Published in final edited form as:
J Stroke Cerebrovasc Dis. 2010 ; 19(4): 290–293. doi:10.1016/j.jstrokecerebrovasdis.2009.06.001.

Analysis of the NINDS t-PA studies following ECASS III patient selection criteria

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Abstract

Background—In 1995 two studies by the NINDS showed that intravenous t-PA was superior to placebo in stroke patients when given less than 3 hours from stroke onset. The recently published ECASS III study introduced new patient selection criteria and treatment between 3 and 4.5 hours. Using these criteria, t-PA was shown effective at the later time window. Both analyses used the 3 month mRS as main primary outcome. We sought to study the effect of applying the ECASS III selection criteria to the original NINDS cohort.

Methods—We analyzed the subgroup of patients from NINDS sample who matched the ECASSS III study criteria and examined 3-month outcomes adjusted and unadjusted for confounding factors.

Results—The NINDS t-PA study included 624 patients. Two hundred in the t-PA treated and 199 in the placebo group were selected after applying ECASS III criteria. Of these selected patients, 52% in the t-PA group versus 31% had an mRS of 0 or 1 at 3 months ($p<0.001$). The unadjusted OR for t-PA treatment versus placebo on day 90 mRS 0–1 versus 2–6 was 2.45 (95% CI: 1.63–3.69) When adjusted for baseline NIHSS, smoking status, time to treatment and history of hypertension the OR was 2.14 (95% CI: 1.34–3.41) ($p<0.001$).

Conclusion—Using the ECASS III patient selection in patient treated in less than 3 hours, 52% of t-PA treated patient had a favorable outcome at 3 months.

Introduction

After many failed attempts in demonstrating a benefit of IV thrombolysis after 3 hours[1–7], the ECASS III study reported the successful use of IV t-PA in patients between 3 and 4.5 hours after stroke.[8] The only other positive studies of IV thrombolysis were those of the NINDS, published in 1995 that proved benefit under 3 hours.[9] Some argued that the ECASS III results might be invalid, since they differ from other longer-window trials[10], but a more likely explanation is the more stringent selection criteria used in ECASS III, compared to other long-window trials.[3] One way to establish the validity of the ECASS III selection criteria is to compare them to the NINDS trial.

Both the NINDS and the ECASS study groups used the same therapy. In addition to a longer time window, ECASS III excluded patients with large strokes, previous anticoagulant therapy,

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previous stroke and diabetes, and patients older than 80 years of age.[8] ECASS III showed that 52.4% of treated patients had a good outcome (mRs 0 or 1) versus 45.2% placebo. The NINDS studies showed 42.6% versus 26.6% of patients with an mRS of 0 01 at 3 months.[9]

The NINDS studies had broader patient selection criteria that allow wider generalization of the results. We sought to determine whether the beneficial effect shown in the NINDS trial remained if the entry criteria were narrowed to those of ECASS III.

Clinical trial results can be applied to patient care when the study selection criteria reflect the overall patient care population. If the inclusion and exclusion criteria are more stringent and patients groups who frequently suffer the condition studied, such as the elderly and diabetics, the study results may only apply to a subgroup of patients.

If the demonstrated benefit in the 3–4.5 hour study ECASS III was largely due to the exclusion of high risk patients, the subgroup of patients treated under 3 hours in the NINDS studies who qualified by ECASS III study criteria would have a significantly different outcome than the overall study groups in NINDS.

Methods

The NINDS t-PA dataset was obtained from a publicly accessible data repository. We analyzed this data following the study criteria used by the ECASS III study group.[8] All patients included in the NINDS t-PA database were reviewed and only patients who were eligible following the ECASS III study criteria were included.

The NINDS study included all patients over age 18 and had no specific stroke severity exclusion. The ECASS III study excluded patients over 80 years of age and an admission NIHSS over 25 or significant early ischemic changes in more than one third of the MCA territory. ECASS III excluded all patients with previous anticoagulant use. The NINDS data set only recorded previous heparin but not other anticoagulant use. We excluded all NINDS t-PA patients with previous heparin use. We excluded patients with known diabetes who had suffered a prior stroke.

The primary outcome is mRS at day 90, 0–1 versus 2–6, compared by rt-PA treatment arm. Groups were compared using the Chi-Square test, with $p<0.05$ considered statistically significant. Results were presented as an unadjusted odds ratio (OR) with a 95% confidence interval (CI). Logistic regression was used to model day 90 mRS by treatment arm, adjusted for baseline NIHSS, smoking status in the previous year (yes versus no), time from stroke onset to treatment and history of hypertension at baseline.

Treatment group effect was presented as an adjusted OR with a 95% CI. All analyses were run with the R statistical software, http://www.r-project.org/, version 2.6.2 (2008–02–08).

Goodness of fit for the model was assessed with the Likelihood Ratio Test (LRT) and Hosmer's Lemeshow's (HL) Chi-Square statistic.[11] The null hypothesis for the LRT is that the fitted model describes the data better than the NULL model with no covariates. The LRT is best for comparing two nested models. The null hypothesis for the HL test is that the model is an adequate fit. Failing to reject the null implies the model describes the data appropriately.

Results

Using the ECASS III study criteria applied to the NINDS t-PA data set, 113 patients in the placebo and 112 in the t-PA treatment group were excluded from our analysis. (Table 1) The exclusion criteria appeared balanced by treatment arm. Based on an unadjusted type I error

significance level of p 0.05, three baseline measures were not balanced by treatment arm: weight, baseline NIHSS and aspirin use before randomization. (Table 2) The treatment arm patients were more likely to weigh less, have lower baseline NIHSS scores and were more likely to have used aspirin before randomization.

Overall, those treated with rt-PA were significantly more likely to have a day 90 mRS of 0–1 (52% versus 31%; p<0.001). (Table 3) The unadjusted OR for rt-PA treatment versus placebo on day 90 mRS 0–1 versus 2–6 was 2.45 (95% CI: 1.63–3.69), and the model passed the HL goodness of fit test (p>0.999).

When adjusted for baseline NIHSS, smoking status in the year prior to stroke onset, time from stroke onset to treatment (or randomization) and history of hypertension, those treated with rt-PA remained significantly more likely to have a day 90 mRS of 0–1 (p<0.001). The adjusted OR for rt-PA treatment versus placebo on day 90 mRS 0–1 versus 2–6 was 2.14 (95% CI: 1.34–3.41). The model passed the HL goodness of fit test (p=0.513) with no apparent outlying observations with an area under the ROC of 0.80.

Discussion

Our analysis shows that patients who matched the ECASS III study criteria and received t-PA less than 3 hours after stroke had an excellent chance of good outcome compared to placebo treated patients. This result suggests that ECASS III was positive, while previous longer-window trials were negative, in part due to the different selection criteria. Previous studies had shown the age >80 years,[12] stroke in diabetics, high NIHSS and areas of early ischemic changes on CT predict poor outcome after t-PA for stroke.[13] Inclusion of such patients in prior trials likely obscured the rt-PA treatment effect. The treatment effect for rt-PA remained similar to that observed in the NINDS study, and did not appear to be attenuated.

The limitations of this analysis are that, in addition to the reportedly different study criteria, both studies were done more than 13 years apart and in different countries. We were not able to account for possible confounding factors such as changes in patient care pattern, treatment of complications and co-morbid factors that may have changed over time and potentially differed between countries.

Thirty-one percent of placebo treated patients from the NINDS studies, which were selected by ECASS III criteria, reached a mRs of 0 or 1 at 3 months. This response rate was 45.2% in the ECASS III trial. This difference may in part be explained by lower average NIHSS and fewer diabetics in the study population of ECASS III.[14] Furthermore, changes in treatment paradigms outside of thrombolytic therapies over the last 13 years may have alerted the outcome as well.

Not all data points used for inclusion and exclusion in the ECASS III study were captured in the NINDS t-PA study. ECASS III excluded all patients who received any anticoagulation before the stroke. The NINDS studies excluded patients who received oral anticoagulants, heparin with an elevated partial-thromboplastin time and patients with a prothrombin time greater than 15 seconds. To match the ECASS III exclusion criteria in the NINDS group, we furthermore excluded patients with any heparin use from our analysis.

In summary, this analysis shows that the ECASS III study criteria did not alter the treatment effect of t-PA less than 3 hours.

Acknowledgments

Grant support : NINDS 2P50NS044148

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Table 1

Exclusion criteria in ECASS III applied to the NINDS sample

	Placebo	t-PA
NINDS overall sample (n)	312	312
Excluded patients:		
Age >80 years	29	40
Baseline NIHSS >25	23	29
Stroke involving >1/3 MCA	43	34
Known diabetic with prior stroke	25	26
Any heparin use	6	5
Final sample size (n)	199	200

Some patient were excluded for more than one reason

Table 2

Demographics

	NINDS-ECASS III* Placebo	NINDS-ECASS III* t-PA	p
n	199	200	
Age (mean±SD)	64.9 (10.8)	66 (10.1)	0.31
Gender (male)	64.8%	59.5%	0.32
Treatment 0–90 min	48.2%	54%	
Treatment 90–180 min	51.8%	46.0%	0.29
Time to treatment (min) (mean±SD)	118.6 (35.7)	117.1 (37.9)	0.69
NIHSS (mean±SD)	13.8 (5.9)	12.1 (6.0)	**0.0055**
Blood pressure (mean±SD)	113.5 (17.6) mmHg	112.8 (17.7) mmHg	0.73
Weight (kg)	81 (18.9)	76.6 (15.3)	**0.012**
Current smoker	36.0%	38.9%	0.63
Diabetes	13.6	14.5	0.92
Prior stroke	25.1	27.5	0.67
Hypertension	64.5	63.8	0.98
Aspirin use	28.6	40	**0.022**
Atrial fibrillation	14.6	14.7	0.92

* Patients from the NINDS sample fulfilling the ECASS III study criteria

Table 3

Modified Rankin Scale at 3 months (unadjusted)

	NINDS** Placebo	NINDS** t-PA	NINDS-ECASS III Placebo	NINDS-ECASS III t-PA
mRS 0–1 (%)	83 (26.6)	133 (42.6)	61 (30.7)	104 (52.0)
mRS 2–6 (%)	229 (73.4)	179 (57.4)	138 (69.3)	96 (48.0)
Total	312	312	199	200

** NINDS Study groups 1 and 2