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Predictive Factors for Hemorrhagic Transformation after Successful Mechanical Thrombectomy in Cerebral Large Vessel Occlusion

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Abstract

Background: Recently, updated guidelines showthat mechanical thrombectomy has high degree evidence to treat acute ischemic stroke due to cerebral large vessel occlusion (LVO). However, hemorrhagic transformation (HT) occurs in some cases after recanalization, and it is associated with poor prognosis. Prevention of HTafter recanalization therapyis thought to be important. In this study, we aimed to investigate factors related to HT after mechanical thrombectomyfor patients with LVO.

Methods: We included patients with cerebral LVO at anterior circulation within 24 hours from onset and presented successful recanalization by mechanical thrombectomy. We divided them into two groups, with HT, and without HT. We compared their characteristics, such as severity of clinical symptom, etiology, radiological findings between these groups.

Results: This study showed that mild white matter lesion (Fazekas scale <2), high Alberta Stroke Program Early CT (ASPECTS) score (>6) were independent factor of absence of HT after mechanical thrombectomy (odds ratio 3.57, p = 0.004, odds ratio 2.82, p< 0.040, respectively).

Conclusion: Severe white matter lesion and low ASPECS score at the time of admission might be predictors for HT after recanalization in patients with LVO.

Keywords: Acute ischemic stroke; Large vessel occlusion; Hemorrhagic transformation; White matter lesion

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Introduction

Recent updated guidelines show that mechanical thrombectomy has high degree evidence to treat patients with acute ischemic stroke (AIS) due to cerebral large vessel occlusion (LVO) at anterior circulation [1,2]. Previous randomized trials showed that mechanical thrombectomy in addition to best medical treatment did not increase the rate of symptomatic intracranial hemorrhage [3-7]. However, hemorrhagic transformation (HT), a known complication of the treatment for AIS patients, can be associated with a higher morbidity and mortality in case of intracranial hematoma with space-occupying effect [8]. In recent trials of mechanical thrombectomy, the rates of HT occurrence after treatment ranged from 5% to 13% of endovascularly treated patients [9]. Because HT is associated with poor prognosis, prevention of HT after mechanical thrombectomy is thought to be important. In this study, we aimed to investigate factors related to PH after mechanical thrombectomy.

Research Methodology

Hemorrhagic transformation and white matter lesion assessment

We performed magnetic resonance image (MRI) scanning systematically 24 to 48 hours after mechanical thrombectomy, and HT was assessed according to the ECASS (European Collaborative Acute Stroke Study) classification [10]. Hemorrhagic infarction type 1 was defined as petechial hemorrhages at the infarct margins, and hemorrhagic infarction type 2 was petechial hemorrhages throughout the infarct, with no space-occupying effect. PH type 1 was defined as blood clots in <30% of the infarcted area with some slight space-occupying effect and PH type 2 (PH2) as blood clots in >30% of the infarcted area with a substantial space-occupying effect. We determined HT as PH1 and PH2 on MR T2* weighted image after mechanical thrombectomy. We also scored white matter lesion (WML) burden on fluid attenuated inversion recovery (FLAIR) image at the time of first MRI scanning by using a Fazekas' scale [11].

Patients

The study was approved by our local institutional review board. This retrospective analysis was based on a prospectively collected registry of consecutive patients between January 2011 and December 2020. We extracted the data of intended patients from the registry. We included patients with AIS due to LVO who were treated by mechanical thrombectomy, and successful recanalization. LVO was determined as occlusion at internal carotid artery or M1 segment of middle cerebral artery (MCA), and successful recanalization was determined as modified Thrombolysis in Cerebral Infarction (mTICI) grade 2C and 3 [12]. Our criterions for mechanical thrombectomy were Alberta Stroke Program Early CT (ASPECTS) score ≥ 6 on diffusion-weighted image (DWI), admission within 24 hours from onset or the last time patient was without symptoms, and without contraindication of mechanical thrombectomy, such as short life expectancy and thrombocytopenia (<30,000/μL). Exclusion criteria were the inability to perform MRI to evaluate WML due to a pacemaker implantation.

We divided our patients into two groups, group HT (with PH after mechanical thrombectomy), and group no-HT (without HTon MRI after mechanical thrombectomy). We compared factors between two groups, including patients' characteristics, severity of neurological deficit, and MRI findings.

Definition and complicated diseases

Continuous variables which were measured at the time of admission are expressed as the mean ± standard deviation. Diabetes mellitus was defined as a hemoglobin A1C (National Glycohemoglobin Standardization Program: NGSP) level greater than 6.5% or the current use of drugs for hyperglycemia. Dyslipidemia was defined as a low-density lipoprotein greater than 140 mg/dL and/or high-density lipoprotein lower than 40 mg/dL, or the current use of drugs for dyslipidemia. Hypertension was defined as the current use of antihypertensive drugs. The etiology of ischemic stroke was diagnosed as cardioembolic stroke or other etiologies proposed by the classification of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria using a 12-channel electrocardiogram, long-term electrocardiogram monitoring, ultrasonography, MRI, and/or digital subtraction angiography.

Statistical analysis

Comparisons were performed using the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables. Statistical significance was defined as $P< 0.05$. We used Bonferroni correction in the comparison of multiple groups. Values of $p < 0.1$ in the univariate analysis were used in the evaluation of the multivariate analysis. To calculate the sensitivity and specificity of the parameters employed to evaluate risk factors associated with HT, we prepared a receiver operating characteristic (ROC) curve **(Figures 1 and 2)**. Cutoff values with the highest sensitivity and specificity were included in the final logistic regression analysis. Results are expressed as adjusted odds ratios and the corresponding 95% confidence interval (CI). Statistical significance was set at $P < 0.05$. All statistical analyses were performed with SPSS Statistics version 26.0 software package (IBM Corporation, Tokyo, Japan).

Results

Between January 2011 and December 2019, 2964 patients with acute stroke were admitted to our hospital, and 456 were diagnosed with LVO. Of these, 175 patients were treated by mechanical thrombectomy, and 137 of them were confirmed successful recanalization on digital subtraction angiography at the time of procedures. Baseline characteristics were shown in **Table 1**. In univariate analysis, frequency of embolic stroke, ASPECTS score and Fazekas' scale were higher in group HT (group no-HT *vs.* group HT, 64.9% *vs.* 90.2%, p = 0.002; 8 *vs.* 7, p = 0.032; 0 *vs.* 2, p = 0.018, respectively). We performed a logistic regression analysis to assess the factors associated with HT after mechanical thrombectomy **(Table 2)**. Fazekas scale ≥ 2 was an independent factor of HT after mechanical thrombectomy (Odds ratio 4.66; 95% CI, 1.79-12.05), and absence of embolic stroke were independent factor of no-HT; p = 0.002, Odds ratio 0.19; 95%CI, 0.056–0.64, P = 0.008).

Discussion

In our study, 29.9% of LVO patients, who were transferred within 24 hours of onset and confirmed successful recanalization by mechanical thrombectomy, presented HT on MRI after treatment. Furthermore, poor functional outcome 90 days after onset was more common in patients with HT (group HT *vs.* group no-HT, 14.6% *vs.* 50.0%, p< 0.001, not shown in this study). Previously reported literature described factors associated with HT after recanalization, such as age, severity of neurological deficit, wake-up stroke, and delayed time from onset to recanalization [13-15]. Our findings suggested that cardioembolic stroke was associated with HT. We speculated that cardioembolic stroke caused sudden occlusion by clot, and progression of ischemic core might faster than the other etiologies. Furthermore, we mentioned MRI

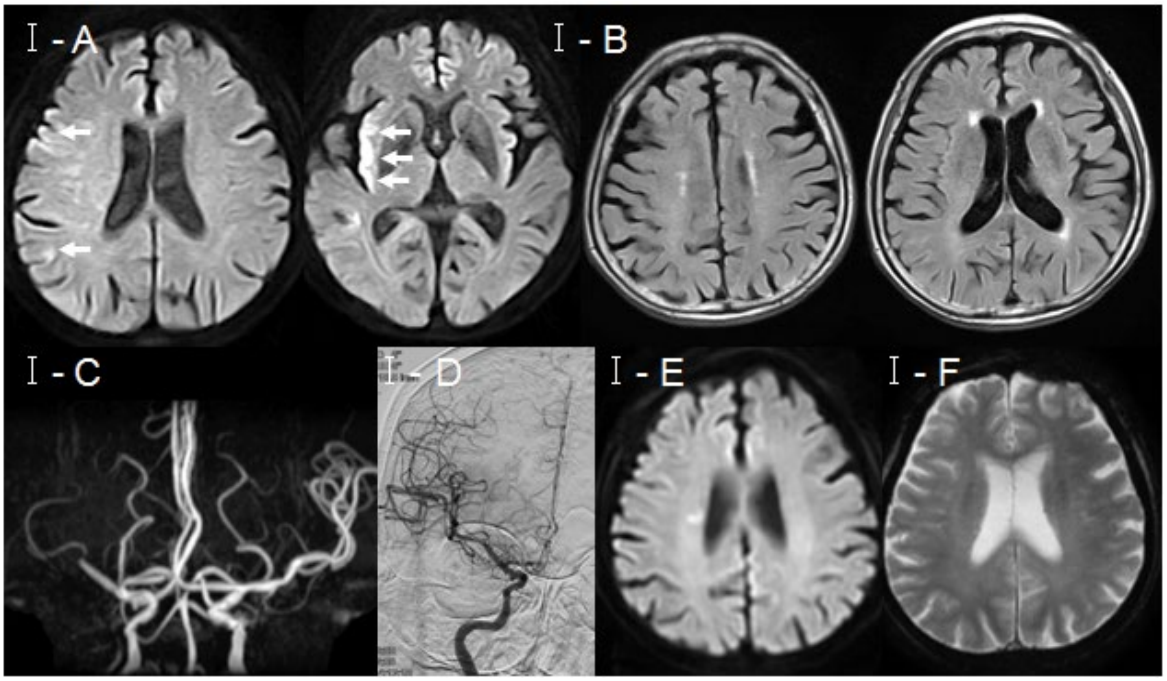

Figure 1 Representative cases of group No-HT (I). I-A: Diffusion-weighted image (DWI); White arrows shows infarct area at territory of right middle cerebral artery (MCA). I-B: Fluid-attenuated recovery image (FLAIR); Sight white matter lesions (WML) are detected at periventricular area. I-C: Magnetic resonance angiography (MRA); Right MCA occlusion can be seen on MRA. I-D: A digital subtraction angiography (DSA); Complete recanalization by mechanical thrombectomy can be confirmed on DSA. I-E: DWI; DWI 24 hours after mechanical thrombectomy shows only spotty infarct area at corona radiata and no infarct area at cortex. I-F: T2*-weighted image (T2*WI); Hemorrhagic transformation cannot be detected.

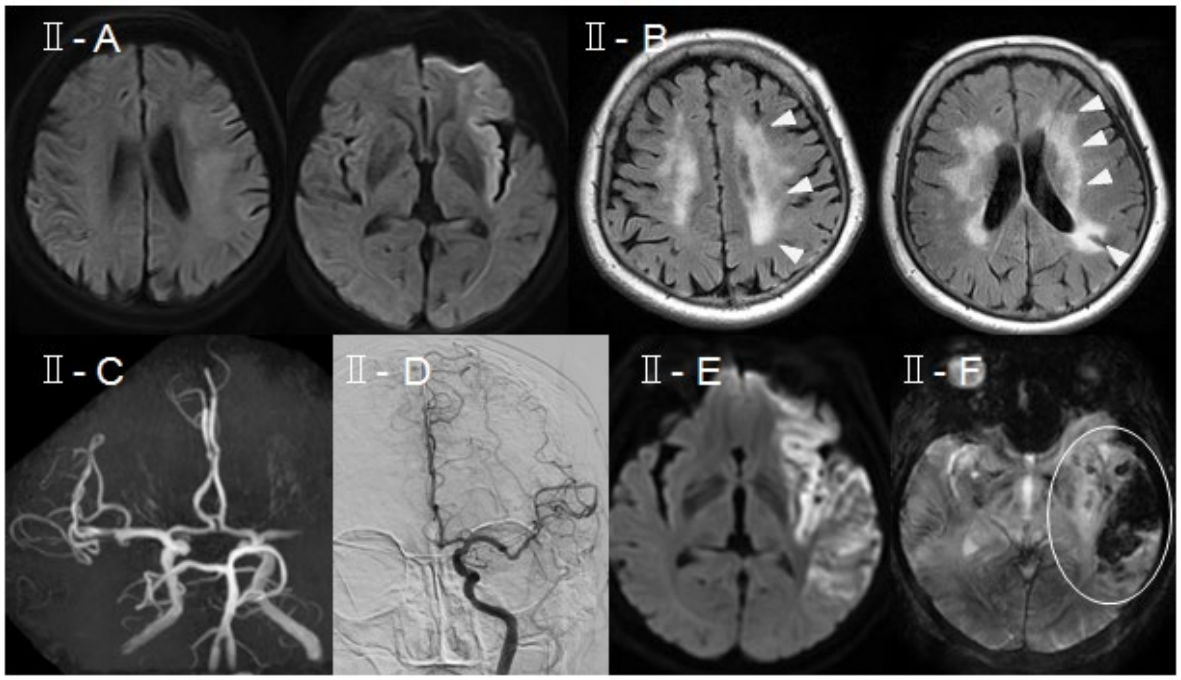

Figure 2 Representative cases of group HT (II). II-A: White arrows shows infarct area at territory of left MCA. II-B: FLAIR shows severe WML (White arrow heads). II-C: MRA; MRA shows left MCA occlusion (White arrow). II-D: Complete recanalization by mechanical thrombectomy can be confirmed on DSA. II-E: Left MCA territory infarct can be detected and enlargement of area relative to that before recanalization. II-F: T2*WI; White circle shows hemorrhagic transformation occupying more than 30 % of infarct area.

Table 1 Baseline characteristics.

Variables	Group no-HT n=96	Group HT n=41	p-value
Age, years	74.3 ± 10.9	78.2 ± 10.8	0.121
Sex, man, n (%)	53 (55.2)	21 (51.2)	0.711
Cardio Embolic stroke, n (%)	62 (64.6)	37 (90.2)	0.002
ICA occlusion, n (%)	45 (46.9)	24 (58.5)	0.264
rt-PA use, n (%)	40 (41.7)	18 (43.9)	0.808
CAD, n (%)	9 (9.3)	4 (9.8)	1
Hypertension, n (%)	42 (43.8)	17 (41.5)	0.636
Dyslipidemia, n (%)	37 (38.5)	17 (41.5)	0.849
Diabetes mellitus, n (%)	17 (17.7)	9 (22.0)	0.636
Current smoking, n (%)	30 (31.3)	18 (43.9)	0.174
O to R, minutes	369.0 ± 247.8	399.0 ± 271.6	0.988
Count of WBC,10^3/µL	7.9 ± 2.8	8.0 ± 2.6	0.739
Count of RBC,10^4/µL	410.0 ± 77.5	401.6 ± 58.1	0.318
Hemoglobin, g/dL	12.7 ± 2.6	12.7 ± 1.9	0.597
Count of Thrombocyte, 10^4/µL	21⍰5 ± 8.2	19.7 ± 5.7	0.348
AST, IU/L	27.1 ± 11.8	26.5 ± 9.2	0.854
ALT, IU/L	18.4 ± 12.9	19.0 ± 11.8	0.788
Total Bilirubin, mg/dL	0.80 ± 0.4	0.87 ± 0.51	0.512
Amylase, IU/L	80.0 ± 35.3	75.0 ± 42.6	0.17
Total Cholesterol, mg/dL	178.2 ± 47.3	171.1 ± 44.5	0.153
BUN, mg/dL	19.5 ± 9.9	20.6 ± 7.2	0.101
Creatinin, mg/dL	0.9 ± 0.8	1.0 ± 0.8	0.417
Na, mEq/L	140.0 ± 1.4	139.6 ± 2.9	0.238
K, mEq/L	4.1 ± 0.9	4.1 ± 0.4	0.42
Cl, mEq/L	106.3 ± 0.9	105.2 ± 0.1	0.137
CRP, mg/dL	0.9 ± 0.8	1.0 ± 0.8	0.764
NIHSS	17.0 ± 8.2	18.4 ± 7.4	0.102
Heart rate, bpm	81.4 ± 18.9	81.4 ± 20.9	0.576
SBP, mmHg	158.4 ± 27.1	155.1 ± 25.8	0.445
DBP, mmHg	86.7 ± 20.0	81.2 ± 19.2	0.474
ASPECTS, median (min, max)	8 (6-10)	7 (6-10)	0.032
Fazekas' score, median (min, max)	0 (0-3)	2 (0-3)	0.018

ICA: Internal Carotid Artery; rt-PA: Recombinant Tissue Plasminogen Activator; CAD: Coronary Artery Disease; O to R: Interval from Onset to Recanalization; WBC: White Blood Cell; RBC: Red Blood Cell; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; BUN: Blood Urea Nitrogen; CRP: C-Reactive Protein; NIHSS: National Institute of Health Stroke Scale; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ASPECTS: Alberta Stroke Program Early CT Score

Table 2 Multivariate analysis.

Variables	OR	95% CI		p-value
Fazekas scale (>2)	4.66	1.78	12.05	0.02
ASPECTS score (>6)	2.25	0.82	6.19	0.116
Blood sugar (>138 mg/dL)	1.9	0.82	4.4	0.134
Age (>75)	1.49	0.63	3.52	0.361
No embolic stroke	0.19	0.06	0.64	0.008

CI: Confidence Interval; ASPECTS: Alberta Stroke Program Early CT Score

findings associated with HT in this study. Severe WML (≥ 2 on Fazekas' scale) was also related to HT. Presence of collateral flow was reported to be associated with ischemic core volume after treatment in patients with LVO [16-20]. We speculated that diffuse small cerebral vessel pathology causing presence of WML may be responsible in some part for poor collateral flow [21]. Although vascular risk factors, such as diabetes mellitus, dyslipidemia, and smoking, were not different in this study, risk factors which were not detected in our patients might contribute to the progression of a WML. These factors also might contribute to collateral vessel

pathology [22,23]. Our study might indicate that AIS patients with severe WML should be treated rapidly rather than patients without WML. Future studies are essential in order to investigate this relationship and mechanisms.

We had several limitations to our study. Patients' data were extracted from a prospectively collected registry; however the image findings were retrospectively evaluated. This retrospective design may have imparted selection bias because of the exclusion of patients who did not undergo advanced evaluation, such as perfusion imaging. Furthermore, the associations of collateral flow, characteristics of thrombus, histology, and methods for treating LVO in those patients were not investigated in this study.

Conclusion

Stroke etiology and the degree of WML may play a role in PH after mechanical thrombectomy for AIS patients with LVO. Additional studies are needed in order to delineate the significance of stroke etiology and degree of WML with regard to PH after treatment.

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