

Combined therapeutic approach of intra-arterial thrombolysis and carotid endarterectomy in selected patients with acute thrombotic carotid occlusion

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Purpose: The feasibility and clinical outcome of intra-arterial thrombolysis followed by carotid endarterectomy (CEA) for acute thrombotic occlusion of the internal carotid artery (ICA) were evaluated.

Methods: Intra-arterial thrombolysis and CEA were performed in four patients with acute thrombotic ICA occlusion. Computed tomography scans, cerebral angiograms, and the severity of carotid plaques were examined, and the patients' clinical outcome was evaluated.

Results: All 4 patients had severe hemiparesis; 3 patients were alert, and 1 patient was lethargic at the time of hospital admission. New lesions were not shown by means of the initial computed tomography scan. ICA occlusion was indicated in all four patients by means of cerebral angiograms; in three patients, middle cerebral artery occlusion was noted. Collateral circulation was manifested in all patients. Partial recanalization of the occluded ICA was obtained in all patients. Two patients with severe residual ICA stenosis underwent an emergency CEA soon after thrombolysis; the other two patients were treated by means of CEA in the subacute or chronic stage. Plaque rupture and intraplaque hemorrhage were seen in all four patients. All four patients recovered completely, and restenosis of the ICA was not shown by means of follow-up angiograms.

Conclusion: Intra-arterial thrombolysis followed by CEA may be an effective therapeutic approach for treating acute thrombotic ICA occlusion. The optimal timing of CEA remains controversial. (J Vasc Surg 2001;34:532-40.)

Acute cervical thrombotic internal carotid artery (ICA) occlusion may result in stroke and be fatal. However, if the blood flow is restored soon after stroke onset, the ischemic brain can be salvaged. Carotid intra-arterial fibrinolysis resulted in dramatic improvements of the neurologic state of patients with ICA occlusion.¹⁻¹² After thrombolysis, residual ICA stenosis or recurring ICA occlusion often led to clinical deterioration that required percutaneous transluminal angioplasty (PTA)^{7,8,11} or carotid endarterectomy (CEA).⁵⁻⁷ Which patients will benefit most from this therapy, its timing, and the optimal combination of therapeutic approaches remain controversial. We report on four patients with acute thrombotic occlusion of the cervical ICA who were successfully treated by means of intra-arterial fibrinolysis followed by CEA. We also present a review of the literature and discuss prognostic indicators for a good clinical outcome.

PATIENTS AND METHODS

Between January 1990 and December 1999, 234 patients with acute ischemic stroke were admitted to our institute within 24 hours after stroke onset. Emergency angiography was performed in patients with profound neurologic deficits. In 20 of 234 patients (8.5%), ICA occlusion was indicated by means of emergency angiograms. If the responsible lesion was not shown by means of the initial computed tomography (CT) scan, we considered performing intra-arterial thrombolysis after diagnostic angiography. Nine of the 20 patients arrived at our institute after some delay; in these cases, a lesion that had precipitated the stroke was identified by means of a CT scan. Those 9 patients were treated conservatively; 6 of them have severe disability, and 3 of them died. The other 11 patients with an acute stroke (4.7% of the 234 patients with an acute stroke) underwent intra-arterial thrombolysis just after diagnostic angiography. Seven of these 11 patients were thought to have embolic ICA occlusion; recanalization was obtained in only 3 of the 7 patients. Of this group, 1 patient recovered moderately, 1 patient was severely disabled, and 5 patients died. The other four patients with an acute stroke (1.7% of the 234 patients with an acute stroke) were thought to have thrombotic ICA occlusion; the combined therapeutic approach consisting of intra-arterial thrombolysis and subsequent CEA was used to treat them. This group comprises 2.5% of the total number of CEAs performed at our institute during the past 10 years.

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Competition of interest: nil.

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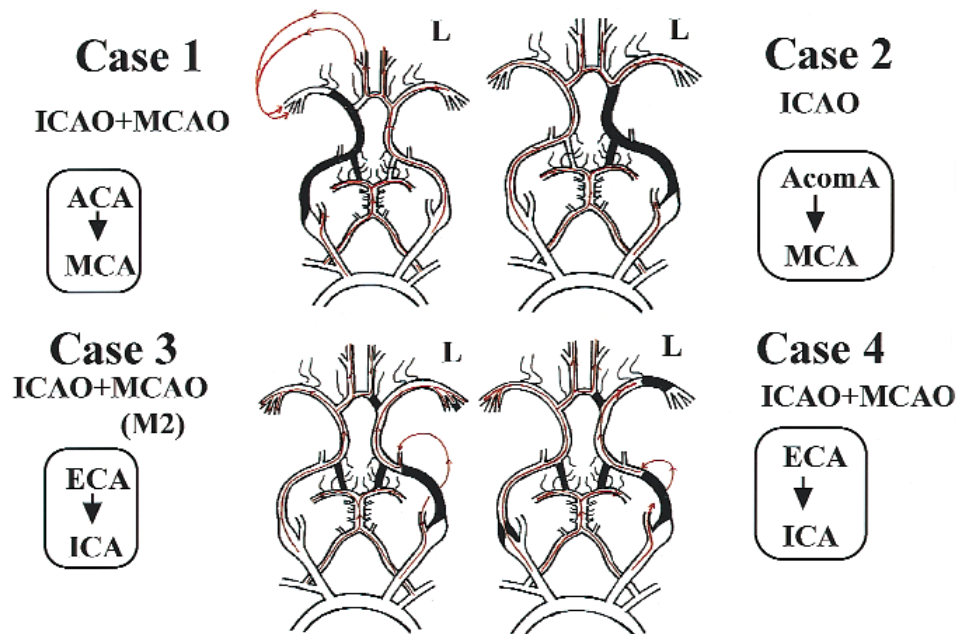


Fig 1. Occlusion sites of internal carotid artery (ICAO) and middle cerebral artery (MCAO) and collateral flow in each of our four patients.

All four of these patients were admitted to our hospital within 2 hours after stroke onset. No patient had a history of arrhythmia or valvular heart disease. Severe hemiparesis was demonstrated in all patients. No new lesions were revealed by means of the initial CT scans. The occlusion sites and the collateral circulation demonstrated by means of cerebral angiograms are illustrated in Fig 1. Occlusion of the ICA was manifested in all patients; in three patients, there was middle cerebral artery (MCA) occlusion. All four patients had evidence of collateral circulation from a leptomeningeal anastomosis, an anterior communicating artery (AcomA), or the external carotid artery (ECA). On the basis of these findings, we diagnosed the cause of the occlusion to be thrombotic.

Intra-arterial thrombolysis was carried out with urokinase or recombinant tissue plasminogen activator (t-PA). Urokinase or t-PA was administered until partial recanalization was obtained; this was achieved in all patients within 4 hours after stroke onset (average, 3.1 hours; range, 2.5-4 hours). In all patients, hemiparesis was improved just after partial recanalization. However, severe residual ICA stenosis at the origin of the ICA was manifested in all patients. In cases 2 and 3, there was moderate residual hemiparesis, and an emergency CEA was performed 6 hours and 8 hours after stroke onset, respectively. The other two patients (cases 1 and 4) underwent CEA more than 3 weeks after stroke onset. Before CEA, no enhanced lesion was shown by means of enhanced CT scans. In all patients, CEA was performed with an internal shunt, and back-flow from the distal ICA was good. New neurologic deficit after CEA was not manifested in any

patient. The plaques removed from all patients showed evidence of plaque rupture and intraplaque hemorrhage. After treatment, all patients were able to live independent lives, and none suffered stroke recurrence. The diagnoses and treatments were performed by our neurosurgical team; neurological examinations were also done by neurosurgeons.

CASE REPORTS

Case 1. A 66-year-old man with severe left hemiparesis was admitted to our hospital 20 minutes after stroke onset. He had a 1-month history of left amaurosis fugax. He was alert, and his blood pressure was 170/80 mm Hg. No abnormal lesion was shown by means of the initial CT scan (Fig 2, *a*). A right ICA occlusion 2 cm from its origin was indicated by means of an emergency cerebral angiogram (Fig 2, *b*). The ipsilateral MCA was not seen through the ICA; however, it was seen through the leptomeningeal anastomosis of the ipsilateral anterior cerebral artery, the supply of which was derived from the AcomA (Fig 1). Urokinase (360 kU) was infused through the 5F catheter placed just proximal to the ICA occlusion site. During the infusion, the patient's hemiparesis almost completely disappeared. Partial recanalization of the right ICA was shown by means of a cerebral angiogram obtained after urokinase infusion. However, severe stenosis of the ICA at its origin (Fig 2, *c*) and proximal MCA occlusion remained (Fig 2, *d*). The interval from onset to recanalization of the ICA was 4 hours. Low density at the right corona radiata was indicated by means of a CT scan (Fig 2, *e*). The patient was given anticoagulants and a cal-

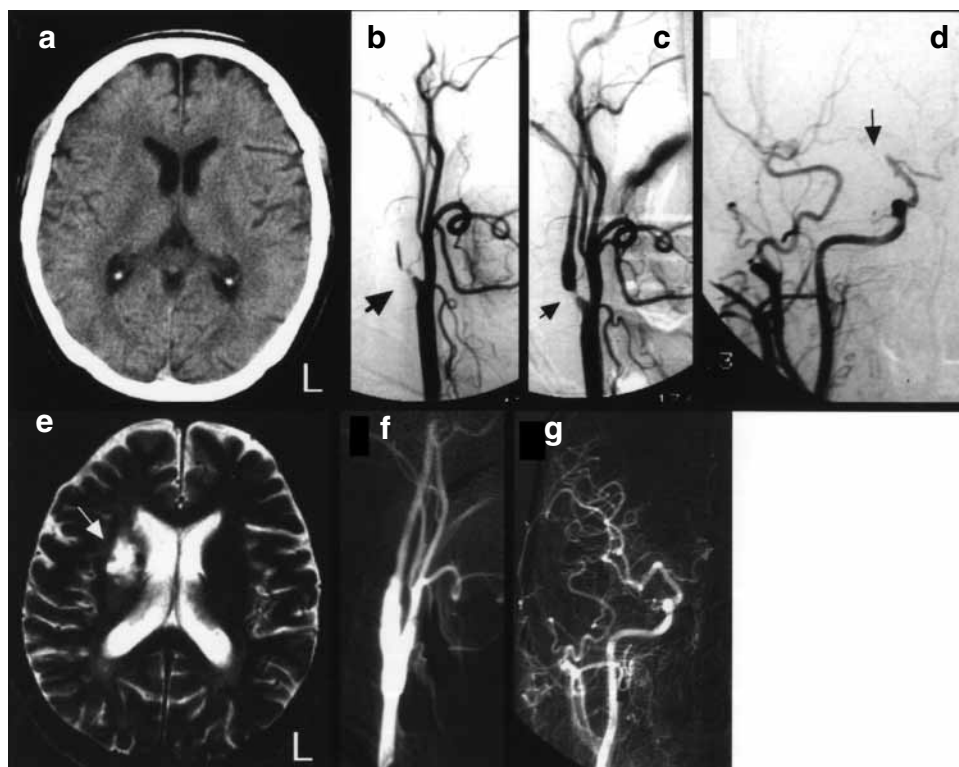


Fig 2. Case 1. **a**, Initial CT scan showing no lesion. **b**, Initial cerebral angiogram showing ICA occlusion on right. **c** and **d**, Serial cerebral angiograms after intra-arterial thrombolysis showing partial recanalization of ICA and residual severe ICA stenosis. Note remaining middle cerebral artery occlusion on right. **e**, Serial CT scan after intra-arterial thrombolysis showing small infarction in right corona radiata. **f** and **g**, Follow-up angiogram after CEA showing good patency of ICA and MCA.

cium antagonist to maintain normal blood pressure (130 to 150/80 to 90 mm Hg) after intra-arterial thrombolysis. The disappearance of the MCA embolus was confirmed by means of a follow-up angiogram obtained 45 days after stroke onset. CEA was performed 54 days after onset. In the pathologic section, plaque rupture and intraplaque hemorrhage were noted. Patency of the right ICA was demonstrated by means of follow-up angiograms (Fig 2, *f*); the MCA was free of stenosis (Fig 2, *g*). The patient was given antiplatelet therapy and was discharged without any neurologic deficits. He continued to do well 8 years after the CEA.

Case 2. A 68-year-old man had right hemiplegia and aphasia when admitted to our hospital 2 hours after stroke onset. Two weeks earlier, he had sustained a transient ischemic attack and mild right hemiparesis. On admission, he was alert; his blood pressure was 180/95 mm Hg. An old small infarction on the bilateral basal ganglia was shown by means of the initial CT scan (Fig 3, *a*). Left ICA occlusion 2 cm from its origin was indicated by means of the initial cerebral angiogram (Fig 3, *b*). The ipsilateral MCA was seen from the AcomA. Intra-arterial thrombolysis was performed with urokinase and a 5F catheter

placed at the occlusion site. After the infusion of 480 kU urokinase, the patient's hemiparesis improved slightly. Partial recanalization of the ICA was shown by means of serial cerebral angiograms; however, severe stenosis at the origin of the ICA persisted (Fig 3, *c* and *d*). Because moderate hemiparesis remained, emergency CEA was performed 6 hours after stroke. Intraplaque hemorrhage and an ulcer were noted. There was a fresh luminal thrombus at the site of rupture of an intraplaque hemorrhage (Fig 4, *A*). In the pathological section, plaque rupture, intraplaque hemorrhage, and luminal thrombi were seen (Fig 4, *B* and *C*). After CEA, the patient's hemiparesis disappeared completely. No new infarction was shown by means of a follow-up CT scan (Fig 3, *e*), and the patency of the ICA was confirmed by means of cerebral angiograms (Fig 3, *f* and *g*). He was given anti-platelet and calcium antagonist therapy to maintain his blood pressure at 130 to 150/80 to 90 mm Hg. He was discharged without any neurologic deficit, and he was well 7.5 years after undergoing CEA.

Case 3. A 77-year-old man had mild right hemiparesis and carotid bruit. At the time of admission, he was alert, and his blood pressure was 158/90 mm Hg. No

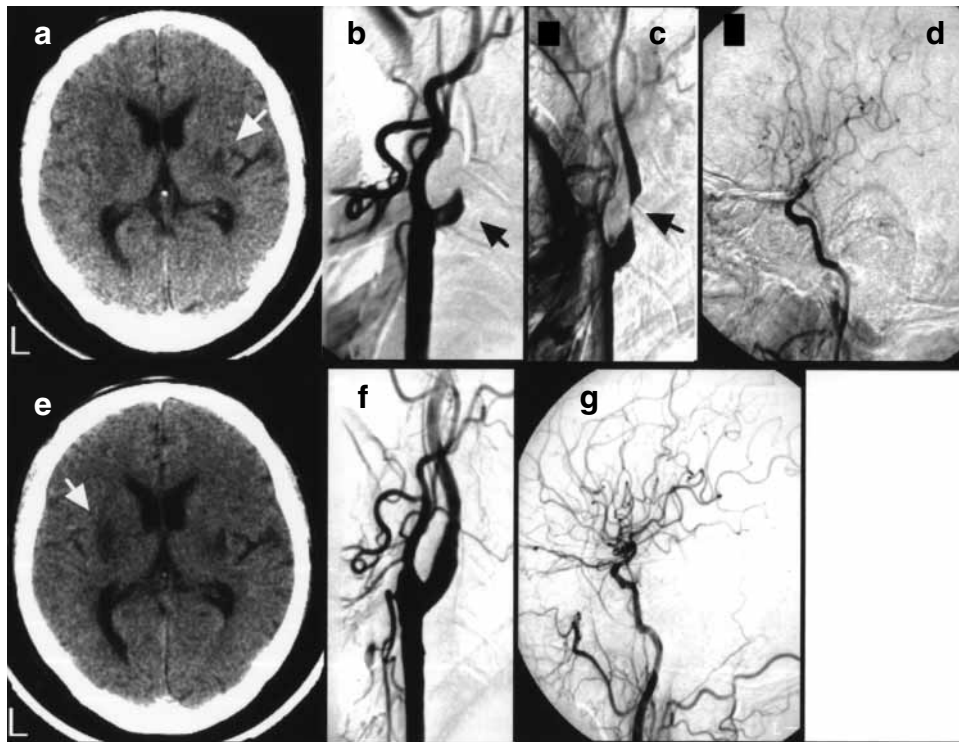


Fig 3. Case 2. **a**, Initial CT scan showing old infarction on bilateral basal ganglia. **b**, Initial cerebral angiogram showing ICA occlusion on left side. **c** and **d**, Serial cerebral angiogram after intra-arterial thrombolysis showing partial recanalization of ICA and residual severe ICA stenosis. MCA was seen through ICA on left. **e**, Serial CT scan after intra-arterial thrombolysis indicating no new lesion. **f** and **g**, Follow-up angiogram after CEA showing good patency of ICA and MCA.

lesion was shown by means of the initial CT scan. Because his hemiparesis improved, he was treated with antiplatelet therapy. A small infarction on the left frontal lobe was shown by means of initial magnetic resonance imaging (MRI) obtained 2 days after stroke onset; severe ICA stenosis at its origin was indicated by means of a magnetic resonance angiography. The patient's state of consciousness and right hemiparesis suddenly worsened 3 days after stroke onset. There was no left carotid bruit. No new lesions were shown by means of a serial CT scan (Fig 5, *a*). Right ICA occlusion was indicated by means of an emergency cerebral angiogram (Fig 5, *b*); the angular artery was occluded at the insular portion. The distal ICA and ipsilateral MCA were seen through the ipsilateral ophthalmic artery from the ECA (Fig 5, *c*). Intra-arterial thrombolysis with t-PA was performed. After an infusion of 6,000,000 units of t-PA, his hemiparesis improved slightly. Partial recanalization of the ICA and severe residual stenosis at its origin was indicated by means of a cerebral angiogram obtained 3 hours after stroke onset (Fig 5, *d*). No change from the earlier CT scan was shown by means of a CT scan obtained after thrombolysis (Fig 5, *e*). Because this patient's moderate hemiparesis did not disappear, an emergency CEA was performed 8 hours after stroke onset. In the plaque removed by means of CEA,

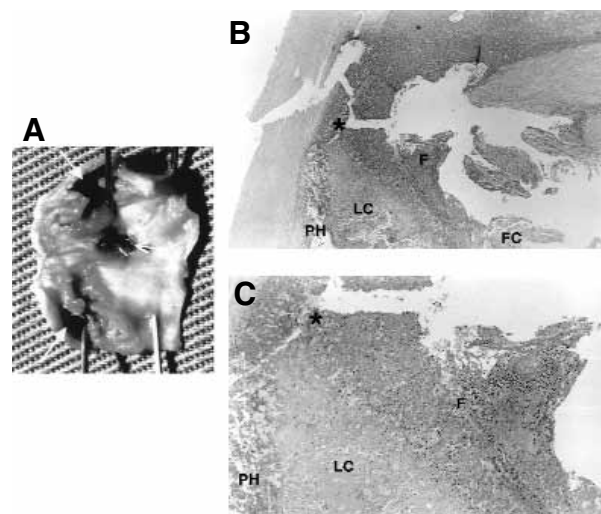


Fig 4. Pathologic features, case 2. **A**, Carotid plaque removed by means of carotid endarterectomy shows intraplaque hemorrhage, ulcer, and luminal thrombus. **B**, Low-power view of atheromatous plaque showing rupture of fibrous cap (FC) and intraplaque hemorrhage (PH). **C**, High-power view of atheromatous plaque showing fibrin (F) on surface of fibrous cap and red cell at plaque rupture point. LC, Lipid core.

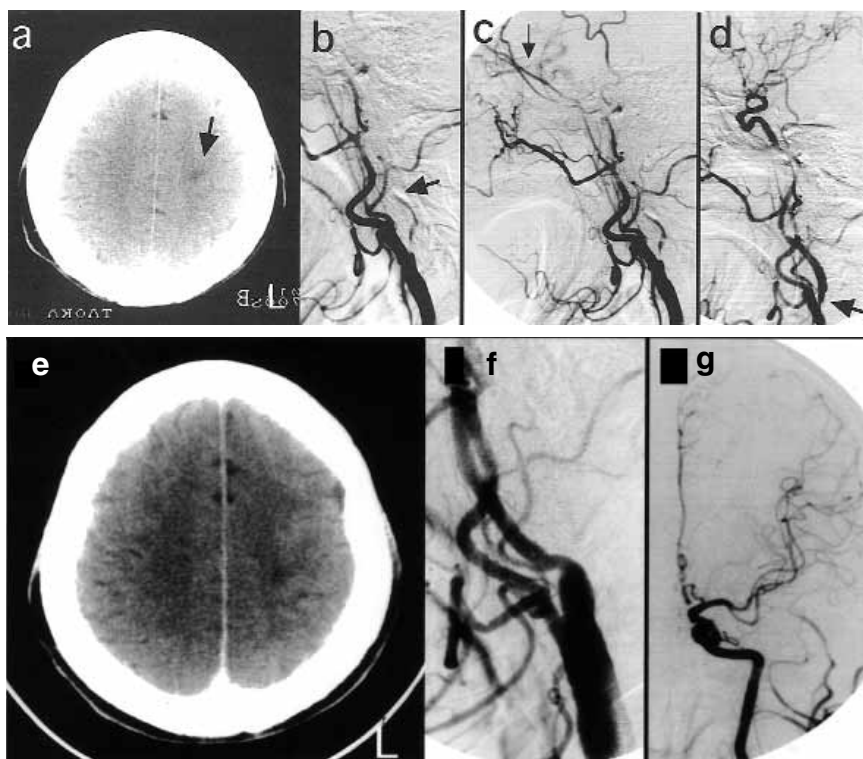


Fig 5. Case 3. **a**, CT scan obtained before initial angiography shows old infarction on left frontal lobe. **b** and **c**, Initial cerebral angiogram demonstrating ICA occlusion and collateral flow through ophthalmic artery on left side. **d**, Serial cerebral angiogram after intra-arterial thrombolysis showing partial recanalization of ICA and residual severe ICA stenosis. **e**, Serial CT scan after intra-arterial thrombolysis indicating no new lesion. **f** and **g**, Follow-up angiogram after CEA showing good patency of ICA and MCA.

plaque rupture and intraplaque hemorrhage were seen. No new lesions were shown by means of a CT scan, and the patient's moderate hemiparesis improved gradually. By 2 months after CEA, the hemiparesis had disappeared. The patient's blood pressure was within reference range, without the administration of drugs. Patency of the ICA was demonstrated by means of follow-up angiograms (Fig 5, *f*). The occlusion of the angular artery was also recanalized (Fig 5, *g*). The patient received antiplatelet agents after CEA, and he was well and leading a normal life 3 years after CEA.

Case 4. A 64-year-old man had severe right hemiparesis and dysarthria; he was admitted to our hospital 1 hour after stroke onset. He was alert, and his blood pressure was 160/90 mm Hg. No lesions were shown by means of the initial CT scan (Fig 6, *a*). Right ICA occlusion (Fig 6, *b*) and ipsilateral MCA occlusion (Fig 6, *c*) were revealed by means of the admission angiogram. There was collateral flow through the ipsilateral ECA; the ICA was seen from the petrous portion (Fig 1). He received intra-arterial thrombolysis with 720 kU of urokinase. Three hours after stroke onset, partial recanalization of the ICA was evident, and the MCA was

recanalized (Fig 6, *d* and *e*). His hemiparesis disappeared completely. He received anticoagulant therapy after intra-arterial thrombolysis. His blood pressure was within reference range without the use of any drugs. A small infarction at the ipsilateral caudate head was shown by means of a CT scan obtained the next day (Fig 6, *f*). CEA was performed 25 days after stroke onset. In the plaque removed by means of CEA, intraplaque hemorrhage, a luminal thrombus, and a deep ulcer were found (Fig 7, *A* and *B*). The patency of the ICA (Fig 6, *g*) and MCA (Fig 6, *h*) were confirmed by means of follow-up angiograms. The patient was given antiplatelet therapy and was discharged without any neurologic deficit. He was able to resume a normal daily life, and he was well 2 years after CEA.

DISCUSSION

The prognosis of patients with acute ICA occlusion is very poor.¹³⁻¹⁵ Meyer et al¹⁵ reviewed the literature on patients with an acute ICA occlusion in whom profound neurologic deficits were manifested. Only 2% to 12% of the patients whom they reviewed experienced a good recovery. Because of the unfavorable natural history of

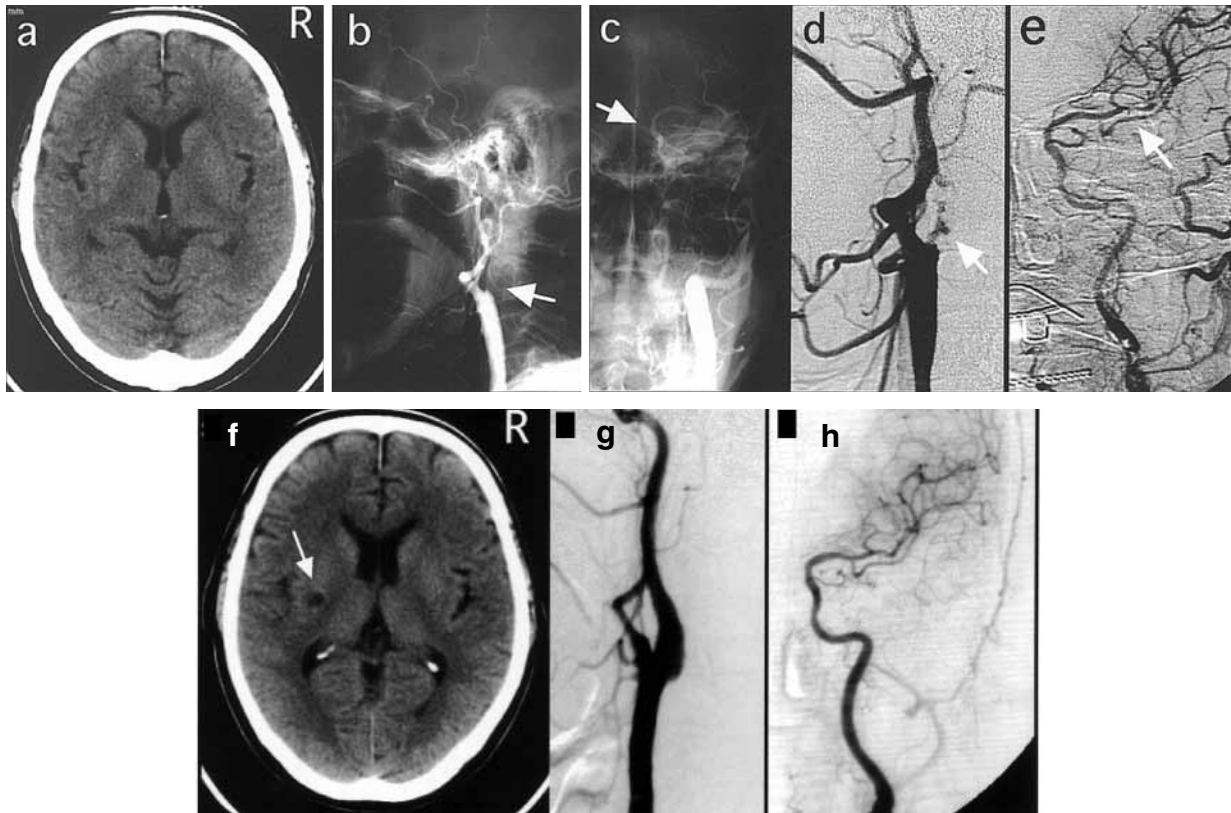


Fig 6. Case 4. **a**, Initial CT scan showing no lesions. **b** and **c**, Initial cerebral angiogram showing ICA occlusion and collateral flow through external carotid artery on left side. **d** and **e**, Serial cerebral angiogram after intra-arterial thrombolysis showing partial recanalization of ICA and residual severe ICA stenosis. MCA was seen through ICA on left. **f**, Serial CT scan after intra-arterial thrombolysis indicating small infarction on left putamen. **g** and **h**, Follow-up angiogram after CEA showing good patency of ICA and MCA.

acute ICA occlusion, patients require aggressive treatment in the acute stage to improve their prognosis.

An emergency CEA was performed in patients with acute ICA occlusion who progressed to stroke or fluctuating neurologic deficits.¹⁵⁻²³ Blaisdell et al¹⁷ performed 50 CEAs for acute ICA occlusion; however, their postoperative mortality rate was 42%. Other authors also reported poor results.^{18,21,23} On the basis of these reports, emergency CEA may appear to be contraindicated in patients with acute ICA occlusion. However, in papers published after 1980, good outcomes were reported.^{15,19,20,22} Meyer et al¹⁵ achieved a good treatment outcome in patients with a good collateral flow. Moreover, the duration of ICA flow stoppage was not a good prognostic factor. Rather, determination of the collateral circulation by means of a preoperative cerebral angiography was a more important means of assessing the indication for emergency CEA. McCormick et al²⁴ also reported that, in patients with thrombotic ICA occlusion, collateral flow from the external carotid artery to the petrous portion of ICA was

an excellent sign of successful vessel opening, and a good outcome could be expected in those patients. Our four patients without arrhythmia had a good collateral flow, and in cases 3 and 4, the petrous portion of the ICA was seen from the vessel providing the collateral. On the basis of our experience and findings reported in the literature, we think thrombotic occlusion should be considered when the occlusion is located at the origin of the ICA, there is angiographic evidence of collateral flow, and the patient is free of arrhythmia.

In our patients, cessation of flow through the ICA lasted for 4 hours and, possibly more important, a collateral flow was manifested in all patients. However, the time lapse between obtaining a cerebral angiogram and performing the emergency CEA (2-3 hours) may be critical in some patients. Like in our cases 2 and 3, intra-arterial thrombolysis fails to produce an adequate effect. Therefore, we performed emergency CEA immediately after thrombolysis. We think, however, that the effect of partial recanalization of the ICA contributed to the mini-

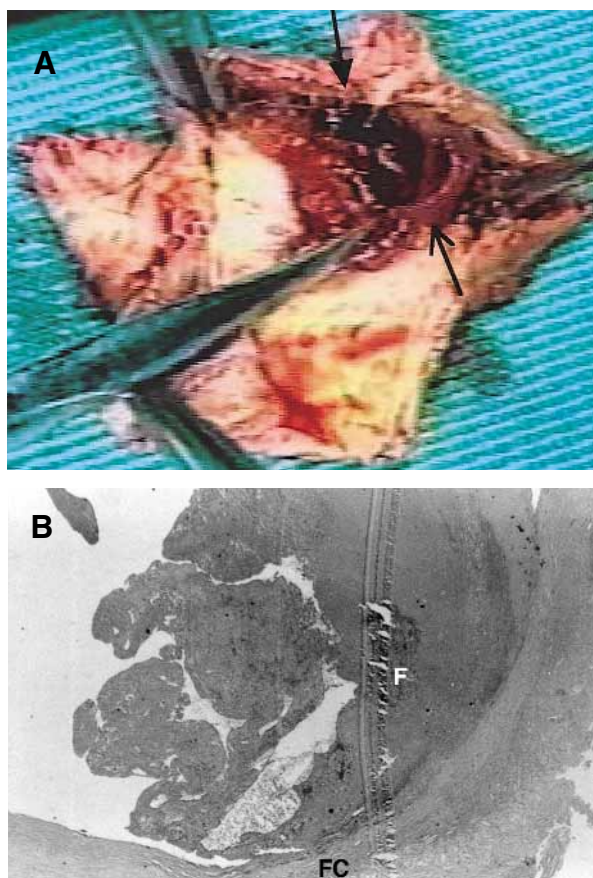


Fig 7. Pathologic features, case 4. **A**, Carotid plaque removed by means of CEA shows intraplaque hemorrhage, ulcer, and luminal thrombus. **B**, Low-power view of atheromatous plaque showing rupture of fibrous cap (**FC**), luminal thrombus, and intraplaque hemorrhage. **F**, Fibrin.

mal cerebral ischemic damage noted in patients who had undergone emergency CEA. In these cases, no new lesions were shown by means of CT scans after CEA. Quick recanalization by means of intra-arterial thrombolysis followed soon thereafter by CEA may have led to the better outcomes we achieved in our patients.

Major complications of intra-arterial thrombolysis for ICA occlusion are dislodging of the thrombus into the intracranial circulation and intracerebral hemorrhage. Horing et al²⁵ indicated that the risk factors for hemorrhagic infarction included late treatment (6 hours after onset), hypertension, and the presence of an area of low density on pretreatment CT scans. Ueda et al²⁶ suggested that a severe decrease of cerebral blood flow on pretreatment single photon emission CT scans could represent a useful parameter for predicting intracerebral hemorrhage and treatment outcome. To avoid intracerebral hemorrhage, we performed intra-arterial thrombolysis in patients in whom no new lesions were shown by means of a CT

scan, who could be treated within 6 hours after onset, and whose blood pressure could be maintained within reference range after thrombolysis. To save time, we did not perform pretreatment single photon emission CT scans. However, when cerebral blood flow study is absolutely necessary, a rapid method such as perfusion-weighted MRI can be used.²⁷ It is very difficult to determine when thrombolysis should be stopped to prevent complications. Aggressive thrombolysis has been used for occlusion of the trunk of the MCA and of the more distal MCA^{28,29}; however, almost all reported patients had an MCA occlusion only. We fear that high doses of thrombolytic agents for full recanalization and a greatly increased blood flow caused by ICA and MCA recanalization increase the risk of intracerebral hemorrhage. Therefore, in our patients, thrombolytic treatment ceased when their neurologic status improved, even when only partial arterial recanalization had been achieved.

We thought that the cause of ICA occlusion in our four patients was thrombotic. This hypothesis is supported by the finding that all the removed atheromatous plaques demonstrated plaque rupture and intraplaque hemorrhage. We posit that plaque rupture caused by intraplaque hemorrhage led to the ICA occlusion and to MCA embolism. Endo et al,³⁰ who evaluated the pathologic features of plaques removed from patients with complete or almost complete thrombotic ICA occlusion, found intraplaque hemorrhages in 37 (92.5%) of 40 plaques. Lusby et al³¹ reported intraplaque hemorrhage in 49 (92.5%) of 53 plaques from patients with symptoms. Persson et al³² also emphasized the correlation between the intraplaque hemorrhage and clinical symptoms. Among 64 patients who underwent CEA during the past 3 years at our hospital, 17 (54.8%) of 31 patients had symptoms, and 7 (21.2%) of 33 patients without symptoms had intraplaque hemorrhage (χ^2 test, $P = .006$). Together, these findings suggest that intraplaque hemorrhage is strongly correlated with symptomatic acute thrombotic ICA occlusion and that PTA in these conditions carries a high risk of embolic cerebral infarction. Therefore, we chose CEA as a means of removing the embolic source completely. Endo et al⁷ and Eckstein et al^{5,6} reported good outcomes in patients who underwent CEA for residual ICA stenosis after thrombolysis.

On the basis of our experience and findings reported in the literature, we consider intra-arterial thrombolysis followed by CEA to be the optimal strategy in patients with profound neurologic deficits caused by ICA occlusion that we suspect to be of thrombotic nature. At present, the indication for this combination therapy is (1) the patient is free of arrhythmia or valvular heart disease; (2) the patient is alert or lethargic, and severe hemiparesis is manifested; (3) no new lesions are identified by means of CT scans; (4) collateral circulation can be seen by means of full cerebral angiograms (if the ICA in petrous portion can be seen through the collateral flow, reopening will be obtained in a high percentage of cases); and (5) intra-arterial thrombolysis can be performed within 6 hours after

stroke onset. Because CT scans taken within 6 hours of stroke onset cannot be relied on as a means of revealing ischemic areas and because diffusion- and perfusion-weighted MRIs were reportedly useful, we examined emergency diffusion- and perfusion-weighted MRI and magnetic resonance angiography in recent patients who sustained an acute stroke.²⁷ On the basis of our results, we added one further criterion: the lesion volume on perfusion-weighted MRI should be larger than that on diffusion-weighted MRI.²⁷ If patients satisfy these six criteria, we expect our combination therapy to produce a good outcome. In patients with embolic ICA occlusion, recanalization was difficult because of the hardness of the emboli.³³ Even when recanalization was obtained, there was a high rate of posttreatment hemorrhagic infarction, and the cerebral infarction was seen because of poor collateral circulation.³³ Thus, the outcome in patients with embolic ICA occlusion may be poorer than that in patients with thrombotic ICA occlusion.

The timing of CEA after intra-arterial thrombolysis remains controversial, and the danger of post-CEA hyperperfusion syndrome must be considered. Although CEA in the subacute or chronic stage may reduce the risk of hyperperfusion syndrome, its delay introduces reocclusion of the ICA or embolic cerebral infarction. CEA should be performed as soon as possible to prevent recurrent stroke; however, to avoid the danger of post-CEA hyperperfusion, it must be delayed until the absence of enhanced lesions at the ischemic site is confirmed by means of an enhanced CT scan. This approach was successful in two of our patients. Finally, it is important to maintain a normotensive blood pressure after CEA to prevent hyperperfusion.

CONCLUSION

Intra-arterial thrombolysis is indicated in the very early stage in a limited number of patients with acute thrombotic ICA occlusion. Furthermore, subsequent CEA may be a reliable treatment for residual ICA stenosis. Only after accumulating more clinical experience will it be possible to determine the optimal timing of CEA after intra-arterial thrombolysis.

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