Widening Time Disparities between Two Paradigms: Tama-REgistry of Acute Endovascular Thrombectomy

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Background: The Tama-REgistry of Acute endovascular Thrombectomy (TREAT) is a multicenter registry of endovascular thrombectomy in the Tama area of Tokyo. The objective of this study was to confirm the real-world status of 2 paradigms of transportation. *Methods:* This was a retrospective analysis of data from TREAT. Patients were divided into 2 groups and 2 periods: directly admitted to an endovascular thrombectomy-capable center (ECC; group D)/secondary transfer from a non-ECC (group S), and the first period/the second period. Transfer distance, workflow metrics, and clinical outcomes were analyzed. *Results:* A total of 326 patients, including 264 in group D and 62 in group S, were analyzed. The median distance from the onset-to-ECC was 3.62 km for group D and 7.87 km for group S ($P < .001$). The median onset-to-needle (OTN) time was longer for group S (168 minutes) than group D (138 minutes; $P = .006$). The median onset-to-reperfusion (OTR) time was significantly shorter for group D (247 minutes) than for group S (304 minutes; $P = .029$). With respect to the 2 periods, there was no significant difference in onset-to-puncture time between the 2 groups in the first period (207 minutes versus 243.5 minutes, respectively, $P = .50$), while there was one in the second period (164 minutes versus 246.5 minutes, respectively, $P = .02$). *Conclusions:* This region-wide registry study showed longer OTN and OTR times, with no improvement of the time course over time in patients transported via non-ECCs. These results should be used to create a regional medical policy for the management of acute ischemic stroke.

Key Words: Emergent large vessel occlusion—acute ischemic stroke—mechanical thrombectomy—transportation—stroke bypass

Introduction

Since December 2014, 5 randomized, controlled trials (RCTs) have reported the efficacy of endovascular thrombectomy in patients with acute ischemic stroke (AIS) caused by large vessel occlusion (LVO).[1-5] Following these 5 RCTs, several ad hoc analyses[6-8] and a meta-analysis[9] were reported. In addition, several studies[10,11] of

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probability models compared 2 systems for transporting patients with suspected stroke: (1) direct admission to the nearest endovascular thrombectomy-capable center (ECC) and bypassing a closer non-ECC; (2) secondary transfer via the closer non-ECC. Some studies pointed out that the time from stroke onset to arterial access was longer in the secondary transfer group.[12-14] The RACECAT trial (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients with Suspected Large Vessel Occlusion)[15] is an ongoing RCT comparing these 2 transport systems. Shortening interval times is a complex problem that needs to take into account the geographical distribution of ECCs and non-ECCs.[7] There is a different solution in every area of medical service delivery. Therefore, to confirm the real-world status of the 2 paradigms of transportation, a multicenter registry (Tama-REgistry of Acute endovascular Thrombectomy [TREAT]) of endovascular thrombectomy to treat AIS with LVO in Western Tokyo was used.

Methods

Study Design and Setting

TREAT is a multicenter registry designed to confirm the real-world status of cases where endovascular thrombectomy was performed at ECC on AIS caused by LVO in the western half of Tokyo, called the Tama area, with a population density of 3650 persons/km^2. In this area, 13 ECCs were stroke centers with 24/7 service for endovascular thrombectomy.[16] Twelve centers except 1 (which included a registry of Kanagawa Prefecture next to Tokyo due to geographical proximity) registered patients who were treated by endovascular thrombectomy. Therefore, it could be considered that most of the patients who underwent thrombectomy in the Tama area were registered in TREAT. The present study was approved by the local ethics committees of each participating institution.

Selection of Participants

Between January 2015 and March 2017, consecutive patients' data registered in TREAT were analyzed. Patients who had symptom onset in the study center were excluded. Subjects were divided into the following 2 groups: directly admitted to an ECC (group D) and secondarily transferred to an ECC via a non-ECC (group S). Baseline characteristics, including demographic characteristics, clinical history, comorbidity, medical history, stroke severity, imaging, occluded site, treatment modality, treatment results, complications, and clinical outcomes were confirmed. To analyze the transportation distance, the real distances between the onset location to the first admitted hospital (nearest non-ECC or nearest ECC), the first hospital to the next ECC, and the hypothetical distance between the onset place location to the ECC bypassing the nearest non-ECC were calculated based on the registered postal codes. The following workflow metrics were defined: (1) time from onset to arrival at the ECC door; (2) time from onset to imaging; (3) time from onset to needle for intravenous recombinant tissue plasminogen activator (iv rt-PA); (4) time from onset to arterial puncture (OTP); and (5) time from onset to complete reperfusion (OTR). Complete reperfusion was defined as achieving thrombolysis in cerebral infarction grade 2b-3. For the safety analysis, any intracranial hemorrhage (ICH) and symptomatic ICH (as defined by a decrease of 4 or more in the National Institutes of Health Stroke Scale [NIHSS]) were confirmed. The clinical outcome was functional independence as defined by a modified Rankin Scale (mRS) score of 0-2 at 90 days. To identify the changes in workflow metrics over time, the numbers of patient were simply divided in half; the first period included the patients treated until April 2016, and the second period included the others.

Statistical Analysis

Baseline characteristics were compared between the groups using the t test for continuous variables with a normal distribution and Fisher's exact test for categorical variables. Time intervals are reported using medians and interquartile ranges, owing to the non-normality of the data; differences between subgroups were tested by the Mann-Whitney U test. For comparison among 3 or more groups, we used nonparametric Kruskal-Wallis test and Steel-Dwass multiple comparison. All P values were 2-sided, and P values $\leq$.05 were considered significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[17] More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Characteristics of Study Subjects

A total of 396 patients were registered during the study periods. In this study, 326 patients whose mRS scores at 90 days were available were evaluated, after exclusion of 49 patients who had AIS in the study center and 21 patients without mRS scores at 90 days. There were 264 cases (81.0%) in group D, and 62 cases (19.0%) in group S. The baseline characteristics of each group are summarized in Table 1. The median age was significantly older in group D (79 versus 75 years in group S, P = .031). The median NIHSS score at admission was significantly worse in group D (18 versus 16 in group S, P = .025). The percentages of patients with unclear onset, including wake-up stroke or unwitnessed stroke, were 40.9% in group D and 24.8% in group S (P = .030). Otherwise, there were no

Table 1. *Baseline characteristics*

	Group D	Group S	*P*
n (%)	264 (81.0)	62 (19.0)	
Age (y), median [IQR]*	79 [70-84]	75 [64.8-82]	.031
Male, n (%)*	156 (59.1)	41 (66.1)	.387
Prestroke mRS score ≤2, n (%)*	226 (85.6)	46 (79.0)	.242
NIHSS, median [IQR]†	18 [13-23]	16 [12-20]	.025
Clear onset, n (%) *	156 (59.1)	46 (74.2)	.030
Cause of stroke, n (%)*			.093
Cardioembolic	206 (78.0)	43 (69.4)	
Atherosclerosis	40 (15.2)	14 (22.6)	
Dissection	2 (.8)	3 (4.8)	
Others	4 (1.5)	0 (0)	
Unknown	12 (4.5)	2 (3.2)	
Clinical history, n (%)*			
Hypertension	161 (62.1)	41 (66.1)	.662
Diabetes	47 (17.8)	12 (19.4)	.855
Hyperlipidemia	62 (23.5)	12 (19.4)	.613
Atrial fibrillation	144 (54.5)	35 (56.5)	.887
Medication, n (%)*			
Antiplatelet	54 (20.5)	13 (21.0)	1
Anticoagulant	52 (19.7)	17 (27.4)	.226
Statin	41 (15.5)	7 (11.3)	.550
Site of occlusion, n (%)*			.353
ICA	82 (31.1)	18 (29.0)	
M1	113 (42.8)	26 (41.9)	
M2/M3	44 (16.7)	7 (11.3)	
ACA	1 (.4)	1 (1.6)	
VA	2 (.8)	1 (1.6)	
BA	20 (7.6)	8 (12.9)	
PCA	2 (.8)	1 (1.6)	
DWI-ASPECTS, median [IQR]†			
(anterior circulation, n = 264)	7 [6-9]	8 [7-9]	.097
PC-ASPECTS, median [IQR]†			
(posterior circulation, n = 33)	7 [6-8]	7 [6-7]	.853
iv rt-PA, n (%)*	135 (51.1)	27 (43.5)	.324

Abbreviations: ACA, anterior cerebral artery; BA, basilar artery; DWI-ASPECTS, Diffusion-Weighted Imaging−Alberta Stroke Program Early Computed Tomography Scores; group D, direct transfer; group S, secondary transfer; ICA, internal carotid artery; IQR, interquartile range; iv rt-PA, intravenous recombinant tissue plasminogen activator; M1, sphenoidal segment of the middle cerebral artery; M2, insular segment of the middle cerebral artery; M3, opercular segment of the middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery; PC-ASPECTS, Posterior Circulation Alberta Stroke Program Early Computed Tomography Scores; VA, vertebral artery.

*Fisher's exact test.

†Mann-Whitney *U* test.

significant differences between groups D and S in the percentage of males (59.1% versus 66.1%, respectively), prestroke mRS score ≤2 (85.6% versus 79.0%, respectively), cause of stroke, comorbidities, past history, anticoagulant or antiplatelet use, and so on. The percentage of patients with occlusion in the anterior circulation was 90.9% in group D and 83.9% in group S ($P = .103$). The median Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography Score[18] with occlusion in the anterior circulation was 7 in group D and 8 in group S ($P = .096$). The median Posterior Circulation Alberta Stroke Program Early Computed Tomography Scores[19] with occlusion in the posterior circulation was 7 in both groups ($P = .853$). The percentage of patients who underwent iv rt-PA was 51.1% in group D and 43.5% in group S ($P = .324$).

Main Results

The median linear distance from the onset location to the ECC was 3.62 km in group D, and 7.87 km was the total linear distance from the onset location to the referral hospital and from the referral hospital to the ECC in group S; there was a significant difference of over 4 km

Table 2. *Distance of each transfer route*

	Group D (n = 259) km [IQR]	Group S (n = 58) km [IQR]	*P*
Distance from onset to ECC*	3.62 [2.27-5.06]	7.87 [5.63-11.44]	<.001
Distance from onset to referral hospital (1)*	3.62 [2.27-5.06]	1.13 [.21-3.66]	<.001
Distance from referral hospital to ECC	-	5.56 [4.35-8.17]	
Distance when assuming that the patient has been transported directly from onset to ECC (2)	-	6.03 [4.68-9.06]	
(2) − (1)	-	4.54 [2.57-5.86]	

Abbreviations: ECC, endovascular capable center; group D, direct transfer; group S, secondary transfer; IQR, interquartile range.
*Mann-Whitney *U* test.

between them ($P < .001$). In group S, the median difference of the distance was only 4.54 km, between the real data via the non-ECC and the assumption of directly transporting to the ECC bypassing the non-ECC (minimum and maximum were −6.32 and 14.26 km). There were 3 paradoxical cases in which the linear distances were shorter when transferred directly to the ECC (Table 2).

As shown in Table 3, the median time from onset to imaging [interquartile range] were 116 [80-256] minutes for group D and 102 [61.5-124.5] minutes for group S, significantly shorter for group S ($P = .002$). However, the median onset-to-needle time was 138 [115-175.5] minutes for group D and 168 [150-187.5] minutes for group S, significantly later for group S ($P = .006$). Patients in group S arrived at the ECC with a median time from onset to arrival at the ECC door of 208 [154-243] minutes, whereas 76 [50-230] minutes in group D ($P < .001$). The median OTP times were 187 [138-337] minutes versus 246.5 [199-303.5] minutes ($P = .002$), and the median OTR times were 247 [189-419] minutes versus 304 [250-388] minutes ($P = .029$) for group D versus group S, respectively (Table 3).

Figure 1 shows each clinical time course in the first and second periods. There was no shortening of any time course for group S between the 2 periods. Thus, there was no significant difference in OTP between the 2 groups in the first period (207 [150.5-343] minutes versus 243.5 [201.3-278.3] minutes, respectively, $P = .50$), but there was 1 in the second period (164 [129-331] minutes versus 246.5 [195.8-366] minutes, respectively, $P = .02$).

No significant differences were observed in the rates of complete recanalization, any ICH, symptomatic ICH, and functional independence at 90 days between the 2 groups (Table 3).

Discussion

In the present study, there was about a 1-hour delay in OTR in group S. However, there was no significant difference in the functional independence rate between the 2 groups. Previous reports had noted that longer OTR was seen with secondary transfer than with direct admission, but it varied according to each registry whether longer OTR affected outcomes.[6,7,12-14,20] In general, a longer time to therapy is considered to result in worse patient

Table 3. *Process times and outcomes**

Time interval (min)†	Group D	Group S	*P*
OTD	76 [50-230]	208 [154-243]	<.001
OTI	116 [80-256]	102 [61.5-124.5]	.002
OTN	138 [115-175.5]	168 [150-187.5]	.006
OTP	187 [138-337]	246.5 [199-303.5]	.002
OTR	247 [189-419]	304 [250-388]	.029
TICI ≥2b‡	209 (79.2)	47 (75.8)	.607
Any ICH‡	73 (27.7)	15 (24.2)	.636
sICH‡	15 (5.7)	4 (6.5)	.767
90-day mRS score ≤2‡	106 (40.2)	23 (37.1)	.773

Abbreviations: ECC, endovascular capable center; group D, direct transfer; group S, secondary transfer; ICH, intracranial cerebral hemorrhage; iv rt-PA, intravenous recombinant tissue plasminogen activator; mRS, modified Rankin Scale; OTD, time from onset to arrival at the ECC door; OTI, time from onset to imaging; OTN, time from onset to needle for iv rt-PA; OTP, time from onset to arterial puncture; OTR, time from onset to complete reperfusion; sICH, symptomatic intracranial cerebral hemorrhage; TICI, thrombolysis in cerebral infarction.
*Data are presented as numbers (percentage) or medians [interquartile range].
†Mann-Whitney *U* test.
‡Fisher's exact test.

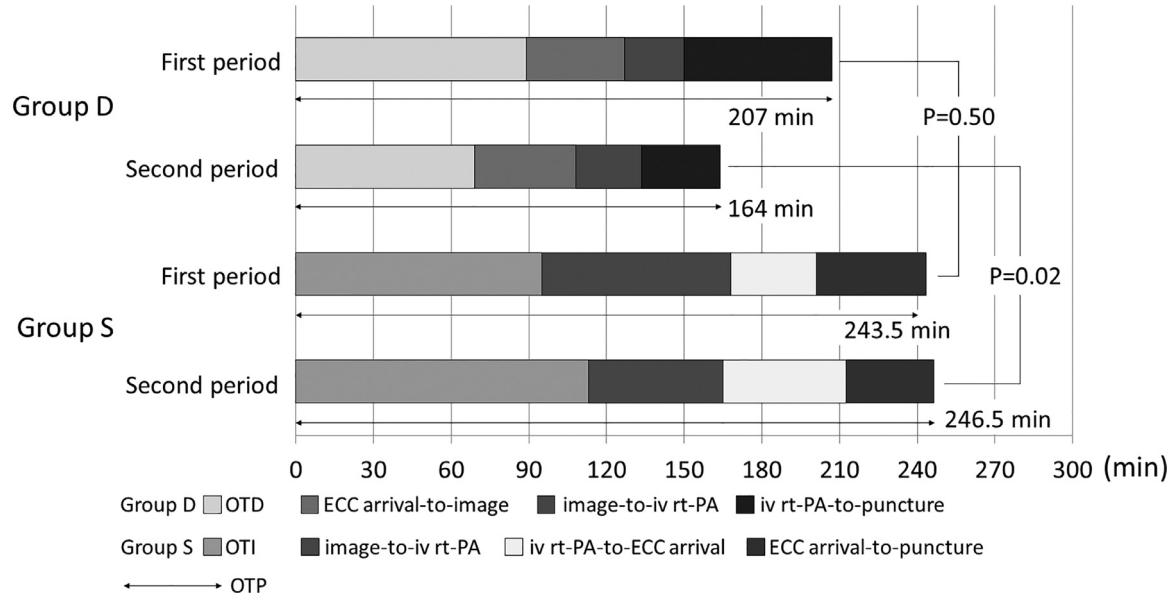

Figure 1. *Median time intervals from onset to arterial puncture (OTP). There is no significant difference in OTP between the 2 groups in the first period (207 minutes versus 243.5 minutes, respectively, P = .50), but there is 1 in the second period (164 minutes versus 246.5 minutes, respectively, P = .02).*

Abbreviations: ECC, endovascular thrombectomy-capable center; group D, direct transfer; group S, secondary transfer; iv rt-PA, intravenous recombinant tissue plasminogen activator; OTD, time from onset to arrival at the ECC door; OTI, time from onset to imaging.

outcomes, because it has been reported that every 1-hour delay of OTR after 210 minutes decreased the probability of functional independence by 20%.[6] The reason why there was no effect of delayed therapeutic time in group S was considered to be due to the decision at the non-ECC of whether to transport the patient to the ECC in this registry cohort. Moreover, at the ECC, a second decision was needed for the patients in group S as to whether they required thrombectomy. Through this 2-stage selection process, the good candidates for thrombectomy probably remained in group S in the present study cohort. For example, in group S, patients were younger and NIHSS were lower compared to group D. To eliminate this effect, univariate analysis and multivariate analysis were performed on the objective variables as functional independence at 90 days, and for explanatory variables as group D or S, age, and NIHSS. Age and NIHSS were associated with functional independence at 90 days, but the group D or S was not related to outcome after age/NIHSS adjustment (Table 4). From this result alone, it is concluded that the secondary transfer system is not always inferior to the direct transfer. In fact, however, since confounding factors should exist in addition to age and NIHSS, we think it is necessary to compare all LVO cases of both ECC and non-ECC in order to correctly compare treatment results of both groups.

The present data suggest that the time of workflow metrics during the second period improved to become faster than in the first period in group D. On the other hand, they were not improved in group S. As to the reason, it is assumed that the medical staff of ECCs has many opportunities to obtain knowledge about mechanical thrombectomy (MT), and they always pay attention to shortening the times of workflow metrics. However, the necessity to shorten the time may seem less important to non-ECC staff because they lack experience with thrombectomy. The probability of a negative effect of lesser experience in the management of patients with acute stroke in non-ECCs was noted previously.[11] As far as we know, this is the first study to report that such undesired consequences occurred in the real-world setting. To prevent a widening disparity, further education about the management of AIS patients should occur at non-ECCs.

A meaningful advantage of our registry is that postal code information of the onset location is collected. That information enables us to know the distance that the emergency medical service (EMS) transfers AIS patients. In a densely populated urban area such as ours, the difference in the distance was only 4.5 km between the case that the patient was transferred to the nearest referral hospital and the case that the patient was transferred to the ECC directly. In addition, the present data showed that some cases were transferred to distant non-ECCs. Availability to administer iv rt-PA more rapidly is emphasized as the advantage of taking patients to the nearest non-ECC.[21] The present data suggested that the difference in the distance between non-ECCs and ECCs was only 4.5 km in our area, so it might be only a 10-minute delay if EMS bypassed the nearest non-ECC to take the patient directly to an ECC. Considering the 20-minute delay of imaging-to-iv rt-PA time at non-ECCs, patients might benefit from a faster start of iv rt-PA if EMS were to take them directly to an ECC. Holodinsky et al[10] proposed a methodology for comparison of 2 options, the "Drip and

Table 4. *Analysis of factors related to functional independence at 90 days*

	Univariate analysis			Multivariate analysis		
	mRS ≤2	mRS ≥3	*P*	OR	95% CI	*P*
Age*	72 [63-80]	81 [74-86]	<.01	.94	.29-.97	<.01
NIHSS*	14 [10-20]	20 [16-24]	<.01	.91	.88-.95	<.01
Secondary transfer	17.8%	19.8%	.77	.56	.29-1.07	.08

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.
*Data are presented as medians [interquartile range].

Ship model" and the "Mothership model," using statistical probability modeling. They gave an example showing that the Drip and Ship model is superior to the Mothership model if door-to-needle times were less than 30 minutes at the non-ECC. It should be noted that this model is unrealistic because the median imaging to iv rt-PA time at the non-ECC was 55 minutes in the present study. The present real-world data provide important information for developing health policy for AIS in the area, and data should be collected continuously.

The following limitations have to be considered. First, this was a retrospective analysis of a single-arm group in which patients were able to undergo MT. In group S, patients were carefully considered for MT twice and were probably good candidates for MT. Therefore, the present study could not conclude which transport system will lead to a better probability of good patient outcomes. To obtain the answer to this question, randomized trials such as the RACECAT trial[15] are needed. Second, the present results are limited to a densely populated urban area, and they may not be applicable to provincial cities or underpopulated areas. The medical administration of each area has its own best solutions to achieve the best outcomes for its AIS patients, and it is essential to have cooperation between related medical facilities to gather real-world data.

Conclusion

In the present study, data from TREAT were analyzed, and the difference in the time course between 2 transportation systems was evaluated. There was no advantage of a faster start of iv rt-PA, which should be provided by taking patients to the nearest non-ECC. The difference in the distance was only 4.5 km between the real data via a non-ECC and the assumption of bypassing the non-ECC. The median OTR was about 1 hour faster for patients in group D. In group S, there was no shortening of the time course over time. Further regional registry data need to be gathered because analysis of such data can provide significant information for creating a medical policy for the management of stroke patients.

This study is recommended by the Japanese Society of Neuroendovascular Therapy.

Appendix

The TREAT enrolling hospitals and Investigators.

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