Evaluation of Local Intra-Arterial Fibrinolytic Therapy for Acute Middle Cerebral Artery Occlusion

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Summary

Fibrinolytic therapy for acute ischaemic stroke has been investigated in several clinical trials, with various protocols. This retrospective study was undertaken to evaluate the efficacy and limitation of local intra-arterial fibrinolytic therapy using urokinase (UK) in patients with acute middle cerebral artery occlusion.

Fifty patients were treated with local intra-arterial fibrinolytic therapy within six hours after onset of symptoms. The median National Institutes of Health Stroke Scale (NIHSS) score was 17 (range, 6 to 28). Two hundred and forty thousand IU of UK was administered through a microcatheter for 20 minutes. When arterial recanalization was not achieved, a second or third infusion was performed. Maximum dosage of UK was 0.96×106 IU. Recanalization efficacy was evaluated at the end of fibrinolytic therapy and intracranial haemorrhage was assessed within 24 hours. Clinical outcome was evaluated three months after ictus with modified Rankin scale (RS).

Thirty-nine patients (78%) obtained recanalization. Twenty-nine of 39 (74%) showed clinical improvement just after treatment. On the other hand, only 18% patients (2/11) who did not recanalize demonstrated improvement. Twenty-five of 50 (50%) patients recovered to RS score 0 or 1, however, only 28% of patients

(5/18) with proximal M1 occlusion obtained good outcome and 39% of them (7/18) died. The mean time interval from onset to treatment did not affect outcome. The overall incidence of haemorrhagic event (HE) within 24 hours was 36%, however, 78% of patients with proximal M1 occlusion showed HE. Only one patient with HE clinically deteriorated.

In conclusion, local intra-arterial fibrinolytic therapy could be a safe and effective method for acute middle cerebral artery occlusion, however, indication of this therapy for patients with proximal M1 occlusion should be carefully decided.

Introduction

Fibrinolytic therapy has been used in patients with acute ischaemic stroke under the hypothesis that recanalization of occluded arteries may reduce brain injury if it is done before the process of infarction has been completed^{1,2}. During the past decade, several fibrinolytic agents have been tested with either intra-arterial³⁻¹³ or intravenous¹⁴⁻²³ administration. However, the protocol, fibrinolytic agents and route of administration of fibrinolytic agents varied widely among these studies. Angiographic evaluation was not performed in some of these studies and the results are also varied.

When high doses of fibrinolytic agent are administered at occluded portion, recanalization can be theoretically accomplished in a short period with a high incidence. However, few reports describe the efficacy of local intra-arterial fibrinolytic therapy for acute thromboembolic stroke^{3-6,9,11,13} and the indications for this procedure in this disease are unknown.

In this report, we retrospectively evaluate the result of 50 cases of acute middle cerebral artery occlusion treated with local intra-arterial fibrinolytic therapy to assess efficacy, safety and limitation of this therapy.

Subjects and Methods

Patients, Inclusion Criteria

From January 1991 to December 1998, 50 patients (16 women, 34 men; age range 43 to 78 years; mean 66) with acute progressing stroke and angiographically demonstrated occlusion of middle cerebral artery (MCA) were treated with fibrinolytic therapy. All patients were admitted to our hospital within six hours after the onset of symptoms.

All patients underwent a complete neurological examination, routine laboratory tests and computed tomography (CT) scans at admission. Angiography of bilateral carotid arteries and a vertebral artery was performed to document the occlusion and collateral flow.

The clinical inclusion criteria for fibrinolytic therapy in this study were as follows: (1) a precisely defined and witnessed onset of stroke within six hours before fibrinolytic treatment; (2) a new onset of focal neurological signs in the MCA distribution and MCA occlusion shown by intra-arterial angiography; (3) a minimum National Institutes of Health Stroke Scale (NIHSS)²⁴ score of 4; (4) informed consent from the patient or patient's relatives. Clinical exclusion criteria included (1) a history of intracranial haematoma within four weeks, (2) clinical presentation suggestive of subarachnoid haemorrhage (even if the initial CT scan was normal), (3) active or recent haemorrhage within two weeks, or (4) known hereditary or acquired haemorrhage diathesis.

CT scan exclusion criteria were evidence of haemorrhage of any degree, or significant mass effect with midline shift or presence of clearly detected infarction. Patients with early changes of ischaemia, such as loss of gray-white matter

junction definition, sulcal obliteration were included.

Angiographic inclusion criteria were complete occlusion (TIMI grade 0)²⁵ or contrast penetration with minimal perfusion (TIMI grade 1) of the M1, M2 or M3 portion of MCA.

Method of local fibrinolytic therapy

A five French non-tapered catheter was advanced into the proximal ICA on the side of the occlusion. Through this catheter, a microcatheter with a single end hole was navigated into the thromboembolus over a 0.014-inch taper guidewire and the tip of microcatheter was placed at just distal of the thrombus. Urokinase (UK) was used as fibrinolytic agent. Two hundred forty thousands IU of UK dissolved in 20 ml of natural saline solution were injected through the microcatheter for 20 minutes. Digital subtraction angiography was carried out to evaluate the degree of clot lysis. If recanalization could not be obtained, mechanical disruption of the thrombus was attempted using microguide wire and injection of UK was repeated until satisfactory recanalization was achieved. The maximum dosage of UK was 960,000 IU. A small dose of heparin (60 to 80 U/kg) was administered intravenously for all patients just before angiography, and additional hourly boluses of heparin (1000 - 1500 U) were given as required.

Radiological assessment

Site of occlusion was divided into four groups; (1) Proximal M1: occlusion of the MCA trunk proximal to the lenticulostriate arteries (LSAs); (2) Distal M1: occlusion of the MCA trunk distal to the LSAs; M2 and M3. Recanalization was assessed by repeated angiography after treatment without delay, and the degree of recanalization was scored in accordance with TIMI grade. Patients with partial (TIMI grade 2) or complete (TIMI grade 3) recanalization were considered "responders".

The initial collateral circulation was evaluated on first angiogram performed just before fibrinolytic therapy and was classified into two groups; good, retrograde collateral supply covered more than 70% of affected areas; poor, less than 70% of affected areas.

CT scans were obtained within 24 hours after

completion of local infusion therapy to assess the occurrence and degree of haemorrhagic transformation. Established definitions of haemorrhagic transformation were applied to all CT scans: Haemorrhagic infarction (HI) was defined as areas of petechial or confluent petechial haemorrhage within regions of more homogeneous ischaemic injury. Parenchymatous haematoma formation (PH) referred to regions of more homogeneous high attenuation that contributed to mass effect or midline shift of cerebral structures or that were associated with intraventricular extension^{1,26}.

Neurological assessment

Neurological assessment was performed before and after therapy to evaluate the effect of recanalization on neurological recovery. The NIHSS score was used as a measure. Clinical improvement was judged by the difference of the NIHSS score obtained immediately prior to and after treatment. Degree of improvement was classified into four groups; marked improvement, decrease in a NIHSS score by three or more; mild by two or one; unchanged by zero; and deteriorated, increase in a NIHSS score after therapy. Clinical outcome was assessed by modified Rankin scale²⁷ three months after ictus and patients who had 0 and 1 scale were assessed as good recovery.

Statistical analysis

The data are presented in raw form as mean $\pm$ standard deviation. Comparison between the differences in the data sets were made by Fisher's exact test or the chi-square test as appropriate. Values < 0.05 were considered statistically significant. Comparison between the difference in the continuous data sets were made using Student's t-test. P values < 0.05 were considered statistically significant.

Results

Patient characteristics, NIHSS, and the site of occlusion are shown in table 1.

Recanalization

The rate of recanalization and the location of the occlusion are shown in table 2. Thirty-nine of 50 (78%) patients showed recanalization.

Complete, partial and no recanalization was achieved in 22 (44%), 17 (34%) and 11 (22%) patients, respectively.

The mean dosage of UK used for the patients with and without recanalization was $(0.61 \pm 0.24) \times 10^6$ IU and $(0.56 \pm 0.28) \times 10^6$ IU, respectively. This difference was not statistically significant.

The mean time interval from onset to start of local infusion therapy was 3.8 ± 1.5 hours in patients with recanalization and 3.6 ± 1.1 in patients without recanalization. No significant difference existed.

Correlation between the degree of clinical improvement and the degree of recanalization are shown in table 3. Of 22 patients who achieved complete recanalization, 19 (86%) had marked or mild improvement. Of 17 patients with partial recanalization, 59% (10/17) had improved and of 11 patients who did not recanalize, only 18% (2/11) improved. There was statistical significance of rate of recanalization between the marked group and unchanged group ($p < 0.0001$) and between the mild group and unchanged group ($p = 0.03$).

Degree of collateral circulation did not influence recanalization. Twelve patients had good collateral circulation and nine of them (75%) showed recanalization. On the other hand, 38 demonstrated poor collateral circulation and 31 of 38 (82%) showed recanalization.

Clinical Outcome

The clinical outcomes are shown in Table 4. Twenty-five of 50 (50%) patients obtained a good recovery. The median stroke severity (NIHSS) measured at admission was 17 (range, 6 to 28). The mean NIHSS score in patients with good outcome (RS 0 to 1) was 14.5 and that in patients with poor outcome (RS > 2) was 19.2. The difference was statistically significant ($p = 0.0003$).

Comparing the outcome of every site of MCA occlusion, 5 of 18 (28%) patients with proximal M1 occlusion, 7 of 11- (64%) patients with distal M1 occlusion and 10 of 18 (56%) patients with M2 occlusion demonstrated good recovery. On the other hand, 7 of 18 (39%) patients with proximal M1 occlusion died.

The median delay from the onset of stroke to treatment did not influence clinical outcome under our inclusion criteria. The mean time in

Table 1 Patient characteristics

	Site of Occlusion				Total
	Proximal M1	Distal M1	M2	M3	
Number	18	11	18	3	60
Age (yr)					
mean	66	62	68	70	66
range	52 - 75	43 - 78	50 - 78	66 - 76	45 - 83
Sex (M / F)	11 / 7	9 / 2	13 / 5	1 / 2	34 / 16
NIHSS					
mean	21	16	15	8	17
range	15 - 28	6 - 24	11 - 19	6 - 11	6 - 28

patients with good outcome was 4.0 ± 1.5 hours and it was in other patients 3.5 ± 1.4 . Eighteen patients received fibrinolytic therapy within three hours after ictus. Fourteen of 18 (78%) patients achieved recanalization and 7 of 18 (39%) had good recovery. On the other hand, 32 patients were treated in three to seven hours after stroke. Twenty-five of 32 (78%) patients could be achieved recanalization and 15 of 25 (60%) had favorable outcome. No significant difference existed between the two groups.

The relationship between clinical outcome and clinical improvement just after the local infusion therapy is shown in table 5. In the patients with marked improvement and mild improvement after local infusion therapy, 15 of 21 (71%) and 7 of 10 (70%) had good outcome, respectively. On the other hand, only 3 of 19 (16%) patients without improvement had a fa-

vorable outcome. Patients with marked improvement and mild improvement showed good recovery significantly ($p=0.0003$ and $p=0.003$, respectively).

Twelve patients demonstrated good collateral circulation on initial angiograms. Among these patients, eight (75%) had a good outcome. On the other hand, 17 of 38 (45%) patients with poor collateral circulation showed a favorable outcome. The difference was not significant, however, good collateral circulation tended to have a good outcome.

Haemorrhagic events

The incidence of intracranial haemorrhagic event (HE) of any degree within 24 hours after the completion of the drug infusion was 36% (18/50). HEs were observed in 14 of 18 (78%) proximal M1 occlusion, 3 of 11 (27%) of distal M1 occlusion, 1 of 18 (6%) of M2 occlusion. Proximal M1 occlusion had a significantly higher incidence of HEs than that of the other portion ($p<0.0001$).

Eighteen of 50 (36%) patients demonstrated HEs. Eleven patients showed HI and seven demonstrated PH. PH was detected in seven patients (14%) (three in proximal M1 occlusion, three in distal M1, one in M2). Only one of these seven patients deteriorated clinically (Rankin scale 4).

The relationship between recanalization and HE was studied. Thirteen of 39 (33%) patients with recanalization had HEs and 5 of 11 (45%) patients without recanalization had HEs. The

Table 2 Rate of recanalization

Site of Occluded Artery		Degree of Recanalization		
		Complete	Partial	No
MCA	Proximal M1	7	6	5
	Distal M1	8	2	1
	M2	6	8	4
	M3	1	1	1
MCA indicates middle cerebral artery; Complete indicates complete recanalization (TIMI grade 3); Partial indicates partial recanalization (TIMI grade 2); No indicates no recanalization (TIMI grade 0 or 1).				

incidence of HEs between the two groups showed no difference, however, 7 of 13 (54%) patients with recanalization showed PHs. On the other hand, all five patients without recanalization demonstrated HIs.

Discussion

The goal of fibrinolytic therapy is to promote the reopening of obstructed arteries as soon as possible after the occlusive events and establish blood flow to rescue the ischaemic brain tissue.

Many reports have described the efficacy of fibrinolytic therapy for acute thromboembolic stroke¹⁻²³. However, not many reports were based on the results of angiography before and after fibrinolytic therapy^{3,7-9,13,19,22,23}. All of the patients in our study demonstrated MCA occlusion angiographically and presented moderate to severe neurological deficit (median NIHSS score = 17). Therefore, our data evaluate the precise efficacy of local fibrinolytic therapy for the acute thromboembolic stroke.

Outcome

The NIHSS score at admission was a good measure of judging stroke severity and it was significantly related to outcome. A similar result was demonstrated in other stroke trials^{13,20}. Gönner et al suggested that an NIHSS score of ≥ 20 was an unfavorable sign¹³.

A significant correlation between clinical outcome and recanalization just after the local fibrinolytic therapy was demonstrated in our study. Other studies in which intra-arterial or intravenous fibrinolysis were used demonstrated that recanalization was also associated with a better prognosis^{8,13,22}. Clinical improvement just after fibrinolytic therapy was also significantly associated with a favorable outcome.

Seventy-one percent of patients (22/31) with clinical improvement had a good recovery in our study. This may reflect the efficacy of recanalization restoring neuronal function in the penumbra²⁸⁻³¹.

Many papers have investigated the efficacy of fibrinolysis with intravenous administration. The rate of favorable outcome varied from 24 to 58%^{14,16,18,20-22}. Many of these trials did not perform angiographic evaluation before fibrinolytic therapy, therefore there is a possibility of including minor stroke cases or already recanalized cases. It is difficult to compare our data directly with those from intravenous fibrinolysis, but our data may be at least as effective as intravenous fibrinolysis with tissue plasminogen activator. Moreover, local intra-arterial fibrinolytic therapy has several advantages¹³. It is possible to evaluate the occluded portion, collateral flow circulation and degree of recanalization; mechanical disruption of the thrombus can be attempted and PTA can be performed if necessary. Summing these factors together, there is a possibility that local intra-arterial fibrinolysis may be superior to intravenous fibrinolytic therapy.

The site of occlusion plays a key role in the outcome of MCA occlusion. Patients with proximal M1 occlusion had the lowest rate of good recovery (28%), highest incidence of haemorrhagic event (78%) and highest rate of mortality (39%). Therefore, it may be better to avoid local fibrinolytic therapy in patients with proximal M1 occlusion.

It is interesting that no significant difference existed between time interval to treatment and outcome in our study. This may be because of our small sample, although the degree of ischaemia may be the most important factor affecting the outcome rather than timing of recanalization within the clinical time window. In

Table 3 Correlation between clinical improvement and recanalization

Degree of Recanalization	Clinical Improvement			
	Marked	Mild	Unchanged	Deteriorated
Complete (TIMI grade 3)	15	4	2	1
Partial (TIMI grade 2)	5	5	6	1
No (TIMI grade 0 or 1)	1	1	9	0
Total	21	10	17	2

Table 4 Clinical outcome

Site of Occluded Artery		Outcome		
		Good (RS 0-1)	Poor (RS 2-5)	Dead
MCA	Proximal M1	5	6	7
	Distal M1	7	3	1
	M2	10	7	1
	M3	3	0	0
Total		25	16	9
<i>RS indicates modified Rankin scale; MCA indicates middle cerebral artery</i>				

general, ischaemic brain tissue is divided into two groups; irreversible injury ones and ischaemic penumbra²⁸⁻³¹. It is necessary for the management of patients with acute stroke to distinguish reversible from irreversible ischaemia, to predict which tissue will evolve to irreversible damage unless blood flow is restored. The aim of fibrinolytic therapy is to restore blood flow for ischaemic penumbra. It has been proposed that combined diffusion weighted MRI (DWI) and perfusion weighted MRI (PWI) could determine the early extent of brain tissue injury and identify the portions of ischaemic penumbra^{32,33}. Marks et al evaluated the relationship between early reperfusion and IV tPA therapy using DWI and PWI³⁴. In this paper, they found that DWI and PWI could guide acute stroke management and PWI lesion > DWI lesion patients may be the best

Table 5 Relationship between outcome and clinical improvement

Clinical improvement	Outcome		
	Good	Poor (RS 0-1)	Dead (RS 2-5)
Marked	15	4	2
Mild	7	2	1
Unchanged	3	8	6
Deteriorated	0	2	0
Total	25	16	9
<i>RS indicates modified Rankin scale</i>			

candidate for fibrinolytic therapy. Ueda et al³⁵ evaluated the usefulness of pretreatment SPECT study to establish the indications for fibrinolytic therapy in acute stroke. According to this study, ischaemic tissue with cerebral blood flow (CBF) greater than 55% of cerebellar flow still may be salvageable with treatment initiated six hours after onset, with CBF greater than 35% of cerebellar flow still may be salvageable with early treatment (within five hours) and with CBF less than 35% of cerebellar flow may be at risk for haemorrhage within the critical time window. Precise evaluation of residual CBF will increase the effectiveness of local fibrinolytic therapy and decrease the risk of haemorrhagic complications.

Haemorrhagic event

HE is one of the serious complications associated with fibrinolytic therapy. HE of brain infarction represents a multiple secondary bleeding into ischaemic tissue ranging from small petechiae and confluent purpura to parenchymal haematoma, with variable clinical sequelae. Comparison of the haemorrhagic rate with natural history in stroke patients is difficult because the rate of very early haematoma formation or haemorrhagic transformation in the absence of fibrinolytic therapy has not been firmly established. Several autopsy studies reported that any kind of spontaneous HE were detected commonly in large volume lesions, with an incidence of up to 71%³⁶⁻³⁸. The incidence of HE in CT studies was variously reported from few to 43% of consecutive patients³⁹⁻⁴¹. The difference depends largely on the diagnostic criteria for HE identification, evolution of in vivo scanning techniques and patient population studied. Meanwhile, it is generally considered that the spontaneous rate of symptomatic HE of the infarction is approximately 5%³⁹ and that the rate of asymptomatic HE is between 15% and 45%⁴². On the other hand, the rate of asymptomatic HE within 24 hours after various fibrinolytic therapy ranges from 4 to 31% and that of symptomatic HE ranges between 0 to 13%^{4,5,9,14,25,43}. The results of our study are similar to the spontaneous rate or to the rate in other fibrinolytic treatment. On the basis of these data, intra-arterial local fibrinolytic therapy does not bring any excess risk of HE.

The relationship between recanalization and

HE was also evaluated and no significant correlation was found. Several authors found similar results. Ogata et al⁴⁴ demonstrated that HE occurred without a reopening of occluded arteries in 14 brains postmortem with cardioembolic stroke. In our study, we could not evaluate the residual CBF in the ischaemic lesion, however, degree of ischaemia may influence the incidence of HE³⁵ and it is also necessary to evaluate the residual CBF before treatment to avoid haemorrhagic complications.

Conclusions

In conclusion, intra-arterial local fibrinolytic therapy with urokinase is a safe treatment and it can achieve a high rate of recanalization and favorable outcome in acute middle cerebral artery stroke patients with moderate to severe neurologic deficit. This study is relatively small and further large open trials are needed. However, this therapy could be an effective method for acute middle cerebral artery occlusion.

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COMMENT

The authors present a study on the evaluation of intra-arterial fibrinolytic therapy by urokinase in acute middle cerebral artery occlusion. This represents an interesting contribution due to the large number of patients included: 50 patients were treated within six hours following ischemic stroke. The results evidence a high recanalisation rate of middle cerebral artery whatever the occlusion site, proximal or distal. These data are consistent with the PROACT I study published in 1998 followed by the publication in 1999 of the PROACT II study, in terms of feasibility and local treatment interest^{1,2}. Complementary information on the clinical benefit according to the inclusion criteria and modern imaging data might, however, significantly improve our understanding. Patients with low NIH score scale were included, which means minimally symptomatic patients. It raises the question of the spontaneous clinical evolution which is potentially favorable in this situation. It is difficult to know how relevant these results are to the local treatment because there is no control group. As far as the imaging is concerned, patients only benefit from CT. Data provided by MRI are missing, especially data from diffusion weighted imaging sequences which allow a precise assessment of the damaged parenchymal volume. Due to the many possibilities of accrual of the Brain Research Institute of Niigata, the authors could have characterized patient sub-groups, more specifically patients who could benefit from intra-arterial fibrinolysis and patients with a high risk of complications, particularly symptomatic haemorrhagic transformation.

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