Randomized, Double-Blinded Multicenter Study

Comparison of Intracoronary Single-Chain Urokinase-Type Plasminogen Activator, Pro-urokinase (GE-0943), and Intracoronary Urokinase in Patients With Acute Myocardial Infarction

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Coronary recanalization rates and changes in the coagulation and fibrinolytic system were evaluated in a randomized fashion in patients with acute myocardial infarction after intracoronary administration of single-chain urokinase-type plasminogen activator (pro-urokinase: GE-0943) or urokinase. Three groups of patients were studied: group H (n=50), 6,000 units pro-urokinase i.c.; group L (n=44), 3,000 units pro-urokinase i.c.; and group U (n=54), 960,000 IU urokinase i.c. Coronary recanalization rates determined angiographically after 45 minutes of intracoronary infusion averaged 90% in group H, 59% in group L, and 61% in group U. The differences were statistically significant between group H and the latter two groups. Pro-urokinase affected plasma proteins of the fibrinolytic system to a lesser degree than urokinase. Bleeding complications were present in one patient in group L, in none in group H, and in five in group U. Thus, intracoronary administration of 6,000 units pro-urokinase is more effective in coronary thrombolysis and causes less systemic fibrinogenolysis than intracoronary administration of urokinase. (Circulation 1988;78:899–905)

Rapid and effective dissolution of intracoronary thrombi by systemic or selective infusion of thrombolytic agents has been demonstrated convincingly in many clinical studies.1–10 In Japan, we initiated a multicenter clinical trial of intracoronary administration of urokinase to aim at early recanalization of the infarct-related coronary arteries in 1982.11 In 1984, a randomized double-blinded, placebo-controlled study was started to assess early recanalization of infarct-related vessels with intracoronary urokinase in patients with acute myocardial infarction.12 The patency rate was 74% for the urokinase group and 17% for the placebo group. However, urokinase possesses little specific affinity for fibrin and, therefore, will activate both circulating and fibrin-bound plasminogen, possibly resulting in serious bleeding complications.

Single-chain urokinase-type plasminogen activator (pro-urokinase: GE-0943)13–15 is a plasminogen proactivator secreted by human embryonic kidney cells,16 which is converted to a two-chain urokinase.17 Pro-urokinase does not significantly activate plasminogen in the absence of fibrin, but the addition of a fibrin clot results in efficient fibrinolysis without fibrinogenolysis.18,19 In a preliminary study,20 we reported that intracoronary administration of pro-urokinase was effective in establishing early recanalization and that the efficacy rate appeared to be dose dependent. No side effects were noted in any patient.
Therefore, we performed this randomized, double-blinded, controlled study to test the efficacy of pro-urokinase and to compare it with urokinase in patients with acute myocardial infarction.

Patients and Methods

Patients

All patients of the 67 participating institutes in Japan who satisfied the following criteria between May 1987 and November 1987 were enrolled: 1) chest pain characteristic of myocardial ischemia for 30 minutes or more; 2) ST segment elevation of at least 0.1 mV on two or more leads of the electrocardiogram; 3) an elapsed time from the onset of chest pain to the administration of the investigational drugs of less than 6 hours; and 4) angiographically documented complete obstruction of the infarct-related artery.

Patients were excluded if they met any of the following criteria: 1) recanalization after intracoronary administration of nitrates; 2) past or present history of gastrointestinal bleeding or hemorrhagic disorder; 3) significant surgical procedure within 2 weeks; 4) presence of rupture in the papillary muscle or interventricular septum, cardiogenic shock, or any other life-threatening systemic diseases; 5) possible or proven pregnancy; 6) uncontrolled hypertension; and 7) other conditions that the attending physicians considered inappropriate for treatment under this protocol.

Study Drugs

Pro-urokinase. Each vial contained 750 or 1,500 units lyophilized pro-urokinase, GE-0943, which is a single-chain urokinase-type plasminogen activator.

Urokinase. Each vial contained 240,000 IU lyophilized urokinase.

The amidolytic activity of pro-urokinase was determined with S-2444, which is a chromogenic substrate for urokinase, before or after activation by plasmin treatment. The amounts of contamination by urokinase in the pro-urokinase preparations were 0% from the amidolytic activities of pro-urokinase preparations before and after activation by plasmin treatment. Three hundred units pro-urokinase (latent activity) described in this paper was estimated to be equivalent to 1×10^3 IU urokinase. Both study drugs were prepared by the Green Cross Corporation, Osaka, Japan, and were identical in appearance.

Study Design

The study comprised the following three groups of patients: group H, four vials of 1,500 units pro-urokinase, 6,000 units in total, were infused during the treatment; group L, four vials of 750 units pro-urokinase, 3,000 units in total, were infused during the treatment; and group U, four vials of 240,000 IU urokinase, 960,000 IU in total, were infused during the treatment.

Three to 10,000 IU heparin were injected intravenously just before coronary arteriography. The coronary artery that was remote to the infarcted zone was visualized first, followed by cineangiography of the infarct-related artery. If coronary arteriography demonstrated total occlusion, nitrates (200 μg or more of nitroglycerin or isosorbide dinitrate) were given intracoronarily. If the nitrates failed to recanalize the occluded artery, the patient was randomized by a double-blinded method to one of the treatment groups. Each vial of the assigned agent was diluted with 20–40 ml normal saline or 5% dextrose-water and infused intracoronarily during a 10-minute period.

After completion of the infusion of each vial, coronary arteriography was repeated to evaluate the degree of recanalization. The degree of recanalization was graded according to the Thrombolysis in Myocardial Infarction trial (TIMI) study as follows: grade 0, no reperfusion; grade 1, thrombolysis without myocardial reperfusion; grade 2, partial reperfusion; and grade 3, full reperfusion.

No concomitant administration of any other plasminogen activator such as urokinase, streptokinase, or tissue-type plasminogen activator was allowed during the period of investigational drug infusion. Subsequent to the coronary cineangiography after the four vials of investigational drug had been given, additional therapies by plasminogen activator, anticoagulation, or percutaneous transluminal coronary angioplasty were permitted if clinically indicated.

Laboratory Tests

Fibrinogen, fibrin(ogen) degradation products, euglobulin lysis time, and α2-plasmin inhibitor were measured on samples taken before treatment and at the conclusion of administration of the fourth vial of the test drug. Complete blood count and routine blood chemistry were measured at baseline and 24 hours after administration of the test drug.

Informed Consent and Statistical Analysis

The study was approved by the human research review committee at each participating institution. Informed consent was obtained from either the patient or the family. Data were expressed as mean ± SD. Analysis of the data was performed with Student’s t test, Kruskal-Wallis’s H test (Sheffe), and χ² test. A p value of less than 0.05 was considered statistically significant.

Results

Patient Data

A total of 164 patients were studied, 53 in group H, 53 in group L, and 58 in group U. Sixteen patients were excluded from data analysis because of cardiogenic shock at the beginning of investigation in eight patients, administration of the drug more than 6 hours after onset of chest pain in three, subtotal occlusion of the infarct-related artery in
TABLE 1. Patient Clinical Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n)</th>
<th>Group H</th>
<th>Group L</th>
<th>Group U</th>
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<td>35</td>
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<tr>
<td>Female</td>
<td>11</td>
<td>9</td>
<td>13</td>
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<td>Symptom onset to treatment initiation (hr)</td>
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<td>&gt;2–4</td>
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<td>Site of infarct</td>
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<td>3</td>
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<td>Hypertension</td>
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<td>Cerebral infarction</td>
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<td>Renal disease</td>
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</table>

Recanalization Rate

Figure 1 and Table 2 demonstrate the coronary recanalization rates after administration of 1, 2, 3, and 4 vials of the test drug for the different groups. Recanalization (TIMI grade 3) was obtained in 76% of the patients in group H, in 36% in group L, and in 43% in group U with statistically significant differences between groups H and L and groups H and U. Recanalization rates differed between the patients in groups H and L and between those in group H and U after the third and fourth vials were administered. Grade 3 or 2 recanalization was attained in 90% of the patients in group H, in 59% in group L,
TABLE 2. Residual Stenosis After Administration of Four Vials of Drug

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (n)</th>
<th>Grade 3</th>
<th>Recanalization Rate (%)</th>
<th>χ² test</th>
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<tbody>
<tr>
<td>H</td>
<td>50</td>
<td>27 (54.0)</td>
<td>11 (22.0)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>L</td>
<td>44</td>
<td>11 (25.0)</td>
<td>5 (11.4)</td>
<td>10 (22.7)</td>
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<tr>
<td>U</td>
<td>54</td>
<td>18 (33.3)</td>
<td>5 (9.3)</td>
<td>10 (18.5)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages.

TIMI, Thrombolysis in Myocardial Infarction trial.
*p<0.01.

and in 61% in group U. Recanalization rates of grade 2 or more differed between the patients in groups H and L after the third and fourth vials were administered, between those in groups U and L after administration of the second vial, and between those in groups H and U after administration of the fourth vial. Recanalization rates increased in a dose-dependent manner for all three groups.

Table 3 indicates the recanalization rates of the different infarct-related arteries, different sites of coronary obstruction, and different intervals between symptom onset to treatment initiation. Infarct-related coronary artery recanalization rates in the patients of group H were 88% in the right coronary artery and 90% in the left anterior descending coronary artery; in group L, rates were 63% in the right coronary artery and 64% in the left anterior descending coronary artery; and in group U, the rates were 59% in the right coronary artery and 65% in the left anterior descending coronary artery. Proximal, middle, and distal obstruction of the coronary arteries demonstrated respective recanalization rates of 96%, 81%, and 89% in group H; 68%, 42%, and 57% in group L; and 77%, 55%, and 25% in group U; the proximal obstruction sites had the highest recanalization rates.

Shorter intervals of symptom onset to treatment initiation did not significantly improve recanalization rates in any study group.

**Laboratory Data**

Table 4 presents fibrinolysis test results. The fibrinogen level was not different before and after treatment in either group H (187 ± 49 vs. 181 ± 42 mg/dl), group L (178 ± 69 vs. 180 ± 78 mg/dl), or group U (181 ± 51 vs. 162 ± 41 mg/dl). Fibrinogen degradation products were significantly increased in group H (15 ± 17 vs. 41 ± 57 μg/ml) and group U (17 ± 25 vs. 186 ± 286 μg/ml) but not in group L (14 ± 14 vs. 36 ± 103 μg/ml).

The euglobulin lysis time was shortened significantly in all three groups: 3.84 ± 1.98 versus 0.46 ± 1.18 hours in group H, 4.08 ± 2.29 versus 0.33 ± 0.76 hours in group L, and 4.02 ± 1.93 versus 0.74 ± 0.54 hours in group U. There was a significant reduction in α₂-plasmin inhibitor in group U (5.68 ± 0.84 vs. 4.40 ± 0.92 mg/dl) and to a lesser degree in group H (5.76 ± 1.16 vs. 4.94 ± 1.12 mg/dl) but not in group L (5.64 ± 1.00 vs. 5.26 ± 0.90 mg/dl).

**Bleeding Complications**

Table 5 presents bleeding complications in six patients (one in group L and five in group U). The patient in group L had bleeding at the puncture site after the catheterization procedure and required a blood transfusion, but immediately after the investigational drug administration, additional heparin and urokinase were infused. The other five patients were administered urokinase with an additional dose of heparin to one patient, urokinase to one, and urokinase and heparin to one.

**Clinical Results 1 Week After Treatment**

There were three reinfarctions (one in group H and two in group U) during the 1-week post-treatment hospitalization. During this period, two patients in
group L died. One died of renal failure, secondary to postoperative complications after surgical closure of a ruptured interventricular septum; the other died of crush syndrome, a complication of the intra-aortic balloon pumping. In group U, three patients died. One death was due to ventricular fibrillation after reinfarction, one was due to cardiac rupture while receiving the second vial of the investigational drug (urokinase), and one was due to renal failure and hematemesis with Mallory-Weiss syndrome.

**Discussion**

Intracoronary administration of urokinase resulted in recanalization rates of approximately 70% in our previous study. In the present study, intracoronary administration of pro-urokinase was used for a comparison with intracoronary urokinase. This study demonstrated an excellent recanalization rate (90%) with high-dose (6,000 units) intracoronary administration of pro-urokinase. A low dose of 3,000 units showed a reduced recanalization rate comparable to that achieved by intracoronary administration of 960,000 IU urokinase, which is the dose currently used in Japan. The present study confirmed that the efficacy of thrombolysis with pro-urokinase was dose dependent up to 6,000 units, a dose that demonstrated a 90% recanalization rate, probably the theoretically expected maximum recanalization rate.

Our previous results also showed that pro-urokinase was an effective thrombolytic and was not associated with systemic activation of the fibrinolytic system, fibrinogen breakdown, or bleeding. Pro-urokinase does not significantly activate plasminogen in plasma in the absence of fibrin, but the addition of a fibrin clot results in efficient fibrinolysis without fibrinogenolysis. In this study, a low dose of pro-urokinase had no significant fibrinolytic effect except on euglobulin lysis time. However, a high dose induced a slight increase in fibrinogen breakdown, and a reduction of euglobulin lysis time and α2-plasmin inhibitor/urokinase. Urokinase showed much more significant generalized effects on the fibrinolytic system.

Bleeding complications were seen in five patients (9%) in group U, but in only one (2.1%) in group L, and in none in group H. Bleeding complications seen in group L occurred after postinvestigational treatment with additional heparin (10,000 IU) and urokinase (240,000 IU i.c.). Furthermore, because no bleeding complications were seen in group H, even after 9,000 units pro-urokinase was administered to four patients (unpublished data from our laboratory), it is unlikely that the current low dose of pro-urokinase induced hemorrhagic complications.

**Table 4. Fibrinolysis Variables**

<table>
<thead>
<tr>
<th>Item</th>
<th>Group</th>
<th>Patients (n)</th>
<th>Before treatment (mean ± SD)</th>
<th>After treatment (mean ± SD)</th>
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<tbody>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>H</td>
<td>38</td>
<td>187 ± 49</td>
<td>181 ± 42</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>39</td>
<td>178 ± 69</td>
<td>180 ± 78</td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>41</td>
<td>181 ± 51</td>
<td>162 ± 41</td>
</tr>
<tr>
<td>Fibrin(ogen) degradation products (μg/ml)</td>
<td>H</td>
<td>39</td>
<td>15 ± 17</td>
<td>41 ± 57*</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>38</td>
<td>14 ± 14</td>
<td>36 ± 103</td>
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<tr>
<td></td>
<td>U</td>
<td>44</td>
<td>17 ± 25</td>
<td>186 ± 286*</td>
</tr>
<tr>
<td>Euglobulin lysis time (hr)</td>
<td>H</td>
<td>38</td>
<td>3.84 ± 1.98</td>
<td>0.46 ± 1.18*</td>
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<tr>
<td></td>
<td>L</td>
<td>38</td>
<td>4.08 ± 2.29</td>
<td>0.33 ± 0.76*</td>
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<tr>
<td></td>
<td>U</td>
<td>41</td>
<td>4.02 ± 1.93</td>
<td>0.74 ± 0.54*</td>
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<tr>
<td>α2-Plasmin inhibitor (mg/dl)</td>
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<td>39</td>
<td>5.76 ± 1.16</td>
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<td>L</td>
<td>39</td>
<td>5.64 ± 1.00</td>
<td>5.26 ± 0.90</td>
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<tr>
<td></td>
<td>U</td>
<td>42</td>
<td>5.68 ± 0.84</td>
<td>4.40 ± 0.92*</td>
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*p < 0.01.

**Table 5. Bleeding Complications**

<table>
<thead>
<tr>
<th>Group</th>
<th>Hemorrhage</th>
<th>Onset of bleeding</th>
<th>Treatment</th>
<th>Results</th>
<th>Drugs administered after study</th>
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<tbody>
<tr>
<td>L</td>
<td>Puncture site (mild)</td>
<td>After heparin and urokinase administration</td>
<td>Blood transfusion</td>
<td>Recovered</td>
<td>Heparin Urokinase</td>
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<td>U</td>
<td>Macroscopic hematuria (mild)</td>
<td>2.5 hours after onset of study</td>
<td>Blood transfusion</td>
<td>Recovered</td>
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<td>U</td>
<td>Hematemesis (moderate)</td>
<td>Next day</td>
<td>Blood transfusion</td>
<td>Recovered</td>
<td>Heparin Urokinase</td>
</tr>
<tr>
<td>U</td>
<td>Puncture site (mild)</td>
<td>At end of treatment</td>
<td>Compression</td>
<td>Recovered</td>
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<td>U</td>
<td>Puncture site (massive)</td>
<td>After urokinase infusion</td>
<td>Blood transfusion</td>
<td>Recovered</td>
<td>Heparin Urokinase</td>
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<tr>
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<td>Hematuria (mild)</td>
<td>After heparin and urokinase administration</td>
<td>Blood transfusion</td>
<td>Recovered</td>
<td>Heparin Urokinase</td>
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<td>Hematemesis (severe)</td>
<td>2.3 hours after onset of study</td>
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Clinical Implications and Questions To Be Answered

Because no significant hemorrhagic tendency was documented, pro-urokinase appears to be much safer and more promising for intravenous administration than urokinase in ordinary medical practice, but the safety and effectiveness of the appropriate intravenous dose needs to be confirmed.

The turnover and clearance of pro-urokinase in rabbits and squirrel monkeys demonstrates a rapid initial half-life of about 3 minutes. The main mechanism of removal from circulation is hepatic clearance.22,23 In humans, a biphasic disappearance rate of natural pro-urokinase with an initial half-life of 6 minutes in plasma has been found.24 In this study, the reinfarction rate during the initial 7 days was low, but the use of prolonged infusion of pro-urokinase for further reduction of residual stenosis and to prevent restenosis merits consideration.

In a rabbit jugular vein thrombosis preparation, significant synergism between tissue-type plasminogen activator and pro-urokinase was observed.25 Preliminary results indicated that tissue-type plasminogen activator and pro-urokinase also act synergistically in patients with acute myocardial infarction.26 Low doses of tissue-type plasminogen activator (10 mg) and pro-urokinase (3 mg) were used in the given combination, and coronary reperfusion was obtained within 50 minutes. This synergism was not associated with systemic fibrinolytic breakdown. The combined use of synergic thrombolytic agents may permit a reduction of total administered doses to one fourth of the dose currently used for each agent alone and further decrease the risk of concomitant fibrinogen breakdown,27 but further investigation will be required for confirmation.

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References


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