Reperfusion Therapy for Acute Middle Cerebral Artery Trunk Occlusion

Direct Percutaneous Transluminal Angioplasty Versus Intra-arterial Thrombolysis

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Summary

The purpose of this study was to test the hypothesis that direct percutaneous transluminal angioplasty (PTA) might reduce the incidence of haemorrhagic complications and might improve recanalization rate and clinical outcome as compared with intra-arterial (IA) thrombolysis in patients with acute middle cerebral artery (MCA) trunk occlusion.

A total of 70 patients with acute MCA trunk occlusion were treated with IA reperfusion therapy. Thirty-six patients were treated with IA thrombolysis alone. In the other 34 patients, direct PTA was selected as the first choice of the treatment and subsequent thrombolysis was added if necessary for distal embolization. The modified Rankin scale (mRS) was used to assess clinical outcome at 90 days.

As compared with IA thrombolysis, direct PTA provided significant increase in the rates of partial or complete recanalization (63.9 vs 91.2%, p< 0.01) and decrease in the incidence of large parenchymal hematoma with neurological deterioration (19.4% vs 2.9%, p=0.03). Despite such favorable effects, direct PTA did not improve the rate of a favorable outcome (mRS score 0 or 1, 41.7% for the IA thrombolysis group vs 52.9% for the PTA group, p=0.48). However, outcome classified in terms of independence (mRS score ≤2) was significantly better in the PTA group (73.5%) than the IA thrombolysis group (50.0%, p=0.04).

In patients with acute MCA trunk occlusion, as compared with IA thrombolysis, direct PTA improved recanalization rate and reduced serious haemorrhagic complications, resulting in a significant increase in independent patients.

Introduction

Intra-arterial (IA) thrombolysis for acute middle cerebral artery (MCA) occlusion has been demonstrated to be effective by a recent randomized controlled trial[1]. However, an increased incidence of serious haemorrhagic complications[1-5] and failure of recanalization in approximately one third of patients[1] are the two major drawbacks for this therapy. Particularly, in patients with MCA trunk occlusion, successful IA thrombolysis may be impeded by the large size of the thrombus and involvement of the lenticulostriate arteries. For a large thrombus, time-consuming thrombolysis with high doses of thrombolytic agents may be required, which may result in unfavorable outcome with haemorrhagic complications[6,7]. Since the lenticulostriate arteries (LSAs) are terminal vessels with poor collaterals, IA infusion of thrombolytic agents into the LSAs territories may be associated with a high risk of haemorrhagic complications[5-7]. Because of such limitations, mechanical recanalization using percutaneous transluminal angioplasty (PTA) has been performed as an adjuvant or alternative to IA thrombolysis[6-10].

In this study, we tested the hypothesis that direct PTA might reduce the incidence of serious haemorrhagic complications and might improve recanalization rate and clinical outcome as compared with IA thrombolysis.

Material and Methods

Seventy patients treated with some reperfusion therapies for acute MCA trunk occlusion over the past nine years were enrolled in this study. In the first four years, 33 patients were treated with IA thrombolysis alone using urokinase or native tissue plasminogen activator (t-PA) (tisokinase, Asahi Chemical Industry Co., Ltd., Tokyo, Japan). Since 1996, to avoid an infusion of thrombolytic agents into the damaged brain tissue, particularly into the LSAs territories, our therapeutic protocol has been altered as reported previously[7,11-13].

In brief, when early CT signs were present and/or the LSAs were involved in ischemia, we preferred direct PTA to IA thrombolysis as the first choice of the treatment. According to this protocol, direct PTA was performed in 34 patients and IA thrombolysis was done in three patients. As the result, the IA thrombolysis group included a total of 36 patients.

An initial CT scan was obtained just after admission on a Quantex RX (Yokogawa Medical Systems, Tokyo, Japan) with a section thickness of 10 mm. Early CT signs were defined according to the following characteristics: obscuration of the margin of the lentiform nucleus, loss of the insular ribbon and cortical effacement[5,14,15].

Angiographic inclusion criteria were complete occlusion (TIMI [Thrombolysis in Myocardial Infarction] grade 0) or contrast penetration with minimal perfusion (TIMI grade 1) of the M1 segment[16].

The detail of our treatment procedure was reported previously[13]. In the IA thrombolysis group, doses of urokinase ranged from 60,000 to 600,000 U, with 10ml of saline/60,000 U, in boluses. Doses of native t-PA ranged from 3.6 to 14.4 mg, with 10 ml of saline/1.8 mg t-PA, in boluses. Direct PTA was performed with a Stealth angioplasty balloon catheter with a maximum diameter of 2.0 to 2.5 mm. The balloon catheter was advanced into the occlusion site and inflated to 2 atm initially and subsequently up to 3 atm. Several inflations of 30 seconds each were performed until recanalization of the MCA trunk was established. After each inflation, repeated angiography was obtained to assess the degree of recanalization and the presence or absence of distal embolic occlusions.

The extent of angiographic recanalization after treatment was classified according to TIMI grades[16]. Complete recanalization (TIMI 3) was defined as normal opacification of all occluded arteries. Partial recanalization (TIMI 2) was defined as recanalization of some but not all the occluded arteries.

Pre-therapeutic neurological status was evaluated with National Institutes of Health Stroke Scale (NIHSS) scores just before the treatment. Clinical outcome was assessed using the modified Rankin Scale (mRS)[17] at 3 months after onset. Favorable outcome was defined as mRS 0 or 1 and mRS ≤ 2 was used as an indicator of functional independence[18,19].

Follow-up CT scans were obtained just after reperfusion therapy, on the next day and again three to seven days after the termination of the reperfusion therapy. Intraparenchymal hyperdense areas were defined as haemorrhages when they did not resolve until > 24 hours later. When hyperdense areas had already disappeared on the next day, they were considered to be extravasation of the contrast medium[12]. Haemorrhagic transformations were subdivided into three types:

1) petechial haemorrhage with spotty and scattered hyperdense areas;
2) small hematoma with a homogenous hyperdense area less than 3 cm in diameter;
3) massive hematoma with neurological worsening (symptomatic haemorrhage)[12].

Continuous variables were analyzed by Mann-Whitney U test and categorical variables were analyzed by χ^2 statistics. We chose a value of $p = 0.05$ as a level of statistical significance. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by a logistic regression analysis to evaluate whether direct PTA is associated with lower incidence of serious haemorrhagic complications and better clinical outcome.

Table 1 **Baseline characteristics of the IA thrombolysis and PTA groups**

	36 patients treated with thrombolysis	34 patients treated with direct PTA	p*
Age, y	69.2 ± 10.4	68.8 ± 9.9	NS
Sex Men / Women	19 / 17	24 / 10	NS
NIHSS	16.0 ± 2.3	16.5 ± 3.0	NS
LSAs involvement	19	25	NS
Early CT signs (+)	28	30	NS
Duration of ischemia, h	3.6±1.4	4.1±1.0	NS
Recanalization (TIMI 2, 3)*	23	31	<0.01
Haemorrhage (Total)	13	10	NS
Petechial	3	6	NS
Small	3	3	NS
Massive*	7	1	0.03
Clinical outcome			
Favorable (mRS 0, 1)	15	18	NS
Independent (mRS≤2)*	18	25	0.04

*LSAs: lenticulostriate arteries; duration of ischemia: time from onset to the termination of the treatment; TIMI: grading scale of recanalization in the Thrombolysis in Myocardial Infarction trial; *χ2 test*

Results

The baseline characteristics of the IA thrombolysis and PTA groups are shown in table 1. There were no significant differences in age, sex, pretherapeutic NIHSS, total rate of early CT signs or LSAs involvement, and duration of ischemia between these two groups. The rates of partial or complete recanalization (TIMI 2+3) were 63.9 and 91.2% in the IA thrombolysis and PTA groups, respectively. There was a significant difference in the recanalization rate between these two groups ($p<0.01$).

Though the incidence of total haemorrhagic transformations was not different between these two groups (36.1% for the IA thrombolysis group vs 29.4% for the PTA group, $p=0.30$), IA thrombolysis group had a significantly higher incidence of massive parenchymal hematoma with neurological deterioration (19.4% vs 2.9%, $p=0.03$, OR 7.97, 95%CI, 0.92 to 68.66) than the PTA group. Despite a higher rate of recanalization and a lower incidence of serious haemorrhagic complications in the PTA group, there was no significant difference in the rate of favorable outcome (mRS score 0 or 1) between these two groups ($p=0.59$). However, when functional independence (mRS score ≤2) was used as the primary outcome measure, direct PTA was associated with significantly better clinical outcome than IA thrombolysis (73.5% vs 50.0%, $p=0.04$, OR 2.78, 95%CI, 1.02 to 7.58).

In the PTA group, there was no arterial injury related to the procedure of PTA, such as arterial rupture or spasm. Among the 31 patients with some degree of recanalization by direct PTA, 20 (64.5%) had crushing of the embolus with distal embolization to the MCA divisions (5 patients) or small cortical arteries (15 patients) and 11 (35.5%) had flattening of the thrombus with residual stenoses of the MCA. Six patients with residual stenoses and two with distal small emboli were considered to have no need for subsequent thrombolytic therapy. Another two patients resulted in M2 occlusion by crushed emboli underwent no additional thrombolytic therapy for fear of haemorrhagic complications. The other 21 patients received additional thrombolytic therapy for distal embolism or residual flattened thrombus, 18 of them received intravenous infusion of 7.2 mg of t-PA. In the other three patients resulted in M2 occlusion, IA infusion of UK (12×10^4 units) or t-PA (1.8 mg) was performed via the balloon catheter after direct PTA.

Discussion

The recanalization rate in our IA thrombolysis group (63.9%) was similar to that in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial (66.0%) [1], indicating that failure of recanalization still occurs in approximately one third of patients by IA thrombolysis alone. Direct or rescue PTA has been thought to be one of the possible procedures to improve recanalization rate [6-10]. Our present study has demonstrated that mechanical crushing or flattening of the thrombus by direct PTA significantly improve the recanalization rate as compared with IA thrombolysis.

Another important issue is whether mechanical recanalization using PTA may reduce the rate of haemorrhagic complications. Although the incidence of total haemorrhagic transformations were not different between IA thrombolysis and PTA groups, the PTA group had a significantly lower incidence of symptomatic haemorrhage (2.9%) than IA thrombolysis group (19.4%). It was similar to that in the non-treated control group in the PROACT II trial (1.9%), suggesting that mechanical recanalization and subsequent infusion of low dose thrombolytic agents might be safe without increase in the risk of symptomatic haemorrhage. The use of thrombolytic agents, particularly IA local infusion of high concentrated or high dose thrombolytic agents into the ischemic tissue, may be the greatest risk factor for haemorrhagic complications [12,20]. Therefore, mechanical clot retrieval without any use of thrombolytic agents may be a possible ideal treatment for acute ischemic stroke. The present catheter technology, however, has not yet provided such an ideal device for mechanical clot retrieval and direct PTA followed by the use of minimum dose thrombolytic agents, if required, may be the best therapeutic strategy of mechanical recanalization for acute MCA trunk occlusion [13].

In spite of such desirable effects as a higher rate of recanalization and a lower incidence of serious haemorrhagic complications, direct PTA could not improve clinical outcome when a favorable outcome as defined by mRS score 0 or 1 was used as the primary outcome measure. While, when mRS score ≤ 2 was used as an indicator of functional independence [18,19], direct PTA provided a significantly higher incidence of functionally independent patients. Since MCA trunk occlusion is often associated with involvement of the LSAs in ischemia and they are terminal vessels with poor collaterals, it is very difficult to save these arterial territories from ischemia even by rapid and complete recanalization. Therefore, as previously reported [1,18,19], functional independence should be chosen as the primary outcome measure rather than complete recovery, particularly when the patient selection is restricted to those with MCA trunk occlusion.

The potential risks associated with direct PTA include arterial rupture, spasm and distal embolization [8,21-24]. In embolic occlusion, the balloon catheter only has to crush the embolus and dilatation force to the vessel wall is not required [10,13]. Therefore, we selected a balloon catheter with the appropriate diameter, which is less than the average inside diameter of the normal artery and inflation of the balloon was performed under leakage of the inflating pressure. In thrombotic occlusion, we set the initial goal of angioplasty at 50% stenosis, keeping the dilatation force within 2 to 3 atm to prevent arterial rupture or spasm. These procedures in our study caused neither arterial rupture nor spasm. The only problem with our procedure was distal embolization. Distal embolization to the MCA divisions may be treated with IA thrombolysis via the end hole of the balloon catheter [7,10,13]. In case of more distal occlusion, intravenous t-PA infusion may be a better approach that can be applied more quickly and safely [10,13]. In our study, recanalization by direct PTA resulted in flattening of the thrombus in 35.5% of patients and distal embolization occurred in 64.5% of patients. Crushed emboli were usually small and distal embolization produced small cortical artery occlusions in 75.0% of patients. Distal embolization to the MCA divisions was seen in only 5 patients. Therefore, in most cases, even intravenous infusion of low dose t-PA may be sufficiently effective to prevent or reduce cortical infarction due to distal embolization.

Conclusions

In conclusion, direct PTA and subsequent thrombolysis with minimum dose thrombolytic agents, if required, may be an effective option for reducing serious haemorrhagic complications and improving recanalization rate and clinical outcome in patients with MCA trunk occlusion.

We believe that mechanical recanalization instead of thrombolysis should become the first choice of the treatment for proximal artery occlusion in the near future.

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