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Original Article

Intraarterial Therapy for Acute Ischemic Stroke : Investigation of Prognostic Factors

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Abstract **Background** : Intraarterial therapy (IAT) for acute cerebral infarction has been proven to be profitable. However, the criteria for the indications, the choice of the thrombolytic agents, and the use of adjunctive agents are controversial. We retrospectively analyzed the prognostic factors of IAT.
Materials and methods : From 1994 to 2003, 28 patients underwent IAT due to middle cerebral artery occlusion (17 women and 11 men ; median age, 69 years old). We evaluated the following prognostic parameters : institution of treatment, degree of paralysis at visit, size of high-intensity area on diffusion-weighted images, dose of intraarterial urokinase administration, elapsed time from symptom onset to completion of IAT, presence of penetration of embolus by microcatheter and microguidewire, recanalization after IAT, intracranial hemorrhage (ICH) within 24 hours after IAT, and intravenous heparin administration after IAT. The outcome was evaluated at discharge and was classified into the following categories according to the modified Rankin Scale : independence (0 to 2), dependence (3 to 5), and death (6).
Results : Seven patients were judged to be independent, 16 patients were judged to be dependent, and five patients died. Patients with recanalization after IAT had a better outcome than those without ($p<0.05$) ; patients with intracranial hemorrhage had a worse outcome than those without ($p<0.05$) ; and patients with intravenous heparin administration after IAT had a better outcome in activities of daily living than those without ($p<0.05$).
Conclusion : In addition to ICH and recanalization, our results suggested that intravenous heparin administration after IAT had a favorable effect on patient outcome.

Key words : Intraarterial therapy, Acute cerebral infarction, Heparin, CT, MRI, Diffusion-weighted image

INTRODUCTION

Following the first reports of the efficacy of intraarterial therapy (IAT) for acute cerebral infarction[1)2)], this intervention has seen gradually increasing use. Previous reports have demonstrated that patients can recover to fully independent function with IAT, while this procedure can result in death due to intracranial hemorrhage in some cases[1)~7)]. Despite the fact that the indications and treatment details for IAT have been developed, there is still no comprehensive methodology for IAT[4)~8)]. It is necessary to analyze the prognostic factors in IAT in order to standardize the treat-

ment. In this study, we retrospectively analyzed our data on IAT for acute cerebral infarction in order to extract prognostic factors.

MATERIALS AND METHODS

From 1994 to 2003, a total of 36 patients underwent angiography to assess their eligibility for IAT for acute cerebral infarction at two hospitals (Kyushu University Hospital and Aso Iizuka Hospital). The indication criteria were as follows: (1) the patient was less than 85 years old, (2) there was no low attenuation area, cerebral edema or hemorrhage on initial plain CT, (3) IAT could be completed within 6 hours of stroke onset, and (4) if possible, MRI including diffusion-weighted images (DWI) had been performed. Patients were excluded when DWI abnormal areas exceeded one-third of the middle cerebral artery (MCA) territory.

Of the 36 patients, 32 presented with MCA occlusion. The remaining patients, including three with vertebrobasilar artery occlusion and one with carotid artery occlusion, were excluded. Of the 32 patients, IAT was not performed due to spontaneous recanalization in one, due to the difficulty of inserting the selective catheter into the responsible artery in two and due to a diagnosis of probable atheroembolism in one. The remaining 28 patients (11 men and 17 women; age range, 46-83 years old; median age: 69 years old; 11 patients treated in Kyushu University Hospital and 17 in Aso Iizuka Hospital) were retrospectively analyzed.

Heparin was routinely administered immediately after sheath insertion (2000 U) and at the beginning of intervention (3000 U). We used either 5F or 6F catheters and 3F microcatheters. Intraarterial (IA) injection of urokinase was performed by a manipulative procedure at a rate of 60,000 U per 5-10 minutes through the microcatheter. The embolus was penetrated by a microcatheter and microguidewire so that the tip of the microcatheter would be located proximal to or, if possible, distal to the occlusion. The criteria for the termination of IA urokinase injection were as follows: (1) a maximum dose of 960,000 U, which was adopted from the dose limit in thrombolysis for myocardial infarction[3], (2) partial or complete recanalization of the occluded artery, (3) improvement of the neurological deficit, and (4) a maximum elapsed time of 6 hours from symptom onset to completion of IAT. Percutaneous transarterial angioplasty (PTA) was optionally performed at the occlusive lesion when a microballoon catheter was available. In a few exceptional cases in which the elapsed time was over 6 hours from onset or the DWI abnormality covered more than one-third of the MCA territory, we tried to perform the penetration of the embolus with the microcatheter and microguidewire without urokinase administration.

CT was performed within 24 hours after IAT in all patients, and thereafter CT or MR were performed as needed. If no intracranial hemorrhage was detected at the initial follow-up CT, intravenous heparin administration of 5,000-15,000 U / day was performed based on the judgment of the primary physician.

We statistically analyzed eight possible prognostic factors: the institution of treatment (Kyushu University Hospital versus Aso Iizuka Hospital; Spearman's rank test), the degree of paralysis at the initial visit (hemiplegia versus hemiparesis or no deficit; Spearman's rank test), the size of the high-intensity area on DWI (equal to or

less than versus greater than one-third of the MCA territory; Spearman's rank test), the dose of IA urokinase administration (Kruskal-Wallis test), the presence of penetration of the embolus by the microcatheter and microguidewire (Spearman's rank test), the presence of recanalization (Spearman's rank test), elapsed time from symptom onset to completion of IAT, and the presence of intracranial hemorrhage within 24 hours after IAT (Kruskal-Wallis test). In addition, we evaluated and statistically analyzed the effect of intravenous heparin administration on patients who had no intracranial hemorrhage within 24 hours after IAT using Fisher's exact probability test. The outcomes were classified into the following three categories according to the modified Rankin Scale[9] (mRS) at discharge: independence (mRS 0 to 2), dependence (mRS 3 to 5), and death (mRS 6).

RESULTS

Of the 28 patients, 21 presented with hemiplegia, six presented with hemiparesis, and one presented with no remarkable motor deficit at the initial visit. MRI was performed in 21 patients, and 19 patients had a DWI abnormality equal to or less than one-third of the MCA territory. The other two patients had a DWI abnormality exceeding one-third of the MCA territory, but underwent IAT (penetration of the embolus by microcatheter and microguidewire without IA urokinase administration) at the strong behest of their families.

Of the 28 patients, IA urokinase was administered to 23 (range; 160,000-960,000 U; median: 180.000 U), including 17 patients who underwent penetration of the embolus by microcatheter and microguidewire and 6 who did not. For 4 of those 23 patients, IAT was started within 6 hours of onset but was completed more than 6 hours after onset as a result of an effort to restore the patency of the occluded artery. For the other 5 of the 28 patients, penetration of the embolus by microcatheter and microguidewire without IA urokinase administration was performed for the following reasons: in 2 patients, DWI abnormalities exceeding one-third of the MCA territory were observed; in 1 patient, successful recanalization was accomplished with only penetration of the embolus; and in 2 patients over 6 hours had elapsed since onset. PTA was optionally performed in 2 patients. Partial or complete recanalization after IAT was observed in 19 patients. The elapsed time from symptom onset to the completion of IAT ranged from 168 to 440 minutes (median: 322 minutes). Intracranial hemorrhage was detected on CT in 7 patients within 24 hours. Of the other 21 patients, follow-up CT was performed in 15 and MR was performed in 3 at over 24 hours after IAT. Of these 18 patients, intracranial hemorrhage was detected in 10. The 3

Table 1 Modified Rankin Scale[9]

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Death

Table 2 Results of the statistical evaluations of prognostic factors

Prognostic factors		Outcome			Total
		Independence	Dependence	Death	
Institution of treatment	(Hospital A)	2	6	3	11
	(Hospital B)	5	10	2	17
Degree of motor deficit	(hemiplegia)	4	12	5	21
	(hemiparesis or no deficit)	3	4	0	7
High intensity area in DWI	(equal to or less than 1/3)	6	10	3	19
	(over 1/3)	0	2	0	2
Dose of urokinase	(range, x 10^4U)	0-96	0-96	6-32	0-96
	(median, x 10^4U)	18	15	18	18
Penetration of embolus	(presence)	6	13	4	23
by microcatheter and microguidwire	(absence)	1	3	1	5
Average elapsed time	(range, x minutes)	181-395	168-440	231-373	168-440
from attack to completion of IAT	(median, x minutes)	298	353	324	322
Partial or complete recanalization*	(presence)	7	8	3	18
	(absence)	0	8	2	10
Intracranial hemorrhage	(presence)	0	4	3	7
within 24 hours after IAT*	(absence)	7	12	2	21

* : $p<0.05$

patients who did not receive additional CT or MR had no deterioration in their neurological conditions. Intravenous heparin administration (5,000-15,000 U / day) after IAT was performed in 11 of 21 patients who were without intracranial hemorrhage within 24 hours after IAT. Five of the 11 patients who underwent heparin administration after IAT had intracranial hemorrhages over 24 hours after IAT. Of those 5 patients, one in whom heparin was discontinued was classified as mRS grade 4, one in whom heparin was discontinued died of intracranial hemorrhage, one with sustained heparin administration due to persistent arrhythmia underwent surgical removal of the intracranial hemorrhage and was classified as mRS grade 4, and the other 2 patients exhibited hemorrhagic findings on an MRI performed after the completion of the dosing period of heparin administration and were classified as mRS grades 0 and 1, respectively.

The outcome was rated as independence in 7 (25%), dependence in 16 (57%), and death in 5 (18%) patients. Of the 5 patients who died, intracranial hemorrhage was detected in 4, and it was considered to be the cause of death in 3. The other 2 patients died of acute cardiopulmonary arrest.

Table 2 summarizes the results of the statistical evaluations of the prognostic factors. The patients with recanalization after IAT had statistically better outcomes than those without ($p<0.05$). The patients with intracranial hemorrhage within 24 hours after IAT had statistically worse outcomes than those without ($p<0.05$). None of the other factors had a significant effect on the outcome.

Table 3 shows the effect of heparin administration after IAT. Between patients with and without intravenous heparin administration after IAT, there was a statistically significant difference in terms of independence vs. dependence or death ($P<0.05$). However, none of the prognostic factors significantly differed in mortality between the group treated with heparin and that treated without heparin.

Figures 1 and 2 show patients with partial and complete recanalization of the occluded artery, respectively.

Table 3 The effect of heparin administration after IAT

Heparin administration after IAT*	Outcome		Total
	Independence	Dependence or Death (Death)	
(presence)	6	5 (1)	11
(absence)	1	9 (1)	10

* : $p<0.05$

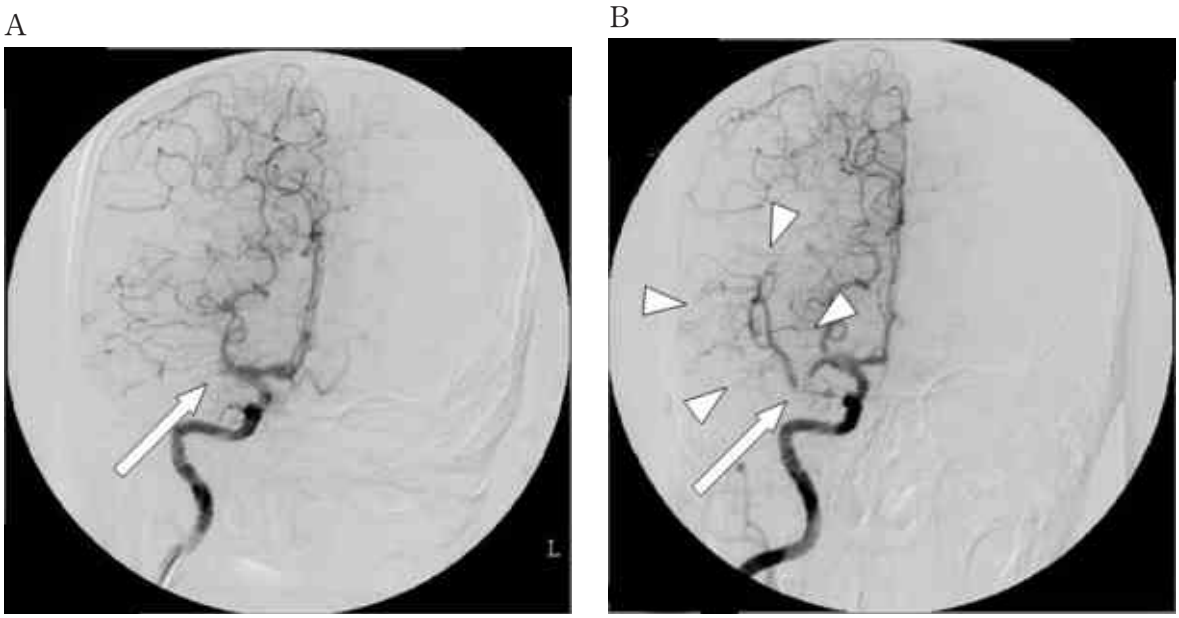

Fig. 1 A 66-year-old female with acute cerebral infarction. The angiographic anteroposterior view image before IAT (A) shows the occlusion of the right MCA (arrow). The following image after IA injection of 180,000 U of urokinase (B) shows the partial recanalization (arrow) with visualization of the distal branches (arrow heads). The patient underwent intravenous heparin administration after IAT and recovered up to mRS grade 0.

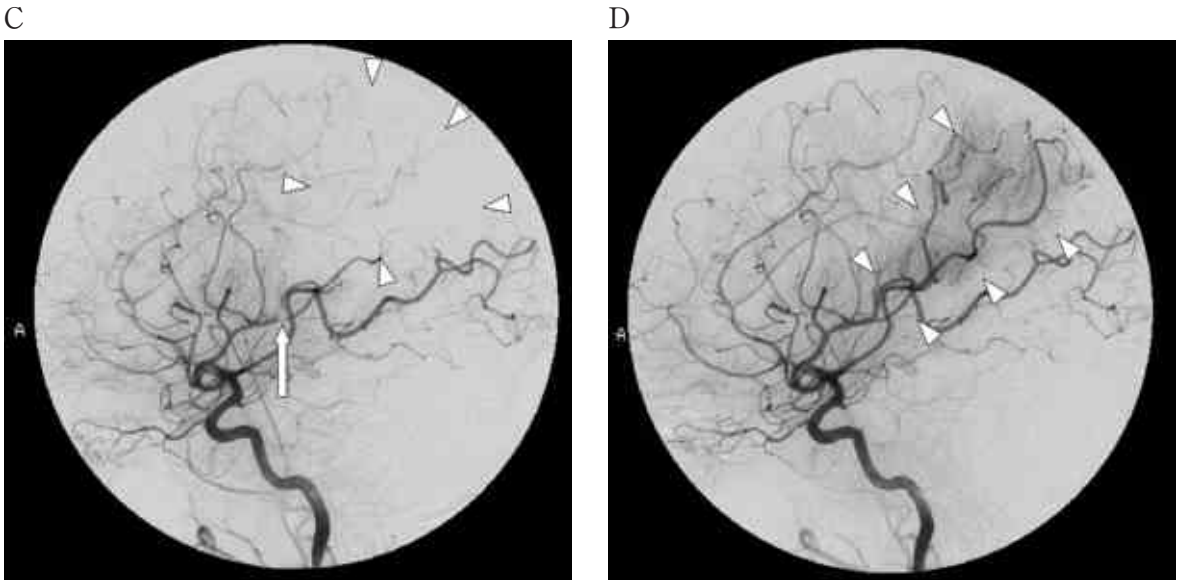

Fig. 2 A 55-year-old female with acute cerebral infarction. The initial angiographic lateral view image (A) shows the occlusion of the cortical branch of the right MCA (arrow) and the absence of the distal branch (arrowheads). The successful penetration of the embolus by microcatheter and microguidewire without urokinase administration resulted in the complete recanalization of the affected artery (B). The patient underwent intravenous heparin administration after IAT and was restored to mRS grade 1.

DISCUSSION

Our results show that patients with recanalization after IAT had significantly better outcomes than those without, and patients with intracranial hemorrhage had significantly worse outcomes than those without. These findings are in agreement with the results of previous reports[1)~7)].

In this study, the patients who received intravenous heparin administration after IAT had statistically better outcomes in terms of activities of daily living than those who did not receive heparin administration. Heparin administration has been performed in the treatment of myocardial infarction with the expectation of having the following effects : (1) prevention of reocclusion of the affected arteries, (2) supplementation of the lytic action exerted on residual thrombus by the thrombolytic agent remaining in the body, (3) inhibition of the regeneration of thrombi, and (4) prevention of deep venous thrombosis or pulmonary embolism[9)]. These effects might be beneficial in the post-IAT period for patients with acute cerebral infarction.

To date, there has been controversy with regard to the effect of heparin administration on patient outcomes[11)~16)]. According to the American Heart Association (AHA) Guidelines, anticoagulation therapy or antiplatelet therapy within 24 hours after intravenous administration of recombinant tissue plasminogen activator (rtPA) is not recommended because it can increase the risk of intracranial hemorrhage[17)]. However, the AHA guidelines also state that the value of adjunctive therapy should be investigated in greater depth, since adjunctive therapy may affect the duration of the lytic action of thrombolytic agents, the extent of recanalization, the rate of reocclusion, and the clinical outcome[17)]. Grond et al reported that additional heparin administration could play a role as an adjunctive therapy in thrombolysis of stroke[14)] as it does in myocardial infarction[9)]. In the European Cooperative Acute Stroke Study trials (ECASS I and II), subcutaneous heparin (not exceeding 10,000 U) was allowed during the first 24 hours for prophylaxis of deep vein thrombosis[18)19)]. Another study reported that it was safe to dispense 100 mg of rtPA with heparin administration of 5,000 U / hour by bolus injection and 1,000 U / hour by continuous infusion[15)].

Though the optimum dose of heparin administration after IAT is unclear, some reports suggest that excessive heparin dosage should be avoided. In the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries trial (GUSTO-I), an activated partial thromboplastin time (APTT) of greater than 70 seconds was significantly related to increased mortality. It was found that the influence on mortality was related mainly to the occurrence of reinfarction, especially after the discontinuation of intravenous heparin, but was only partially related to intracranial hemorrhages or other serious hemorrhagic events[20)]. Our results support the hypothesis that intravenous heparin can be an effective adjunctive therapy in IAT for acute cerebral infarction.

Our study has some limitations. First, 6 patients had protocol violations, including 4 patients in whom IAT was completed more than 6 hours after the onset of symptoms and 2 patients in whom IAT was commenced more than 6 hours after the onset of symptoms. However, we included these patients in order to estimate practical indicators for prognosis, because these kinds of protocol violations can sometimes occur in

clinical practice and may affect the prognosis. Second, the primary physician decided whether to administer the intravenous heparin after IAT in a given patient based on conditions such as the degree of neurological deficits after IAT, the amount of urokinase administration in IAT, the size of the irreversible ischemic area after IAT, and so on ; these decisions may have resulted in a selection bias. Third, a small number of patients (28, attends) were evaluated by univariate analysis in our study. The inclusion of a larger number of patients and the use of multivariate analysis are necessary to establish the prognostic factors.

In conclusion, it is well known that IAT can dramatically improve functional recovery in cases of acute cerebral infarction. To further improve prognosis, it is important to establish a comprehensive strategy of treatment that includes adjunctive therapy.

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SELECTED ABBREVIATIONS AND ACRONYMS :

IAT = intraarterial therapy
ICH = intracranial hemorrhage
mRS = modified Rankin Scale
IA = intraarterial
MCA = middle cerebral artery
DWI = diffusion-weighted images
PTA = percutaneous transarterial angioplasty
rtPA = recombinant tissue plasminogen activator
AHA = American Heart Association
APTT = activated partial thromboplastin time