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Original Article

Pre-Therapeutic Factors Predicting for the Necessity of Rescue Treatments in Mechanical Thrombectomy

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Objective: Mechanical thrombectomy for acute large vessel occlusion (LVO) is currently widely performed. However, rescue treatment (RT), such as percutaneous transluminal angioplasty (PTA) and stenting, is occasionally required, particularly in the case of atherothrombotic brain infarction (ATBI) or dissection. As RT requires higher levels of therapeutic skills and additional devices, early prediction of its performance and preparation are important. We retrospectively investigated the pre-therapeutic factors for predicting the necessity of RT.

Methods: We reviewed 149 consecutive patients who underwent mechanical thrombectomy for acute LVO between April 2014 and December 2019. Eight patients were excluded because of missing clinical data. RT was performed when severe stenosis was observed in occluded vessels or proximal to them during mechanical thrombectomy. We investigated pre-therapeutic neurological, laboratory, and radiological findings in the 141 remaining patients, and compared them between RT and non-RT groups.

Results: RT was performed on 23 of the 141 patients. We found four pre-therapeutic factors with significantly different rates between RT/non-RT as follows: (1) Atrial fibrillation 8.7%/71.1% ($p < 0.001$), (2) diabetes mellitus 39.1%/19.5% ($p = 0.04$), (3) susceptibility vessel sign (SVS) by T2-weighted imaging 17.4%/66.1% ($p < 0.001$), and (4) tapered occlusion by magnetic resonance angiography (MRA) 47.8%/11.9% ($p < 0.001$). The plasma level of brain natriuretic peptide (BNP) was also significantly different between the two groups. When the BNP level was less than 70 pg/mL, the sensitivity for being in the RT group was 86.9% and the specificity was 83.5%.

Conclusion: Pre-therapeutic findings, such as diabetes mellitus, tapered occlusion, absence of atrial fibrillation, negative SVS, and BNP level less than 70 pg/mL, are predictors of RT in mechanical thrombectomy.

Keywords ▶ mechanical thrombectomy, percutaneous transluminal angioplasty, pre-therapeutic factor, rescue treatment, stenting

Introduction

Mechanical thrombectomy for acute large vessel occlusion (LVO) has recently become a standard procedure following the development of aspiration catheters and stent retrievers. In patients with cardiogenic embolism, which may be involved in the mechanism in most cases, favorable reperfusion rates have been obtained.[1)] However, rescue treatment (RT), such as percutaneous transluminal angioplasty (PTA) and stenting, for the stenotic site of a responsible blood vessel is occasionally required in acute LVO related to atherothrombotic brain infarction (ATBI) or cerebral artery dissection. Early intervention by physicians who are able to manage such a condition is needed.[2,3)] To perform mechanical thrombectomy smoothly, preoperative disease-type differentiation is important, but a consensus regarding accurate evaluation has not been established.

In this study, we compared preoperative findings between RT and non-RT groups in our series to investigate predictive factors for a disease type requiring RT during surgery based on examination findings obtained in a limited

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time before mechanical thrombectomy. We report the results and review the literature.

Materials and Methods

The subjects were 149 consecutive patients who underwent mechanical thrombectomy for a diagnosis of acute ischemic stroke due to acute LVO between April 2014 and December 2019. Patients in whom PTA or stenting was conducted during mechanical thrombectomy were included to the RT group, and the other patients (those in whom mechanical clot disruption was performed, or an aspiration catheter or stent retriever alone was used) were included to the non-RT group. RT was indicated for patients with severe stenosis of an occluded blood vessel or its proximal part (cervical carotid artery: NASCET ≥70%; intracranial artery: WASID ≥70%),[4] which was considered to be an etiological factor for distal blood flow disturbance. We excluded eight patients in whom it was impossible to evaluate the items described below due to a lack of hematological parameters or the absence of magnetic resonance imaging (MRI) (**Fig. 1**). We retrospectively investigated the National Institutes of Health Stroke Scale (NIHSS) score before mechanical thrombectomy, risk factors (atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia, smoking, chronic kidney disease, coronary artery disease, and presence of ischemic stroke), hematological data (brain natriuretic peptide (BNP), D-dimer, and hemoglobin A1c), and MRI findings (Alberta Stroke Programme Early CT Score on diffusion-weighted imaging (DWI-ASPECTS),[5] susceptibility vessel sign (SVS) on T2-weighted imaging, and tapered occlusion on time-of-flight (TOF) magnetic resonance angiography (MRA) in the RT and non-RT groups. Each factor was compared between the two groups and those characteristics of the RT group were analyzed.

For comparison, the chi square or Fisher's test was used. Continuous variables with a normal distribution were expressed as the mean ± standard deviation and compared using the t-test. Those with a non-normal distribution were expressed as the median (interquartile range) and compared using Wilcoxon's test. A p value of 0.05 was regarded as significant. Concerning the BNP level, a receiver operator characteristic (ROC) curve was prepared, and the cut-off value, sensitivity, specificity, and area under the curve (AUC) were calculated using Youden's index. The presence of SVS and tapered occlusion on MRI was evaluated by three neurosurgeons who were not involved in this study, with blinding of other clinical information (Fleiss' k value = 0.699). For statistical analysis, we used JMP pro ver. 14 (SAS Institute, Cary, NC, USA).

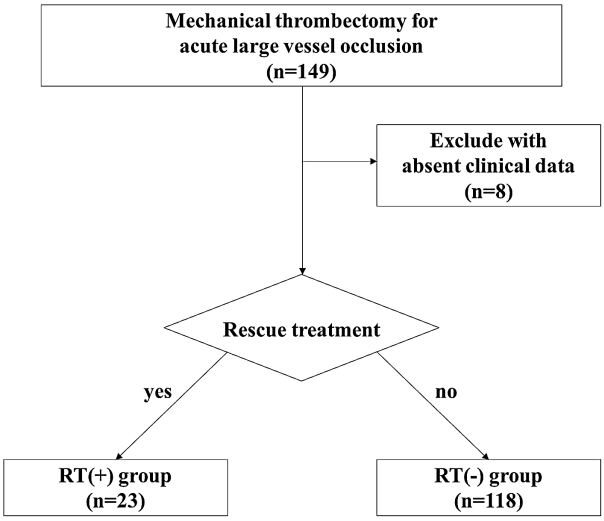

Fig. 1 Study flow diagram. After excluding eight patients because of missing clinical data, 141 patients with LVO who underwent mechanical thrombectomy were divided into the RT group (23 patients) and non-RT group (118 patients). LVO: large vessel occlusion; RT: rescue treatment

Results

Of a total of 141 patients, the RT group consisted of 23 patients (16.3%) and the non-RT group consisted of 118 (83.7%). In the RT group, 10 patients required RT for cervical carotid artery stenosis. In the other 13 patients, severe stenosis of the intracranial artery was observed, requiring RT. In this group, ATBI was suggested in 21, whereas the possibility of cerebral artery dissection was considered in 2 because a severe headache was present at the time of onset and stenting led to prompt vasodilation.

The patient background, morbidity rates of underlying diseases obtained before surgery, hematological data, and MRI findings are shown in **Table 1**. There were no significant differences in the age, sex, or preoperative NIHSS score between the RT and non-RT groups. However, concerning the occluded blood vessel, the rate of patients with occlusion of the middle cerebral artery was slightly higher in the non-RT group. Regarding underlying diseases, the morbidity rate of diabetes mellitus was significantly higher in the RT group (39.1 vs. 19.5%, respectively, p = 0.04). Furthermore, the morbidity rate of dyslipidemia and the rate of patients with a history of ischemic stroke were slightly higher. On the other hand, in the non-RT group, the morbidity rate of atrial fibrillation was significantly higher (8.7 vs. 71.1%, respectively, p <0.001). There were no significant differences

Table 1 Patient characteristics (n = 141)

	RT(+)	RT(–)	p value
Case number	23	118	
Age, mean (SD)	72.1 (10.4)	73.7 (11.0)	0.55
Female, n (%)	6 (26.1)	33 (28.0)	0.54
NIHSS, median (IQR)	15 (10.5-19.5)	18 (13-20)	0.28
Occlusion vessel, n (%)			
ICA	13 (56.5)	52 (44.1)	0.07
MCA	6 (26.1)	57 (48.3)	
VA, BA	4 (17.4)	9 (7.6)	
Risk factors, n (%)			
Af	2 (8.7)	84 (71.1)	**<0.001**
DM	9 (39.1)	23 (19.5)	**0.04**
Hypertension	18 (78.3)	74 (62.7)	0.15
Dyslipidemia	9 (39.1)	26 (22.0)	0.08
Current smoking	6 (26.1)	16 (13.6)	0.13
CKD	5 (21.7)	15 (12.7)	0.26
Coronary disease	8 (34.8)	38 (32.2)	0.81
Ischemic stroke	8 (34.8)	21 (17.8)	0.07
Labolatory data			
BNP (pg/mL), median (IQR)	34.9 (18.3-57.9)	165.2 (94.6-308.6)	**<0.001**
BNP<70pg/mL, n (%)	20 (87.0)	19 (16.1)	**<0.001**
D-dimer (ng/mL), median (IQR)	1.1 (0.5-2.8)	1.6 (0.9-3.0)	0.17
HbA1c (%), median (IQR)	5.9 (5.6-6.6)	5.9 (5.6-6.2)	0.84
MRI findings			
DWI-ASPECTS	8 (7-9)	8 (5-9)	0.17
SVS	4 (17.4)	78 (66.1)	**<0.001**
Tapered occlusion	11 (47.8)	14 (11.9)	**<0.001**

Af: artrial fibrillation; BA: basilar artery; BNP: brain natriuretic peptide; CKD: chronic kidney disease; DM: diabetes mellitus; DWI-ASPECTS: Alberta Stroke Programme Early CT Score on diffusion-weighted imaging; IQR: interquartile range; HbA1c: hemoglobin A1C; ICA: internal carotid artery; MCA: middle cerebral artery; NIHSS: National Institutes of Health Stroke Scale; SVS: susceptibility vessel sign; VA: vertebral artery

in the morbidity rates of hypertension or ischemic heart disease between the two groups. Concerning hematological data, the plasma level of BNP was significantly lower in the RT group (median: 34.9 vs. 165.2 pg/mL, respectively, p <0.001). On the other hand, there were no significant differences in the D-dimer or HbA1c levels between the two groups. Regarding MRI findings, the detection rate of tapered occlusion on TOF-MRA was significantly higher in the RT group (47.8 vs. 11.9%, respectively, p <0.001). In the non-RT group, the detection rate of SVS on T2-weighted imaging was significantly higher (17.4 vs. 66.1%, respectively, p <0.001). There was no significant difference in the DWI-ASPECTS between the two groups.

The ROC curve using plasma BNP level as an independent variable and regarding the RT group as positive is presented in **Fig. 2**. The AUC was 0.83. The cut-off value for BNP was 69.2 pg/mL. The sensitivity of the RT group at this point was 86.9% and its specificity was 83.5%.

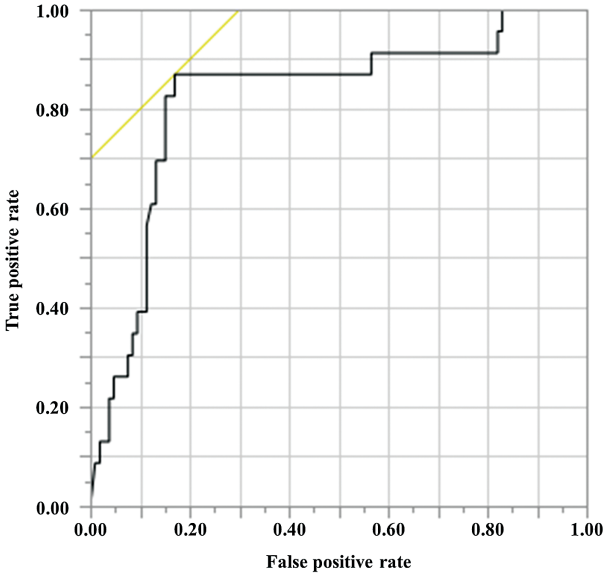

Fig. 2 ROC curves for prediction of being in the RT group based on the plasma level of BNP. The cut-off value for BNP was 69.2 pg/mL. The sensitivity for being in the RT group was 86.9% and the specificity was 83.5%. BNP: brain natriuretic peptide; ROC: receiver operator characteristic

Case Presentation

An 82-year-old woman with left hemiplegia and right conjugate deviation was brought to our hospital 2 hours after onset. She previously received drug therapy at a local clinic for hypertension, diabetes mellitus, and hyperlipidemia. On arrival, the Glasgow Coma Scale score was E3V4M6 and the NIHSS score was 14. On hematology, the BNP, HbA1c, and D-dimer levels were 28.1 pg/mL, 6.3%, and 0.9 ng/mL, respectively. The DWI-ASPECTS on MRI was 9 and TOF-MRA demonstrated tapered occlusion at the M1 segment of the right middle cerebral artery (**Fig. 3A**). No SVS was observed on T2-weighted imaging (**Fig. 3B**). In addition to the administration of recombinant tissue plasminogen activator, mechanical thrombectomy was performed. A 9Fr balloon guide catheter was inserted into the cervical internal carotid artery. Right internal carotid angiography revealed severe stenosis at the right M1 segment leading to a diagnosis of ATBI (**Fig. 3C**). PTA with a 2.0 × 9 mm balloon dilation catheter was performed. Favorable peripheral recanalization was achieved (**Fig. 3D** and **3E**). As restenosis did not occur during a 30-minute waiting period, stenting was not performed. After surgery, the symptoms improved and MRA after 7 days confirmed a favorable peripheral blood flow signal, although mild stenosis of the right middle cerebral artery remained (**Fig. 3F**). The modified Rankin Scale score after 90 days was 3.

Discussion

This study revealed significant differences in the presence of atrial fibrillation and diabetes mellitus, plasma BNP level, and presence of SVS and tapered occlusion between the RT and non-RT groups. The specificity of the RT group was 100% when all of the following five items were met: (**1**) Atrial fibrillation is absent, (**2**) diabetes mellitus is present, (**3**) the BNP level is <70 pg/mL, (**4**) there is no SVS, and (**5**) tapered occlusion is present. When ≥4 items were met, the sensitivity of the RT group was 52.2% and its specificity was 90.7%. These may be appropriate as parameters for preparing specialists or instruments for RT.

ATBI accounts for the greater portion of disease types requiring RT. As mechanisms, thrombus formation associated with plaque enlargement/rupture at the site of stenosis or distal vascular occlusion related to artery-to-artery embolism may be involved in ATBI-related occlusion.[3] According to previous reports, risk factors for ATBI include hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease. In particular, patients with ATBI are characterized by a history of cerebral infarction or the presence of transient ischemic attacks.[6–8] In this study, the morbidity rate of diabetes mellitus was significantly higher in the RT group, and the morbidity rate of dyslipidemia and the rate of patients with a history of ischemic stroke were slightly higher. These results were consistent with those of previous studies. On the other hand, atrial fibrillation is a primary etiological factor for cardiogenic cerebral infarction. A previous study found that atrial fibrillation is present in approximately 11% of ATBI patients.[9] In this study, two patients in the RT group had atrial fibrillation. Thus, the presence of atrial fibrillation does not always lead to cardiogenic cerebral infarction.

Based on this study, a high plasma BNP level strongly suggests the non-RT group. BNP is routinely used as a parameter of the diagnosis/severity of heart failure or therapeutic effects. At the same time, previous studies reported that its level significantly increased in the patients of cardiogenic cerebral infarction.[10] The BNP level is high not only in the presence of chronic atrial fibrillation but also it rapidly increases upon the development of atrial fibrillation in those with paroxysmal atrial fibrillation. If there is an increase in the BNP level despite sinus rhythm on arrival, the possibility of cardiogenic embolism related to paroxysmal atrial fibrillation should be considered.[11] On the other hand, even in the RT group, patients with chronic heart disease had a high BNP level, but the rate of increase in the BNP level was less than that in the non-RT group; the BNP level was <70 pg/mL in 87.0% of the patients in the RT group. Meanwhile, patients with a low BNP level in the non-RT group included Trousseau syndrome in cancer-bearing patients or antiphospholipid syndrome as an underlying disease. As other hematological parameters suggestive of ATBI, high D-dimer and HbA1c levels were reported. However, in this study, there were no significant differences in either parameter between the RT and non-RT groups.[12,13]

MRI findings are also useful. Regarding SVS, an embolus is visualized as low signal intensity on T2-weighted imaging (gradient recalled echo) and SVS is more sensitive than a hyper-dense MCA sign on CT.[14] According to previous studies, SVS is an accessible clinical biomarker that is observed in approximately 72.5%–77.5% of patients with cardiogenic embolism.[15,16] In this study, SVS were detected in approximately 70% of patients with cardiogenic embolism,

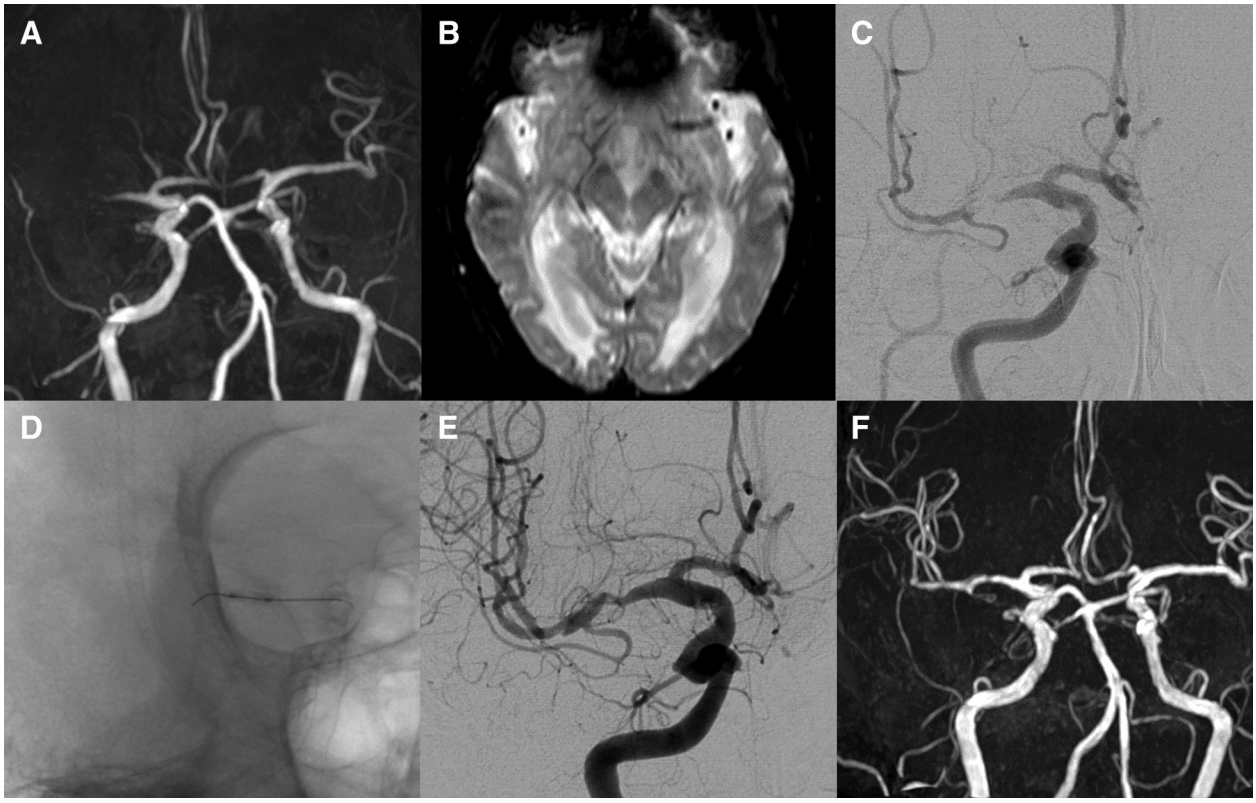

Fig. 3 Initial TOF-MRA demonstrated tapered occlusion at the M1 segment of the right MCA (**A**). Axial T2* gradient-echo imaging revealed a negative SVS at the occluded portion (**B**). Right ICA injections (anteroposterior view) revealed severe stenosis in the right M1 segment (**C**). Angioplasty using the 2.0 × 9 mm balloon (**D**) improved the caliber of the right M1 segment, and angiography demonstrated flow restoration of Thrombolysis in Cerebral Infarction grade 3 (**E**). On MRA after treatment, mild stenosis remained at the M1 segment, but good signal intensity in the right MCA was noted (**F**). ICA: internal carotid artery; MCA: middle cerebral artery; SVS: susceptibility vessel sign; TOF-MRA: time-of-flight magnetic resonance angiography

which was similar to the percentage previously reported. However, even in the RT group, SVS was detected in approximately 20%; RT cannot always be excluded based on the presence of SVS. Similarly, tapered occlusion of an occluded blood vessel on TOF-MRA suggests the necessity of RT. It reflects afferent plaque-related stenosis of the vascular lumen in the presence of ATBI or dissection-related true lumen blood flow disruption.[17] A previous study reported that tapered occlusion was observed in approximately 55% of patients with ATBI and in approximately 18% of non-ATBI patients.[18] In this study, tapered occlusion was also significantly more frequent in the RT group, but it was observed in some patients in the non-RT group.

Thus, it is difficult to predict whether RT is necessary based on each finding alone. However, it would be highly predictable by comprehensive evaluation based on numerous findings, as described above. For further studies, predictive factors should be investigated in a larger number of patients and the accuracy should be improved.

Conclusion

Based on this study, the absence of atrial fibrillation/SVS, a BNP level of <70 pg/mL, and presence of diabetes mellitus/tapered occlusion of a blood vessel as preoperative findings in patients with acute LVO were factors that suggest the necessity of RT during mechanical thrombectomy. These may be useful as indices for preparing therapeutic intervention by skilled physicians or instruments in the early phase.

Ethics Approval

Prior to this study, its protocol was approved by the ethics review board of a medical institution to which the main author belonged (Approval No. 5074). Information on the subjects was obtained using the opt-out system and used such that individuals cannot be identified.

Disclosure Statement

The authors declare no conflict of interest.

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