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The efficacy of IV tissue plasminogen activator for restoring cerebral blood flow in the hours immediately after administration in patients with acute stroke

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Abstract

Background and Purpose: Timely restoration of tissue-level cerebral blood flow is the goal of thrombolytic therapy in patients presenting with an acute ischemic stroke. We aimed to identify the incidence and predictors of reperfusion immediately following treatment with intravenous recombinant tissue plasminogen activator (IV rt-PA).

Methods: This study included patients with acute ischemic stroke triaged using MRI with perfusion weighted imaging (PWI) and treated with IV rt-PA that were subsequently enrolled in our natural history study and underwent repeat MRI with PWI approximately 2 hours post treatment. Early reperfusion was defined as >80% decrease in the size of initial perfusion deficit on the 2 hours follow up MRI. Demographics, stroke risk factors, presenting NIHSS score and location of the thrombosis were compared between patients with and without early reperfusion.

Results: Of the 49 patients included in this study, 21 (43%) had early reperfusion. The mean age for patients with early reperfusion was significantly lower in comparison to the patients without early reperfusion (64 vs 76, $p=0.01$). The prevalence of hyperlipidemia was significantly lower among patients with early reperfusion (24% vs 54%, $p=0.036$). Patients with early reperfusion were less likely to have large vessel occlusion (internal carotid artery terminus or proximal middle cerebral artery) (24% vs 50%, $p=0.06$). In a multivariate analysis, the presence of a LVO was an independent predictor of lack of early reperfusion [OR (95%CI): 0.13 (0.019-0.89), $p=0.038$].

Conclusion: Early reperfusion was found in a substantial percentage of the patients treated with IV rt-PA. It was more common in patients without large vessel occlusion.

Keywords

Early reperfusion; intravenous recombinant tissue plasminogen activator; ischemic stroke; large vessel occlusion; perfusion MRI

Introduction

Intravenous recombinant tissue plasminogen activator (rt-PA) is the standard of care for eligible patients with acute ischemic stroke presenting within 4.5 hours from the time of symptom onset. IV rt-PA is shown to improve clinical outcome in stroke patients when compared with placebo.^{1,2} The presumed mechanism of improved outcome after treatment with rt-PA is accelerated lysis of the culprit thrombus with restoration of blood flow to the ischemic brain tissue. Previous studies looking at the efficacy of rt-PA on clot lysis have focused on the resolution of vascular occlusion, finding 13% to 52% rates of recanalization on vessel imaging depending on the location of intracranial occlusion.^{3,4} Recanalization of the target vascular occlusion is associated with improved functional outcome and reduced mortality.⁵ Changes in tissue level perfusion have also been associated with good clinical outcome,^{6,7} and rt-PA has been shown to accelerate such reperfusion.⁸ However the ability of rt-PA to establish early, extensive, tissue-level reperfusion has not been described in a quantitative fashion. The purpose of this study was to identify the incidence and predictors of early reperfusion using MR perfusion as a biomarker for IV rt-PA efficacy.

Methods

This study was a retrospective analysis of prospectively collected data from institutional review board-approved National Institutes of Health (NIH) Natural History of Stroke (NHS) study. The study identification number for this protocol is NCT00009243. Written informed consent was obtained from all participants (or their surrogate) of this study. Patients enrolled in the study during 2013 and 2014 were screened for inclusion in this analysis. The inclusion criteria for our study were 1) treatment with IV rt-PA, 2) an MRI with PWI prior to treatment with IV rt-PA, 3) an MRI with PWI approximately 2 hours after treatment, and 4) a quantifiable PWI lesion on the pretreatment MRI. There was no minimum PWI volume requirement. Patients who received endovascular therapy prior to the 2-hour MRI, were excluded. Of note, the enrollment period for this study was prior to the advent of endovascular therapy as standard of care for large vessel occlusion.⁹

MRI Parameters

Images were acquired on a 1.5T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI), a 3T Siemens Skyra scanner (Siemens AG, Munich, Germany), or a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands). Image sequences and typical parameter ranges were: Diffusion tensor imaging (TR 4461-10500msec, TE 61.6-91.3 msec, 3.5mm slice thickness, 40 slices) used to generate trace diffusion weighted images (DWI) using three orthogonal directions ($b = 0$ and 1000 s/mm²) and apparent diffusion coefficient (ADC) maps; dynamic susceptibility contrast (DSC) PWI (TR 1-1.5 sec, TE 25-45 msec, 7mm slice thickness, 20 slices, 40-80 dynamics), which was collected during the injection of a weight-based dose of gadolinium (0.1mmol/kg of gadolinium-DPTA, Magnevist; Bayer Schering Pharma, Whippany, New Jersey or gadolinium-BOPTA Multihance, Bracco Diagnostics, Monroe Township, New Jersey); FLAIR imaging (TR 9000 msec, TE 120-145 msec, 3.5 mm slice thickness, 40 slices); time-of-flight magnetic resonance angiography (MRA) images (TR 18-23 msec, TE 3.43-6.8 msec, 0.75-1.4 mm

slice thickness, 73-95 slices); gradient recall echo (GRE) images (TR 700-800 msec, TE 12-20.4 msec, 3.5-7mm slice thickness, 20-40 slices).

Image Processing

Images were processed using Matlab software (Mathworks, Natick, MA, USA) and image co-registration¹⁰ was implemented using Diffeomap software (mrstudio.org). The pretreatment PWI scan was processed to identify a region of interest (ROI) defined as having a time-to-peak (TTP) gadolinium concentration of greater than 4 seconds beyond normal tissue from the unaffected hemisphere. This ROI, which represents the pretreatment perfusion lesion, was then moved into the 2 hour PWI using transformation matrices extracted from the image co-registration process.¹¹ The percentage of the ROI that no longer had a TTP greater than 4 seconds was used to define the percent reperfusion (Figure-1). This can be described with the equation:

$$\text{Percent Reperfusion} = [1 - (\text{2hr ROI volume}) / (\text{Pretreatment ROI volume})] * 100 \quad (1)$$

Early reperfusion for this study was defined as >80% percent reperfusion at 2 hours as described above.

The location of vascular occlusion was assessed by one reviewer, ANS, who was blinded to the other results of the study. Large vessel occlusion (LVO) was defined as a cut off or absence of the internal carotid artery (ICA) or M1 segment of the middle cerebral artery (MCA) on time-of-flight MRA. For more distal occlusions, in the absence of a vascular cutoff on MRA, the location of the thrombus was estimated from the PWI based on standard vascular territories.

Statistics

Successful reperfusion was defined as >80% reperfusion at 2 hours and treated as a dependent binary variable. Demographic characteristics, vascular risk factors including hypertension, diabetes, hyperlipidemia, atrial fibrillation, congestive heart failure, and smoking, stroke severity through National Institutes of Health Stroke Scale (NIHSS) score, time interval from symptom onset to IV rt-PA administration and status of large vessel occlusion (defined as distal ICA, M1 segment of middle cerebral artery occlusion) were compared among patients with and without >80% reperfusion at 2 hours.

Chi-square test and t-test were used for categorical data and for continuous data, respectively with a p-value <0.05 considered significant. A multivariate logistic regression model was created to identify the independent predictors of >80% reperfusion at 2 hours using variables with p<0.10 from the univariate analysis. A second multivariate analysis also included two typical modifiers of stroke outcome (NIHSS and time-to-treatment) that were not identified in the univariate analysis. The SAS 9.3 software (SAS Institute, Cary, NC) was used for the analysis.

Results

Of the 131 treated patients enrolled in the NIH NHS study during the two-year period, 93 patients had a MRI 2 hours after treatment, of which 73 had perfusion imaging. Of these 49 had a quantifiable perfusion deficit on their pretreatment MRI and did not received endovascular therapy thus meeting the inclusion criteria for this analysis. The median age of the cohort was 71 and 47% were women. The mean perfusion volume prior to treatment was 72 cc and the average percent reperfusion (equation 1) was 65%. In this cohort, 43% (21/49) of the patients had near total reperfusion (>80%) immediately (~2 hours) after treatment with IV rt-PA. The table-1 displays the demographics, risk factors, and clinical characteristics of the entire population and the individual groups of those who did and did not have early reperfusion.

We found that the average age of the patients with reperfusion at 2 hours was significantly lower than the patients without reperfusion (64 ± 16 vs 76 ± 14 , $p=0.01$). There was no significant difference between the two groups regarding gender, the rate of hypertension, diabetes, prior stroke, atrial fibrillation and congestive heart failure. However, the patients with >80% reperfusion at 2 hours had significantly lower prevalence of hyperlipidemia (24% vs 54%, $p=0.04$). Lesion volume measured in ADC sequence of baseline MRI was not different in patients with early reperfusion and those without it (11 ml vs. 17 ml, $p=0.34$). The median time intervals from symptom onset to IV rt-PA administration were not different between the two groups. Similarly, the mean size of initial perfusion deficit measured on MR perfusion study was not significantly different between the two groups.

Patients with a large vessel occlusion (LVO) tended to be less likely to have early reperfusion after treatment with IV rt-PA at 2 hours (24% vs 50%, $p=0.06$). Multivariate analysis including variables with $p<0.10$ from the univariate analysis did not find age ($p=0.36$), HLD ($p=0.33$), smoking ($p=0.26$), or LVO ($p=0.13$) to be independent predictors of reperfusion. Adding initial NIHSS and time interval from symptom onset to IV rt-PA, since these are common modifiers of outcome, to the multivariate model resulted in the presence of a large vessel occlusion becoming an independent predictor of not achieving >80% reperfusion at 2 hours MRI [OR (95% CI): 0.13 (0.019-0.89), $p=0.038$]. However, of the 19 patients who had a LVO, 5 (26%) had early reperfusion. Thus, while the majority of patients with LVO did not have early reperfusion, 1 in 4 patients with LVO were successfully treated with IV rt-PA alone. In patients without LVO, 16 patients out of 30 (53%) had early reperfusion.

Discussion

In this analysis we found that IV rt-PA was effective at its intended task in 43% of stroke patients presenting with a blood flow abnormality detected on MRI. Current practice is for patients with LVO to be taken for endovascular therapy after treatment with IV rt-PA; thus, the LVO population no longer depends on thrombolysis for reperfusion. For the population of patients presenting without a LVO, this study found that over half responded favorably to IV rt-PA.

For patients presenting with a LVO in this study, our analysis supports the results of prior studies that demonstrated this population is less likely to respond to IV rt-PA.^{12,13} It is also now recognized by the field that endovascular therapy improves outcome in this population.¹⁴ However some LVO patients are not treated with endovascular therapy due to an exclusion such as poor baseline functional status, or due to lack of access to a tertiary care center. Thus, it is reassuring to know that 25% of the patients in our study presenting with LVO were successfully treated with IV rt-PA alone. The enrollment period for our study population included time before introduction of endovascular therapy as standard of care for patients with LVO and we excluded patients who had endovascular therapy prior to 2-hour MRI. Therefore, early reperfusion rate in patient with IV rt-PA plus endovascular therapy compared to those with only endovascular therapy needs to be addressed in separate study. Nevertheless, our results should discourage the practice of withholding IV rt-PA from patients with LVO in favor of pursuing endovascular therapy alone and support current guidelines and literature endorsing bridging therapy in eligible patients with LVO.^{15,16}

Previous studies have demonstrated a strong correlation between radiographic recanalization and good functional outcome in acute stroke patients.⁵ Even modest reductions in perfusion deficits have been associated with improved outcome.⁶ In our study we focused on the efficacy of rt-PA on the target occlusion rather than on functional outcome since the latter could be influenced by both reperfusion and recovery.

Published literature on examining response to rt-PA has typically focused on recanalization of the proximal vessel. Yeo et al³ measured early recanalization as any change in transcranial Doppler (TCD) at 2 hours and found 51% of patients met this definition, which was similar to our results. A meta-analysis⁴ of 20,163 patients treated with IV rt-PA that incorporated a variety of methods for detecting early recanalization found an overall rate of 33%, which is lower than our findings, however when they restricted the analysis to distal occlusions they found a 52% rate of early recanalization which is similar to what we found for non-LVO patients. For M1 segments they reported 35%, and for ICAs they report 13%, which when taken together is probably similar to our finding of 26% for LVOs in our study.

Two studies have quantitatively looked at reperfusion based on PWI for patients treated with rt-PA in an extended time window.^{17,18} A meta-analysis of these studies found that rt-PA approximately doubled both the recanalization and reperfusion rates over placebo, reporting a 67% reperfusion rate for treated patients.¹⁹ However the definition of reperfusion varied between studies to account for difference in the timing of follow up imaging. Our study used both a strict definition of reperfusion (>80%) and an early follow up image (2 hours). These stricter criteria may account for our lower reperfusion rate of 43%. In contrast to those studies, this study assesses early, extensive reperfusion of patients treated with rt-PA in a standard treatment window.

There are several limitations to this study. It has a relatively small sample size; thus, the reported reperfusion rates may not be generalizable to a larger population. Several variables were tested and the multivariate analysis may suffer from over fitting. Also, considering retrospective nature of our analysis, selection bias might exist in our analysis. The lack of

association with reperfusion in some cases, such as for the time-to-treatment, may be related to limited power rather than a true lack of association.

In conclusion we found that, for the population enrolled in this study, acute stroke patients presenting with a perfusion deficit detected on MRI who were treated with IV rt-PA alone experienced early, near complete resolution of the perfusion deficit in 43% of all cases and 53% of cases with distal occlusion. The presence of a LVO, as well as other risk factors, may reduce the likelihood of response to rt-PA, however it was still effective in approximately one in four cases. Although the sample size for this study was relatively small, our findings are in agreement with the published literature on the topic. While endovascular therapy has largely replaced the need for effective thrombolysis in patients with LVO, many patients do not have access to immediate endovascular therapy. This study supports the use of rt-PA in patients with and without a large vessel occlusion and highlights the importance of the “drip-and-ship” model.

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Figure-1:

The figure shows an example of how percent reperfusion was calculated by moving perfusion deficits between time points. Panel A shows a pre-treatment perfusion weighted image (PWI) with bright signal reflecting increased time-to-peak (TTP). Panel B shows the region of interest (ROI) determined by thresholding the TTP map at greater than 4 seconds. Panel C shows the ROI in isolation. Panel D shows the ROI after the co-registration matrix between the time points is applied to the ROI. Panel E shows the PWI from the 2 hour time point when the lesion has reperfused. Panel F shows the transformed ROI superimposed on the 2 hour PWI. The percent reperfusion is calculated as the percent of the ROI in panel F that is no longer greater than 4 seconds on the 2 hour TTP map

Table-1:

Population and group characteristics

	All Patients N=49	Patients with early reperfusion N=21 (43%)	Patients without early reperfusion N=28 (57%)	p-value
Age- Mean($\pm$SD)	71 $\pm$ 16	64 $\pm$ 16	76 $\pm$ 14	0.01
Median (range)	73 (30-102)	67 (30-92)	76 (47-102)	
Gender-Female (%)	23 (47%)	9 (43%)	14 (50%)	0.62
Baseline NIHSS				
Mean($\pm$ SD)	12 $\pm$ 8	11 $\pm$ 8	13 $\pm$ 8	0.31
Median (range)	10 (1-31)	7 (1-30)	13 (1-31)	0.31
Hypertension	40 (82%)	16 (76%)	24 (86%)	0.39
Diabetes	12 (24%)	6 (29%)	6 (21%)	0.56
Hyperlipidemia	20 (41%)	5 (24%)	15 (54%)	0.036
Atrial fibrillation	21 (43%)	8 (38%)	13 (46%)	0.56
Heart Failure	6 (12%)	2 (10%)	4 (14%)	0.61
Prior stroke	5 (10%)	1 (5%)	4 (14%)	0.25
Alcohol abuse	2 (4%)	1 (5%)	1 (4%)	0.86
Smoking	5 (10%)	4 (19%)	1 (4%)	0.08
Carotid artery stenosis	2 (4%)	1 (5%)	1 (4%)	0.86
Initial systolic blood pressure	151 $\pm$ 25	153 $\pm$ 22	149 $\pm$ 27	0.67
Glucose	130 $\pm$ 45	140 $\pm$ 62	122 $\pm$ 26	0.22
Platelet	233 $\pm$ 71	230 $\pm$ 59	235 $\pm$ 80	0.81
Time interval from LKN to IV rt-PA treatment				
Median number of minutes (range) *	135 (54-1030)	165 (62-1030)	125 (54-864)	0.12
Initial perfusion deficit volume (ml)				
Mean($\pm$ SD)	72 $\pm$ 73	57 $\pm$ 59	83 $\pm$ 81	0.22
Median (range)	50 (0.2-284)	37 (0.2-208)	57 (0.6-284)	0.19
Percent Reperfusion** (%)				
Mean($\pm$ SD)	65 $\pm$ 29	93 $\pm$ 7	43 $\pm$ 18	<.0001
Median (range)	64 (0-100)	96 (80-100)	43 (0-76)	<.0001
Large vessel occlusion	19	5 (24%)	14 (50%)	0.06
Location of the thrombosis				0.001
ICA thrombosis	7 (14%)	1 (5%)	6 (21%)	0.098
M1 thrombosis	12 (24%)	4 (19%)	8 (29%)	0.44
M2 thrombosis	10 (20%)	2 (10%)	8 (29%)	0.12
Distal MCA thrombosis	20 (41%)	14 (67%)	6 (21%)	0.001

Abbreviations used: SD: standard deviation, NIHSS: National Institutes of Health Stroke Scale, LKN: last known normal, IV rt-PA: intravenous recombinant tissue plasminogen activator, ml: milliliter, ICA: internal carotid artery, MCA: middle cerebral artery, M1: proximal segment of middle cerebral artery, M2: insular segment of middle cerebral artery

* The cohort includes the patients who presented as wake up stroke and were treated with IV rt-PA with LKN within 24 hours and symptom discovery within 4 hours from the time of IV rt-PA administration

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