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Greater effect of stroke thrombolysis in the presence of arterial obstruction

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Abstract

Objective—Recanalization of arterial obstruction is associated with improved clinical outcomes. There are no controlled data demonstrating whether arterial obstruction status predicts the

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treatment effect of intravenous (IV) tissue plasminogen activator (tPA). We aimed to determine if the presence of arterial obstruction improves the treatment effect of IV tPA over placebo in attenuating infarct growth.

Methods—We analyzed 175 ischemic stroke patients treated in the 3-6 hour time window from the EPITHET trial (randomized to IV tPA or placebo) and DEFUSE study (all treated with IV tPA). Infarct growth was calculated as the difference between baseline DWI and final T2 lesion volumes. Baseline arterial obstruction of large intracranial arteries was graded on magnetic resonance angiography (MRA).

Results—Among the 116 patients with adequate baseline MRA and final lesion assessment, 72 had arterial obstruction (48 tPA, 24 placebo) and 44 no arterial obstruction (33 tPA, 11 placebo). Infarct growth was lower in the tPA than placebo group (median difference 26mL, 95% CI 1 to 50) in patients with arterial obstruction, but was similar in patients with no arterial obstruction (median difference 5mL, 95%CI -3 to 9). Infarct growth attenuation with tPA over placebo treatment was greater among patients with arterial obstruction than those without arterial obstruction by a median of 32 mL (95%CI 21to 43, $p<0.001$).

Interpretation—The treatment effect of IV tPA over placebo was greater with baseline arterial obstruction, supporting arterial obstruction status as a consideration in selecting patients more likely to benefit from IV thrombolysis.

Introduction

The aim of stroke thrombolysis is recanalization of an arterial obstruction with subsequent reperfusion leading to infarct growth attenuation with the ultimate goal of better clinical outcomes. Intravenous (IV) stroke thrombolysis has a narrow therapeutic window with decreasing benefit and escalating risk with increasing time from onset. [1] Attempts to widen the therapeutic window have employed selection criteria that include profiles with greater potential for benefit and exclude those with increased risk of symptomatic intracerebral hemorrhage (sICH).

Arterial obstruction has been proposed as a selection criterion for stroke thrombolysis, supported by data showing recanalization with IV tissue plasminogen activator (tPA) improves clinical outcomes. [2-3] Post-hoc Desmoteplase In Acute Ischemic Stroke (DIAS) II trial data demonstrated a trend for clinical benefit with IV desmoteplase in a subgroup with arterial obstruction. [4] Patient selection based on arterial obstruction was used in the intra-arterial Prolyse in Acute Cerebral Thromboembolism (PROACT) II study which included patients with high grade stenosis/ occlusion of the middle cerebral artery (MCA) M1 or M2 segment), [5] and is currently being employed in the DIAS III and IV trials which include those with high grade stenosis or occlusion of proximal arteries. [6-7]

The presence of arterial obstruction has been shown to result in larger infarct growth and poorer clinical outcomes in patients not treated with thrombolysis [8-9] and in cohorts including patients who did and did not undergo thrombolytic treatments. [10-11] There are no published data demonstrating that arterial obstruction influences the impact of IV tPA versus placebo. We aimed to test the hypothesis that the presence of arterial obstruction improves the treatment benefit of IV tPA over placebo in terms of infarct growth attenuation.

Methods

This is a post-hoc study including pooled data from the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study. EPITHET is a multicenter, randomized, double blinded, controlled trial of IV tPA versus placebo in the 3-6 hour window. [12] The

DEFUSE study is a multicenter prospective cohort treated with IV tPA also in the 3-6 hour window. [13] Informed consent was obtained from all participants in EPITHET and DEFUSE, both of which were approved by the ethics committees of the individual participating centers.

In both EPITHET and DEFUSE, patients underwent baseline magnetic resonance imaging (MRI) prior to treatment, including magnetic resonance angiography (MRA), diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) sequences. Final lesion was assessed on follow-up MRI at day 30 in DEFUSE and day 90 in EPITHET, using T2-weighted sequences.

We performed uniform standardized assessment of arterial obstruction for the EPITHET and DEFUSE cohorts by consensus of three investigators masked to clinical factors. Arterial obstruction was graded as no obstruction, partial obstruction or complete occlusion of the artery corresponding to the acute infarction. [3] For these analyses, arterial obstruction was defined as partial obstruction and completed occlusion.

Baseline DWI, baseline PWI and final T2 lesions were assessed using the original EPITHET and DEFUSE protocols. [12-13] PWI lesions were defined as Tmax delay of 2 seconds or more from Tmax maps generated using deconvolution algorithms using arterial input function selected from the contralateral middle cerebral artery. [12-13] Mismatch was defined as a profile with PWI lesion larger than DWI lesion volume by 20% and at least 10mL, as per the original EPITHET and DEFUSE definitions. Infarct growth was the absolute difference between final T2 lesion and baseline DWI lesion volumes. Functional outcome was assessed at day 90 using the modified Rankin score (mRS) with good outcome defined as mRS 0-2.

We compared the baseline characteristics based on arterial obstruction status using the Pearson's Chi-square and Wilcoxon-Mann-Whitney rank-sum tests. The difference in infarct growth between treatment arms for subgroups with and without arterial obstruction was estimated by Hodges-Lehman nonparametric shift estimator. A median regression model with treatment-by-obstruction status interaction term was employed to determine the influence of arterial obstruction on infarct growth attenuation between treatment arms.

Results

There were 101 patients in EPITHET and 74 in DEFUSE. Of these 175 patients, 154 had adequate MRA data (MRA not performed for 1 and of poor quality for 14). Among these, the final lesion could be assessed for 116 patients (final MRI not performed for 37 and of poor quality for 1). In this 116 cohort with data analyzed, 72 had baseline arterial obstruction (48 tPA, 24 placebo) and 44 no obstruction (33 tPA, 11 placebo). Among the 72 with arterial obstruction, 45 had complete occlusion and 27 partial obstruction. The site of obstruction was the internal carotid artery for 22, MCA M1 for 43, M2 for 4 and posterior cerebral artery for 3.

Table 1 shows the comparison of baseline characteristics based on arterial obstruction status. Patients with arterial obstruction were younger than those with no obstruction [median age 70 (IQR 58 to 78) vs 76 (IQR 71 to 83) years, p=0.004]. As expected, those with arterial obstruction had a higher National Institutes of Health Stroke Scale (NIHSS) score [median 14 (IQR 9 to 17) vs 9 (IQR 7 to 14) mL, p=0.001], larger DWI [median 18.5 (IQR 5.0 to 39.0) vs 9.9 (IQR 3.0 to 18.30) mL, p=0.017], PWI [median 134.8 (IQR 63.5 to 228.4) vs 57.9 (IQR 5.0 to 95.5) mL, p<0.001] and mismatch [median 102.0 (IQR 36.0 to 195.5) vs 35.8 (IQR 0 to 75.0) mL, p<0.001] volumes as well as higher prevalence of the mismatch profile (84% vs 57%, p=0.003).

The treatment effect of infarct growth attenuation was greater among patients with arterial obstruction than those with no arterial obstruction on MRA. Among those with arterial obstruction, there was less infarct growth in the tPA compared to placebo arms by a median difference of 26 mL (95% CI 1 to 50, p=0.03) (Table 2), as estimated by Hodges-Lehman nonparametric shift estimator. Infarct growth was similar between placebo and tPA arms in the patients with no arterial obstruction (median difference 5mL 95% CI -3 to 9, p=0.22). Using median regression models, the median difference in infarct growth attenuation with tPA over placebo between patients with and without arterial obstruction was 32 mL (95% CI 21 to 43, p<0.001). This remained significant with a median difference of 33 mL (95% CI 22 to 43, p<0.001) with adjustment for age.

Among the 24 patients who had no arterial obstruction but had the mismatch profile, infarct growth appeared attenuated in the tPA group (median -1.94 IQR -6.36 to 5.72 mL) compared to the placebo groups (median 5.24 IQR -2.90 to 10.31 mL) but the difference was not statistically significant (Hodges-Lehmann median difference -4.86 95% CI -13.56 to 6.33 mL, p=0.320). Infarct growth was significantly lower among patients who achieved good functional outcome (median 0 IQR -2.63 to 5.15 mL) compared to those who did not (17.70 IQR 0.68 to 63.34 mL) by a Hodges-Lehmann median difference of -18.35mL (95% CI -31.90 to -8.40mL, p<0.001). Using logistic regression, for 1mL of absolute infarct growth, the OR of good functional outcome was 0.97 (95% CI 0.95 to 0.98). Among patients without arterial obstruction, good functional outcome occurred in 66% (25) treated with tPA and 42% (5) in the placebo arm (OR 2.69, 95%CI 0.59 to 12.85). Among patients with arterial obstruction good functional outcomes occurred in 43% (32) treated with tPA and 34% (10) in the placebo arm (OR 1.44, 95%CI 0.55 to 3.98).

Discussion

The beneficial effect of IV tPA over placebo on infarct growth attenuation was significantly greater in patients with arterial obstruction than those with no arterial obstruction. Potential reasons for this finding include the larger hypoperfusion and diffusion-perfusion mismatch lesions among patients with arterial obstruction that are potentially salvageable with recanalization. Alternatively, spontaneous recanalization may have occurred with no potential for further infarct growth. The infarct growth difference of a median 32 mL is sizeable. This difference is expected to influence the likelihood of good functional outcome which was reduced by 3% for every 1mL of absolute infarct growth.

This study's data support the concept of arterial obstruction as a selection criterion to identify patients more likely to benefit from IV tPA, particularly beyond the 3 hour time window. Assessment of arterial obstruction status using MRA may be easier and faster to ascertain than the presence of ischemic penumbra delineated by diffusion-perfusion mismatch, another candidate selection criterion for stroke thrombolysis. This is particularly important with the time pressure to minimize the duration from stroke onset to initiation of thrombolysis. One strength of diffusion-perfusion mismatch over arterial obstruction status as a selection criterion is that features of the ischemic penumbra such as the malignant profile can predict risk of sICH complications. [13] Within 3 hours of stroke onset, arterial obstruction status may not influence the treatment effect of IV tPA and its assessment may unnecessarily delay time to thrombolysis.

The presence of arterial obstruction does not equate to that of an ischemic penumbra. [9, 14] This is evidenced by our data showing that 16% with arterial obstruction did not have a mismatch profile. Arterial obstruction may occur without any corresponding tissue hypoperfusion due to alternative arterial supply via collaterals and communicating arteries, early completed infarct growth into the ischemic penumbra or recanalization of a tandem

arterial obstruction. [9, 14] On the other hand, tissue hypoperfusion may be evident despite no obstruction of large arteries due to involvement of arteries too small to be imaged with MRA, partial spontaneous recanalization or the no-reflow phenomenon. [9, 14] In this study, among patients with no arterial obstruction, 57% had a mismatch profile with a median mismatch volume of 35.8 mL (IQR 0 to 75.0). Among patients with the mismatch profile but no large arterial obstruction, tPA appeared to have some beneficial effect in attenuating infarct growth compared to placebo, but these findings were underpowered and not statistically significant. Thus, larger studies are required to verify this. There are currently no published data comparing arterial obstruction and diffusion-perfusion mismatch as selection criteria for stroke thrombolysis. Use of the dual target selection criteria of both arterial obstruction and diffusion-perfusion mismatch has been proposed but there is a paucity of evidence for this strategy. [14]

We confirm that infarct growth correlated with functional outcomes in this pooled dataset, consistent with findings from the EPITHET trial and DEFUSE study. [12-13] Although the rate of good functional outcome was higher in the tPA versus placebo arms for both groups with and without arterial obstruction, the differences were not statistically significant. This is expected as the EPITHET trial and these post-hoc analyses were not powered for clinical outcomes.

The main strengths of this study were the placebo control arm which allows for assessment of treatment effect, adequate sample size with pooling of EPITHET and DEFUSE data, and uniform assessment of arterial obstruction status. There were some limitations. First, infarct growth attenuation is a surrogate outcome measure. Although infarct growth is strongly correlated with clinical outcomes, [12] these findings need to be confirmed with clinical outcomes. Second, MRA has its own limitations as a modality for assessment of arterial obstruction, including overestimation of degree of obstruction and poor resolution for smaller arteries particularly as it was not performed with contrast. Third, in view of the post-hoc nature of the analyses, these findings should be interpreted with caution and replicated in other studies.

In the pooled EPITHET and DEFUSE cohort, the treatment benefit of IV tPA over placebo using an imaging surrogate of infarct growth attenuation was greater in patients with arterial obstruction on MRA versus those with no arterial obstruction. Thus, arterial obstruction status might provide additional or complementary information in treatment selection for IV tPA, particularly in the wider time windows.

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Table 1
Baseline characteristics of patients by baseline arterial obstruction status

	No arterial obstruction N=44	Arterial obstruction N=72	P value
Median Age (IQR) - years	76 (71-83)	70 (58-78)	0.004
Male gender	50%	50%	0.999
Hypertension	66%	63%	0.711
Diabetes	18%	25%	0.393
Hyperlipidemia	41%	29%	0.194
Smoking	36%	43%	0.476
Atrial Fibrillation	30%	28%	0.838
Median NIHSS (IQR) - mL	9 (7-14)	14 (9-17)	0.001
Median PWI volume (IQR) - mL	57.9 (5.0 to 95.5)	134.8 (63.5 to 228.4)	<0.001
Median DWI volume (IQR) - mL	9.9 (3.0 to 18.3)	18.5 (5.0 to 39.0)	0.017
Median mismatch volume (IQR) -mL	35.8 (0 to 75.0)	102.0 (36.0 to 195.5)	<0.001
Mismatch (>20% and 10mL)	57%	84%	0.003

IQR: Interquartile range
NIHSS: National Institutes of Health Stroke Scale score
PWI: Perfusion-weighted imaging
DWI: Diffusion-weighted imaging

Table 2
Median infarct growth in mL (95% CI) by baseline arterial status and treatment arm

	Placebo	tPA	Median difference in treatment effect: (placebo-tPA)*	Median difference in treatment effects between patients with and without arterial obstruction#
Arterial Obstruction (N=72)	N=24 37 (1 to 83)	N=48 6 (0 to 29)	26 (1 to 50) p=0.03	32 (21 to 43) p<0.001
No arterial obstruction (N=44)	N=11 5 (-3 to 8)	N=33 0 (-2 to 2)	5 (-3 to 9) p=0.22	

*Hodges-Lehman nonparametric shift estimator

#Obtained by median regression model with an arterial obstruction status by treatment group interaction term

CI: Confidence Interval
tPA: tissue plasminogen activator