Effects of Intravenous Administration of Tissue Plasminogen Activator Before Thrombectomy in Patients With Acute Myocardial Infarction

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Background Myocardial salvage after acute myocardial infarction (AMI) largely depends on the removal of infarct-related thrombus. Although both thrombolysis and thrombectomy are effective strategies to remove thrombus, there is a paucity of reports regarding the benefit of the combination therapy. Therefore, the efficacy of intravenous administration with mutant tissue plasminogen activator (Mt-PA) before thrombectomy and ordinary percutaneous coronary intervention (PCI) was evaluated.

Methods and Results Consecutive 44 AMI patients without contraindication of Mt-PA were enrolled in the study and randomly assigned to thrombectomy with Mt-PA pre-administration (group T) or thrombectomy alone (group N). Although Thrombolysis in Myocardial Infarction (TIMI) grade before PCI and TIMI myocardial perfusion grade immediately after PCI were significantly greater in group T ($p < 0.05$), there was no improvement of left ventricular ejection fraction immediately and 6 months after PCI.

Conclusions These results suggest that intravenous administration with Mt-PA before thrombectomy had no significant benefit in the salvage of infarcted myocardium over thrombectomy alone, despite improvement of coronary microcirculation immediately after PCI. (*Circ J* 2006; 70: 243–247)

Key Words: Acute myocardial infarction; Human recombinant tissue plasminogen activator; Percutaneous coronary intervention; Thrombectomy; Thrombolysis in Myocardial Infarction (TIMI)

Percutaneous coronary intervention (PCI) for patients with acute myocardial infarction (AMI) carries a risk of distal embolization of atheromatous and thrombotic debris. These adverse effects of PCI potentially result in so-called ‘no-reflow phenomenon’, which is characterized by impaired myocardial perfusion, despite reopening of the epicardial coronary arteries.^{1,2} Embolization of plaque and thrombotic debris induced by PCI can lead to the obstruction of distal coronary arteries, limiting the efficacy, and the extent of myocardial reperfusion.³ The impaired coronary microcirculation after PCI causes persistent abnormality in myocardial metabolism and increased cardiomyocyte death, which might limit myocardial salvage gained by PCI.^{3–5}

A number of techniques to protect against distal embolization during PCI have developed in recent years. Of these, several studies have emphasized the efficacy of thrombectomy before PCI in reducing distal embolization and improving coronary microvascular perfusion.^{6,7} However, the efficacy of thrombectomy is limited by the fact that complete aspiration of thrombus before PIC is not possible and residual thrombus are liberated during PCI.⁸

Therefore, we designed a prospective and randomized trial to test the hypothesis whether thrombolysis by intra-

venous administration with mutant tissue plasminogen activator (Mt-PA) improves the outcome of thrombectomy and PCI in patients with AMI. The rationale for using Mt-PA before thrombectomy and PCI in patients with AMI is 2-fold. First, this facilitated PCI technique might enhance the efficacy of PIC by earlier reopening of infarction-related artery (IRA). Second, thrombolysis by Mt-PA before thrombectomy might allow more complete aspiration of thrombotic debris by thrombectomy devices, thereby improving the efficacy of thrombectomy to protect coronary microcirculation. The results of our trial suggest that although the use of Mt-PA before thrombectomy improves coronary microcirculation immediately after PCI, it is not superior in improving left ventricular (LV) function over thrombectomy alone.

Methods

Subjects

Consecutive 44 patients who were admitted in our coronary care unit for the first onset of ST-segment elevation AMI without contraindication for Mt-PA were enrolled in the study. These patients received the initial therapy by oral administration with 100 mg of aspirin and 100 mg of ticlopidine and intravenous administration with 60 units/kg of heparin and, when necessary, they received intravenous isosorbide dinitrate and/or propranolol. They were, then, randomly assigned to either thrombectomy with Mt-PA pretreatment (group T; $n = 23$) or thrombectomy alone (group N; $n = 21$) using an envelope method. Group T patients received a bolus half-dose of alteplase (13,750 IU/kg) intravenously. The protocol of the study was approved by

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Table 1 Baseline Clinical Characteristics

	Group N	Group T	p value
Patients (n)	21	23	
Age (years)	62±8	58±10	0.26
M/F (n)	17:4	19:4	0.89
Risk factors, n (%)			
Diabetes	4 (19)	14 (61)	0.005
Dyslipidemia	19 (90)	15 (65)	0.046
Hypertension	12 (52)	11 (48)	0.54
Smoking	17 (81)	17 (74)	0.58
Time from the onset to arrival (h)	2.1±1.3	3.1±3.1	0.71
Time from the arrival to PCI (min)	89±50	80±17	0.81
Time from Mt-PA administration to PCI		48±10	

Group N, patients received thrombectomy and percutaneous interventions (PCI); Group T, patients received the half-dose of mutant tissue plasminogen activator (Mt-PA) before thrombectomy and PCI. The unpaired Wilcoxon non-parametric test was used to compare continuous variables and is expressed as mean±SD. The chi-square test was used to compare categorical variables.

Table 2 Baseline Angiographic Data

	Group N	Group T	p value
Patients (n)	21	23	
Infarction related artery, n (%)			0.63
RCA	10 (48)	10 (43)	
LCX	1 (5)	3 (13)	
LAD	10 (48)	10 (43)	
TIMI grade before PCI, n (%)			0.0007
0	16 (76)	7 (30)	
1	3 (14)	1 (4)	
2	2 (10)	15 (65)	
3	1*	0	

Group N, patients received thrombectomy and percutaneous interventions (PCI); Group T, patients received the half-dose of mutant tissue plasminogen activator before thrombectomy and PCI; RCA, right coronary artery; LCX, left circumflex artery; LAD, left anterior descending artery; TIMI, Thrombolysis in Myocardial Infarction.

*Because patients with TIMI grade 3 are not indicated for acute phase PCI, this patient was excluded from the study.

the Institutional Ethical Committee at Kansai Medical University, and written informed consent was obtained from all patients.

Exclusion Criteria

Exclusion criteria was age over 75 years, the presence of active bleeding (intracranium, gastrointestinal tract, or urinary tract), intracranial lesion (tumor, aneurysm, or arteriovenous malformation), intracranial or spinal operation or injury within 2 months, persistent high blood pressure after the initial therapy (systolic pressure over 180 mmHg or diastolic pressure over 110 mmHg), and post-cardiopulmonary resuscitation.

Coronary Angiography and Interventions

Coronary angiography was performed using standard techniques. Quantitative antegrade flow in the IRA was assessed before and after PCI according to Thrombolysis in Myocardial Infarction (TIMI) grading system.⁹ TIMI frame count (TFC) and TIMI myocardial perfusion (TMP) grade was assessed after PCI according to the previously defined methods^{10,11} by a single observer who was blinded to treatment assignment and clinical outcome. Only patients whose angiography failed to show TIMI 3 flow received PCI. To facilitate angioplasty, additional heparin (total 10,000 IU) was administered and a 6-Fr guiding catheter was inserted. A standard 0.014-inch guide wire was then used to cross the lesion. The 6-Fr thrombectomy catheter (Thrombuster, Kaneka, Japan) was carefully advanced and withdrawn over the wire repeatedly through the thrombotic site under

negative suction until the 20 ml suction syringe was filled. This process was repeated 2 or 3 times until thrombus disappeared angiographically. After thrombectomy, PCI (stent implantation with or without pre-balloon angioplasty) was done by an ordinal manner. We did not perform left ventriculography (LVG) in any patients undergoing PCI to reduce the dose of contrast medium.

All patients received ticlopidine (200 mg/day) and aspirin (100 mg/day) for 6 months after the procedure. Clinical events were monitored throughout hospitalization and patients were followed up after discharge for 6 months. Quantitative-gated tomographic scintigraphy (QGS) using ^{99m}Tc-Sestamibi¹² was done to evaluate LV ejection fraction (LVEF) within 3 days after the onset of AMI. Follow-up catheterizations were performed 6 months after the onset of AMI in 30 patients (12 patients in group N and 18 patients in group T).

Statistical Analysis

All statistical analysis was calculated using JAMP (SAS Institute). The unpaired Wilcoxon non-parametric test was used to compare continuous variables and expressed as mean±SD. The chi-square test was used to compare categorical variables. A p-value <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics with respect to gender, age, body height, and body weight were similar between group

Table 3 Post Procedural Angiographic Data

	Group N	Group T	p value
Patients (n)	21	23	
Procedural time (min)	64±21	57±22	0.21
TIMI grade 3, n (%)	18 (86)	22 (96)	0.25
TFC (15 Fps)	18±12	17±9	0.94
TMP grade, n (%)			0.013
0/1	1 (5)	1 (4)	
2	17 (81)	9 (39)	
3	3 (14)	13 (57)	

Group N, patients received thrombectomy and percutaneous interventions (PCI); Group T, patients received the half-dose of mutant tissue plasminogen activator before thrombectomy and PCI; Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) and TIMI myocardial perfusion (TMP) grade were evaluated as described in the Methods. Fps, frames per second.

Table 4 Post-Procedural Creatine Kinase Release and Left Ventricular Function

	Group N	Group T	p value
Patients (n)	21	23	
Peak CK release (IU/L)	3,038±2,000	3,147±2,085	0.99
LVEF (%)			
QGS (1-3 days after PCI) (n)	48±12 (16)	53±12 (17)	0.31
LVG (6 months after PCI) (n)	56±10 (12)	59±8 (18)	0.57

Group N, patients received thrombectomy and percutaneous interventions (PCI); Group T, patients received the half-dose of mutant tissue plasminogen activator before thrombectomy and PCI. CK, creatine kinase; LVEF, left ventricular ejection fraction; QGS, quantitative gated tomographic scintigraphy; LVG, left ventriculography.

N and group T (Table 1). Although dyslipidemia was more frequently observed in group N, diabetes was more frequently observed in group T. The number of patients who currently smoked was not different between these groups. The time from the onset of chest pain to the hospital arrival was similar between group N (2.1±1.3 h) and group T (3.1±3.1 h). The time from hospital arrival to PCI was 89±50 min in group N and 81±17 min in group T. The time from administration of Mt-PA to PCI ranged from 31 to 75 min (mean: 48±10 min) in group T.

IRA were similar between these groups (Table 2). There was no patient with TIMI grade 3 before PCI in group T. Only 1 patient in group N was found to be TIMI grade 3 and this patient did not receive PCI and was excluded from the study. However, the number of patients with TIMI grade 2 was significantly ($p<0.01$) greater in group T.

The procedural time was not significantly different between group N (64±22 min) and group T (57±22 min) (Table 3). TIMI grade 3 after PCI was obtained in 86% (18/21) in group N and 96% (22/23) in group T. All of 4 patients without TIMI grade 3 after PCI showed TIMI grade 2, which was almost equivalent to TIMI grade 3. TFC grade after PCI was not significantly different between these groups. However, TMP grade was significantly greater in group T patients.

The level of peak creatine kinase (CK) release was not significantly different between group N and group T (Table 4). LVEF measured by a QGS technique within 3 days after PCI was also similar between these groups. LV EF measured by LVG 6 months after PCI was not significantly different between these groups (56.2±9.8% in group N and 59.1±7.8% in group T).

We could follow up 14 patients in group N and 19 patients in group T during 6 months after PCI. The 6-month occurrence of death, re-infarction, re-intervention, emergency coronary artery bypass grafting, or stroke was not significantly different between group N and group T. At 6 months' follow-up, there was no death in both groups. No

re-infarction occurred in group N, but 1 patient in group T. In this patient, the IRA of the second AMI was different from that of the first AMI. Four patients in both groups received re-intervention of the IRA, but no patient underwent coronary artery bypass grafting. No major bleeding event including stroke was observed in both groups.

Discussion

We performed a prospective and randomized trial to examine the effect of thrombolysis by intravenous administration with Mt-PA before thrombectomy and PCI on myocardial perfusion and LV function in patients with AMI. The results demonstrated that although better TIMI grade at first angiography and better TMP grade immediately after PCI were obtained in patients pretreated with Mt-PA, there was no significant difference in peak CK release and LV function early after PCI and no superior improvement of LV function in this group of patients over those with thrombectomy and PCI alone during the intermediate follow-up period. These results suggest that the combination therapy using Mt-PA pretreatment and thrombolysis is effective in improving coronary microcirculation, but this does not reflect on the improvement of LV function in patients with AMI.

There should be many reasons to explain the failure of thrombolysis to enhance the outcome of PCI in patients with AMI in our series. The disparity between improved coronary microcirculation immediately after PCI and the lack of improvement of immediate and follow-up LV function after PCI by pretreatment with Mt-PA suggests that the improvement of tissue-level perfusion immediately after PCI is not always associated with myocardial salvage. Although we evaluated coronary flow restoration immediately after PCI by TFC and TMP grade, only TMP grade was improved in group T patients. We can not explain the mechanism for the disparate results between TFC and TMP grade immediately after PCI. However, it has been demon-

strated that TMP grade is a more useful marker of the degree of perfusion at tissue level myocardium achieved with PCI and a more sensitive indicator of the efficacy of PCI strategies in patients with AMI compared to TFC grade.¹³ Therefore, we chosen TMP grade as an index for coronary microvascular function. However, it has been claimed that the assessment of TMP grade should be performed 1–2 weeks after reperfusion therapy,¹³ because coronary microvasculature undergoes a series of changes leading to microvascular dysfunction early after AMI, such as ischemic and reperfusion injury and atheroembolism, in addition to distal thromboembolism. Indeed, it has been demonstrated that both basal and peak flow velocities increased at 2 weeks, compared with values obtained immediately after PCI in patients with AMI.¹⁴ Thus, initial improvement of TMP grade does not confer long-term superiority of microvascular function and it is possible that microvascular function in patients with thrombectomy and PCI alone caught up with those pretreated with Mt-PA during the follow-up period and, therefore, no difference in LV function could be found between these 2 groups of patients late after PCI.

In addition to temporal differences in the recovery of microvascular function after PCI in patients with AMI, disproportional recovery of coronary microvascular perfusion and LV function could occur when infarcted myocardium undergoes irreversible injury before restoration of coronary perfusion. It is conceivable that these 2 groups of patients were subjected to a similar extent of ischemic injury before restoration of coronary perfusion, because the time from the onset of AMI to the end of PCI was equivalent between these 2 groups. Alternatively, similar extent of myocardial salvage was obtained by thrombectomy and PCI in these groups of patients irrespective of whether pretreatment with Mt-PA was performed or not. The time between the administration of Mt-PA and PCI ranged from 31 to 75 min (mean: 48 ± 10 min) in group T patients. We found that there was no significant correlation between the interval from administration of Mt-PA and PCI and any parameters of perfusion grade or LV function (TFC and TMP grade and LVEF measured by QGS and LVG). This time interval might be too short to elicit the advantage of thrombolysis achieved by reopening the IRA at an earlier stage. It is expected that when the time between administration of Mt-PA and PCI is prolonged, the efficacy of pretreatment with Mt-PA might be uncovered. Moreover, the procedural time was similar between these groups. A recent study showing the efficacy of facilitated PCI in patients with AMI documented that the procedural time was significantly shorter in patients pretreated with Mt-PA.¹⁵ In our series, the procedural time tended to be negatively correlated with LVEF 6 months after PCI in both group N ($p=0.1$) and group T ($p=0.08$) and highly significant negative correlation was found when group N and group T were combined ($p<0.01$). Thus, the procedural time might be a critical determinant of improvement of LV function by thrombectomy and PCI in patients with AMI irrespective of whether these patients received pretreatment with Mt-PA and the benefit by pretreatment with Mt-PA might depend on abbreviation of the procedural time.

Another possible explanation for the failure of thrombolysis to salvage myocardium before thrombectomy and PCI might be related to only partial success of epicardial flow restoration by thrombolysis. It should be noted that there was no patient with TIMI grade 3 in group T before

thrombectomy and PCI, indicating that the infarcted myocardium remained ischemic in this group of patients until TIMI grade 3 was achieved by PCI. It has been demonstrated that the efficacy of facilitated PCI in improving LV function depends on whether TIMI grade 3 is obtained by thrombolysis before PCI.¹⁶ The dose of Mt-PA used in our series might be too small to obtain successful thrombolysis. We used a half-dose of Mt-PA to reduce the risk of bleeding complication, which was often associated with a full-dose administration with Mt-PA.¹⁷ The dose of Mt-PA used in the present study was comparable to that used in other series of study demonstrating the efficacy of facilitated PCI.¹⁶ Although we do not know the reason for less successful recanalization by our thrombolysis protocol, it is reasonable to conclude that the limited coronary flow restoration by thrombolysis before thrombectomy and PCI might be responsible for the failure to improve LV function. Risk and benefit analysis with respect to bleeding complication and the extent of recanalization in the face of thrombectomy and PCI should be carried out in future using larger doses of Mt-PA.

Although we were unable to evaluate the efficacy of pretreatment with Mt-PA in facilitating aspiration of thrombotic debris during thrombectomy, it is reasonable to assume that pretreatment with Mt-PA was at least partially effective in fulfilling this role, because coronary microvascular function immediately after PCI was significantly improved by pretreatment with Mt-PA, despite incomplete restoration of epicardial coronary flow before thrombectomy. Thrombectomy is our preferable choice in preventing distal embolization during PCI for patients with AMI primarily because it is technically easier than using distal protection procedures. However, the efficacy of thrombectomy is limited by the fact that complete aspiration of thrombus before PCI is not possible and residual thrombus are liberated during PCI.⁸ Therefore, distal protection devices have emerged as an alternative technique to prevent no-reflow during emergency PCI in patients with AMI. A recent retrospective study demonstrated that a distal embolic protection device is more effective than an aspiration catheter in improving tissue-level perfusion during PCI in patients with AMI.¹⁸ Although distal occlusion and aspiration permits a more complete retrieval of debris, the use of distal protection devices entails myocardial ischemia and the inability of simultaneous angiographic delineation of the culprit lesion. A recently conducted prospective randomized trial demonstrated that a distal balloon occlusion and aspiration system effectively retrieves embolic debris during primary PCI or rescue intervention after failed thrombolysis in most patients with AMI, but such distal embolic protection did not result in improved microvascular flow, greater reperfusion success, reduced infarct size, or enhanced event-free survival.¹⁹ In contrast, when using filtration devices, the extent of coronary microembolism is probably underestimated from the retrieved material, because a filter with a pore size of $100 \mu\text{m}$ can not retrieve the size of particles that caused substantial microembolism in the experimental studies. Also, data from randomized studies to compare the effects of these devices on myocardial reperfusion during direct PCI have not been reported so far.²⁰ Therefore, it is premature to conclude that a certain distal protection technique is better over others.

Study Limitation

This study was a single-center experience in a limited

number of patients. As a result, some baseline characteristics differed between the groups, despite a randomized nature of this trial. For example, more diabetic patients were enrolled in group T, whereas more hyperlipidemic patients were enrolled in group N. This might have affected the outcome after PCI. The previous study showed that patients with diabetes are more likely to have abnormal myocardial and microvascular perfusion after PCI.²¹ In the present study, however, microvascular function as assessed by TMP grade was significantly better in group T after PCI. Therefore, it is unlikely that existence of microvascular abnormalities in group T patients negatively affected the outcome of facilitated PCI in the present trial. However, the effect of dyslipidemia on the outcome of PCI in patients with AMI has not been fully elucidated. One available study demonstrated that the presence of hyperlipidemia negatively correlated with mortality of reperfusion therapy.²² Thus, hyperlipidemia might have favorably affected the early and intermediate follow-up LV function in group N, although the mechanism for favorable outcome in dyslipidemic patients is uncertain. Another limitation of our study is a study design. The present study did not restrict the type of the IRA that might produce much variation in the size of the risk area caused by AMI. Therefore, it would be difficult to detect small differences in peak CK release and LV function between these groups. Moreover, we evaluated LV function by a QGS technique within 3 days after PCI and by LVG after 6 months after PCI. Therefore, direct comparison of LV function between the early and the late follow-up periods was difficult. This lack of evaluation of the change in LV function might have overlooked notable improvement of LV function during the follow-up period in certain patients. Larger clinical trials are warranted to address the impact of thrombolysis before thrombectomy and PCI on microvascular function and LV function in the future.

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