Confirmation of tPA Treatment Effect by Baseline Severity-Adjusted End Point Reanalysis of the NINDS-tPA Stroke Trials

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Background and Purpose—Baseline severity-adjusted end point analysis, an emerging approach to the evaluation of primary end points in acute stroke trials, offers a novel means of adjusting trial analysis for baseline imbalances in presenting stroke severity among treatment groups, a factor that has complicated interpretation and reception of the results of the pivotal National Institute of Neurological Disorders and Stroke tissue plasminogen activator (NINDS-tPA) trials.

Methods—The sliding scale dichotomy end point responder analysis applied in recent acute ischemic stroke clinical trials was used to analyze NINDS-tPA stroke trials 1 and 2. Good outcomes were: 3-month Rankin scale=0 if pretreatment NIHSS scores were 1 to 7; 3-month Rankin scale=0 to 1 if pretreatment NIHSS scores were 8 to 14; 3-month Rankin scale=0 to 2 if pretreatment NIHSS scores were >14.

Results—Both of the NINDS-tPA stroke trials showed a statistically significant beneficial treatment effect of tPA. In unadjusted analyses, in trial 1, good outcomes in tPA versus placebo patients were 39.6% versus 28.6% (odds ratio 1.64, P=0.049); in trial 2, 35.7% versus 24.2% (odds ratio 1.74, P=0.024). Among all 624 patients in trials 1 and 2 combined, good outcomes occurred in 37.5% versus 26.3% patients (odds ratio 1.68, P=0.0034). In the 91- to 180-minute onset to treatment time subgroup of patients among whom baseline severity imbalance was particularly severe, good outcomes were noted in 36.1% versus 24.0% (odds ratio 1.80, P=0.021). Odds ratios favoring tPA generally further increased after adjustment for 12 additional covariates known to predict acute stroke outcome.

Conclusion—Baseline-adjusted severity end point reanalysis of the NINDS Stroke tPA trials confirms a beneficial treatment effect of intravenous tPA. (Stroke. 2007;38:414-416.)

Key Words: acute care ■ acute Rx ■ acute stroke ■ clinical trials ■ emergency medicine ■ stroke ■ stroke care ■ therapy ■ thrombolysis ■ thrombolytic Rx

Baseline severity-adjusted end point analysis is an emerging approach to the evaluation of primary end points in acute stroke trials. Prognosis-adjusted end points allow enrolled patients to be assessed on achievable goals given their presenting stroke severity rather than a fixed target outcome inappropriate for individuals with very mild or very severe presenting stroke deficits.1-3

Severity-adjusted analysis also offers a novel means of adjusting trial analysis for baseline imbalances in presenting stroke severity among treatment groups. Baseline imbalance in prognostic factors has complicated interpretation and reception of the results of the pivotal National Institute of Neurological Disorders and Stroke tissue plasminogen activator (NINDS-tPA) trials.4,5 Whereas some baseline imbalances favored the placebo group (eg, younger age), others, particularly aspects of presenting stroke severity, favored the treatment group.4 The median NIHSS stroke severity score at entry showed a trend toward a difference between the tPA and placebo groups (15 versus 14, P=0.10), and more extremely mild severity stroke patients were randomized to the placebo group. Among patients with NIHSS scores of 0 to 5, 72% were assigned to the tPA group versus 28% in the placebo group. This difference was particularly pronounced among patients in the 91 to 180 minute time window from onset to treatment.

This study was undertaken to determine whether NINDS-tPA study data indicate a beneficial treatment effect of tPA when a severity-adjusted end point analysis is applied to correct for imbalances in baseline stroke severity.

Methods

The sliding scale dichotomy end point applied in recent acute ischemic stroke clinical trials was used.1,2 Good outcomes were defined as: 3-month Rankin scale=0 if pretreatment NIHSS scores were 1 to 7; 3-month Rankin scale=0 to 1 if pretreatment NIHSS scores were 8 to 14; 3-month Rankin scale=0 to 2 if pretreatment NIHSS scores were >14. Data were obtained from the publicly available dataset of the results of NINDS trials 1 and 2.

Analyses were performed on the following data groups: trial 1, trial 2, all patients from trials 1 and 2 combined, 0- to 90-minute
onset to treatment patients from trials 1 and 2 combined, and 91- to 180-minute onset to treatment patients from trials 1 and 2 combined. Analyses were performed on both raw data and on data after adjustment for baseline variables predictive of outcome. The following 12 variables identified in previous studies, including the NINDS study itself, as determinants of prognosis or treatment response in acute ischemic stroke were covariates in the adjusted analysis, using logistic regression: age, sex, history of hypertension, history of diabetes, current smoking, pre-existing disability, mean arterial pressure, serum glucose, stroke subtype, baseline CT hypodensity, baseline CT intravascular thrombus, and baseline CT mass effect. Age, mean arterial pressure, and glucose level were treated as continuous variables, and the remaining factors were treated as binary variables. In an additional analysis, baseline NIHSS was adjusted for in addition to the other 12 predictor variables.

Power to detect a treatment effect was good in the combined analysis and moderate in the subgroup analyses. To detect a treatment effect that increased the odds ratio of good outcome to 1.8, power was 0.94 in the combined analysis, from 0.66 to 0.72 in the half population (trial part, time window) subgroup analyses, and from 0.29 to 0.69 within each tertile.

Results
In unadjusted analyses, both of the NINDS tPA stroke trials showed a statistically significant beneficial treatment effect of tPA. Among all 624 patients in trials 1 and 2 combined, good outcomes occurred in 37.5% versus 26.3% patients (odds ratio [OR], 1.68; \(P = 0.0034\); Figure). In trial 1, good outcomes in tPA versus placebo patients were 39.6% versus 28.6% (OR, 1.64; \(P = 0.049\)); in trial 2, 35.7% versus 24.2% (OR, 1.74; \(P = 0.024\)). In the 0- to 90-minute patients from both trials, good outcomes in tPA versus placebo patients were noted in 38.9% versus 29.0% (OR, 1.56; \(P = 0.089\)); in the 91- to 180-minute cohort, 36.1% versus 24.0% (OR, 1.80; \(P = 0.021\)).

ORs favoring tPA in unadjusted analyses generally further increased after adjustment for the 12 additional covariates known to predict acute stroke outcome (Table). Additionally adjusting for baseline NIHSS within each tertile did not substantially alter the findings (trials 1 and 2 combined, adjusting for the 12 non-NIHSS variables, OR, 1.85 [1.27 to 2.69], versus also adjusting for NIHSS, OR, 1.75 [1.2 to 2.57]).

Discussion
Baseline-adjusted severity end point reanalysis of the NINDS Stroke tPA trials confirms a beneficial treatment effect of intravenous tPA. In this reanalysis, benefit was demonstrated in each of the 2 independent trials. Benefit was also demonstrated in the 91- to 180-minute time window, which has been the focus of greatest concern regarding severity imbalance at entry.

The findings of this reanalysis complement those from several groups who have applied more traditional statistical approaches to adjust for baseline imbalances in prognostic factors to the NINDS tPA study data. These approaches

| ORs for Responder Analysis-Defined Good Outcome in tPA vs Placebo Patients in Unadjusted and Adjusted Analyses |
|---------|---------|---------|
|          | N     | Unadjusted | Adjusted |
| Part 1   | 291   | 1.64 (1.00, 2.67) | 1.56 (0.90, 2.69) |
| Part 2   | 333   | 1.74 (1.08, 2.79) | 2.32 (1.36, 3.95) |
| Time to treatment 0–90 | 302     | 1.56 (0.96, 2.52) | 1.67 (0.97, 2.89) |
| Time to treatment 90–180 | 322     | 1.80 (1.11, 2.91) | 2.10 (1.26, 3.68) |
| Parts 1 and 2 combined | 624   | 1.68 (1.20, 2.37) | 1.85 (1.27, 2.69) |

Distribution of an adjusted, 90-day modified Rankin outcomes among the tPA and placebo groups in each of the 3 tertiles of stroke severity at entry. In each row, the proportion of patients with Rankin 0 outcomes is shown in the leftmost box, with Rankin 1 in the next box to the right, Rankin 2 the next further box to the right, etc, through Rankin 6 in the rightmost box. Unshaded boxes indicate patients considered to be responders with good outcomes, given their entry stroke severity. Within each tertile, ORs for good outcomes were: NIHSS 1 to 7, OR 1.41 (0.65 to 3.08); NIHSS 8 to 14, OR 1.90 (1.06 to 3.4); and NIHSS >14, OR 1.55 (0.93 to 2.60).
included logistic regression analysis, risk adjustment effect analysis, interaction tests, analysis within tertiles and quintiles, and analysis of defined minor stroke categories. All found a beneficial effect of tPA after taking into account imbalances in baseline stroke severity.

Traditional statistical adjustment approaches can generally be conceptualized as adjusting the starting point for each patient based on their stroke severity, and then determining if treatment allows the patient to attain a good outcome state. The sliding scale dichotomy applied in this study can be conceptualized as adjusting the finish line for each patient based on their stroke severity, and then determining if treatment allows the patient to attain a good outcome. That both approaches show congruent findings provides additional confirmation that tPA is beneficial when administered within 3 hours of onset to patients with acute cerebral ischemia.

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References
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