1. Antithrombolytic Therapy for Sclerotic Diseases

3) Ischemic Heart Disease (Coronary Thrombolysis)

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Key words: coronary thrombolysis, reperfusion rate, long-term follow up, survival rate

It is well known that early reperfusion therapy for patients with acute myocardial infarction improves left ventricular systolic function and survival rate. Thrombolytic agents such as urokinase, pro-urokinase and tissue plasminogen activator (t-PA) are used via intracoronary or intravenous routes in Japan.

Recanalization rates

When these agents were injected into the infarct related coronary arteries, reperfusion rates in double blind multi center trials in Japan, as follows: about 70% by urokinase, 85% by tisokinase (tissue culture t-PA) and 92% by pro-urokinase. When these agents were administered via the intravenous route, reperfusion rates (TIMI grade 2 or 3 flow) were shown in Fig. 1. The reason of lower reperfusion rate by urokinase was due to low doses such as 960,000 IU for over 30 minutes.

It was the most interesting fact that single bolus of E6010 (mutant t-PA) showed a high reperfusion rate.

E6010, mutant t-PA, has an amino-acid substitution at 84th in kring domain, resulting in a longer half-life and increased fibrin specificity. In E6010 double blind trial in Japan, 97 patients received a single bolus of E6010 t-PA over 2 minutes.

At 30 minutes, the recanalization rate (TIMI grade 2 or 3 flow, 62%) was higher than tissue cultured t-PA (AK124). Final recanalization rate at 60 minutes after bolus injection was significantly higher than those of AK124 (TIMI 2 or 3 grade flow, 79% vs 65%) (1).

Intracoronary thrombolysis was performed only in the beginning of 1980's, in Europe and United States of America. Afterward, coronary thrombolysis was mainly performed via the intravenous route.

On the other hand, intracoronary and intravenous thrombolysis was performed for a long time in Japan, but this high reperfusion rate by intravenous single bolus injection of mutant t-PA should change the methodology from intracoronary to intravenous route in the near future.

Intracoronary or intravenous thrombolysis alone was performed in the initial 366 patients who were admitted to our hospital within 6 hours from the onset of chest pain. Recanalization rate of thrombolysis alone was 71.3% overall (Fig. 2).

Upon obtaining this result, rescue or sequential PTCA (percutaneous coronary angioplasty) was added after thrombolysis for a higher expected recanalization rate. Final recanalization rate after rescue PTCA was increased to 92.8% (n=424 patients) (Fig. 2) (2).

Short-term results after coronary thrombolysis

The comparison of in hospital mortality between the groups of thrombolysis alone and thrombolysis plus emergency (rescue) PTCA is shown in Fig. 3.

There was no significant difference between the groups, however the tendency was lower in the group of thrombolysis

Figure 1. Reported by double blind multi-center trial in Japan.

Figure 2. Comparison of recanalization rates: Thrombolysis alone vs Thrombolysis plus rescue PTCA.

Figure 3. Comparison of in-hospital mortality: Thrombolysis alone vs Thrombolysis plus Emergency PTCA.

plus emergency PTCA. These mortality rates were similar to ISIS-3 and GUSTO trials (3, 4).

Long-term results

The results of long-term follow-up after coronary thrombolysis was not reported, because of the natural progression of coronary atherosclerosis and the addition of several coronary interventions such as PTCA or stenting.

The comparison of survival rates between these two groups is shown in Fig. 4. Only the patients who were followed up in our hospital after discharge, were examined for long-term results. The follow-up ratio was 97%. There were high survival rates at 5 years in both groups.

Figure 4. Comparison of survival rates: Thrombolysis alone vs Thrombolysis plus Emergency PTCA.

Table 1. Comparison of intravenous thrombolysis: Japan vs US and Europe.

	Japan	US and Europe*
Reocclusion		
UK or SK	5%	8%
t-PA	10%	13.5%
Intracranial Hemorrhage		
UK or SK	0.1%	0.3%
t-PA	0.3%	0.6%

*Topol EJ: Textbook of Interventional Cardiology, 1994
Granger CB: Drug 44, 1992 and GUSTO: N Engl J Med 329, 1993

Complications after thrombolysis

The reocclusion rates after thrombolysis in the acute phase were 5% in the urokinase group and 10% in the group of t-PA injection in Japan (Table 1). These ratios were lower than those of United States and Europe.

Intracranial hemorrhage is a serious complication, it occurred in 0.1% in the urokinase group and in 0.3% in the t-PA injection group. The percentage of intracranial hemorrhage was also lower in Japan compared to the United States and Europe.

These differences are due to the low doses of urokinase and t-PA used in Japan which are about one-half or one-third those used in the United States and Europe (Table 2). Old aged women with diabetes mellitus and a low body weight and hypertension showed a higher percentage of intracranial hemorrhage.

Table 2. Comparison of intravenous thrombolysis: Japan vs US and Europe.

	Japan	US and Europe*
Dose		
UK	0.96 mU/60 min	2 mU/bolus, 3 mU/90 min
t-PA	0.5~0.75 mg/kg/60 min	≥70 mg/60 min
(Accelerated Alteplase)		and/or 100 mg/90 min
Pro UK	40 mg/60 min	80 mg/60 min

*Topol EJ: Textbook of Interventional Cardiology, 1994

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2. Cardiogenic Cerebral Embolism Associated with Atrial Fibrillation

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Key words: nonvalvular atrial fibrillation (NVAF), cerebral embolism, warfarin, aspirin

Nonvalvular atrial fibrillation (NVAF) as an important cause of embolism

Cardiogenic embolism is recognized to account for about 15% to 20% of all ischemic strokes in clinical studies. As cardiac sources of embolic strokes, atrial fibrillation, especially nonvalvular atrial fibrillation (NVAF) is the most common cardiac source, accounting for approximately 50% of embolic strokes (Table 1) (1). From an autopsy study in the elderly, 28% of the cerebral infarctions were embolic strokes of cardiac origin, 56% of which were caused by NVAF (2).

Atrial fibrillation (AF) increases in incidence with increasing age. Kuramoto et al reported that 10% of all autopsied patients had chronic AF, 7% had paroxysmal AF, most of which were non-rheumatic AF or NVAF (3). Approximately 35% of patients with AF will experience an ischemic stroke during their lifetime. Åberg indicated that 42% of autopsied AF patients without valvular or congenital heart diseases had systemic

embolism, half of which were brain embolism (4). Twenty-two percent of the AF patients had large cerebral infarctions, and 15% had medium-sized cortical infarctions at the autopsy (3). NVAF is an important cause of fatal massive cerebral infarctions in the elderly. Approximately half of the patients with fatal massive cerebral infarctions who died within 2 weeks after the strokes had embolic infarctions due to NVAF (5).

Prophylactic therapy for the prevention of recurrent embolic stroke

Cardiogenic embolic brain infarctions recur frequently. Sage and Uiter reported the high risk of recurrent cerebral infarctions over the long-term in NVAF stroke patients who had no anti-coagulant therapy (6). From an autopsy study, we indicated frequent recurrences in embolic strokes over the long-term with NVAF (7). Although the risk of early recurrences is well known in cerebral embolism of cardiac origin, these data show that the

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