Risk of Distal Embolization in Acute Large Arterial Occlusion Prior to Endovascular Stroke Treatment in Neurological Institute of Thailand

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Abstract

Objective: Distal embolization was observed in patients presenting with acute ischemic stroke (AIS) with large vessel occlusion (LVO). There are several studies show that the exposure of patients to intravenous tissue-type plasminogen activator (IV tPA) increases the risk of distal embolization and associated with inaccessibility of clot removal by mechanical thrombectomy (MT). In this study, we aimed to investigate the incidence of clot migration, distal embolization, and their risk factors.

Methods: To identify risk factors for and clinical outcomes in the setting of distal embolization and clot migration, the records of all patients with AIS due to anterior circulation LVO treated with MT at Neurological Institute of Thailand between 1 July 2015 and 31 December 2021 were retrospectively reviewed. Clot location was assessed by pretreatment computed tomography angiogram (CTA) and was compared with clot location identified by digital subtraction angiography (DSA) before planned MT. Univariate logistic model were performed to evaluate risk factors of distal embolization and clot migration.

Results: A total of 112 patients were eligible for the analysis, and clot migrations were reported in 19 patients (17.0%). Baseline demographics, underlying diseases, vital signs, NIHSS, CBC, INR, blood sugar, lipid profile, Hounsfield unit ratio (rHU), and history of IV tPA administration were similar between the 2 groups. No correlation between IV tPA administration, high rHU and clot migration (p value 0.789, 0.569 respectively). Because of small sample size (n=17), we cannot identify correlation between each variable factor and distal embolization. However, there is no significant

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difference in clinical outcome between clot migration group and no clot migration group in clinical improvement at discharge (change of NIHSS; 4 vs 8, *p*-value 0.783) and 90-day mRS (2 vs 2, *p*-value 0.642).

Conclusion: Our results show that IV tPA administration, high Hounsfield unit ratio and other variables are not associated with a risk of clot migration. In distal embolization group, we could not identify risk factor because of a few patients but IV tPA administration tend to be a risk factor of distal embolization. We recommend that future research required more sample size. However, there were no significant differences in clinical outcome at discharge and long-term outcome. When possible, use of IV tPA in combination with MT should remain first line treatment for LVO.

Keywords: Distal embolization, Clot migration, Large Vessel Occlusion, Mechanical Thrombectomy, Intravenous tissue plasminogen activator (IV tPA)

Introduction

At present, the treatment of acute ischemic stroke (AIS) is with intravenous tissue plasminogen activator (IV tPA) and mechanical thrombectomy (MT) is classified in the treatment guidelines for AIS. However, it was found that the administration of IV tPA has the potential to cause blood clot to move to the distal vessel.[1-4,7] Causing the inability to continue inserting the catheter through the blood vessels.

In this research, the authors intended to study retrospective data from the medical records of patients diagnosed with AIS due to large vessel occlusion (LVO) and received treatment at Neurological Institute of Thailand (NIT) both in the emergency room and were transferred from other hospitals to consider treatment with mechanical thrombectomy. Computed Tomography Angiography (CTA) method when patients first arrived at the hospital compared with Digital Subtraction Angiography (DSA) at NIT. To determine the correlation of clot migration and distal embolization with the administration of IV tPA and other factors.

Materials and Methods

We performed a retrospective, single-center study to assess risk factors for clot migration and distal embolization before MT of anterior circulation LVO. The records of all patients with AIS, who were treated with MT between 1 July 2015 and 31 December 2021 were reviewed. Patients with posterior circulation interventions and those with no CTA before DSA were excluded. We accept CTA from both NIT and other hospitals in this study. All historical, clinical, laboratory data, radiographic data, clinical outcome and follow-up information was obtained from the medical record at NIT. The modified Rankin Scale (mRS) assessed at 90+/-15 days poststroke was determined in the majority of cases from retrospectively recorded mRS in OPD card. Patients who did not receive IV tPA before MT were either presented late after 4.5 h or there was a contraindication for IV-tPA administration (i.e., patients on anticoagulation). Treatment dose of IV tPA in this study is 0.9 mg/kg (not to exceed 90 mg total treatment dose) infused over 60 minutes. 10% of the total treatment was administered as an initial bolus over 1 minute. The remaining treatment dose was infused intravenously over 60 minutes.

Location of clots was categorized into 6 segments based on their location in anterior cerebral circulation, including intracranial ICA, proximal M1, distal M1, M2, M3 & beyond and ACA. The clot location after the first run of contrast during DSA, before any intervention, was identified by neuroradiologist following the same rule of categorization.

In this study, clot migration was defined by the observation of clot having moved from 1 segment to another and distal embolization was defined a prior as a change in thrombus location into ACA, M2, M3& beyond on DSA which causes the inability to continue inserting the catheter through the blood vessel to remove blood clot. For cases of distal embolization to 2 or more locations, the most proximal clot location was recorded. Adjudication of clot location on CTA and DSA was performed by direct review of the neuroimaging studies specifically for this study by board-certified neuroradiologist who were blinded to IV tPA administration status, demographic data and clinical outcome.

Clot characterization in CT scans

Clot attenuation was determined in 1-mm thick axial reconstructions of nonenhanced CTs by placement of regions of interest. Because of interindividual differences in blood density (anemia, polycythemia), clot attenuation is represented in Hounsfield unit ratio in affected to the unaffected side (rHU=HU Clot / HU contralateral middle cerebral artery).

Statistical Analyses

Continuous variables were presented as the mean and standard deviation or the median and interquartile range. Categorical variables were described as percentages. The differences between groups were analyzed using an independent sample t-test for continuous variables and Fisher's Exact test for categorical variables. A univariate logistic model was used to examine the individual relationship between each variable and clot migration. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to illustrate the association between potential risk factors and clot migration. All probability values were two-sided and the level of significance was set at a p-value < 0.05. Statistical analyses were performed using SPSS for Windows version 16.0 (IBM, Armonk, NY). Ethics Committees of the Neurological Institute of Thailand approved this study no. 65020.

Subgroup Analysis

We performed a subgroup analysis for patients who underwent clot migration to evaluate the risk factor of distal embolization.

Outcome

The primary outcome measure identified risk factors of distal embolization. The secondary outcome measure was a change of NIHSS (before-after) and the 90-day mRS.

Results

A total of 112 patients were eligible for the analysis, and clot migrations were reported in 19 patients (17.0%). Baseline demographics, underlying diseases, vital signs, initial NIHSS, CBC, INR, blood sugar, lipid profile, radiographic data, and history of IV tPA administration were similar between the 2 groups. Patients with clot migration had no significant risk factor compared to no clot migration group (n=93). There is no significant difference in clinical outcome between clot migration group and

no clot migration group in clinical improvement at discharge (change of NIHSS; 4 vs 8, *p*-value 0.783) and 90-day mRS (2 vs 2, *p*-value 0.642). (Table 1)

Among 19 patients who were recorded as clot migration had initial CTA show the most site of occlusion is distal M1(n=6, 31.6%), proximal M1(n=5, 26.3%), intracranial ICA (n=5, 26.3%) and M2(n=3, 15.8%) respectively. (Figure 1)

Distal embolization was seen in 17 cases (15.2% of total, 89.5% of clot migration group). 13 patients in distal embolization group received IV tPA administration (76.5%) and half of no distal embolization group (n=2) received IV tPA administration (50.0%). (Figure 2)

Table 1 Demographics, clinical, laboratory data, radiographic data, and outcomes between clot migration vs. no clot migration groups.

	Clot migration n = 19(17.0%)	No clot migration n = 93(83.0%)	*p*-value
General data			
Age, year (IQR)	64(50-77)	64(52-73)	0.923
Sex			
• Male, n (%)	11(57.9)	50(53.8)	0.804
• Female, n (%)	8(42.1)	43(46.2)	
Underlying diseases			
• Hypertension, n (%)	11(57.9)	62(66.7)	0.598
• DM, n (%)	2(10.5)	23(24.7)	0.235
• Atrial fibrillation, n (%)	12(63.2)	41(44.1)	0.141
• History of TIA, stroke, n (%)	3(15.8)	14(15.1)	1.000
• History of MI, CAD, n (%)	3(15.8)	14(15.1)	1.000
Initial Systolic BP, mmHg (IQR)	149(129-183)	150(136-169.0)	0.810
Initial Diastolic BP, mmHg (IQR)	92(71-113)	86(76-100)	0.415
Initial NIHSS (IQR)	15(13-22)	15(12-18)	0.453
LAB			
Hb, g/dL (IQR)	13(12-14)	13(11-15)	0.659
Hct, % (IQR)	37(34-42)	39(34-43)	0.789
WBC, /mcL (IQR)	8450(7300-11100)	9500(7460-10825)	0.507
Neutrophil, % (IQR)	74(63-84)	71(58-80)	0.411
Lymphocyte, % (IQR)	22(13-29)	20(13-33)	0.592
Platelet, x10^3 mcL (IQR)	250(220-309)	240(207-283)	0.317
INR (IQR)	1.0(1.0-1.0)	1.0(0.9-101)	0.471
Blood sugar, mg/dL (IQR)	110(94-162)	121(103-150)	0.323
Neutrophil/ Lymphocyte ratio (IQR)	3.41(2.2-6.0)	3.8(1.8-6.0)	0.762
Platelet /Lymphocyte ratio (IQR)	131.9(93.4-176.1)	146.1(98.8-194.6)	0.742
Cholesterol, mg/dL (IQR)	175(153-208)	172(144-207)	0.558
Triglyceride, mg/dL (IQR)	84(64-100)	92(70-112)	0.319
HDL, mg/dL (IQR)	45(38-57)	45(38-51)	0.424
LDL, mg/dL (IQR)	110(93-138)	110(82-134)	0.644
IV tPA administration, n (%)	14(73.7)	64(68.8)	0.789

Table 1 Demographics, clinical, laboratory data, radiographic data, and outcomes between clot migration vs. no clot migration groups. (cont.)

	Clot migration n = 19(17.0%)	No clot migration n = 93(83.0%)	*p*-value
At NIT			
Systolic BP, mmHg (IQR)	144(126-156)	152(135-175)	0.113
Diastolic BP, mmHg (IQR)	92(71-98)	86(79-101)	0.917
Radiographic data			
rHU (IQR)	1.31(1.18-1.61)	1.35(1.17-1.47)	0.569
After treatment			
NIHSS at discharge (IQR)	7(4-17)	7(4-13)	0.638
ΔNIHSS (before-after) (IQR)	4(2-11)	8(2-12)	0.783
90-day mRS (IQR)	2(1-4)	2(1-4)	0.642

DM: diabetic mellitus, TIA: transient ischemia attack, MI: myocardial infarction, CAD: coronary artery disease, BP: blood pressure, Hb: hemoglobin, Hct: hematocrit, INR: international normalized ratio, HDL: high density lipoprotein, LDL: low density lipoprotein, NIT: Neurological Institute of Thailand, rHU: Hounsfield unit ratio, NIHSS: national institute of health stroke scale, mRS: modified rankin scale

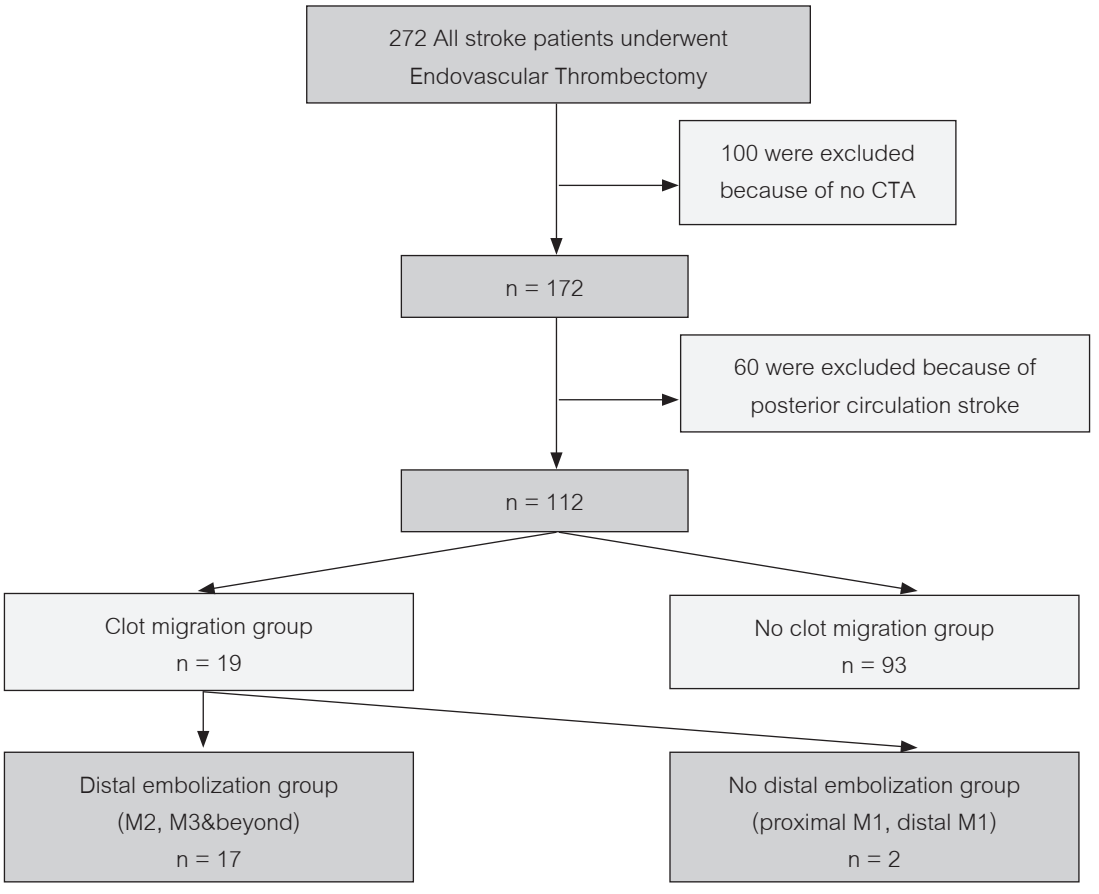
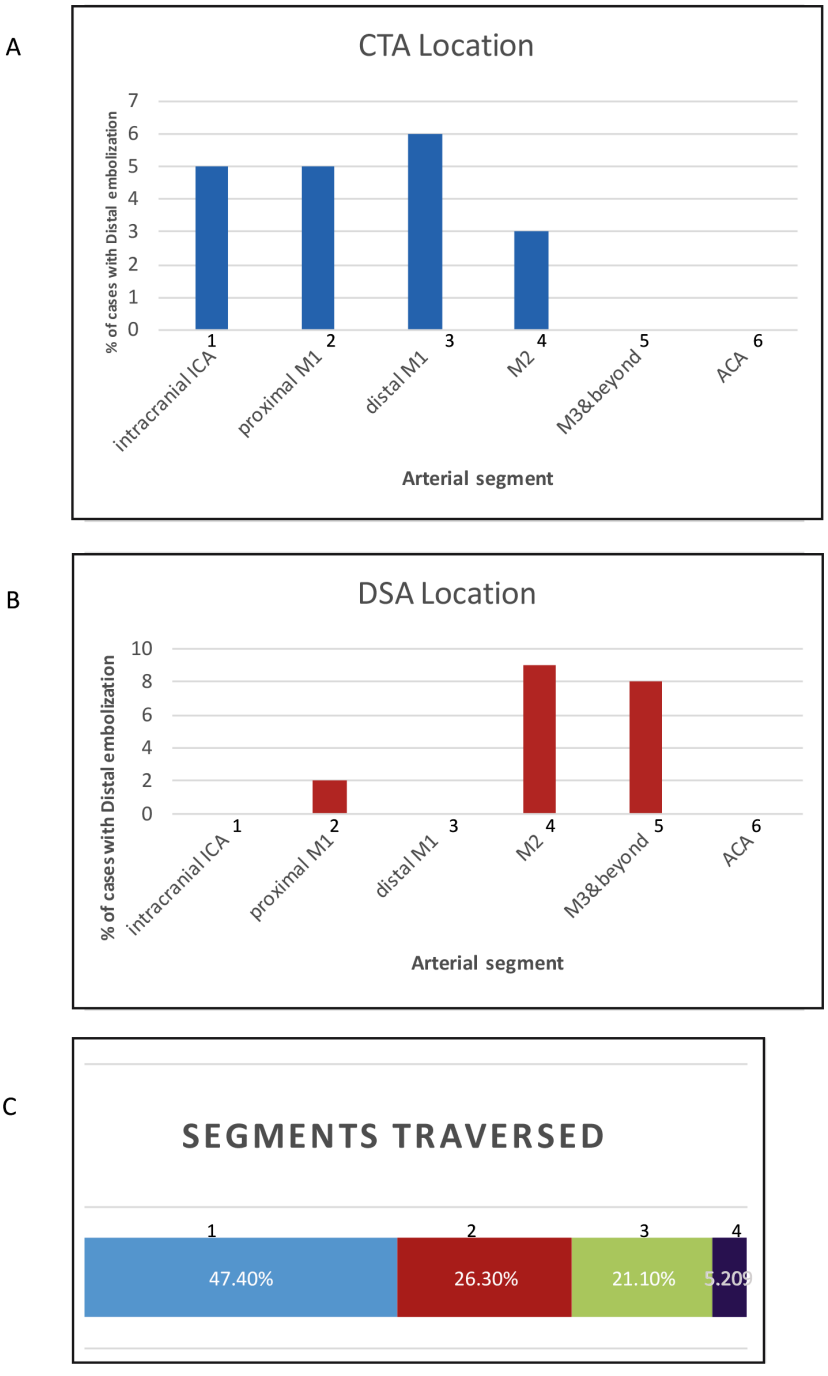


Figure 1 Methodology



A, Initial clot location on CT angiogram (CTA) in the anterior circulation cases where clot migration went on to occur (n=19). Anterior circulation clot locations on the x-axis (1-6) correspond to the following sequential locations: 1= intracranial ICA, 2=proximal M1 segment MCA, 3= distal M1 segment MCA), 4=M2 segment MCA, 5=M3 segment MCA & beyond, 6=ACA
B, Subsequent clot location on digital subtraction angiogram (DSA) in the same cases. Anterior circulation clot locations on the x-axis are coded as shown in (A).
C, Distribution of the number of arterial segments traversed in the same cases. Segments are defined according to the clot locations as described in (A). For example, a case in which the clot embolized from the proximal M1 MCA (location 2 on CTA) to the M3 MCA (location 5 on DSA) traversed 3 segments. In case of clot migration from intracranial ICA (location 1 on CTA) to ACA (location 6 on DSA) was categorized as traversed 1 segment.

Figure 2 Clot migration by arterial segment in the anterior circulation.

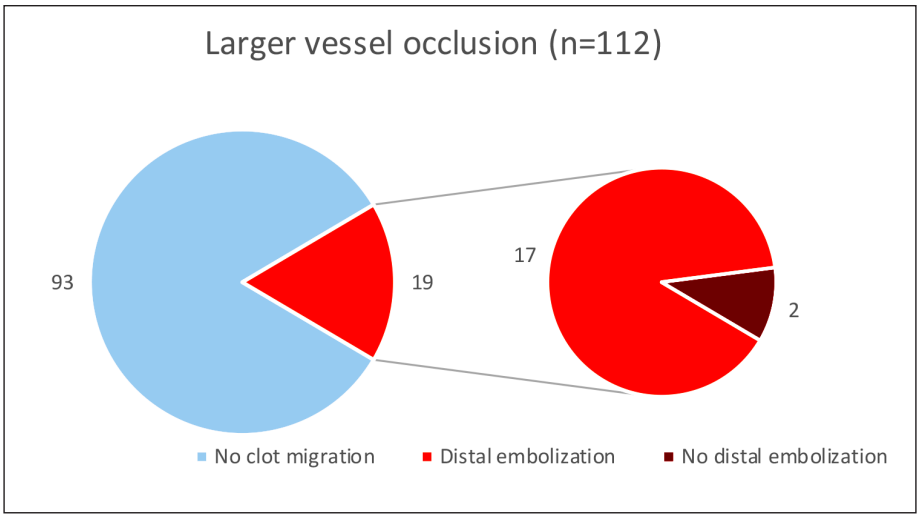


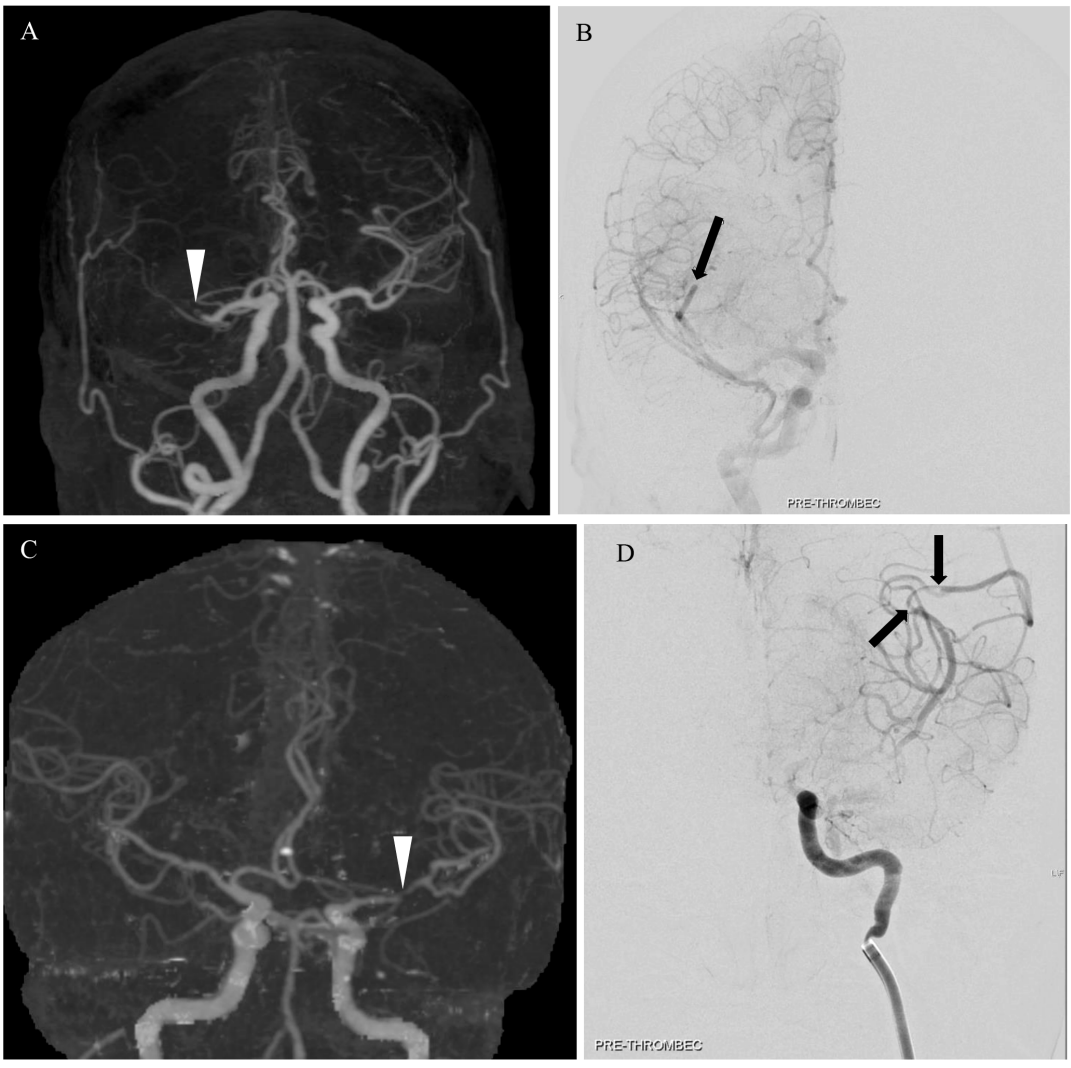
Figure 3 Proportion of clot migration and distal embolization in large vessel occlusion patients

Angiographic clot location compared with clot location on prior CTA, with or without intravenous IV tPA (tissue-type plasminogen activator) administration (n=112). No change in clot location was seen in 93 subjects, clot migration (movement of clot from CTA location to a more distal location on DSA) was seen in 19 subjects, and distal embolization was seen in 17 subjects.

Table 2 number of clot migration were detected in CTA and DSA each case.

CTA	DSA	n
Intracranial ICA	proximal M1	2
	distal M1	0
	M2	2
	M3&beyond	1
Proximal M1	distal M1	0
	M2	3
	M3&beyond	2
Distal M1	M2	4
	M3&beyond	2
M2	M3&beyond	3

ICA: internal carotid artery



A, Initial proximal M1 segment of right MCA clot location on CTA, indicated by white arrow.

B, DSA indicted clot migrated to M2 segment of right MCA, indicated by black arrow.

C, Initial distal M1 segment of left MCA clot location on CTA, indicated by white arrow.

D, Subsequent distal embolization to 2 locations on DSA, M2 and M3 segment of left MCA, indicated by black arrows. For cases such as this with 2 locations of distal embolization (clot fragmentation), the more proximal clot location (in this case, M2) was used in the analysis by segments shown in Figure 2.

Figure 4 Examples of distal embolization comparing CTA to DSA (front cover)

Discussion

In this study, we found that clot migration occurred in 17.0% of all patients presented with AIS. The incidence of clot migration was not increased by administration of IV tPA before MT. This result is similar to the previous study.[5] and there is no correlation between other factors and clot migration. It seems that upon discharge from the hospital, clinical improvement of no clot migration group is better but not statistically significant. However, there were no significant differences in clinical outcome

in 90-day mRS between clot migration and no migration group. This result is similar to previous studies.[1,3,7,9]

We found that 17 patients (15.2%) in clot migration group had a change in location of clot to M2, M3 & beyond as defined as distal embolization and most of them (76.5%) had IV tPA administration. Because of small sample size, we cannot identify correlation between each variable and distal embolization. However, it seems IV tPA administration tends to be a potential risk factor for distal embolization. We suggest that larger studies will be necessary to determine if IV tPA administration is truly risk factor for distal embolization.

In radiologic data, hyperdense artery sign was represented in high Hounsfield Unit ratio (rHU) and Brinjikji W shows that high Hounsfield Unit is associated with RBC-rich thrombi[14] which is predictor for clot migration.[8,9] however we did not find an association between high rHU and clot migration in this study.

Strengths of this study include the completeness of data and inclusion of all anterior circulation AIS. Because of a few previous studies which looked for risk of distal embolization, we hope our study will provide the result to those interested in distal embolization and clot migration in the future. In addition, several limitations of this study need to be addressed. First, the retrospective nature of this study may generate system bias. Second, the study was conducted in a single center where patients shared similar demographic backgrounds which caused selection bias. Third, the interpretation of both CTA and DSA images was done by one neuroradiologist. Furthermore, the differences between M2 and M3 clot location may be better appreciated on DSA than CTA and patients without initial CTA were excluded. Therefore, the actual incidence of clot migration and distal embolization could be higher than in this study. In addition,

NIHSS is an established measure of neurological impairment; however, it can award more points for tests of presumed left-hemisphere function than for tests of right-hemisphere function. This difference may be important if patients with right-sided stroke may have a low NIHSS despite substantial infarction volume.[15] Thus, prospective evaluation after MT should be required for both clinical outcomes and imaging outcomes in distal embolization and clot migration group for assessment of stroke severity. Finally, histopathology of clot is important for predicting clot migration.[8,9] we suggest record levels of erythrocytes, fibrins and embolus length for future study.

Conclusion

Our results show that IV tPA administration, high Hounsfield unit ratio are not associated with a risk of clot migration. In distal embolization group, we could not identify risk factor because of a few patients but IV tPA administration tend to be a risk factor of distal embolization. We recommend that future research requires more sample sizes. However, there were no significant differences of clinical outcome at discharge and long-term outcome. When possible, use of IV tPA in combination with MT should remain first line treatment for large vessel occlusions.

Acknowledgement

We thank the statisticians from Neurological Institute of Thailand research center for their support with the statistical analysis.

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