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Efficacy of "drive and retrieve" as a cooperative method for prompt endovascular treatment for acute ischemic stroke

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Abstract

Background and purpose—

Outcomes of endovascular treatment for acute ischemic stroke depend on the time interval from onset to reperfusion. Although the centralized “mothership” method is considered preferable, the required transportation time increases the risk that a stroke patient may not receive intravenous or endovascular therapy. In contrast, “drive and retrieve” describes a system wherein doctors from comprehensive stroke centers travel to primary stroke centers and provide endovascular treatment for acute ischemic stroke. In this report, we verified the effects of this novel collaboration among facilities.

Methods—

This nonrandomized, single-arm study retrospectively analyzed patients who met the inclusion criteria for endovascular treatment provided through a drive and retrieve system. Among the 122 patients treated via this system, we analyzed the time of onset to recanalization as the primary outcome. We also analyzed the efficacy of the drive and retrieve system using geographic information system analysis.

Results—

The median time from onset to recanalization was 229 minutes (interquartile range: 170–307 min, 95% confidence interval: 201–252 min). The upper limit of the 95% confidence interval for the time from onset to recanalization was shorter than the median times reported in two previous trials. Geographic information system analysis revealed an upward trend in the population coverage rate in each secondary medical area after the drive and retrieve method was introduced.

Conclusion—

The drive and retrieve method may be an effective form of cooperation between facilities located within 1 hour of a comprehensive stroke center.

Introduction

Endovascular thrombectomy is an effective treatment for patients with acute ischemic stroke (AIS) with major vessel occlusion [1-5]. However, successful outcomes depend on the time from onset to reperfusion[6]. A subanalysis of the Hermes collaboration found that outcomes following endovascular treatment were superior to those of standard medical treatment within 7.3 hours from onset to puncture[7]. Furthermore, a subanalysis of the MR CLEAN trial demonstrated that endovascular treatment was effective if the time from onset to reperfusion was within 6 hours, 18 minutes, and the absolute difference in the risk of achieving a higher modified Rankin score (mRS) decreased by an average of 6.4% for every 1-hour delay in reperfusion[8]. Therefore, a system of medical cooperation that specializes in endovascular treatment for AIS is needed to ensure prompt treatment initiation and to reduce the time from onset to reperfusion.

Several potential cooperative systems have been proposed including the "drip and ship method"[9-11], although studies have reported better results with centralized direct transport ("mothership" method) because of the required time for transportation[12] and potential reductions in mortality rates[13]. However, full centralization throughout our country is currently difficult because of economics and lack of personnel. An additional limitation is that the mothership method could potentially prevent stroke patients from receiving intravenous or endovascular therapy because of the longer distances and travel times[14].

Our country also faces challenges related to the ambiguous distinction between primary stroke centers (PSCs) and comprehensive stroke centers (CSCs), which is attributed to a failure of the national health system to clearly define each type of center. Furthermore, many PSCs have access to angiography equipment 24 hours per day, but facilities lack a certified neurointerventionist who has completed the required and lengthy training and thus, many centers cannot currently administer endovascular treatment. Despite this limitation,

many PSCs in our country are currently equipped with facilities and other staff that meet the requirements for a CSC. This has led to the construction of a collaborative system wherein neurointerventionists travel from CSCs to PSCs to perform endovascular treatment ("drive and retrieve" method).

The efficacy of the drive and retrieve method relative to the drip and ship and mothership paradigms remains unclear. In this report, we describe the drive and retrieve system and verify the effects of this novel collaboration on outcomes in patients with AIS.

Materials and methods

Study design

This study was approved by the Institutional Review Boards of the participating institutes. All patients provided written informed consent. This retrospective, nonrandomized, single-arm study was based on the effective zone for mobile stroke team (EZO) trial. The primary aim of the current study was to show that our mobile stroke team could treat AIS patients with endovascular thrombectomy within a reasonable time. The secondary aim of this study was to map the effect of the drive and retrieve method using a geographic information system (GIS).

Inclusion criteria

The EZO trial registry includes patients who underwent endovascular treatment via the drive and retrieve system from July 2015 to March 2016. Patients with AIS and major vessel occlusion in the internal carotid artery, middle cerebral artery horizontal portion (M1), insular portion (M2), or basilar artery, with symptom-diffusion mismatch at the initial institution were treated with endovascular thrombectomy. The inclusion criteria were as follows: age > 20 years and National Institutes of Health Stroke Scale score > 8 points.

We left additional inclusion criteria to the discretion of each facility.

Exclusion criteria

We excluded patients who received endovascular treatment via drip and ship or mothership systems.

Facilities

Facilities were required to meet the following conditions to participate in the EZO registry: designated stroke center located within a 60-km radius around our city (drive time: ~1 hour), availability of recombinant tissue plasminogen activator, endovascular equipment for catheter thrombectomy, and enough paramedical staff to perform thrombectomy 24 hours per day. When we initiated research in 2015, 10 affiliated institutes fulfilled these conditions; however, at that time only three institutes employed neurointerventionists. Accordingly, these three institutes supported the institutes without neurointerventionists by helping them perform procedures using the drive and retrieve method. All institutes were located within a 1-hour drive of an institute with a staff neurointerventionist.

Drive and retrieve protocol

The neurointerventionists' weekly schedules were updated and distributed to the participating institutions by e-mail. Patients were transferred to PSCs mainly by ambulance. If a staff physician diagnosed AIS requiring endovascular treatment, they consulted the neurointerventionists' weekly schedules and called the appropriate individual. If available, the neurointerventionist evaluated the imaging data via telemedicine. If a telemedicine system was not available, physicians at the PSC made decisions regarding the use of endovascular recanalization treatment. Simultaneously, the interventionist began to travel to the relevant PSC, and the doctor at the PSC began preparations for endovascular recanalization treatment, such as performing a femoral puncture, setting up a continuous saline infusion pump and

guiding catheter, inserting the guiding catheter into the carotid artery, and preparing the thrombectomy device. The PSC physicians received off-the-job training in these preparations, which do not require a high level of experience with endovascular treatment. Upon arrival at the PSC, the neurointerventionist initiated the endovascular recanalization treatment.

Study variables

We evaluated the time from onset to recanalization as the primary outcome. Other procedural time courses, including the time from onset to door, door to imaging, door to puncture, onset to puncture, and puncture to recanalization, were evaluated as secondary outcomes. Additionally, we evaluated patients' background data, pretreatment Alberta Stroke Program Early CT (ASPECT) scores, occluded vessel sites, thrombolysis in cerebral infarction grades after embolectomy, and mRS scores 90 days after onset.

Geographic Information System (GIS)

We calculated the population of individuals (aged ≥ 65 years) who resided inside the service areas of facilities providing mechanical thrombectomy and used the calculated percentage for each secondary medical area as an evaluation index of spatial accessibility. Based on previous research, we defined the service areas as the driving times that allowed for transportation to medical facilities within 30-, 60-, and 90 minutes[15]. We used the ArcGIS 10.5 Network Analyst (SRI, Redlands, CA, USA) to determine the ranges of facilities providing mechanical thrombectomy and the ArcGIS Data Collection Road Network 2012 Hokkaido regional version (Esri Japan Corporation, Tokyo, Japan) to obtain information about roadways, as described previously[16].

The target population was defined as individuals aged ≥ 65 years with a high incidence of cerebral infarction. We applied a 1-km^2 mesh based on the 2010 census to the target area

and performed intersect processing to extract overlapping regions that fell within the 30-, 60-, and 90-minute driving times and secondary medical areas. As a result, we obtained the population of individuals aged ≥ 65 years for the calculated area. We then calculated the proportions of individuals aged ≥ 65 years who resided within 30-, 60-, and 90-minute driving times. In cases involving a partial overlap between the driving-time area and the mesh, the total population of the mesh was added because even if the total population is the largest estimate, if the value is low, the impact on health policy makers is high.

Statistics

We performed a statistical power simulation to calculate the required number of patients to reach significance. We adopted the variables in the Multi MERCI study [17] to set the threshold for the median time from puncture to recanalization because we planned the current study prior to the publication of a major randomized clinical trial (RCT), and our study was not an RCT. Multi MERCI was the largest retrospective cohort study at that time. In addition, it was difficult to set the number of patients because the data distribution was unknown, with only median values reported previously, which was another reason we adopted the variables in the Multi MERCI study. According to the Multi MERCI study, the median time (interquartile range) from puncture to recanalization was 96 minutes (range, 18–282 minutes)[17], and the median time (interquartile range) in a pilot study by our group performed in a single facility was 76 minutes (range, 57.5–99.5 minutes) (data not published). In the current study, we set 96 minutes as the threshold for the median time from puncture to recanalization. A 95% confidence interval (CI) upper limit of the median value below the threshold indicated efficacy of the drive and retrieve system. Because the current study was performed at multiple facilities, we set the number of patients by simulation assuming that the required number, with a median time (interquartile range) of 86.5 minutes

(range, 65.0–117.0 minutes), which was above the median of the pilot studies, was approximately twice as large as that of the pilot study. Based on 100 000 simulations, more than 99 patients were required to confirm the probability that the 95% CI upper limit of the median value would fall below the threshold to ≥ 90%. Considering a slight dropout rate, the target sample size was set at 110 patients.

Continuous variables are expressed as mean ± standard deviation. For time courses, we calculated the medians and 95% CIs and compared the upper limit of the 95% CIs from the current study with the medians reported in five previous major RCTs. If our upper limit was lower than the previous medians, we concluded that our time course was comparatively shorter than those in the RCTs.

Results

Demographics and baseline characteristics

Patients' demographics are listed in Supplemental Table 1.

Ten patients were excluded because they had received treatment in either a mothership or drip and ship system. A final total of 122 patients with a mean age of 79 ± 11 years were deemed eligible. Patients were 48% male and had a median pretreatment ASPECT score of 7 (5.9–9). The most frequent occlusion site was the proximal middle cerebral artery, horizontal portion (M1) (42%).

Time course for the procedures

Supplemental Table 2 presents the median, interquartile range, and 95% CI for each procedural time course in this study. Specifically, the median times (95% CIs) from onset to recanalization, onset to door, door to imaging, door to puncture, onset to puncture, and puncture

to recanalization were 229 (201–252) minutes, 50 (45–59) minutes, 15 (13–18) minutes, 80 (70–95) minutes, 145 (130–165) minutes, and 67 (57–79) minutes, respectively. Table 1 compares the outcomes of previous clinical trials with those of our study.

Table 1. Comparison of median time courses of endovascular treatment for AIS between the present and previous studies

	MR clean[1]	REVASCAT[4]	ESCAPE[3]	SWIFT prime[5]	EXTEND IA[2]	Present study median (95% CI)
Onset to puncture (minutes)	260	269	200	224	210	145 (130–165)
Door to puncture (minutes)	NR	109	NR	90	113	80 (70–95)
Puncture to recanalization (minutes)	NR	59	30	24	43	67 (57–79)
Onset to recanalization (minutes)	332	355	241*	252*	248	229 (201–252)

*First reperfusion. CI, confidence interval

Notably, our 95% CI upper limits for the time from onset to recanalization and the time from door to puncture were shorter than those of two previous trials, and our 95% CI upper limit for the time from onset to puncture was shorter than those in all previous published trials. However, our 95% CI upper limit for the time from puncture to recanalization was longer than that reported in previous trials, and our 95% CI upper limits for the times from onset to puncture and from onset to recanalization were shorter than those in the Hermes collaboration[7 18].

Treatment outcome

In the present study, the recanalization rate was 70%. mRS of 6 at 90 days was 12.3%, and 25% of patients had an mRS of 0–2 at 90 days. These results were comparable to those of the five previous RCTs shown in Supplemental Table 3.

GIS analysis

Figure 1 shows the distribution of individuals aged ≥ 65 years, the mothership model population coverage ratios (only three facilities), and the drive and retrieve model coverage ratios (10 participating facilities). In each secondary medical area, the medical area offering general medical service excluded special medical care, and the population coverage rate showed an upward trend after the drive and retrieve method was introduced (Table 2 and 3),

Table 2. Numbers and percentages of the population living within 30-, 60-, and 90 minutes of the institute providing neuroendovascular treatment before the implementation of the drive and retrieve method.

	≥65 years	90 minutes n (%)	60 minutes n (%)	30 minutes n (%)
Sapporo	594,555	593,860 (100)	593,175 (100)	513,746 (86)
Shiribeshi	76,374	55,707 (73)	48,306 (63)	17,918 (23)
Minamisorachi	58,872	58,173 (99)	47,066 (80)	7 (0)
Nakasorachi	41,097	29,256 (71)	0 (0)	0 (0)
Kitasorachi	13,168	385 (3)	0 (0)	0 (0)
Nishiiburi	65,367	2,012 (3)	0 (0)	0 (0)
Higashiiburi	59,286	54,788 (92)	4,464 (8)	0 (0)
Total area	1,558,387	794,181 (51)	693,011 (44)	531,671 (34)

Table 3. Numbers and percentages of the population living within 30-, 60-, and 90 minutes from the institute providing neuroendovascular treatment after the implementation of the drive and retrieve method.

	≥65 years of age	90 minutes n (%)	60 minutes n (%)	30 minutes n(%)
Sapporo	594,555	593,860 (100)	593,416 (100)	588,409 (99)
Shiribeshi	76,374	67,335 (88)	55,690 (73)	47,482 (62)
Minamisorachi	58,872	58,872 (100)	58,248 (99)	46,575 (79)
Nakasorachi	41,097	41,076 (100)	31,725 (77)	173 (0)
Kitasorachi	13,168	12,961 (98)	841 (6)	0 (0)
Nishiiburi	65,367	39,206 (60)	0 (0)	0 (0)
Higashiiburi	59,286	59,122 (100)	54,544 (92)	3,153 (5)
Total area	1,558,387	924,553 (59)	794,464 (51)	685,792 (44)

with Minamisorachi showing the greatest increase in the population coverage rate. The arrival area within 30 minutes increased from 0% before introducing the drive and retrieve method, to 79% after introduction (Table 3).

Discussion

We identified two major findings in our study. First, the drive and retrieve method yielded a reasonable time course for thrombectomy, which requires the obstructed blood vessel to be reopened as soon as possible. Second, the relationships among hospitals increased the area accessible within a reasonable driving time and thus improved the population coverage rates. In particular, our study findings suggest that our procedural times, especially onset-to-door time, were shorter than those reported in clinical trials promoting drastic changes to AIS treatment. Conversely, the puncture-to-recanalization time was longer than that in previous studies. This is a drawback of the drive and retrieve method; however, we included the initial data from the beginning of our study, in the final analysis. Initially, we were not accustomed to this system, and initial times may have been longer. Once staff at each facility become accustomed to the drive and retrieve system, procedure times are expected to shorten.

The guidelines of eight societies in United States and European countries have recommended time courses for endovascular treatment, including a time from door to imaging of < 25 minutes, time from door to puncture of < 120 minutes, and time from puncture to recanalization of within 90 minutes[19]. Comparatively, the time courses in our study were shorter, suggesting that our system is a reasonable approach to the prompt execution of endovascular treatment.

The efficacy of the drive and retrieve system can be attributed to the simultaneous collaboration of PSC and CSC staff, as described previously[14]. In our study, and in previous

studies[14], parallel efforts of the staff of both institutions enabled prompt treatment. Additionally, the drive and retrieve system may lead to earlier thrombectomy compared with the drip and ship method. In a retrospective review, Caspar et al. compared the drive and retrieve and drip and ship methods and concluded that the former was preferable because the latter delayed the start of treatment by a median of 148 minutes[20]. Consistent with that report, our system allowed rapid treatment initiation.

Our study also showed that areas within 30-, 60-, or 90 minutes from institutes that could perform endovascular treatment for AIS increased dramatically after the drive and retrieve system was applied. GIS analysis before introducing the drive and retrieve system provided the area covered within a specific time only for direct transport (mothership system) to the current CSC in the area. Our results matched those of a previous report in which direct transport increased the risk of delayed AIS treatment initiation[21]. In contrast, our system, which relies on an inter-facility network composed of metropolitan and small suburban cities, is considered highly suitable for providing AIS treatment. To our knowledge, our study is unique in that it was the first to analyze the effects of the drive and retrieve method using GIS, whereas a previous study used GIS only to evaluate inter-facility cooperation regarding tissue plasminogen activator[15]. GIS analysis allowed us to evaluate the effectiveness of the drive and retrieve system regarding population coverage and mapping. Accordingly, we could evaluate effectiveness in both metropolitan areas and in other regions (e.g., rural). Therefore, this analysis method could be used to propose optimal inter-facility cooperation in any area.

The results of recent large-scale clinical studies of thrombus retrieval therapy for cerebral infarction secondary to large vessel occlusion[1-5] have highlighted the importance of establishing inter-institutional cooperative systems, given the association of an improved prognosis with a reduced time from onset to completion of recanalization. Specifically, a previous report showed each 1-hour delay of reperfusion corresponded to a 6% decrease in the

absolute risk of a good outcome[8]. Similarly, the Hermes collaboration also indicated that each 1-hour delay in reperfusion was associated with a less favorable degree of disability and reduced functional independence[7]. We note that the drive and retrieve system, which was shown to be effective in our study, does not require institutions to purchase additional angiography equipment or to hire additional personnel; therefore, significant expenditures are not required. Moreover, the system can be established promptly and is thus suitable for the dissemination of treatment as soon as possible. This system is also flexible regarding inter-facility cooperative efforts; i.e., the drive and retrieve system may be complementary to both the drip and ship and mothership systems. For example, drive and retrieve is useful when angiography is not available because other operations are being performed at CSCs using a mothership system.

This study has certain limitations. First, the study was not an RCT, and we did not compare the efficacy of the drive and retrieve system with the drip and ship and mothership methods within the same registry. A large-scale RCT is needed to evaluate the effectiveness of the drive and retrieve system. Second, the drive and retrieve system cannot be established unless certain conditions are satisfied. The participating PSCs near our city possess the equipment and medical staff (other than neurointerventionists) required to provide intravascular treatment round-the-clock. In addition, the area near our city is urban and densely populated, with facilities located within a 1-hour drive of each other. Therefore, the effects of cooperation among facilities located at longer distances from the CSC are unknown. Future studies should evaluate these aspects in areas with more widely-varied characteristics.

Conclusion

This study explored a newly-proposed form of inter-institutional collaboration for the prompt endovascular treatment of AIS. Our findings demonstrated that the drive and retrieve system

may be an effective method of cooperation between facilities located within 1 hour of a CSC.

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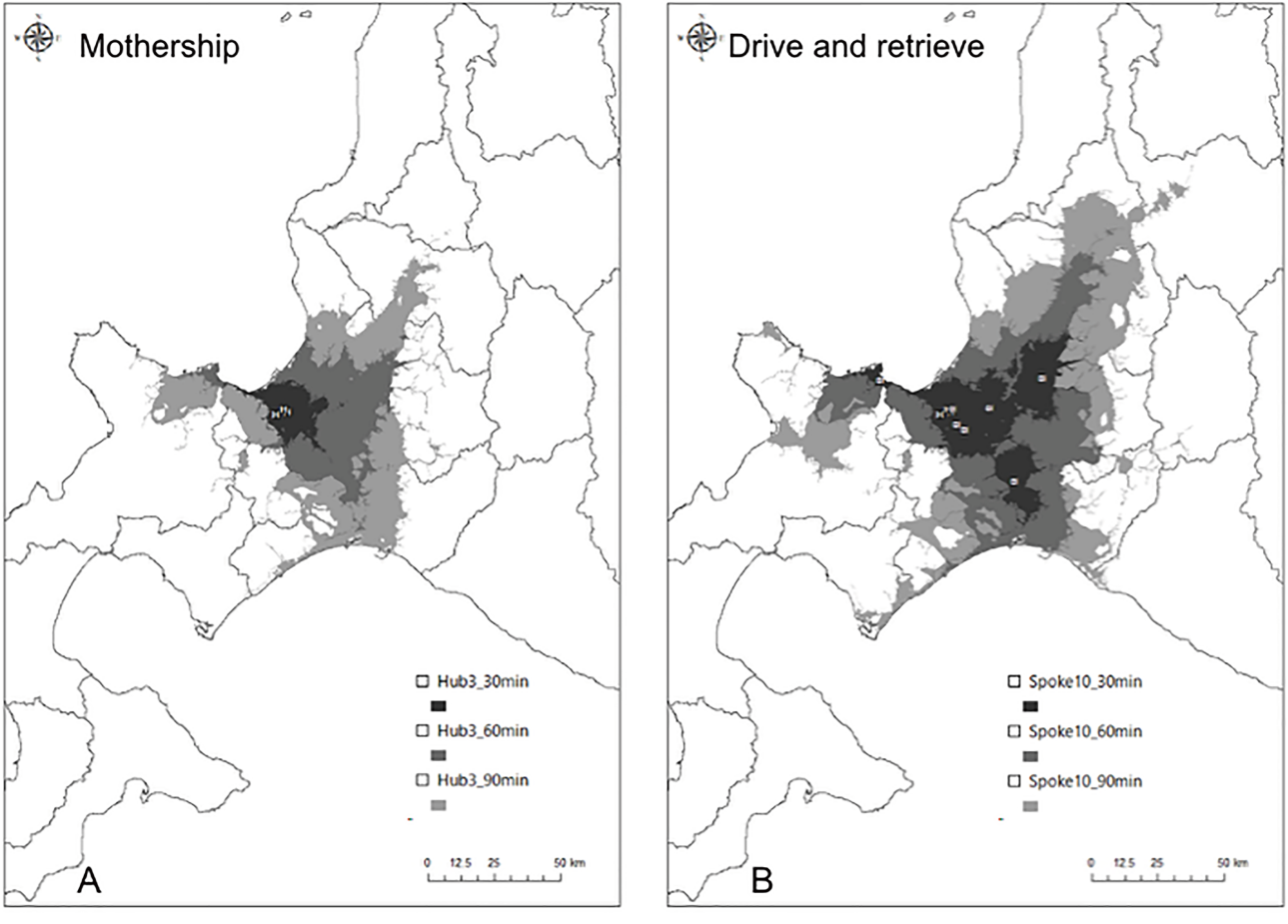
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Figure legends

Figure 1. Map of the area surrounding Hokkaido prefecture.

The areas within 30-, 60-, and 90 minutes from the institute providing endovascular treatment for AIS are marked in light gray, darker gray, and black, respectively. When the mothership method was used in only three institutes, these areas are narrow (A). In contrast, the areas dramatically increased in size after implementing the drive and retrieve method (B).

AIS, acute ischemic stroke.


Mothership
Hub3_30min
Hub3_60min
Hub3_90min
0 12.5 25 50 km
A
Drive and retrieve
Spoke10_30min
Spoke10_60min
Spoke10_90min
0 12.5 25 50 km
B