Clot Migration Is Associated With Intravenous Thrombolysis in the Setting of Acute Ischemic Stroke

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Background and Purpose—Clot migration to distal intracranial arterial segments was observed in patients presented with acute large vessel occlusions. It is postulated that the exposure of patients to intravenous thrombolysis (IVT) increases the risk of clot migration and associated with inaccessibility of the clot by endovascular thrombectomy (EVT). In this study, we aimed to investigate the incidence of clot migration and its association with IVT before EVT.

Methods—We conducted a single-center retrospective analysis of patients who had EVT during the period 2009 to 2016. Patients who fulfilled clinical criteria were treated with bridging IVT and those who did not were treated with direct EVT. Clot position was assessed by pretreatment computed tomography angiogram or magnetic resonance angiogram and was compared with clot position identified by digital subtraction angiography before planned endovascular thrombectomy.

Results—Of 314 included patients, clot migration occurred in 43 patients (13.7%). The proportion of clot migration was 18.7% (39 of 209) in patients who had bridging IVT with EVT compared with 3.8% (4 of 105) in direct EVT (P=0.001). Of the 39 patients who had clot migration in the bridging IVT with EVT, 59.0% (23 of 39) demonstrated clot inaccessibility compared with 25.0% (1 of 4) in clot migration cases in the direct EVT group (P=0.011).

Conclusions—The incidence of clot migration was significantly increased in the setting of bridging IVT before EVT, leading to increased proportion of clot inaccessibility by EVT. **(*Stroke*. 2018;49:3060-3062. DOI: 10.1161/STROKEAHA.118.022751.)**

Key Words: computed tomography angiography ■ incidence ■ stroke ■ thrombectomy ■ thrombosis

Bridging intravenous thrombolysis (IVT) with endovascular thrombectomy (EVT) is the current standard of care for patients who present with acute large vessel occlusions within 4.5 hours of symptoms onset.[1] This treatment has steadily increased in number after the publication of several landmark randomized clinical trials.[2] In animal studies, clot migration to distal intracranial arterial segments was associated with thrombolysis therapy.[3] It followed that occurrence of distal clot migration after IVT,[3–5] may lead to inaccessibility of clot by EVT. However, no previous study has investigated the incidence of clot migration in acute ischemic stroke (AIS) patients with large artery occlusion eligible for bridging IVT and EVT.

The aim of this study was to investigate the association of IVT with clot migration in patients presenting with AIS with large artery occlusion. We hypothesized that standard bridging IVT with EVT, as compared with direct EVT, was associated with increased risk of clot migration.

Methods

Authors declare that all supporting data are available within the article and in the online-only Data Supplement. Extra data are available from the corresponding author on reasonable request.

Study Population

This was a retrospective analysis of patients with AIS of anterior cerebral circulation who presented to Royal Melbourne Hospital (Victoria, Australia) between June 2009 to September 2016. All patients underwent digital subtraction angiography (DSA) with the intention of EVT. All patients had preceding computed tomography angiography (CTA) or magnetic resonance angiogram of brain before administration of IVT and EVT. Patients were excluded if: (1) no adequate images for assessment, (2) complete clot resolution on DSA, and (3) no administration time of IVT were documented. Baseline information was obtained from clinical records collected. This study was approved by the Royal Melbourne Hospital Human Research Ethics Committee and waived the need for patient consent.

IVT and Endovascular Treatment

All enrolled patients were treated according to the current guideline for AIS.[1] Eligible patients who were confirmed to have AIS based on radiological evidence (initial CTA/magnetic resonance angiogram) within 4.5 hours of symptoms onset received bridging IVT (intravenous tissue-type plasminogen activator) before EVT. Direct EVT was performed in patients whereby time of onset was beyond 4.5 hours of stroke onset or had contraindications for IVT.

Image Analysis

Initial clot position was identified by researcher (Dr Ren) on patients' initial CTA or magnetic resonance angiogram after onset of AIS.

Received March 31, 2018; final revision received September 17, 2018; accepted September 25, 2018.

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The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.022751.

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Position of clots was categorized into different groups based on their location in cerebral circulation, including common carotid artery, internal carotid artery, internal carotid artery terminus junction (also termed internal carotid artery T junction), middle cerebral artery and its segments, anterior cerebral artery, and its segments. Of note, M1 segment was defined as from the origin of middle cerebral artery to the bifurcation/trifurcation.[6] The clot position after the first run of contrast during DSA, before any intervention, was identified by Dr Ren following the same rule of categorization. The IVT status of patients was not known to Dr Ren at the time of evaluating clot positions. Clot migration was defined by the observation of clot having moved from 1 category to another (example shown in the Figure). Finally, randomly selected 20% of the study population was independently assessed by senior neuroradiologist (B. Yan) and interrater agreement of clot position was calculated.

Statistical Analysis

Statistical analysis was performed using Stata 13IC (StataCorp, College Station, TX). Individual characteristics of the patients with and without clot migration were summarized as medians and interquartile ranges for continuous characteristics and as counts (proportions) for categorical characteristics and compared using Wilcoxon-Mann-Whitney rank sum test and Fisher exact test, respectively. Interrater agreement was estimated using Cohen kappa. The association between presence/absence of bridging IVT and clot migration was investigated using logistic regression modeling with clot migration (yes/no) as the dependent variable, absence versus presence of bridging IVT as an independent variable and age, clot positions, and time between symptoms onset to DSA as prior chosen treatment covariates. Firth penalized likelihood regression was used to investigate low-incidence outcome. For all analyses, 2-tailed *P* values below 0.05 were interpreted as indicative of statistical significance.

Results

Study Population

The study population consisted of 314 patients and their baseline information was presented in Table I in the online-only Data Supplement. There were no significant differences between direct IVT group and IVT with EVT group in terms of age, sex, baseline National Institutes of Health Stroke Scale, risk factors of stroke (diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, ischemic heart disease, and previous stroke) and time between symptoms onset to DSA were identified.

Clot Position and Clot Migration

The interrater agreement on clot migration was high (κ=0.819; 95% CI, 0.621–1.000), which demonstrated reproducibility of the adjudication method for clot migration. A total of 43 (13.7%) patients were found to have clot migration among all patients presented with AIS. Of the patients who had bridging IVT, 39 patients had clot migration (Table II in the online-only Data Supplement). In contrast, only 4 patients had clot migration in the direct EVT group which was significantly lower than IVT group (odds ratio, 5.79; 95% CI, 2.01–16.69; *P*=0.001). Variables including age, clot side, and clot positions other than internal carotid artery had no significant statistical association with clot migration. For those patients who had clot migration, M2 (n=21) was the most common final clot location on DSA followed by M3 and beyond (n=15). Furthermore, 23 of 39 clot migration patients in IVT with EVT group failed to

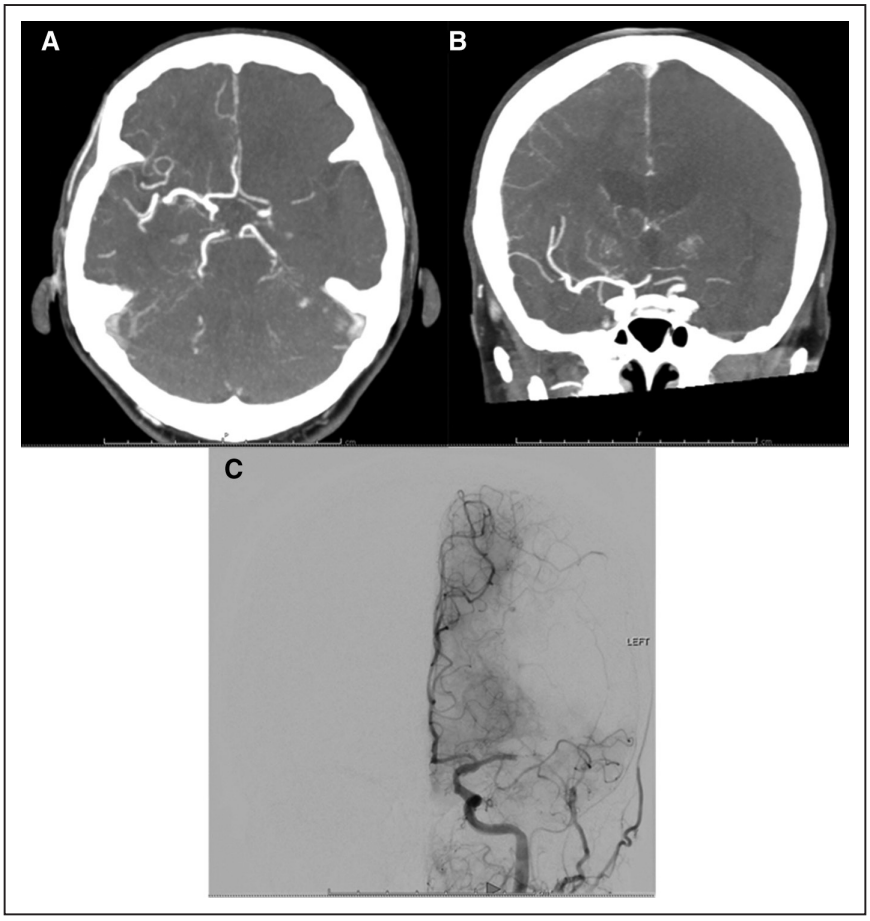

Figure. Example of clot migration comparing computed tomography angiography (CTA) to digital subtraction angiography (DSA). **A** and **B**, axial and coronal CTA indicated clot located in left internal carotid artery terminus junction. **C**, Coronal DSA indicted clot migrated to M1 segment of left middle cerebral artery (MCA).

receive EVT because of clot migrated to distal arteries. This was significantly higher than only 1 patient in direct EVT group had clot migrated beyond the reach of EVT devices (adjusted odds ratio, 8.77; 95% CI, 1.66–46.53; *P*=0.011). However, no significant differences were found in term of 90 days modified Rankin Scale between direct EVT and IVT with EVT (*P*=0.077). Furthermore, clot migration did not show a significant impact on 90 days modified Rankin Scale compared with no clot migration group (*P*=0.741).

Discussion

In this study, we found that clot migration occurred in 13.7% of all patients presented with AIS. The incidence of clot migration was significantly increased by administration of bridging IVT before EVT (18.7%) compared with direct EVT (3.8%). Of note, 11.0% (n=23) of IVT patients did not receive EVT because of clot migrated to distal arteries, whereas only 1.0% (n=1) of direct EVT patients had clot migration beyond capacity of current EVT. This suggests bridging IVT before EVT may lead to worse recanalization outcome comparing to direct EVT. However, there were no significant differences of clinical outcome at 90 days between direct EVT and IVT with EVT group, as well as between clot migration and no migration group.

Of note, 5 patients were excluded in the study because of complete recanalization (Thrombolysis in Cerebral Infarction grade 3) on DSA. This recanalization rate followed by administration of IVT was lower than those of the large randomized trial.[7,8] The recanalization rate in the IMS III trial (International Management of Stroke; partial or complete) in all anterior circulations were higher than our results.

Strengths of this study include the completeness of data and inclusion of all anterior circulation AIS. 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 single center where patients shared similar demographic background which caused selection bias. Furthermore, the interpretation of both CTA and DSA images were done by the same researcher (Dr Ren). Although interrater agreement was evaluated statistically, image analysis was primarily performed by nonblinded single researcher which may resulted in bias. In addition, the differences between M2 and M3 clot position may be better appreciated on DSA than CTA. Finally, although we did not observe any significant differences (*P*=0.077) between the clinical outcome between clot migration and no clot migration, we cannot exclude the possibility that this is affected by the relatively small sample size of clot migration patients.

Conclusions

We found that of the patients, who were treated with bridging IVT with EVT, demonstrated clot migration of 18.7%. A significant proportion of cases with clot migration was associated with inaccessibility of the clot by EVT. We recommend that future research is required to answer the question whether direct EVT without IVT leads to decreased clot inaccessibility and improved outcomes.

Disclosures

None.

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