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Original Research

Initial experience of balloon catheter disruption of the thrombus in an unrecanalized intracranial artery after intravenous recombinant tissue plasminogen activator

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●Abstract●

Objectives: This report documents initial experiences with balloon catheter disruption (BCD) of a thrombus for an unrecanalized intracranial artery, even after intravenous recombinant tissue plasminogen activator (IV-rtPA).

Methods: From August 2006 to February 2008, 12 patients with acute major vessel occlusion underwent IV-rtPA, and recanalization of the affected artery was not obtained in 8 patients. Seven of these 8 patients underwent BCD immediately after the completion of continuous rtPA infusion without the addition of thrombolytic agents.

Results: Of the 7 patients that underwent BCD, 4 patients (57%) showed complete or partial recanalization and relatively favorable clinical outcomes were obtained compared to patients without recanalization. No technical complications were observed in these patients.

Conclusions: Although the number of patients was limited, intra-arterial rescue therapy, BCD, may be effective for patients with an unrecanalized intracranial artery after IV-rtPA therapy.

●Key Words●

acute stroke, endovascular therapy, recanalization, tissue plasminogen activator

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Introduction

Intravenous (IV) administration of recombinant tissue plasminogen activator (rtPA) for hyperacute stroke was approved in Japan in October 2005, based on the National Institute of Neurological Disorders and Stroke (NINDS) rtPA study[21)] and Japan Alteplase Clinical Trial (J-ACT)[23)]. Introduction of IV-rtPA has had a great impact on early treatment for acute stroke in Japan.

However, the NINDS study included all ischemic stroke subtypes and no continuous vascular monitoring was performed[21)]. Early recanalization after IV-rtPA therapy has been recently shown to correlate with a smaller infarct size[8,14-16,23)]. In addition, the timing of arterial recanalization is also correlated with clinical recovery from stroke[1,4,8,10,23)]. More recently, rescue recanalization therapies after IV-rtPA, such as mechanical thrombectomy or additional intra-arterial (IA) infusion of thrombolytic agents, have been reported to be effective[7,9,11,13,17)].

In our institute, cerebral angiography has been performed for all patients before and after IV-rtPA therapy in order to determine whether the affected artery is recanalized after treatment, as the dosage of rtPA approved in Japan is less than that of the NINDS protocol. In addition, as an intra-arterial rescue treatment, balloon catheter disruption (BCD) of the thrombus was performed in 7 patients whose occluded artery was not recanalized after IV-rtPA therapy. To our knowledge, this is the first report of BCD as rescue therapy after IV-rtPA in Japan.

The purpose of this study was to determine the recanalization rate of the major intracranial artery after IV-rtPA, plus to evaluate the feasibility, safety, and efficacy of rescue BCD after IV-rtPA for hyperacute ischemic stroke.

Methods and Materials

1. Patients and treatment protocol

From August 2006 to February 2008, regular IV-rtPA therapy was performed for 12 patients with acute major vessel occlusion according to the standard protocol in Japan (0.6mg/kg dose, 10% bolus, 90% continuously infused over 60 minutes)[24)].

However, recanalization of the affected artery on the

Table 1 Summary of the patients with unrecanalized vessels on the angiogram just after intravenous rtPA infusion

Case No.	Age	Sex	Time to tPA (min)	NIHSS score	Occlusion side	Occlusion site	TIMI grade 1 hour after tPA	BCD	TIMI grade after BCD	mRS at 1 month
1	56	f	69	11	right	M1	0	yes	3	0
2	71	m	105	9	left	M1	0	yes	3	0
3	64	m	116	26	left	M1	0	yes	2	2
4	59	m	120	16	left	M1	0	yes	2	1
5	57	f	164	20	left	M1	0	yes	0	4
6	80	m	135	11	left	M1	0	yes	0	5
7	70	f	155	21	left	IC	0	yes	0	dead
8	70	m	175	21	right	M2	0	no	-	5

Note BCD : balloon catheter disruption, IC : internal carotid artery, M1 : M1 segment of the middle cerebral artery, mRS : modified Rankin Scale, NIHSS : National Institute of Health Stroke Scale, TIMI : Thrombolysis in Myocardial Infarction, tPA : tissue plasminogen activator.

angiogram just after completion of IV-tPA infusion was not obtained in 8 of 12 patients (67%) in the present study (**Table 1**). In our institute, IA rescue therapy, BCD of the intraluminal thrombus was approved by the institutional review board. Therefore, when the affected artery was not recanalized on the angiogram at the end of rtPA infusion, BCD was immediately performed without the addition of thrombolytic agents.

Of the 8 patients with unrecanalized vessels after IV-rtPA, 7 patients underwent BCD (Cases 1-7, **Fig. 1**). BCD was not performed in a patient (Cases 8) due to refusal of family members.

2. BCD procedure

A 6 Fr angiosheath was newly inserted into the femoral artery, as cerebral angiography was usually performed transbrachially. After administration of intravenous heparin, a 6 Fr guiding catheter was introduced into the internal carotid artery (ICA) of the affected side. A double-lumen percutaneous transluminal angioplasty (PTA) balloon (Gateway, Boston Scientific, Fremont, CA, USA) measuring 2.0 or 2.5mm in diameter or a single-lumen compliant balloon catheter (Sentry, Boston Scientific; Hyperglide, ev3 Neurovascular, Irvine, CA, USA) was navigated into the occluded vessel. These balloons were carefully inflated over 1 minute with less than 2 atm, or with minimal hand pressure to avoid vessel injury. Regardless of balloon type, angiography was performed to observe recanalization of the vessel after each inflation/deflation of the balloon. When the thrombus was moved to the M2 segment, this procedure was repeated at the new occlusion site using a smaller-sized balloon if possible. However, when the thrombus moved to the M3 segment or no flow was observed after 3 attempts at appropriate inflation at the target site, then no more balloon inflation was performed. In this study, no additional thrombolytic agent was administered intra-arterially. A hemostatic device (Angio-Seal, St Jude Medical, St. Paul, Minnesota, USA) was used for the puncture site of the femoral artery.

3. Postprocedural assessment

Recanalization of the target vessel was assessed on angiograms obtained just after the procedure, according to Thrombolysis in Myocardial Infarction (TIMI) grades[22], as follows: no perfusion, TIMI grade 0; minimal perfusion, 1; partial perfusion, 2; and complete perfusion, 3. A CT scan was routinely obtained just after and within 24 hours after the procedure to evaluate postprocedural hemorrhage and infarction. The outcome was assessed by neurosurgeons, with a clinical examination at 1 month after the procedure, using the modified Rankin scale (mRS).

Results

In the 7 patients that received BCD (Cases 1-7, **Fig. 1**), partial to complete recanalization (TIMI grade 2-3) was obtained in 4 of 7 patients (57%). The neurological outcome of these patients with recanalization (Cases 1-4) was relatively favorable compared to patients without recanalization after BCD (Cases 5-7), or without BCD (Cases 8). On the other hand, in 3 of the 7 patients, recanalization was not obtained, even after BCD. Reasons were remaining thrombus despite balloon disruption in 2 cases, and unable to penetrate the thrombus by a guidewire in one case. The reason for poor prognosis in Case 7 was severe

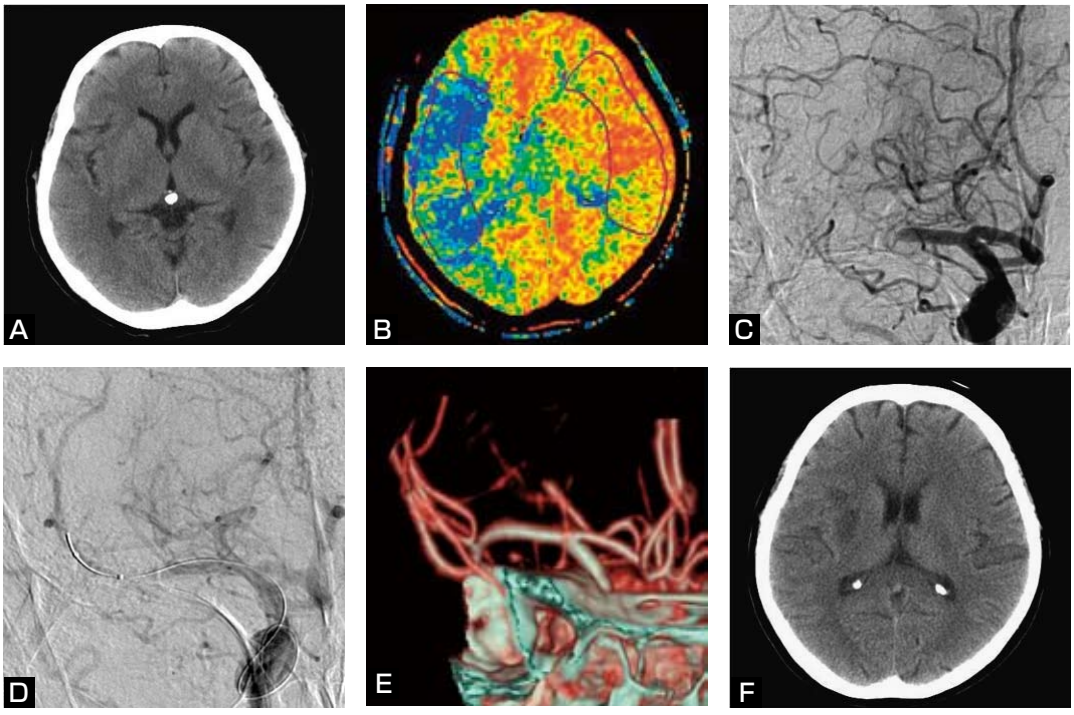

Fig. 1 Case 1. A 56-year-old female

A : An initial CT scan showing no low density area in the right frontal lobe.
B : A pretreatment perfusion CT showing marked elongation of the mean transit time in the right MCA territory.
C : A right carotid angiogram just after IV-rtPA continuous infusion showing occlusion of the MCA.
D : A right carotid angiogram showing antegrade flow in the MCA after balloon angioplasty.
E : A 3D-CT angiogram after the procedure showing complete recanalization of the right MCA.
F : A CT scan obtained 1 day after treatment showing a limited low density area in the right MCA territory.

brain swelling due to cerebral infarction in the ICA territory. There were no serious technical complications, such as intracranial hemorrhage, in this series.

Discussion

In our early experience, recanalization rate just after IV-rtPA therapy was low (33%) (unpublished data). Similar recanalization rates, 22-34%, after IV-rtPA therapy, have previously been reported[4,10]. Early recanalization correlates with a favorable outcome[1,10,23], and various IA rescue therapies have been attempted[7,9,13,15,17]. In the present study, 4 of 7 patients (57%) that received BCD showed partial to complete recanalization, and the clinical outcome of these patients was relatively favorable (**Table 1**). These results suggest that BCD is a potentially useful rescue therapy for patients that do not respond to IV-rtPA treatment. However, appropriate timing and method of rescue therapy still need to be characterized.

1. Timing to initiate rescue recanalization therapy

An ideal time to initiate rescue therapy is when brain exposed to hypoperfusion is reversible and thrombolytic effect of rtPA administered intravenously is reduced. In local IA thrombolysis, 6 hours after ischemic symptom onset is the generally accepted therapeutic window[4,12]. Ribo et al. reported that the recanalization rate rapidly decreased after IV-rtPA therapy, based on monitoring with transcranial Doppler ultrasound, and suggested that rescue reperfusion therapy should be considered if no flow improvement is observed by 60 minutes after the rtPA bolus injection, i.e., just after continuous infusion of the rtPA[15]. Therefore, the same timing was set for the present study. However, Qureshi et al. and Sugiura et al. reported more aggressive trials in which mechanical disruption was started as soon as IV-rtPA bolus injection was administered[13,20].

Above all else, it is most important to elucidate the recanalization rate of the major artery occlusion and clinical outcome of the current IV-rtPA protocol in Japan. Based on these results, appropriate timing for IA recanalization therapy will be determined.

2. Other additional therapies in conjunction with IV-rtPA

Various additional therapies other than mechanical disruption in conjunction with IV-rtPA have been reported:

1) IA injection of thrombolytic agents with IV-rtPA[5,7,11], and 2) mechanical thrombus removal[2,3,6,18,19].

1) IA injection of thrombolytic agents with IV-rtPA[5,7,11,17]

In the Emergency Management of Stroke (EMS) bridging trial, combined IV/IA treatment provided better recanalization, but was not associated with improved clinical outcomes[11]. In the Interventional Management of Stroke (IMS) study[5], patients had a significantly better outcome at 3 months than NINDS placebo-treated subjects for all outcome measures. However, Kim et al. reported efficacy of rescue localized IA thrombolysis for non-responsive patients after IV-rtPA therapy[7]. Shaltoni et al. also reported efficacy and safety of IA thrombolysis after full-dose IV-rtPA, but that symptomatic intracranial hemorrhage occurred in 4 of 69 (5.8%) patients; 3 of which were fatal[17]. It is therefore necessary to perform a randomized trial of standard IV-rtPA compared to a combined IV/IA approach.

2) Mechanical thrombus removal after IV-rtPA[2,3,7,9,18,19]

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial reported efficacy of the Merci Retriever for opening intracranial vessels in patients ineligible for IV-rtPA within 8 hours of stroke symptom onset[18]. This trial demonstrated that mechanical thrombectomy after IV-rtPA is as safe as mechanical thrombectomy alone[19]. Thrombus removal is theoretically more effective than other treatments and is a mainstream therapy in Europe and the USA, but is not currently available in Japan. If this device is approved in Japan, it is expected to become a powerful tool for patients with a thrombus non-responsive to either thrombolytic agents or mechanical disruption.

Conclusion

The number of patients with hyperacute ischemic stroke treated by IV-rtPA is increasing in Japan, but its clinical effect on patients with major vessel occlusion is still unknown. It is extremely important to elucidate the recanalization rate of the major artery and clinical outcome after IV-rtPA treatment in the current protocol in Japan. Further efforts are required to assess efficacy and safety of additional therapies after IV-rtPA.

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