Direct Percutaneous Transluminal Angioplasty for Acute Middle Cerebral Artery Trunk Occlusion
An Alternative Option to Intra-arterial Thrombolysis

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Background and Purpose—The purpose of this study was to evaluate the safety and efficacy of direct percutaneous transluminal angioplasty (PTA) for patients with acute middle cerebral artery (MCA) trunk occlusion.

Methods—Over the past 9 years, a total of 70 patients with acute MCA trunk occlusion were treated with intra-arterial reperfusion therapy. In the last 5 years, 34 patients were treated with direct PTA, and subsequent thrombolytic therapy was added if necessary for distal embolization. The other 36 patients, mainly in the first 4 years, were treated with thrombolytic therapy alone and were used as controls. Pretherapeutic neurological status was evaluated with National Institutes of Health Stroke Scale scores. The modified Rankin Scale (mRS) was used to assess clinical outcome at 90 days.

Results—There were no significant differences in pretherapeutic National Institutes of Health Stroke Scale score and duration of ischemia between the 2 groups. The rate of partial or complete recanalization in the PTA group was 91.2%, whereas that in the thrombolysis-alone group was 63.9% (P<0.01). The incidence of large parenchymal hematoma with neurological deterioration in the PTA group was 2.9%, while that in the thrombolysis-alone group was 19.4% (P=0.03). Although direct PTA did not improve the rate of favorable outcome (mRS score 0 or 1; 41.7% for the thrombolysis-alone group versus 52.9% for the PTA group; P=0.48), outcome in terms of independence (mRS score 0, 1, 2) was significantly better in the PTA group (73.5%) than in the thrombolysis-alone group (50.0%; P=0.04).

Conclusions—Although definitive conclusions on the comparative merits of these 2 therapies cannot be drawn because of an open trial, direct PTA may be an effective alternative option to intra-arterial thrombolysis for acute MCA trunk occlusion. (Stroke. 2002;33:lll-lll.)

Key Words: angioplasty ▪ cerebral ischemia ▪ hemorrhage ▪ middle cerebral artery ▪ thrombolysis

The effectiveness of intra-arterial thrombolytic therapy for acute middle cerebral artery (MCA) occlusion has been demonstrated by a recent randomized controlled trial.1 However, the drawbacks of this therapy include an increased incidence of serious hemorrhagic complications1–5 and failure to achieve arterial recanalization in approximately one third of patients.1 In patients with embolic MCA trunk occlusion, the embolus is often so large as to be resistant to thrombolysis, and time-consuming thrombolytic therapy with high doses of thrombolytic agents may be required, which may result in an unfavorable outcome with hemorrhagic complications.6,7 On the other hand, in patients with atherothrombotic MCA occlusion, the greatest disadvantages of thrombolytic therapy are the low rate of recanalization and the risk of reocclusion.8 Because of these limitations, there has been increasing interest in the use of percutaneous transluminal angioplasty (PTA) as an adjuvant or alternative to thrombolytic therapy, particularly in patients with MCA trunk occlusion.6–7,9,10 Direct PTA is therefore advocated by some authors7,10 as the preferred treatment for MCA trunk occlusion, particularly in patients with risk factors of hemorrhagic complications such as early CT signs or involvement of the lenticulostriate arteries. Although distal embolization by small crushed fragments is a noteworthy complication of direct PTA for embolic MCA occlusion, thrombolysis of these small fragments has been reported to be easy with intravenous infusion of small amounts of tissue plasminogen activator (tPA).10

In this study we evaluated the safety and efficacy of direct PTA for patients with acute MCA trunk occlusion.

Subjects and Methods

Patients
Since 1993, we have performed reperfusion therapy in 140 patients with acute MCA occlusion; 114 of them were treated with intra-arterial reperfusion therapy. Seventy of these 114 patients were treated...
within 6 hours after onset for acute MCA trunk occlusion and were enrolled in this study. Among these 70 patients, 33 patients were treated with intra-arterial local thrombolytic therapy alone with urokinase or native tPA (tisokinase, Asahi Chemical Industry Co, Ltd) in the first 4 years. Since 1996, to avoid an infusion of highly concentrated thrombolytic agents into the ischemic territory, particularly into the lenticulostriate artery territory, our therapeutic protocol has been altered as reported previously.11,12 In brief, when early CT signs were present and/or lenticulostriate arteries were involved in ischemia, we preferred direct PTA to thrombolytic therapy as the first choice of treatment. According to this protocol, direct PTA was performed in 34 patients, and intra-arterial thrombolytic therapy was performed in 3 patients. As a result, the thrombolysis-alone group included a total of 36 patients. We have reviewed the treatment result of the direct PTA group using the thrombolysis-alone group as controls.

An initial CT scan was obtained just after admission of the patient on a Quantex RX (Yokogawa Medical Systems) with a section thickness of 10 mm. The initial pretherapeutic CT reading was performed by 2 or 3 neurosurgeons on duty to exclude the patients with early CT signs on less than one third of the MCA territory. The angiographic inclusion criterion was complete occlusion (Thrombolysis in Myocardial Infarction [TIMI] grade 0) or contrast penetration with minimal perfusion (TIMI grade 1) of the M1 segment.13 Angiographic sites of arterial occlusion were divided into 3 types: (1) type 1, MCA trunk occlusion at its origin; (2) type 2, MCA trunk occlusion with partial involvement of the lenticulostriate arteries; and (3) type 3, MCA trunk occlusion distal to the lenticulostriate arteries.14

Pretherapeutic neurological status was evaluated with National Institutes of Health Stroke Scale (NIHSS) scores just before the treatment.

**Treatment Procedure**

In both groups, a microcatheter was introduced beyond the thrombus, and local angiography was performed to assess the size of thrombus or the precise site of occlusion before the initiation of reperfusion therapy. Just before the initiation of reperfusion therapy, 5000 U heparin was administered intravenously. An additional 1000 U heparin was administered intravenously. An additional 1000 U heparin was administered at 1-hour intervals during the reperfusion therapy procedure.

In the thrombolysis-alone group, doses of urokinase ranged from 60 000 to 600 000 U, with 10 mL of saline per 60 000 U, in boluses. Doses of native tPA ranged from 3.6 to 14.4 mg, with 10 mL of saline per 1.8 mg tPA, in boluses. After each infusion, repeated angiography was obtained to assess the degree of recanalization.

In the direct PTA group, 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 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.13 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 of the occluded arteries.

For partial recanalization (TIMI 2) or residual severe stenosis without intraparenchymal hyperdense areas on posttherapeutic CT, an intravenous continuous infusion of 10 000 to 15 000 U heparin per day was administered for 7 days. When complete recanalization (TIMI 3) was achieved or intraparenchymal hyperdense areas were seen on posttherapeutic CT, we performed strict blood pressure control to <160/90 mm Hg with neither anticoagulation nor antiplatelet treatment after reperfusion therapy.

**Outcome Assessment**

Clinical outcome was assessed with the modified Rankin Scale (mRS)15 at 3 months after onset. Favorable outcome was defined as an mRS score 0 or 1, and mRS score ≤2 was used as an indicator of functional independence.16,17

**Radiological Assessment**

Initial CT images were retrospectively analyzed by 3 neurosurgeons (S.N., T.I., and T.Y.) together. They had known only the side of hemiparesis, and CT images were read in an unblinded fashion. To minimize false-negative or -positive interpretation, the presence of early CT signs was considered when all 3 neurosurgeons were in accord after discussion.15,16 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.17 Early CT signs in the deep MCA territories were classified according to their anatomic extent, as follows: (1) grade I, normal basal ganglia with subtle hypodensity localized to the insula; (2) grade II, partial obscuration of the posteroslateral part of the putamen; and (3) grade III, hypodensity of the entire lentiform nucleus.17

Follow-up CT scans were obtained just after reperfusion therapy, on the next day, and again 3 to 7 days after termination of the reperfusion therapy. Follow-up CT scans were evaluated by 2 or 3 neurosurgeons in charge of the reperfusion therapy. Intraparenchymal hemorrhagic areas were defined as hemorrhages when they did not resolve until >24 hours later. Hemorrhagic transformations were subdivided into 3 types: (1) petechial hemorrhage with spotty and scattered hyperdense areas; (2) small hematoma with a homogeneous hyperdense area <3 cm in diameter; and (3) massive hematoma with neurological worsening (symptomatic hemorrhage).18 When hyperdense areas had disappeared by the next day, they were considered to be extravasation of the contrast medium.18

**Statistical Analyses**

Continuous variables were analyzed by Mann-Whitney U test, and categorical variables were analyzed by χ² statistics. When appropriate, odds ratios (ORs) and their 95% CIs were calculated by logistic regression analysis. We chose a value of P = 0.05 as a level of statistical significance.

**Results**

In the thrombolysis-alone group, all 36 patients received intra-arterial urokinase infusion, with a mean dose of 21.3×10⁴ U (range, 6 to 60). Among them, 15 patients received additional intra-arterial tPA infusion, with a mean dosage of 7.7 mg (range, 3.6 to 14.4) (Table 1). In 10 of the 36 patients, thrombolytic therapy was discontinued for fear of hemorrhagic complications because of the appearance of early venous filling from the lenticulostriate arteries to the thalamostriate vein. In contrast, the PTA procedure was discontinued in only 3 patients without any recanalization. Among the other 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 2 with

| TABLE 1. Mean Dosage of Thrombolytic Agents in the Thrombolysis and PTA Groups |
|---------------------------------|-----------------|-----------------|
| Treatment                       | Patients Treated With Thrombolysis (n = 36) | Patients Treated With Direct PTA (n = 34) |
| Intra-arterial urokinase (×10⁴) | 21.3 ± 12.4 (6–60, n = 36) | 12 (n = 2) |
| Intra-arterial tPA, mg           | 7.7 ± 4.1 (3.6–14.4, n = 15) | 1.8 (n = 1) |
| Intra-arterial tPA, mg           | —                | 7.2 (n = 18) |
Distal small emboli were considered to have no need for subsequent thrombolytic therapy. In 2 patients with both type 1 occlusion and grade III early CT signs, direct PTA resulted in M2 occlusion by crushed emboli, but additional thrombolytic therapy was not performed for fear of hemorrhagic 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 tPA. In the other 3 patients with M2 occlusion, intra-arterial infusion of urokinase (12–10^4 U) or tPA (1.8 mg) was performed via the balloon catheter after direct PTA (Table 1).

The baseline characteristics of the thrombolysis-alone and PTA groups are shown in Table 2. There were no significant differences in age, sex, pretherapeutic NIHSS score, proportion of occlusive site, rate of early CT signs, and duration of ischemia between these 2 groups. The median baseline NIHSS score was 16 in both groups. The median times from onset to termination of the intra-arterial thrombolysis and PTA procedures were 3.6 and 4.1 hours, respectively. The rates of partial or complete recanalization (TIMI 2 and 3) were 63.9% and 91.2% in the thrombolysis-alone and PTA groups, respectively. There was a significant difference in the recanalization rate between these 2 groups (P<0.01, χ^2 test; OR, 5.84; 95% CI, 1.49 to 22.73).

Posttherapeutic hyperdense areas just after the treatment were seen in 63.9% of the thrombolysis-alone patients and in 47.1% of the PTA patients (P=0.10, χ^2 test); approximately half of them in each group were proved to be extravasation of the contrast medium instead of hemorrhage. There was no significant difference in the rate of hemorrhagic conversion of posttherapeutic hyperdense areas between these 2 groups (P=0.80, χ^2 test). However, in the thrombolysis-alone group, 29.2% of hyperdense areas progressed to massive parenchymal hematoma, whereas this occurred in only 6.3% in the PTA group (P=0.08, χ^2 test). All hemorrhagic transformations except 2 petechial hemorrhages in the PTA group were diagnosed as posttherapeutic hyperdense areas just after the treatment. These 2 petechial hemorrhages in the lentiform nucleus appeared 3 to 7 days after the treatment for all no-contrast extravasation.

Although the incidence of total hemorrhagic transformations was not different between these 2 groups (36.1% for the thrombolysis-alone group versus 29.4% for the PTA group;

| TABLE 2. Baseline Characteristics of the Thrombolysis and PTA Groups |
|------------------------|------------------------|------------------------|
| Patients Treated With Thrombolysis (n=36) | Patients Treated With Direct PTA (n=34) | P* |
| Age, y | 69.2±10.4 | 68.8±9.9 | NS |
| Sex | | | |
| Male | 19 | 24 | NS |
| Female | 17 | 10 | NS |
| NIHSS | 16.0±2.3 | 16.5±3.0 | NS |
| Occlusive Site | | | |
| Type 1 | 2 | 7 | |
| Type 2 | 17 | 18 | |
| Type 3 | 17 | 9 | |
| Early CT signs (+) | 28 | 30 | NS |
| Deep MCA territory | | | |
| Grade I | 10 | 6 | |
| Grade II | 15 | 16 | |
| Grade III | 1 | 6 | |
| Cortical effacement | 7 | 12 | NS |
| Duration of ischemia, h | 3.6±1.4 | 4.1±1.0 | NS |
| Recanalization (TIMI 2, 3)* | 23 | 31 | <0.01 |
| Posttherapeutic hyperdensity | 24 | 16 | NS |
| Extravasation only | 11 | 8 | NS |
| Hemorrhage | 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 0, 1, 2)* | 18 | 25 | 0.04 |

Duration of ischemia is time from onset to the termination of the treatment; TIMI, grading scale of recanalization in the Thrombolysis in Myocardial Infarction trial; mRS, modified Rankin Scale. *

χ^2 test.

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$P=0.14$, $\chi^2$ test), the thrombolysis-alone group had a significantly higher incidence of massive parenchymal hematoma with neurological deterioration (19.4% versus 2.9%; $P=0.03$, $\chi^2$ test; OR, 7.97; 95% CI, 0.92 to 68.66) than the PTA group. Despite a higher rate of recanalization and lower incidence of serious hemorrhagic complications in the PTA group, there was no significant difference in the rate of favorable outcome (mRS score 0 or 1) between these 2 groups ($P=0.34$, $\chi^2$ test). However, when mRS score $\leq 2$ was used as the primary outcome measure, direct PTA was associated with significantly better clinical outcome than thrombolysis alone (73.5% versus 50.0%; $P=0.04$, $\chi^2$ test; OR, 2.78; 95% CI, 1.02 to 7.58).

**Discussion**

Although this study is an open trial with the use of retrospective controls and the 9-year study duration allows for technical development, we believe that this study indicates the usefulness of direct PTA as a safe and effective procedure for acute MCA trunk occlusion. Compared with intra-arterial thrombolytic therapy, direct PTA provided a significantly higher rate of recanalization (91.2% versus 63.9%; $P<0.01$) and a lower incidence of serious hemorrhagic complications (2.9% versus 19.4%; $P=0.03$). Despite such desirable effects, direct PTA could not provide a significant increase in a favorable outcome as defined by mRS score of 0 or 1. This may be because of high baseline stroke severity in patients with MCA trunk occlusion.1 However, when mRS score $\leq 2$ was used as an indicator of functional independence,16,17 direct PTA was associated with a significantly higher incidence of functionally independent patients (73.5% versus 50.0%; $P=0.04$). Since MCA trunk occlusion is often associated with involvement of the lenticulostriate arteries 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. Because of the inevitable subcortical infarction in the lentiform nucleus or the corona radiata, successful recanalization does not always result in complete neurological recovery. Therefore, as previously reported,16,17 we also agree that functional independence should be chosen as the primary outcome measure rather than complete recovery, particularly when selection of patients is restricted to those with MCA trunk occlusion.

The recanalization rate in our thrombolysis-alone group (63.9%) was consistent with that in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial (66.0%).1 Although these recanalization rates with intra-arterial thrombolysis may be superior to those with no or intravenous thrombolysis, failure of recanalization still occurs in approximately one third of patients. Direct or rescue PTA has been thought to be one of the possible procedures to improve recanalization rate.7–10 Our present study also demonstrated that mechanical crushing or flattening of the thrombus by direct PTA significantly improved the recanalization rate compared with thrombolysis alone. In our study direct PTA failed to crush the embolus in only 3 patients, probably because large or hard thrombus could not be crushed into enough small pieces to move distally beyond the MCA bifurcation.

The potential risks associated with direct PTA include arterial rupture, spasm, and distal embolization.5,20–23 In embolic occlusion, the balloon catheter only has to crush the embolus, and dilatation force to the vessel wall is not required.10 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 intra-arterial thrombolytic therapy via the end hole of the balloon catheter.7 In case of more distal occlusion, intravenous tPA infusion may be a better approach that can be applied more quickly and safely.10 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 tPA may be sufficiently effective to prevent or reduce cortical infarction due to distal embolization.

The rates of total hemorrhagic transformation and symptomatic hemorrhage with neurological deterioration in our thrombolysis-alone group (36.1% and 19.4%) were within the range of those in the recent controlled clinical trials of thrombolytic therapy for acute ischemic stroke.1,16,17,24–28 Compared with the rate of symptomatic hemorrhage in the PROACT II trial (10.2%),1 however, that in our study may be higher (19.4%), probably because the study group was restricted to patients with MCA trunk occlusion. On the other hand, the rate of symptomatic hemorrhage in our PTA group (2.9%) was similar to that in the untreated 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 hemorrhage. The use of thrombolytic agents, particularly intra-arterial local infusion of highly concentrated or high-dose thrombolytic agents into the ischemic tissue, may be the greatest risk factor for symptomatic hemorrhage. Therefore, mechanical clot removal without any use of thrombolytic agents may be an ideal treatment for acute ischemic stroke. The present catheter technology, however, has not yet provided such an ideal device for mechanical clot removal, 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.

In conclusion, direct PTA and subsequent thrombolysis with minimum-dose thrombolytic agents, if required, may be an effective alternative option to intra-arterial thrombolytic therapy for acute MCA trunk occlusion. Although this study
is preliminary, it is possible that direct PTA may reduce serious hemorrhagic complications and may improve clinical outcome compared with intra-arterial thrombolytic therapy alone. Our present results encourage us to perform further randomized trials.

References
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