Angiographic Study of Mutant Tissue-Type Plasminogen Activator Versus Urokinase for Acute Myocardial Infarction

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The effects and problems of intravenous thrombolytic therapy with a bolus injection of mutant tissue plasminogen activator (t-PA) were investigated in 34 patients with first acute myocardial infarction (AMI). In contrast, 114 patients were selected from 1,003 patients with AMI for treatment using intravenous infusion urokinase (UK). Angiography of these 148 patients revealed a complete occlusion of infarct-related artery with no clear contraindications to the study treatment. With the exception of thrombolysis in myocardial infarction (TIMI-3) recanalization 60 min after a bolus injection of mutant t-PA, the patients were given intracoronary UK in addition to mutant t-PA. The study comparisons were assessed using the following criteria: (1) 60-min assessment of recanalization rates, mutant t-PA vs UK; (2) time interval from initiation of thrombolysis to recanalization, mutant t-PA vs UK; (3) angiographic reocclusion rates within 1 month, mutant t-PA alone vs UK vs mutant t-PA plus UK; and (4) intracerebral hemorrhage rates, mutant t-PA alone vs UK vs mutant t-PA plus UK. There were no significant differences in the recanalization rates between mutant t-PA and UK, but there was a significant reduction in the time to recanalization with mutant t-PA (31.8 ± 12.7 min) compared with UK (56.5 ± 6.3 min). There was a significant difference in the reocclusion rates among the 3 treatment groups (20% mutant t-PA alone vs 4% UK vs 0% mutant t-PA plus UK). On the other hand, no significant differences in intracerebral hemorrhage rates among the 3 treatments were observed. In conclusion, thrombolytic therapy with a bolus injection of mutant t-PA achieved more rapid recanalization, but treatment with mutant t-PA led to a high rate of reocclusion. (*Jpn Circ J* 1998; 62: 111–114)

Key Words: Thrombolysis; Acute myocardial infarction; Mutant t-PA; Urokinase

Evidence for the beneficial effect of intravenous thrombolytic therapy in acute myocardial infarction (AMI) is incontrovertible. It has been demonstrated that over 90% of patients with AMI have previously suffered coronary thrombotic occlusion and, in addition, pivotal randomized trials in the 1980s proved that thrombolytic therapy could reduce mortality^{1–7}. In the 1990s, the Fibrinolytic Therapy Trial⁸ and Lincoff and Topol⁹ confirmed that the time window for reperfusion therapy should be extended to 12 h, rather than the 6-h boundary previously suggested, and that early thrombolytic treatment conveyed great benefits to the patient with AMI. Although this major transformation is now taken for granted, substantial refinements continue to be made regarding the approach to AMI patients. One of these refinements is the selection of a thrombolytic agent. Recently, we had the opportunity to use the mutant tissue-type plasminogen activator (t-PA), which is the second generation of t-PA for AMI. In this study, we performed coronary angiography to examine the effects and problems of thrombolytic therapy using mutant t-PA.

Patients and Methods

Between April 1984 and March 1993, 1,003 patients who had an AMI in the previous and who consented to treatment in our Coronary Care Unit were given reperfusion therapy using thrombolytic agents or percutaneous transluminal coronary angioplasty. Emergency coronary angiography had shown that 656 patients with first AMI had complete occlusion of the infarct-related artery and, of these, 34 patients who had agreed to participate in this study and who lacked infarct-related artery of the left main trunk had undergone thrombolytic therapy with a bolus injection of mutant t-PA. In contrast to these patients, all 114 patients given intravenous infusion of urokinase (UK) and without infarct-related artery of the left main trunk were selected from the 656 patients with first AMI. Finally, 148 patients who were still within 12 h of onset of first AMI and with complete angiographic occlusion of the infarct-related artery and no clear contraindications to thrombolytic agents were entered into this retrospective study.

The dose of mutant t-PA was 0.05–0.5 mg/kg as a bolus injection and that of UK was 10,000 U/kg during the first 10 min and 10,000 U/kg over the next 50 min of the injection. At 15-min intervals for 1 h, infarct vessel patency was assessed by coronary angiography and the criteria of successful recanalization were either those of TIMI-2 (almost without filling delay), denoting slightly delayed filling of contrast media, or those of TIMI-3 (brisk flow)^{10,11}. However, with the exception of TIMI-3

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Table 1 Baseline Patient Characteristics

	Mutant t-PA (n=34)	UK (n=114)
Age (years)	59.8±10.3	60.6±10.9
Gender (male/female)	29/5	92/22
Infarct-related artery		
LAD	22	64
RCA	11	39
LCX	1	11
Time to thrombolysis* (min)	243±97	301±187
Preinfarction angina (%)	52.9	51.8
Good collateral (%)	14.7	17.5
Two or 3 vessel disease (%)	23.5	25.4
Killip class ≥2 (%)	23.5	21.9
Risk factors (%)		
Hypertension	52.9	55.3
Diabetes mellitus	20.6	22.8
Hyperlipidemia	47.1	48.2
Smoking	79.4	80.7

LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; *, time interval from symptom onset to initiation of thrombolysis.

recanalization at 60 min after a bolus injection of mutant t-PA, the patients were given intracoronary UK (240,000 U/15 min ×4) in addition to mutant t-PA. When TIMI-3 recanalization with intracoronary UK was confirmed, UK infusion had been completed. The maximum dose of intracoronary UK was 960,000 U.

Treatment comparisons were made for the following parameters via cineangiogram examination: (1) 60-min assessment of recanalization rates, mutant t-PA vs UK; (2) time interval from initiation of thrombolysis to recanalization without failed thrombolysis, mutant t-PA vs UK; (3) angiographic reocclusion rates within 1 month after AMI, mutant t-PA alone vs UK vs mutant t-PA plus UK; and (4) intracerebral hemorrhage rates mutant t-PA alone vs UK vs mutant t-PA plus UK.

Statistical Analysis

Values were expressed as means±SD. Statistical analysis was performed using Student's t test, the chi-square test, Fisher's exact probability test, and multiple comparisons. A value of $p < 0.05$ was considered statistically significant.

Patient Characteristics

Baseline characteristics of patients given mutant t-PA or UK are shown in Table 1. No significant difference was observed between the 2 groups regarding age, sex, infarct-related artery, time interval from symptom onset to initiation of thrombolysis, preinfarction angina, collateral, vessel disease, Killip class, or risk factors.

Results

Angiographic Recanalization Rate

The 60-min angiographic assessment of successful recanalization rates with a bolus injection of mutant t-PA was 64.7% (22/34), and that of UK infusion was 71.1% (81/114). In addition, the TIMI-3 recanalization rate of mutant t-PA was 44.1% (15/34) and that of UK was 42.1% (48/114). No significant differences were observed

Fig 1. Comparison between mutant t-PA and Urokinase at 60 min angiographic recanalization rate. No significant differences were observed between mutant t-PA and UK.

Fig 2. Time interval from initiation of thrombolysis to recanalization. A significant difference was observed between mutant t-PA and UK.

Fig 3. Reocclusion rates within 1 month after AMI. A significant difference existed among the 3 thrombolytic therapies.

between the 2 thrombolytic agents (Fig 1). However, among 12 patients given intracoronary UK for failure of recanalization after treatment with mutant t-PA, 7 experienced successful recanalization within 60 min of starting UK.

Time Interval From Initiation of Thrombolysis to Recanalization

For the 2 thrombolytic therapies, a significant difference was observed in the time interval from initiation of thrombolysis to successful recanalization without failed treatment (Fig 2). Time to recanalization with a bolus injection of mutant t-PA was shorter than that with infusion of UK (mutant t-PA 31.8 ± 12.7 min vs UK 56.5 ± 6.3 min)

Angiographic Reocclusion Rate

All surviving patients (136/148) were followed up by coronary angiography in the chronic phase (1 month after AMI). Angiographic reocclusion rates within 1 month after AMI were significantly different among the 3 thrombolytic therapies (Fig 3). The reocclusion rate resulting from treatment with mutant t-PA alone was higher than that which occurred with UK alone or with mutant t-PA plus UK [mutant t-PA alone 20% (3/15) vs UK 3.9% (3/76) vs mutant t-PA plus UK 0% (0/14)]. All cases of reocclusion in patients treated with mutant t-PA alone occurred within 24 h after thrombolytic therapy and resulted in recurrent chest pain. On the other hand, among patients in whom reocclusion occurred after treatment with UK, there were silent occlusions that were confirmed by elective coronary angiography 1 month after AMI.

Intracerebral Hemorrhage Rate

Intracerebral hemorrhage within 1 month after AMI was not observed as a complication among the 3 thrombolytic treatment groups [mutant t-PA alone 0% (0/15) vs UK 0% (0/114) vs mutant t-PA plus UK 0% (0/19)].

Discussion

The class of thrombolytic agents known as plasminogen activators are the proteases, which are directly or indirectly responsible for fibrinolysis. The specific group consists of t-PA and a single-chain urokinase plasminogen activator; the relatively non-specific proteases include streptokinase (SK), an isolated streptokinase plasminogen activator complex (APSAC), and UK. Recently, the fibrin specificity of t-PA has led to some advantages as well as disadvantages. On the positive side, t-PA lyses clot more rapidly than SK, as shown previously through experimental studies and clinical trials.¹² However, this early and high recanalization rate is accompanied by an even higher rate of reocclusion, and this fibrinolytic potency appears to induce hemorrhagic stroke.¹³ Therefore, mutant (modified) t-PA, in which the disadvantages of t-PA were modified through biotechnological procedures, was developed^{14–16} and has now entered the stages of clinical trials.^{17,18} The omission of kringle-I has led to a prolonged half-life exceeding that of t-PA by approximately 2- to 3-fold, permitting a bolus injection of mutant t-PA, and thus facilitating its administration, a practical advantage not available with other thrombolytic agents. Nevertheless, the effects, problems, procedures, and optimal doses of mutant t-PA have yet to be determined.

Consequently, the aim of this retrospective clinical trial was to examine the effects and problems of single-bolus injection of mutant t-PA using coronary angiography. Criteria for successful recanalization have commonly

included either TIMI-2 or TIMI-3. But subsequently the GUSTO investigators reported that the patency of TIMI-2 demonstrated more failed recanalization than successful recanalization.¹⁹ We believe that TIMI-2 flow can be divided into 2 categories: moderate delayed filling and slightly delayed filling (TIMI-2 almost without filling delay). Successful recanalization incorporates TIMI-2 with almost no filling delay, as TIMI-2 with almost no filling delay at 60 min after optimal doses of thrombolytic agents restores brisk flow.²⁰

However, the optimal doses of mutant t-PA in this trial were unclear, and the achievement of infarct vessel patency without TIMI-3 60 min after a bolus injection of mutant t-PA still required additional intracoronary thrombolysis with UK. At 60 min, the successful recanalization rate with a bolus injection of mutant t-PA (64.7%) was less than that achieved by UK infusion (71.1%). Nonetheless, if the optimal dose of mutant t-PA is defined, the successful recanalization rate will be higher because, among 12 patients who were given intracoronary UK after failed recanalization attempts using mutant t-PA, 7 patients experienced successful recanalization. Finally, the successful recanalization rate with mutant t-PA and mutant t-PA plus additional UK exceeded 85%.

The time interval from initiation of mutant t-PA treatment to recanalization was approximately 30 min, a significant improvement compared with that of UK, which was approximately 60 min. On the other hand, mutant t-PA alone led to a high rate of reocclusion (20%) compared with UK and mutant t-PA plus UK, and reocclusion, together with chest pain, usually occurred within 24 h after a bolus injection of mutant t-PA. To prevent reocclusion, a double bolus injection of mutant t-PA has been attempted,¹⁷ but this procedure proved too costly.

In 1992, Granger et al¹³ performed a meta-analysis of angiographic reocclusion rates from randomized trials, comparing t-PA with non-fibrin-specific agents (SK, APSAC, or UK), and demonstrated that reocclusion rates were significantly higher after t-PA. Stump et al²¹ reported that this reocclusion was associated with a lack of fibrinogen depletion. During this time, the combination of t-PA and UK or of t-PA and SK led to a very low rate of reocclusion without a significant increase in bleeding complications.^{22–27} In this study, combination of mutant t-PA plus UK also had the same effects. In 1994, the National Heart Attack Alert Program suggested that time is a crucial factor in the thrombolytic therapy of patients with AMI, and that the fundamental barrier to timely treatment of individuals with symptoms and signs of AMI was mainly delay – by the patient, in the emergency medical service facility, and in the emergency department. The program further recommends that eligible AMI patients should be treated with thrombolytic therapy within 30–60 min of their arrival at the emergency department.²⁸ A bolus injection of mutant t-PA, which could bring about earlier recanalization, was proposed to be the most convenient thrombolytic therapy for AMI in emergency situations. However, the fact remains that the criteria that determine the ideal thrombolytic agent are its rapid, complete, and sustained effects accompanied by minimal or no side-effects.

In conclusion, thrombolytic therapy with a bolus injection of mutant t-PA achieved more rapid recanalization despite a higher rate of reocclusion.

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