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ORIGINAL ARTICLE

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Reperfusion strategy for acute myocardial infarction in elderly patients aged 75 to 80 years

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Abstract The increasing elderly population will influence the treatment policies adopted in cases of acute myocardial infarction. Considering reperfusion therapy in elderly patients with acute myocardial infarction, we compared three strategies, as follows: primary percutaneous coronary intervention (primary PCI: $n = 26$), facilitated PCI with half the standard dose of mutant tissue-type plasminogen activator (t-PA) (half + PCI: $n = 24$), and facilitated PCI with a standard dose of mutant t-PA (standard + PCI: $n = 15$) between patients 75 and 80 years of age. The rate of acquisition of thrombolysis in myocardial infarction (TIMI-3) flow on initial coronary arteriography was significantly lower in the primary PCI group than in the other two groups (7.7% in the primary PCI group vs 60% in the half + PCI and 66.7% in the standard + PCI group). The incidence of hemorrhagic complications including blood transfusion was not significantly different between primary PCI and facilitated PCI. Considering reperfusion therapy in elderly patients with acute myocardial infarction, we concluded that facilitated PCI may be effective in elderly patients aged 75–80 years.

Key words Reperfusion therapy · Acute myocardial infarction · Elderly patients · Facilitated percutaneous coronary intervention · Thrombolysis

Introduction

It is widely recognized that mortality associated with acute myocardial infarction is higher in the elderly than among younger patients.[1] With current advances in the techniques of reperfusion therapy, including in-stent placement, the time has probably come to evaluate the most suitable treatment strategy for myocardial infarction in the elderly. The guidelines established by the American Heart Association (AHA) and American College of Cardiology (ACC) recommend that to obtain the best results in patients with myocardial infarction under 75 years of age, the door-to-needle time in thrombolysis should be at the most 30 min, and the door-to-balloon time in primary percutaneous coronary intervention (PCI) should be at the most 90 ± 30 mins.[2–5] Since the report on the "A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction," the PACT trial, was first published,[6] several reports[7–9] have also indicated good results obtained by facilitated PCI, in which PCI is conducted in addition to thrombolysis in suitable candidates. However, the benefits of these procedures have not yet been confirmed in elderly patients aged 75 years or older. Two groups of patients in our study group, who were diagnosed as having had acute myocardial infarction immediately after arrival at our hospital, were treated by intravenous (i.v.) bolus injection of mutant tissue-type plasminogen activator (t-PA), and were then examined by coronary arteriography (CAG). Percutaneous coronary intervention was then conducted in patients in whom thrombolysis in myocardial infarction (TIMI)-3 flow was not achieved on the initial CAG. Thus, we have obtained good results by structuring the treatment strategy, fibrinolysis and subsequent transluminal (FAST) therapy. FAST therapy was assessed in the FAST-1[10] and FAST-2[11] trials, which used t-PA and mutant t-PA, respectively, and has reduced the incidence of myocardial injury and the consequent risk of complications. If the benefits of the FAST trials can also be confirmed in elderly patients, excellent results, overall, could also be obtained in this subset of patients. Therefore, to determine how early TIMI-3 flow can be safely achieved in elderly patients, we compared the results of FAST with those of primary percutaneous transluminal coronary intervention (primary PCI) in elderly patients, 75 years of age or older, with acute

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myocardial infarction. The appropriate dose of the thrombolytic agent used for thrombolysis prior to the PCI was also comparatively investigated.

Subjects and methods

Subjects

The subjects were 65 patients with ST-elevation myocardial infarction (STEMI) within 12 h of the onset of symptoms, between April 2002 and March 2004. Patients with symptoms persisting for at least 30 min who had the following finding on a 12-lead electrocardiogram (ECG) were enrolled in the study: a 0.2 mV or greater elevation of the ST segment in limb leads and a 0.1 mV or greater elevation of the ST segment in at least two adjacent chest leads. The following patients were excluded from the study: (1) patients under 75 years or over 80 years of age, (2) those with a past history of cranial nerve diseases, recent MI, coronary revascularization, or bypass operation, (3) patients with a hemorrhagic tendency or active hemorrhagic lesions, (4) patients with a recent history of trauma or major surgery, and (5) patients with a systolic blood pressure of 180 mmHg or more or a diastolic blood pressure of 110 mmHg or more in the emergency room. Other exclusion criteria included: (1) cardiogenic shock on arrival at the emergency room, (2) bundle branch block on the ECG at the emergency room, (3) elevation of the serum creatinine kinase level (CK) beyond the upper limit of normal level even before the administration of a thrombolytic agent, and (4) those who refused consent for participation in the study. Informed consent was obtained from each subject before the administration of a thrombolytic agent.

Study protocol

The protocol of the present study is shown in Fig. 1. ECG findings were evaluated in patients who presented with ischemic chest pain in the emergency room. After assessing whether they were suitable candidates for thrombolysis, the patients were assigned to one of the following three treatment groups: primary PCI, in which PCI was performed after oral administration of 100–200 mg of aspirin (with no prior administration of thrombolytic agent); half + PCI group, in which a thrombolytic agent was administered as a bolus i.v. injection at half the standard dose used for Japanese persons (13.75 kIU of monteplase per kg body weight, or 3.25 kIU of pamiteplase per kg body weight), prior to PCI; Standard + PCI group, in which a thrombolytic agent was administered as a bolus i.v. injection at the standard dose used for the Japanese (27.5 kIU of monteplase per kg or 6.5 kIU of pamiteplase per kg), prior to PCI. The patients were assigned to these groups according to the month in which they were admitted to the facilities; e.g., those who were admitted in January were assigned to the primary PCI group, those who were admitted in February were assigned to the half + PCI group, and those who were admitted in March were assigned to the standard + PCI group. Emergency CAG was implemented following the administration of the thrombolytic agent. If TIMI-3 flow was achieved, no further treatment was planned. If TIMI-0 to -2 was achieved, PCI was conducted in addition to thrombolysis. Heparin (60 U/kg) was administered as a bolus injection once before the initial CAG was performed. Thereafter, the accelerated clotting time (ACT) was monitored at regular time intervals (for 2–8 h after the heparin administration). To reach the target ACT of 150–200 s, heparin was administered i.v., continuously for 2 days. The CAG findings were evaluated by the coronary artery team of the Nihon University School of Medicine.

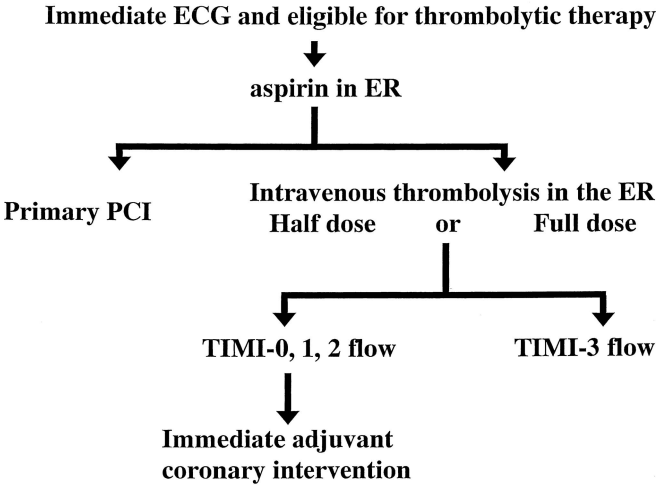

Fig. 1. Protocol. On arrival at the emergency room, patients with ischemic-type chest discomfort were evaluated immediately by electrocardiography. After assessing whether they were suitable candidates for thrombolysis, the patients were assigned to one of the following three treatment arms: primary percutaneous coronary intervention (*PCI*), in which PCI was performed after oral administration of 100–200 mg of aspirin (with no prior administration of thrombolytic agent); half + PCI group, in which a thrombolytic agent was administered as a bolus i.v. injection at half the standard dose used for Japanese persons, prior to PCI; standard + PCI group, in which a thrombolytic agent was administered as a bolus i.v. injection at the standard dose used for Japanese persons, prior to PCI. If thrombolysis in myocardial infarction (TIMI)-3 flow was achieved, no further treatment was planned. If TIMI-0, -1 or -2 flow was observed in the infarct-related artery, then rescue PCI was performed immediately

Study end-points

The primary end-points included changes in the parameters of myocardial injury (i.e., peak CK, peak CK-MB, and peak troponin-T (TnT)), the rate of achievement of TIMI-3 flow, and the time to acquisition of TIMI-3 flow. The blood levels of CK, CK-MB, and peak TnT were measured every 3–12 h after the arrival of the patient at the emergency room, for at least 4 days. The secondary end-points included the mortality rate at 30 days after the onset of myocardial infarction, and the incidence of complications during the 30-day period after the occurrence of myocardial infarction.

Statistical analysis

The patients were divided into three groups according to the month of hospitalization. The numerical data were expressed as the mean ± standard deviation (SD) or as a percentage. The chi-square test and analysis of variance (ANOVA) were used for statistical comparisons among the groups, and Dunnett's test was used as a post hoc test. All the data were analyzed using StatView (Ver. 5.0) software. Differences at $P < 0.05$ were considered as indicating statistical significance.

Results

There were 65 elderly patients with acute myocardial infarction between 75 and 80 years of age, who satisfied the criteria for inclusion in the present study protocol, between April 2002 and March 2004. Table 1 shows the background characteristics of the patients classified according to the treatment arm to which they were assigned. There were no significant differences among the three groups of patients in terms of sex, Killip's class, incidence of anterior infarction associated with acute myocardial infarction, or coronary risk factors. There were also no significant differences among the three groups in the time taken for the transport of the patient to the emergency room from the time of symptom onset.

While the time taken from the arrival of the patient at the emergency room to the achievement of TIMI-3 flow was significantly longer in the primary PCI group, there were no significant differences among the three groups in the time from the symptom onset to the achievement of TIMI-3. There were no significant differences among the three groups in the length of hospital stay (Table 2), changes in the parameters indicative of the infarction volume (i.e., peak CK, peak CK-MB, and peak TnT), or in relation to the secondary end-points (i.e., the mortality rate at 30 days after the occurrence of myocardial infarction and the incidence of hemorrhagic complications) (Table 3). There were no differences in the incidence of hemorrhagic complications in relation to the dose of the thrombolytic agent administered prior to PCI. The eventual cause of death was heart failure in all three groups.

The rate of achievement of TIMI-3 flow on initial CAG was significantly lower in the primary PCI group than in the two facilitated PCI groups (Fig. 2). The rate of achievement of TIMI-3 flow on final CAG was not significantly different among the three groups (Fig. 3). Comparison of the incidence of hemorrhagic complications between the primary PCI group ($n = 26$) and the two facilitated PCI groups ($n = 39$) revealed no statistically significant differences between the groups (Fig. 4).

Discussion

Primary PCI vs thrombolytic therapy

The rate of achievement of TIMI-3 flow on initial CAG was significantly lower in the primary PCI group than in the

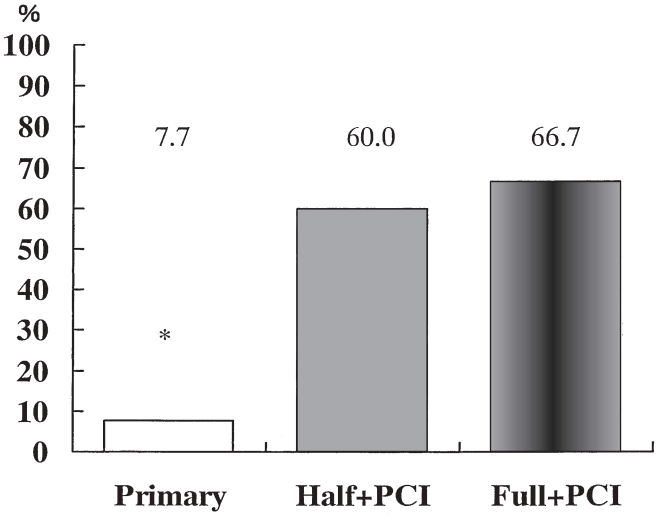

Fig. 2. Comparison of the rate of TIMI-3 flow at the initial angiography according to strategy. *$P = 0.0035$ vs Half + PCI; $P = 0.005$ vs Full + PCI

Table 1. Baseline characteristics according to strategy

Strategy	Primary PCI ($n = 26$)	Half + PCI ($n = 24$)	Full + PCI ($n = 15$)
Age (years)	77.2 ± 2.0	76.5 ± 1.5	77.6 ± 1.7
Sex (M/F)	23/3	15/9	11/4
Initial clinical findings			
Killip class I (%)	88.5	83.3	80.0
Killip class II or III (%)	11.5	16.7	20.0
Anterior MI (%)	64.0	50.0	53.3
Coronary risk factor			
Hypertension (%)	65.4	54.2	53.3
Diabetes (%)	30.8	37.5	33.3
Hyperlipidemia (%)	57.7	50.0	53.3
Smoking (%)	50.0	54.2	46.7
Time interval			
Onset to ER (min)	270.7 ± 288.1	252.0 ± 272.8	225.5 ± 142.9

PCI, percutaneous coronary intervention; MI, myocardial infarction; ER, emergency room

Table 2. Relationship between the time required for the achievement of TIMI-3 flow and length of hospital stay according to strategy

Strategy	Primary PCI	Half + PCI	Full + PCI
Time interval			
ER–TIMI-3 flow (min)	146.7 ± 53.2*	116.5 ± 53.3	100.4 ± 45.7
Onset—TIMI-3 flow (min)	417 ± 293.0	348.6 ± 288.4	325.9 ± 156.3
No. of days in hospital	27.5 ± 10.1	31.9 ± 22.2	29.5 ± 9.9

TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention; ER, emergency room
* $P = 0.0238$ vs full + PCI

Table 3. Relationships between the serum cardiac marker, the incidence of complications, and 30-day mortality according to strategy

Strategy	Primary PCI	Half + PCI	Full + PCI
Serum cardiac markers			
Peak CK (U/l)	2043 ± 1588	2914 ± 2505	2917 ± 2259
Peak CK-MB (U/l)	221 ± 255	213 ± 145	306 ± 227
Peak Troponin T (ng/dl)	12.4 ± 12.2	11.0 ± 6.6	13.5 ± 12.8
Complication			
Intracerebral bleeding (%)	0	0	0
Minor bleeding (%)	0	0	1 (6.7)
Blood transfusion (%)	0	3 (12.5)	1 (6.7)
30-day mortality (%)	4 (15.4)	6 (25)	2 (20)

Minor bleeding: bleeding on punctal site without blood transfusion
CK, creatine kinase

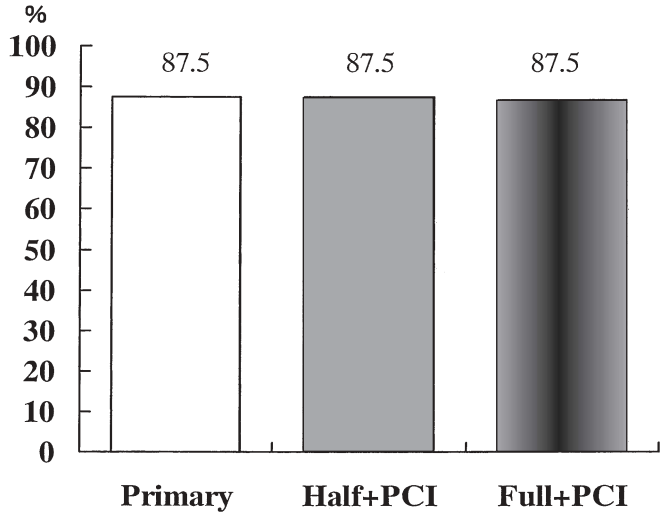

Fig. 3. Comparison of the rate of TIMI-3 flow at the final angiography according to strategy

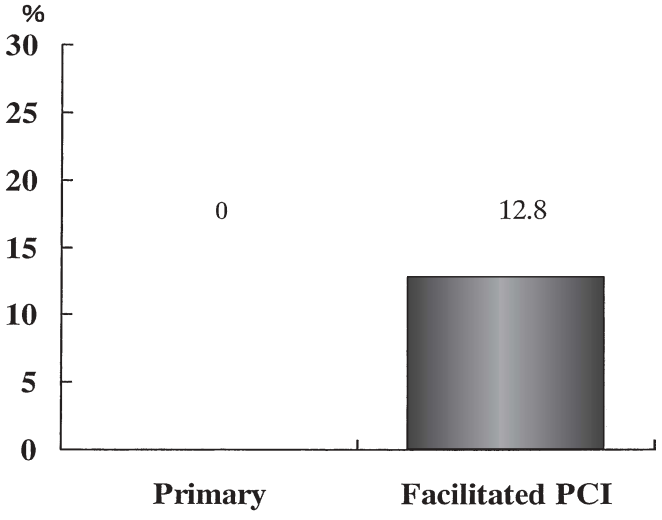

Fig. 4. Comparison of the incidence of hemorrhagic complications between primary and facilitated PCI

two facilitated PCI groups. However, one additional outcome was not proved in facilitated PCT. Intracerebral bleeding is a serious complication that we must never be allowed to develop. Intracerebral bleeding did not occur in this study, because of the small number of patients enrolled.

Our data did not show that facilitated PCI caused any higher rate of hemorrhagic complications than primary PCI. However, we cannot prove that facilitated PCI in elderly patients is safe. It has been reported previously that the rate of intracerebral bleeding in elderly patients after treatment with thrombolytic therapy occurred at a higher frequency.[12–14] Therefore, we should consider the dosage of drug administration.

Facilitated PCI

Since the results of the PACT trial[6] demonstrated for the first time that good results may be obtained by combined

use of PCI and thrombolysis, administration of a thrombolytic agent prior to PCI has been increasingly adopted. The reason for the increasing attention being paid to this treatment strategy is that a therapeutic outcome equivalent or even superior to that following primary PCI may be obtained even at facilities not equipped to conduct PCI, if reperfusion by thrombolysis is conducted prior to transfer of suitable patients to an appropriate facility for PCI. We have devised a protocol in order to shorten the time from the onset of AMI to reperfusion; in this protocol, a thrombolytic agent (mutant t-PA: monteplase) is administered to patients with acute myocardial infarction upon arrival at the hospital, and PCI is subsequently performed if TIMI-3 flow is not achieved. We have since reported the benefits and safety of this treatment protocol.[11] The benefits are marked when the door-to-TIMI-3 time is short; in particular, when it is 55 min or less.[15] In the results of the present study, a significantly long period of time elapsed between arrival of the patient at the emergency room and achievement of TIMI-3 flow in the primary PCI group, suggesting that ways must be devised to shorten this interval. One of the methods to achieve this may be administration of a thrombolytic agent prior to PCI. In a multi-institutional study[16] investigating the usefulness of PCI preceded by thrombolysis with monteplase at a low dose, the rate of achievement of TIMI-3 flow was higher in the group receiving prior administration of monteplase, followed by PCI in suitable candidates at an appropriate facility; the benefits of this protocol were especially marked at facilities that lacked an adequately equipped emergency medical room. This result may indicate the importance of facilitated PCI in Japan. However, these benefits have not yet been confirmed in elderly patients. The GUST-1 trial[17] reported that the beneficial effects of thrombolysis using t-PA are not affected by age, while a meta-analysis by the FTT collaborative group[18] suggested the absence of any benefits of this treatment protocol in patients over 75 years of age. According to the AHA/ACC guidelines, the most suitable candidates for thrombolysis and primary PCI are patients under 75 years of age. One reason for this would appear to be that the incidence of hemorrhagic complications and heart rupture following thrombolysis alone is increased in patients who are 75 years of age or older, and the risks of the harmful effects of the procedure outweigh the benefits that might be accrued. However, based on an assessment of the usefulness of facilitated PCI according to the age group of patients, we confirmed that there were no significant differences in the rate of achievement of TIMI-3 flow on the initial CAG among age groups under 80 years of age, and that there were also no differences in the final rate of achievement of TIMI-3 flow after the addition of PCI among different age groups.[19] At facilities where primary PCI is conducted aggressively, achievement of TIMI-3 flow in the implicated coronary artery before PCI has been reported to have a good influence on the outcome, indicating that it may be of utmost importance to achieve TIMI-3 flow at the earliest opportunity.[20] In the present study, our data demonstrated the efficacy of facilitated PCI in patients with acute myocardial infarction over 75 years of age.

Conclusion

In Japan, where the average longevity of humans has increased, it may be expected that the steady increase in the population of the elderly will influence the treatment policies adopted in cases of acute myocardial infarction. More aggressive countermeasures against myocardial infarction in the elderly are anticipated. Under these circumstances, with advances in reperfusion techniques, including stent placement, we considered it necessary to reassess the efficacy of the various reperfusion strategies available in elderly patients with acute myocardial infarction. In the present study, we were able to confirm the efficacy of facilitated PCI in elderly patients aged 75–80 years. We concluded that facilitated PCI may be a useful strategy in elderly patients with acute myocardial infarction.

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