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IV rt-PA Improves Arterial Recanalization Rates and Reduces Infarct Volumes in Subjects with Hyperdense Artery Sign on Baseline CT

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Abstract

Background and Purpose—To evaluate arterial recanalization as measured by changes in the presence of the Hyperdense Artery Sign (HAS) on initial and 24 hour CT scans in patients treated with rt-PA or placebo, and to assess the effect of rt-PA on patient outcomes in this population.

Methods—Subjects in the NINDS rt-PA Stroke Trial composed the study group. We determined the percentage of HAS subjects in rt-PA and placebo-treated groups who had persistence (HAS +/+) or resolution (HAS +/−) of the HAS on 24-hour CT, and compared outcomes in those with resolution or persistence of the sign in these treatment groups.

Results—Baseline HAS occurred in 79/604 eligible subjects (13%). The two treatment groups were similar, though rt-PA treated patients were significantly older. Of the 79 patients with HAS on baseline CT scan, 14/37 (38%) treated with rt-PA had resolution of the HAS at 24 hours compared to 7/42 (17%) treated with placebo (p=0.03). Infarct volumes at 24 hours were significantly smaller in rt-PA treated patients with resolution of the sign, compared to those who had persistence of the sign (p=0.004). In our analysis, functional outcomes were not significantly improved based on resolution of HAS in either treatment group. There were 4 symptomatic ICHs in the rt-PA treated group with HAS as compared to 2 in the placebo-treated group.

Conclusion—Among patients with HAS at baseline in the NINDS rt-PA Stroke Trial, IV rt-PA increased recanalization as measured by resolution of HAS and reduced infarct volumes at 24 hours.

Keywords

Acute stroke; tPA; hyperdense artery; recanalization; stroke volume

BACKGROUND

Hyperdense artery sign (HAS) is a finding on CT scan that is an excellent marker of clot in the proximal middle cerebral artery (MCA).[1,2] Further, resolution of clot in the MCA has been correlated with the disappearance of the sign.[3–5] A hyperdense MCA also correlates with a

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poor functional outcome,[6] therefore it has been suggested that patients with a HAS be considered for intraarterial thrombolysis as opposed to IV treatment alone.[7]

The National Institute of Neurological Diseases study of recombinant tissue plasminogen activator (rt-PA) in ischemic stroke showed that the use of intravenous rt-PA produces better functional outcomes at 3 months than placebo.[8] Further, intravenous rt-PA treatment demonstrated a trend favoring a reduced stroke lesion size, as measured on CT scan,[9] and showed clinical benefit within the subset of patients with HAS on initial CT scan.[10]

We evaluated the effect of IV rt-PA on arterial recanalization as determined by changes in HAS on CT imaging performed at baseline and 24 hours in subjects treated in the NINDS rt-PA Stroke Trial. We specifically examined whether treatment with rt-PA or placebo increased the rate of arterial recanalization, and if resolution of HAS was associated with clinical outcomes and/or infarct volumes.

METHODS

Our study comprised subjects treated as part of the NINDS rt-PA in ischemic stroke trial. Briefly, the NINDS rt-PA trial was a multicenter, prospective, double-blind, placebo-controlled, randomized trial of intravenous rt-PA for acute ischemic stroke.[8] Patients were randomized to receive intravenous rt-PA at 0.9 mg/kg or placebo within 3 hours of stroke onset.

Scans were performed at baseline, 24 hours, 7 to 10 days, 3 months, and 1 year after randomization. CT scan standards were determined at the beginning of the trial.[9] Briefly, images were obtained using either 3rd or 4th generation CT scanners. The CT scans were obtained with 10-mm slice thickness with the specifications of 120 kV, 170 mA, matrix size of 512 × 512, and scanning time for 3 seconds for the posterior cranial fossa and 2 seconds for the supratentorial compartment from the level of the foramen magnum to the high vertex region. Hard copies of the CT scan were sent to the coordinating center for review after the on-site investigators had examined them for evidence of hemorrhage. A coordinating center neuroradiologist reviewed all CT scans centrally. Calculation of infarct volumes used an intention to treat algorithm, as previously described.[9] This method maximizes the number of subjects for analysis, has been shown to be reliable, and reduces potential bias that could be introduced by not including missing data from patients who have died.

For the initial review the coordinating center neuroradiologist was blinded to the treatment assignment, clinical findings, and other CT scans for each subject. As part of a separate analysis for early ischemic changes, baseline CT scans were reanalyzed by an interpreting physician who was given clinical information regarding the subject, but remained blinded to the treatment arm.[11] Because the 24-hour CT scans on this review were not reanalyzed for the presence of a hyperdense artery sign, we confined our analysis to the initial, blinded interpretation of the presence of a hyperdense artery sign on baseline and 24-hour CT scans.

After identifying those subjects with hyperdense artery sign on initial CT scan, we compared groups with regard to age, sex, time to treatment, hypertension, admission blood pressure and blood glucose, and presenting NIHSS. We defined arterial recanalization as resolution (+HAS baseline/−HAS 24-hours) or continued presence (+HAS baseline/+HAS 24-hours) of a hyperdense artery sign, and compared the rates of recanalization between rt-PA treated and placebo treated subjects.

We compared outcomes within the rt-PA treated and placebo treated groups with regard to the presence of HAS on initial and 24 hour CT scans. Outcomes were defined by a 90-day modified Rankin Scale (mRS) of 0–2, mRS of 0–1, Barthel index of 95–100, death, intracerebral hemorrhage, and median infarct volume. Subjects that died prior to the 90-day follow-up were

given the worst outcome score. Lesion volumes were compared at 24-hours between rt-PA treated subjects and placebo treated subjects.

STATISTICAL ANALYSIS

Data were managed and analyzed using SAS® version 9.1 (SAS Institute, Cary, NC). Baseline characteristics were compared between the rt-PA and placebo subjects using chi-square, t-test and Wilcoxon Rank Sum as appropriate. Chi-square was used for comparison of the groups with respect to the bivariate outcome of 24-hour hyperdense artery sign. Comparison of lesion volumes was made using Wilcoxon Rank Sum test due to the distribution of that variable and values are reported as median and interquartile range.

RESULTS

There were 624 subjects in the NINDS rt-PA trial, 312 received rt-PA and 312 received placebo. Two of the subjects had no hyperdense artery sign designation at either baseline or 24 hours, six were missing hyperdense artery sign just at baseline, and twelve at 24 hours. Thus 604 subjects were eligible for this analysis; 300 treated and 304 placebo subjects.

Hyperdense artery sign was found on baseline scan in 79 of 604 (13%) subjects who had both initial and 24-hour CT scan data. Table 1 lists the baseline characteristics for placebo and rt-PA treated subjects. Placebo-treated subjects were significantly younger, but otherwise there were no significant differences between placebo and rt-PA treated groups with regard to sex, time to treatment, hypertension, diabetes, admission blood pressure and blood glucose, or presenting NIHSS.

Of the 79 subjects with HAS on baseline CT scan, 14/37 (37.8%) treated with rt-PA had resolution of the HAS at 24 hours compared to 7/42 (16.7%) treated with placebo (p=0.03).

Functional outcomes were not significantly improved in our analysis based on resolution of HAS although the small number of subjects limits statistical comparison (Table 2).

Among 37 rt-PA treated subjects with a baseline HAS treated, the 14 without HAS at 24 hours had smaller infarct volumes than the 23 with persistent HAS. Infarct volumes were non-significantly larger in the placebo treated group with resolution of the HAS as compared to those without resolution (p = 0.20) at 24-hours.

There were 9/37 (24%) deaths in the rt-PA group and 10/42 (23%) in the placebo group. There were 4/37 (10.8%) symptomatic ICHs in the rt-PA group with HAS as compared to 2/42 (2.4%) in the placebo group (p=0.18).

DISCUSSION

The clinical benefit of rt-PA extends to patients presenting with a HAS sign on CT scan, as previously described.[10] Our analysis demonstrated the effect that intravenous rt-PA has on arterial recanalization as measured by the resolution of HAS. Recanalization rates found in other studies are similar, with recanalization by IV rt-PA treatment shown by angiography or transcranial Doppler ultronsonography (TCD) to be between 17% and 38%. Recent analysis confirms that some of this recanalization may be within the first 30–60 minutes after rt-PA treatment.[12–16] Advances in CT and MR angiography as well as TCD now allow non-invasive evaluation of patency and recanalization of intracranial arterial occlusions not available in the mid-1990's.

The NINDS trial is one of the last studies to evaluate placebo treatment within 3 hours of onset in patients eligible for rt-PA treatment. The rates of spontaneous reperfusion in placebo treated patients in the Desmoteplase in Acute Ischemic Stroke (DIAS) and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trials were similar to our rate of placebo treated spontaneous recanalization.[17,18] Direct extension or comparison cannot be made, however, as those patients were selected based on the presence of diffusion-perfusion mismatch. The Third International Stroke Trial will still include some placebo patients in the 0–3 hour time window.

Lesion volumes were reduced with rt-PA treatment in subjects with baseline HAS which is consistent with earlier and more frequent recanalization with rt-PA as compared to placebo. Reperfusion likely reduces the territory of ischemic damage by salvaging penumbral tissue. Interestingly, resolution of HAS in placebo-treated patients was associated with a larger volume of ischemic brain at 24 hours, though the number of patients was small. Recanalization that occurs after tissue is already dead may be associated with increased edema and potentially poorer outcome.[19] At the same time, reperfusion may also increase the rate of both asymptomatic and symptomatic ICH, an effect that is compounded by the lytic action of rt-PA.[20] The effect of rt-PA on lesion volumes at three months was still present although did not reach statistical significance. The loss of subjects in both treatment groups between 24 hours and three months led to much more use of imputation in the lesion volume analysis. The rate of death among patients presenting with HAS is similar to other trials with high presenting NIHSS scores.[15,21–23]

Limitations of our analysis include that it is a post-hoc analysis. Additionally, smaller numbers of subjects limits statistical comparisons in terms of outcomes. Analysis of the same data set was previously completed and supported a clinical benefit in patients with HAS, as stated earlier.[10] Our analysis likely did not find the same effect due to variability in the interpretation of HAS. In the analysis by Qureshi et al, HAS was defined using reanalyzed CT scans. Because there was no reanalysis of the 24 hour CT scans, we thought it more reliable to use both blinded initial and 24 hour CT scans. The result of using different CT scans for interpretation of the HAS is the inclusion of 21 patients in our analysis that were not included in the prior analysis by Qureshi (9 placebo and 12 rt-PA treated), and the exclusion of 32 patients from our analysis (21 placebo and 11 rt-PA treated). We also performed our analysis using only those patients with initial HAS positive scans and HAS reanalyzed scans, and found similar results as reported here. There were only 59 patients available for this analysis, however, and statistical significance was not reached in any of the outcome measures listed previously in Table 2. Outcomes at 90-days using only those 59 patients above did show a trend toward benefit from IV rt-PA treatment, which is concordant with results previously reported by Qureshi.[10]

The assertion that intraarterial therapy with or without prior IV rt-PA may be more effective than IV rt-PA alone in the subset of stroke patients with HAS remains to be determined. Balancing the use of IV therapy, which can usually be administered sooner for practical reasons, with intraarterial therapies that can increase recanalization rates will remain a challenge for the stroke community as a whole, especially when the time to achieving these goals are considered. Our results add to the data that IV rt-PA recanalizes large artery occlusions better than placebo, and that this effect results in smaller infarcts. Our data also suggest that recanalization at later times in patients treated with placebo may not be beneficial and can be associated with larger infarcts. Thus the timing of recanalization is critical in ongoing trials of intra-arterial therapy, with or without prior IV rt-PA. The ongoing IMS III trial will address this issue by comparing IV rt-PA treatment within 3 hours with IV rt-PA treatment followed by IA approaches aimed at recanalization within 5 hours.

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Table 1

Baseline characteristics in subjects with HAS on baseline CT by treatment group

Subject characteristics	rt-PA (n=37)	Placebo (n=42)	p-value
Age	69.6 ± 10.9	63.7 ± 11.7	0.02
Sex (female)	22 (59.5%)	31 (73.8%)	0.18
Time to treatment (hours)	1.95 ± 0.59	1.94 ± 0.58	0.94
Hypertension	22 (59.5%)	25 (61.0%)	0.89
Diabetes	4 (10.8%)	7 (16.7%)	0.45
Presenting NIHSS	20 (17, 24)	18 (15, 23)	0.20
Admission MAP	105.8 ± 13.6	108.4 ± 13.5	0.40
Glucose (mg/dL)	137.8 ± 48.4	162.8 ± 87.7	0.12

Data presented as mean ± standard deviation, n (%), or median (25^{th}, 75^{th} percentiles)

Table 2

Outcomes in subjects with HAS on baseline CT by treatment group.

	rt-PA (n=37)			Placebo (n=42)		
	HAS 24 hours	**No HAS 24 hours**	**p-value**	**HAS 24 hours**	**No HAS 24 hours**	**p-value**
N	23	14		35	7	
Rankin 0–1	3 (13.0%)	3 (21.4%)	0.65	6 (17.1%)	1 (14.3%)	1.00
Rankin 0–2	4 (17.4%)	4 (28.6%)	0.44	10 (28.6%)	2 (28.6%)	1.00
Barthel Index 95+	7 (30.4%)	5 (35.7%)	1.00	11 (31.4%)	2 (28.6%)	1.00
SICH	3 (13.0%)	1 (7.1%)	1.00	0 (0%)	1 (14.3%)	0.17
Death	4 (17.4%)	5 (35.7%)	0.25	7 (20.0%)	3 (42.9%)	0.33
Median (IQR) 24 hour Volume	107.4 (68.0, 229.1)	16.1 (6.6, 53.0)	0.004	49.0 (12.4, 138.9)	105.6 (52.4, 204.5)	0.20
Median (IQR) 3 month Volume	130.6 (63.3, 238.1)	60.6 (7.1, 136.6)	0.06	103.8 (5.9, 148.3)	55.8 (28.6, 170.4)	0.60

Data presented as mean ± standard deviation, median (25^{th}, 75^{th} percentiles), or n (%)