mmol/h for 24 h; and (3) Group C: neither nicorandil nor magnesium was given. Left ventriculography was performed immediately after reperfusion and 3 months later. There was no significant change in regional wall motion (RWM) in either Group C or M, whereas that of group N improved significantly. The change in RWM in Group N was significantly greater than in Group C (Group N: 0.92±0.92, Group M: 0.44±0.80, Group C: –0.01±0.65, p<0.05).

Conclusions The early administration of nicorandil as an adjunct to reperfusion is useful for cardioprotection in AMI, but magnesium is not. (Circ J 2004; 68: 192–197)

Key Words: Acute myocardial infarction; Magnesium; Nicorandil; Reperfusion therapy

Reperfusion therapy is effective in limiting the extent of infarction and preserving ventricular function in patients with acute myocardial infarction (AMI). However, some patients do not experience these benefits even when early reperfusion is established, perhaps because of so-called reperfusion injury, that is, restoration of blood flow to ischemic but reversibly injured cardiac cells may result in irreversible injury to those cells. This reperfusion injury constitutes a major hurdle in the current era of reperfusion therapy.

Nicorandil [N-(2-hydroxyethyl)-nicotinamide nitrate; Chugai Pharmaceutical Co Ltd, Tokyo, Japan] is a hybrid of an ATP-sensitive potassium channel (KATP) opener and a nitrate, and it is being used as an anti-ischemic drug. Magnesium is a physiologic calcium antagonist that inhibits the calcium influx to myocardial cells. Previous experimental studies using ischemia–reperfusion models have demonstrated that both nicorandil and magnesium induce a striking enhancement of myocardial salvage and improvement of ventricular function. In some clinical studies, the administration of nicorandil with reperfusion therapy had a beneficial effect on the left ventricular function in AMI patients. On the other hand, 2 large randomized clinical trials using magnesium for AMI gave conflicting results on mortality and it has been demonstrated that magnesium improved ventricular function in AMI patients who did not undergo reperfusion therapy. However, there has not been a previous study that compared the cardioprotective effect of nicorandil and magnesium for AMI, which was the aim of the present study.

Methods

Study Patients The present study included patients with AMI who were admitted to the Chiba Emergency Medical Center and underwent emergency coronary angiography (CAG) with stand-by PCI between June 1997 and September 1998. The diagnosis of AMI was made on the basis of chest pain lasting at least 30 min and ST-segment elevation electrocardiogram in 2 or more adjacent leads. Inclusion criteria were: (1) admission within 24 h of he onset of symptoms, (2) total or subtotal occlusion (Thrombolysis in Myocardial Infarction flow grade (TIMI) 0 or 1) of the proximal or mid-left anterior descending coronary artery (LAD), (3) no prior myocardial infarction, (4) no or mild congestive heart failure (Killip I or II), (5) serum creatinine <2.0 mg/dl, and (6) age <80 years. In total, 40 consecutive patients were enrolled.
Cardiographic ST-segment elevation in the V4 lead, and (4) decrease of systolic blood pressure, (3) additional vasodilators, angiotensin-converting enzyme inhibitors and indefinetly. Calcium channel blockers, nitrates were given if necessary for the treatment of myocardial ischemia or hypertension.

Three months later, follow-up CAG and LVG were performed. Of the 40 patients, 4 had not undergone baseline LVG and 2 did not undergo follow-up LVG, so the comparison of baseline and follow-up LVG was performed in 34 patients.

Data Analysis
Quantitative CAG analysis was performed by experienced angiographers not involved in the imaging procedure, using the coronary end-diastolic frames from both acute and chronic CAG and a computer-assisted cineanalyzer (CCIP-310, Cathex, Tokyo, Japan). Successful reperfusion was defined as both diameter stenosis ≤50% and TIMI 3 flow on final baseline CAG and restenosis was defined as diameter stenosis >50% on follow-up CAG. To evaluate coronary blood flow after reperfusion, the TIMI frame count of LAD was calculated using the final baseline CAG.16

All LVGs were analyzed with the same system as for CAG using the 30° right anterior oblique projection. The end-diastolic volume index (EDVI) and end-systolic volume index (ESVI) were measured by the area-length method on well-opacified LVG frames during normal sinus beats in the acute and chronic phases. The global ejection fraction (EF) was calculated as 100(EDV–ESVI)/EDV.

Statistical Analysis
Results are expressed as mean±SD or number (%). Statistical analysis among the 3 groups were performed by Analysis of Variance (ANOVA) or chi-square analysis followed by the Scheffe-type multiple comparison method.
Serial changes in global and regional ventricular function were estimated by two-way repeated measure ANOVA. A probability value of <0.05 was considered significant.

Table 2  Reperfusion Phenomena

<table>
<thead>
<tr>
<th></th>
<th>Group N (n=13)</th>
<th>Group M (n=13)</th>
<th>Group C (n=14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain increase</td>
<td>8 (62%)</td>
<td>6 (46%)</td>
<td>9 (64%)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure decrease</td>
<td>6 (46%)</td>
<td>6 (46%)</td>
<td>11 (79%)</td>
<td>NS</td>
</tr>
<tr>
<td>ST elevation (mV)</td>
<td>0.34±0.25</td>
<td>0.44±0.38</td>
<td>0.51±0.30</td>
<td>NS</td>
</tr>
<tr>
<td>Reperfusion arrhythmia</td>
<td>2 (15%)</td>
<td>3 (23%)</td>
<td>6 (43%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3  Analysis of Left Ventriculography

<table>
<thead>
<tr>
<th></th>
<th>Group N (n=10)</th>
<th>Group M (n=12)</th>
<th>Group C (n=12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDVI (ml/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>104.6±24.8</td>
<td>100.4±17.2</td>
<td>96.7±17.2</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>119.7±37.8</td>
<td>122.2±25.2*</td>
<td>126.0±22.8**</td>
<td>NS</td>
</tr>
<tr>
<td>∆</td>
<td>15.1±26.2</td>
<td>21.7±29.5</td>
<td>29.3±19.6</td>
<td>NS</td>
</tr>
<tr>
<td>ESVI (ml/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>46.2±13.8</td>
<td>44.2±17.4</td>
<td>43.1±13.8</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>51.2±55.9</td>
<td>42.7±18.3</td>
<td>59.9±23.4*</td>
<td>NS</td>
</tr>
<tr>
<td>∆</td>
<td>5.0±29.1</td>
<td>-1.5±24.1</td>
<td>16.8±19.4</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>54.3±14.1</td>
<td>56.5±13.5</td>
<td>55.2±14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>59.7±20.2</td>
<td>65.9±59.7</td>
<td>53.0±14.2</td>
<td>NS</td>
</tr>
<tr>
<td>∆</td>
<td>5.4±19.6</td>
<td>9.4±17.3</td>
<td>-2.1±15.4</td>
<td>NS</td>
</tr>
<tr>
<td>RWM (SD/chord)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-3.76±0.66</td>
<td>-3.32±0.61</td>
<td>-3.43±0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-2.84±1.08*</td>
<td>-2.88±0.65</td>
<td>-3.44±0.93</td>
<td>NS</td>
</tr>
<tr>
<td>∆</td>
<td>0.92±0.92</td>
<td>0.44±0.80</td>
<td>-0.01±0.65</td>
<td>0.032</td>
</tr>
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*p<0.05 vs baseline, **p<0.01 vs baseline.

Fig 1. Change in regional wall motion (RWM) (follow-up RWM– baseline RWM). Group N showed greater improvement than Group C, with significant difference. In contrast, there was no significant difference between Groups M and C.

**Results**

**Patient Characteristics**

The baseline characteristics were similar among the 3 groups (Table 1). The mean reperfusion time was 363 min from onset of AMI, and 82.5% of the patients were reperfused within 8 h. All patients underwent PCI successfully, and coronary stents were placed in 25.0% of patients. The mean peak serum creatine kinase was 6,635±2,742 IU/L. There was no significant difference in the use of cardio-protective agents such as ß-adrenergic blocking agents or angiotensin-converting enzyme inhibitors.

Exacerbation of chest pain intensity, additional ST-segment elevation and reperfusion arrhythmia were observed with less frequency in the 2 treated groups than in Group C; however there was no significant difference (Table 2). All patients were discharged alive, but 1 patient in Group C died because of congestive heart failure after discharge.

**CAG and LVG**

There were no significant differences in restenosis rates (Table 1). The TIMI frame count of LAD on the baseline CAG was similar among the 3 groups (Group N: 26.8±9.9, Group M: 25.3±8.5, Group C: 28.9±12.7; NS).

Among the 3 groups, there was no significant difference in EDVI, ESVI or EF on both baseline and follow-up. In Groups C and M, a substantial increase in the EDVI from baseline to follow-up was observed. In contrast, there was no significant change in the EDVI of Group N. A considerable increase in the ESVI from baseline to follow-up was also observed in Group C, whereas there was no significant change in the ESVI of Groups N and M. A substantial improvement in EF was not observed in any of the groups. There was no significant difference in RWM among the 3
groups; however, a significant improvement of RWM from baseline to follow-up was demonstrated in Group N, but not in Groups M and C (Table 3). The change in RWM (follow-up RWM–baseline RWM) in Group N was significantly greater than that in Group C, but not in Group M (Fig 1). There was no significant difference in the change of RWM between Groups M and C.

Discussion
The present study is the first randomized clinical trial to compare nicorandil and magnesium as adjunct cardioprotective agents to PCI in anteroseptal AMI. In spite of its design for multiple comparisons and the small study population, the results demonstrate that early administration of nicorandil as an adjunct to PCI improves the RWM of the infarcted area and prevents enlargement of the left ventricle in patients with AMI without any adverse effects and to a greater extent than either magnesium or no treatment.

Previous Studies of Reperfusion Injury
There is a large body of experimental evidence indicating that reperfusion has deleterious effects on viable myocardium, the so-called reperfusion injury. The precise pathogenesis is still unclear, but various possibilities, including calcium overload, oxygen free radicals, neutrophils, cytokines and microcirculatory disturbances, have been considered.

Although various pharmacological agents have been reported to reduce infarct size in ischemia–reperfusion models, many of them, such as diltiazem, 

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RWM after reperfusion and Ito et al. ascertained that continuous intravenous infusion of nicorandil prior to reperfusion prevented the no-reflow phenomenon and preserved left ventricular function. Because of these 2 important roles, it is considered that nicorandil is more effective than magnesium as a cardioprotective agent against reperfusion injury. Recently, the IONA study demonstrated that oral administration of nicorandil reduced the incidence of major coronary events and improved the long term outcome of patients with stable angina, and it is expected that previous use of nicorandil will reduce the deleterious complications at the onset of AMI.

Study Limitations

The present study was designed for multiple comparisons and was carried out in a small study population. In expectation of the prevention of reperfusion injury during PCI, we decided that the initial dose of each drug would be higher than in previous studies. Despite intracoronary administration prior to reperfusion and the higher initial dose of nicorandil, the present study did not demonstrate additional cardioprotective effects more conclusively than previous studies. Because early administration of nicorandil improved RWM without preventing reperfusion phenomena such as exacerbation of chest pain intensity, additional ST-segment elevation and reperfusion arrhythmia, it is impossible to certify that the cardioprotective effect of nicorandil resulted from treatment of reperfusion injury. It is expected that early administration of nicorandil will improve the clinical outcome of AMI patients, but this study was too small to determine the long-term efficacy. Although magnesium failed to show any beneficial effects in this present study, it does not mean that the usefulness of magnesium for AMI is in any way criticized. The dose of magnesium administered after reperfusion therapy was lower than in either the LIMIT-2 or ISIS-4, study because we had previously experienced an extreme elevation of serum magnesium concentration when we administrated magnesium under the same protocol as those studies. Further randomized trials are needed to accurately evaluate the indication and appropriate dose of magnesium therapy for AMI as an adjunct to PCI.

We used the TIMI frame count to evaluate coronary flow and we failed to find improvement in coronary perfusion. Serial investigations of myocardial perfusion using contrast echocardiography, Doppler flow wire or radionuclear perfusion scanning may reveal the contribution of the 2 agents to microcirculatory integrity.

Conclusions

As an adjunct to PCI, nicorandil was useful for preserving the contractility of the infarcted myocardium and preventing an enlargement of the left ventricle in AMI without any adverse effects. On the other hand, magnesium failed to show a cardioprotective effect in this study. Early administration of nicorandil prior to reperfusion therapy in AMI may prevent reperfusion injury.

References


