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## Does Study Enrollment Delay Treatment With Intravenous Thrombolytics for Acute Ischemic Stroke?

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### Abstract

**Background and Purpose**—Enrollment in acute stroke trials at a stroke center with multiple study protocols may delay the initiation of intravenous thrombolytics in patients who present within 3 hours of symptom onset.

**Methods**—We studied all patients presenting with acute ischemic stroke over the past 3.5 years who qualified for thrombolysis within 3 hours of symptom onset. We collected demographics, baseline National Institutes of Health Stroke Scale scores, CT findings, and arrival-to-treatment times and compared patients treated with intravenous thrombolytics in a clinical trial with patients who received standard of care intravenous tissue plasminogen activator.

**Results**—Of 290 treated patients, 19 were enrolled in prelytic studies, 46 were enrolled in postlytic studies, and 225 were treated with standard intravenous tissue plasminogen activator. There was no significant difference in age, gender, National Institutes of Health Stroke Scale score, admission glucose, or changes on CT. There was no difference in onset-to-arrival time or arrival-to-treatment time between patients enrolled in clinical studies and those who received standard treatment. However, among study patients, prelytic randomization led to a significantly longer arrival-to-treatment time by 13 minutes ( $P=0.028$ ).

**Conclusion**—We found that trials requiring prethrombolytic randomization can lead to a delay in the initiation of treatment. Future studies are needed to determine if such a delay is clinically significant and can be shortened by improved enrollment strategies.

### Keywords

acute stroke; clinical trials; thrombolytic treatment

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There is a pressing need to develop additional and better therapies for the treatment of acute ischemic stroke. Tissue plasminogen activator (tPA) remains the only proven therapy, but its efficacy is limited and its approval remains restricted to patients who present within 3 hours of symptom onset.

Many new treatments are being trialed as adjuvants or alternatives to thrombolytic therapy. Some trials require enrollment and randomization before or during thrombolysis. Evaluation of potential study candidates requires rapid decision-making. Potential sources for delay

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include securing an exact time of onset. Knowing that the patient is “in the window” for tPA is not sufficient for clinical trial participation. The emergent history and review of systems is more comprehensive as various inclusion/exclusion criteria are screened. A complete and well-executed examination using the National Institutes of Health Stroke Scale must be done because many studies require minimum or maximum severity scores or specific findings. Some studies require defined abnormalities on transcranial Doppler. Each of these factors could add minutes to the initial assessment.

The treating physician can be distracted by the flurry of activities of eligibility assessment and consent and not be aware that all criteria for tPA treatment have been met. Additional delay could be introduced in situations when the patient is not consentable and the treating physician is told that the family member is “just a few minutes away.”

Studies of adjunctive therapy allow for tPA to be given before enrollment. Adjuvant treatments, however, are time-linked to the tPA bolus. Knowing that the patient will be enrolled at the time of tPA bolus enables initiation of subsequent steps in trial enrollment such as randomization, gathering of equipment, and notification to the pharmacy of the urgent need to prepare study medications. If a patient is eligible for alternative thrombolytic therapy, enrollment and randomization are required before treatment. These procedures could pose delays to treatment, particularly at a stroke center with multiple study protocols.

The time from symptom onset to thrombolysis is important for response rate.<sup>1</sup> Delays in reperfusion not only limit tissue salvage, but also may impair the detection of clinical improvements from study treatments. Enrollment in acute stroke trials, therefore, particularly at a stroke center with multiple study protocols, may delay the initiation of intravenous thrombolytics in patients who present within 3 hours of symptom onset. The purpose of this study was to determine if the process of enrollment increases the arrival-to-treatment time in thrombolysis clinical trials.

## Methods

At our center, the stroke team is notified about a potential acute stroke before the patient arrives to the emergency department. A series of codes are entered into the stroke team pager that put transcranial Doppler and our research team on alert. The stroke team attending or fellow quickly screens the patients for acute cerebrovascular event and assesses the patient's ability to consent. If the patient is not able to provide informed consent, a family member is urgently sought. If the patient is a potential study candidate, nurse coordinators are paged immediately.

Study enrollment is limited to weekdays from 8 AM to 5 PM, when our nurse coordinators are available. A study eligibility log records the reasons why patients presenting within 3 hours of symptom onset during study enrollment periods were not enrolled in clinical studies. This log was reviewed to determine the major reasons eligible patients were not enrolled in clinical trials.

Patients presenting to the emergency department who qualified for intravenous thrombolysis over the past 3.5 years were examined. Demographics, baseline National Institutes of Health Stroke Scale scores, CT findings, and arrival-to-treatment times were collected. Comparison was made between patients enrolled in a clinical trial and patients receiving the standard of care intravenous tPA. Patients enrolled in a trial requiring prelytic consent (eg, study of alternative thrombolytic agent compared with standard tPA) were compared with those enrolled in trials allowing postlytic consent (eg, study of adjunctive treatment in addition to standard tPA).

## Statistical Analysis

Categorical variables were compared using  $\chi^2$  or Fisher exact tests where appropriate. Continuous variables were compared using 2-sample *t* tests or Mann–Whitney *U* tests where appropriate.

## Results

Over the study period, we treated 290 patients with intravenous thrombolytics. Our study participants represented 22.4% of treated patients (n=65). The major reason why patients were not enrolled in clinical trials was time of presentation during “off hours” for enrollment (44%). Among the daytime treatments, declining study participation (51%), inability to obtain consent (21%), and minimal deficit on National Institutes of Health Stroke Scale (19%) were the most common reasons a patient with acute stroke was not enrolled into a study. Table 1 shows the baseline demographics and variables that may predict outcomes after acute ischemic stroke. There were no significant differences in these variables in our study patients compared with patients receiving standard-of-care intravenous tPA.

Table 2 shows that the arrival-to-treatment times were nearly identical in study and nonstudy patients. The treatment times were analyzed again after dividing study patients into groups based on whether enrollment was required before treatment with thrombolytics (Table 3). There was no significant difference in arrival-to-treatment time in patients participating in studies allowing for thrombolytic treatment before enrollment compared with standard-of-care patients ( $P=0.57$ ). We found, however, a statistically significant prolongation in the arrival-to-treatment time in patients who were enrolled and randomized before treatment compared with patients who were treated with intravenous tPA before enrollment ( $P=0.028$ ). In addition, we also found a shorter median time from symptom onset-to-arrival time (nonsignificant) in the patients enrolled and randomized before thrombolysis.

## Discussion

We found that patients participating in our trials are representative of our overall population of patients with acute ischemic stroke. When assessing all patients treated with thrombolytics, we found that participation in acute stroke clinical trials does not lead to delays in initiation of therapy. However, we did find that the symptom onset to arrival time was shorter for those patients enrolled in clinical studies versus those who were given the standard of care. This may indicate that our treatment team is more prone to enroll patients who arrive earlier in the treatment window compared with patients who present later in the treatment window.

We also found that the subset of patients participating in trials requiring prethrombolytic randomization had a delay in the initiation of treatment. The clinical significance of this delay is unproven but theoretically is meaningful.<sup>2</sup> Future studies are needed to determine if such a delay is clinically significant and can be shortened by improved enrollment strategies. It should be noted, however, that a treatment that takes longer to initiate may still ultimately be more effective than treatments that can be administered more quickly.

We use several strategies to reduce arrival-to-treatment time during enrollments. One team member is designated as the “tPA person.” This person alerts the treating physician when necessary imaging and laboratory tests are available to meet criteria for tPA. One team member, usually the first contact, is designated as the “study pitcher” who introduces the opportunity of clinical trial participation and the concept behind the offered study. We use a study rotation system to minimize the time period during which eligibility is being determined and to limit “cherry picking” patients for particular studies. Our research team works rapidly to coordinate the subsequent steps in enrollment, randomization, and treatment to minimize delays and

notifies the pharmacy even before enrollment of a potential study patient to reduce delays in drug preparation. Drug preparation after pharmacy receipt of the consent form and randomization number is another source of the delay in alternative thrombolytic studies. Although these strategies may help to reduce delays, rapid enrollment raises the concern about the extent to which the impaired patient with stroke or their surrogates understand the informed consent sheets, which are 4 to 9 pages long at our stroke center.

Using these strategies, we hope that we are minimizing the loss of brain cells and the chance of losing a signal of efficacy of the therapies under investigation. Clinical trialists should be cognizant of the potential for introducing delays in treatment and should share strategies thought to be helpful in reducing delay in treatment. Despite our efforts, we still exceed the established guidelines on arrival-to-treatment time. However, we cannot generalize our experience at a single center to the larger acute stroke research community. Delay in tPA administration because of trial enrollment is potentially a clinically significant problem that warrants further investigation.

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**Table 1**  
Baseline Characteristics of Standard-of-Care Patients and Study Patients

Variable	Not Enrolled (n=225)	Enrolled		Total Enrolled Patients (n=65)
		Postlytic Enrollment (n=46)	Prelytic Enrollment (n=19)	
Age, median (range)	63 (19–91)	64 (38–89)	70 (46–91)	65 (38–91)
Gender, % male	56.4	52.2	47.4	50.8
Race, %				
Black	38.7	32.6	31.6	32.3
Hispanic	14.2	17.4	5.3	13.8
White	44.9	43.5	63.2	49.2
Other	2.2	6.6	0	4.5
Admission glucose, median (range)	122 (62–536)	137 (82–414)	125 (78–252)	135 (78–414)
Early ischemic changes on initial CT, %	15.6	15.2	21.1	16.9
Baseline National Institutes of Health Stroke Scale score, median (range)	12 (0–39)	13 (3–26)	10 (4–23)	13 (3–26)

All *P* values comparing nonenrolled with enrolled patients and patients with postlytic with prelytic enrollment were nonsignificant.

**Table 2**  
Onset-to-Treatment and Arrival-to-Treatment Times in Standard-of-Care Patients and Study Patients

Variable	Not Enrolled	Enrolled	P Value
Onset-to-treatment, median (range)	135 (64–180)	127 (64–180)	0.636
Arrival-to-treatment, median (range)	62 (20–131)	61 (23–135)	0.725

**Table 3**

Onset-to-Treatment and Arrival-to-Treatment Times in Patients Who Received Standard of Care tPA Compared With Patients Participating in Clinical Studies That Either Required Prelytic or Postlytic Enrollment

Variable	Not Enrolled	Studies With Postlytic Enrollment	Studies With Prelytic Enrollment	P Value
	(N=225)	46/65 (70.8%)	19/65 (29.2%)	
Onset-to-arrival, median (range)	66 (17–137)	60 (25–120)	59 (15–116)	NS
Onset-to-treatment, median (range)	135 (64–180)	126 (64–180)	128 (92–178)	NS
Arrival-to-treatment, median (range)	62 (20–131)	59 (23–135)	72 (52–111)	0.027 <sup>*</sup>
				0.56 <sup>†</sup>
				0.028 <sup>‡</sup>

NS indicates nonsignificant.

\* Comparison of nonenrolled patients with patients that were enrolled in prelytic studies.

† Comparison of nonenrolled patients with patients that were enrolled in postlytic studies.

‡ Comparison of patients enrolled in pre- versus postlytic studies.