Thrombectomy for Stroke at 6-24 hours without Perfusion CT Software for Patient Selection

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Background: Although, thrombectomy for stroke more than 6 hours after onset supported by automated perfusion computed tomography (CT) software (RAPID, iSchemaView) is effective, this software is not available in Japan. This study aimed to elucidate the efficacy of thrombectomy 6-24 hours after onset in our patient cohort using conventional imaging mismatch. *Methods:* Of 586 ischemic stroke patients who underwent thrombectomy registered from January 2015 to December 2017, patients with occlusion of the intracranial internal carotid artery or middle cerebral artery, who had last been known to be well 6-24 hours earlier and who had a prestroke modified Rankin scale (mRS) score 0 or 1 were enrolled. Clinical outcomes were the scores of the utility-weighted (UW) mRS, which ranges from 0 (death) to 10 (no symptom or disability), and the rate of functional independence (mRS score of 0-2) at 90 days. *Results:* This study sample included 31 patients. The median baseline National Institutes of Health Stroke Scale score was 17 (interquartile range [IQR], 13-20), and the median Diffusion-Weighted Imaging-Alberta Stroke Program Early CT Score was 7 (IQR, 5-8). The median interval between the time that the patient was last known well and revascularization was 741 (IQR, 641-818) minutes. The mean UW mRS score at 90 days was 5.3, the rate of functional independence was 32%, and the 90-day mortality rate was 13%. *Conclusions:* Thrombectomy 6-24 hours after onset which can be performed with conventional imaging mismatch might be secured for improving functional independence in stroke patients.

Key Words: Atrial fibrillation—cerebral infarction—emergency medicine—endovascular therapy—RAPID

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Scores; CT, computed tomography; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IQR, interquartile ranges; IV tPA, intravenous tissue plasminogen activator; LVO, large vessel occlusion; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage; TICI, thrombolysis in cerebral infarction

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Background

Endovascular thrombectomy has been shown to be effective for the treatment of acute ischemic stroke in patients with large vessel occlusion (LVO) of the middle cerebral artery (MCA) or internal carotid artery (ICA) if treatment is initiated within 8 hours.[1] Recently, according to 2 thrombectomy trials that treated patients 6-24 hours after stroke onset (DAWN [DWI or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with Trevo] and DEFUSE 3 [endovascular therapy following imaging evaluation for ischemic stroke-3]), time-extended thrombectomy (up to 24 hours) showed enough benefit over medical therapy alone.[2,3] These studies were based on infarct volume imaging for patient selection, and infarct volume was assessed by diffusion-weighted magnetic resonance imaging (MRI) or perfusion computed tomography (CT) and was measured with the use of RAPID automated software (iSchemaView). However, this automated software was not available in Japan. Conventionally, the Diffusion-Weighted Imaging (DWI)-Alberta Stroke Program Early CT Score (ASPECTS) has been used to confirm brain infarction volume and imaging mismatch, which was superior to noncontrast CT images, and permits earlier intravenous tissue plasminogen activator or thrombectomy if required.[4] Therefore, a retrospective study to elucidate the efficacy and safety in patients selected by conventional imaging mismatch without automated software for thrombectomy at 6-24 hours after stroke was conducted using the Tama REgistry of Acute endovascular Thrombectomy (TREAT) database.

Methods

Patients

This study was a retrospective, observational study using data from TREAT (UMIN-CTR: UMIN000026888), a multicenter registry of mechanical thrombectomy for acute LVO in the Tama area of Tokyo, Japan.[5] The survey covered 586 patients with LVO who underwent acute thrombectomy between January 2015 and December 2017. Occlusion sites of the ICA, MCA, anterior cerebral artery, vertebral artery, and basilar artery were included. All patients were registered retrospectively. Participating facilities were 12 of the 13 recanalization therapy-capable stroke centers in the Tama area.

This study was approved by the ethics committee of each participating hospital, but written consent was waived due to its retrospective nature. The stroke patients described above were allocated to mechanical thrombectomy based on the decisions of the attending stroke specialists who had been certified by the Japanese Society for Neuroendovascular Therapy.

All eligible patients met the following criteria: (1) 18 years of age or older; (2) time last known to be well to hospital arrival was 6-24 hours; (3) presenting with a baseline National Institutes of Health Stroke Scale (NIHSS) score greater than or equal to 5; (4) prestroke modified Rankin Scale (mRS) score of 0 or 1; and (5) LVO in the arterial circulation (ICA or MCA). Of these patients, the decision for treatment was based on the NIHSS score, occlusion site by imaging, and DWI-fluid-attenuated inversion recovery (FLAIR) mismatch by the stroke specialists and emergency thrombectomy was performed within 24 hours after the onset.

Data collection

The demographic, clinical, and neuroimaging data were retrieved from the TREAT database. The following characteristics were noted from the database of all eligible patients: age, sex, vascular risk including hypertension, diabetes, lipid metabolism abnormalities, atrial fibrillation, medications, baseline NIHSS score, mRS scores (prestroke, 90 days), CT or MRI imaging, DWI-ASPECTS, time last seen well to revascularization, modified Thrombolysis in Cerebral Infarction (TICI) score, symptomatic intracranial hemorrhage (sICH) at 24 hours, and 90-day mortality.

Endovascular Thrombectomy

For endovascular thrombectomy, a stent retriever (Solitaire, Covidien/ev3, Dublin, Ireland; Trevo, Stryker Neurovascular, Mountain View, CA; and REVIVE, Johnson & Johnson, NJ) or Penumbra MAX system (Penumbra Inc., Alameda, CA) were available in Japan at the time. These devices were used for treatment at the discretion of the attending stroke specialist.

Outcomes

The primary efficacy outcome included the mean score for disability on the utility-weighted (UW) mRS at 90 days.[6] To determine the UW score, the score on the mRS is weighted according to average values calculated from the DAWN trial criteria.[3] The following weights are assigned to scores 0-6 on the mRS: 10.0, 9.1, 7.6, 6.5, 3.3, 0, and 0, respectively. The UW-mRS ranges from 0 (death)-10 (no symptoms or disability). The second efficacy outcome was functional independence, which was defined as an mRS score of 0-2 at 90 days. Patients' mRS scores at 90 days were retrieved from the TREAT registry database, available either by telephone follow-up or outpatient visit. In the present study, 2 patients were lost to follow-up; thus, the 90-day mRS score was replaced by the discharge mRS (scores of 3 and 4) for these patients. The technical outcome of thrombectomy was defined as a modified TICI score of 2b (50%-99% reperfusion) or 3 (complete reperfusion) according to the recommendation of Zaidat et al[7] The safety outcomes included the incidence of sICH at 24 hours according to the definition by the SITS-MOST

Table 1. *Baseline characteristics of the patients and the time course for acute stroke care*

Variable	n = 31
Age − yr	74 ± 9
Age ≧80 yr − n (%)	9 (29)
Male sex − n (%)	22 (71)
Artrial fibrillation − n (%)	15 (48)
Diabetes mellitus − n (%)	5 (16)
Hypertension − n (%)	25 (81)
Lipid metabolism abnormalities −n (%)	14 (45)
Medication use	
Antiplatelet	8 (26)
Anticoagulant	5 (16)
Statin	6 (19)
Prestroke modified Rankin scale score − n (%)	
0	28 (90)
1	3 (10)
Baseline NIHSS score	
Median	17
Interquartile range	13-20
10-20 (n [%])	25 (81)
Type of stroke onset − n (%)	
On awakening	19 (61)
Unwitnessed stroke	9 (29)
Witnessed stroke	3 (10)
Type of stroke − n (%)	
Cerebral embolism	25 (81)
Atherothrombotic	4 (13)
Others	2 (6)
Imaging − n (%)	
CT + MRI	3 (10)
MRI	28 (90)
DWI-ASPECTS	
Median	7
Interquartile range	5-8
Occlusion site − n (%)	
Intracranial ICA	10 (32)
1st segment of middle cerebral artery	16 (52)
2nd segment of middle cerebral artery	5 (16)
Time last seen well to hospital arrival (min)	
Median	606
Interquartile range	475-748
Time last seen well to imaging (min)	
Median	628
Interquartile range	506-772
Time from hospital arrival to arterial puncture (min)	
Median	76
Interquartile range	55-94
Time from imaging to arterial puncture (min)	
Median	49
Interquartile range	38-60
Time last seen well to arterial puncture (min)	
Median	689
Interquartile range	559-821
Time last seen well to revascularization (min)	
Median	741
Interquartile range	641-818

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Scores; CT, computed tomography; DWI, Diffusion-Weighted Imaging; ICA, internal carotid artery; MRI, magnetic resonance imaging; NA, none available; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

(Safe Implementation of Thrombolysis in Stroke-Monitoring Study) and ECASS (the European-Australasian Acute Stroke Study) trials and 90-day mortality.[8,9]

Statistical Analysis

Data from all eligible patients were analyzed. Continuous variables are shown as median values with interquartile ranges (IQRs). Between-group differences were assessed using Fisher's exact test for categorical variables. The Spearman correlation coefficient was used to identify correlations between the evaluated parameters. All statistical analyses were performed using Prism version 6.0a statistical software (GraphPad Software, San Diego, CA). Categorical variables were calculated as the ratio (percentage) of the frequency of occurrence. A probability *P* value of less than .05 was considered significant.

Results

Descriptive Analysis in the TREAT Database

The patients' demographics and clinical characteristics are shown in Table 1. This study sample included 31 patients who had a prestroke mRS score of 0 or 1 and who underwent endovascular thrombectomy at 6-24 hours after stroke. The mean age was 74 years (range, 48-90 years), and 71% of the participants were male. In 90% of the participants, the prestroke mRS score was 0, while 10% had a prestroke mRS score of 1. The median baseline NIHSS score was 17 (IQR, 13-20), and 81% of the participants had NIHSS scores of 10-20. The median interval between the time that the patient was last known to be well and hospital arrival was 606 minutes (IQR, 475-748 minutes), and the median interval between the time that the patient was last known to be well and imaging was 628 minutes (IQR, 506-772 minutes).

Characteristics of Imaging and Endovascular Thrombectomy

All participants underwent MRI, while 3 underwent CT imaging before MRI. The median DWI-ASPECTS was 7 (IQR, 5-8). The median interval between imaging and arterial puncture was 49 minutes (IQR, 38-60 minutes), and the time between arterial puncture and revascularization was 55 minutes (IQR, 33-77 minutes). The median interval between the time that the patient was last known to be well and revascularization was 741 minutes (IQR, 641-818 minutes).

Table 2. *Efficacy outcomes of the patients*

Outcome	n = 31
Score on utility-weighted modified Rankin scale at 90 days	5.3 ± 3.4
Modified Rankin scale score at 90 days − n (%)	
0-2	10 (32)
0-3	16 (52)
4-6	15 (48)
Grade of 2b or 3 on TICI scale − n (%)	24 (77)
Complications	
Stroke-related death at 90 days − n (%)	4 (13)
Death from any cause at 90 days − n (%)	0
Symptomatic Intracranial hemorrhage at 24 h − n (%)	3 (10)
HI-1	4 (13)
HI-2	1 (3)
PH-1	0
PH-2	3 (10)
RIH	0
IVH	0

Abbreviations: EVT, endovascular therapy; HI, hemorrhagic infarction; IVH, intraventricular hemorrhage; NA, none avaiable; PH, parenchymal hematoma; RIH, remote intracranial hemorrhage; TICI, thrombolysis in cerebral infarction.

Clinical and Safety Outcomes

Clinical and safety outcomes are shown in Table 2. After thrombectomy, 2 (6%) patients had a TICI score of 0, 5 (16%) had a score of 2a, 8 (26%) had a score of 2b, and 16 (52%) had a score of 3. The mean score for disability on the UW-mRS scale at 90 days was 5.3, and the rate of functional independence with an mRS score of 0-2 was 32% (Fig 1). The rate of sICH within 24 hours after finishing thrombectomy was 10%, and the 90-day mortality rate was 13%.

In subgroup analyses defined according to the occlusion site, the onset time of stroke, age, NIHSS score, and DWI-ASPECTS, there were no significant differences in functional independence between the groups (Fig 2, A-D). However, there was a significant difference in 90-day mortality between the group with DWI-ASPECTS less than or equal to 5 and that with DWI-ASPECTS greater than or equal to 6. A positive correlation was found between the UW-mRS score and DWI-ASPECTS (Spearman's r = .4, P = .02) (Fig 3).

Discussion

Although the most important issue for stroke patients is to shorten the time from the onset of stroke to revascularization, which is essential to achieve good functional outcomes, the expansion of the time window is a great challenge for unknown or wake-up stroke worldwide. The DAWN trial followed by the DEFUSE 3 trial had a

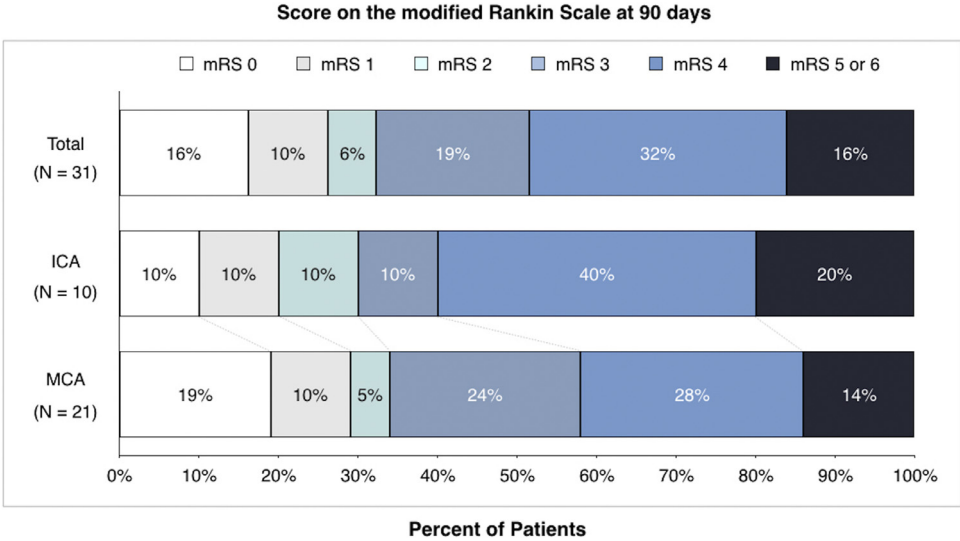

Figure 1. *Scores on the modified Rankin Scale at 90 days. Scores for disability on the modified Rankin scale range from 0-6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Scores; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale. (Color version of figure is available online.)*

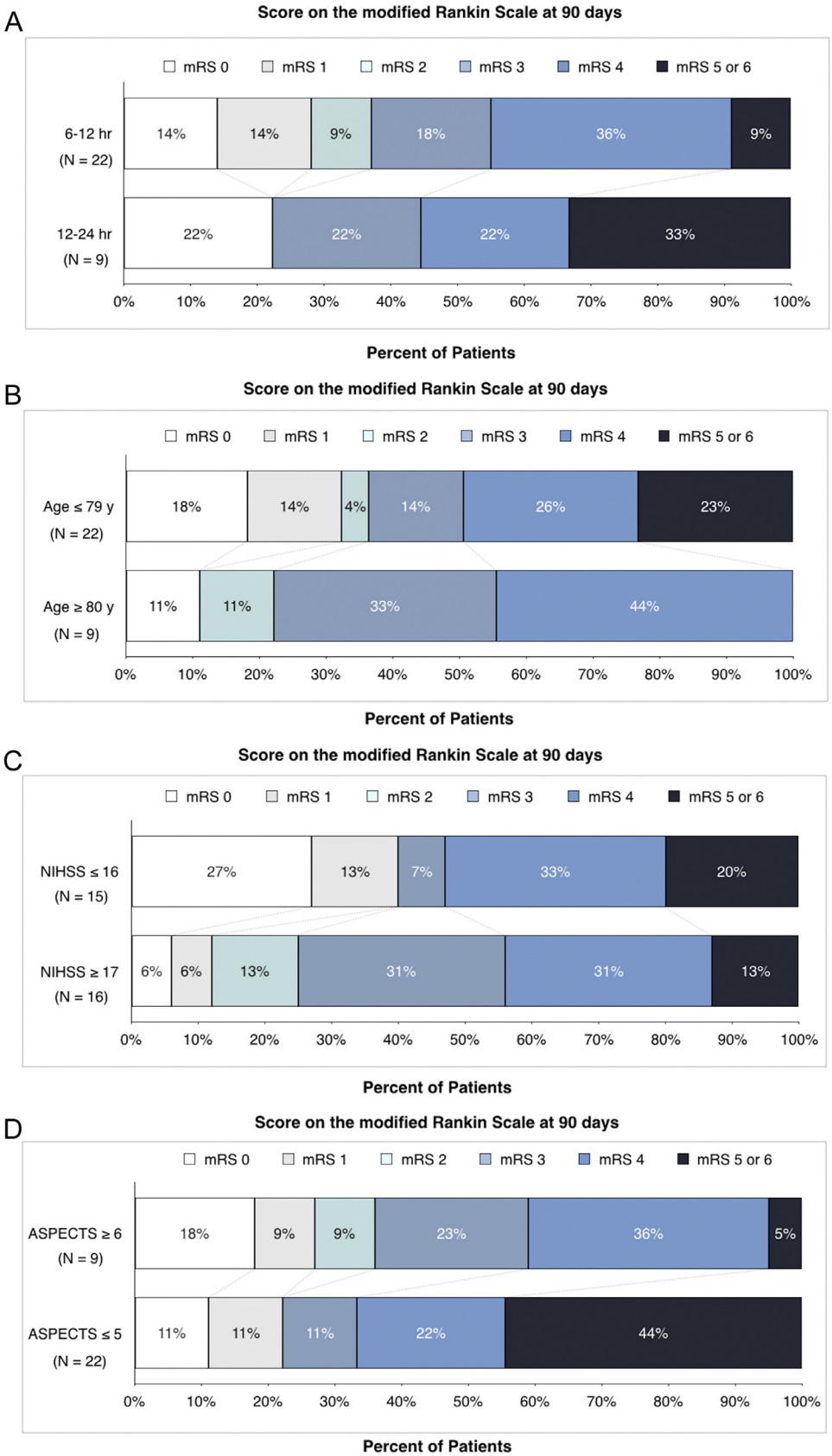

Figure 2. *Subgroups defined according to the time of stroke onset (A), age (B), National Institutes of Health Stroke Scale score (C), and Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography Scores (D). The numbers in the bars are percentages of patients who had each score; the percentages may not sum to 100 because of rounding. (Color version of figure is available online.)*

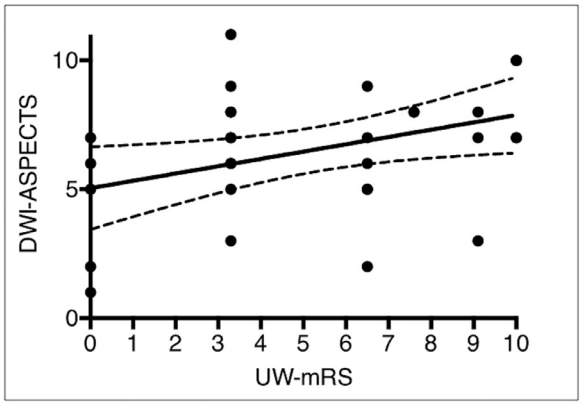

Figure 3. *Correlation between the utility-weighted modified Rankin Scale score and Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography Scores.*

new concept to more precisely evaluate irreversible tissue damage using the RAPID software than previous studies, and the 90-day functional independence rate was 48% if treated, compared with 13% if not treated. Therefore, endovascular thrombectomy at 6-24 hours is a higher priority for acute stroke than not to treat. In the present study, the rate of functional independence was 32%, which was 2.5 times higher than the nontreated patients in the DAWN trials, and the UW-mRS score was similar to that in the treated patients.

In the present study, the safety outcomes were acceptable, with a rate of sICH at 24 hours of 10% and 90-day mortality of 13%, which are consistent with the rates reported by the DAWN trial (6% and 16%) and DEFUSE 3 (7% and 14%). Furthermore, the present study showed no significant differences in 90-day mortality by LVO site (ICA versus MCA), time of onset (6-12 hours versus 12-24 hours), age (≤80 versus >80 years), and NIHSS score (≤16 versus ≥17).

There was also no clinically significant difference in 90-day mortality between patients with DWI-ASPECTS less than or equal to 5 and DWI-ASPECTS greater than or equal to 6. Furthermore, there was a positive correlation between DWI-ASPECTS and UW-mRS. Several studies (ESCAPE trial [endovascular treatment for small core and proximal occlusion ischemic stroke] and REVASCAT trial [randomized trial of revascularization with solitaire FR device versus best medical therapy in the treatment of acute stroke due to anterior circulation LVO presenting within 8 hours of symptom onset]) excluded patients with DWI-ASPECTS less than 6, because patients with DWI-ASPECTS less than 6 have poor outcomes (mRS score 4-6) with intravenous tissue plasminogen activator therapy.[1,10] However, Desilles et al recently reported that, if thrombectomy was successful with TICI greater than or equal to 2b, 90-day disability in patients with a DWI-ASPECTS of 5 or 6 could be reduced sufficiently.[11] There has been marked progress in the revascularization rate of thrombectomy with aspiration catheters or stent retrievers over the past decade. Furthermore, there are a variety of factors to improve functional outcomes i.e., imaging and clinical decision-making. We should increase our efforts to advance revascularization by thrombectomy in the clinical setting.

DWI-ASPECTS and infarct volume were relatively correlated in stroke patients, and Schröder et al demonstrated that DWI-ASPECTS less than or equal to 6 was equal to infarct volume greater than or equal to 100 mL.[12] The criteria of the DAWN trial included the core infarct volume associated with the NIHSS score, which had a relatively small infarct volume. Although patients with larger core infarct volumes were treated using DWI-FLAIR mismatch in the present study compared with DAWN trial participants, the functional and safety outcomes were acceptable. Although Fahed et al showed limited repeatable clinical decisions related to thrombectomy based on assessing DWI-ASPECTS and DWI-FLAIR mismatch by clinicians, the clinical utility of thrombectomy based on assessing clinical imaging mismatch was demonstrated in the present study.[13] Further investigations to evaluate optimal efficacy in patients with moderate infarct volume are warranted.

Limitations

There are several limitations to this study, most notably the retrospective design and small number of cases. The most notable weaknesses were the use of a posthoc hypothesis, and that endovascular thrombectomy by stroke specialists was not assessed in a randomized trial against controls. Second, patients were allocated to treatments at the discretion of the attending stroke specialist, so the possibility of bias cannot be excluded. Second, although patients with NIHSS scores greater than or equal to 5 were enrolled in this study, patients who had NIHSS scores less than 10 were not determined. There was insufficient information about patients who had NIHSS scores less than 10. Shang et al demonstrated the efficacy of endovascular thrombectomy within 24 hours after onset of acute stroke in patients with NIHSS scores of 0 to 8, with an excellent rate of functional independence.[14] Third, we used the UW-mRS as patient-centered primary outcome to compare that of DAWN trial, which utilities based on the European Quality of Life Scale (EQ-5D) were assigned to the mRS health states. The UW-mRS showed similar statistical power to detect treatment utility compared with the ordinal mRS analysis in past large stroke trials, and this approach was more effective in outcome analysis than conventional dichotomous mRS analysis.[6,15] Chaisinanunkul et al also mentioned that caregivers and patients who did not support collapsing mRS 5-6 consider the mRS 5 being worse than the mRS 6, and the mRS 5 is not valued as higher than the mRS 6 (death) in the UW-mRS. However, the Japanese caregivers and primary

healthcare professionals of noncommunicative patients are challenged to consider the mRS 5 being worse than the mRS 6, because this decision can directly relate to the patients' lives owing to cultural habits, e.g., the physician tended to view the value of maintaining the lives of noncommunicative patients in terms of the relationships of such patients with others.[16,17] Recently, the EQ-5D values demonstrated in stroke trials might not reflect valuation of health states in Japanese populations. Recently, the Japanese value sets for EQ-5D-5L was developed to calculate quality of life with the Japanese sense of values, and Japan's economic evaluation guideline recommends the use of measures with this value sets.[18-20] Therefore, the Japanese version of UW-mRS in which utilities based on the Japanese style of EQ-5D-5L are assigned to the mRS might be essential as a patient-centered primary outcome in Japan.

Conclusions

In the TREAT database, thrombectomy at 6-24 hours after onset performed based on conventional clinical imaging mismatch produced good technical success and its clinical utility might be secured for improving functional independence in stroke patients. Further investigations to better improve functional outcomes among patients with moderate infarct volume are warranted.

Authors' Contributions

The experiments were conceived and designed by T.J., O.T.

The experiments were performed and the data was analyzed by T.J., J.H., and O.E.

Interpretation of data was done by T.J., O.E., J.H., and O.T.

The manuscript was critically revised by S.K., A.T., S.Y., and A.T.

The final version to be submitted was approved by T.J., J.H., O.E., O.T., S.K., A.T., S.Y., and A.T.

Appendix

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