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Results of Urgent Thrombolysis in Patients with Major Stroke and Atherothrombotic Occlusion of the Cervical Internal Carotid Artery

Shunro Endo, Naoya Kuwayama, Yutaka Hirashima, Takuya Akai, Michiharu Nishijima, and Akira Takaku

PURPOSE: **Atherothrombotic occlusion of the cervical internal carotid artery (ICA) without collateral flow is one of the most critical forms of acute ischemia. We report the results of urgent thrombolytic treatment of patients with major stroke in this clinical category.**

METHODS: **Clinical findings and outcome in 33 patients were investigated. All patients had suffered a major stroke, with a score of 24 or higher on the NIH Stroke Scale on admission. Ischemic abnormalities were not detected on initial CT studies. Diagnoses were made at angiography, and patients were treated by intravenous or intraarterial local thrombolysis within 6 hours of stroke onset.**

RESULTS: **Recanalization was accomplished in eight patients with intraarterial local thrombolysis; four of these patients had a good clinical outcome. Two factors characteristic of those whose treatment was successful were dramatic improvement of symptoms after partial recanalization achieved within 3 hours of onset and stabilized improvement after subsequent percutaneous transluminal angioplasty or carotid endarterectomy for residual atherosclerotic stenosis at the ICA origin.**

CONCLUSION: **The results of this study suggest that urgent intraarterial local thrombolysis may be a successful treatment method for some patients in this critical clinical category if the treatment can be accomplished within 3 hours of ictus and followed by either angioplasty or endarterectomy for residual stenosis.**

Several approaches to the treatment of acute ischemic stroke have been used and investigated, including thrombolytic therapy and surgical or endovascular revascularization (1–5). In a recent report from the National Institute of Neurological Disorders and Stroke (NINDS) Study Group (6), an important positive result was presented in which intravenous recombinant tissue plasminogen activator (rTPA) improved clinical outcome after stroke when administered within 3 hours of stroke onset in carefully selected patients. However, the effectiveness and propriety of urgent therapy for patients with profound neurologic deficits have not been universally accepted. In the NINDS study (6), patients with a National Institutes of Health (NIH) Stroke Scale score above 22 (7) were excluded from the evaluated subgroups (8–11).

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From the Department of Neurosurgery, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama, 930-01, Japan. Address reprint requests to Shunro Endo, MD.

Occlusion of the cervical internal carotid artery (ICA) without collateral flow is one of the most critical forms of acute ischemia. Patients suffer profound neurologic deficits from the time of onset, and the rate of major morbidity and mortality is extremely high. A review of the literature by Meyer et al (12) revealed that 16% to 55% of patients with acute ICA occlusion and profound neurologic deficits will die of complications from infarction, 40% to 60% will be left with severe neurologic disability, and only 2% to 12% will make a good recovery. Carotid endarterectomy (CEA) combined with distal thrombectomy is a radical surgical option for patients with acute symptomatic ICA occlusion. While high rates of successful recanalization have been reported, the clinical outcome of emergency CEA has been far from ideal. Lack of collateral flow associated with profound neurologic deficits has been an exclusion criterion in most recent studies (12–14). Despite the development of thrombolytic therapies, few studies that focus on this clinical category have been presented, and the results in those that have been reported are controversial (15, 16). Nevertheless, a few authors have described patients who had a dramatic improvement in their

TABLE 1: Profiles of eight patients with successful recanalization after intraarterial local thrombolysis

Case No.	Age, y/ Sex	Treatment	Onset to Recanalization, h	Thrombolytic Agent	NIHSS Score		
					Initial	After LT	At 1 Month
1	66/M	LT alone	2.5	Urokinase, 120,000 IU	27	7	Died of reocclusion
2	65/M	LT alone	4.0	rTPA, 20 mg	26	26	20
3	64/M	LT alone	5.0	rTPA, 15 mg	26	26	Dead of intracerebral hemorrhage
4	57/M	LT and PTA	2.0	rTPA, 20 mg	27	6	0*
5	76/M	LT and PTA	2.0	Urokinase, 360,000 IU	25	5	0
6	49/M	LT and PTA	2.5	rTPA, 20 mg	27	12	1
7	73/M	LT and CEA	3.0	rTPA, 20 mg	27	4	1
8	65/M	LT and PTA	3.5	rTPA, 20 mg	26	20	12

Note.—LT, Local thrombolysis; CEA, carotid endarterectomy; PTA, percutaneous transluminal angioplasty; rTPA, recombinant tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale.

* CEA 6 months later for an asymptomatic restenosis.

symptoms after recirculation by CEA or thrombolysis within 1 or 2 hours after stroke onset (14, 15, 17–20). We report our therapeutic experiences with intravenous or intraarterial local thrombolysis in patients with acute atherothrombotic cervical ICA occlusion with poor collateral flow.

Methods

Between 1991 and 1996, 120 consecutive patients with acute cerebral stroke due to major cerebral artery occlusion were treated with intravenous or intraarterial thrombolysis in our hospital. Thirty-three of these patients were included in this study. They were identified as having acute atherothrombotic cervical ICA occlusion without collateral flow and were treated with thrombolysis within 6 hours of stroke onset. Patients with ICA occlusion that was diagnosed as cardioembolism (21) were not included in this series. The patients were all men, 49 to 78 years old (mean age, 68 years), and all had suffered serious stroke and were admitted to the hospital through a local emergency service. On admission, they showed impairment of consciousness and severe hemispheric neurologic deficits, including hemiplegia, aphasia, and often conjugate deviation of the eyes. The NIH Stroke Scale score was more than 24 points, but hypodense areas were not detected on initial CT scans. Three- or four-vessel digital substraction angiography, including a delayed venour phase, performed on an emergency basis, revealed complete occlusion at the origin of the ICA with no development of collateral flow through the anterior communicating artery, posterior communicating artery, or external carotid arteries.

The first 12 patients were treated only by constant intravenous urokinase (60,000 to 240,000 IU) or rTPA (alteplase, 40 to 80 mg) infusion without other aggressive measures. Posttreatment recanalization was defined by angiography or sonography. In the remaining 21 patients, intraarterial local thrombolysis was performed immediately after diagnostic angiography. The tip of a 3F microcatheter was advanced coaxially into the thrombus through a 6F guiding catheter, which was placed in the common carotid artery under systemic heparinization. The thrombolytic agent was then injected into the thrombus. The initial injection, which included 60,000 IU of urokinase or 5 mg of rTPA dissolved in 10 mL of physiological saline, was given manually in a pulse spray fashion for 10 minutes. Injection of the thrombolytic agent was repeated until angioanatomic recanalization was achieved up to the maximum dose of 960,000 IU of urokinase or 40 mg of rTPA. Patients in whom recanalization of the ICA was successful were managed by intravenous drip infusion of heparin (500 U/h) during the subsequent 24-hour period. In some of these patients, percutaneous transluminal angioplasty (PTA) or CEA was subsequently performed for persistent severe stenosis at the origin of the ICA. PTA was performed immediately after recanalization. Systolic blood pressure was maintained at less than 150 mm Hg after treatment. Ticlopidine (100 mg/d) and aspirin (80 mg/d) were administered from the day after treatment, when no intracranial hemorrhage or systemic bleeding was observed.

Criteria for exclusion from cerebral angiography and from the treatment described above included positive baseline CT findings related to the ischemic events; age over 80 years; deep coma; gradually improving symptoms; critical cardiac, pulmonary, renal, or hepatic condition; known contraindication to fibrinolysis; and inability to obtain informed consent. At angiography, a finding of pseudoocclusion with a long "string sign" in the distal ICA was a criterion for exclusion from further treatment (22, 23). Cerebral blood flow (CBF) was not routinely measured as a means to shorten the time before treatment.

The neurologic status of the 33 patients was evaluated according to the NIH Stroke Scale immediately after initial thrombolysis and related treatment and again at 24 hours, 7 days, and 1 month. CT scans were generally obtained within 1 hour after treatment and again at 24 hours, 5 to 7 days, and 1 month. They were also obtained any time that clinical deterioration was observed. CBF measurements by single-photon emission CT were also obtained at 5 to 7 days and at 1 month after treatment. Functional outcomes of the 14 surviving patients were evaluated 1 month after treatment with the following criteria: excellent = a normal neurologic examination; good = a minor deficit on examination (these patients were functionally independent and employable); fair = a moderate hemiparesis or aphasia (these patients were functionally independent); and poor = marked neurologic deficit (these patients were incapable of independent living). In patients with successful recanalization and an excellent or good outcome, conventional or MR angiography was performed 3 to 6 months after treatment.

Representative Cases

Case 1: Local Thrombolysis Alone

This 66-year-old man (Case 1 in Table 1; Fig 1) was hospitalized 1 hour after symptom onset in a stuporous state with left hemiplegia and severe dysarthria. Angiography revealed occlusion of the right ICA, and 120,000 IU of urokinase was promptly administered locally. Neurologic symptoms improved immediately after recanalization was detected angiographically at 2.5 hours after onset of ictus. Forty hours later, the patient suffered another stroke, with profound neurologic deficits. Repeat angiography revealed reocclusion of the ICA. Recanali-

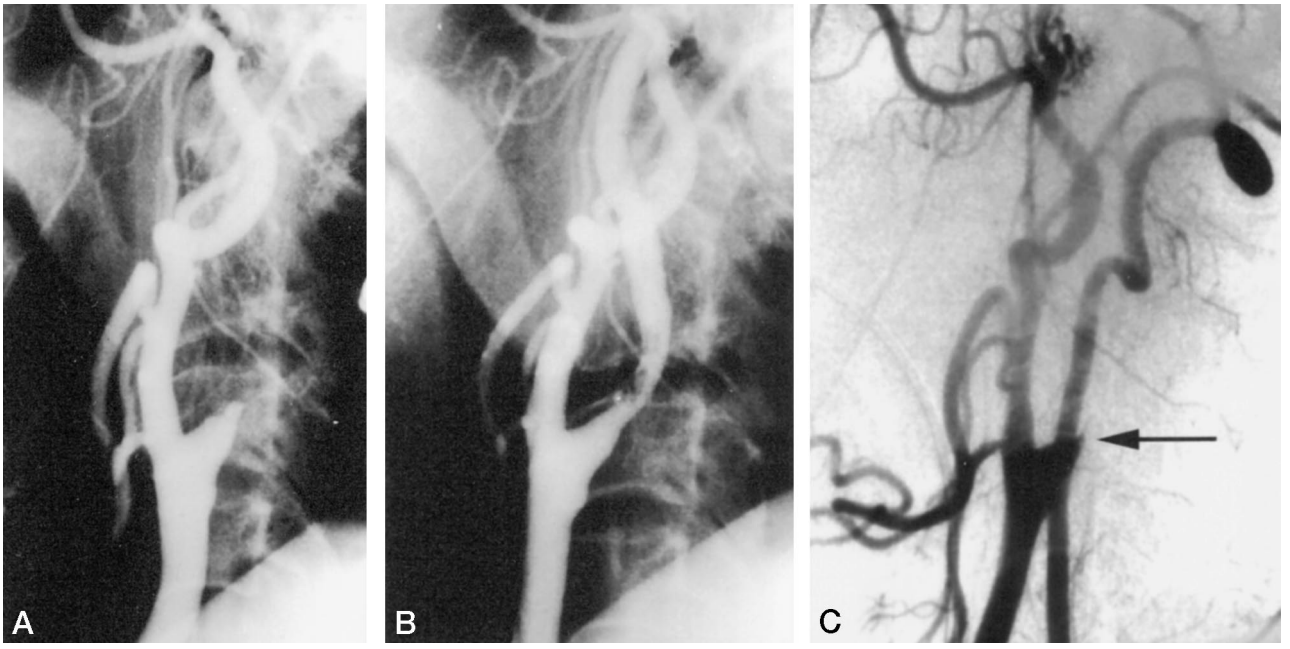

FIG 1. Case 1. Right carotid angiograms (lateral view) show occlusion at the origin of the ICA before treatment (*A*), partial recanalization just after local thrombolysis (*B*), and reocclusion (*arrow*) 40 hours after recanalization (*C*).

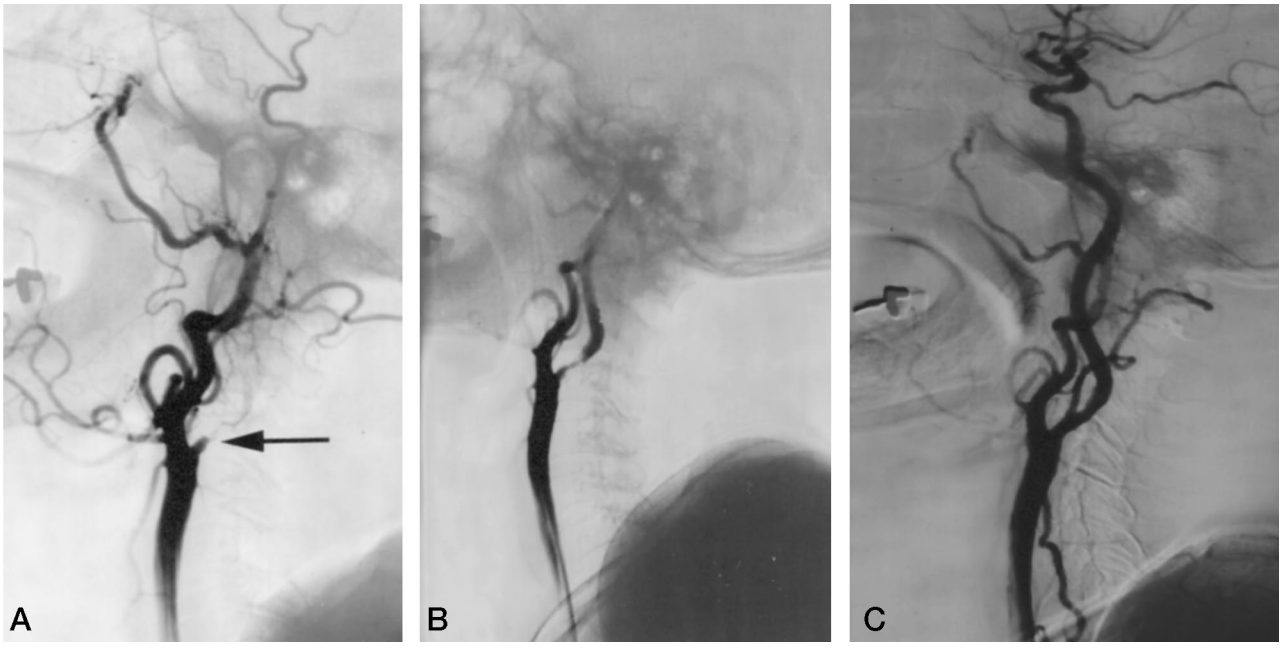

FIG 2. Case 2. Right carotid angiograms (lateral view) show occlusion at the origin of the ICA (*arrow*) before treatment (*A*), partial recanalization just after local thrombolysis (*B*), and further dilatation after transluminal angioplasty (*C*).

zation could not be obtained by repeat intraarterial local thrombolysis, and the patient died, without improvement of clinical symptoms, of secondary mass effect from infarction.

Case 2: Local Thrombolysis Followed by PTA

This 76-year-old man (Case 5 in Table 1; Fig 2) was hospitalized 1 hour after symptom onset in a drowsy state with left hemiplegia. Angiography revealed occlusion of the right ICA, and 360,000 IU of urokinase was promptly administered locally. Neurologic symptoms improved quickly after recanalization was detected angiographically at 2 hours after onset of ictus. PTA was performed immediately in the portion of the artery with severe residual stenosis, which was dilated to 50% of the stenotic diameter. Symptoms continued to improve after PTA, and the patient was discharged 3 weeks later without neurologic deficit.

Case 3: Local Thrombolysis Followed by CEA

This 73-year-old man (Case 7 in Table 1; Fig 3) was hospitalized 1.5 hours after symptom onset in a stuporous state with right hemiplegia and complete aphasia. Angiography revealed occlusion of the left ICA, and 20 mg of rTPA was promptly administered locally. Neurologic symptoms improved dramatically after recanalization was detected angiographically 3

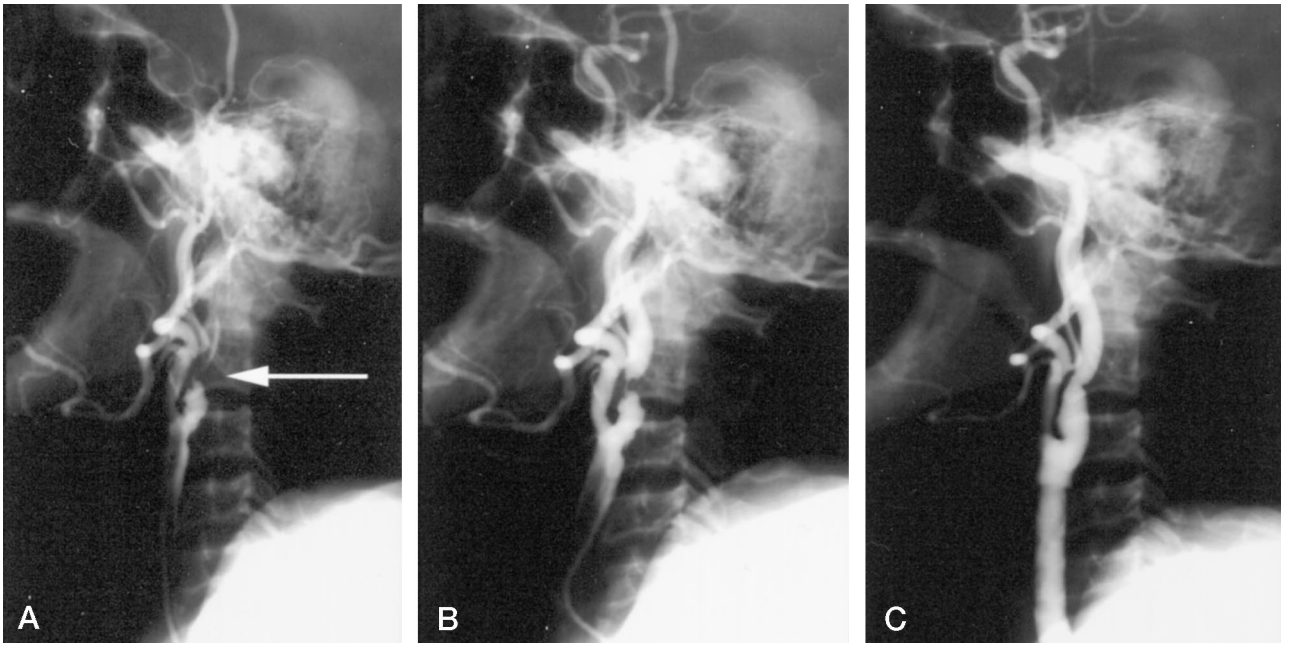

FIG 3. Case 3. Left carotid angiograms (lateral view) show occlusion at the origin of the ICA (*arrow*) before treatment (*A*), partial recanalization just after local thrombolysis (*B*), and total revascularization after carotid endarterectomy (*C*).

TABLE 2: Outcome of 33 patients after urgent thrombolytic therapy

Treatment	No. of Cases	Outcome				
		Excellent	Good	Fair	Poor	Dead
Intravenous thrombolysis	12	0	0	0	3	9
ILT alone (no recanalization)	13	0	0	0	5	8
ILT alone (recanalization)	3	0	0	0	1	2*
ILT and PTA/CEA	5	2*	2*	1	0	0

Note.—ILT, Intraarterial local thrombolysis; PTA, percutaneous transluminal angioplasty; CEA, carotid endarterectomy.
* Five patients showed prompt improvement just after ILT performed within 3 hours of symptom onset.

hours after onset of ictus. CEA was performed 8 hours later, and thick atheroma at the site of residual stenosis was resected. Symptoms improved after surgery, and the patient was discharged 2 weeks later with minimum functional impairment of the right fingers.

Results

Table 2 shows the results of treatment for all 33 patients immediately and at 1 month after treatment. In the 12 patients with intravenous thrombolysis, recanalization and improvement of symptoms were not observed. Three patients had poor outcomes and nine patients died. In 13 of 21 patients who underwent intraarterial thrombolysis, recanalization was not successful and their outcome was poor (vegetative state, n = 5) or fatal (n = 8). In the 25 patients who had no recanalization, posttreatment CT scans revealed diffuse hemispheric infarction and brain edema. The causes of death or major morbidity were primary damage and secondary mass effect from infarction and/or pulmonary/heart failure. No intracranial or systemic hemorrhagic complications were encountered.

In the eight patients treated by intraarterial local thrombolysis, partial recanalization was accomplished and angiographic filling of the distal ICA and intracranial arteries without distal embolism was confirmed, although a moderate to severe stenotic lesion at the ICA origin persisted in all of them. The outcome for the three patients who underwent thrombolysis alone was poor or fatal. On the other hand, five patients who were treated with PTA or CEA had a satisfactory outcome (excellent or good in four and fair in one). Recanalization was accomplished with 360,000 IU of urokinase or 20 mg or less of rTPA.

Table 1 shows the clinical profiles of the eight patients in whom recanalization was successfully accomplished by local thrombolytic therapy. In one of the three patients who underwent thrombolysis alone (case 1), symptoms improved rapidly 2.5 hours after onset, but a repeat stroke caused by recurrent ICA occlusion occurred 2 days later and the patient died (see representative case 1). In the other two patients (cases 2 and 3), recanalization occurred 4 or 5 hours after onset, but symptoms became aggravated as a result of severe hemispheric infarction and/or massive intracerebral hemorrhage. In four of five patients who underwent subsequent PTA or CEA (cases 4

through 7), symptoms improved dramatically immediately after recanalization, which was accomplished within 3 hours after their onset. Further improvement and stabilization of symptoms were obtained by adding PTA or CEA. These four patients returned to their normal lives with or without minimum neurologic dysfunction (see representative cases 2 and 3). In the remaining patient (case 8), 3.5 hours transpired before recanalization was accomplished, and neurologic deficits persisted, resulting in a fair outcome. These five patients had no clinical change during the 24- to 60-month follow-up period, but one patient underwent CEA 6 months later because of an asymptomatic severe restenosis. The effectiveness of intraarterial local thrombolysis within 3 hours of symptom onset and with subsequent PTA or CEA treatment was significantly better than that of other treatments ($P < .01$ by χ^2-test).

Discussion

Of the 33 patients with major stroke and atherothrombotic ICA occlusion in our study, 29 had poor clinical outcomes despite urgent intravenous thrombolysis or unsuccessful intraarterial thrombolysis, illustrating the devastating clinical course of this disease. However, four patients with intraarterial local thrombolysis had a good result, which could not be expected before treatment. Two factors characteristic of those whose outcomes were successful were dramatic improvement of symptoms after partial recanalization within 3 hours of symptom onset and further improvement and stabilization of symptoms by subsequent PTA or CEA treatment for residual atherosclerotic stenosis at the origin of the ICA.

Intraarterial Local Thrombolysis

Intraarterial thrombolysis for intracranial arterial occlusion has been performed with ICA infusions and/or direct local thrombolysis. Techniques used and amounts of thrombolytic agent administered have varied widely among reported studies (10, 24–27). A review of the literature by Nesbit et al (28) suggested that intraarterial thrombolysis might have a higher rate of recanalization (58% to 100%) and clinical improvement (53% to 94%) than intravenous treatment (36% to 89% and 26% to 85%, respectively), without significant increase in hemorrhagic transformation (16, 29–33) (however, these data are drawn mainly from case reports and small open clinical trials). For both proximal and distal ICA occlusion, though, data supporting the effectiveness of thrombolytic therapy have not been sufficiently evaluated. The low recanalization rate and the risk of distal arterial embolism and subsequent hemorrhagic complications must be considered more seriously than with intracranial distal arterial occlusion (3, 26). Guidelines for thrombolytic therapy for acute stroke presented in 1996 by the American Heart Association Stroke Council (10) summarized recent studies of intraarterial thrombolysis, stating that rates of recanalization are lower for occlusion of the ICA than for occlusion of branches of the middle cerebral artery, that there is no evidence that intraarterial thrombolysis is superior or inferior to intravenous therapy, and that there is no evidence that one thrombolytic drug is superior to another in terms of rate of recanalization or safety when used for intraarterial thrombolysis.

Previously reported macroscopic or histopathologic investigations have revealed that lesions of atherothrombotic ICA occlusion often have a thick atheroma plaque associated with fresh thrombus. McCormick et al (34) reviewed the findings in 42 patients with surgically managed symptomatic ICA occlusion and presented three different phenomena observed at the point of arteriotomy: 1) the clot spontaneously expressed itself with good back flow: 2) the clot did not spontaneously exit and no back flow was observed, and 3) a small amount of clot exited with weak back flow. In some patients who displayed the latter two phenomena, they used Fogarty balloon catheter techniques to remove organized thrombus with distal extension. In a recent pathologic study of nine patients with acute ICA occlusion who underwent emergency CEA, Endo et al (35) reported that five patients had massive intraluminal fresh thrombus extending distally and three had only small thrombus localized to the site of occlusion. These atherosclerotic thrombi were associated with disrupted intraplaque hemorrhage of the thick atheroma.

With thrombolytic therapy, the amount of distal ICA thrombus (clot) related to the advanced atherosclerotic changes should be a determining factor for the success of recanalization, although such determination is difficult with currently used routine studies. In our patients, recanalization was successful in fewer than half of those treated by intraarterial local thrombolysis, and higher doses of thrombolytic agent did not contribute to the success rate. In addition, angiographic findings after recanalization uniformly showed a stringlike flow at the origin of the ICA, with a relatively complete filling of the distal ICA. These results may suggest that recanalization can be achieved only in a restricted group of patients who have a small localized thrombus at the origin of the ICA, and that aggressive intraarterial local thrombolysis or angioplasty should be more effective than intravenous treatment of advanced atherothrombotic occlusion (16, 26). In patients with massive intraluminal thrombus extending distally, it is strongly believed that sufficient recanalization may be unattainable by any thrombolytic therapy.

Timing and Degree of Recanalization

For recanalization of acute ischemic stroke to be successful, the duration of ischemia should be shorter and the residual CBF in the territory of occluded vessels should be greater than the levels at which the viability of neuronal cells and vascular endothelial cells are lost. Numerous experimental and clinical studies have addressed the timing of recanalization, and the consensus is that 6 hours is the maximum

time before infarction or hemorrhagic complications are likely to occur in cases of middle cerebral artery territory occlusion. The recent findings of the NINDS Study Group showed that intravenous rTPA improved outcome after stroke when given within 3 hours of symptom onset in selected patients (6, 20, 36).

A few exceptional cases of good outcomes have been reported in patients in whom establishment of flow was achieved in less than 1 or 2 hours after symptom onset (14, 16–20). In eight patients in our series, partial recanalization of the occluded ICA was accomplished by intraarterial local thrombolysis within 5 hours after symptom onset. Five of these patients had dramatic improvement of neurologic symptoms immediately after partial recanalization was obtained within 3 hours of onset. The other three patients, in whom recanalization occurred 3.5 to 5 hours after onset, experienced deterioration of symptoms and did not have acceptable outcomes. Hemorrhagic complications, especially serious intercerebral hemorrhage, are important considerations when evaluating the possibility of urgent treatment of acute ischemic stroke. In our series, intracranial hemorrhage did not occur, except for a fatal intracerebral hemorrhage in one patient who had recanalization 5 hours after symptom onset. We believe that mild reflow due to partial recanalization may also lessen the risk of hemorrhage.

Our findings suggest that the permissible duration of ICA occlusion is extremely limited, but it may be extended to about 3 hours, and even partial recanalization may supply blood flow sufficient to improve symptoms in the most critical conditions in which there is no collateral flow. If this 3-hour treatment window is adequate for transportation and examination of patients, urgent treatment of ICA occlusion should be reconsidered. Intraarterial local thrombolysis, which can be performed immediately after angiographic diagnosis, should be an alternative treatment method in this clinical category. With CEA, recanalization rates are higher than this endovascular treatment but the time from onset to flow restoration by arterial repair or replacement of shunt is limited. In this series, we performed three- or four-vessel angiography before starting the treatment to confirm the status of the intracranial arterial circulation. This procedure may be considered dispensable to reduce the time to treatment; however, we recommend employing this simple and minimal study so that recanalization may be performed more safely and accurately.

Treatment after Recanalization

As mentioned above, findings of macroscopic and histopathologic investigations reveal that most lesions of the atherothrombotic ICA occlusion have a thick atheromatous plaque associated with fresh thrombus at the origin of the ICA. These atheromatous lesions will remain after clearance of the thrombus by thrombolysis and will continue to reduce CBF or cause reocclusion and distal embolism. Definitive management of residual stenotic lesions after thrombolysis should be required, but this option has not been sufficiently investigated (16, 28, 37). In our series, excellent results by intraarterial local thrombolysis were obtained in four patients who underwent subsequent PTA or CEA after partial recanalization. One patient treated only with thrombolysis suffered reocclusion and died. Although our experience is limited, our findings suggest that treatment to remove or decrease the residual stenotic lesion should routinely be considered after successful recanalization. The means for selecting the optimal method and timing for achieving the best treatment results are still obscure. We advocate PTA as one means of treating this acute and critical condition, although its effectiveness remains a matter of controversy (16, 24, 38, 39). CEA is an established treatment for high-grade ICA stenosis, but the time delay and surgical risks in cases of critical ischemia are unknown.

Another important determinant of the result of local thrombolysis is the perioperative risk of intracranial arterial embolism (12). In our series of patients with no collateral flow, identification of intracranial arterial occlusion before and during surgery was impracticable, but eight patients with ICA recanalization had no finding of occlusion in the distal intracranial artery. However, it is clear that this method of inserting the catheter into the thrombus itself carries a significant risk of producing a distal embolism (40, 41). Komiyama et al (37) and Speaman et al (16) reported their experience with successful endovascular treatment of acute thrombotic ICA occlusion associated with embolic middle cerebral artery occlusion. Nesbit et al (28) also reported a series of four patients successfully treated by intracranial intraarterial thrombolysis facilitated by microcatheter navigation through an occluded cervical ICA.

Conclusion

Our results should encourage further attempts to initiate urgent therapy for patients with major stroke and ICA occlusion with no development of collateral flow. However, this study is preliminary and further investigation and more extensive clinical experience are required to know the true effectiveness and limitations of this treatment.

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