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Intra-carotid Thrombolytic Therapy in Acute Ischemic Stroke of Carotid Arterial Territory

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Intra-carotid urokinase (UK) infusion in 20 patients with acute internal carotid artery (ICA) territorial ischemic stroke acheived immediate recanalization in 45% and the clinical outcome in patients with recanalization was superior to that of patients without recanalization. The procedure was most effective in patients with smaller arterial occlusions : 7 of 10 patients with MCA branch occlusions (M2 to M4) achieved recanalization compared to only 2 of 10 with distal ICA or M1 occlusions, which should be an important issue for the critical evaluation of the efficacy of thrombolytic therapy (TT). Hemorrhagic transformation was observed in 9 patients on CT scan; petechial hemorrhage in 5 and intraparenchymal hematoma formation in 4. Among 4 patients with hematoma formation, clinical deterioration was seen in 3 cases and the angiography at the immediate end of the UK infusion showed recanalization in only one patient. The average dose of UK in patients with parenchymal hematoma formation was higher than that of patients without hemorrhagic transformation (123.3×10^4 units vs 101×10^4 units). The administration of a large dose of UK, probably more than 100×10^4 units, and the absence of immediate recanalization seemed to increase the risk of parenchymal hematoma formation. Despite the effort of investigators, the in-hospital time delay for the TT was significant which was mainly related to the time consuming preparation for angiography especially during night. A more effective system for the earlier intervention of acute ischemic stroke needs to be devecoped.

Key Words: Thrombolytic therapy, Urokinase, recanalization, hemorrhagic transformation

The concept of "ischemic penumbrae" has recently raised much interest for the early management of ischemic stroke (Jones *et al.* 1981; Astrup *et al.* 1981). Among various approaches for the early intervention of acute ischemic stroke, thrombolytic therapy (TT) has attracted the most attention due to its theoretical simplicity as well as its well documented clinical benefits in patients with acute myocardial infarction (MI). TT is now a routine procedure in acute MI with a reported in-hospital mortality rate reduction of 25% and a significant improvement of myocardial function when the treatment starts approximately within 4 hours of symptom onset (Collen and Gold, 1990). However, the direct application of TT in acute ischemic stroke has been discouraged mainly due to the increasing risk of life threatening hemorrhagic transformation of initially pale infarction. In fact, the earlier clinical trials of TT in acute ischemic stroke conducted before the CT era reported increased incidences of clinical deterioration probably related to the hemorrhagic transformation, which has led to a general contraindication of TT in stroke (Meyer *et al.* 1964; Fletcher *et al.* 1975).

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Renewed interests for TT in acute ischemic stroke was initiated by Zeumer *et al.* (1983) who reported the successful recanalization of an occluded vertebrobasilar artery in a patient with acute ischemic stroke by using an intra-arterial administration of streptokinase (SK). Compared to the previous use of an intravenous administration of thrombolytic agents, SK or urokinase (UK), an intraarterial route should be more effective for the lysis of occluding blood clots by introducing a much higher concentration of thrombolytic agents close to the clot. In addition, repeat angiography may provide the information about the efficacy of TT by demonstrating the degree of recanalization. Del Zoppo *et al.* (1988) conducted an intra-arterial administration of either UK or SK by using a superselective angiocatheter in 20 patients with acute ischemic stroke in the internal carotid artery (ICA) territory. TT was started within 8 hours of onset and 15 patients (75%) showed complete recanalization with subsequent clinical improvement in 10 patients. Hemorrhagic transformation was seen in 4 patients, but was not associated with any evidence of clinical deterioration. Mori *et al.* (1988) studied 22 patients with acute ischemic stroke in the MCA territory. They administered UK through a conventional angiocatheter placed in the high ICA and the mean time from the clinical onset to the start of infusion was 4.5 hours. Immediate recanalization was achieved in 10 patients (45 %) with a significantly better neurological outcome and smaller volume of infarction measured by CT scan compared to that of the patients without recanalization. Hemorrhagic transformation occurred in four patients; one in the recanalized group and three in the non-recanalized group, with symptomatic deterioration in two patients. They suggested that the restoration of CBF by thrombolytic recanalization was the most important factor for the clinical outcome of MCA stroke. Intra-arterial TT was also investigated in patients with vertebrobasilar occlusion by Hacke *et al.* (1988). Nineteen of 43 patients who received intra-arterial UK or SK achieved successful recanalization and 14 of them survived. On the other hand, all 24 patients without evidence of recanalization died. Only 3 of 22 patients who recieved conventional treatment survived. Therefore, the results from major studies of intra-arterial TT could be summarized as (i) recanalization of arterial occlusion was accomplished in about half of the patients (range 44% to 75 %), (ii) arterial recanalization was associated with significantly better clinical improvement, and (iii) the risk of hemorrhagic transformation seemed small and often associated with no apparent clinical deterioration.

Recently, the interests for TT in acute ischemic stroke have shifted to the relatively fibrin-specific thrombolytic agents; tissue-type plasminogen activator (t-PA), single chain urokinase-type plasminogen activator (scu-PA), and acylated plasminogen streptokinase activator complex (APSAC). These agents apparently have more attractive theoretical advantages such as their effectiveness by intravenous administration and less likelihood of inducing systemic hypocoagulability. However, their clinical experience is still quite limited and they are either too expensive or not readily available in many countries yet. In addition, it is still not determined whether the fibrin-specific thrombolytic agent is superior to intra-arterial UK or SK in their safety and efficacy.

We report our clinical experiences with intra-carotid UK therapy in patients presented with acute ischemic stroke in the ICA territory.

SUBJECTS AND METHODS

Patients

The study was conducted at the Severance Hospital of Yonsei University College of Medicine from January, 1989 to June, 1991. The selection criteria for the study patients consisted of following: i) abrupt onset of focal neurological deficits clinically considered as the carotid artery territorial ischemia, ii) age younger than 70 yr-old, iii) notified to the neurology residents within 4 hours of onset, iv) absence of apparent focal hypodensity in the CT scan of the head v) no contraindication of UK infusion (past history of G-I bleeding, uncontrolled hypertension, etc). Patients with only minimal neurological deficits or symptoms suggestive of la-

cunar infarction were excluded from the study. Twenty patients met the selection criteria and were included in the study.

Procedures

A consent form was obtained before the procedure. After routine labarotory tests including CBC, UA, coagulation battery, Chest PA, SMA12 and EKG, CT scan of the head without contrast infusion was taken immediately. When the patients met the selection criteria, they were transferred to the cerebral angiography suite.

Emergency cerebral angiography was performed by a femoral approach to identify the occlusion of the internal carotid artery or its branches. Contralateral carotid arterial angiography was not considered necessary to save the therapeutic time window. After the identification of arterial occlusion, the catheter was advanced to just below the cavernous portion of the ICA. Initially, 600,000 units of UK was administered through the catheter continuously for 30 minutes by using a syringe infusion pump, which was followed by the repeat angiography. If the recanalization was not established, an additional dose of UK was administered in a similar method and the angiography was repeated again. The total dose of UK used varied from 60 to 150×10^4 units. Upon completion of UK infusion, the patient was transferred to the neurology ward for close observation. CT scan was repeated within 24 to 48 hours after the end of TT and again at the seventh day of hospitalization.

Ancillary Medical Management

Following the initial neurological evaluation, before the start of TT, low molecular weight dextran (LMWD) was started at a rate of 500 ml over 4 hours, which was followed by 500 ml of LMWD over 24 hours for 3 days.

Anticoagulation therapy was withheld until the second CT scan was available. In cases where the second CT scan revealed no evidence of hemorrhagic transformation heparin anticoagulation started immediately by using a continuous IV drip method to maintain the partial thromboplastin time value at 2 times the control. Antiplatelet agents were prescribed immediately at the end of TT in patients who had atherosclerotic thromboembolism.

Outcome Measurement

The angiography repeated immediately after UK infusion was reviewed by the neuroradiologists to evaluate the degree of reperfusion. Reperfusion was graded as 0; no reperfusion, 1; occlusion with minimal reperfusion, 2; partial reperfusion, 3; complete reperfusion. Grade 2 and 3 were considered as effective recanalization.

CT scans obtained within 24 to 48 hours after the UK infusion were reviewed by neuroradiologists. Hemorrhagic transformations were divided into petechial hemorrhage (PH) and parenchymal hematoma (HA). The focal hypodensities were graded as small (S), moderate (M), and large (L) according to the size, and localized as subcortical (Sc), cortical (C), and both subcortical and cortial (Sc+C). The mass effect of the focal hypodensities was also graded as 0: no mass effect; +: obliteration of sulci and mild compression of the ventricle; ++: minimal midline shift; +++: moderate to severe midline shift.

The clinical outcome was evaluated by using the canadian neurological scale (CNS; Cote *et al.* 1986) during the hospitalization. The flow sheet was filled at admission, the first, third, seventh day, and at the time of discharge. The patient's functional status was evaluated at the end of the third month follow up, which was graded as Excellent: no neurological deficits; Good: slight neurological deficit remained but social life possible; Fair: independent domestic life possible; Poor: assistance required for domestic life, and Death.

Statistics

statistical analysis employed the two tailed Fisher's exact test and two way ANOVA

RESULTS

The clinical, angiographic, and outcome features of the study patients are summarized in table 1.

Table 1. Clinical, angiographic, and outcome features in 20 patients recieved intra-carotid urokinase infusion therapy

Case/Sex/Age	Cause	Occlusion	Dose of UK ($\times 10^4$ unit)	Recanalization		Time interval (minutes)	CNS score			CT			Complication	Late outcom
				Artery	Degree		P	D1	D7	F.H.	M.E.	H		
1/F/42	CE (VHD)	Rt ICA	60	ACA.PCA.M1	2	p:150								
			120	NR	2	S:420	2.5	5.0	5.0	Sc	+	N	N	Fair
2/F/33	CE (VAE)	Lt ICA	60	PCA	1	P:60								
			120	NR	1	S:370	5.0	7.0	0	Sc	++	N	R.S. CHF	Dead
3/F/33	CE (VAE)	Rt ICA	60	NR	0	P:50								
			120	A.Ch.A	1	S:310	6.5	6.5	6.5	Sc+C	+	N	N	Fair
4/M/67	CE (NVAF)	Rt ICA	60	NR	0	P:75								
			120	NR	0	S:360	1.5	1.5	0	Sc+C	+++	N	T.H.	Dead
5/M/67	CE (NVAF)	Rt ICA	60	NR	0	P:30								
			100	NR	0	S:260	4.5	1.5	0	Sc+C	+++	N	T.H	Dead
6/F/68	CE (NVAF)	Rt ICA	60	ACA	1	P:80								
			100	NR	1	S:270	4.0	3.5	0	Sc+C	+++	NA*	T.H	Dead
7/M/48	AT	Rt M1	60	NR	0	P:140								
			90	NR	0	S:300	6.0	6.0	6,0	Sc	+	N	N	Fair
8/M/40	AT	Rt M1	60	NR	0	P:50								
			120	NR	0	S:300	5.0	5.0	5.0	Sc+C	++	HA	N	Fair
9/M/61	EU	Rt M1	60	NR	0	P:60								
			120	NR	0	S:330	4.5	4.5	5.0	Sc+C	++	PH	N	Poor
10/M/67	EU	Lt M1	60	NR	0	P:60								
			90	M1	2	S:330	3.0	3.0	4.0	Sc+C	+	N	MI	Dead
11/F/61	CE (NVAF)	Rt M2	60	NR	0	P:100								
			120	Partial	2	S:510	1.5	1.5	1.5	Sc+C	+++	HA*	N	Poor
			150	complete	3									
12/M/52	AE	Lt M2	60	NR	0	P:100								Excel-
			120	M1	2	S:280	3.0	8.5	10	C	0	N	N	lent
			150	complete	3									
13/F/56	CE (VHF)	Rt M2	60	NR	0	P:80								
			120	NR	0	S:380	1.5	1.5	1.5	C	+	PH	CHF Pneumonia sepsis	Dead

Table 1. Continued

Case/Sex/Age	Cause	Occlusion	Dose of UK ($\times 10^4$ unit)	Recanalization		Time interval (minutes)	CNS score			CT			Complication	Late outcom
				Artery	Degree		P	D1	D7	F.H.	M.E.	H		
14/M/55	CE	Lt M2	60	NR	0	P:180								
	(VHD)		120	NR	0	S:420	6.5	6.5	7.5	C	+	PH	N	Good
15/M/63	EU	Lt M2	60	M2	2	P:135								Excel-
			90	complete	3	S:400	5.5	5.5	9.5	C	+	N	N	lent
16/M/60	CE	Lt M2	60	M2	2	P:120								
	(NVAF)					S:270	3.0	3.0	7.0	C.	+	N	N	Good
17/M/42	AE	Lt M2	60	NR	0	P:40								
			120	NR	0	S:280	6.5	1.5	5.0	−	++	HA*	Surgery	Fair
18/M/54	CE	Lt M4	60	M3	2	P:30								Excel-
	(VHD)	Lt M3	120	NR	2	S:390	4.5	5.5	7.5	C mul	0	PH	N	lent
19/M/70	CE	Rt M3	60	NR	0	P:120								
	(NVAF)	Rt M3	120	complete	3	S:450	6.0	6.0	7.5	C mul	+	N	N	Fair
		Rt M4												
20/F/61	CE	Lt M3	60	NR	0	P:180								
	(VHD)		90	complete	3	S:450	4.0	6.0	8.5	C	0	PH	R.S CHF	Died

Lt: left, Rt: right, F.H: focal hypodensity, M.E: mass effect, HT: hemorrhagic transformation, CE: Cardiogenic embolism, AT: atherosclerotic thrombosis, AE: artery to artery embolism. EU: embolism of unknown source, VHD: valvular heart disease, VAF: valvular atrial fibrillation, NVAF: non-valvular atrial fribrillation, ACA: anterior cerebral artery, PCA: posterior cerebral artery, A.ch.A: anterior choroidal artery, P: time interval from onset to the initial presentation, S: time interval from onset to the start of UK infusion, Sc: subcortical, C: cortical, Sc+C: both subcortical and cortical, mul : multiple, HA: intraparenchymal hemorrhage(HA*: associated with symptomatic deterioration), PH: petechial hemorrhage, R.S.: recurrent stroke, CHF: congestive heart failure, T.H.: transtentorial herniation, MI: myocardial infarction

Patient Characteristics

Intra-carotid UK infusion was performed in 20 patients. Although patient #12 had the procedure twice for recurrent stroke, which occurred one month apart with excellent outcome each, the second procedure was not included in the analysis. Eleven events occurred in the right hemisphere and 9 were in the left hemisphere. On the basis of angiographic findings and cardiac abnormalities, cardiogenic embolism was considered responsible for the event in 13 cases, atherosclerotic thromboembolism in 4 patients, and embolism of unknown etiology in 3 cases. Among 13 cases with cardiogenic embolism, valvular or non-valvular atrial fibrillation (AF) was present in 8 cases, and valvular heart disease without AF in 5 cases. Of 4 patients with atherosclerotic thromboembolism, two patients showed MCA branch embolic occlusion secondary to ICA atherosclerosis and two others were atherosclerotic thromboocclusion at the MCA stem.

Location of arterial occlusion

The angiographically defined arterial occlusions were distributed in the distal ICA in 6 cases, MCA stem (M1) in 4 cases, major branches of MCA (M2) in 7 patients and distal branches of MCA (M3 and M4) in 3 cases. Two patients with distal MCA occlusions involved two and three branch occlusions each.

Dose of UK and Recanalization

The average dose of UK in the study was 114×10^4 units (range: 60 to 150×10^4 units). Complete recanalization was achieved in 5 patients, effective partial recanalization in 4 patients, minimal recanalization in 3 patients, and no recanalization in 8 patients. The average dose of UK in patients who achieved effective recanalization (class 2 or 3:9 cases) was 110×10^4 units compared to 113.6×10^4 units in the non-recanalized group (class 0 or 1:11 cases), which was not much different. After the initial administration of 60×10^4 units of UK, no patients achieved complete recanalization but effective partial recanalization was seen in 4 patients and minimal recanalization in 2 patients. After the second dose of UK (30 to 60×10^4 units), 6 of 14 patients (42.8%) without any evidence of recanalization after the first dose showed evidence of recanalization (class 1:1 patient, class 2:3 patients, class 3:2 patients). On the other hand, only 1 of 6 patients (16.6%) with evidence of recanalization after the first dose showed further recanalization. Two patients who received the third dose of UK (30×10^4 units) had shown effective partial recanalization at the end of the second infusion, which became complete by the third dose of UK.

In this study, the sites of arterial occlusion seemed to be important for predicting the degree of recanalization. In 10 patients with large arterial occlusions (distal ICA or MCA stem), complete recanalization was achieved in none and effective partial recanalization in only two cases, while 7 of 10 patients with smaller arterial occlusions (M2 or M3-4) achieved either complete (5 patients) or effective partial recanalization (2 patients). Although it was not statistically significant ($P=0.069$, Fisher's exact test), probably due to a small number of patients, the findings might suggest that the size of embolic material was

Table 2. Summary of relations between clinical outcomes, site of arterial occlusions, and recanalization

		Early Neurological* improvement	Long term** outcome
Large artery (10)	R (2)	$+1.75\pm1.06$	○ △
	NR (8)	-1.81 ± 2.13	△△△ ○○○○○
Small artery (10)	R (7)	$+3.43\pm2.24$	●●●● △ ○○
	NR (3)	-0.17 ± 1.26	● △ ○

*: average difference of CNS scores between presentation and 7th hospital day.

**: ●: favorable outcome
△: fair outcome
○: worse outcome

R: effective recanalization, NR: non-recanalization

( ): number of patients

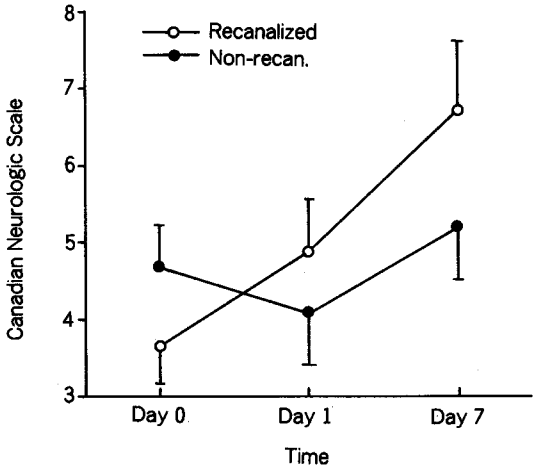

Fig. 1. Changes of CNS scores during early hospitalization in patients with and without immediate recanalization. Vertical bar indicates standard error.

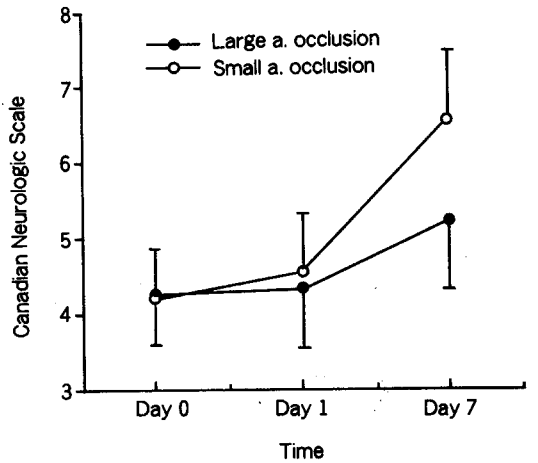

Fig. 2. Changes of CNS scores during early hospitalization in patients with large and small arterial occlusions. Vertical bar indicates standard error.

one of the factors determining the recanalization by intra-carotid TT.

Neurologic Outcome

The early and long term neurological outcomes are summarized in table 2. The early neurological outcome of TT was evaluated by using CNS. Average CNS scores at the time of initial evaluation was 4.23±1.70 at the initial presentation, 4.45±2.18 on the first day, and 4.85±3.31 on the 7th day of hospitalization. In the recanalized group, the initial CNS score was 3.67±1.46, and it improved to 4.89±2.09 on the first day and then to 6.72±2.75 on the 7th day of hospitalization. On the other hand, in the non-recanalized group, the mean CNS scores at the initial presentation was 4.68±1.81, which decreased to 4.09±2.28 on the first day and further decreased to 3.32±3.01 on the 7th day of hospitalization (Fig. 1). The changes of the CNS score on the first and 7th day of hospitalization between the two groups were significantly different ($P=0.04$ and $P=0.0002$ respectively) When we analyzed the early neurological outcome in patients with different arterial occlusions (Fig. 2), the CNS scores decreased from 4.25±1.55 at the time of initial presentation to 3.15±2.80 on the 7th day in patients with larger arterial occlusions in contrast to the improvement from 4.2±1.92 to 6.55±2.99 respectively in patients with smaller arterial occlusions, which was significant ($P<0.01$). Therefore, the early neurological improvement seen in patients with recanalization seemed to be at least partly related to the smaller arterial occlusions. However, further statistical analysis (two way ANOVA) for measuring the independent influence of the arterial occlusion sites and the recanalization on the early neurological outcome (7th day) disclosed no significant influence of the occlusion sites ($P=0.14$) but statistical significance of the recanalization ($P<0.004$).

Six patients died during the study period. All of 4 patients who died during the early period of hospitalization (<7th day) had ICA occlusions and did not achieve effective recanalization. One died of recurrent stroke and congestive heart failure (CHF) and the remaining 3 patients due to transtentional herniation with associated parenchymal hematoma formation in one. Two other patients died during the convalescent phase due to sudden MI in one and CHF associated with pnemonia and sepsis in the other. The long term outcome at 3 months follow-up showed an excellent outcome in 3 patients, good in 2,

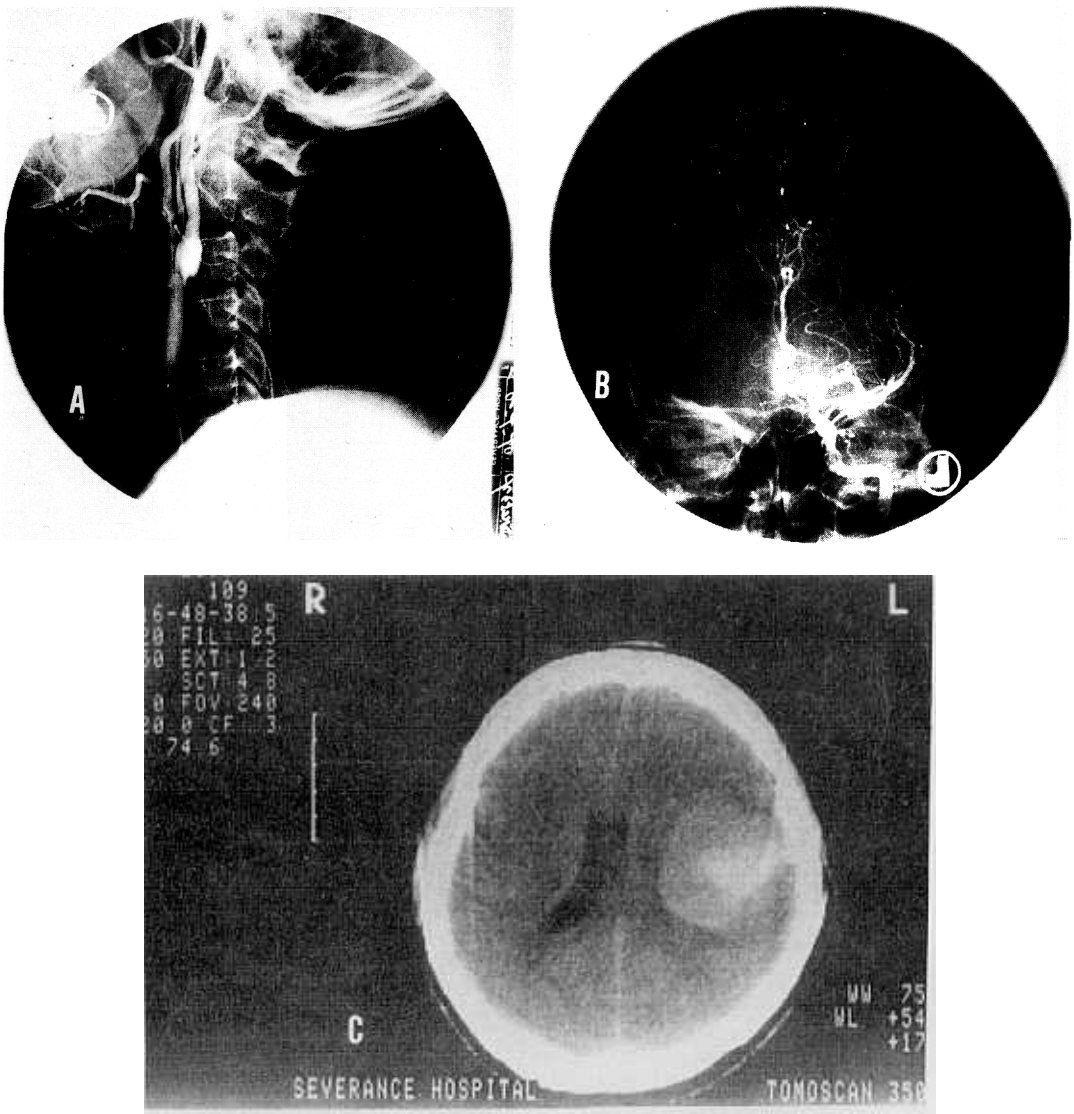

Fig. 3. *Angiographic and CT findings of patient 17.*

A: moderate sized atheromatous plaque with ulceration in the internal carotid artery at the bifurcation.

B: left carotid angiography taken after the infusion of 120×10^4 unit of UK. Arrow indicates persistent arterial occlusion at M2 segment of MCA.

C: CT scan taken immediately after sudden clinical deterioration shows a large intraparenchymal hematoma with minimal midline shift. The hemorrhage is more dense in the central region supplied by the occluded MCA branches.

fair in 6, poor in 2, and dead in 6 patients (Table 2). Among 9 patients who achieved recanalization, favorable outcome (excellent or good) was seen in 4, fair in 2, and worse outcome (poor or dead) in 3. In 3 patients with worse outcome, intraparenchymal hematoma formation was responsible in one while remote complications were responsible in two. In 11 patients without effective recanalization, favorable outcome was seen in

only one, fair in 4, and worse outcome in 6.

As predicted, the size of focal hypodensities in the CT scans obtained within 24 to 48 hours after the intra-carotid UK infusion was strongly correlated with both the sites of arterial occlusions and the recanalization. Subcortical focal hypodensities with or without associated cortical lesions were universal features in large arterial occlusions (distal ICA and M1), related to the absence of collateral circulations in the lenticulostriate arteries.

Among 10 patients with large arterial occlusions, 8 patients without recanalization showed large focal hypodensities in 7 and moderate sized focal hypodensities in 1. Two patients with recanalization showed moderate sized focal hypodensities. In 10 patients with smaller arterial occlusions, subcortical structures were spared except one (#11) who showed symptomatic large intraparenchymal hemorrhage involving both cortical and subcortical regions. In patients with M2 occlusions, with the exception of case #11, the size of focal hypodensities was smaller in patients who achieved effective recanalization.

Apparently, the mass effect in the CT scan was correlated with the size of focal hypodensities but not with the degree of recanalization.

Hemorrhagic Transformation

Repeat CT scan revealed evidence of hemorrhagic transformation in 9 patients (45%), 4 patients developed intraparenchymal hematoma formation (HA) and 5 petechial hemorrhagic transformation (PH). Among 4 patients with HA formation, 3 patients were associated with clinical deterioration: two in the non-recanalized group and one in the recanalized group. The hemorrhagic complication developed in case # 17 was quite instructive. He developed motor aphasia and right hemiplegia related to M2 occlusion. Repeat angiography after the infusion of 120×10^4 units of UK did not show any evidence of recanalization. However, his neurological deficits began to improve rapidly to almost complete recovery over two hours after UK infusion, when his condition suddenly deteriorated again. The immediately taken CT scan showed a large HA formation in the region of ischemia (figure 3). Although recanalization was not demonstrated at the repeat angiography it was speculated that the arterial occlusion was probably recanalized shortly after the UK administration with rapid recovery of his neurological deficit but was complicated by the subsequent development of hemorrhage in the ischemic region due to reperfusion. Stereotactic evacuation of hematoma was performed but he was left with a right hemiplegia.

All five patients with PH did not show any associated clinical deterioration. The average doses of UK in patients with and without hemorrhagic transformation were 117.8×10^4 units and 107.3×10^4 units respectively. For 4 patients with HA formation, the average dose of UK was 123.3×10^4 units and all of them recieved 100×10^4 units of UK or more. None of 5 patients who received less than 100×10^4 units of UK developed HA formation but PH developed in one patient.

Time Interval

The average time interval from the clinical onset to the initial neurological evaluation in the study patients was 92 minutes (range: 30 to 180 min), and the UK infusion was started 354 minutes (range: 260 to 510 min) after the clinical onset with the average time interval between the initial evaluation and the start of UK being 262 minutes (range: 150 to 410 min). Therefore, only 10 patients started UK infusion and 5 of them finished TT within 6 hours of clinical onset, which was commonly quoted as the limit of the therapeutic time window in humans. However, there was no correlation between the time interval and the neurological outcomes: The average time intervals from the onset to the end of UK infusion were 428 min in the group with good or excellent outcomes, 420 min for the fair outcomes and 442 min for the poor or worse outcome. There was also no correlation between the time interval and the hemorrhagic transformation; the average time interval in patients with and without hemorrhagic transformation was 341 ± 19 min and 370 ± 19 min respectively. Even in the patients with HA, it was 340 ± 57 min.

DISCUSSION

Although the administration of thrombolytic agents may decrease the blood viscosity by decreasing the level of plasma fibrinogen, the major purpose of TT is the restoration of CBF in the ischemic penumbral zone by recanalizing the arterial occlusion. The intra-arterial administration of thrombolytic agents may provide much higher concentration of thrombolytic agents at the vicinity of arterial occlusions with subsequently more rapid and effective recanalization than the intravenous route of administration.

In our study, the recanalization rate was 45 % and both acute and chronic neurological outcomes were significantly better in the recanalized group than the non-recanalized group and the recanalization was the single important factor in the two way ANOVA, which was in agreement with the results of Mori *et al.* (1988).

However, the interpretation of our data required great caution because the recanalization rate was somewhat dependent on the sites of arterial occlusion: 7 of 10 cases with M2 or M3-4 branch occlusions achieved effective recanalization in contrast to only 2 of 10 cases with distal ICA or M1 occlusions. On the other hand, the initial CNS scores at the onset of stroke were not significantly different between the patient groups with larger arterial occlusions and with smaller arterial occlusion. Therefore, although the independent influence of the arterial occlusion sites on the neurological outcome was not significant in this study, it seemed inappropriate to compare the clinical outcomes between the two groups with and without recanalization in the absence of adequate control patients.

In fact, the poor recanalization rate in large arterial occlusions have been observed in other studies of TT. Mori *et al.* (1991), by using the same regional UK infusion as ours, reported that the recanalization rate was only 12.5% in ICA occlusions. Partial or complete recanalization was observed in 50% of the patients with M1 or M2 occlusions, which was comparable to 25% in M1 occlusion and 57% in M2 occlusions of our study.

In recent studies of intravenous t-PA therapy, Kummer and Hacke (1992) observed immediate recanalization at the end of intravenous infusion of antiplase (100 mg) in 8 of 29 cases (27.6%) with large arterial occlusions and in 3 of 3 cases (100%) with smaller arterial occlusions. In the study of del Zoppo *et al.* (1992), the recanalization rate in the occlusions of ICA, M1, M2, and M3 were 8%, 26.1%, 35%, and 39.7% respectively. Mori *et al.* (1992) also reported a poor recanalization rate in patients with ICA or multiple arterial occlusions after intravenous t-PA infusion, which was seen in only one of 10 patients. Therefore, it seems clear that the site of arterial occlusion is an important factor for the recanalization in the regional as well as intravenous TT.

On the other hand, the 75% recanalization rate in both ICA and MCA occlusions by del Zoppo *et al.* (1988) seemed outstanding compared to the other studies. In fact, 7 of 8 patients with distal ICA occlusions achieved complete recanalization and the one remainning patient had partial recanalization. The high recanalization rate in distal ICA occlusion in their study might be related to the use of different techniques because they apparently adopted a superselective angiographic techiques to infuse thombolytic agent at the very site of occlusion, which should be more effective in maintainning higher concentrations of thromobolytic agents at the surface of the occluding blood clot.

As Zeumer *et al.* (1984) recognized previously, most thrombolytic agents administered by the intra-carotid approach may be diverted from the site of arterial occlusion due to a low flow-state in the lesional arterial segment resulting in a less optimal concentration of thrombolytic agents at the occlusion site. Therefore, for more effective recanalization of arterial occlusions, especially in larger arterial occlusions, a superselective angiographic technique should be seriously considered although it may require more technical demands.

Other factors to be considered for the critical evaluation of TT may include collateral circulation, therapeutic time window, and complications related to TT. The therapeutic time window is the critical issue in TT. Experimentally, 2 to 3 hours have been

shown to be the critical time limit for effectiveness of reperfusion in smaller animals (Jones *et al.* 1981), which may be prolonged to 3 to 6 hours in larger animals (del Zoppo *et al.* 1990; Sundt *et al.* 1969). Although the therapeutic time window in humans is still unknown, most clinical trials adopted 6 hours of starting TT in patients without any apparent focal hypodensities in the CT scan (Wardlaw and Warlow, 1992). However, considering that the therapeutic time window is proportional to the CBF in the ischemic region (Heiss and Rosner, 1983), it is most likely that the therapeutic time window varies in individual patients according to the state of collateral circulation. Therefore, 6 hours of therapeutic time window may be too late in some patients with poor collateral circulation and TT in those patients may do more harm than benefit.

In fact, collateral circulation was an important prognostic factor in the study of emergency embolectomy (Meyer *et al.* 1985), and the importance of collateral circulation in TT was recently stressed by Kummer and Hacke (1992) and Ringelstein *et al.* (1992) in the prospective clinical trial of intravenous t-PA therapy. In the study of Kummer and Hacke (1992), the clinical outcome was good in 12 of 15 patients with good collateral circulation and in only 2 of 17 patients with poor collateral circulation. Immediate recanalization was achieved in 8 of 15 patients with good collateral circulation and in only 3 of 17 patients with poor collateral circulation, which may also suggest the important role of collateral circulation for the recanalization, which is probably related to the delivery of t-PA to the site of arterial occlusion. The clinical outcome in cases without immediate recanalization was also strongly influenced by the collateral circulation as 5 of 7 patients with good collateral circulation achieved good clinical outcome compared to only one of 14 patients with poor collateral circulation. Therefore, a thorough evaluation of collateral circulation seems to be a critical factor for evaluating the efficacy of TT, which has not been properly addressed in the clinical trials of intra-arterial TT including the present study. Hemorrhagic transformation of pale infarction is certainly the most important concern for TT. The natural incidence of hemorrhagic transformation varied widely in different studies, which may be related to multiple factors including the etiology of stroke, size of stroke, age, or use of anticoagulants. In prospective studies used serial CT scans, Hornig *et al.* (1986) and Ogata *et al.* (1989) reported the incidence of 43% and 40.6% respectively. However, most of the hemorrhagic transformations were petechial hemorrhages which were not clinically important. The incidence of intraparenchymal hematoma formation in these studies, associated with clinical deterioration, was around 4 % to 5%. The incidence of hemorrhagic transformation in various studies of TT also varied greatly. According to Wardlow and Warlow (1992), the average incidence of clinically important symptomatic hematoma formation was 5% for SK, 3% for UK, and 8% for t-PA. In our study, the hemorrhagic transformation was found in 9 of 20 patients; petechial hemorrhage in 5 patients and intraparenchymal hemorrhage in 4 patients. Symptomatic deterioration was noticed in 3 cases with intraparenchymal hematoma formation, one in the recanalized group and two in the non-recanalized group. This was comparable to the study of Mori *et al.* (1988) who used a similar intra-carotid TT as ours. They reported 3 cases of intra-parenchymal hematoma formation in 22 study patients with symptomatic deterioration in two patients: one in the recanalized group and the other in the non-recanalized group.

These were, however, somewhat higher than the study of Hacke *et al.* (1988) and del Zoppo *et al.* (1988). Especially the incidence of symptomatic hemorrhagic transformation was zero in the study of del Zoppo *et al.* The reasons for the difference are not clear and may be related to multiple factors.

The dose of UK was much higher in intra-carotid UK infusion studies, which was 104×10^4 units in our study and 92.7×10^4 units in Mori *et al.* (1988) compared to 40×10^4 units in Hacke *et al.* (1988) and less than 30×10^4 units in del Zeppo *et al.* (1988). In our study, the average dose of UK in 3 patients with symptomatic hematoma formation was 123.3×10^4 units compared to 101×10^4 units in 11 patients without hemorrhagic transformation.

Mori *et al.* (1988) stated that the incidence of hemorrhagic transformation was not sig-

nificantly different between patients who received lower and higher doses of UK but the severity of hemorrhage was increased in the higher dose group. The infusion of more than 108×10^4 units of UK was associated with a severe systemic hypocoagulable state, which may affect the severity of hemorrhagic transformation. Therefore, infusion of more than 100×10^4 units of UK seems to increase the risk of symptomatic hematoma formation. In fact, the correlation between hemorrhagic transformation and the dose of thrombolytic agents was demonstrated in a t-PA study by Brott et al(1992). A dose of t-PA higher than 0.85 mg/kg was significantly associated with intraparenchymal hemorrhage. The relationship between the timing of UK infusion and hemorrhagic transformation is unclear but a recent t-PA study by del Zoppo *et al*(1992) has suggested a higher incidence of hemorrhagic transformation in patients who received a later TT. Considering that the major mechanisms of hemorrhagic transformation are the restoration of blood flow(Fisher and Adams, 1951), which could cause diapedesis through ischemic endothelium and disruption of collateral vessels in or around the infarcted area, the delay of recanalization beyond the critical time window, after the complete disruption of the ischemic blood vessel, may increase the risk of hemorrhagic transformation. In our study, intra-carotid UK infusion was started at an average of 338 minutes after the onset of stroke, which was delayed by almost an hour compared to 270 minutes of Mori *et al*(1988), which might have contributed to the slightly increased incidence of hemorrhagic transformation. However, the average time interval was not different between the patient groups with and without hemorrhagic transformation in this study. On the other hand, the patient who developed HA after complete recanalization started TT at 510 min after clinical onset, which was markedly delayed compared to the other 3 patients without immediate recanalization (range: 270 to 300 min). This may suggest that the timing of recanalization, not the timing of TT, may be more related with the risk of HA formation. Both the studiy of Mori et al and our studiy suggested that the absence of immediate recanalization at the end of intracarotid UK infusion may carry more risks of HA formation, which was probably related to the delayed recanalization in the state of UK induced hypocoagulable state as seen in case # 17. Further clinical investigations employing the technique of serial arterial blood flow measurement such as transcranial doppler, may help clarify the subject. In our study, the in-hospital time delay for TT was significant and this was mainly related to the time consuming preparation for angiography especially during night. A more effective system for the earlier intervention of acute ischemic stroke needs to be developed. Otherwise, intravenous t-PA therapy may be more appropriate.

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