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Effect of Antiplatelet Preparation Before Endovascular Thrombectomy for Cerebral Infarction on Procedural Thromboembolism

Taek Min NAM, Ji Hwan JANG, Young Zoon KIM, Kyu Hong KIM, Seung Hwan KIM

Sungkyunkwan University School of Medicine, Samsung Changwon Hospital, Department of Neurosurgery, Changwon, Republic of Korea

Corresponding author: Seung Hwan KIM 🗵 aajechtkskim@hanmail.net

ABSTRACT

AIM: To compare an antiplatelet-preparation group with a no-preparation group to evaluate the effect of the antiplatelet preparation on procedural thromboembolism during endovascular thrombectomy (EVT) with diffusion-weighted imaging (DWI), retrospectively.

MATERIAL and METHODS: From January 2017 to April 2020, EVT was performed in 60 patients with cerebral infarction. Patients were categorized into the antiplatelet-preparation group (n=25) or the no-preparation group (n=35). Procedural thromboembolism was defined as new DWI-positive lesions in other areas of the occluded artery after EVT.

RESULTS: The antiplatelet-preparation and no-preparation groups did not differ in the rate of procedural thromboembolism occurrence (6/25 [24.0%] vs. 6/35 [17.1%]; p=0.532). Procedural thromboembolism was associated with age (74.4 \pm 6.95 years vs. 65.7 \pm 12.9 years; p=0.028), atherosclerotic occlusion (66.7% vs. 29.2%; p=0.022), and procedural time (97.4 \pm 45.7 min vs. 60.1 \pm 28.8 min; p=0.001). Multivariable logistic regression analysis showed that factors affecting procedural thromboembolism during EVT for cerebral infarction were old age (odds ratio [OR], 1.133; 95% confidence interval [CI], 1.009-1.273; p=0.035), atherosclerotic occlusion (OR, 7.434; 95% CI, 1.272-43.431; p=0.026), and longer procedural time (OR, 1.023; 95% CI, 1.001 - 1.046; p=0.006).

CONCLUSION: The antiplatelet preparation had no significant protective effect on procedural thromboembolism during EVT for cerebral infarction. Old age, atherosclerotic occlusion, and longer procedural time were independent risk factors for procedural thromboembolism during EVT for cerebral infarction.

KEYWORDS: Endovascular thrombectomy, Cerebral infarction, Antiplatelet, Procedural thromboembolism

ABBREVIATIONS: IV: Intravenous, EVT: Endovascular thrombectomy, DWI: Diffusion-weighted imaging, CTA: Computed tomography angiography, MRA: Magnetic resonance angiography, NIHSS: National Institutes of Health Stroke Scale, mRS: Modified Rankin Scale, TICI: Thrombolysis in cerebral infarction, ROC: Receiver - operating characteristic, ICA: Internal carotid artery, OR: Odds ratio, CI: Confidence interval, AUC: Area under the curve

INTRODUCTION

Intravenous (IV) thrombolysis with tissue plasminogen activator administered within 4.5 hours after the onset of cerebral infarction and endovascular thrombectomy (EVT) for cerebral infarction caused by a major vessel occlusion have been considered as standard treatment options for cerebral infarction (3,4,7,12,19,21). When patients are not suitable candidates for IV thrombolysis, EVT for cerebral infarction caused by a major vessel occlusion is planned, and antiplatelet drug preparations can be considered before EVT to achieve better clinical and radiological outcomes and

 Taek Min NAM
 Image: bit is 0000-0002-9596-4659

 Ji Hwan JANG
 Image: bit is 0000-0001-6364-3992

 Young Zoon KIM
 Image: bit is 0000-0001-9724-3081

 to reduce the risk of reocclusion, in situ thrombosis, and procedural thromboembolism (9,22).

The effects of periprocedural antiplatelet treatment on the outcomes of EVT for cerebral infarction are well known. The administration of antiplatelet agent before EVT is associated with better angiographic results and lower mortality rates; it also does not increase the risk of hemorrhagic complications (9,22). However, previous studies have focused only on the radiological and clinical outcomes and the risk of intracerebral hemorrhage. The effect of antiplatelet treatments before EVT on thromboembolism risk has not been studied.

This study aimed to evaluate the effect of antiplatelet treatment on procedural thromboembolism during EVT for cerebral infarction, based on diffusion-weighted imaging (DWI) findings after EVT. This study also aimed to evaluate the factors affecting procedural thromboembolism during EVT for cerebral infarction.

MATERIAL and METHODS

Study Population

The study was conducted from January 2017 to April 2020. We reviewed the data of patients with cerebral infarction who underwent EVT at our hospital. A total of 178 patients who met the inclusion criteria were enrolled. The inclusion criteria were as follows: 1) cerebral infarction with symptoms; 2) large artery occlusion confirmed by computed tomography angiography (CTA) or magnetic resonance angiography (MRA); 3) period of less than 24 hours from symptom onset to treatment; 4) more than one-half mismatch between the cerebral blood volume and the cerebral blood flow map on magnetic resonance perfusion imaging with color-coded threshold maps; and 5) treatment with EVT.

Of the 178 patients, 118 were excluded for the following reasons: 1) no DWI within 2 days after EVT (n=70), as the purpose of this study was to use DWI after EVT to evaluate the effect of antiplatelet agent on procedural thromboembolism; and 2) use of IV thrombolysis (n=48), as antiplatelet preparation is not considered after the use of IV thrombolysis because of the risk of intracerebral hemorrhage. Therefore, 60 consecutive patients were included in the study.

Data Collection and Patient Characteristics

The patients' medical records and imaging data, including patient characteristics, procedural details, and clinical and radiological outcomes, were reviewed. The institutional review board reviewed and approved the study protocol (SCMC 2020-04-012). Patient characteristics included sex; age; past medical history, such as hypertension, diabetes mellitus, and atrial fibrillation; smoking history; occlusion site; stroke etiology; National Institutes of Health Stroke Scale (NIHSS) score on admission; the time from symptom onset to groin puncture; and the use of an antiplatelet preparation. Procedural details included the total number of EVT attempts; the procedural time; use of an intermediate catheter; use of a balloon guiding catheter; use of rescue treatments, such as angioplasty or stenting; and incidence of procedural

thromboembolism. The clinical outcome was the 3-month modified Rankin Scale (mRS) score, and the radiological outcome was the thrombolysis in cerebral infarction (TICI) grade.

Stroke etiology was classified based on the Trial of ORG 10172 in Acute Stroke Treatment criteria. The NIHSS score of each patient was assessed upon admission. Patients administered aspirin and/or clopidogrel were categorized as the antiplatelet-preparation group, and patients who were administered neither aspirin nor clopidogrel were classified as the no-preparation group. The procedural time was the total time taken from groin puncture to recanalization. Procedural thromboembolism was defined as new DWI-positive lesions in other areas of the occluded artery after EVT. Successful recanalization was defined as a TICI grade of 2b or 3. A good clinical outcome was defined as a 3-month mRS score between 0 and 2.

EVT Procedures

EVT for cerebral infarction was performed through the femoral artery while the patient was under conscious sedation. The primary EVT modality was determined by the surgeon. EVT was performed using catheter aspiration or a stent retriever. When residual stenosis in atherosclerotic occlusion was observed on post-EVT angiography, rescue treatments, including balloon angioplasty or stenting, were considered.

Statistical Analysis

Patient characteristics, procedural details, and radiological and clinical outcomes were compared between the antiplatelet-preparation and no-preparation groups and in terms of whether procedural thromboembolism occurred. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the Student's t-test or Mann - Whitney U test. Multivariable logistic regression analysis was used to evaluate factors affecting procedural thromboembolism during EVT for cerebral infarction. Statistical significance was set at p<0.05. The cutoff value of the univariate analysis for inclusion in the logistic regression analysis was p<0.05. The cutoff value of the variables for predicting procedural thromboembolism was obtained by using the receiver - operating characteristic (ROC) curve. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 60 patients (37 men, 23 women; mean age, 67.4 years; range, 33 - 84 years) who presented with cerebral infarction and were treated with EVT at our hospital were enrolled in the study. Among the 25 patients in the antiplatelet preparation group, 9 were administered 300 mg of aspirin and 300 mg of clopidogrel before EVT, 4 were administered 100 mg of aspirin and 75 mg of clopidogrel before EVT, and 12 were administered 300 mg of aspirin alone before EVT. There were 55 anterior circulation occlusions, including cervical to cavernous internal carotid artery (ICA) occlusions (n=3), ICA bifurcation occlusions (n=8), M1 occlusions (n=31), M2

occlusions (n=5), and cervical ICA and MCA occlusions (n=8); as well as 5 posterior circulation occlusions, including vertebral artery occlusions (n=2) and basilar artery occlusions (n=3).

The patient characteristics, procedural details, and radiological and clinical outcomes of the antiplateletpreparation and no-preparation groups are detailed in Table I. None of the patient characteristics, except for stroke etiology and NIHSS score on admission, differed significantly between the antiplatelet-preparation and no-preparation groups. An increased association with atherosclerotic occlusion was seen in the antiplatelet-preparation group than the no-preparation group (14/25 [56.0%] vs. 8/35 [22.9%]; p=0.014). Further, the antiplatelet-preparation group had lower NIHSS scores on admission than the no-preparation group (9.64 \pm 5.52 vs. 12.9 \pm 6.44; p=0.046). The incidence of procedural thromboembolism was not significantly different between the antiplatelet-preparation and the no-preparation groups (6/25 [24.0%] vs. 6/35 [17.1%]; p=0.532).

The TICI grades were as follows: TICI 0, n=4; TICI 1, n=2; TICI 2a, n=10; TICI 2b, n=2; and TICI 3, n=42. The mRS scores were as follows: mRS 0, n=13; mRS 1, n=11; mRS 2, n=13; mRS 3, n=7; mRS 4, n=5; mRS 5, n=4; and mRS 6, n=7. The antiplatelet-preparation group achieved better clinical outcomes than the no-preparation group $(18/25 \ [72.0\%] vs. 19/35 \ [54.3\%])$; however, the difference was not statistically significant (p=0.189). Successful recanalization did not differ significantly between the two groups $(18/25 \ [72.0\%] vs. 26/35 \ [74.3\%]; p=1.000)$.

Among the 60 patients who underwent EVT for cerebral infarction, procedural thromboembolism occurred in 12 patients (20.0%). These 12 patients showed small and focal new DWI-positive lesions. A case of EVT for cerebral infarction with procedural thromboembolism is shown in

Table I: A Comparison of Patient Characteristics, Procedural Details, and Radiological and Clinical Outcomes Between the Antiplatelet

 Preparation and No-Preparation Groups

		Antiplatelet- preparation group (n=25)	No-preparation group (n=35)	р
	Gender (male)	18 (72.0%)	19 (54.3%)	0.189
	Age (years) (mean ± SD)	67.2 ± 11.0	67.6 ± 13.5	0.894
	Hypertension	8 (32.0%)	20 (57.1%)	0.069
	Diabetes Mellitus	6 (24.0%)	8 (22.9%)	1.000
Patient characteristics	Atrial fibrillation	5 (20.0%)	11 (31.4%)	0.386
	Smoking history	12 (48.0%)	10 (28.6%)	0.175
	Occlusion site (anterior circulation)	23 (92.0%)	32 (91.4%)	1.000
	Stroke etiology			0.014
	Atherosclerosis	14	8	
	Non-atherosclerosis	11	27	
	NIHSS score on admission (mean \pm SD)	9.64 ± 5.52	12.9 ± 6.44	0.046
	The time from symptom onset to groin puncture (mean \pm SD)	400.5 ± 259.3	501.5 ± 280.6	0.161
	Total number of EVT attempts (mean \pm SD)	2.88 ± 1.81	2.63 ± 1.88	0.606
	The procedural time (mean \pm SD)	73.6 ± 37.0	2.88 ± 1.81 2.63 ± 1.88	0.273
	Intermediate catheter	18 (72.0%)	26 (74.3%)	1.000
Procedural details	Balloon guiding catheter	4 (16.0%)	7 (20.0%)	0.748
	Rescue treatment	3 (12.0%)	%) 26 (74.3%) %) 7 (20.0%)	0.640
	Procedural thromboembolism	6 (24.0%)	6 (17.1%)	0.532
Radiological and clinical	Successful recanalization	18 (72.0%)	26 (74.3%)	1.000
outcomes	Good clinical outcome	18 (72.0%)	19 (54.3%)	0.189

NIHSS: National institutes of health stroke scale.

Figure 1A-F. Regarding patient characteristics (Table II), the procedural thromboembolism group was comprised of older patients than the no procedural thromboembolism group (74.4 \pm 6.95 years vs. 65.7 \pm 12.9 years; p=0.028) and was more associated with atherosclerotic occlusion than the no procedural thromboembolism group (8/12 [66.7%] vs. 14/48 [29.2%]; p=0.022).

Regarding procedural details, the procedural thromboembolism group had longer procedure time than the no procedural thromboembolism group (97.4 \pm 45.7 min vs. 60.1 \pm 28.8 min; p=0.001). The procedural thromboembolism and no thromboembolism groups had no significant differences in radiological and clinical outcomes.

The multivariable analysis of factors affecting procedural thromboembolism during EVT for cerebral infarction revealed that older age (adjusted odds ratio [OR], 1.133; 95% confidence interval [CI], 1.009-1.273; p=0.035), atherosclerotic occlusion (adjusted OR, 7.434; 95% CI, 1.272-43.431; p=0.026), and longer procedural time (adjusted OR, 1.023; 95% CI, 1.000-1.046; p=0.006) were independently associated with procedural thromboembolism during EVT for cerebral infarction (Table III).

The ROC curve analysis revealed that the cutoff age for predicting procedural thromboembolism was \geq 72 years (area under the curve [AUC], 0.715; 95% Cl, 0.570-0.860; p=0.022), while the cutoff procedural time for predicting procedural thromboembolism was \geq 109 minutes (AUC, 0.740; 95% Cl, 0.577-0.904; p=0.010).

DISCUSSION

Procedural thromboembolism is a major complication in the field of neurointervention, and previous studies have investigated the effect of antiplatelet drugs on procedural thromboembolism (8,14,18). However, these studies have focused mainly on the endovascular approach for intracranial aneurysms and carotid stenosis. Recanalization is the major goal of EVT for cerebral infarction, and procedural thromboembolism has not been considered important. Procedural thromboembolism during EVT for cerebral infarction has rarely been studied.

Antiplatelet therapy is generally delayed after IV thrombolysis because of the concern of intracerebral hemorrhage. A randomized controlled trial showed an increased risk of

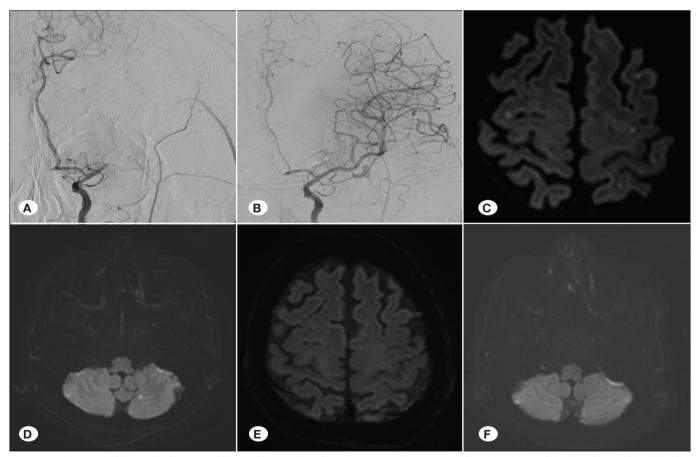


Figure 1: A case of M1 occlusion treated by endovascular thrombectomy. A 76-year-old male patient visited our hospital with right hemiparesis. A) Proximal M1 occlusion was observed. B) Successful recanalization was achieved in the left M1 occlusion with stent retrievers. Diffusion-weighted imaging 1 day after endovascular thrombectomy for acute ischemic stroke showed multifocal diffusion restriction in the right hemisphere (C) and left cerebellum (D), which was not observed on diffusion-weighted imaging before endovascular thrombectomy for acute ischemic stroke (E, F).

Table II: A Comparison of Patient Characteristics, Procedural Details, and Radiological and Clinical Outcomes Between Procedural
Thromboembolism Group and no Procedural Thromboembolism Group After Mechanical Thrombectomy

		Procedural Thromboembolism		
	-	Yes (n=12)	No (n=48)	– р
Patient characteristics	Gender (male)	7 (58.3%)	30 (62.5%)	1.000
	Age (years) (mean ± SD)	74.4 ± 6.95	65.7 ± 12.9	0.028
	Hypertension	5 (41.7%)	23 (47.9%)	0.756
	Diabetes Mellitus	4 (33.3%)	10 (20.8%)	0.448
	Atrial fibrillation	3 (25.0%)	13 (27.1%)	1.000
	Smoking history	7 (58.3%)	15 (31.3%)	0.102
	Occlusion site (anterior circulation)	12 (100.0%)	43 (89.6%)	0.572
	Stroke etiology			0.022
	Atherosclerosis	8	14	
	Non-atherosclerosis	4	34	
	NIHSS score on admission (mean \pm SD)	13.0 ± 4.39	11.2 ± 6.61	0.367
	The time from symptom onset to groin puncture (mean \pm SD)	401.9 ± 282.0	473.8 ± 273.5	0.422
	Antiplatelet preparation	6 (50.0%)	19 (39.6%)	0.532
Procedural details	Total number of EVT attempts (mean \pm SD)	2.58 ± 1.31	2.77 ± 1.96	0.755
	The procedural time (mean ± SD)	97.4 ± 45.7	60.1 ± 28.8	0.001
	Intermediate catheter	8 (66.7%)	36 (75.0%)	0.716
	Balloon guiding catheter	0	11 (22.9%)	0.099
	Rescue treatment	2 (16.7%)	3 (6.3%)	0.259
Radiological and clinical	Successful recanalization	9 (75.0%)	35 (72.9%)	1.000
outcomes	Good clinical outcome	7 (58.3%)	30 (62.5%)	1.000

NIHSS: National Institutes of Health Stroke Scale.

 Table III: Multivariable Logistic Regression Analysis of Factors

 Affecting Procedural Thromboembolism During EVT for Cerebral

 Infarction

Adjusted OR	Adjusted 95% CI	р
1.133	1.009-1.273	0.035
7.434	1.272-43.431	0.026
1.023	1.001-1.046	0.006
	1.133 7.434	7.434 1.272-43.431

EVT: Endovascular thrombectomy, **OR:** Odds ratio, **CI:** Confidence interval

intracerebral hemorrhage with the early administration of aspirin after IV thrombolysis (23). Therefore, antiplatelet preparations before EVT for cerebral infarction can be considered when IV thrombolysis is not available. Previous studies on the use of antiplatelet drug preparations before EVT have shown that the administration of antiplatelet therapy before EVT is associated with better functional outcomes and improved recanalization rates, and it does not increase the risk of hemorrhage (9,22). However, the effect of antiplatelet preparation before EVT on procedural thromboembolism has not been studied.

In this study, the antiplatelet-preparation and no-preparation groups did not show a significant difference in the incidence of procedural thromboembolism (24.0% vs. 17.1%; p=0.532). Hwang et al. reported on thromboembolic complications during the coiling of unruptured aneurysms between the antiplatelet-preparation and no-preparation groups (2.1% vs. 3.4%; p=0.085) (10). The incidence of procedural thromboembolism in our study was higher than that reported in their study. This result can be partially explained by the large proportion of older patients in our study who had substantial comorbidities and poor vascular health, such as such as tortuous vessels, calcification, widespread atheroma, and

occlusive disease (1). Our results suggest that a higher risk of procedural thromboembolism should always be considered during EVT procedures for cerebral infarction, even when antiplatelet preparations are used.

Our results showed that all procedural thromboembolism were small and focal new DWI-positive lesions. Kang et al. reported that many DWI-positive lesions are significantly associated with symptomatic ischemic complications (13). Kim et al. reported that asymptomatic procedural thromboembolism may be associated with cognitive dysfunction, stroke, and mortality (14). Therefore, it is important to reduce the risk of procedural thromboembolism and identify the underlying causes of procedural thromboembolism (16).

Our results also showed that the procedural thromboembolism group was older than the no procedural thromboembolism group (74.4 \pm 6.95 years vs. 65.7 \pm 12.9 years; p=0.028) and the cutoff age for predicting procedural thromboembolism was \geq 72 years. These results may have been associated with poor vascular health with tortuous vessels, calcification, and widespread atheroma (1). In this study, although the statistical significance was not sufficient, the procedural thromboembolism group required rescue treatments more often than the no procedural thromboembolism group (16.7% vs. 6.3%; p=0.259). Because rescue treatments including balloon angioplasty and stenting, require a longer puncture-to-reperfusion time and require more types of devices and device passes (5,20), they can be associated with procedural thromboembolism.

New DWI-positive lesions after neurointerventional procedures may be due to fragmented atherosclerotic plaques and tiny thrombi. Hydrophilic coating materials or air bubbles from catheters and wires can also cause new DWI-positive lesions (11.17). Our multivariable analysis revealed that procedural thromboembolism had a significant relationship with procedural time (adjusted OR, 1.023; 95% CI, 1.000-1.046; p=0.006), and our ROC curve analysis revealed that the cutoff value of the procedural time in predicting procedural thromboembolism was ≥ 109 minutes. A longer procedural time can increase the risk of dislodging a thrombus and introducing hydrophilic coating materials or air bubbles during neurointerventional procedures (15). A procedural time over 1 hour or 3 retrieval attempts during EVT can decrease the rate of good clinical outcomes and increase the risk of hemorrhage (2,6). Our results also suggest that a procedural time of greater than 1 hour is associated with an increased risk of procedural thromboembolism.

This study has several limitations. First, our study had a retrospective design, and therefore an inevitable selection bias. In addition, the types and doses of antiplatelet drugs were heterogeneous in the antiplatelet-preparation group. Second, the sample size was small; thus, the statistical power may be low. Third, we defined procedural thromboembolism as new DWI-positive lesions in other areas of the occluded artery after EVT. However, new DWI-positive lesions after EVT may be due to systemic embolic sources as well as procedural thromboembolism. For new DWI-positive lesions in other areas of the occluded artery after areas of the occluded artery after areas of the occluded artery after EVT.

procedural thromboembolism from new systemic embolic infarction is difficult. Therefore, we used our definition, which may have limitations in representing real procedural thromboembolism. Fourth, late procedural thromboembolism was not considered. We focused only on the analysis of acute procedural thromboembolism based on DWI after EVT. In our hospital, we use magnetic resonance imaging, including DWI and MRA, to evaluate re-occlusion and postprocedural hemorrhage within 2 days after EVT, and this study is a retrospective study analyzing these results. Thus, this may lead to underestimation of the incidence of procedural thromboembolism, because late thromboembolism, which can occur after 2 days was not considered. Further studies with longer-term follow-up and larger sample sizes are necessary to validate these preliminary results.

CONCLUSION

In our study, when IV thrombolysis was unavailable, antiplatelet preparation did not have a significant protective effect on procedural thromboembolism during EVT for cerebral infarction. Additionally, procedural thromboembolism was independently associated with older age, atherosclerotic occlusion, and longer procedural time. Future studies are needed to validate these preliminary results.

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