



Strategy to Achieve Faster Recanalization for Acute Ischemic Stroke in a University Hospital with Many Constraints

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Objective: It is essential to improve the in-hospital system and arrangement to achieve recanalization as soon as possible in acute cerebral artery occlusion. In Saitama Prefecture, the stroke emergency transport system began to operate in January 2018 under the prefectural government initiative. At our hospital, also, a trial aiming at rapid, safe, and effective recanalization was initiated in August 2017 in a team consisting mainly of doctors and co-medical staff of the Stroke Center. In this report, the results of the 17-month trial are reviewed.

Methods: In all, 127 patients with acute cerebral artery occlusion who underwent endovascular treatment between January 2016 and December 2018 (56 treated before and 71 treated after the initiation of the time-reducing trial) were compared. Interdepartmental conferences and simulations were frequently held with participation primarily by physicians, radiology technicians, and nurses, and information about treatments, operations by various professionals, and therapeutic approaches was shared. The diagnostic and therapeutic processes of the cases experienced were also promptly evaluated and modified for improvements.

Results: The time from the arrival of the patient to the injection of recombinant tissue plasminogen activator (rt-PA) was significantly reduced from 90 to 75 minutes, time from the arrival to puncture from 99 to 74 minutes, procedure time from 63 to 50 minutes, and time from the arrival to eventual recanalization from 165 to 130 minutes. The rate of effective recanalization was higher after the initiation of the trial (62% vs. 76%), but the difference was not significant. The percentage of patients with a favorable outcome was also higher after the initiation of the trial (25% vs. 39%).

Conclusion: The results of this study indicate that the time of emergency treatment for acute cerebral artery occlusion can be shortened even in a large-scale university hospital with many constraints by sharing of information among departments and making sure that the medical staff of stroke center is well-informed of the standardized therapeutic approach.

Keywords ▶ acute cerebral artery occlusion, mechanical thrombectomy, stroke team approach, rapid recanalization, therapeutic time

Introduction

Since the effectiveness of endovascular treatment (mechanical thrombectomy, [MT]) for emergent large vessel occlusion (ELVO) was demonstrated by randomized controlled trials

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Received: January 7, 2019; Accepted: August 1, 2019

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(RCTs) in 2015,¹⁻⁵⁾ improvement in the recanalization rate and reduction in the time until recanalization have become extremely important. The conclusions of these recent RCTs can be summarized as follows: (1) early recanalization leads to a favorable outcome, (2) MT using a stent retriever (SR) is safe and effective, (3) patient selection using imaging modalities is important, and (4) development of an in-hospital system (team work) is vital for achieving prompt recanalization.⁶⁾ In Saitama Prefecture, the stroke emergency transport system began to operate under the prefectural government initiative in January 2018. Our hospital, which is a large-scale university hospital, has many regulations, and is vertically divided (lacks inter-department communications), was also designated as a foundation hospital and began to be required more than ever to organize an in-hospital system for prompt recanalization as an institution

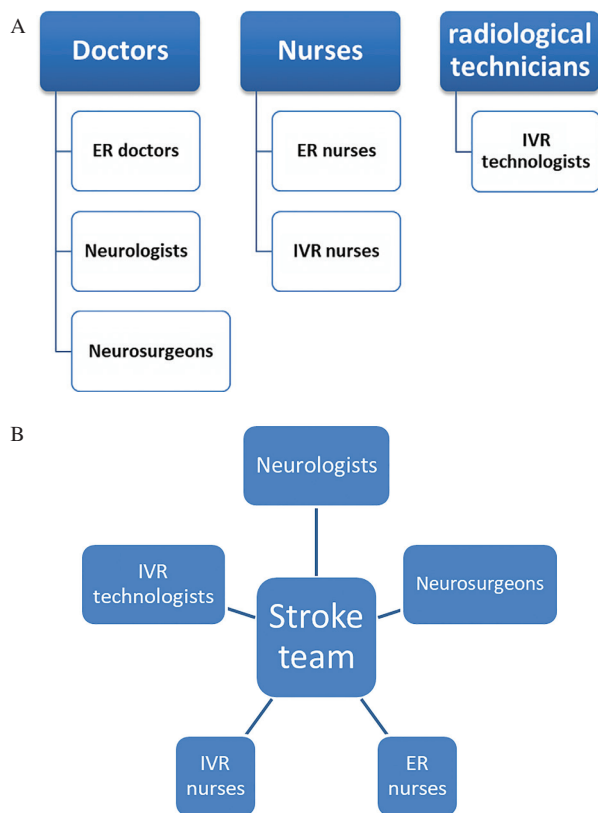


Fig. 1 (A) There is vertical sectionalism and not a horizontal connection in our university hospital. (B) The making of a stroke team which can exchange information freely between sections. ER: emergency room; IVR: interventional radiology

that can handle emergency recanalization therapy. We established a stroke team primarily staffed by endovascular neurosurgeons, neurologists, nurses, and radiology technicians and initiated a trial to implement prompt, safe, and effective recanalization (**Fig. 1**). Here, we review the results of our efforts for a year at a university hospital with many constraints.

Materials and Methods

Subjects: The subjects were 127 patients with acute cerebral artery occlusion who underwent endovascular treatment for recanalization in the acute period between January 2016 and December 2018. In all, 56 patients (Group 1) treated by July 31, 2017, before the trial to shorten therapeutic time, and 71 patients (Group 2) treated since August 1, 2017, after the trial were compared.

Treatment: At our hospital, plain CT and MRI of the head are performed in all patients, in principle, to evaluate the indication of recanalization therapy. Recombinant tissue plasminogen activator (rt-PA) was administered to those

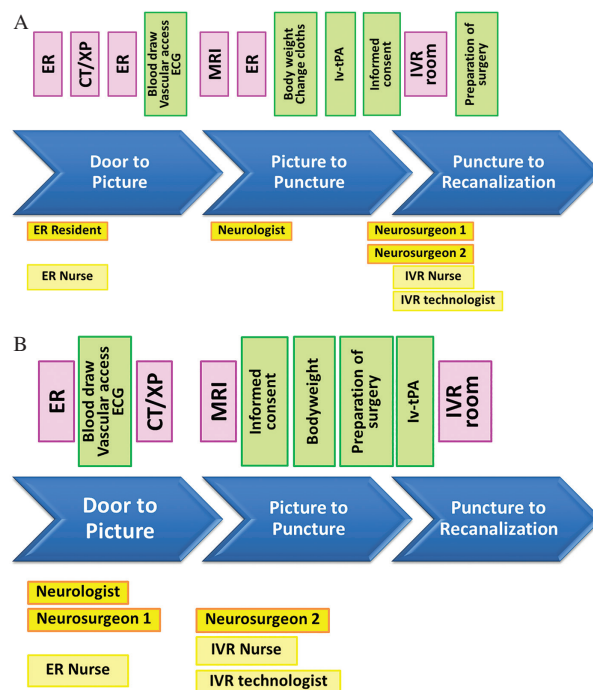


Fig. 2 Implemented revision of the time-reducing program at our hospital. Protocol of before (A) or after (B) trying to reduce the time from hospital admission to recanalization. ER: emergency room; IVR: interventional radiology; XP: X-ray Photograph; ECG: electrocardiogram; Iv-tPA: intravenous tissue type plasminogen activator

with indications without omissions. As endovascular treatment, retrieval using SR or aspiration of thrombi was selected depending on the site of occlusion. All treatments were performed under local anesthesia.

Time-reducing measures: A diagnostic and therapeutic in-hospital aiming at prompt initiation of rt-PA injection therapy and endovascular procedures in patients who need recanalization therapy for major intracranial artery occlusion was formulated (**Fig. 2**). The circumstances at our hospital before the time-reducing scheme were as follows: A request to accept a patient is received via the hot line. After the arrival of the patient, the intravenous (IV) line is secured, and blood is sampled simultaneously. The patient is transferred to the X-ray room, and chest radiography is performed. Then, the patient is transferred to the CT room, plain CT of the head is performed, and, if intracranial hemorrhage is excluded, the patient is brought back to the emergency room, and moved to the MRI room for examination. If the patient is judged to have an indication for rt-PA, he/she is transferred back to the emergency room again, endovascular neurosurgeons are contacted, the patient is weighed, the administration of rt-PA is initiated, the patient is transferred to the cerebral angiography room, and preparations for endovascular treatment are initiated.

In addition, there was no communication among the endovascular neurosurgery and neurology departments, emergency room nurses, nurses of the endovascular treatment team, and radiologists, and the necessity of time reduction was not understood. There were frequent personnel relocations, and the staff was poorly informed. When we decided to conduct a time-reducing trial, we appointed one to two members in charge of acute cerebral infarction therapy in each section or department, and conferences attended by endovascular neurosurgeons, neurologists, nurses (of the emergency and angiography rooms), radiology technicians, and pharmacists in charge were held to establish close inter-department communication. Problems that would interfere with time reduction in each department were shared, and the members in charge tried to disseminate information such as the importance of time reduction and points to be changed. It was arranged that, at the time of contact by the ambulance crew about patient transport, the endovascular neurosurgeons, neurologists, radiology technicians, nurses, and pharmacists on duty are informed and prepared to cooperate by sharing information. Concerning change in the route of patient transfer, following chest X-ray and head CT, the patient is immediately transferred for head MRI so that, even during MRI, the preparation of the drug can be initiated as soon as the judgment of whether there is an indication for rt-PA is made. Emphasis was placed on efficient use of time during imaging examinations, additional diagnostic information is provided during the examinations, and, in patients who may have an indication for recanalization therapy, it is explained to the family, and the procedure to obtain consent to the treatment is carried out, simultaneously with the examinations by dividing the assignments within the team. The arrangements after the examinations are that rt-PA is performed in patients with an indication and that patients with occlusion of a major cerebral artery are transferred to the angiography room while administering rt-PA or administered rt-PA in the angiography room. Consciousness of the staff about time is enhanced by having them write down the time needed for each step in a chart indicating the target times. Simulation is performed periodically in the stroke team to make the team always capable of rapidly carrying out the standardized workflow. The course of treatment in each patient is reviewed according to the chart in which times are written down, the operations are brushed up at each review, and operations in which time is wasted are modified. Since there are a wide variety of physicians because of the characteristics as a university hospital, the methods

for the preparation of devices and selection of devices according to the site of occlusion are standardized. In principle, aspiration using the Penumbra (Penumbra Inc., Alameda, CA, USA) (a direct aspiration first pass technique [ADAPT]) is adopted as the first choice for occlusion of the internal carotid artery to the proximal part of the middle cerebral artery, a combination of SR and the Penumbra system as the first choice for M1 distal occlusion, and SR alone as the first choice for occlusion distal to the M2 or the posterior circulation.

Analysis: The times from the arrival of the patient to the beginning of head CT (door to CT), from the arrival to the beginning of MRI (door to MRI), from the arrival to the beginning of the administration of rt-PA (door to needle), from the arrival to puncture (door to puncture), from puncture to recanalization (puncture to recanalization), and from the arrival to eventual recanalization (door to recanalization) were calculated in each patient. In each group, the age, severity at the onset (National Institutes of Health Stroke Scale [NIHSS] score), Alberta Stroke Program Early CT Score (ASPECTS) in the diffusion-weighted image (DWI) before treatment, presence or absence of hypertension, diabetes, and atrial fibrillation, percentage of patients with symptomatic intracranial hemorrhage who showed 4-point or greater exacerbation of NIHSS score 48 hours after the onset, site of the occluded vessel, recanalization, NIHSS scores 24 hours after treatment and at discharge, and outcome at discharge (modified Rankin scale [mRS]) were compared. Recanalization was considered successful when the modified thrombolysis in cerebral infarction (mTICI) score was 2b-3. The outcome at discharge was considered favorable when the mRS was 0-2 and poor when it was 3-6. Statistical analysis was performed using IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA). The patient demographics and outcomes were compared using the chi-square test and Fisher's exact test. The NIHSS score, ASPECTS + W, age, and durations of various intervals were compared using the Mann-Whitney U-test. A p value of <0.05 was considered significant in all tests.

Results

Patient demographics and baseline characteristic of the two groups are shown (**Table 1**). The median age was 74 (33-92) years in Group 1 and 76 (45-92) years in Group 2 with no significant difference ($P = 0.82$). There was no significant difference in the percentage of patients with hypertension, diabetes, hyperlipidemia, coronary artery disease,

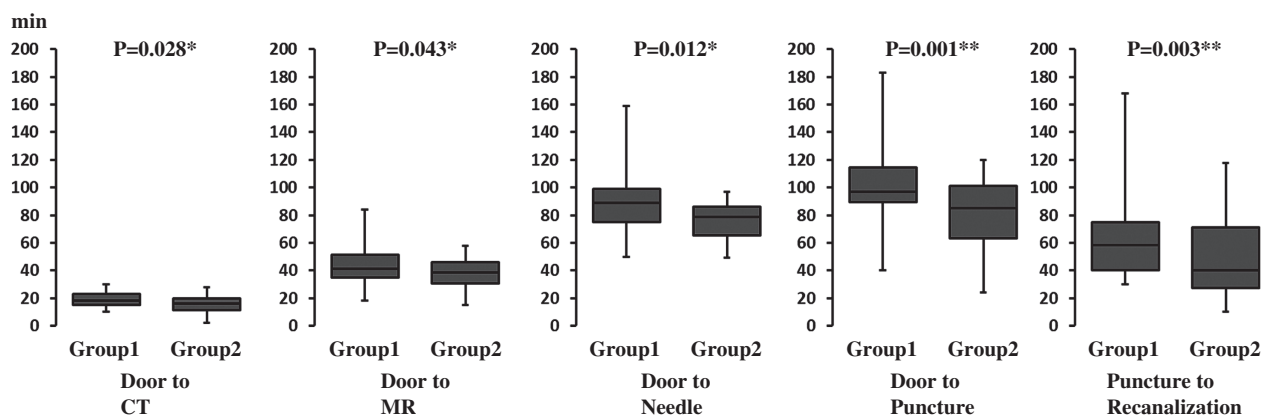
Table 1 Patient demographics and baseline characteristics between before (Group 1) and after (Group 2) trying reduction in time from hospital admission to recanalization

	Group 1	Group 2	P value
Number of patients	56	71	
Median age, years (range)	74 (33–92)	76 (45–92)	0.82
Hypertension, n (%)	32 (57.1)	42 (59.2)	0.38
Diabetes, n (%)	12 (21.4)	18 (25.4)	0.30
Hyperlipidemia, n (%)	14 (25.0)	15 (21.1)	0.89
Atrial fibrillation, n (%)	35 (62.5)	36 (50.7)	0.18
Stroke type, n (%)			
Atherosclerotic	8 (14.3)	18 (25.4)	0.12
Cardiogenic	43 (76.8)	48 (67.6)	0.25
Dissection	3 (5.4)	1 (1.8)	0.21
Other	2 (3.6)	4 (5.7)	0.59
NIHSS on admission (median)	14	15	0.31
Modified Rankin Scale (%)			
Score 0	40 (71.4)	58 (81.7)	0.17
Score 1	6 (10.7)	5 (7.0)	0.47
Score 2	5 (8.9)	4 (5.6)	0.47
Score >2	5 (8.9)	4 (5.6)	0.47
ASPECTS-DWI (median)	7	7	0.53
rt-PA (%)	34 (60.7)	43 (60.6)	0.99
Occluded vessel (%)			
ICA	20 (35.7)	26 (36.6)	0.91
MCA M1 proximal	9 (16.1)	14 (19.7)	0.59
MCA M1 distal	15 (26.8)	20 (28.2)	0.86
MCA M2	4 (7.1)	6 (8.5)	0.78
BA	7 (12.5)	4 (5.6)	0.19
VA	1 (1.8)	1 (1.4)	0.87

ASPECTS-DWI: Alberta Stroke Program Early CT score diffusion-weighted imaging;

BA: basilar artery; ICA: internal carotid artery; MCA: middle cerebral artery; NIHSS: National Institute of Health Stroke Scale; rt-PA: intravenous tissue plasminogen activator;

VA: vertebral artery

**Fig. 3** The duration of each time interval before and after the time-reduction measure is shown. The duration of each time interval between the arrival of a patient and CT, MRI, needle and puncture was significantly reduced after the measures were implemented, also a significant difference was observed in the puncture to recanalization time (* $P < 0.05$, ** $P < 0.01$).

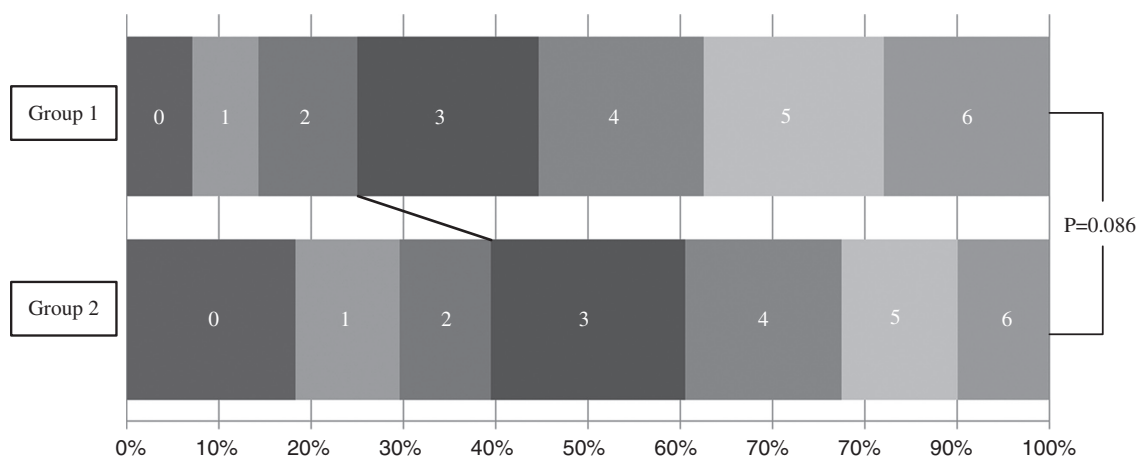
or atrial fibrillation between the two groups. The median NIHSS score on admission was 14 in Group 1 and 15 in Group 2 with no significant difference ($P = 0.31$). Similarly, no significant difference was noted in mRS before admission, pathogenesis of cerebral infarction, site of

occlusion, or percentage of patients treated with rt-PA. The median door to image (CT) time (interquartile range) was 18 (15–23) minutes in Group 1 and 16 (11.5–20) minutes in Group 2 ($P = 0.028$), the door to image (MRI) time was 41.5 (34.75–51.5) minutes in Group 1 and 38.5 (30.75–46)

Table 2 Outcome of patient between before (Group 1) and after (Group 2) trying reduction in time from hospital admission to recanalization

	Group 1	Group 2	P value
Treatment			
SR	38 (67.9)	21 (29.6)	0.0017**
Penumbra system (ADAPT)	5 (8.9)	28 (39.4)	0.0099**
SR + Penumbra system	13 (23.2)	22 (31.0)	0.33
Recanalization rate			
mTICI 0	1 (1.8)	0 (0)	0.26
mTICI 1	7 (12.5)	3 (4.2)	0.09
mTICI 2a	13 (23.2)	14 (19.7)	0.63
mTICI 2b	16 (28.6)	23 (32.4)	0.64
mTICI 3	19 (33.9)	31 (43.7)	0.26
Number of passes			
1	29 (51.8)	51 (71.8)	0.021*
2	20 (35.7)	15 (21.1)	0.067
≥3	7 (12.5)	5 (7.0)	0.296
Intracranial hemorrhage (%)			
Asymptomatic	2 (3.6)	2 (2.8)	0.81
Symptomatic	1 (1.8)	1 (1.4)	0.87

P values <0.05 were considered statistically significant. ADAPT: a direct aspiration first pass technique; mTICI: modified thrombolysis in cerebral infarction; SR: stent retriever

**Fig. 4** Outcome of patients between before (Group 1) and after (Group 2) trying to reduce the time from hospital admission to recanalization. Modified Rankin Scale at discharge of each group.

minutes in Group 2, showing a significant reduction ($P = 0.043$). The door to needle time was 89 (75–98.75) minutes in Group 1 and 78.5 (65.25–86) minutes in Group 2, being significantly shortened in Group 2 ($P = 0.012$), the door to puncture time was 97 (89.5–114.5) minutes in Group 1 and 85 (63–101) minutes in Group 2 ($P = 0.001$), the puncture to recanalization time was 58.5 (40.5–74.75) minutes in Group 1 and 40 (27.5–71) minutes in Group 2, being significantly shortened in Group 2 ($P = 0.003$), and the door to recanalization time was shortened by about 30 minutes (**Fig. 3**). **Table 2** shows the results of treatment. In Group 1, 38 (67.9%) were treated with SR alone, 5 (8.9%) were treated by ADAPT using the Penumbra, and 13 (23.2%)

were treated with SR and aspiration using the Penumbra. In Group 2, 21 (29.6%) were treated using SR alone, 28 (39.4%) were treated by ADAPT using the Penumbra, 22 (31.0%) were treated with SR and aspiration using the Penumbra, and significant differences were observed in the devices used. Satisfactory recanalization with mTICI $\geq 2b$ was achieved in 35 (62.5%) in Group 1 and more frequently in 54 (76.1%) in Group 2, but the difference was not significant (**Table 2**). The number of device passes was significantly smaller in Group 2 ($P = 0.021$) (**Table 2**). The number of patients with symptomatic intracranial hemorrhage who showed 4-point or greater exacerbation in the NIHSS 48 hours after the onset was 1 (1.8%) in Group 1

and 1 (1.4%) in Group 2 with no significant difference in their frequency. Also, the percentage of patients with asymptomatic intracranial hemorrhage was 2 (3.6%) in Group 1 and 2 (2.8%) in Group 2 with no significant difference in their frequency. The outcome at discharge was favorable in 14 (25%) in Group 1 and 28 (39.4%) in Group 2, and despite the higher percentage in Group 2, the difference was not significant ($P = 0.086$) (**Fig. 4**).

Discussion

Recently, shortening of the time of each stage of MT for ELVO from transport to recanalization has been emphasized in RCTs. Patient selection based on CT rather than MRI has become the mainstay, and a regimen consisting of rt-PA therapy and MT has been adopted, resulting in the mean time from the initial imaging examination to puncture of 100 minutes in Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), 93 minutes in Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA), 58 minutes in SWIFT PRIME, and even 51 minutes in Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE).⁷⁻⁹⁾ At our institution, following the society of neurointerventional surgery (SNIS) guidelines,¹⁰⁾ goals were set at 30 minutes for the door to needle time, 60 minutes for the door to puncture time, and 90 minutes for the door to recanalization time. Based on the results of five RCTs,¹⁻⁵⁾ attempts to reduce the time of various procedures for recanalization of major arteries of the brain have also been reported from institutions in Japan.¹¹⁾ Increasingly, institutions have begun to evaluate indications by CT alone without MRI, which is more time-consuming,¹²⁾ and the Solitaire Flow Restoration Thrombectomy for Acute Revascularization (STAR) trial reported that MRI delays recanalization by 18 minutes.¹³⁾ In addition, our institution has two 3T and one 1.5T MRI system but no MRI to be used specifically for emergency medicine, and MRI systems are fully booked daily during the daytime. During the day time, emergency MRI is performed during the intervals of patient shifts in the waiting room. In the nighttime, MRI can be performed smoothly without a waiting time. We have one 64-row CT system specifically allocated to emergency imaging, and imaging can be made smoothly without a waiting time during the daytime or nighttime. There are two angiography systems specifically for the neurosurgery department, one each installed in the

operation room and emergency room. During the daytime, the one in the operation room is used for endovascular surgery, and the one in the emergency room is used for examination (performed 2–4 times/day). At the arrival of a request for admission of a patient suspected to have acute cerebral infarction by the ambulance crew, the scheduled examination is postponed, and the emergency case is smoothly accepted. Change of the modality of early imaging evaluation to CT is an issue to be evaluated in the future. However, the assessment by CT is more dependent on the experience of the physician than the assessment by MRI and involves the risk of adversely affecting complications and the outcome. Since the evaluation of indications by CT alone is occasionally difficult at a university hospital, where there are inexperienced doctors, such as those in the late training phase, information obtained by MRI is considered important for avoiding misdiagnoses. Therefore, we concluded for the time being that MRI is indispensable at our institution and decided to use the time more efficiently by performing the procedure of informed consent, preparing the rt-PA, etc., during MRI. In retrospect, sorting and sharing of necessary information among neurologists, endovascular neurosurgeons, radiology technicians, and nurses during MRI, evaluating indications by multiple physicians, explaining the condition to the family, and making preparations to promptly initiate treatment after the examination are considered to have contributed to time reduction and safer implementation of rt-PA and MT. In patients with an indication for IV thrombolysis with rt-PA, also, MT was promptly initiated without waiting for drug dispensation, and the time for preparation of the device could be significantly shortened by always keeping a stock of thrombectomy kits in the endovascular treatment room. Nurses of the emergency room, pharmacists, radiology technicians, and interventional radiology (IVR) nurses play important roles in the processes to the initiation of rt-PA and puncture, and time reduction greatly owes to their cooperation. The shortening of the door to puncture time is considered to be a result of correction of sectionalism unique to a university hospital, establishment of the stroke team, sharing of information among departments and sections, consultation about points that needed improvements based on accumulation of experience and case conferences among departments and sections, quick and repeated minor modifications, and making the staff well informed and capable of implementing the workflow through simulation. However, the time that can be shortened by individual efforts of physicians, radiology technicians, nurses, and pharmacists is limited, and top-down radical

reform involving the entire hospital including the introduction of an imaging system (such as MRI) exclusively used for stroke and additional allocation of the personnel is considered necessary.

The puncture to recanalization time was considered to depend primarily on the performance of the device and skill of the surgeon, and the selection of the device and procedure was left to the judgment of the operator before the time-reducing trial. Before the reform, SR was used alone in 65% of the operations, followed by procedures with the concomitant coaxial use of the Penumbra system and SR, and ADAPT using the Penumbra system alone was performed least frequently because SR can be guided to the site of occlusion relatively easily, thrombi can be captured efficiently, and the use of SR was considered a reason for the usefulness of thrombectomy therapy in an RCT reported in 2015. Satisfactory recanalization could be achieved in 62.5% of the patients. Turk et al.¹⁴⁾ reported, along with the usefulness of ADAPT, that the percentage of outcomes rated as mTICI score 3 was high with Penumbra 5MAX Ace with an increased internal tip diameter compared with the conventional Penumbra 5MAX ACE. Lapergue et al.¹⁵⁾ compared the results of ADAPT using Penumbra 5MAX Ace with those using SR and reported that there was no difference in time until recanalization or the clinical outcome but that the rate of mTICI score 2B or better recanalization was significantly higher after ADAPT. In addition, procedures by the concomitant use of Penumbra and SR have been reported to achieve recanalization more rapidly and effectively than procedures using a single device,^{16,17)} and this advantage is partly ascribed to the concomitant use of the Penumbra, which serves as an intermediate catheter and enables withdrawal of SR parallel with the course of the blood vessel.¹⁸⁾ In reality, however, when the Penumbra could not be delivered to the M1, the length of the microcatheter was insufficient, and it occasionally failed to reach the site of occlusion distal to the M2. From these experiences, the device to be used was standardized after the time-reducing trial: ADAPT using Penumbra 5MAX Ace 68 was selected for IC to M1 proximal occlusion, SR and the Penumbra system were used in combination for M1 distal occlusion, and SR alone was used for occlusion of other sites as the first choices. This resulted in successful recanalization in 76% of the patients. Moreover, the percentage of recanalization achieved by a single pass was 51.8% before the time-reducing trial but was 71.8% after the trial ($P = 0.021$). At a university hospital, where there is frequent reshuffle of doctors, and there are many doctors uncertified as specialists, standardization of the device

according to the indication saves the time and trouble of device selection, and sharing of the workflow between the operator and the supporting staff has led to shortening of the time for preparation and improvement of the learning curve. The puncture to recanalization time could be shortened by about 23 minutes compared with that before the trial ($P = 0.003$), the rate of successful recanalization could be improved, and the number of device passes could be reduced.

By a review about 1.5 years after the beginning of a time-reducing trial with standardization of the treatment procedure and device, the time from the arrival of the patient to recanalization could be shortened by about 33 minutes compared with that before the trial. In addition, the percentage of successful recanalization and the percentage of patients with a favorable outcome at discharge also increased. Not only time reduction but also advances in surgical techniques and devices are considered to have contributed to the improvement in the outcome, but these results achieved at a university hospital, in which there are frequent reshuffles of the staff, and many staff members are inexperienced doctors in training and non-specialists, are considered to owe greatly to systematic efforts involving the entire team. Even at a university hospital, where there are many rules, and major change is difficult to make, time reduction was possible by accumulating minor improvements. It is considered important to create a protocol suited for the staff and environment at each institution and constantly modify it by case conferences. Formerly, information was not shared among departments due to sectionalism characteristic of a university hospital, but dismantling of the wall between sections by establishing a stroke team, permeation of a standardized workflow in all staff members, and a steep learning curve of the entire staff brought about by standardization of the procedure are considered to have induced major changes. The significance of the achievement of time reduction and improvement in outcome by a team approach is considered to be great.

Conclusion

The results of this study suggest that considerable time reduction is possible even at a large-scale university hospital with many restrictions by sharing of information among departments and having a standardized therapeutic approach fully understood by the entire staff.

Disclosure Statement

The first author and all of the coauthors have no conflicts of interest.

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