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The Potential Impact of Maintaining a 3-Hour IV Thrombolysis Window: How Many More Patients can we Safely Treat?

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Abstract

Background—In 2008, the European Cooperative Acute Stroke Study-3 (ECASS-3) demonstrated that intravenous-tissue plasminogen activator could be safely administered for acute stroke patients presenting between 3 and 4.5 hours from symptom onset. Recently, the Food and Drug Administration rejected expansion of this time window in the United States. We sought to determine how many fewer patients would be treated by maintaining this restricted time window.

Methods—We reviewed charts from patients who received intravenous thrombolysis at the University of Alabama at Birmingham between January 2009 and December 2011. Patients were divided into two groups (treated within 3 hours of onset, treated between 3 and 4.5 hours from onset). Demographics, stroke severity and protocol deviations according to the ECASS-3 trial were collected. Our safety measures were any hemorrhagic transformation, symptomatic intracerebral hemorrhage and systemic hemorrhage.

Results—Two hundred and twelve patients were identified, of whom 192 were included in our analysis. A total of 36 patients (19%) were treated between 3 and 4.5 hours. No statistical differences were seen between age (p=0.633), gender (p=0.677), race (p=0.207) or admission stroke severity (p=0.737). Protocol deviations from the ECASS-3 criteria were found in 20 patients (56%). These were primarily age > 80 and aggressive blood pressure management. Despite these deviations, we did not see significant increases in the rates of adverse events in patients treated in the extended time window.

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Conclusions—Our data are consistent with previously reported international data that IV thrombolysis can safely be used up to 4.5 hours from symptom onset. Restricting the time window to 3 hours would have resulted in almost one-fifth fewer patients treated at our center.

Keywords

Ischemic Stroke; Thrombolysis; Safety; Hemorrhage

INTRODUCTION

Currently, intravenous tissue plasminogen activator (IV-tPA) is the only FDA approved treatment for acute ischemic stroke (AIS) in the United States [1]. In 2008, the European Cooperative Acute Stroke Study-3 (ECASS-3) trial demonstrated that tPA could be safely administered in patients presenting between 3 and 4.5 hours from symptom onset [2]. Despite a higher rate of symptomatic intracranial hemorrhage (sICH) in this group (2.4% vs. 0.2%), patients treated beyond 3 hours demonstrated improved clinical outcomes. Since ECASS-3, additional international trials have provided further support for the expansion of the tPA time window [3–6].

Although these trials have resulted in a modest increase (2%) in IV thrombolysis use in the United States, [7] overall tPA utilization rates remain below five percent [8]. While there are many factors that influence tPA use including drug label contraindications, [9] the majority of patients are excluded because of presentation to emergency rooms beyond the 3 hour treatment window [10]. This may be due to lack of symptom awareness by the patient, [11,12] failure to access emergency services [13] or geographic inaccessibility to hospitals capable of delivering acute stroke care [14].

Expanding the tPA window has the potential to increase the proportion of patients who are eligible for treatment in the United States [15]. However, without an FDA approval of treatment beyond 3 hours, many providers, particularly those outside major stroke centers, may be reluctant to offer this therapy. The objective of this study was to determine the safety of expanding the tPA window to 4.5 hours in a tertiary care hospital in the US Stroke Belt, including patients with and without ECASS-3 protocol deviations, and to assess how many patients would have been denied treatment by restricting time window to 3 hours.

METHODS

Study Population

After approval by the University of Alabama at Birmingham (UAB) Institutional Review Board, we retrospectively analyzed all AIS patients treated at UAB between January 2009 and December 2011. Our center utilizes an expanded IV tPA treatment protocol that includes use of the 4.5 hour window. Informed consent (from patient or surrogate) was obtained prior to treatment on all patients who received tPA after 3 hours. Demographic data, stroke severity as measured by the National Institute of Health Stroke Scale (NIHSS), and IV thrombolytic data were obtained from our prospectively collected stroke registry. Retrospective chart review was performed on all patients who received IV tPA at our center to obtain additional clinical, laboratory, imaging, and treatment data. In addition, charts were reviewed to determine when IV thrombolysis was initiated relative to symptom onset and to determine if there were any deviations from the published inclusion and exclusion criteria in the ECASS-3 trial [2].

Patients with an uncertain time of symptom onset (i. e., wake up strokes) and those who received tPA beyond the 4.5 hour window were excluded from the analysis. We also

excluded patients treated at other institutions and then transferred to our center since documentation of treatment times and management of blood pressure during transfer were inconsistently documented. Use of aggressive blood pressure control was defined in the ECASS-3 trial as the need for continuous infusion of an antihypertensive agent.

Safety Outcomes

Our primary safety outcome was symptomatic intracerebral hemorrhage (sICH). We defined sICH as a hemorrhage not seen on previous imaging coupled with >4 point neurologic deterioration on the NIH Stroke Scale [16]. Our two secondary outcomes were any hemorrhagic transformation (HT) on CT or MRI and systemic hemorrhage.

Statistical Analysis

Categorical data were compared using Pearson Chi-squared or Fisher exact test where appropriate. Continuous data were compared using Wilcoxon Rank Sum test. All tests were two sided and an alpha of 0.05 was considered significant. As this was an exploratory analysis, no adjustments were made for multiple comparisons [17].

RESULTS

We identified 212 patients in our registry who received tPA from 2009 to 2011. We excluded 20 patients because of missing data. Of the 192 patients with complete data, 156 patients were treated within 3 hours and 36 patients were treated between 3 and 4.5 hours. Table 1 compares the baseline demographics between these groups. Fewer patients in the extended time window group were on an antiplatelet agent prior to admission, otherwise there were no significant differences between groups.

We assessed the 36 patients in the extended time window group for protocol deviations according to the ECASS-3 trial. One or more deviations were found in 20 patients (56%, Table 2). The two most frequent deviations were age greater than 80 (22%) and aggressive blood pressure management using nicardipine hydrochloride (14%). Four patients were on oral anticoagulation therapy with warfarin; however, only one of these patients had an INR greater than 1.7. There were no patients on novel anticoagulants (e. g., dabigatran). Two patients had a clinically severe stroke as defined by the ECASS-3 trial involving more than a third of the MCA territory on the initial CT scan. One patient was treated when their glucose was 536 mg/dL and one patient had recent gastrointestinal bleeding.

The proportion of patients in each group with sICH, HT and systemic hemorrhage is displayed in Table 3. Symptomatic ICH was rare and occurred in only one patient (3%) in the extended time window group, compared to two patients (1%, p=0.468) in the group treated within three hours. Similarly, HT without clinical deterioration was noted in 8 patients (22%) in the extended time window group, compared to 22 patients (14%, p=0.233) in the group treated within three hours. No patients developed systemic hemorrhage in the extended time window group.

DISCUSSION

Our study suggests that expanding the IV t-PA time window to 4.5 hours in a tertiary care hospital in the Stroke Belt of the United States is safe, although some patients had deviations from the ECASS-3 protocol. If a 3 hour cut off was used, 36 fewer patients (19% of our treatment population during this time period) would have been denied treatment. This is slightly higher than the experience reported at other centers [18]. Within these 36 patients, nearly half had ECASS-3 protocol deviations, however safety outcomes did not significantly differ from patients treated within 3 hours.

In spite of clinical trials and guidelines [3,4,19] supporting the safety and efficacy of tPA beyond 3 hours, this practice is still considered to be "off-label" in the United States. While the percentage of patients treated between 3 and 4.5 hours has increased by 2%, [7] there may be continued reluctance to adopt this practice outside of major academic centers with stroke expertise. Since tPA is the only medical treatment available to these patients, [1] it is imperative to minimize barriers to its delivery [20]. Many of the tPA contraindications are overly restrictive [21–23]. Regardless of the other contraindications, arrival beyond the treatment window remains the largest barrier [10]. While reasons for delayed arrival certainly need to be addressed, the reality is that a 3 hour time window is going to continue to be a barrier to acute stroke treatment.

Our data are consistent with previous research showing that tPA can be safely delivered up to 4.5 hours after symptom onset. Large international trials such as the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) and the Third International Stroke Trial (IST-3) have shown that an extended time window beyond 3 hours may be beneficial for many patients although outcomes are less favorable [3,4] The CASES registry in Canada also found that tPA is beneficial in the extended window although they found a trend towards higher sICH rates and death [5]. Similar to the contraindications used with the 3 hour window, the exclusion criteria used in the ECASS-3 trial warrant further study to determine if they should be applied to all patients in the extended time window. At our center, we found that the most common protocol deviations in the extended time window were age >80 and aggressive blood pressure control using IV agents. Currently, there are conflicting data for tPA use in elderly patients (within 3 hours) [24–27] although the IST-3 trial suggested that the benefit is not diminished [4]. Martin-Schild et al. demonstrated that aggressive IV blood pressure control for patients treated within three hours is relatively safe and does not appear to be associated with worse outcomes [23]. Prospective studies are needed to further explore the effects of aggressive blood pressure control in the setting of tPA. Overall, even with protocol deviations, patients treated in the extended time window have safety outcomes similar to those treated within 3 hours.

Our study is limited by its retrospective design. Our small sample size may have prevented us from detecting existing differences in groups. Additionally, our sample included patients admitted to a single, tertiary care center where patients were treated following evaluation by trained stroke neurologists who are comfortable with tPA use. Our experience may not be generalizable to smaller, more rural facilities. Furthermore, we only examined patients presenting directly to our emergency room and did not consider alternate forms of tPA administration (e. g., "drip and ship," telemedicine). Our outcomes were limited to the short-term, only accounting for morbidity occurring during the hospitalization. Additional study is needed to assess long-term outcomes in patients treated in the extended time window. Despite these limitations, our study is the first to describe the effects of an extended time window in the US Stroke Belt.

In conclusion, despite ECASS-3 protocol deviations in the majority of patients treated in the 3 to 4.5-hour window, our study found that tPA can be safely delivered in patients presenting in the 3 to 4.5-hour window without significant increases in sICH. Our results are in keeping with the findings of ECASS-3 and other international trials, suggesting that treatment within the extended time window may be both safe and beneficial in select patients. Adherence to a 3 hour time window would have resulted in almost one-fifth of patients being denied IV tPA at our center. Further research will be required to determine which contraindications remain necessary to help better select patients for IV thrombolysis beyond three hours.

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Table 1

Comparison of the Demographics and Baseline Characteristics of Treatment Groups.

Variable	Less than 3 Hours (n=156)	3–4.5 Hours(n=36)	P-value
Age	68 (IQR 55, 82)	68 (IQR 54, 79)	0.633
Gender (Male)	54% (84)	50% (18)	0.677
Race			0.207
White	57% (89)	72% (26)	
Black	41% (64)	14% (10)	
Asian/Pacific Islander	2% (3)	0% (0)	
Ethnicity			
Non-Hispanic	100% (156)	100% (36)	N/A
Past Medical History			
Diabetes	28% (43)	14% (5)	0.133
HTN	77% (120)	67% (24)	0.200
HLD	32% (50)	28% (10)	0.618
Afib	18% (28)	31% (11)	0.090
CHF	15% (23)	6% (2)	0.176
CKD	6% (10)	0% (0)	0.213
Medications			
Oral Hypoglycemics	16% (25)	11% (4)	0.608
Antihypertensives	64% (100)	50% (18)	0.117
Antiplatelet Agent	41% (64)	22% (8)	0.036
Current Smoker	28% (44)	33% (12)	0.542
Admission NIHSS	8 (IQR 5, 15)	8 (IQR 5,13)	0.737

IQR=Interquartile Range; HTN=Hypertension; HLD=Hyperlipidemia; Afib=Atrial Fibrillation; CHF=Congestive Heart Failure; CKD=Chronic Kidney Disease; NIHSS=National Institutes of Health Stroke Scale

Table 2

Frequency of ECASS-3 Protocol Deviations in Patients Treated between 3–4.5 Hours.

Deviation Type	Percentage of Patients with Deviations (n=36)
Age >80	22% (8)
Aggressive Blood Pressure Treatment Required	14% (5)
Oral Anticoagulant Treatment	11% (4)
Imaging with >33% MCA Territory Involvement	6% (2)
Seizure at Onset	3% (1)
Combination of Diabetes and Previous Stroke	3% (1)
Other Disorders with an Increased Bleeding Risk	3% (1)
Platelets <100,000	3% (1)
Glucose <50 or >400	3% (1)
NIHSS >25	0% (0)
Trauma or Major Surgery within 3 Months	0% (0)
Stroke or Serious Head Trauma within 3 Months	0% (0)
Elevated PT/PTT	0% (0)
SBP >185 or DBP >110	0% (0)
Symptoms Resemble SAH	0% (0)

MCA=Middle Cerebral Artery; NIHSS=National Institutes of Health Stroke Scale; PT=Prothrombin Time; PTT= Partial Thromboplastin Time; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; SAH= Subarachnoid Hemorrhage

Table 3

Safety Outcomes based on Treatment Times.

Outcome	Less than 3 Hours (n=156)	3–4.5 Hours (n=36)	P-value
Symptomatic ICH	1% (2)	3% (1)	0.468
Any HT on MRI or CT	14% (22)	22% (8)	0.233
Systemic Hemorrhage	4% (7)	0% (0)	0.351

ICH=Intracerebral Hemorrhage; HT= Hemorrhagic Transformation; MRI=Magnetic Resonance Imaging; CT=Computed Tomography