ATLANTIS Trial
Results for Patients Treated Within 3 Hours of Stroke Onset

Gregory W. Albers, MD; Wayne M. Clark, MD; Kenneth P. Madden, MD, PhD; Scott A. Hamilton, PhD

Background and Purpose—Only a single study has demonstrated beneficial effects of intravenous tissue plasminogen activator (tPA) for treatment of acute stroke.1 In the NINDS study, effects of intravenous tissue plasminogen activator (tPA) for treatment of acute stroke were documented.2–5 The ATLANTIS study was designed to enroll patients within 3 hours of symptom onset.6–8 The ATLANTIS study, failed to document clear benefits of intravenous tPA administered beyond 3 hours of stroke onset.9,10 The ATLANTIS study was initially designed to evaluate the efficacy and safety of intravenous tPA in patients with acute stroke who could be treated within 6 hours of symptom onset. After December 1993, the ATLANTIS study design was changed to enroll patients within 5 hours of symptom onset because of safety concerns in patients enrolled between 5 and 6 hours. The study design was further modified in 1996 to a 3- to 5-hour time window after the results of the NINDS tPA study were published.1 One hundred forty-two patients were enrolled before December 1993 and were considered to be in part A of the study.5 Most of the patients (n=613) were enrolled in the 0- to 5-hour and 3- to 5-hour time windows and are reported as part B of the study.4 During the course of the entire ATLANTIS study, 61 patients were enrolled within 3 hours of stroke onset. We evaluated the clinical outcomes of these patients using the prespecified primary and secondary hypotheses of the ATLANTIS part B trial.

Methods

All patients enrolled within 3 hours of symptom onset in either part A or B of ATLANTIS were included in this analysis. The full methods of both parts of the ATLANTIS trial have previously been published.4,5 Acute ischemic stroke patients were randomized to receive either intravenous tPA (0.9 mg/kg) or a placebo. One hundred forty university and community hospitals in the United States entered a total of 755 patients in these trials within 6 hours of symptom onset. The inclusion and exclusion criteria for the ATLANTIS trial4,5 were similar to those of the NINDS trial1 with the exception of the longer time window and an age limit of 79 years.

Outcome Measures

The primary end point was the percentage of patients who had a complete recovery defined as a National Institutes of Health Stroke Scale (NIHSS) score of ≤1 at 90 days. The secondary end points included a global outcome test to determine whether there was a significant difference between the tPA and placebo groups in the proportion of patients with an NIHSS score of ≤1, a Barthel Index score of ≥95, a modified Rankin Scale score of ≤1, and a Glasgow Outcome Scale score of 1 at 90 days. Additional secondary end points included an analysis of excellent outcomes on the 3 functional scales (modified Rankin Scale, Glasgow Outcome, and Barthel Index) at 90 days considered as separate variables. Comparisons between treatment groups were performed with χ² tests.

The sample size in this analysis was too small for stable multivariate modeling to adjust for important prognostic factors or baseline imbalances. However, in previous acute stroke trials, stroke severity at baseline has consistently been among the most important predictors of outcome. Therefore, to examine the consistency of the

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treatment effect, we analyzed the primary end point after stratification for baseline stroke severity (NIHSS ≤10 and NIHSS >10). The Wilcoxon rank-sum test was used for comparisons of treatment effects on the basis of NIHSS scores.

Results

In general, the baseline characteristics and prior medical conditions of patients randomized to the tPA and placebo groups were well matched (see Table 1). There was a higher percentage of men in the tPA group (P<0.05). Most of the patients were white.

Time to treatment was slightly longer in the tPA group (mean, 161 minutes) compared with the placebo group (mean, 144 minutes; P=0.08; see Table 1). Although the mean baseline NIHSS scores were identical (12), a larger percentage of tPA patients had baseline NIHSS scores >21. A higher percentage of tPA patients also had relatively low baseline NIHSS scores (3 through 7) (see Table 1). Placebo-treated patients more frequently had baseline scores of moderate severity (8 through 21).

Clinical outcomes at 90 days are presented in Table 2 and the Figure. Patients treated with tPA were significantly more likely to have a very favorable outcome (score of ≤1) on the NIHSS (P=0.01). Compared with the placebo group, the tPA group had a 35% absolute increase in the number of patients with an NIHSS score of ≤1. Modified Rankin and Glasgow Outcome scales were not available for all patients because these outcomes were not collected throughout the entire duration of part A of ATLANTIS. Among the patients who had these scales performed, nonsignificant trends in favor of tPA were detected (see Table 2). The global outcome test indicated that the odds ratio for a favorable outcome in the tPA group was 2.0; however, this result did not reach significance (95% CI, 0.8 to 4.9; P=0.14).

When the data were stratified on the basis of stroke severity, about half of the patients (n=30) had a stroke of mild to moderate severity at baseline (NIHSS ≤10). Of these, 79% of the patients who received tPA had a complete recovery at 90 days (NIHSS, 0 to 1) compared with 56% of the placebo patients (OR, 2.9; 95% CI, 0.6 to 14.3). Among the 31 patients with moderate to severe strokes (baseline NIHSS >10), 33% of the tPA patients recovered completely compared with 5% of the placebo patients (OR, 10.5; 95% CI, 0.9 to 120.3).

Safety Analyses

A significant increase in the rate of symptomatic intracerebral hemorrhage was seen in the tPA-treated patients with a rate of 13% (95% CI, 2.8 to 33.6) in the tPA group (see Table 3). All 3 symptomatic intracranial hemorrhages occurred in tPA-treated patients and were fatal. The baseline NIHSS scores in these patients were 8, 16, and 20. There was a nonsignificant trend toward an increased death rate at both 30 and 90 days in the tPA group.

![NIHSS Scores at 90 Days (%)](image-url)

Outcome at 90 days based on NIHSS score. Scores of 0 to 1 were considered to indicate a very favorable outcome.
TABLE 3. Safety Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=38), n (%)</th>
<th>tPA (n=23), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ICH through day 10</td>
<td>0 (0)</td>
<td>3 (13)</td>
<td>0.05</td>
</tr>
<tr>
<td>Asymptomatic ICH through Day 10</td>
<td>0 (0)</td>
<td>2 (8.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td>0 (0)</td>
<td>3 (13)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fatal brain herniation without hemorrhage</td>
<td>2 (5.3)</td>
<td>1 (4.3)</td>
<td>0.40</td>
</tr>
<tr>
<td>Death at 30 d</td>
<td>2 (5.3)</td>
<td>4 (17.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Death at 90 d</td>
<td>2 (5.3)</td>
<td>4 (17.4)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

ICH indicates intracranial hemorrhage.

Discussion

The FDA approval of tPA for treatment of acute ischemic stroke within 3 hours of symptom onset was based on the NINDS trial. Only minimal data are available regarding the efficacy of intravenous tPA therapy administered within 3 hours of stroke onset from other trials. In ECASS, only 49 patients were treated with tPA within 3 hours, and only 81 were treated within this time window in ECASS II.2,3,6 Our results for patients treated with tPA within 3 hours are more favorable than the results for patients treated between 3 and 5 hours.4 The findings of the Australian Streptokinase Trial7 were similar to ours: Patients treated within 3 hours had a more favorable response to streptokinase than those treated between 3 and 4 hours. These clinical findings are compatible with data from animal stroke models, indicating that ischemic brain tissue rapidly becomes irreversibly injured after stroke onset and that therapeutic interventions provide greater benefit when administered early. The recently published subgroup analysis of the NINDS trial suggests that this concept applies even within the first 3 hours after stroke symptom onset. Patients in the NINDS trial who were treated within 90 minutes of symptom onset had a more favorable response to tPA than those treated between 91 and 180 minutes.8

Data from the subgroup of patients treated within 3 hours of symptom onset in the ATLANTIS trial support both the beneficial effects of tPA and the increased risk of symptomatic intracranial hemorrhage documented in the NINDS study. Although a trend toward increased mortality in tPA-treated patients was seen at both 30 and 90 days, we suspect that this finding was related to the small sample size and possibly imbalances in baseline prognostic factors. No significant difference in mortality was found in the much larger cohort of patients treated between 3 and 5 hours in the ATLANTIS trial,4 and a trend toward reduced mortality in tPA-treated patients was noted in the NINDS trial.1

Our analysis is limited by the small number of patients treated within 3 hours of stroke onset; therefore, the results should be interpreted with caution. Although the mean baseline NIHSS scores were identical in both the tPA and placebo groups, more tPA-treated patients had both mild (NIHSS, 3 to 7) and severe (NIHSS ≥21) strokes. This imbalance may have contributed to an overestimation of both the benefits and risks of tPA. Analysis of favorable outcome stratified by baseline stroke severity showed a consistent treatment benefit. This data set supports the current recommendation to administer intravenous tPA to eligible ischemic stroke patients who can be treated within 3 hours of symptom onset.9

Acknowledgment

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References


Thrombolysis for Stroke: Defining the Time Window

Despite their small sample size, the positive results using tissue plasminogen activator (tPA) within 3 hours in the ATLANTIS Trial provide further confirmation that this is an appropriate time window for thrombolysis.1 The substudy showed that excellent outcomes were increased by one third, an identical finding to that of the NINDS investigators.2

Editorial Comment

Thrombolysis for Stroke: Defining the Time Window

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Together with the earlier ATLANTIS report of lack of benefit of tPA in the 3- to 5-hour time window, these findings emphasize that the timing of thrombolytic intervention is critical and that, indeed, “time is brain.”

Several thrombolytic trials have now shown that earlier treatment is associated with better outcome. In the Australian Streptokinase Trial, there was a strong trend toward better outcomes using streptokinase <3 hours of stroke onset, compared with those treated 3 to 4 hours, an a priori hypothesis. The NINDS trial(s) provided definitive evidence of the benefit of tPA administered within 3 hours, half the patients treated within a remarkably short 90 minutes. The NINDS Investigators initially reported no significant differences between these two time strata, but later analysis showed that those treated <90 minutes had increased odds of favorable outcome. In the ECASS I and ECASS II trials, a 6-hour treatment window was used, and most patients were treated beyond 3 hours. In an analysis of the 87 patients treated <3 hours in ECASS I, the results favored tPA and also appeared very similar to the NINDS outcomes. Meta-analysis of the sub-3-hour data from NINDS, ECASS I, and ECASS II demonstrated a clear benefit for tPA, the odds of death or dependency at outcome reduced by 45% (OR [odds ratio] 0.55; 95% CI 0.41 to 0.72).

The link between the efficacy of thrombolysis and time to treatment is supported by pathophysiological information about the ischemic penumbra, the variable region of functionally deranged, but potentially salvageable, peri-infarct tissue. Using 13O PET, the increased oxygen extraction fraction, which defines the likely penumbra, declines over time. Similarly, the rate of hypoxic tissue in the putative penumbra, measured by increased 18F-FMISO PET, is time-linked. Heiss and colleagues used PET to show that a large volume of critically hypoperfused tissue, defined by cerebral blood flow <12 mL/100g/min, could be salvaged by tPA within 3 hours. The penumbra, defined as perfusion greater than diffusion mismatch on MRI, is found in 80% of patients <6 hours and its frequency rapidly diminishes with time. In such patients, treatment with tPA within 6 hours has been associated with significantly increased reperfusion and reduced outcome infarct size. Individualization of the variable time window and the opportunity for thrombolytic therapy might well be facilitated by this use of MRI. A prospective randomized trial is under way to test this hypothesis.

What about time to treatment and safety? Is there any evidence that earlier treatment with tPA is associated with a lesser risk of hemorrhagic transformation and mortality? There has been a remarkable consistency among all thrombolytic trials, using streptokinase or tPA, of a 3- to 4-fold increased odds of the development of symptomatic intracranial hemorrhage. In contrast to the link between efficacy and earlier time to treatment, the risk of hemorrhagic transformation is not lower. It was a substantial 13% in the sub-3-hour ATLANTIS cohort, but the small sample size must be emphasized. For mortality alone, meta-analysis of the tPA trials alone shows no significant difference in those treated 0 to 3 and 3 to 6 hours. For now, the ATLANTIS subset results provide some further reassurance that the 3-hour time window is appropriate in selecting thrombolytic treatment and that earlier treatment with tPA indeed appears better. However, earlier treatment is not safer, and this should underline the need for institutional surveil-

lance of protocol adherence, hemorrhage, and mortality rates in patients treated with tPA.

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References
1. Albers GW, Clark WM, Madden KP, Hamilton S. The ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Stroke. 2002;33:
13. Heiss WD. 18F-FDG PET and the University of Melbourne Melbourne, Australia

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