



# Clinical Outcomes of Mechanical Thrombectomy for Acute Ischemic Stroke in Transfer Cases

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**Objective:** There are regional disparities in endovascular thrombectomy, and problems with emergency transport systems and hospital collaboration when transferring need to be addressed. In this study, the clinical outcomes of endovascular thrombectomy for transferred patients were analyzed.

**Methods:** Acute ischemic stroke patients who underwent endovascular thrombectomy between January 2016 and March 2019 were enrolled. They were retrospectively reviewed and divided into the direct group and transfer group, and we compared treatment results and clinical outcomes between them.

**Results:** In all, 122 patients met the inclusion criteria, comprising 93 patients in the direct group and 29 patients in the transfer group. The time from onset to door of our hospital was longer in the transfer group than in the direct group (73 minutes vs. 158 minutes,  $P = 0.80$ ), but the time from arrival to reperfusion was significantly shorter in the transfer group (139 minutes vs. 106 minutes,  $P = 0.001$ ). As the time from onset to reperfusion did not differ significantly between the two groups (220 minutes vs. 256 minutes,  $P = 0.60$ ), there was no significant difference in good outcome at discharge (38.7 vs. 41.3%,  $P = 0.79$ ).

**Conclusion:** Clinical outcomes of transferred patients for endovascular thrombectomy may be equivalent to those of directly transported patients. Promoting close hospital cooperation may improve clinical outcomes and resolve regional disparities.

**Keywords** ▶ endovascular thrombectomy, acute stroke, transfer, secondary medical service area

## Introduction

A meta-analysis of several randomized controlled trials (RCTs)<sup>1–5</sup> revealed that the rate of patients with a favorable outcome after the combination of tissue plasminogen activator (t-PA) therapy and mechanical thrombectomy for acute ischemic stroke was higher than that after each therapy alone. Furthermore, the duration of mechanical thrombectomy has been increased based on the results of the Diffusion Weighted Image (DWI) or CTP assessment

with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN)<sup>6</sup> and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DIFFUSE3)<sup>7</sup> studies, and this procedure has been selected as the standard treatment for indicated patients.

On the other hand, there are regional differences in the number of physicians or institutions able to perform mechanical thrombectomy. Patients with large vessel occlusion who are transported to institutions where mechanical thrombectomy cannot be performed must be promptly referred to hospitals where it is possible. A previous study reported the usefulness of the “Drip, Ship and Retrieve” system in which patients for whom mechanical thrombectomy should be indicated are referred to hospitals where this procedure is possible after the start of t-PA therapy.<sup>8</sup>

Several studies reported that the clinical outcome was better in patients with shorter intervals from onset until diagnosis, puncture, and recanalization.<sup>9–11</sup> However, transfer to another hospital requires a longer interval from onset until recanalization than direct transportation, and

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the rate of patients with a favorable outcome after 90 days is significantly lower according to one study.<sup>12)</sup> Which of two systems, “Drip & Ship” and “Mother Ship”, is more advantageous remains controversial.

In this study, we retrospectively examined the results of mechanical thrombectomy for patients referred to our hospital.

## Subjects and Methods

The subjects were 122 consecutive patients who had undergone mechanical thrombectomy at our hospital between January 2016 and March 2019. They were divided into two groups: directly transported patients (direct group) and those referred from other hospitals (transfer group). For initial image assessment, magnetic resonance imaging (MRI) had been selected as a first-choice procedure, but computed tomography (CT)/CT angiography (CTA) was adopted for patients for whom MRI was contraindicated or for those for whom a specific interval was required until imaging. In our hospital, the emergency consultation room is adjacent to the MRI/CT and angiography rooms.

Indication criteria for mechanical thrombectomy included an interval of  $\leq 8$  hours from onset or final onset-free time, a DWI-The Alberta Stroke Program Early CT Score (ASPECTS) of  $\geq 5$ , and the following sites of occlusion: internal carotid artery (ICA), middle cerebral artery M1-M2, basilar artery (BA), or posterior cerebral artery P1.

### Management of directly transported patients

The patients were accepted in the emergency consultation room based on requests on admission from the ambulance crew. After arrival, whether mechanical thrombectomy was indicated was evaluated through image assessment using MRI as a first-choice procedure, and each patient was transferred to the angiography room. The ambulance crew responsible for patient transportation to our hospital did not employ scoring to evaluate large vessel occlusion.

### Management of patients referred from other hospitals

Requests for referral were made through hospital-to-hospital stroke hotlines or telephone contacts mediated by the regional cooperation room or hospital clerks. For patients referred from two affiliated institutions, it was possible to share MRI (DWI, Fluid-attenuated Inversion Recovery (FLAIR), and MRA) information using in-hospital Local Area Network (LAN) prior to arrival. However, there was

no system for sharing images with other institutions, and images from a previous hospital were evaluated after arrival. For some patients, imaging procedures were additionally performed at our hospital. For patients in whom an occluded blood vessel was clear, image reassessment was omitted, and they were admitted to the angiography room. On the other hand, MRI or CT/CTA was performed for those in whom an occluded vessel or indication was unclear, and they were admitted to the angiography room. Informed consent was received after a physician responsible for endovascular treatment or superior physician explained the content of treatment to each patient or his/her family after arrival.

### Mechanical thrombectomy

Mechanical thrombectomy was performed under local anesthesia in all patients. As an access route, right transfemoral approach was adopted. As a rule, a balloon guiding catheter was used. Stent retrievers, such as a Solitaire FR (Medtronic, Minneapolis, MN, USA) and Trevo Provue (Stryker, Kalamazoo, MI, USA), were selected as first options, but each stent retriever was combined with a Penumbra system (Penumbra, Inc., Alameda, CA, USA) when recanalization was not achieved by a single pass or in accordance with individual patients at an appropriate time. Recanalization was evaluated using the Thrombolysis in Cerebral Infarction (TICI) grade. Patients with TICI 2b or 3 recanalization were regarded as achieving effective recanalization.

### Analytical methods

We compared the patient background, treatment methods, recanalization rate, time-related factors, presence of intracranial hemorrhage, and clinical outcomes between the two groups.

Neurological findings were assessed using the National Institutes of Health Stroke Scale (NIHSS). Patients with a modified Rankin Scale (mRS) score of 0 to 2 on discharge from our hospital or referral to other hospitals were regarded as having a favorable outcome. The hospital-to-hospital distance on referral was calculated using Google maps.

The data were compared between the two groups using the chi square test and Mann–Whitney U test. We used JMP10.0 software for statistical analysis (SAS Institute, Inc., NC, USA). A P value of 0.05 was regarded as significant. Prior to this study, its protocol was approved by the ethics review board of our hospital (Approval No.: Shibyo-hatsu No. 13, date of approval: June 24, 2019).

**Table 1** Clinical backgrounds in direct group and transfer group

Variables	Direct (n = 93)	Transfer (n = 29)	P value
Age, median (IQR), y	77.0 (69–85)	79.0 (74–86)	0.60
Male sex, n (%)	51 (54.8)	14 (48.2)	0.53
Pre-stroke mRS 0-1, n (%)	82 (88.1)	22 (75.8)	0.097
Occlusive artery, n(%)			
ICA	30 (30.0)	9 (30.0)	1
MCA M1	48 (48.0)	16 (53.3)	0.60
BA	5 (5.3)	3 (10.3)	0.31
Clinical characteristics, median (IQR)			
NIHSS score on admission	17 (12–23)	20 (16–22)	0.16
DWI-ASPECTS	8 (6.5–9)	7 (5–8.2)	0.10
*n	n = 78*	n = 22*	
IV-tPA therapy, n(%)	53 (56.9)	12 (41.3)	0.14

\*Number of patients evaluated using DWI-ASPECTS. BA: Basilar artery; DWI-ASPECTS: diffusion-weighted MRI Alberta Stroke Program Early CT Score; ICA: internal carotid artery; IQR: interquartile range; MCA: middle cerebral artery; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; TICl: Thrombolysis in Cerebral Infarction; tPA: tissue plasminogen activator

**Table 2** Clinical outcome in direct group and transfer group

Variables	Direct (n = 93)	Transfer (n = 29)	P value
Time parameters, min, median (IQR)			
Onset to door	73 (45–200)	158 (75–283)	0.80
Door to puncture	80 (63–93)	59 (45–72)	0.001
Door to reperfusion	139 (113–165)	106 (82–135)	0.001
Onset to reperfusion	220 (160–343)	256 (213–400)	0.60
Successful reperfusion (TICl2b≥), n (%)	73 (78.0)	24 (82.7)	0.61
median mRS at discharge	4 (2–4)	3 (2–4)	0.88
mRS, n (%)			
0–2 (independent)	36 (38.7)	12 (41.3)	0.79
3–5 (disabled)	51 (54.8)	15 (51.7)	0.76
6 (dead)	6 (6.4)	2 (6.8)	0.93
Reperfusion hemorrhage, n (%)			
Any type of hemorrhage	21 (22.5)	8 (27.5)	0.58
Symptomatic ICH	2 (2.1)	2 (6.8)	0.21

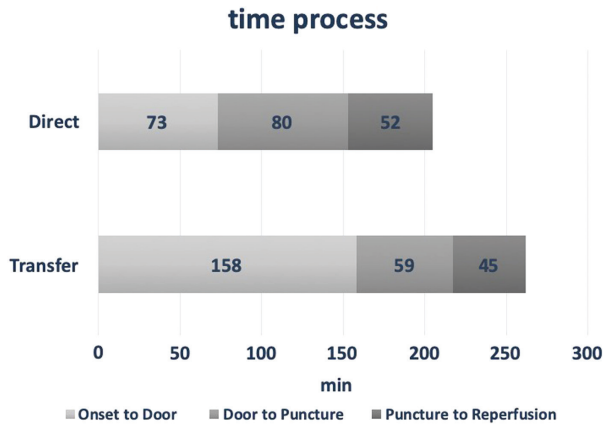
ICH: intracerebral hemorrhage; IQR: interquartile range; mRS: modified Rankin Scale; TICl: Thrombolysis in Cerebral Infarction

## Results

The subjects consisted of 93 patients in the direct group and 29 in the transfer group. Of the 29 patients in the latter, 12 had been hospitalized in other hospitals, and 2 developed acute ischemic stroke upon consulting the outpatient clinic of a previous hospital. Furthermore, the 29 patients were referred from a total of 13 institutions, with a median transfer distance of 7.2 km (1.4–12.2 km). On all referred patients, mechanical thrombectomy was performed, but one with low DWI-ASPECTS on arrival was excluded from this study.

The patient background in the direct and transfer groups is presented in **Table 1**. In the transfer group, patients under treatment for cerebral infarction or heart failure in

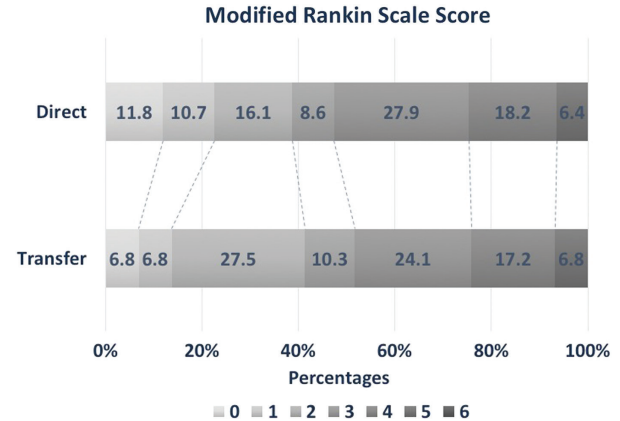
other hospitals were included, and the rate of patients with an mRS score of 0 to 1 before onset was lower, but there was no significant difference (88.1 vs. 75.8%, respectively,  $P = 0.09$ ). There were no significant differences in any other parameter. In the direct group, t-PA therapy was combined with mechanical thrombectomy in 53 patients (56.9%), but of them, t-PA was not administered to 9 mild-status patients with an NIHSS score of  $\leq 4$  or requiring careful administration due to a history of trauma or to 2 in whom loading with two antiplatelet drugs was conducted in the initial phase, considering emergency carotid artery stenting (CAS). In the transfer group, t-PA therapy was performed for 12 patients (41.3%), but 1 was referred from a previous hospital after t-PA therapy (Drip & Ship).



**Fig. 1** Time course of the direct group and transfer group. The time from onset to door of our hospital was longer in the transfer group than in the direct group. The time from arrival to puncture was significantly shorter in the transfer group than in the direct group. Thus, the time from onset to reperfusion did not differ significantly between the groups

The time courses in the direct and transfer groups are presented in **Table 2** and **Fig. 1**. The median onset-to-door time (O2D) was 73 and 158 minutes, respectively (interquartile range: 45–200 and 75–283 minutes, respectively,  $P = 0.80$ ); a longer time was required in the transfer group, but there was no significant difference. On the other hand, the median door-to-reperfusion time (D2R) was 139 and 106 minutes, respectively (113–165 and 82–135 minutes, respectively,  $P = 0.001$ ); it was significantly shorter in the transfer group. Furthermore, the median onset-to-reperfusion time (O2R) was 220 and 256 minutes, respectively (160–343 and 213–400 minutes, respectively,  $P = 0.60$ ); there was no significant difference. There was no significant difference in the TICI 2b or higher reperfusion rate (78.0 vs. 82.7%, respectively,  $P = 0.61$ ). There was no significant difference in the rate of patients with a mRS score of 0 to 2 (favorable outcome) on discharge between the two groups (38.7 vs. 41.3%, respectively,  $P = 0.79$ , **Table 2** and **Fig. 2**). In the transfer group, patients referred under a diagnosis of large vessel occlusion from previous hospitals accounted for 37.9% (11/29). In nine of them, image assessment after arrival to our hospital was omitted, and the median D2R was 75 (65–112) minutes. For the other two patients, mechanical thrombectomy was performed after reassessment using MRI (DWI and FLAIR), and the median D2R was 90 (88–92) minutes.

The transfer group was divided into three subgroups based on the distance of transportation: <10 km, 18 patients; <20 km, 7 patients; and  $\geq 20$  km, 4 patients. Of these patients, 11 were transported beyond the secondary medical area. In the <10 km and <20 km groups, the median O2D



**Fig. 2** Distribution of modified Rankin Scale scores at discharge in the direct group and transfer group

was 114 and 175 minutes, respectively (70–227 and 138–322 minutes, respectively,  $P = 0.08$ ); a longer time was required in the latter. In the  $\geq 20$  km group, it was 251 (120–372) minutes; the time was further prolonged (**Fig. 3**).

In the <10 km and <20 km groups, the median O2R was 252 and 270 minutes, respectively (214–351 and 211–407 minutes, respectively,  $P = 0.45$ ); there was no significant difference. When comparing the former with the  $\geq 20$  km group, it was 252 and 348 minutes, respectively (214–351 and 220–461 minutes, respectively,  $P = 0.34$ ); a longer time was required in the latter, but there was no significant difference (**Fig. 3**).

On the other hand, when examining the mRS score on discharge with respect to the distance of transportation, there were no distance-related differences in the outcome. Of the 11 patients transported beyond the secondary medical area, the outcome was favorable in 4 (36%) (**Fig. 4**).

## Discussion

Several studies have suggested that the outcomes of patients referred from other hospitals are less favorable than those of directly transported patients.<sup>4,12</sup> The Systematic Evaluation of Patients Treated With Stroke Devices for Acute Ischemic Stroke Registry (STRATIS) registry found that the O2R for patients directly transported to a comprehensive stroke center (CSC) was shorter than that for those transported via a primary stroke center (PSC), and that the rate of patients with a favorable outcome after 90 days was significantly higher in the former.<sup>12</sup> Assuming that all patients referred from other hospitals were directly transported, it was estimated that mechanical thrombectomy could have been started 91 minutes earlier, suggesting the

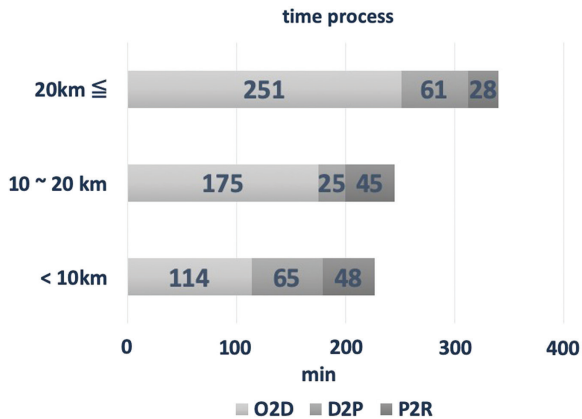


Fig. 3 Time course of the transfer group classified by transfer distance

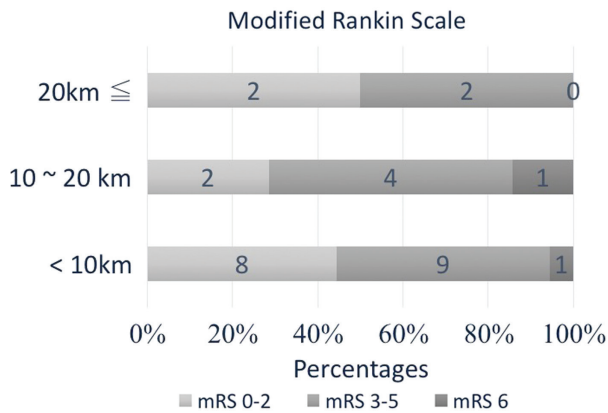


Fig. 4 Distribution of modified Rankin Scale scores at discharge in the transfer group classified by transfer distance

necessity of arranging a direct CSC transportation system. Furthermore, the SWIFT PRIME subanalysis also suggested the usefulness of direct transportation.<sup>4)</sup> Concerning the “Drip & Ship” system, the incidence of symptomatic intracranial hemorrhage is high (5.7%), and the hospital mortality rate is high (10.9%).<sup>13,14)</sup>

On the other hand, in our study, there was no difference in the rate of patients with a favorable outcome between the direct and transfer groups. This may have been because there was no difference in the O2R. Hiyama and Aoki et al. also reported that there was no difference in the rate of patients with a favorable outcome by maintaining an O2R similar to that for directly transported patients for those referred from other hospitals. In this study, there was only one “Drip & Ship” patient, but the O2R for patients referred from other hospitals and the rate of patients with an mRS score of 0 to 2 (favorable outcome) were similar to those previously reported in Japan.<sup>8,15)</sup>

For 38% of the patients in the transfer group, the D2P and D2R were shortened by omitting imaging procedures after arrival. As other factors to shorten the time, patient information (image data and medical history) was shared among physicians/nurses/hospital clerks before arrival for patients referred from other hospitals, facilitating the preparation of devices, such as sheaths and guiding catheters, in the angiography room/waiting by physicians responsible for endovascular treatment, pre-arrival indication of a flow from arrival until admission to the angiography room and necessary examinations, and preparation of articles for treatment and drugs by co-medical staff such as nurses. A previous study reported a protocol for shortening the time for patients referred from other hospitals<sup>15)</sup>; therefore, at our hospital, a protocol regarding patients referred from other hospitals must be prepared. The clinical outcomes were reported to be poor at a transportation distance of >20 km,<sup>16)</sup> but as for why there were no differences in the O2R or rate of patients with a favorable outcome in our study, the median distance of transportation was 7.2 km, being relatively short. On the other hand, the O2D and O2R slightly increased according to the distance of transportation. If the number of patients increases in the future, there may be transportation-distance-related differences in the prognosis.

In the transfer group, there was only one “Drip & Ship” patient, but this was because the previous hospital was not a stroke-specializing institution responsible for t-PA therapy. To perform t-PA therapy even in regional stroke-specialist-free hospitals, the establishment of a telestroke network is recommended by the 2018 The American Heart Association and American Stroke Association (AHA/ASA) guidelines.<sup>17)</sup> Patient transportation/mechanical thrombectomy after the start of t-PA therapy using telemedicine has been reported.<sup>18)</sup> This issue should be examined in the future.

Furthermore, attempts to shorten the O2R for patients referred from other hospitals have been reported. Aoki et al. presented initial evaluation free patient transfer to the angiography room through ambulance acceptance in the CT room.<sup>15)</sup> Jadhav et al.<sup>19)</sup> shortened the O2P through ambulance acceptance in the angiography room without performing cephalic imaging procedures.

In the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES) study, the interval from onset until recanalization for “Drip & Ship” patients was ≥2 hours longer than that for directly transported patients, suggesting an insufficient patient transportation system.<sup>20)</sup>



The time may be shortened by omitting/simplifying the preparation of medical information-providing documents or image data at hospitals from which patients are referred. In the future, the O2D must be shortened by preparing a transfer protocol for mechanical thrombectomy with hospitals from which patients are referred or standardizing an informed consent form.

In this study, Endovascular Therapy (EVT) was performed on all patients referred from other hospitals. However, mechanical thrombectomy may not be indicated for the following patients through image reassessment after arrival, and this must be considered between hospitals when referring patients: patients with symptom amelioration and recanalization, those with symptom exacerbation and enlargement of an infarcted focus (DWI-ASPECTS: <5), and those with a transportation time of  $\geq 90$  minutes.<sup>21)</sup>

Strategies for stroke care consolidation were presented by affiliated societies, but “medical areas free from specialists in neuroendovascular treatment” reportedly account for 36.5% (61/167). Indeed, there are regional differences in the distribution of such specialists who are unevenly distributed in urban areas.<sup>22)</sup> The referral/transportation system plays a role in the correction of disparities.

This study has three limitations. First, the median O2D in the transfer group was 158 minutes (short). The subjects included patients who had been hospitalized in previous hospitals and those who developed acute ischemic stroke on consultation at the outpatient clinic of the previous hospital. In addition, the distance of transportation was relatively short. These factors may have influenced the results; the O2D was shorter than that previously reported in Japan for patients referred from other hospitals.<sup>8,15)</sup> Second, the patients in the transfer group included those who had been hospitalized due to other diseases, and the rate of patients with a pre-mRS score of 0 to 1 was low. Third, this was a single-center retrospective study. For patients referred from other hospitals, outcomes of mechanical thrombectomy similar to those of directly transported patients may be obtained. Increased cooperation with hospitals in adjacent areas may further shorten the time, improving the results of treatment.

## Conclusion

For patients referred from other hospitals, outcomes of mechanical thrombectomy similar to those of directly transported patients may be obtained. Close hospital cooperation may further improve the results of treatment, reducing regional differences in stroke care.

## Disclosure Statement

We declare no conflict of interest.

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