Preprocedure Intravenous Recombinant Tissue Plasminogen Activator and Risk of Distal Embolization with Thrombectomy in Acute Ischemic Stroke

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Background: Intravenous recombinant tissue plasminogen activator (IV rt-PA) prior to thrombectomy may reduce the risk of intraprocedural distal embolization in acute ischemic stroke patients. *Methods:* We analyzed the diffusion-weighted imaging acquired with 1.5- or 3-T magnetic resonance imaging (MRI) scans obtained within 24 hours of thrombectomy in consecutive acute ischemic stroke patients. An independent physician identified distal embolization, defined as discrete foci of restricted diffusion independent of the primary area of infarction on MRI scan. Patients were stratified based on whether they had or did not receive IV rt-PA prior to thrombectomy. *Results:* Distal embolization was seen in 59 (ipsilateral in 56) of 63 patients (mean age ± SD; 64.6 ± 15.3 years) who underwent thrombectomy (mean number 8.6; range 0-32). There was no difference in mean number of ipsilateral hemispheric distal embolization between the 2 groups (7.9 ± 6.1 versus 7.5 ± 7.6, P = .82). After adjusting for age, admission National Institutes of Health Stroke Scale score, the time interval between symptom onset and thrombectomy, there was no association between receiving IV rt-PA prior to thrombectomy and number of ipsilateral distal emboli (P = .90). There was no relationship between the number of ipsilateral emboli and rates of favorable outcome after adjusting for other confounders (adjusted odds ratio 1.0; 95% confidence interval .89 - 1.0; P = .40). *Conclusions:* Although distal embolization is very common after thrombectomy, IV rt-PA prior to procedure does not reduce the risk of intraprocedural distal embolization.

Key Words: Thrombectomy—activase—recombinant tissue plasminogen activator—distal embolization—acute ischemic stroke—magnetic resonance imaging

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Introduction

The use of stent retrievers and aspiration devices for endovascular treatment of ischemic stroke may result in thrombus fragmentation and downstream migration of smaller embolic particles.[1] These, however, are usually undetected by conventional digital subtraction angiography, and their true prevalence and effect on the clinical outcome is unclear. The presence of embolic complications has been associated with worse outcomes in acute ischemic stroke treatment.[2] The reported rates of distal embolization range from 0% to 12.5% to new arterial territories, and up to 22.8% within the same territory.[3] The risk of embolic complications following thrombectomy is of particular concern since emboli can impair collateral blood supply to the affected territory, accelerate penumbral tissue loss, and cause additional ischemic lesions.[4] Theoretically, preprocedural administration of intravenous recombinant tissue plasminogen activator (IV rt-PA) may reduce the rate or consequences of this type of complication by lysing the smaller embolic fragments. In most studies, recanalization rates in patients treated with thrombectomy are not influenced by preprocedural administration of IV rt-PA, although this subset of patients seems to show a higher rate of favorable outcomes.[5-8] However, such a potential benefit remains largely unproven, and a review of 20 studies encompassing 5279 patients showed only a nonsignificant trend of higher functional independence at 90 days and no difference in rates of successful recanalization.[9] Still, it is plausible that IV rt-PA may improve the clinical results of thrombectomy by reducing the rates of distal embolization. We performed this study to evaluate the effect of IV rt-PA on rates of distal embolization in acute ischemic stroke patients undergoing thrombectomy.

Methods

We identified all patients with acute ischemic stroke who underwent thrombectomy at the University of Missouri Hospital between 2016 and 2018. We selected those patients who underwent magnetic resonance imaging (MRI) studies within the 24 hours following thrombectomy and included them in our study population. All patients in the study population who met standard treatment criteria, had received IV rt-PA, in accordance with current guidelines.[10] The patients who did not qualify for IV rt-PA mainly because of presenting outside the recommended time window were considered for mechanical thrombectomy. The decision to proceed with thrombectomy as part of the treatment did not influence the administration of IV rt-PA, and was based on the following criteria: (1) identification of a large arterial occlusion on computerized tomographic angiography in patients who presented within 6 hours of the estimated time of onset, or (2) identification of salvageable tissue using computerized tomographic perfusion (CTP) in those who presented between 6 and 24 hours. The salvageable tissue was identified based on the standard CTP parameters, where mean transit time (MTT) is elevated in both penumbra and infarct core, whereas cerebral blood volume (CBV) is typically diminished only in the infarct core. Thus, MTT-CBV mismatch is commonly thought to reflect the ischemic penumbra.[11]

Qualifying Imaging Protocol

Immediately following standard noncontrast head computed tomography (CT), CTP study of the brain was obtained using a timed (40 cc) bolus of nonionic intravenous iodinated contrast. Perfusion CT was performed by monitoring only the first pass of an iodinated contrast agent bolus through the cerebral circulation.[12] It involved continuous cine imaging for 45 seconds over the same slab of tissue (1-32 sections) during the dynamic administration of a small (50 mL), high-flow contrast material bolus (injection rate, 4-5 mL/s). The contrast agent passed through the brain tissue, causing a transient hyperattenuation that is directly proportional to the amount of contrast material in the vessels and blood in that region. This principle was used to generate time-attenuation curves for an arterial region of interest, a venous arterial region of interest, and each pixel.

Color-coded perfusion maps showing CBV, MTT, and cerebral blood flow (CBF) are obtained.[12] The quantification of these parameters is based on the equation CBF = CBV/MTT. MTT was calculated by performing a mathematical technique called deconvolution on the regional time-attenuation curve of each pixel with respect to the arterial curve (arterial input function).[12] CBV was calculated by dividing the area under the curve in a parenchymal pixel by the area under the curve in an arterial pixel. CBV map depicts the lesions seen at diffusion MRI, helping predict the infarcted brain tissue that is not salvageable despite reperfusion. Hence, the salvageable brain tissue is equivalent to CBF − CBV. The MTT, CBF, and CBV maps were calculated using the commercial software Syngo, Siemens.

Thrombectomy Procedures

All thrombectomies were carried out via 6-8 French (Fr) introducer sheath in the common femoral artery. A diagnostic angiogram was immediately performed to confirm the position of the introducer sheath in anticipation of the placement of closure device postprocedure. A 6-Fr multipurpose device guide catheter was introduced into the internal carotid or vertebral arteries, depending on the target vessel being treated. Once the target arterial occlusion was confirmed, a microcatheter ranging in diameter from 1.4 to 2.7 Fr (Excelsior XT-27 Microcatheter or Excelsior SL-10 Microcatheter or 3MAX Reperfusion Catheter or Prowler Select Plus 0.021-inch 2-tip Microcatheter) was advanced over a 0.014-inch microwire (SYNCHRO-II

guidewire) into the vessel of interest, and used to traverse the occlusion. Thrombectomy was performed using stent retrievers (Solitaire or Trevo). Aspiration thrombectomy was used infrequently (n = 45 patients) and intra-arterial thrombolytics were also used as needed (n = 17 patients). Intra-arterial thrombolytics were used regardless of whether patient had received IV rt-PA. Stents (Neuroform Atlas 4.5 × 24 mm stent or ACCULINK Carotid Stent System 6-8 × 40 mm or CODMAN ENTERPRISE 2 Vascular Reconstruction Device 4 × 39 mm) were used (5 patients) in the event of underlying stenosis and/or re-occlusion. Combination of various modalities was used consistent with contemporary practices. The principles of postprocedure care were similar to those used in patients receiving IV rt-PA such as maintaining systolic blood pressure less than 180 mm Hg and avoidance of antiplatelet agents. Antiplatelet agents were infrequently used if stents were placed.

MRI Assessment Protocol

All MRI studies were acquired using either 1.5 (Siemens – Magnetom Aera) or 3 Tesla (Siemens - Magnetom Vida/Skyra) magnets and included diffusion-weighted imaging (DWI) sequences. All images were obtained within 24 hours of thrombectomy. The single-shot echo-planar technique was used at b-values of 0-1000 s/mm^2 to perform the MRI. The MRI protocol followed for the ischemic stroke included; Axial FLAIR (fluid-attenuated inversion recovery), Axial T2, Axial susceptibility-weighted images and Axial DWI. T1-weighted Magnetization Prepared Rapid Gradient Echo sequence with coronal and sagittal reconstructions was used.

Identification of Distal Embolization

The DWI images were reviewed by one of the 2 independent stroke and neurointerventional physicians (E.A., J.L.) who were unaware whether the patient had received IV rt-PA or not. The physicians identified distal embolization related foci of restricted diffusion on ipsilateral and contralateral hemispheres. Distal embolization was defined as discrete foci of restricted diffusion independent of the primary area of infarction on MRI. The number of lesions was determined regardless of the distribution patterns of the lesions (see Fig 1).

Data Collected

The presence of cardiovascular risk factors including active cigarette smoking history, hypertension, atrial fibrillation, coronary artery disease, hyperlipidemia, diabetes mellitus, prior transient ischemic attack or ischemic stroke; and the time interval between symptom onset and endovascular intervention, and use of IV rt-PA were ascertained as previously described.[13] We recorded admission, 24-hour post-treatment, and discharge National Institutes of Health Stroke Scale (NIHSS) scores.

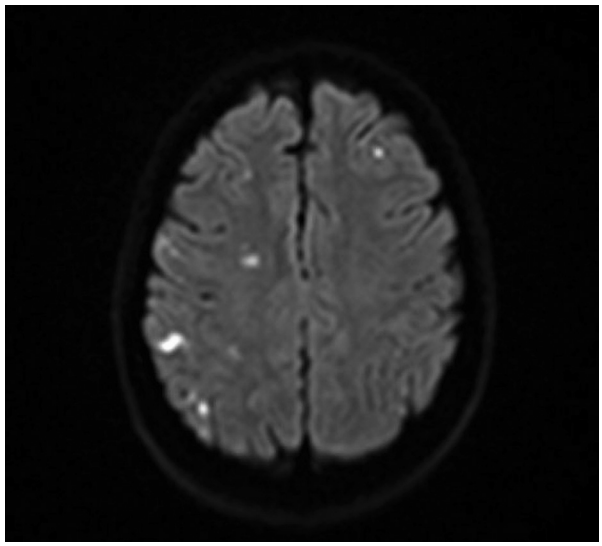

Figure 1. *MRI scan (DWI sequence) illustrating the distal embolization related foci of restricted diffusion on ipsilateral and contralateral hemispheres. Abbreviations: DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging.*

We also recorded any occurrence of postprocedure intracerebral hemorrhage (ICH) and in-hospital mortality. Symptomatic ICH was defined as a noncontrast CT scan documented ICH resulting in neurological deterioration (≥4 points worsening on an NIHSS score compared with the previous clinical assessment). Outcome at the time of discharge was assessed using a modified Rankin scale (mRS) ascertained using detailed descriptions provided by the vascular neurology team, and occupational, speech, and physical therapists. Favorable functional outcome was defined by mRS of 0-2 at discharge. Procedural time was defined by the time interval between femoral artery catheterization and partial or complete recanalization or procedure termination. The times were identified by reviewing the angiographic images and recording the individual times of microcatheter placement and recanalization or completion of the procedure. Angiographic occlusion and recanalization were classified by the treating physician by using either the thrombolysis in myocardial infarction (TIMI) grading scale[14] or the Qureshi grading scale.[15] Complete recanalization was defined by post-treatment TIMI grade[16] of 3 which is equivalent to thrombolysis in cerebral infarction reperfusion grade[17] of 3 or by Qureshi grade of 0. Partial recanalization was defined by an improvement of 1 grade or more on either the TIMI or Qureshi grading scale. This methodology has been used in previous publications.[18,19]

Statistical Analysis

All data was descriptively presented using mean ± standard deviation for continuous data and frequencies for categorical data. The frequency of baseline demographic and clinical characteristics, admission NIHSS

score, the time interval between symptom onset and initiation of thrombectomy, distal embolization (total, ipsilateral, and contralateral), rates of symptomatic ICH and favorable outcome at discharge were compared among patients who received or did not receive IV rt-PA prior to thrombectomy. We performed a multivariable linear regression analysis evaluating the independent effect of receiving IV rt-PA prior to thrombectomy on the number of ipsilateral distal emboli after adjusting for age and admission NIHSS score (used as a continuous variable) and any other variables identified in the univariate analysis. We performed a multivariable logistic regression analysis evaluating the independent effect of ipsilateral emboli on the favorable outcome at discharge after adjusting for age and admission NIHSS score and the time interval between symptom onset and thrombectomy. We performed another multivariable logistic regression analysis evaluating the independent effect of all (ipsilateral and contralateral) emboli on the favorable outcome at discharge after adjusting for age and admission NIHSS score and the time interval between symptom onset and thrombectomy. We performed another multivariable logistic regression analysis evaluating the independent effect of ipsilateral emboli on the favorable outcome at discharge after adjusting for above-mentioned confounders. We also repeated the analysis only including patients with near complete or complete recanalization to identify the effect of distal embolization in absence of unsuccessful recanalization (another prognostic factor). A P value <.05 was considered significant. All data analysis was performed using IBM Corp. IBM SPSS Statistics for Windows, version 23.00 64-bit edition Armonk, NY.

Results

A total of 63 acute ischemic stroke patients (mean age ± SD; 64.6 ± 15.3 years; 37 were men) underwent thrombectomy and underwent an MRI within 24 hours postprocedure. IV rt-PA was administered in 27 (43%) of 63 patients with a mean time interval (±SD) of 2 hours (±0.69) between symptom onset and IV rt-PA administration. The mean time interval (±SD) between symptom onset and thrombectomy was 8.7 hours (±12.8). The mean time interval (±SD) between IV rt-PA administration and thrombectomy was 3.2 hours (±1.3) in 27 patients.

Table 1 compares the baseline demographic and clinical variables between patients who did and did not receive IV rt-PA prior to thrombectomy. The mean age was similar among patients who did and did not receive IV rt-PA

Table 1. *Baseline demographic and clinical variables between acute ischemic stroke patients who did and did not receive IV rt-PA prior to thrombectomy*

Variables	Patients who received IV rt-PA (%)	Patients who did not receive IV rt-PA (%)	P value
Total	27	36	
Age years (mean ± SD)	62.8 ± 15.2	65.9 ± 15.4	.52
Women	11 (41)	15 (42)	.94
Hypertension	17 (63)	27 (75)	.31
Cigarette smoking	7 (26)	15 (42)	.20
Atrial fibrillation	6 (22)	18 (50)	.02
Coronary artery disease	6 (22)	12 (33)	.34
Hyperlipidemia	10 (37)	19 (53)	.22
Diabetes mellitus	6 (22)	10 (28)	.62
Admission NIHSS score strata			
NIHSS score 0-10	5 (18)	9 (25)	
NIHSS score 11-19	17 (63)	18 (50)	
NIHSS score 20-42	5 (18)	9 (25)	
Treatment times			
Time interval between symptom onset and thrombectomy (mean ± SD)	5.3 ± 1.5 h	11.3 ± 16.5 h	.06
Number of emboli			
Total (mean ± SD)	8.7 ± 5.9	8.6 ± 7.8	.93
Ipsilateral (mean ± SD)	7.9 ± 6.1	7.5 ± 7.6	.82
Contralateral (mean ± SD)	.80 ± 1.4	1.1 ± 1.6	.50
Angiographic recanalization			
Partial or complete	21 (78)	27 (75)	.80
ICH symptomatic	0	0	N/A
Favorable outcome at discharge (mRS 0-2)	14 (52)	13 (36)	.25

Abbreviations: ICH, intracerebral hemorrhage; IV rt-PA, intravenous recombinant tissue plasminogen activator; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

(62.8 ± 15.3 versus 65.9 ± 15.4 years, $P = .52$). There were no differences in the proportion of patients with hypertension, coronary artery disease, cigarette smoking, hyperlipidemia, or diabetes mellitus among patients who did and did not receive IV rt-PA. Atrial fibrillation as a risk factor was significantly different between the 2 groups [6 (22%) versus 18 (50%), $P = .02$]. The mean time interval between symptom onset and thrombectomy was greater in those who did not receive IV rt-PA (11.3 ± 16.5 and 5.2 ± 1.5, $P = .06$). Patients who received IV rt-PA had similar rates of complete or partial recanalization [21 (81%) versus 27 (75%), $P = .80$] but nonsignificantly higher rates of favorable outcomes [mRS 0-2] at discharge [14 (51%) versus 13 (36%), $P = .25$].

Distal embolization (both ipsilateral and contralateral) was seen in 59 of 63 patients (mean age ± SD; 64.6 ± 15.3 years) who underwent thrombectomy (mean number 8.6; range 0-32). Ipsilateral emboli were seen in 56 of 63 patients. The mean number of distal embolization was not significantly different between patients who had and those who did not receive IV rt-PA prior to thrombectomy (8.7 ± 5.9 versus 8.6 ± 7.8; $P = .93$ by ANOVA). There was no difference in the mean number of ipsilateral hemispheric distal embolization between the 2 groups (7.9 ± 6.1 versus 7.5 ± 7.6, $P = .82$ by ANOVA). There was no relationship between mean number of emboli and age of the patient (regression coefficient −0.069; $P = .59$) or time interval between symptom onset and thrombectomy (regression coefficient −0.023; $P = .86$) on linear regression analyses.

In multivariable analysis, after adjusting for age, admission NIHSS score, the time interval between symptom onset and thrombectomy, there was no association between receiving IV rt-PA prior to thrombectomy and number of ipsilateral distal emboli ($\beta = -0.2$, S.E = 1.8, 95% confidence interval (CI) for β −3.4 to 3.9; $P = .90$). There was no association between receiving IV rt-PA prior to mechanical thrombectomy and number of overall (ipsilateral and distal) emboli (β .2, S.E = 3.7, 95% CI for β −7.2 to 7.6; $P = 1.00$), after adjusting for above-mentioned confounders. There was no relationship between the number of ipsilateral emboli and rates of a favorable outcome after adjusting for age, admission NIHSS score, the time interval between symptom onset and thrombectomy (adjusted odds ratio (OR) 1.0; 95% CI 0.89-1.0; $P = .40$). There was no effect of number of overall (ipsilateral and contralateral) emboli and rates of a favorable outcome after adjusting for abovementioned confounders (adjusted OR 1.0; 95% CI 0.93- 1.1). Limiting the analysis to only those patients with near complete or complete recanalization did not change the results.

Discussion

We found a very high rate of embolization on MRI in patients undergoing thrombectomy for acute ischemic stroke. We did not find any evidence to support that IV rt-PA use prior to thrombectomy reduces the risk of distal embolization. A previous study by Kaesmacher et al[20] demonstrated similar results. The definition of distal embolization was based on angiographic occlusion distal to the site of primary occlusion after recanalization. Administration of IV rt-PA was associated with fewer endovascular maneuvers, and shorter time to primary recanalization, but the sum of overall emboli was higher among those who received IV rt-PA. The lack of relationship between IV rt-PA prior to thrombectomy and occurrence of emboli may be related to the short half-life of rt-PA (3-5 minutes)[21] which may result in near complete hepatic based clearance of IV rt-PA by the time thrombectomy was performed.

One of the challenges has been that how is distal embolization defined? There are angiographic criteria and MRI criteria looking at thrombi in distal arteries. Both criteria may provide overlapping but not the same results. Angiographically visible distal embolization may not always result in ischemia and restricted diffusion. MRI evidence of ischemia and restricted diffusion may identify consequences of embolization in small arteries not visible on angiographic images. Janjua et al[22] defined distal embolization" based on the appearance of occlusion on a downstream vessel. The study found that distal embolization occurred in 16% of the 91 patients treated in 4 prospective protocols. Janjua et al[22] also reported that distal embolization can occur in patients who receive only intra-arterial thrombolytics without any thrombectomy.[21] Todo et al[23] used the same definition and found that 30% of the 20 patients treated with Penumbra suction device based thrombectomy had distal embolization. Kaesmacher et al[20] using the angiographic definition as mentioned above reported that 49 (57.6%) out of 85 patients had distal embolization but the study only included those in whom thrombus was retrieved for histological analysis. Klinger-Gratz et al[3] identified emboli based on areas of tubular or dot-like signal drop on postprocedural susceptibility-weighted images. New embolic lesions were found in 13 of 57 patients (22.8%), and were located outside of the infarct core (defined by post-treatment DWI images) in 9 patients and inside in 4 patients. Lee et al[24] using the angiographic definition of distal embolization reported that distal embolization was less frequent when the occlusive balloon guide catheter used as an adjunct to thrombectomy with stent retriever (6.8% versus 31.8%). We used the presence of small infarctions independent of the primary lesion on DWI as markers of distal embolization. A small proportion of patients with acute ischemic stroke (16-29%) can have multiple acute brain infarctions in the absence of thrombectomy.[25,26] Such infarctions are thought to be secondary to emboli although can occur in the setting of regional hypoperfusion.[27] The appearance of a primary contiguous infarction with multiple small infarctions noncontiguous to primary infarction is

uncommon. However, our methodology is insensitive to emboli that are released within the primary infarcted region, as the restricted diffusion by primary lesion will mask such small areas.

We did not find a relationship between the number of emboli on rates of a favorable outcome at discharge. It is possible that distal emboli are more amenable to intrinsic thrombolytic systems and shear force of the proximal flow and cause small infarctions, which are inconsequential to the outcome. Janjua et al[22] reported that rates of mRS 0-2 at 1-3 months were lower among the subgroup with distal embolization compared with those without it (13% versus 36%; $P = .09$), though this difference was only significant when patients who never experienced recanalization were excluded. In the multivariate analysis, distal embolization was not significantly associated with mRS 3-6 at 1-3 months (OR 3.0, $P = .09$). Kaesmacher et al[20] reported that higher rate of substantial neurologic improvement defined as either NIHSS score at the day of discharge less than or equal to 1 or the difference between NIHSS scores on admission and NIHSS score at the day of discharge greater than or equal to 8 was seen in patients with lower frequency, proximal ($P = .029$) and intermediate emboli ($P = .018$). Todo et al[23] reported that the rates of patients who achieved an mRS of 0-2 were lower in those with distal embolization (16.7% versus 42.9%). The mean NIHSS score decrease was only 2.3 in patients with distal embolization versus a decrease of 10.6 in patients without distal embolization among stroke survivors. One of the factors that confound the relationship between distal embolization and outcome may be due to additional treatment offered for distal embolization that occurs in large arteries beyond the site of initial occlusion during the procedure as part of achieving angiographically defined complete recanalization.[28,29] Smaller emboli that are distal or not apparent on digital subtraction angiography may not receive additional treatment but may not affect the outcome. Atrial fibrillation was present in higher proportion of patients who did not receive IV rt-PA in our analysis. This disproportionate distribution was by chance because presence of atrial fibrillation was not used to exclude patients from receiving IV rt-PA. However, we cannot exclude the possibility that thrombi generated due to atrial fibrillation may be more susceptible to IV rt-PA and less prone to distal embolization. Therefore, disproportionate distribution may have confounded part of our observations. The relative time interval between receiving IV rt-PA and performance of mechanical thrombectomy may have limited our ability to detect a benefit of IV rt-PA in reducing distal embolization. It is possible that if mechanical thrombectomy was performed very quickly after receiving IV rt-PA (may not be practical), a beneficial effect could have been detected.

Conclusion

The current observation adds new information regarding the (lack of) therapeutic value of preprocedure IV rt-PA on distal embolization in acute ischemic stroke patients undergoing thrombectomy. Our current study and other studies[5-8] have also shown that the rate of angiographic recanalization does not improve with preprocedure IV rt-PA in acute ischemic stroke patients undergoing thrombectomy. These observations highlight the need for critically determining the value of preprocedure IV rt-PA in acute ischemic stroke patients undergoing thrombectomy.

Declaration of Competing Interest

Nothing to disclose and no conflict of interest.

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