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Does Reducing the Duration from Symptom Onset to Recanalization Improve the Results of Intracranial Mechanical Thrombectomy in the Elderly?

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Abstract

Endovascular recanalization for acute major cerebral artery occlusion is effective within a short time after symptom onset. However, its efficacy in the elderly remains unknown. We assessed the efficacy of our comprehensive stroke center's reduction of this time in 28 consecutive patients for elderly patients (defined as patients aged ≥75 years) with acute major cerebral artery occlusion treated with intravenous injection of tissue plasminogen activator, followed by thrombus retrieval by endovascular therapy. The patients were divided into groups according to whether they were treated before implementation of the time reduction measure (from January 2012 to May 2014) or after (from June 2014 to May 2015). The onset-to-door, onset-to-needle, onset-to-recanalization (O2R), door-to-image (D2I), door-to-needle (D2N), door-to-puncture (D2P), door-to-recanalization (D2R), and puncture-to-recanalization time intervals were compared between the two groups. There were 14 patients (including 8 elderly patients ≥80 years) before and 14 patients (including 10 elderly patients ≥80 years) after the time reduction measure. The mean duration of each of the following time intervals was significantly reduced after the time reduction measure ($P < 0.05$). To reduce the O2R time, the D2P time is the first time interval that can be reduced. At our center, conferences were regularly held to raise awareness among staff and make specific changes in the workflow, and overall time reduction was achieved. Similar results were obtained in elderly patients.

Key words: mechanical thrombectomy, aged, acute occlusion

Introduction

Endovascular recanalization therapy for acute occlusion of major cerebral arteries is reportedly associated with a high recanalization rate, and reducing the time from symptom onset to recanalization is important because time reduction affects prognosis.[1)] However, the efficacy of time reduction in elderly patients remains unknown. This study evaluated the current status of a measure aimed at reducing the time to recanalization at a comprehensive stroke center and the effects of the measure on treatment outcomes overall, including elderly patients.

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Materials and Methods

Participants included in the analyses were 42 consecutive patients (including 28 elderly patients ≥75 years) with acute occlusion of major cerebral arteries who were treated with intravenous (IV) injection of tissue plasminogen activator (t-PA) within 4.5 hours of stroke onset, followed by retrieval of the thrombus by endovascular therapy during the period in which the Penumbra System® was introduced, from January 2012 to May 2015.

The patients were divided into two groups according to whether they were treated before the start of the time reduction measure (from January 2012 to May 2014) or after (from June 2014 to May 2015). The onset-to-door (O2D), onset-to-needle (O2N),

onset-to-recanalization (O2R), door-to-image (D2I), door-to-needle (D2N), door-to-puncture (D2P), door-to-recanalization (D2R), and puncture-to-recanalization (P2R) time intervals were statistically compared and analyzed between the two groups for elderly patients, defined as aged ≥75 years.

In addition, these two groups were also compared and analyzed for sex; age; stroke severity at onset (using the National Institutes of Health Stroke Scale [NIHSS] score); modified Alberta Stroke Program Early Computed Tomography Score (ASPECTS + W) on diffusion-weighted imaging (DWI) before treatment;[2] the presence or absence of hypertension, diabetes mellitus, or atrial fibrillation; stroke type; proportion of patients with symptomatic intracranial hemorrhage (sICH) who showed a worsened NIHSS score by ≥4 points 36 hours after onset; the frequency of the use of equipment; location of occluded blood vessels; degree of recanalization (using the Thrombolysis in Cerebral Infarction [TICI] grade);[3] and outcomes at the time of discharge and 90 days after onset (using the modified Rankin scale [mRS]). The proximal occlusion was defined as proximal occlusion of the internal carotid (IC) and middle cerebral (M1 proximal and distal) arteries.[4] Successful recanalization was defined as procedural success with TICI grade 2B to 3. As for outcomes, functional independence was defined as an mRS score of 0–2 and good outcome as mRS score of 0–3.[5]

It should be noted that, in all cases at the time that stent retrievers were used for procedures, the Penumbra 5MAX® (Medicos Hirata, Japan) or Penumbra ACE® (Medicos Hirata, Japan) was used as combined aspiration and stent retrieval technique for thrombectomy.[6]

Development of the time-reducing program at our hospital

The first step for admission to our stroke center is that a request for patient admission is received through the Stroke Care Unit hotline. After the patient's arrival, establishment of vascular accesses for infusion and blood collection is first simultaneously performed. Then, the patient is transferred to the radiology suite for chest radiography and to the computed tomography (CT) suite for a head CT. When hemorrhagic diseases are ruled out by head CT, the patient is temporarily brought back to the emergency room. A nurse examines the patient using a checklist to determine the appropriateness of magnetic resonance imaging (MRI). Subsequently, the patient is transferred to the MRI suite and examined. Because the MRI suite is located in the basement of the outpatient emergency department, the use of an elevator is necessary to transfer a patient from the emergency room, located on the first floor, to the MRI suite. When IV t-PA injection is indicated, the patient is brought back to the emergency room on the first floor. Then, the patient's body weight is measured, and the t-PA is prepared. The patient stays in the emergency room for 1 hour after the start of IV t-PA injection. If IV t-PA injection is ineffective, the patient is transferred to the cerebral angiography suite, which is located on the opposite side of the corridor from the emergency room, and preparation for endovascular therapy is begun.

This workflow was examined for possible time-reduction measures. Whenever a patient was treated according to this workflow, the clinical course was reviewed, and revisions necessary for time reduction were applied to the workflow after each case.

Implemented revisions

Regarding blood collection after patient arrival, we decided that only items necessary for determining the applicability of IV t-PA injection (eg, platelet count, prothrombin time, and blood glucose) would be first ordered separately. Regarding workflow changes, we decided that CT scans would be continuously performed from the head to trunk to rule out aortic dissection at the process of plain CT, and chest radiography was omitted. Moreover, changes were made so that IV t-PA injection would be prepared as soon as it was determined to be indicated by measuring the patients' body weight before they were transferred to the MRI suite for head MRI. The imaging sequence for head MRI was also reviewed. After the time-reduction measure, we decided that imaging would be performed in the following order: DWI, magnetic resonance angiography (MRA), fluid-attenuated inversion recovery (FLAIR) MRI, T_2-weighted MRI*, T_1-weighted MRI, and T_2-weighted MRI, and that, whenever IV t-PA injection was determined to be indicated, MRI would be discontinued even before the completion of the imaging sequence. For patients with occluded major arteries, we decided to transfer the patient to the angiography suite while injecting t-PA, or to inject t-PA while the patient was in the angiography suite. We also decided that, before patients were transferred to the angiography suite, a few vascular accesses for infusion would be established so that intubation and sedative therapy could be performed without delay, even in patients who could not stay still or had difficulty in staying still (e.g., those with lesions in the left side and those who were agitated and severely restless) (Table 1).

Regarding statistical analyses, the χ^2 test or Fisher's exact test was performed to compare patient characteristics. Among them, NIHSS, ASPECTS + W, and mRS scores were compared by the Mann-Whitney *U*-test.

Table 1 Implemented revisions of the time-reducing program at our hospital

Work flow changes	Pre-time reduction	Post-time reduction
Blood collection	Order the items necessary for hospitalization in a single	Separate order only the minimum necessary ones for the judging of IV t-PA enforcement
CT usage	The patient is transferred to the radiology suite for chest radiography and to the CT suite for head CT	Continuously performed from the head to trunk at the process of plain CT
MRI protocols	Performed all in the order of DWI FLAIR T_1 T_2 T_2^* MRA	Performed in the order of DWI MRA FLAIR T_2^* T_1 T_2. It ends when it is determined that the adaptation of t-PA administered
Timing of measurement of body weight	After transferred to the MRI suite	Before transferred to the MRI suite
After the start of IV t-PA injection	Stays in the emergency room for 1 hour	Moves while administration t-PA, or t-PA administered in a angiography suite
Securing vascular access	Not specified	Before transferred to the angiography suite, a few vascular accesses would be established

Moreover, the Student t-test was used to compare time intervals. For all analyses, a *P* value of less than 0.05 was considered to indicate a significant difference.

Results

There were 130 patients who experienced acute cerebral infarction during the study period. Of those, 72 patients underwent IV t-PA alone, and 42 underwent acute recanalization therapy with endovascular treatment in addition to IV t-PA. There were 26 patients who underwent acute recanalization therapy, without IV t-PA. There were 24 patients with functional independence and 33 patients with good outcomes who underwent IV t-PA therapy alone at discharge. For patients undergoing acute recanalization therapy with endovascular treatment in addition to IV t-PA, the successful recanalization rate was 50%, and there were 8 patients with functional independence and 14 patients at discharge.

For patients undergoing acute recanalization therapy with endovascular treatment without IV t-PA, the successful recanalization rate was 68.4%, and there were 2 patients with functional independence and 5 patients at discharge. For patients undergoing acute recanalization therapy, the Penumbra System® alone was used in 28 cases and a stent retriever with the Penumbra System® was used in 16 cases. In acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, the successful recanalization rate using the Penumbra System® alone was 57%, and the mRS score at discharge for these patients was 14%. The effective recanalization rate for a stent retriever with the Penumbra System® was 100%, and with respect to outcomes, the mRS score at discharge was 28%.

Patient characteristics for elderly patients aged ≥75 years underwent acute recanalization therapy with endovascular treatment in addition to IV t-PA therapy are shown in Table 2.

The pre-time-reduction group included 14 elderly patients (included 8 elderly patients aged ≥80 years), while the post-time-reduction group included 14 elderly patients (included 10 elderly patients aged ≥80 years). The mean age was 80.9 years in the pre-time-reduction group and 82.2 years in the post-time-reduction group, which was not significantly different. Regarding sex, the pre-time-reduction group included 7 men and 7 women, while the post-time-reduction group included 6 men and 8 women. No significant difference was observed with respect to sex distribution between the two groups. Hypertension was observed in 7 elderly patients in the pre-time-reduction group and in 10 elderly patients in the post-time-reduction group; diabetes mellitus was observed in 3 and 4 elderly patients, respectively; and atrial fibrillation in 10 and 7 elderly patients, respectively. No significant differences were observed in the prevalence of these diseases between the two groups.

Regarding the type of cerebral infarction, the pre-time-reduction group included 12 cases of cardiogenic embolism and 2 cases of brain embolism of unknown cause, while the post-time-reduction group included 13 cases of cardiogenic embolism and 1 case of atherothrombosis, which was not significantly different.

The occlusion sites are shown in Table 3. The pre-time-reduction group included 5 cases involving the internal carotid artery, 3 involving the middle cerebral artery (M1 proximal), 1 involving the middle cerebral artery (M1 distal), 4 involving the basilar artery, while the post-time-reduction group included 4 cases involving the internal carotid artery, 4 involving the middle cerebral artery (M1 proximal), 3 involving the middle cerebral artery (M1 distal),

Table 2 Characteristics of elderly patients aged ≥75 years before and after the time reduction measure

	Before time reduction measure	After time reduction measure	*P* value
	N = 14	*N* = 14	
Mean age (standard deviation)	80.9 (±3.9)	82.2 (±6.1)	
Sex (men)	7 (50%)	6 (43%)	1
Hypertension (present)	7 (50.0%)	10 (71.4%)	0.4401
Diabetes mellitus (present)	3 (21.4%)	4 (28.6%)	1
Atrial fibrillation (present)	10 (71.4%)	7 (50.0%)	0.4401
Median NIHSS score (range)	25.5 (8–38)	20 (12–40)	0.5194
Occlusion site (IC and M1 proximal, distal)	10 (71.4%)	10 (71.4%)	0.114
Median ASPECTS + W (range)	8 (3–11)	7.5 (3–11)	0.8586
Recanalization level (TICI 2B and 3)	2 (20.0%)	11 (78.6%)	0.0111*
Symptomatic ICH	3 (21.4%)	3 (21.4%)	1
90 days modified RS (≦2)	0 (0%)	3 (21.4%)	0.2222
90 days modified RS (≦3)	2 (15.4%)	7 (50.0%)	0.1032

*$P < 0.05$

ASPECTS + W: Alberta Stroke Program Early Computed Tomography Score, ICA: Internal Carotid Artery, Symptomatic ICH: Symptomatic intracerebral hemorrhages, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, TICI: Thrombolysis in Cerebral Infarction.

Table 3 Comparison between before and after the time reduction measure of occlusion site for elderly patients aged ≥75 years

	Before time reduction measure	After time reduction measure
	N = 14	*N* = 14
BA	4	0
IC	5	4
M1p	3	4
M1d	1	3
M2	0	2
M2, A2	0	1

A2: anterior cerebral artery A2 segment, BA: Basilar Artery, ICA: Internal Carotid Artery, M1d: middle cerebral artery M1 distal segment, M1p: middle cerebral artery M1 proximal segment.

2 involving the middle cerebral artery (M2), and 1 involving the anterior cerebral artery (A2) and middle cerebral artery (M2).

The Penumbra System® alone was used in 7 cases (50.0%) and none of the cases used a stent retriever with the Penumbra System® in the pre-time-reduction group, and the Penumbra System® was alone used in 5 cases (35.7%) and a stent retriever with the Penumbra System® was used in 8 cases (57.1%) in the post-time-reduction group.

The median NIHSS score before onset was 25.5 in the pre-time-reduction group and 20.0 in the post-time-reduction group, which was not significantly different. Successful recanalization was performed for 2 elderly patients in the pre-time-reduction group and 11 elderly patients in the post-time-reduction group, which was significantly different. The proximal occlusion site was observed in 10 elderly patients in the pre-time-reduction group and in 10 elderly patients in the post-time-reduction group. No significant difference was observed between the two groups.

The mean duration of each of the following time intervals was significantly reduced: from 64 to 39 minutes for D2I, from 115 to 82 minutes for D2N, from 186 to 125 minutes for D2P, from 320 to 220 minutes for D2R, and from 379 to 290 minutes for O2R ($P < 0.005$). Moreover, the P2R time was reduced from 134 to 94 minutes (Fig. 1).

The outcomes are shown in Fig. 2. Although none of the patients in the pre-time-reduction group had functional independence and there were 2 patients with good outcomes, there were 3 patients with functional independence and 7 patients with good outcomes in the post-time-reduction group at 90 days after onset. Although the difference at 90 days after onset was not statistically significant, improvement was observed.

Discussion

The measure aimed at reducing the time to recanalization at our center resulted in significant reduction in the D2P time for patients of all ages, including elderly patients aged ≥75 years and ≥80 years, whereas no difference was observed in the P2R time.

When treatment outcomes were compared between the pre- and post-time-reduction groups, although the difference at 90 days after onset was not statistically significant, improvement was observed.

Overseas randomized controlled trials[7–12] include both those without an upper limit for age and those with an exclusion criterion of patients aged ≥80 years. For example, in the Third Interventional Management of Stroke (IMS III) trial,[8] eligible

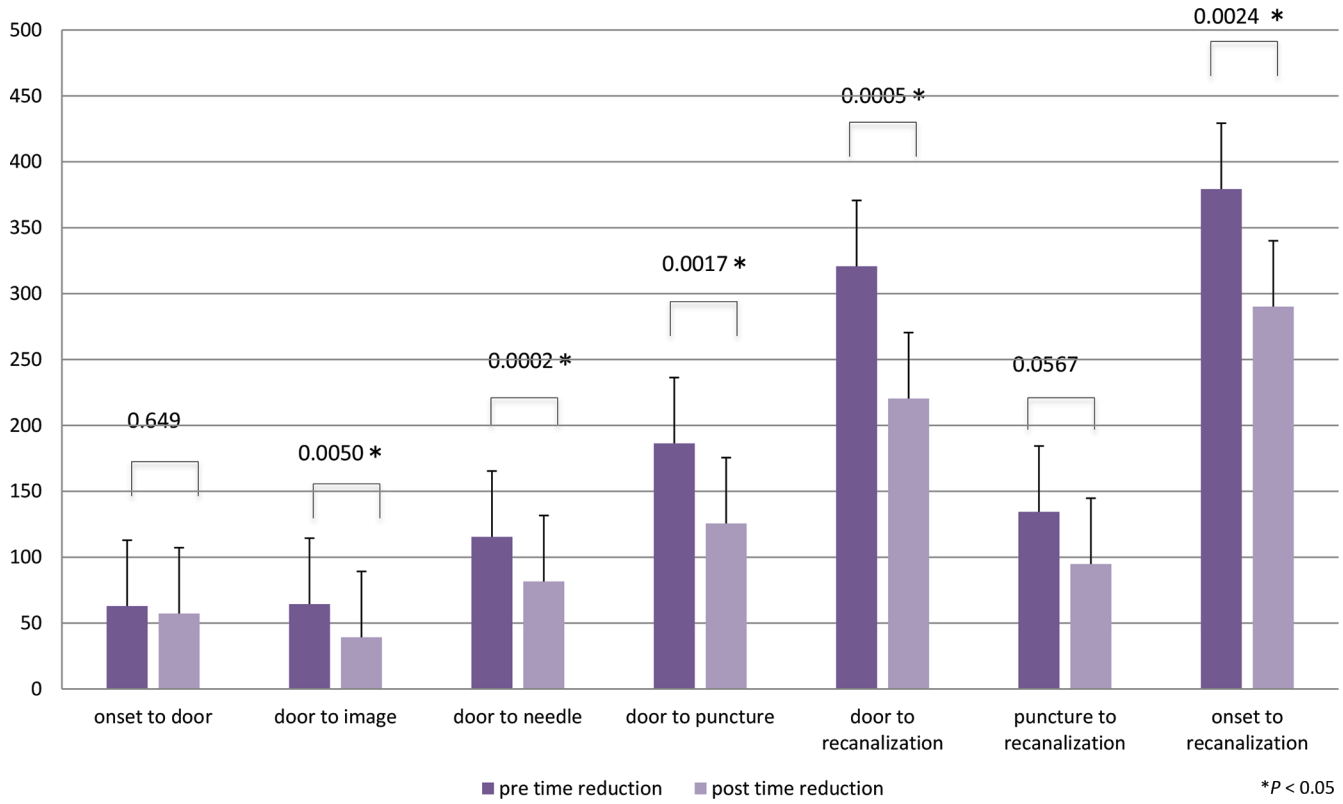

Fig. 1 Comparison of time intervals before and after the time reduction measure in elderly patients aged ≥75 years: The mean duration of each time interval between the arrival of a patient and puncture was significantly reduced after the measures were implemented, whereas no difference was observed in the P2R time.

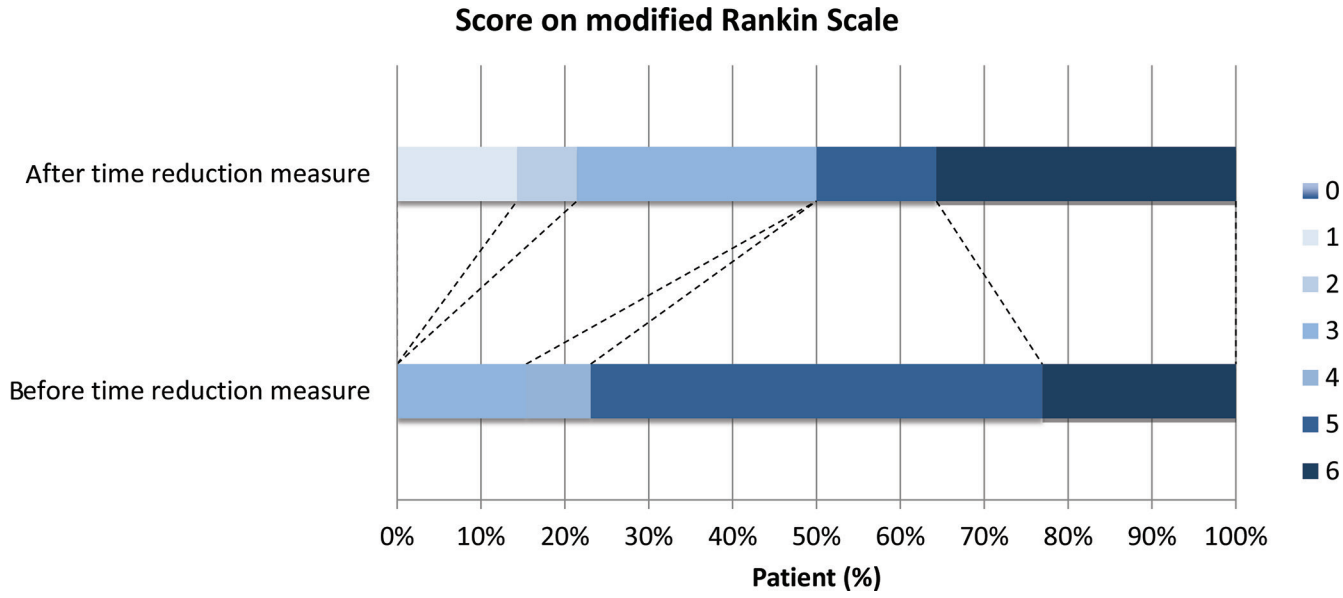

Fig. 2 Distribution of functional scores at 90 days: Although the difference at 90 days after onset was not statistically significant, improvement was observed.

patients were limited to those aged ≤82 years. In the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial,[11] the eligibility age is limited to ≤80 years. According to a meta-analysis of studies reported between 1990 and 2012 that compared outcomes of endovascular therapy for acute cerebral infarction by age (≥80 years vs <80 years),[13] the younger group included significantly more patients with favorable outcomes (mRS 0–2) at 90 days (odds ratio [OR], 2.69; 95% confidence interval [CI], 1.94–3.74, $P < 0.001$), and sICH and death were more frequently observed in the elderly group (OR, 1.60; 95% CI, 1.01–2.54; $P = 0.04$ and OR, 3.70; 95% CI, 2.52–5.42; $P < 0.001$, respectively).

Moreover, in elderly patients, because of severely curved and tortuous arteries and severe *atherosclerotic* lesions, the risk of perioperative complications of endovascular therapy tends to be high, and the recanalization rate tends to be low. Compared to younger patients, fewer elderly patients achieve favorable outcomes because of underlying diseases and complications.

Meanwhile, the North American Solitaire Stent Retriever Acute Stroke registry (NASA) study[14] has reported outcomes of acute recanalization treatment performed only in elderly patients. According to this study, comparison of the outcomes at 90 days between two groups divided at the age of 80 years showed that younger patients followed a more favorable clinical course. However, no significant difference was reported with respect to the time to recanalization, recanalization rate, and incidence of sICH between the two groups. On the basis of these findings, it can be assumed that recanalization is associated with only a few technical disadvantages, even for elderly patients. Moreover, multivariate analysis identified age of ≥80 years as the only factor for poor prognosis, while the factors for favorable prognosis included a mild condition (low NIHSS score at onset), prior administration of IV t-PA injection, and short time to recanalization. In patients aged ≥80 years, the independent predictors for death were identified as NIHSS scores at onset, recanalization status, use of rescue therapy, and presence or absence of sICH.

Among our patients in the present study, including those with previous IV t-PA injection, good outcomes were obtained only in patients with a moderate or mild condition, as indicated by an NIHSS score of ≤26 at onset. Moreover, the time to recanalization was shorter in patients with better outcomes than in the others. These findings are consistent with those described in previous reports. In addition, outcomes were poor in patients with severe conditions, those treated with additional endovascular procedures (such as percutaneous transluminal angioplasty), and those with unsuccessful recanalization.

In this study, the improvement of the recanalization rate is considered to have influenced outcomes, which may be attributable to the increased use of stent retrievers in the post-time-reduction group. The effective recanalization rate with the use of the Penumbra System® alone is 57% in our hospital, but the effective recanalization rate with the use of a stent retriever with the Penumbra System® was as high as 100%. In the post-time-reduction group, a stent retriever was used in ≥50% of patients of all ages, including elderly patients aged ≥75 and ≥80 years.

A factor that did not lead to a significant difference in observed outcomes for each age group may be a difference in the technical capabilities of the surgeons performing the procedure.

Although not limited to the elderly, improving the teamwork of the medical care team by standardizing procedures, such as using a stent retriever for all cases, may also decrease the time from a puncture to recanalization.

In the present study, favorable results appeared to be associated with the inclusion of patients with previous IV t-PA injection and reduced time to recanalization based on the time-reduction measure. However, there is a little number of cases at present, and the accumulation of the case is expected in future. Meanwhile, the higher successful recanalization rate in the elderly after the time reduction compared to the before the time reduction measure, that might appear to be associated with the improvement of procedures of our stroke team and the difference of use of thrombectomy device. Thus, the positive effect of time reduction was observed even in elderly patients. Our results suggest that rapid and successful recanalization might contribute to maintaining activities of daily living. If transition to home care is also targeted to patients for whom independent activities of daily living are not achievable, acute recanalization treatment should be aggressively considered, even for elderly patients.

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Conflicts of Interest Disclosure

Yoshiaki Shiokawa has received payment for development of educational presentations from Daiichi-Sankyo-Seiyaku.

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Koichiro Komatsubara, Tomohisa Dembo, Hiroo Sasamori, Masataka Torii and Eishi Sato declare that they have no conflicts of interest.

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