Review Article

Endovascular Treatment of Acute Ischemic Stroke: Honolulu Shock and Thereafter

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Recently, use of mechanical clot retrievers for acute stroke has gradually spread. However, 3 recent randomized controlled trials failed to show superiority of endovascular treatment compared to intravenous recombinant tissue plasminogen activator (IV rt-PA) alone or standard care. On the other hand, a Japanese nationwide survey demonstrated the efficacy of endovascular treatment in the IV rt-PA failed and ineligible patients, especially with the proximal artery occlusion such as the internal carotid artery. Earlier initiation and higher reperfusion of endovascular treatment seemed to be the main reason for the better result in this survey compared with the reported randomized studies. Because next-generation devices such as stent retrievers have been shown to provide better effects in terms of clinical outcomes compared with the Merci retriever, the efficacy of endovascular treatment is expected to be confirmed again by randomized controlled trials in the near future. **Key Words:** Acute stroke—clot retriever—tissue plasminogen activator—randomized trial.

Background

Despite the increasing use of intravenous recombinant tissue plasminogen activator (IV rt-PA), the large number of patients deemed ineligible for treatment because of time restrictions, or in whom treatment is ineffective because of cerebral large vessel occlusion, is now becoming recognized as problematic. Endovascular treatment has therefore been performed as rescue therapy in these patients.

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Three randomized controlled trials were recently conducted to evaluate the efficacy of endovascular treatment in acute ischemic stroke,[1-3] but failed to show the superiority of endovascular treatment, a finding now called as the "Honolulu shock." This article analyzes the results of those randomized trials and discusses the future of treatment for these patients.

Problems with IV rt-PA

One problem with IV rt-PA is the large number of patients who are ineligible for treatment. Less than 5% of all patients with acute ischemic stroke are eligible for treatment with IV rt-PA. In the European Cooperative Acute Stroke Study III randomized trial of patients with a delayed time window for eligibility, IV rt-PA was effective even at 3-4.5 hours after stroke onset.[4] Those results led to a slight reduction in the number of ineligible patients, but major improvement of this issue has not yet been achieved.

Another problem is the low efficacy rate in patients with cerebral large vessel occlusion. In particular, favorable

Table 1. *Summary of 3 recent randomized controlled trials regarding endovascular treatment for acute stroke*

	IMS III			MR RESCUE			SYNTHESIS expansion		
	Endovascular treatment	IV t-PA only	*P*	Endovascular treatment penumbral	Standard care penumbral	*P*	Endovascular treatment	IV t-PA only	*P*
Number of patients	434	222		34	34		181	181	
Favorable outcome*	40.8%	38.7%	.25	21.0%	26.0%	.48	30.4%	34.8%	.37
Mortality	19.1%	21.6%	.52	18.0%	21.0%	.75	14.4%	9.9%	.22
Symptomatic ICH	6.2%	5.9%	.83	9.0%	6.0%	.24	6%	6%	.99

Abbreviations: ICH, intracranial hemorrhage; IMS III, Interventional Management of Stroke III; IV t-PA, intravenous tissue plasminogen activator; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; SYNTHESIS, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke.

*Modified Rankin scale 0-2 in IMS III and MR RESCUE; 0-1 in Synthesis expansion.

outcome rates of only 10%-20% have been reported with internal carotid artery occlusion. In all cases, this was due to a failure to recanalize the occluded vessel,[5] representing a limitation of treatment with IV rt-PA.

Endovascular Treatment

The Merci Retriever was the first thrombus retrieval device, which is indicated within 8 hours of stroke onset in patients with large vessel occlusion or in those ineligible for or in whom IV rt-PA has proven ineffective. In the Multi MERCI trial,[6] the successful recanalization rate (Thrombolysis In Myocardial Infarction score, 2-3) was 68%, and the favorable outcome rate (modified Rankin Scale [mRS], 0-2) after 90 days was 36%. On the other hand, the Penumbra System, which was subsequently approved, achieves recanalization by thrombus aspiration. In a prospective study, the recanalization rate (Thrombolysis In Myocardial Infarction score, 2-3) was 82%, and the favorable outcome rate (mRS 0-2) was 25%.[7] Favorable computed tomography findings at baseline and recanalization within 5 hours were reported as good prognostic factors.[8]

Results of Randomized Controlled Trials

The results of the 3 randomized controlled trials of endovascular treatment in acute ischemic stroke were announced at the 2013 International Stroke Conference held in Honolulu, Hawaii. These included the Interventional Management of Stroke III (IMS-III) study[1] evaluating the effectiveness of endovascular treatment in addition to IV rt-PA, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) study[2] evaluating the effectiveness of endovascular treatment based on imaging diagnosis, and the Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) Expansion study[3] comparing IV rt-PA and endovascular treatment (Table 1).

IMS-III

IMS-III was a multicenter, randomized controlled trial evaluating the effectiveness of endovascular treatment in addition to IV rt-PA.[1] Patients were assigned in a 2:1 ratio to an additional endovascular treatment group and IV rt-PA alone group. The primary end point was the mRS 0-2 rate after 90 days.

The study was expected to enroll 900 patients, but was stopped early after no additional effectiveness was being shown in the results from 656 patients. The primary end point did not differ significantly between groups (additional endovascular treatment group, 40.8%; rt-PA alone group, 38.8%; 95% confidence interval [CI], −6.1 to 9.1). Even in a subgroup analysis comparing mild stroke (National Institutes of Health Stroke Scale score 8-19) and severe stroke (score ≥20), there was still no significant difference. Furthermore, no significant differences were identified in mortality after 90 days ($P = .52$) or the rate of symptomatic intracranial hemorrhage after 30 hours ($P = .83$).

However, the IMS-III study had the following problems: (1) large vessel occlusion was not confirmed in more than half of the enrolled patients; (2) the mean time from IV rt-PA to endovascular treatment was 127 minutes (Table 2); and (3) the recanalization rate (Thrombolysis in Cerebral Infarction [TICI] grade, 2B-3, which means perfusion of half or greater of the vascular distribution of the occluded artery) with endovascular treatment was low, at only about 40% (Table 2).

Based on these results, endovascular treatment should of course target large vessel occlusions, and shortening the time until recanalization and higher rate of recanalization are important to achieve higher recanalization rates.

MR RESCUE

In the MR RESCUE study, patients treated within 8 hours of stroke onset who had large vessel occlusion (anterior circulation only) were evaluated by magnetic resonance imaging perfusion imaging to demonstrate a penumbra region and randomly assigned to an endovascular treatment group or standard treatment group.[2] Outcome was assessed according to the 90-day mRS.

Table 2. *Comparison of time to puncture and reperfusion after endovascular treatment in IMS III, MR RESCUE, and RESCUE-Japan registry*

0	IMS III	MR RESCUE	RESCUE-Japan registry
Onset to puncture		370 minutes	210 minutes
IV t-PA to puncture	127 minutes		70 minutes
Reperfusion: TICI 2B-3*	ICA: 38%M1: 44%	Total: 27%	Total: 53%ICA: 56%M1: 60%

Abbreviations: ICA, internal carotid artery; IMS III, Interventional Management of Stroke III; IV t-PA, intravenous tissue plasminogen activator; M1, middle cerebral artery M1 portion; MR RESCUE, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; SYNTHESIS, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke; TICI, thrombolysis in cerebral infarction.

*TICI 2B, perfusion of half or greater of the vascular distribution of the occluded artery, TICI 3, complete reperfusion.

Also evaluated was whether endovascular treatment was more effective in patients with a larger penumbra (penumbral pattern).

The results showed no difference in mean 90-day mRS score, which was 3.9 in both groups. Moreover, endovascular treatment was no more effective even in the group showing a penumbral pattern. However, this study had the following limitations: (1) the mean time from stroke onset to initiation of endovascular treatment was 370 minutes and (2) the recanalization rate (TICI 2B-3) with endovascular treatment was only 27% (Table 2).

In this study, large vessel occlusion was confirmed by magnetic resonance angiography before randomization, no effectiveness was demonstrated. The reason of failure seemed to be the long time until initiation of endovascular treatment and a low recanalization rate.

SYNTHESIS Expansion

The SYNTHESIS Expansion study randomized patients with acute ischemic stroke within 4.5 hours of onset to endovascular treatment or IV rt-PA.[3] The primary end point was defined as mRS 0-1 after 3 months (Table 2).

The results showed no significant difference between groups in the proportion of patients with a good outcome of mRS 0-1 ($P = .16$). The rate of symptomatic intracranial hemorrhage was 6% in both groups. Median time from onset until initiation of treatment was 3.75 hours in the endovascular treatment group and 2.75 hours in the IV rt-PA group ($P < .001$). Endovascular treatment was thus performed 1 hour later.

The major limitation in the SYNTHESIS study, as in the IMS-III study, was that large vessel occlusion was not confirmed before randomized assignment. Therefore, among the 181 patients in the endovascular treatment group, 165 actually received treatment. Among these, 109 received intra-arterial rt-PA and 56 underwent mechanical thrombolysis. In other words, about 10% of patients did not receive endovascular treatment after randomized assignment, and the modality in two thirds of those patients who did was intra-arterial rt-PA.

These study results, representing the so-called "Honolulu shock," were announced at the 2013 International Stroke Conference. However, all 3 studies had significant flaws in their designs and procedures. By addressing these faults, new directions for better treatment can come into view.

Rescue-Japan Registry

The Rescue-Japan Registry is the first nationwide, prospective registry of acute cerebral large vessel occlusion in Japan.[9] This study was performed to assess the impact of endovascular treatment on clinical outcome following approval of a mechanical clot retriever in Japan. The study demonstrated that endovascular treatment significantly improved clinical outcomes in IV t-PA-failed and -ineligible patients with proximal artery occlusion such as internal carotid artery.

In this registry, endovascular treatment was started much earlier (210 minutes after onset in RESCUE-Japan versus more than 360 minutes in MR RESCUE), and the reperfusion rate was higher than those of IMS III and MR RESCUE (TICI 2b-3: 52.5% in RESCUE-Japan versus 26% in MR RESCUE) (Table 2). The reason for the higher rate of reperfusion in the present study might be due to unlimited use of endovascular devices such as clot retrievers, intracranial/extracranial stents, balloons, thrombolytic agents, and their combinations, whereas a single device was allowed to use in IMS III. Another possible reason is that, in Japan, mechanical clot retrievers are allowed to be used by a board physician of the Japanese Society of NeuroEndovascular Therapy, which requires 100 or more neuroendovascular experience and passing the board examination. These differences should be considered when designing future comparative studies.

New Devices

Currently, the most promising new devices are stent-like thrombus retrieval devices. Stent retrievers allow thrombectomy to be performed by pulling back the deployed stent into the guide catheter, whereby the struts of the stent engage the thrombotic material. The device is applicable repeatedly and can be used even in small peripheral vessel branches. In contrast with conventional stent systems, stent retrievers require no anticoagulation

or antiplatelet treatment because the stent is not deployed permanently.

The main devices are the stent retrievers such as Solitaire (ev3) and the Trevo (Concentric Medical). Multicenter, prospective, randomized controlled trials comparing Solitaire and Merci (SWIFT study)[10] and comparing Trevo and Merci (Trevo 2 study)[11] have already been conducted, and superiority to the Merci Retriever has been demonstrated. Because these new devices achieve higher recanalization rates than previous devices, and the procedure times are shorter, this type of treatment is expected to become mainstream in the future.

Conclusions

Three recent randomized controlled studies found no effectiveness of endovascular treatment in acute ischemic stroke. However, limitations in the 3 studies included that large vessel occlusion was not yet confirmed, initiation of treatment was delayed, and recanalization rates were low. We believe that with the advent of new devices, controlled studies with modified protocols will demonstrate the superior effectiveness of endovascular treatment, thus further advancing the treatment of acute ischemic stroke.

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