Percutaneous Transluminal Coronary Angioplasty, Alone or in Combination With Urokinase Therapy, During Acute Myocardial Infarction

Shuichi Oshima, MD; Taro Saito, MD; Shota Nakamura, MD; Katsuo Noda, MD; Haruhiko Date, MD; Seiji Hokimoto, MD; Izumi Taniguchi, MD; Nobuyasu Yamamoto, MD

To investigate the effect of pre-treatment of a thrombus with a low dose of urokinase on establishing patency in a persistent infarct-related artery (IRA) during direct percutaneous coronary angioplasty (PTCA), the frequency of acute restenosis during direct PTCA, alone, or in combination with the intracoronary administration of urokinase, was examined in a consecutive nonrandomized series of patients with acute myocardial infarction (AMI). Two hundred and seventy-two successful PTCA patients (residual stenosis <50%) were divided into 2 groups: 88 patients received pre-treatment with intracoronary urokinase following PTCA (combination group); 184 received only direct PTCA without thrombolytic therapy (PTCA group). In the present study, after achievement of a residual stenosis of less than 50%, IRA was visualized every 15 min to assess the frequency of acute restenosis, which was defined as an acute progression of IRA with more than 75% restenosis after initially successful PTCA. In the patients with a large coronary thrombus, the frequency (times) of acute restenosis was significantly lower in the combination group than in the PTCA group (0.98±0.19 vs 2.92±0.32, p<0.0001). On the other hand, in the patients with a small coronary thrombus, the frequency of acute restenosis showed no difference in either group. The present study indicates that in patients with AMI, PTCA combined with pre-treatment of a low dose of urokinase is much more effective than PTCA alone, especially for those patients who have a large coronary thrombus. (Jpn Circ J 1999; 63: 91–96)

Key Words: Acute myocardial infarction; Acute restenosis; Direct PTCA; Intracoronary thrombolysis

T here is increasing evidence that coronary thrombosis plays a pivotal role in the pathogenesis of acute myocardial infarction (AMI).1–4 Large controlled clinical trials have demonstrated that early coronary thrombolysis (ECT) reduces mortality in patients with AMI.5–8 ECT for patients with AMI, however, is associated with several major unresolved problems: (1) 20–30% of the occluded coronary arteries may not be opened by lytic therapy;9–11 (2) reinfarction, or reocclusion, occurs in 10–20% of patients in whom reperfusion was initially successful;8,12–15 and (3) subsequent revascularization is often necessary because of severe residual stenosis and a persistently unstable clinical course. Therefore, methods of treatment for achieving and maintaining reperfusion continue to evolve.

Direct percutaneous coronary angioplasty (PTCA) is also used for recanalization of an infarct-related coronary artery in patients with AMI16–18 and with such patients there are studies reporting an advantage of direct PTCA over ECT.16,17 The theoretical benefits associated with PTCA include the reopening of occluded arteries more promptly than with ECT, the reopening of arteries when thrombolytic therapy has failed, and a reduction in the severe stenosis that frequently persists after thrombolysis. However, direct PTCA for AMI, compared with elective PTCA for patients with stable angina, has disadvantages with lower initial success rates (87% vs 94%, p<0.01) and higher clinical in-hospital reocclusion rates (9% vs 3%).19 This difference in clinical course after PTCA may result either from an instability of the endothelial surface of the infarct-related plaque and/or from the effects of thrombus in the coronary vessels.20

In the present study, we investigated the effect of pre-treatment of the thrombus with a low dose of urokinase on establishing persistent infarct-related artery (IRA) patency during direct PTCA by comparing PTCA alone without thrombolysis. It describes the frequency of acute restenosis or acute occlusion during the PTCA procedure and the clinical in-hospital reocclusion rates in patients who had initially successful and persistent patency during the 30 min immediately after PTCA.

Methods

Patient Population

The study population consisted of 297 patients with AMI referred to Kumamoto Central Hospital, between January 1986 and June 1995, within 12h after the onset of symptoms who were enrolled consecutively in a protocol of emergency coronary angioplasty. These patients were not randomized. All patients were diagnosed as having AMI on the basis of the following criteria: persistent chest pain lasting for at least 30min with ST-segment elevation...
of >0.2 mV in 2 contiguous leads on a standard 12-lead electrocardiogram, and an elevation of the creatine kinase MB isoenzyme to a level of at least twice the upper limit of the normal range. Some patients satisfying these entry criteria were excluded from the protocol if they had a contraindication to urokinase, which was demonstrated by any of the following: (1) recent history of gastrointestinal bleeding, stroke, major surgery, or trauma; (2) history of a bleeding diathesis; (3) proliferative diabetic retinopathy; or (4) severe uncontrolled hypertension. Patients were also excluded from the study for PTCA if they displayed any of the following: (1) stenosis of the left main coronary artery of more than 70%; (2) critical 3- vessel disease; or (3) morphologic features of a lesion known to indicate high risk.

Written informed consent was obtained from each patient and, where appropriate, the family in the early phase of AMI. The study protocol was in agreement with the guidelines of the ethics committee at our institution.

**Definitions**

Persistent patency of the IRA was considered to be present if the vessel was completely perfused at the end of the procedure (Thrombolysis in Myocardial Infarction trial TIMI grade 3). The coronary angioplasty was defined as follows: successful if the residual stenosis was less than 50%; or unsuccessful if the residual stenosis was greater than 50% but less than 100% or if the infarct-related coronary arteries remained occluded. After achievement of a residual stenosis of less than 50%, IRAs were visually inspected every 15 min to assess the acute progression of the IRAs. Acute restenosis was defined as an acute progression of infarct-related coronary arteries with more than 75% residual stenosis up to total occlusion after an initially successful PTCA. Large thrombus was defined as over 2 cm and small thrombus was defined as under 2 cm, using the PTCA balloon length of 2 cm as a guide. Cardiogenic shock was defined as systolic blood pressure of less than 80 mmHg that was unresponsive to volume expansion and necessitating immediate intraaortic balloon therapy.

**Angioplasty Protocol**

In the emergency room or coronary care unit, each patient received nitrate either sublingually or intravenously. The patients were then immediately transferred to the cardiac catheterization facility. Cardiologists experienced in angioplasty and a cardiac catheterization team were on call 24 h a day. In the cardiac catheterization facility, 7F sheaths were placed in the femoral artery and vein. The patient was administered 10,000 units of heparin at the beginning of the procedure and this initial dose was supplemented with a bolus of 2,000 units per each hour in a long procedure. A 5F balloon-directed temporary pacemaker was inserted from the femoral vein and was advanced to the right ventricle if conduction disturbances or bradycardy occurred during this procedure. In patients experiencing cardiogenic shock or receiving cardiopulmonary resuscitation, coronary angiography and balloon angioplasty were performed simultaneously with vasopressor therapy or intra-aortic balloon counterpulsation.

For the angiography, the noninfarct related coronary artery was opacified first in order to assess the degree of collateral circulation to the infarct-affected region. The IRA was then opacified in multiple views. Coronary angioplasty was performed using a 7F thin-wall guiding catheter and a low-profile balloon catheter. After crossing the occluded site with the 0.014 inch guide wire and/or noninflated balloon catheter, the IRA was opacified to assess the size of thrombus. If combination therapy was selected by the senior cardiologist, 240,000 to 480,000 units of urokinase/50 ml saline was administered through the guiding catheter between 10 and 20 min to partially lyse or macerate the thrombus before balloon angioplasty. The aims of this pretreatment of the thrombus were as follows: (1) to perform PTCA with an understanding of the characteristics of the underlying coronary anatomy; (2) to minimize the distal embolization of the thrombus after balloon inflation; and (3) to prevent thrombus regrowth. Therefore, acute progression after PTCA due to large and/or spiral dissection, which needed stent implantation, meant exclusion from this study. The decision to perform pretreatment of the thrombus by lytic agent before PTCA was dependent on the size of thrombus or the urgency for flow restoration, and not on any specific research protocol. The balloon was advanced across the lesion and inflated to 5–7 atm for 1–2 min. In all cases, an attempt was made to restore the vessel to a normal diameter or to at least achieve a residual stenosis of less than 50% by visual estimate. If, after several balloon inflations, significant narrowing was still present, the lesion was usually recrossed and retreated with a larger balloon.

After achievement of a residual stenosis of less than 50%, IRAs were visualized every 15 min to assess the frequency of acute restenosis, mainly by thrombus regrowth. If acute restenosis was present, a repeat dilation of the lesion was performed. The end-point of emergency angioplasty was persistent perfusion with TIMI 3 flow during the 30 min from the last inflation, with a residual stenosis of less than 50%.

**Postangioplasty Protocol**

After the procedure, a Swan-Ganz catheter was inserted and the patient was sent to the cardiac care unit for observation. Heparin infusion was maintained at 500–1,000 units/h, adjusted by keeping the partial thromboplastin time at 1.5–2.0 times the control level for at least 48 h. Routine cardiac care unit management included bedside hemodynamic monitoring for 24 h or until the patient was considered to be stable. A calcium blocker, diltiazem (90–120 mg/day), was started immediately after the reperfusion procedure; if a contraindication to diltiazem existed, nifedipine was administered. The calcium blocker, as well as antiplatelet therapy with aspirin and persantine, was continued throughout the period of hospitalization.

Electrocardiographic monitoring was continued for 72–96 h and patients were constantly observed for signs or symptoms of recurrent ischemia. When there was clinical evidence suggesting reocclusion, patients underwent repeat emergency angiography.

**Follow-up Catheterization**

To critically evaluate the final patency status of the IRA, repeat cardiac catheterization was sought in surviving patients not referred for coronary-aorto bypass graft (CABG) before hospital discharge as a part of the study protocol. Surviving non-CABG patients in whom initial angioplasty failed (n=25) were also excluded. Two hundred and forty-one (88.6%) of the remaining 272 patients underwent repeat cardiac catheterization 14±5.5 days after the onset of symptoms.
Statistical Analysis
The frequency of acute restenosis during the waiting period of 30 min after initial successful recanalization and the frequency of reocclusion at follow-up coronary angiography before hospital discharge were compared between the combination therapy group and the PTCA group. The clinical characteristics were compared using the unpaired t-test for continuous data and the Chi-square test for group data between the combination therapy group and the PTCA group; or the frequency of acute restenosis was compared between the large-thrombus group and the small-thrombus group. A p value of less than 0.05 was considered statistically significant. Data were expressed as mean±SD.

Results
Twenty-five of the 297 study patients underwent an unsuccessful PTCA procedure; 16 of these patients had greater than 50% but less than 100% residual stenosis after PTCA and 9 had coronary occlusion after PTCA. Three of these 25 patients with failed PTCA were sent for emergency bypass surgery because of sustained ischemic symptoms. There were 5 deaths: 3 were due to cardiogenic shock, 1 was due to cardiac rupture and another was caused by refractory ventricular fibrillation. The remaining 17 patients were asymptomatic and were believed to have a complete infarction. These patients were transferred to the coronary care unit and were treated medically.

Successful PTCA (residual stenosis <50%) was achieved in 91.6% (272/297). These successful PTCA patients were divided into 2 groups: 88 of 98 patients received pre-treatment with intracoronary low-dose urokinase followed by PTCA (success rate 89.8%, combination group); 184 of 199 received only direct PTCA without thrombolytic therapy (success rate 92.5%, PTCA group). Patient characteristics and angiographic characteristics in patients with successful PTCA in the 2 groups are shown in Table 1. There were significantly more female patients in the combination group than in the PTCA group (p<0.05). There were significantly more patients with a large thrombus in the combination group than in the PTCA group (p<0.01). Two hundred and forty-one (88.6%) of the 272 patients with successful PTCA underwent repeat cardiac catheterization before hospital discharge (75 patients in the combination group and 166 in the PTCA group). There was no significant difference in reocclusion rates between the 2 groups (Table 2). The overall reocclusion rate of all patients who underwent repeat cardiac catheterization for the first time after PTCA was 3.3%. Table 2 shows in-hospital hemorrhagic complications; there were no significant differences between the 2 groups (Table 2).

Fig 1. The frequency of acute restenosis during the first 30 min after achievement of a residual stenosis of less than 50% by PTCA. In all study patients, the frequency (%) of acute restenosis was significantly lower in the combination group than in the PTCA group (68.6 vs 80.1, p<0.01) (left panel). When the frequency of acute restenosis was compared by the thrombus size, the frequency (%) was significantly lower in the combination group than in the PTCA group (60.5 vs 82.0, p<0.001) (middle panel) in patients with a large thrombus. On the other hand, the frequencies (%) were not different between the combination group and the PTCA group in the patients with a small thrombus (74.4 vs 79.2, respectively) (right panel).

Fig 2. In all study patients, the cumulative times of acute restenosis during emergency PTCA were significantly lower in the combination group than in the PTCA group (left panel). The times were significantly lower in the combination group than in the PTCA group in the patients with a large coronary thrombus (middle panel). On the other hand, in the patients with a small coronary thrombus, the times were slightly lower in the combination group than in the PTCA group, but the difference was not significant (right panel).
the frequency of acute restenosis was significantly lower in coronary thrombolysis. The present study indicated that safety of PTCA are enhanced in selected patients with vessels. Recent reports indicate that the effectiveness and result from the effects of the thrombus in the coronary slightly lower in the combination group than in the PTCA patients with a small coronary thrombus, the frequency was in the patients with a large coronary thrombus. In the (p<0.0001). The frequency was also significantly lower in the combination group than in the PTCA group vs 79.2, respectively).

When the frequency of acute restenosis was compared by the thrombus size, the frequency (%) was significantly lower in the combination group than in the PTCA group (60.5 vs 82.0, p<0.001) in the patients with a large thrombus (>2 cm). On the other hand, the frequencies (%) were not different between the combination group and the PTCA group in the patients with a small thrombus (<2 cm) (74.4 vs 79.2, respectively).

Fig 2 shows the cumulative frequency of acute restenosis during emergency PTCA in both groups. In all study patients, the frequency of acute restenosis was significantly lower in the combination group than in the PTCA group (p<0.0001). The frequency was also significantly lower in the combination group than in the PTCA group (p<0.0001) in the patients with a large coronary thrombus. In the patients with a small coronary thrombus, the frequency was slightly lower in the combination group than in the PTCA group, but the difference was not significant (p=0.07).

Discussion

Emergency PTCA in patients with AMI, compared with elective PTCA patients with stable angina, has potential disadvantages: lower initial success rates and higher reocclusion rates. This difference after PTCA may partially result from the effects of the thrombus in the coronary vessels. Recent reports indicate that the effectiveness and safety of PTCA are enhanced in selected patients with visual coronary thrombus when PTCA is preceded by intra-coronary thrombolysis. The present study indicated that the frequency of acute restenosis was significantly lower in the combination therapy group than in the PTCA group. Our results also demonstrated that pre-treatment with urokinase was more useful in patients with a large coronary thrombus than in patients with a small coronary thrombus, which may lend credence to previous reports. On the other hand, a previous large-scale trial demonstrated the efficacy of abciximab, a blocker of the platelet surface-membrane glycoprotein IIb/IIIa receptor, in reducing complications among patients at high risk during coronary intervention because of unstable ischemic syndromes. This new strategy should be carried out in AMI patients with a large coronary thrombus.

Administration of thrombolytics with PTCA may increase the risk of plaque hemorrhage or stimulate new thrombus formation at the dilated site and result in unfavorable outcomes in patients with unstable angina. On the other hand, prolonged infusion of thrombolytic agents has been effective in dissolving large amounts of thrombus in saphenous vein grafts and native coronary arteries or in preventing intimal hyperplasia, permitting angioplasty to proceed without complications. A recent trial demonstrated that PTCA after a recent myocardial infarction was associated with a lower incidence of thrombus after an infusion of urokinase, and also that the difference between unstable angina and myocardial infarction in the thrombotic or plaque substrate may be responsible for apparently divergent responses to urokinase. The present study indicated that the frequency of acute restenosis in patients with a small coronary thrombus displayed no statistical difference when comparing the combination group with the PTCA group. Therefore, the data suggest that PTCA without thrombolytic therapy may result in favorable outcomes without complications in patients with a small amount of thrombus.

In the present study, successful PTCA was achieved in 91.6% of patients. Clinically evident reocclusion occurred in 1% and was treated with repeat PTCA. Silent reocclusion was diagnosed on follow-up catheterization before discharge in 8 of 241 patients (3.3%). Our data indicated similar success rates and lower reocclusion rates compared with previous reports. The incidence of acute reocclusion during or shortly after PTCA has been reported to be higher in patients with AMI than in those without AMI undergoing elective PTCA. We previously reported that acute restenosis occurred within 30 min after initial successful PTCA in 40 of 43 patients with AMI. If patients with initial successful PTCA had been not observed during the 30 min after the procedure, and if those patients had been not retreated when the regrowth of thrombus occurred, the occlusion rates at the chronic phase might increase. The present study also indicated that such a strategy, such as persistent patency lasting for at least 30 min in the acute phase of AMI, may result in a lower reocclusion rate in the chronic phase even in the PTCA alone group.

Some reports demonstrated that primary stenting is safe and feasible in patients with AMI having small or moderate amounts of thrombus. However, the use of coronary stents in patients with AMI having large amounts of thrombus is considered controversial because of the thrombogenic potential of stents and concern about subsequent stent thrombosis; therefore, primary stenting with pretreatment with thrombolytic agents may be useful if a large thrombus is present in the coronary artery in patients with AMI.
Study Limitations

This study is a retrospective analysis of the incidence and management of acute restenosis during PTCA from a consecutive series of patients with AMI undergoing PTCA between January 1986 and June 1995. There was no rigid, prospectively designed protocol to treat occluded coronary arteries in the acute phase of AMI, although the initial step in our institution for the treatment with occluded coronary arteries was primary PTCA. This study is also a non-randomized study. The decision to perform the thrombolytic therapy before PTCA was dependent on the size of the thrombus and based upon subjective physician preference; consequently it is thought that there were significantly more patients with a large thrombus in the combination group than in the PTCA group. Furthermore, thrombolytic therapy or PTCA may predispose the thrombus to embolization: this originates from the culprit lesion and no-reflow phenomenon should be examined in future studies. Additionally, a randomized trial should be carried out comparing PTCA with pretreatment by thrombolytic agents versus primary PTCA in the treatment of AMI patients with a large amount of coronary thrombus.

Conclusions

In patients with a large coronary thrombus, the frequency of acute restenosis during emergency PTCA was significantly lower in the combination group than in the PTCA group. Therefore, the present study indicates that PTCA with pretreatment by a low dose of urokinase is more useful than direct PTCA alone in patients with AMI, especially for those who have large amounts of coronary thrombus. This study also indicates that persistent patency lasting for at least 30 min in the acute phase may result in a lower reocclusion rate in the chronic phase.

References