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Thrombolytic Therapy Followed by Rescue Percutaneous Coronary Intervention for Acute Myocardial Infarction

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ABSTRACT

Objective : We investigated the benefit of thrombolytic therapy with the tissue plasminogen activator (t-PA) monteplase before percutaneous coronary intervention (PCI) for early reperfusion in patients with acute myocardial infarction (AMI).

Method : Eighty patients who presented within 12 hours of symptom onset with ST segment elevation consistent with AMI at admission were enrolled and randomly assigned to treatment with monteplase followed by rescue PCI (monteplase group) or with PCI alone (primary PCI group). PCI was performed if the initial coronary angiogram showed flow of Thrombolysis In Myocardial Infarction (TIMI) grade 2 or less.

Results : Baseline characteristics did not differ between the two groups. In the monteplase group more patients had TIMI grade 3 flow, and fewer patients required PCI. The peak creatine kinase value in the monteplase group among patients with anterior wall myocardial infarction was lower, but no difference was observed among patients with inferior wall myocardial infarction. The rates of hemorrhagic complications and other in-hospital complications did not differ between the groups.

Conclusion : These findings suggest that administration of the t-PA monteplase before PCI for AMI is an effective treatment, facilitating early recanalization in patients with AMI without causing adverse events. (Jikeikai Med J 2006 ; 53 : 23-9)

Key words : acute myocardial infarction, percutaneous coronary intervention, thrombolytic therapy, monteplase

INTRODUCTION

Early reperfusion therapy after acute myocardial infarction (AMI) improves left ventricular function and provides a better overall clinical course than does conservative treatment[1-5]. Despite these advantages, there has been a long-standing controversy over the effectiveness of thrombolysis versus primary percutaneous coronary intervention (PCI). A recent randomized trial of facilitated PCI found that pretreatment with a tissue plasminogen activator (t-PA) improves the preprocedural coronary patency but is associated with a higher rate of bleeding complications and had no effect on ejection fraction (EF) or clinical outcome[6]. Accordingly, the purpose of the study was to investigate the clinical benefits and

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safety of antecedent thrombolytic therapy with the standard dose of a mutant t-PA, monteplase, before PCI for early reperfusion in patients with AMI.

METHODS

Selection of patients

This randomized, double-blind study was performed at 4 institutions affiliated with The Jikei University School of Medicine. Patient eligibility criteria included: 1) ischemic chest pain lasting 30 minutes or more within 12 hours of symptom onset, 2) ST segment elevation consistent with AMI at admission, and 3) age less than 75 years. Exclusion criteria were cardiogenic shock, severe left ventricle dysfunction (Killip III/IV), acute bleeding or bleeding diathesis within the previous month, left main trunk obstruction, severe renal insufficiency, and known contraindications to aspirin, heparin, or contrast medium. This study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients gave written informed consent to participate in the study.

Study protocol

The protocol is shown in Fig. 1. All eligible patients received 162 mg of chewable aspirin and 5,000 U of intravenous heparin. Patients were randomly assigned with the envelope method to either the monteplase group, which received 27,500 U/kg intravenous monteplase (the standard dose), or the primary PCI group. Patients were to undergo coronary angiography as soon as possible. PCI was performed if the initial coronary angiogram indicated flow of Thrombolysis In Myocardial Infarction (TIMI) grade 2 or less. If the infarct-related artery showed TIMI grade 3 flow, PCI was not performed. Aspirin was continued throughout the hospitalization, and intravenous heparin injection was continued for at least 72 hours. Left ventriculography was performed (right anterior oblique) with a radiopaque ball filmed in the left upper the clavicle for calibration. Creatine kinase (CK) and CK-MB were measured every 3 to 12 hours for at least 3 days after the patient arrived at the emergency room. Angiography was repeated 2 to 4 weeks later to evaluate left ventricular function. The EF was calculated with the area-length method. Adverse outcomes were defined as in-hospital death, intracranial hemorrhage, recurrent ischemic events, and bleeding complications producing a decrease in blood hemoglobin concentration of 3 g/dl or more.

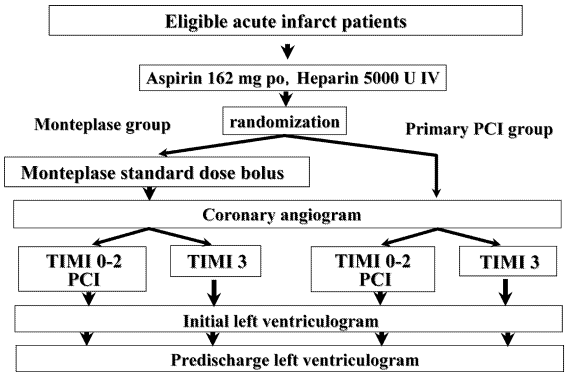

Fig. 1. Study Protocol. IV, intravenous; PO, oral

Statistical analysis

Variables are expressed as means±standard deviations (SD). Variables were compared between groups by means of unpaired t-tests. Differences with a p value less than <0.05 were considered statistically significant.

RESULTS

From May 2000 through September 2001, 80 consecutive patients were enrolled. The baseline characteristics of the two groups of patients are shown in Tables 1 and 2. The groups did not significantly with regard to sex, gender, coronary risk factor, previous angina or infarction, infarct location, or angiographic characteristics.

Of the enrolled patients, more than 90% were Killip class I at admission. The culprit artery was the right coronary artery (RCA) in 50% of patients in the monteplase group and 40% of patients in the primary PCI group. The left anterior descending (LAD) artery was the culprit artery in 35% and 48% of patients, respectively, in the monteplase group and the primary PCI group. Despite this being a randomized, double-blind study, time from onset to admission was significantly longer in the monteplase group (216±152

Table 1. Baseline characteristics (1)

	Monteplase (n=40)	Primary PCI (n=40)	P value
Age (years)	58±9	59±10	NS
Sex (male %)	85	88	NS
Body Mass Index	24±3	24±3	NS
Coronary risk factor			
Hypertension (%)	63	75	NS
Diabetes (%)	38	23	NS
Dyslipidemia (%)	63	45	NS
Smoking (%)	72	76	NS
Previous angina (%)	28	20	NS
Previous myocardial infarction (%)	5	5	NS

Table 2. Baseline characteristics (2)

	Monteplase (n=40)	Primary PCI (n=40)	P value
Site of the AMI ant/inf/lat/post (%)	35/58/10/0	48/43/8/5	NS
Killip classification Class I/II	98/3	92/8	NS
Infarct-related artery RCA/LAD/LCX (%)	50/35/15	40/48/13	NS

ant, anterior ; inf, inferior ; lat, lateral ; post, posterior ; Cx, circumflex.

minutes) than in the primary PCI group (143±120 minutes ; p=0.019). However, time from admission to coronary angiography did not differ between the groups. Although the time from admission to TIMI grade 3 flow did not differ between the groups, time from onset to TIMI grade 3 flow was slightly but not significantly longer in the monteplase group (358±185 minutes) than in the primary PCI group (287±147 minutes ; p=0.08). This difference was due to the longer time from onset to admission in the monteplase group than in the primary PCI group.

Figure 2 shows the patency of the infarct-related artery at initial coronary angiography. Upon arrival at the catheterization lab, the percentage of patients with TIMI grade 3 flow was approximately three times as high in the monteplase group (43%) as in the primary PCI group (15%).

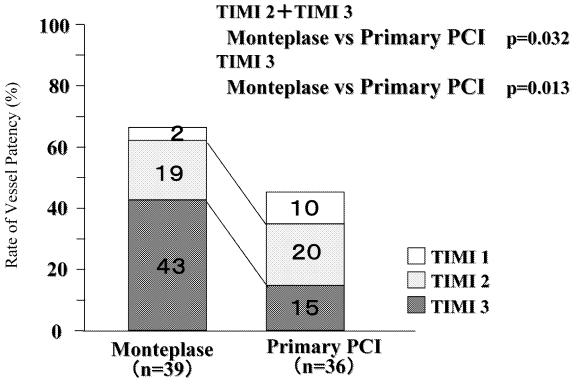

Fig. 2. Infarct-related artery patency at the time of the initial coronary angiography ; M, monteplase group ; P, primary PCI group.

Table 3 shows procedural outcomes in the acute phase. Because TIMI grade 3 flow was observed in more patients in the monteplase group than in the primary PCI group, fewer PCI procedures were performed in the monteplase group. Coronary stent implantation was the main intervention, used in approximately 70% of patients in each group. The final results of PCI did not differ between the groups. More than 80% of patients finally achieved TIMI grade 3 flow.

Table 4 shows the initial and predischarge left ventricular function in the groups. Analyzable initial

Table 3. Procedural outcomes in acute phase

	Monteplase ($n=40$)	Primary PCI ($n=40$)	P value
Total of PCI (n)	24	38	<0.001
POBA/STENT/POBA+STENT (n)	7/13/4	11/14/13	NS
Final results of PCI			
TIMI 3/2/1 (n)	18/5/1	34/2/1	NS
Rate of TIMI 3 (%)	85	90	NS

POBA, plain old balloon angioplasty.

Table 4. Initial and predischarge LV function

	Monteplase	Primary PCI	P value
Initial Outcome			
EF (%)	59±11	60±11	NS
EDVI (ml/m²)	63±10	59±11	NS
ESVI (ml/m²)	26±9	25±11	NS
Predischarge Outcome			
EF (%)	59±9	59±12	NS
EDVI (ml/m²)	64±13	61±14	NS
ESVI (ml/m²)	28±11	25±9	NS

left ventriculograms were obtained from 56 patients and showed no significant difference in EF, end-diastolic volume index (EDVI), or end-systolic volume index (ESVI) between the groups. Analyzable predischarge left ventriculograms were obtained in 37 patients and showed no significant difference in EF, EDVI, or ESVI between the groups.

The mean peak CK value was slightly but not significantly lower in the monteplase group (2,746±1,735 IU) than in the primary PCI group (3,589±3,554 IU; $p=0.183$). Peak CK values were significantly lower in the monteplase group among patients with anterior myocardial infarction, but no difference was observed among patients with inferior wall myocardial infarction (Fig. 3).

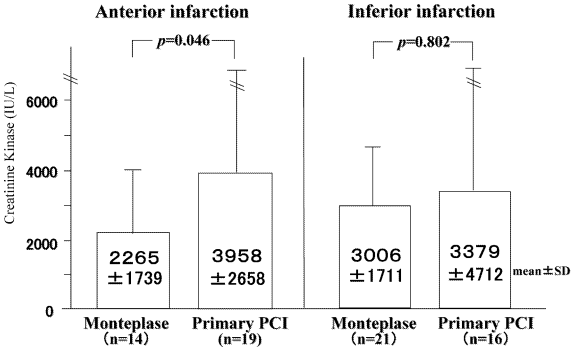

Fig. 3. Peak CK values of patients with anterior and inferior myocardial infarction.

Table 5 shows the adverse outcomes observed during hospitalization. The rates of adverse events did not differ between the groups. Major hemorrhage occurred in 5% of patients in the monteplase group and 8% of patients in the primary PCI group. Intracerebral bleeding occurred in only 1 patient in the monteplase group. Blood transfusion was required by 2 patients in the primary PCI group and was associated with insertion of an intra-aortic balloon pump. Abrupt closure occurred in only 1 patient in the monteplase group.

DISCUSSION

Achieving earlier reperfusion after symptom onset is critical in the treatment of AMI[7]. Early reperfusion after AMI reduces infarct size and improves cardiac function and long-term prognosis, and the sooner reperfusion is achieved, the greater is the benefit[8,9]. In the United States and Europe, throm-

Table 5. Adverse outcomes during hospitalization

	Monteplase ($n=40$)	Primary PCI ($n=40$)	P value
Major hemorrhage	2	3	NS
Intracerebral bleeding	1	0	NS
Transfusion	0	2	NS
Reocclusion	1	0	NS
Reinfarction	1	0	NS
Postinfarct angina	1	0	NS
New heart failure	1	0	NS
Ventricular tachycardia	2	5	NS
Ventricular fibrillation	0	1	NS
In-hospital death	0	1	NS

bolytic therapy is routinely performed, whereas in Japan, PCI predominates because many medical institutions have PCI facilities. Thrombolytic therapy is simple to perform but has several disadvantages, including a risk of bleeding complications, a low rate of achieving TIMI grade 3 flow, and a high reocclusion rate. In contrast, PCI achieves TIMI grade 3 flow in a higher percentage of patients, but requires an experienced team and appropriate facilities and takes a longer time to achieve reperfusion.

A long-standing controversy concerns whether thrombolytic therapy or PCI should be performed first. One large-scale trial combining thrombolysis with immediate PCI or rescue PCI has demonstrated that administration of a thrombolytic agent before PCI is associated with a decreased PCI success rate and an increased risk of bleeding complications; the authors of this study have concluded that the antecedent use of thrombolytic agents is not effective[10-14]. However, recent developments in PCI techniques and devices, particularly the introduction of stents, have increased PCI success rates. Recently, the Plasminogen-activator Angioplasty Compatibility Trial (PACT) has found that earlier reperfusion can be achieved using low-dose t-PA combined with PCI performed as needed and that this combination therapy is effective and safe[6].

Monteplase, used in the present study, is a t-PA developed in Japan that has a prolonged half-life allowing bolus administration[15]. Although the standard dose of monteplase was used to increase reperfusion rates before PCI, no increase in adverse events (such as hemorrhage) occurred. At initial angiography, 43% of patients receiving monteplase achieved TIMI grade 3 flow and 62% of patients achieved TIMI grade 2 or 3 flow; these rates were significantly higher than those in the primary PCI group. The initial success rates (for achieving TIMI grade 3 flow) after PCI were similar in patients who did or did not receive the antecedent thrombolytic agent. Stents were used in more than 70% of patients who underwent PCI, and this is one factor likely contributing to the different results in a large-scale trial conducted before the introduction of stents. Long-term assessment of cardiac function in the PACT study revealed no significant difference between patients receiving monteplase and those undergoing primary PCI same as our study. The possible reasons in outcome from our study are that follow-up left ventriculography was performed after an average of 3 weeks, which may have been too early for full restoration of cardiac function, and that more than half of the patients did not undergo left ventriculography owing to problems associated with the amount of contrast agent used.

Peak CK values were slightly but not significantly lower in the monteplase group. However, when assessed by infarct area, peak CK values were significantly lower in patients of the monteplase group with anterior infarction. This finding suggests that greater myocardial salvage was achieved in patients with anterior infarction. This result may be related to the infarct-related artery in anterior infarction being the LAD artery, which has a larger myocardial perfusion area than does the RCA or the circumflex

artery such that the LAD artery infarct size is larger if reperfusion is not achieved at an early stage. Furthermore, despite the longer time from onset to admission in the monteplase group than in the primary PCI group, peak CK values were significantly lower in patients of the monteplase group with anterior infarction, suggesting that antecedent t-PA may be beneficial.

The bleeding complication of cerebral hemorrhage occurred in one patient in the monteplase group. This patient complained of a headache after receiving t-PA, and cerebral hemorrhage was confirmed by computed tomography on day 12. The patient eventually recovered and was discharged on day 28. Blood transfusions were required by 2 patients in the primary PCI group but by no patients in the monteplase group. One patient in the monteplase group had reocclusion. Further investigation is needed to determine whether PCI (stenting) or thrombolytic therapy or both should be performed in patients, including those achieving TIMI grade 3 flow before coronary angiogram to prevent reocclusion.

STUDY LIMITATION

The most important limitation of our study was the significant differences between the groups in the time from onset to admission. The reason for this difference is not clear. The study enrolled 80 patients, which was a relatively small number, so the difference might have been due to chance. If a larger number of patients had been enrolled, there may have been no differences in time from onset to admission.

CONCLUSION

An antecedent full dose of the mutant t-PA monteplase produced early patency without an increase in adverse events and reduced infarct size in patients with anterior wall myocardial infarction.

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