

Outcome Evaluation of Intra-arterial Infusion of Urokinase for Acute Ischemic Stroke¹

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Purpose: To evaluate the results of intra-arterial urokinase thrombolysis in cases of acute ischemic stroke and to define the factors affecting prognosis.

Materials and Methods: Forty-eight patients with angiographically proven occlusion of the intracranial arteries were treated with local intra-arterial infusion of urokinase within six hours of the onset of symptoms. Neurologic status was evaluated on admission and on discharge using the NIH(National Institute of Health) stroke scale score (SSS). When the SSS decreased by at least four points, this was considered indicative of an improved clinical outcome.

Results: Complete recanalization was achieved in 17/48 patients (35%), including 8 of 13 (62%) with occlusion of the vertebrobasilar artery (VBA), 9 of 20 (45%) with occlusion of the middle cerebral artery (MCA), and none of 15 with occlusion of the internal carotid artery (ICA). Neurologic status improved in 12 (60%) of patients with MCA occlusion, in five (38%) of those with VBA occlusion and in three (20%) of those with ICA occlusion ($P < 0.05$). Patients in whom occluded MCA was completely recanalized showed greater clinical improvement than those with partial or no recanalization ($P < 0.05$). The overall mortality rate was 21%, 43% (9/21) in patients in whom CT revealed signs of early infarct, but only 4% (1/27) in those without this sign ($P < 0.05$). The mortality rate of patients with parenchymal hematoma (4/5) was higher than that of those with hemorrhagic infarct (3/9) or without hemorrhage (3/34) ($P < 0.05$).

Conclusion: In patients in whom occluded MCA was completely recanalized, the clinical outcome was better, while patients with VBA occlusion did not benefit from recanalization. The presence on CT scans of signs of early infarct and of parenchymal hematoma after thrombolysis correlated with a high mortality rate.

Index words : Brain, blood flow
Brain, ischemia
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Acute occlusion of the intracranial artery probably causes sudden severe neurological ischemic change, and

the prognosis is poor (1, 2). In patients with acute ischemic stroke, intra-arterial infusion of urokinase has

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generally been thought to be effective if administered within 6 hours of stroke onset (2 - 11).

Because of differences in the causes of occlusion, territory involved, functional importance, resistance to ischemia, collaterals, and therapeutic method, intra-arterial thrombolytic outcome varies according to the vessels involved. In the literature, the majority of the cases described have involved either the anterior or posterior circulatory system (3, 5, 7 - 11). It has been demonstrated that after intra-arterial thrombolysis, the prognosis is usually better in patients with occlusion of the middle cerebral artery(MCA) than in those with occlusion of either the internal carotid artery(ICA) or vertebrobasilar artery(VBA) (2 - 11). There were contrary results in series reported by both Sasaki (12) and Huang-Hellinger (13), where complete recanalization and marked clinical improvement were more frequently obtained in patients with VBA occlusion than in those with MCA occlusion.

We retrospectively reviewed our experience of cases of intra-arterial thrombolysis in patients with acute ischemic stroke, using urokinase, and analyzed the factors affecting the outcome of thrombolytic therapy, with emphasis on the effect at various sites of vascular occlusion.

Materials and Methods

Between December 1995 and January 1998, 48 patients with acute ischemic stroke (22 men and 26 women; age range 34 - 81, mean 65.8 years) who had undergone brain CT and showed neither definite abnormality nor early infarction, and angiographically demonstrated intracranial arterial occlusion in the expected area, underwent local intra-arterial infusion of urokinase. Among these patients, there were 15 with occlusion of the ICA, 20 with occlusion of the MCA, and 13 with occlusion of the VBA. All were admitted to the neurologic intensive care unit with symptoms and signs consistent with acute cerebral arterial occlusion. The interval between the onset of symptoms and thrombolytic therapy ranged from 2.5 to 6 (mean, 4.6) hours. The status of each patient was documented by neurologic examination on admission (baseline) and on discharge, using the NIH (National Institute Health) stroke scale score (SSS) (14). We rated clinical status as improved if there was a four-point decrease of SSS, aggravated if there was a four-point increase, and stationary if between these two limits.

Each patient underwent CT brain scannings immedi-

ately before angiography, and if CT revealed definite low density corresponding to clinical features, and parenchymal hematoma, was excluded from angiography and thrombolytic therapy. The early infarct sign on CT before thrombolytic therapy was defined as present if any of the following signs were noted: loss of gray-white interfaces, sulcal effacement, or a slight decrease in tissue attenuation. In every patient, follow-up CT scans were obtained within two hours and at 24 hours after thrombolytic therapy. Hemorrhage as seen on CT after thrombolysis was classified as one of two types. If nonhomogeneous, petechial or speckled with unclear margins, and limited to the same region as the involved vascular distribution, it was defined as hemorrhagic infarction. If homogeneously dense with round or oval configuration and sharp, distinct borders, it was classified as a parenchymal hematoma. The extravasation of contrast medium with parenchymal hyperdensity in the areas treated could be distinguished from hemorrhage because the former was absorbed more quickly, usually within 24 hours.

Every patient or their family gave informed consent before angiography. A 5-F Headhunter catheter (Cook, Bjæverskov, Denmark) was then introduced femorally, and in order to save time, an arterial sheath was not usually used. In 32 patients, a full diagnostic angiogram, including the anterior and posterior circulation, was obtained before treatment. In 16 patients whose clinical status was poor, pretreatment angiography involving only the occluded vessel was performed according to clinical evaluation, while angiography of other vessels was performed immediately after thrombolysis. Once a diagnosis of thromboembolism was confirmed, a plan for thrombolytic therapy was agreed between the neurointerventional radiologist, the neurologist, and the patient's family. During the procedure, systemic anticoagulation was initiated, using intravenous heparin bolus (3,000 - 4,000IU), but supplementary heparin was not used.

A Tracker-18 microcatheter (Target Therapeutics, Cal., U.S.A.) was advanced through the 5-F angiographic catheter to the site of occlusion. If possible, the thrombus was mechanically disrupted using a microwire, and the microcatheter was then embedded within the clot. Otherwise, the microcatheter was guided as close to the clot surface as possible. 200,000 IU of urokinase (Nokshibza, Seoul, Korea) were diluted in 10 ml of normal saline and infused using a Flo-Gard 6200 infusion pump (Baxter Healthcare Corporation, Ill., U.S.A.) or by

hand, for 15 to 20 minutes. Angiography was then performed through the microcatheter. If recanalization was not complete, urokinase infusion and angiography were repeated. The infusion of urokinase was terminated when complete recanalization had been achieved or when there was no response after the infusion of 400,000 IU of urokinase. The total dose of urokinase ranged between 200,000 and 1,000,000 IU, the upper limit (mean 523,000 IU).

Recanalization was assessed and divided into "complete" (all main branches and most of distal branches recanalized), "partial" (at least one main branch opened), and "no response" (no main branches recanalized). If there was a history of cardiac dysrhythmia or valve disease, and sudden onset, the stroke mechanism was regarded as a cardiogenic embolus. Data was statistically analyzed using the χ^2 and Mann-Whitney tests.

Results

Clinical data are summarized in Table 1. Patient age, time interval between the onset of symptoms and the

start of thrombolytic therapy, neurologic status on admission, the presence of the early infarct sign on initial CT, and the dose of urokinase infused did not differ significantly among the four groups ($P > 0.05$). The SSS range on admission was 7 to 25 (mean 15.3).

Fourteen patients had a history of cardiac dysrhythmia or valve disease, and sudden onset of symptoms. Among these, ICA occlusion was present in eight patients, MCA occlusion in three, and VBA occlusion in three. Occlusion caused by cardiogenic emboli was more common in the ICA ($P < 0.05$). Arterial stenosis was found after thrombolysis of the occluded vessel in 16 patients (Fig. 1). Stenosis of the VBA was found in eight patients (57%), but that of the ICA in only two (13%) ($P < 0.05$). Using a balloon microcatheter, two patients with tight stenosis in the ICA or vertebral artery underwent angioplasty.

Clinical outcomes are shown in Table 2. The overall mortality rate was 21% (10/48). The mortality rate after thrombolysis was 33% in the ICA group, 10% in the MCA and 23% in the VBA. Twelve patients (60%) with MCA occlusion experienced improvement after throm-

Table 1. Summary of the Clinical Data According to the Various Sites of Occlusion

Occlusion Site	Patient No.	Sex M/F	Age (years)	Infarct on CT		Stroke Mechanism			UK Dose (1,000IU)*	Baseline SSS*
				no	yes	Cardiac Embolic	Stenosis	Unknown		
ICA	15	6/9	70.2	7(47)	8(53)	8(53) [†]	2(13)	5(34)	520 ± 248	15.6 ± 3.5
MCA	20	7/13	65.5	13(65)	7(35)	3(15)	6(30)	1(5)	470 ± 213	150.0 ± 7.2
VBA	13	9/4	60.9	7(54)	6(46)	3(23)	8(62) [‡]	2(15)	596 ± 292	15.2 ± 6.3
Total	48	22/26	65.8	27(56)	21(44)	14(29)	16(33)	18(38)	523 ± 242	15.3 ± 5.8

Note.-Values in parentheses are percentages. No. = number. M/F = male/female. UK = urokinase. SSS = stroke scale score.

*Data are the mean ± standard deviation.

[†]Difference from number in MCA group or VBA group was significant ($p < .05$).

[‡]Difference from number in ICA group or MCA group was significant ($p < .05$).

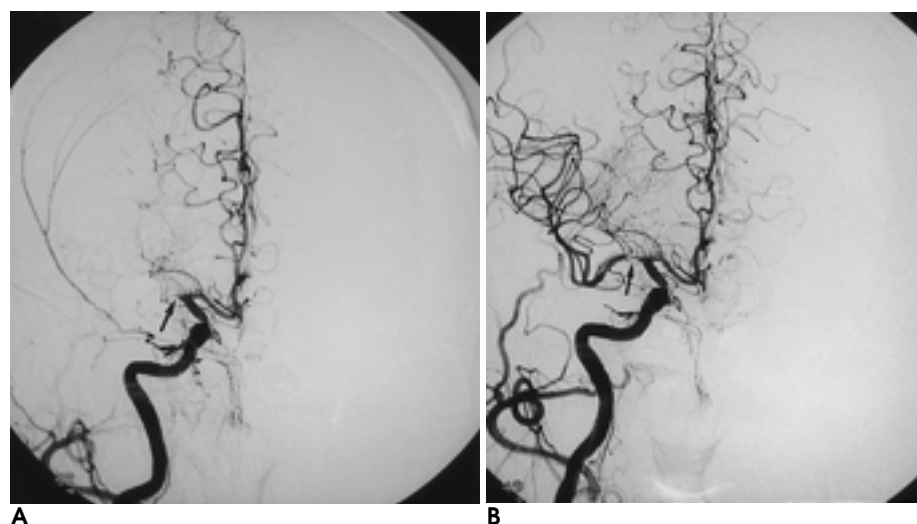


Fig. 1. A 73-year-old woman received thrombolytic therapy 4 hours after onset of hemiparesis and dysarthria. Initial frontal projection on the right common carotid angiogram shows complete occlusion of the proximal middle cerebral artery (arrow) (A). After arterial infusion of 1,000,000 IU of urokinase, there is complete recanalization with residual stenosis (arrow) in the M1 segment (B). Immediate follow-up CT shows normal findings (not shown). Her SSS decreased from 11 point before treatment to 1 point 8 days after thrombolytic therapy.

bolysis, whereas three (20%) with ICA occlusion and five (38%) with VBA occlusion improved. Clinical improvement was thus more common in patients with MCA occlusion than in those with ICA or VBA occlusion ($P < 0.05$).

Complete recanalization was more common in cases involving VBA or MCA occlusion than in those involving ICA occlusion ($P < 0.05$) (Table 2). In no patient with ICA occlusion was complete recanalization achieved, but in nine (45%) with MCA occlusion and in eight (62%) with VBA occlusion, this was the outcome. The extent of complete recanalization did not vary significantly between MCA and VBA occlusions. Clinical improvement was noted in 11 of 17 (65%) patients with complete recanalization, in 7 of 20 (35%) with partial recanalization and in 2 of 11 (18%) with no response; there were, thus, significant differences ($P < 0.05$). Eight of nine patients with complete MCA recanalization showed improved clinical status, a greater proportion than the 3 of 8 with incomplete recanalization or the 1 of 2 with no response ($P < 0.05$). However, only 3 of 8 patients with complete VBA recanalization showed clinical improvement, so in those with VBA occlusion, recanalization did not correlate with clinical outcome (Fig. 2) ($P > 0.05$).

Stroke mechanism and baseline neurologic status did not correlate with recanalization and clinical outcome. Among the 14 patients with cardiogenic emboli, complete recanalization was achieved in five (36%), and five showed clinical improvement, results which did not differ significantly from those obtained in 16 cases with pre-existing arterial stenosis (50% and 56%, respectively) ($P > 0.05$).

Although a few more patients with the early infarct sign on pretreatment CT (43%) achieved complete recanalization than those without the sign (30%) ($P > 0.05$), clinical improvement was noted in fewer patients with the sign (28%) than in those without the sign (52%)

($P > 0.05$). Among the ten patients who died, nine exhibited this early sign. The mortality rate was 43% in patients in whom the early infarct sign was seen on pretreatment CT, but only 4% in those without the sign ($P < 0.05$).

Hemorrhagic complications after thrombolysis occurred in 14 patients (29%), including five (10%) with parenchymal hematoma (Fig. 3) and nine (19%) with hemorrhagic infarction. The incidence of parenchymal hematoma in patients with ICA occlusion after thrombolysis was 27% (4/15), which was significantly higher than that in patients with either MCA (0/20) or VBA occlusion (1/13) ($P < 0.05$). The incidence of hemorrhagic infarction was not related to the site of occlusion, and hemorrhage was not associated with degree of recanalization. No patient with parenchymal hematoma showed clinical improvement, but three of the nine with hemorrhagic infarction (33%) improved clinically. The mortality rate of patients with parenchymal hematoma was 80% (4 of 5), which was significantly higher than that of those with hemorrhagic infarction (33%) and without hemorrhage (9%). Neither the angiographic nor clinical results of patients with hemorrhagic infarction differed greatly from those of patients without hemorrhage. In addition, contrast extravasation was resolved by immediate follow-up CT in four patients.

Discussion

In patients with acute ischemic stroke, many factors affect the outcome of intra-arterial thrombolysis. One of the most important of these is the location of the occlusion, and in our series, the characteristics and results of occlusions in different locations were evaluated. Other than the cause of occlusion, the patients' baseline characterizations for occlusion in various arteries were not distinctly different, and we therefore believe that the comparison of these results is relatively reliable. The

Table 2. Outcomes of Patients with Various Types of Artery Occlusion after Thrombolytic Therapy

Occlusion Site	Patient No.	Recanalization			Clinical Outcome			
		Complete	Partial	No Response	Improved	Stationary	Aggravated	Death
ICA	15	0*	9(60)	6(40)	3(20)	5(33)	2(14)	5(33)
MCA	20	9(45)	8(40)	3(15)	12(60) [†]	6(30)	0	2(10)
VBA	13	8(62)	3(23)	2(15)	5(39)	3(23)	2(15)	3(23)
Total	48	17(35)	20(42)	11(23)	20(42)	14(29)	4(8)	10(21)

Note.-Values in parentheses are percentages. No. = number.

*Difference from number in MCA group or VBA group was significant ($p < .05$).

[†]Difference from number in ICA group or VBA group was significant ($p < .05$).

cause did not, however, correlate with recanalization, clinical improvement or mortality.

Patients with MCA occlusion exhibited better recanalization and outcome than those with ICA occlusion. In our study, 45% of patients with MCA occlusion achieved complete recanalization, and 60% showed clinical improvement. This result was consistent with other reports (3, 5 - 7, 12, 13). Huang-Hellinger et al. (13) compared the clinical outcomes of patients with arterial occlusion in different locations, finding that 5 of 16 patients with MCA occlusion (31%) had good outcomes, but that this was not the case in any of the seven with ICA occlusion. In a series described by Sasaki et al. (12), 8 of 10 patients with ICA occlusion demonstrated complete ($n=2$) or partial ($n=6$) recanalization, but none showed clinical improvement.

In our study, no patients with ICA occlusion achieved complete recanalization. Only 20% of these patients showed clinical improvement, and the mortality rate was 33%. These results were similar to those of Jansen

et al., in which only one patient showed a good clinical outcome after thrombolytic therapy and 9 of 16 patients (56%) with acute occlusion of ICA bifurcation died (5). Jansen explained that the poor prognosis was due to the size and composition of the blood clot which obstructed the ICA lumen. A large, organized and rigid clot is likely to occlude a large vessel, such as the ICA. Small or large soft emboli, which can squeeze through the narrow vascular segment, or pass through it by fragmenting, lead primarily, to MCA occlusion. Moreover, even though the composition of the clot was similar in the ICA and MCA, it is more difficult because of clot size, to lyse a clot in the ICA. In addition, ICA occlusion involves a large territory and important functional branches such as the lenticulostriate and other perforating arteries (5).

There have been several reports of thrombolysis in the vertebrobasilar system (2, 6, 9 - 11), and in most of these series, the overall mortality rate after thrombolysis varied between 46% and 75%. The mortality rate of patients in whom recanalization was achieved ranged from

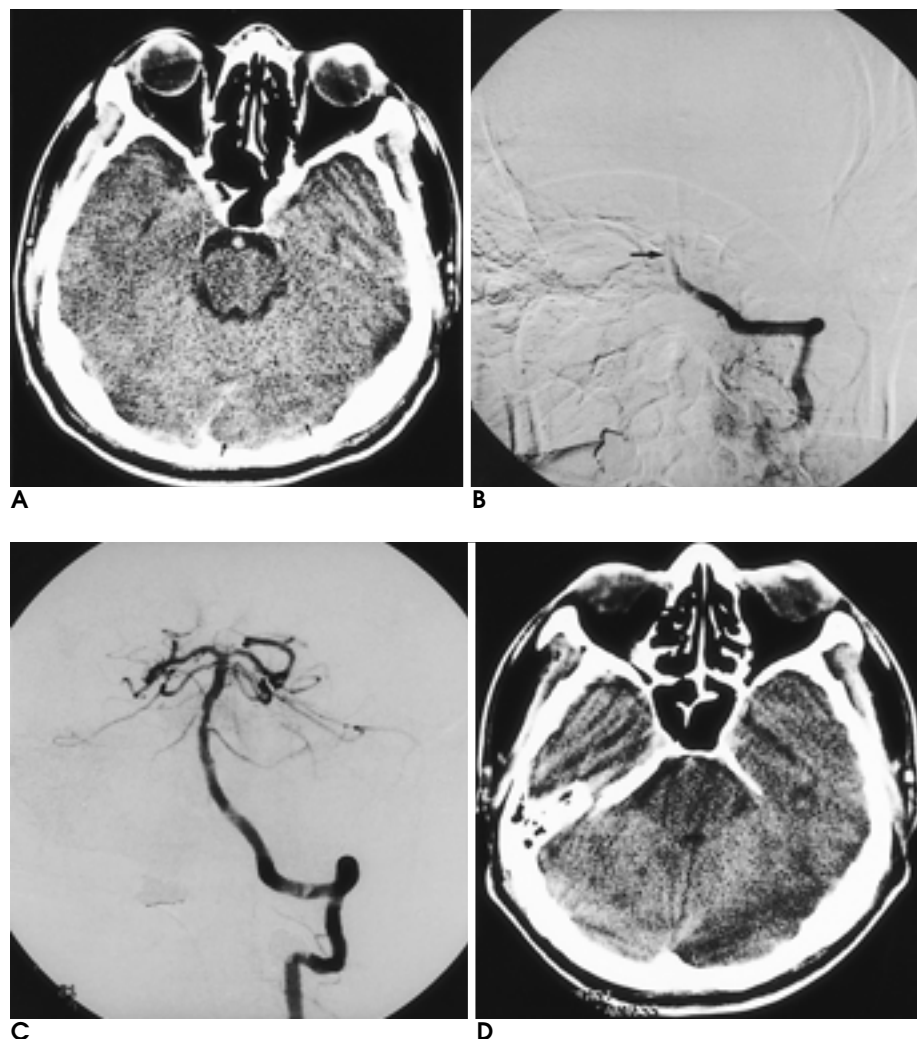


Fig. 2. A 50-year-old man with right-sided weakness and deeply drowsy state received thrombolytic therapy 4 hours after onset of symptoms. Pretreatment CT (**A**) shows suspicious hypodensity (arrows) in the left occipital lobe. Frontal projection on the vertebral angiogram (**B**) shows complete occlusion of the proximal basilar artery (arrow). After infusion of 600,000 IU of urokinase, complete recanalization is obtained (**C**). CT 24 hours after thrombolysis (**D**) shows acute infarct in the brainstem and the territory of both posterior cerebral arteries. The patient died of brainstem infarct 4 days after thrombolytic therapy.

26% to 60%. Becker *et al.* (9) reported that in 13 patients with VBA thromboses, the overall mortality rate was 75%, although ten patients (77%) underwent recanalization after local intra-arterial thrombolysis, and the mortality rate was 60% in those in whom recanalization was successful. Among the 20 patients with basilar thromboses reported by Cross III (11), complete recanalization was achieved in 50%, and the overall three-month survival rate was 35%. Even though recanalization can be achieved after thrombolytic therapy, the outcome obtained in patients with VBA occlusion are poor; this is probably because damage to brain stem tissue is more serious than that to other brain tissue and it is therefore more difficult for such patients to recover (9). In our series, there was a similar trend: fewer patients with VBA occlusion exhibited clinical improvement than did those

with MCA occlusion, even though the occluded VBA was recanalized more easily than the MCA. Yet the outcome of VBA thrombolysis in our study was better than in most previous reports, a fact probably related to neurological status before thrombolytic therapy, to the site of occlusion, or to the time between onset of symptoms and thrombolysis. Patients with VBA occlusion had a similar baseline SSS to those with occlusion in the carotid system and were also treated within six hours. Among our 13 patients, eight (62%) achieved complete recanalization, five (38%) showed neurologic improvement, and only three (23%) died. In patients with VBA occlusion, we found no distinct correlation between recanalization and clinical outcome, including clinical improvement and mortality, a result which differed from those obtained in cases involving occlusion of the carotid

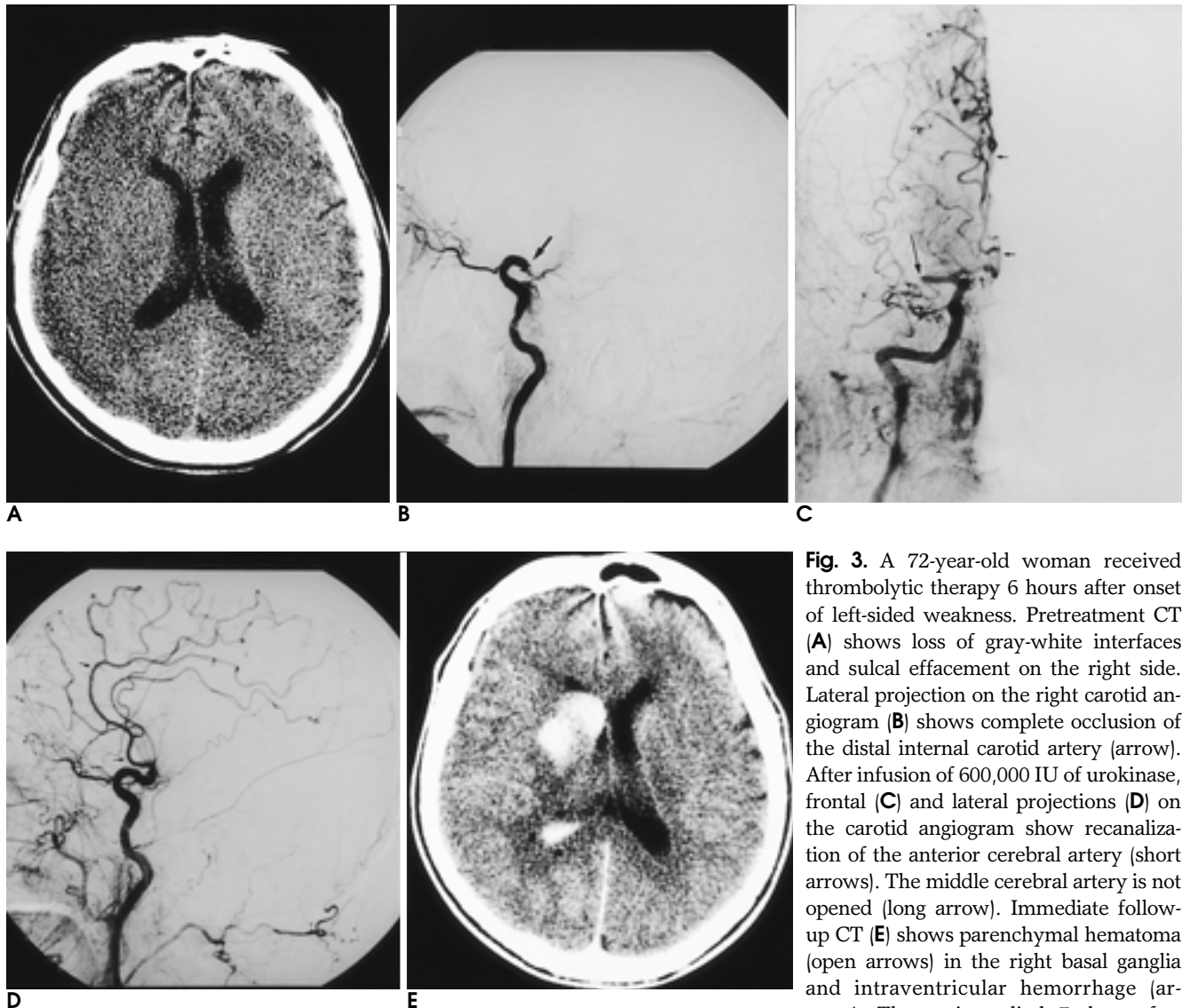


Fig. 3. A 72-year-old woman received thrombolytic therapy 6 hours after onset of left-sided weakness. Pretreatment CT (**A**) shows loss of gray-white interfaces and sulcal effacement on the right side. Lateral projection on the right carotid angiogram (**B**) shows complete occlusion of the distal internal carotid artery (arrow). After infusion of 600,000 IU of urokinase, frontal (**C**) and lateral projections (**D**) on the carotid angiogram show recanalization of the anterior cerebral artery (short arrows). The middle cerebral artery is not opened (long arrow). Immediate follow-up CT (**E**) shows parenchymal hematoma (open arrows) in the right basal ganglia and intraventricular hemorrhage (arrows). The patient died 7 days after thrombolytic therapy.

system. It has been concluded by other authors that among the factors affecting clinical outcome after VBA thrombosis and intra-arterial thrombolysis, the best predictor is distal basilar occlusion (9 - 11). In our series, on the other hand, in two of the three patients who died after thrombolysis, the occlusions were located in the distal basilar arteries. The different results obtained by Sasaki et al. (12) indicated that patients with VBA occlusion achieved better recanalization (78%) and more favorable clinical outcomes (67%) than those with MCA occlusion (56% and 28%, respectively). In a series of 36 patients described by Huang-Hellinger (13), the results were similar, though they did not analyze the causes.

In accordance with the findings of other studies (2 - 11), we found that complete recanalization of the occluded vessel significantly improved a patient's neurological status. Neurological improvement was seen in 65% of patients in whom recanalization was complete, in 35% of those with incomplete recanalization, but in only 18 % of those without recanalization. Meta-analysis of controlled clinical trials has shown that for the active treatment of acute ischemic stroke, early recanalization of an obstructed vessel is a promising approach (15). The purpose of thrombolysis in intracranial vascular occlusion is to preserve threatened brain tissue, not to repair tissue which is already damaged. After acute occlusion of a major cerebral artery, infarction of cortical and subcortical structures can be prevented by rapid opening of the leptomeningeal collateral. Progressive brain swelling in an irreparably damaged area may cause secondary failure of these collaterals and may thus increase the size of the infarction. Early recanalization may help prevent enlargement of the infarct by compensating for the failure of the collaterals to function properly (15). Because of the poor prognosis in such cases, patients in whom the early infarct sign is seen on CT should be selected for thrombolytic therapy only after careful consideration.

We classified intracerebral hemorrhage as either hemorrhagic infarction or parenchymal hematoma. In our series, the incidence of hemorrhage was 29%, including five patients (10%) with parenchymal hematoma; this was similar to the rate seen in other series in which thrombolytic therapy was employed (5, 12), and in series involving spontaneous hemorrhagic transformation of the infarction (16, 17). The frequency of hemorrhage was unrelated to the presence or absence of recanalization. Parenchymal hematoma, which most often occurred in patients with ICA occlusion, usually resulted in death. By means of CT scanning we differentiated be-

tween parenchymal hyperdensity caused by blood and that caused by contrast extravasation; the latter, with a higher density than that of hemorrhage, nearly disappeared on CT within 24 hours of thrombolysis, whereas hemorrhage persisted for several days (18).

In conclusion, in cases of acute ischemic stroke, intra-arterial thrombolysis was an effective therapy. Patients with ICA occlusion rarely achieved complete recanalization after intra-arterial infusion of urokinase, and their prognosis was poor. Patients with MCA occlusion in whom recanalization was complete showed greater neurological improvement than those whose recanalization was incomplete or nonexistent. In patients with VBA occlusion, there was no correlation between recanalization and clinical outcome, though recanalization was easier in those with VBA occlusion than in those with MCA occlusion. The presence of the early infarct sign on pretreatment CT scans, and parenchymal hematoma after thrombolysis, correlated with high mortality.

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