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Intravenous Thrombolysis in Expanded Time Window (3-4.5 hours) in General Practice with Concurrent Availability of Endovascular Treatment

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Abstract

Introduction: A randomized double-blind trial (ECASS III) demonstrated that intravenous (IV) recombinant tissue plasminogen activator (rt-PA) administered between 3 and 4.5 hrs after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke. In May 2009, the American Stroke Association guidelines recommended the use of IV rt-PA for patients presenting within 3 and 4.5 hrs after symptom onset.

Objective: To determine the rate of patients treated with IV rt-PA within the 3- and 4.5-hr time window and associated comparative outcomes in general practice.

Methods: We retrospectively reviewed all patients who were treated with IV rt-PA at two comprehensive stroke centers from September 1, 2008 to July 31, 2010 and identified a total of 98 patients. In addition, we identified patients who arrived to the ED of those centers within 2.5 to 4 hrs of symptom onset between January 1, 2007 and June 30, 2010 and received only endovascular treatment. We compared the rates of favorable outcome (determined by using modified Rankin scale 0-2 at discharge and 3-month follow-up), and National Institutes of Health Stroke Scale (NIHSS) score improvement by ≥ 4 points or 0 at discharge among patients treated with IV rt-PA within 3-4.5 hrs with those who received IV rt-PA within 0-3 hrs, and subsequently with patients presenting at similar time window treated only with endovascular treatment.

Result: Out of the total 98 IV rt-PA treated patients, 84 of them were treated within 0-3 hrs, and 14 within the 3--4.5 hrs. Twelve patients received endovascular treatment only for the specified time window. Mean admission NIHSS score ± standard deviation (SD) was 11.90 ± 6.72, 8.57 ± 5.40, and 11.75 ± 8.06, for the 0--3, 3--4.5 hrs, and endovascular only treatment groups, respectively. Favorable clinical outcome at discharge (50% vs. 56%, p=0.77), 3 months (64% vs. 64%, p=1.0), and NIHSS score improvement (43% vs. 58%, p=0.38) were not different between those treated within 3-4.5 and 0-3 hrs time windows. There appeared to be a non-significantly higher rate of favorable outcomes at discharge (25% vs. 50%, p=0.24), and at 3 months (42% vs. 64%, p=0.43) among patients treated with IV rt-PA within 3-4.5 hrs compared with those treated with primary endovascular treatment.

Conclusion: An additional 14% of patients received IV rt-PA because of treatment window expansion from 3 to 4.5 hrs. Outcomes were comparable to those treated within 3 hrs of symptom onset. The shift of those patients from primary endovascular treatment does not appear to adversely affect patient outcomes.

Introduction

The pivotal NINDS clinical trials led to FDA approval of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) in 1996 for administration within 3 hrs of symptoms onset in patients with acute ischemic stroke. [1] Despite the fact that IV rt-PA is currently recommended by AHA/ASA Stroke Council [2] and Brain Attack Coalition [3] and considered a quality parameter by Joint Commission [4], utilization of this effective treatment remains very low – around 2-3%. [5,6] Only about 15--20 % of patients with acute stroke symptoms

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present to the hospital within 3 hrs of symptom onset. [6,7,8] Delayed arrival to health care facilities is the most common reason for patients to be excluded from IV rt-PA treatment. [9,10,11]

There has been considerable interest in expanding the time window for administration of IV rt-PA to increase the number of patients who can benefit from this treatment [12–15]. The initial studies focused on recruiting patients in whom treatment could be initiated between 3 and 6 hrs after symptom onset. However, a meta-analysis of clinical trials found that the benefit of IV rt-PA was limited only to patients in whom treatment was initiated within 4.5 hrs after symptom onset. [16] The European Cooperative Acute Stroke Study III (ECASS III) trial [17] was the first randomized double-blind placebo controlled trial that demonstrated IV rt-PA administered between 3 and 4.5 hrs after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke. Concurrently, "thrombolysis with alteplase 3-4.5 h after acute ischemic stroke" (SITS-ISTR) [18] was an observational study which also confirmed similar outcomes between patients treated within 3 hrs and those treated within 3-4.5 hrs after symptom onset.

In May 2009, a science advisory from the American Stroke Association [19] recommended the use of IV rt-PA for patients presenting within 3 and 4.5 hrs after symptom onset. Subsequently, a meta-analysis of ECASS III, ATLANTIS, NINDS, and EPITHET trials confirmed a higher rate of favorable outcomes among patients treated with rt-PA compared with those treated with placebo within 3-4.5 hrs after symptoms onset. [20,21,22] Bluhmki et al. [23] performed a sub group analysis of the ECASS III data and demonstrated consistent benefit of IV rt-PA in patient subgroups based on age or initial NIHSS score.

The impact of these studies and professional guidelines in general practice is not known. The first objective of our study is to determine the rate of patients treated with IV rt-PA within the 3- and 4.5-hr time window and associated outcomes in general practice.

It is known that prior to the results of ECASS III, patients presenting between 3 and 6 hrs at many institutions were offered direct endovascular acute stroke treatment option. As active endovascular treatment institutions [24], we provide comparative analysis of outcomes among ischemic stroke patients who received IV rt-PA within 3-4.5 since ECASS III results were published, against those who presented in similar time window and received only endovascular treatment prior to ECASS III - which is the second objective of our study.

Methods

We identified all patients who were treated with IV rt-PA at two comprehensive stroke centers from September 1, 2008 to July 31, 2010 using prospectively collected databases of all acute ischemic stroke patients who receive either IV rt-PA and/or endovascular intervention. The databases are updated and maintained on a daily basis by staff personnel in our institutions, and then cross-checked against the acute ischemic stroke admission diagnosis reports that are provided by the coding departments of the participating hospitals at the end of each month. These reports are based on International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes where primary diagnostic codes (433,434, 436, 437.0, and 437.1) are used to identify the patients admitted with ischemic stroke.

We collected relevant information for each patient from the individual hospital records. Demographic data including age, sex, and race/ethnicity was collected from patient profile documented during admission registration. We collected data regarding stroke risk factors present before onset of stroke symptoms (as mentioned in the admission and/or discharge notes), e.g., hypertension, dyslipidemia, diabetes mellitus, cigarette smoking, atrial fibrillation, and coronary artery disease. Data regarding severity of stroke and baseline function at presentation was obtained by the admission National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) respectively. Door-to-needle time for IV rt-PA treated patients was obtained from thrombolytic administration records, whereas onset-to-hospital time was collected from emergency room and/or EMS service records for both IV rt-PA and endovascular treated patients.

IV rt-PA was administered in a dose of 0.9 mg/kg using standard dosing protocol after a non-contrast computerized tomography (CT) ruled out intracerebral hemorrhage. A follow-up head CT was obtained in all patients 24 hrs after IV rt-PA treatment. Similarly, non-contrast head CT scan was performed in all endovascular treatment patients prior to treatment to exclude any intracranial hemorrhage, obvious or significant cerebral infarction or cerebral edema which would have excluded them from such treatment. In addition, non-contrast head CT scan was performed immediately and 24 hrs after completion of endovascular treatment. Neurology house staff evaluated each patient before and after each treatment,

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and follow-up neurological exam was performed on a daily basis during each patient's hospital stay, and at 3 months of follow-up. The NIHSS score was recorded on admission, during hospitalization, and upon discharge.

Occurrence of intracerebral hemorrhage – symptomatic (sICH) or asymptomatic, was obtained from the radiological reports, hospital course, and/or discharge summary records for each patient. sICH was defined as computed tomography scan documented bleeding either in the area of the qualifying stroke and related to neurological deterioration or associated with new neurological deficits (greater than or equal to 4 point worsening on the NIHSS score compared with previous global clinical assessment) . Asymptomatic hemorrhagic transformation was defined as computed tomography-documented bleeding without neurological deterioration after bleeding. In-hospital mortality included patients who died after being placed on comfort care or secondary to a medical complication following treatment.

Favorable clinical outcome in our analysis was defined by modified Rankin scale 0-2 at discharge or 3-month follow-up, or NIHSS score improvement by ≥ 4 points or 0 at 24 hrs. Data regarding functional outcome was obtained for all patients by looking at their discharge or 3-month follow-up mRS. We obtained such information through review of medical records from follow-up in stroke or other specialty clinics, emergency room visits, re-admissions, or telephone conversations conducted by one of the investigators with the patient or patient representatives. Information whether or not a patient is deceased during the 3-month follow-up period was also obtained in a similar way. The protocol for collecting data was reviewed and approved by the institutional review board at each institution as part of a standardized database.

Comparison with endovascular treated patients

We selected a matched group by time of presentation, of controls stroke patients who arrived to the emergency department (ED) of the two centers within 2.5 to 4 hrs of symptom onset between January 1, 2007 and June 30, 2010 and received only endovascular treatment. The reason for selecting the 2.5 to 4 hrs ED arrival time limit for the endovascular group is that, first, we think 2.5- to 4-hr time window represents a comparable time frame of arrival against patients who received IV rt-PA within 3-4.5 hrs. Second, patients who arrive to the ED within this window would only be offered endovascular treatment prior to the ECASS III results as they would fall out of the conventional 3-hr time window by the time their evaluation for stroke is completed. However, since ECASS III results, they may qualify for the expanded 3-4.5 hrs window IV rt-PA treatment.

Endovascular treatment of acute ischemic stroke

Endovascular treatment technique for acute ischemic stroke treatment is well described in previous reports [25,26], and we only give a summary of the key portions of the procedure. Through a femoral access, a 6-French introducer sheath is advanced in either femoral artery and secured in place. A guide-catheter was then introduced through the sheath into the proximal potion of the target vessel – carotid or vertebral artery. Once the location and extent of occlusion was assessed by a diagnostic injection, a micro-catheter was introduced over a micro-wire and positioned closer to the clot/thrombus. The micro-wire was then advanced through the clot/thrombus and the micro-catheter followed through past the occluded segment into the distal patent portion of the vessel. The length of the occluded segment was assessed by simultaneous contrast injection through the guide-catheter and micro-catheter. A thrombolytic agent was then infused through the micro-catheter distal to, within, and proximal to the clot/thrombus as the micro-catheter was withdrawn.

Different thrombolytic agents such as alteplase (rt-PA), reteplase (r-PA), or tenecteplase (TNK), and doses were used during endovascular treatments of acute ischemic stroke. The choice of an agent mainly depended on institutional protocols and availability. Intra-arterial (IA) dosing of alteplase and reteplase did not exceed 22 mg and 4 units, respectively in all cases, whereas the dose of TNK ranged from 1.5 mg to 10 mg. Mechanical thrombectomy using MERCI retriever or snare device, or balloon angioplasty was performed when appropriate, either in conjunction with a thrombolytic agent, or alone for patients who were not candidates or had contraindications for IA thrombolysis. Detailed description of the technical aspect of mechanical thrombectomy/balloon angioplasty is described in other reports. (25, 26)

Statistical analysis

We assessed if risk factors, severity of disease, and time to presentation were similar between patients treated with IV rt-PA within 3 hrs, 3-4.5 hrs and endovascular treatment only. All data were descriptively presented using mean ± standard deviation (SD) for continuous data and frequencies for categorical data. Statistical

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association was assessed with ANOVA and chi-square test for categorical variables. We compared the rates of favorable clinical outcome, sICH, and in-hospital mortality, between patients treated with IV rt-PA within 3-4.5 hrs and those within 0-3 hrs. We also compared the rates of favorable clinical outcome, sICH, and in-hospital mortality between patients treated with IV rt-PA within 3-4.5 hrs and those presenting at similar time window and treated only with endovascular therapy.

Result

There were 98 patients that were treated with IV rt-PA during the study duration. Of the 98, 84 received IV rt-PA within 0-3 hrs, and 14 were treated within 3-4.5 hrs. The number of matched endovascular treated patients was 12 for the respective study period. The baseline demographic and clinical characteristic for each group is presented in Table.1, and these were not significantly different among all comparison groups, although there was a trend towards less severe neurological deficits (mean NIHSS score) and higher rates of cigarette smoking in patients treated with IV rt-PA in 3-4.5 hrs time window.

All patients in the 3-4.5 hrs group, and majority of patient in the remaining two categories had computerized tomography (CT) perfusion studies as part of the initial stroke work-up. On CT angiogram, middle cerebral and internal carotid arteries were the most common sites of occlusion for all categories. No arterial occlusion was found in 21% and 29% of IV rt-PA treated patients in the 0-3 and 3-4.5 hrs categories, respectively. Follow-up endovascular treatment was performed in 31% and 36% of IV rt-PA treated patients in the 0-3 and 3-4.5 hrs categories, respectively.

The rate of NIHSS score improvement (43% vs. 58%, p=0.38) was not different between those treated within 3-4.5 and 0-3 hrs time windows. There was also no statistically significant difference in the rates of sICH, asymptomatic intracerebral hemorrhage, and in-hospital mortality between the two groups. (Table. 1) Favorable clinical outcome at discharge (50% vs. 56%, p=0.77), and at 3 months (64% vs. 64%, p=1.0) were not different between those treated within 3-4.5 and 0-3 hrs time windows.

The rates of favorable outcomes at discharge (25% vs. 50%, p=0.24), and at 3 months (42% vs. 64%, p=0.43) were also not significantly different among patients treated with IV rt-PA within 3-4.5 hrs compared with those treated with primary endovascular treatment in comparable time window (Table. 1). In addition, the rates of sICH, asymptomatic intracerebral hemorrhages, and in-hospital mortality appeared similar between these two groups as well.

Discussion

We found in our retrospective analysis of patients with acute ischemic stroke that 14% of the patients who received IV rt-PA were treated between 3 to 4.5 hrs. Although this trend in increased utilization is probably true for most stroke centers in the US, our result is comparable with the recently published (SITS-ISTR) registry implementation and outcomes data, which shows utilization increase by about 10%. [27]. It appears that the reported increase in rt-PA utilization impacts a relatively smaller percentage (10-15%) of all patients who receive IV rt-PA; however, the impact is actually significant given the proportion of acute ischemic stroke patients who present to emergency departments within 3-6 hrs is only about 11% [28].

We also found that clinical outcome on discharge and at 3 months of follow-up, and rates of ICHs and in-hospital mortality were similar among patients who were treated with rt-PA within 3-4.5 hrs and those treated within 3 hrs after symptom onset. The comparative outcomes in these time windows in the original (SITS-ISTR) observational study [29] showed no significant differences between the 3-4.5 h cohort and the within 3 hrs cohort for any outcome measure including rate of symptomatic ICHs, mortality and independence. Ahmed et al [27] also looked at ICHs rates between patients treated in 0-3 and 3-4.5 hrs and did not find a significant difference between the two groups.

The rates of sICH for all of our comparison groups were in the range of 7-8 %. sICH rate in the original NINDS rt-PA trial was 6.4% in patients who received IV rt-PA within 3 hrs of symptom onset. The rates of sICH in patients treated in the ECASS II were 7% and 11% among patients who received IV rt-PA with 0-3 and 3-6 hrs after symptom onset, respectively. The ECASS III found a rather lower rate (2.4%) of sICH for the patients who received IV rt-PA in 3-4.5 hrs after symptom onset, but the pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials found a 5.2% rate of large intracranial hemorrhage (Parenchymal Hematoma type 2) among those treated between 3 and 4.5 hrs after symptom onset [16]. The variance in rates is partly attributable to different definitions used in various studies.

An important question to ask at this point may be why should outcomes between patients who are treated

Table. 1.

Baseline demographic and clinical characteristics and outcomes among patients treated with thrombolysis at our institutions.

Variables	Patients treated with IV rt-PA between 0 and 3 hours	Patients treated with IV rt-PA between 3 and 4.5 hours	Patients treated with intra-arterial thrombolytics and/or mechanical thrombectomy between 2.5 and 4 hours
Number	84	14	12
Women	41 (48.60%)	6 (42.90%)	3 (25%)
Age years (mean ±SD)	65.49 ± 16.64	68.8 ± 18.47	67.75 ± 17.11
Admission NIHSS score (mean ±SD)	11.90 ± 6.72	8.57 ± 5.40	11.75 ± 8.06
Hypertension	54 (64.29%)	10 (71.43%)	9 (75%)
Diabetes	17(20.24%)	1 (7.14%)	1 (8.33%)
Coronary artery disease	17 (20.24%)	3 (21.43%)	4 (33.33%)
Dyslipidemia	33 (39.29%)	7 (50%)	5 (41.67%)
Atrial fibrillation	20 (23.81%)	5 (35.71%)	3 (25%)
Smoking	18 (21.43%)	6 (42.86%)	2 (16.67%)
CTA diagnosed arterial occlusion *			
Internal carotid artery	20 (23.8%)	2 (14.3%)	2 (16.7%)
Middle cerebral artery	43 (51.2%)	5 (35.7%)	10 (83.3%)
Posterior cerebral artery	1 (1.2%)	3 (21.4%)	0
Vertebral and basilar arteries	2 (2.4%)	0	0
No major vessel occlusion	18 (21.2%)	4 (28.6%)	0
CT Perfusion	65 (77.4%)	14 (100%)	8 (66.7%)
IV plus IA treatment*	26 (31%)	5 (35.7%)	0
Favorable outcome at discharge	47 (55.95%)	7 (50%)	3 (25%)
NIHSS score Improvement	48 (58.54%)	6 (42.86%)	6 (50%)
In-hospital mortality	10 (11.9%)	0	3 (25%)
Favorable mRS at 3 months	54 (64.29%)	9 (64.29%)	5 (41.67%)
ICH symptomatic	7 (8.33%)	1 (7.14%)	1 (8.3%)
ICH asymptomatic	7 (8.33%)	1 (7.14%)	0

within 0-3 hrs and 3-4.5 hrs be similar despite evidence suggesting exponential loss of benefit with increasing time interval between IV rt-PA initiation and symptom onset [16]. However, there is evidence that strokes of lesser severity tend to present after 3 hrs of symptom onset [17,28]. The mean NIHSS score for the 3-4.5 hrs group in our analysis is also slightly lower than the other comparator groups (Table.1). In addition, the 3-4.5 hrs rt-PA treated group may have received additional benefit from follow-up endovascular treatment performed in 36% of the patients (Table.1)

Another major issue is that in many stroke centers, treatment of patients with IV rt-PA between 3 and 4.5 hrs may replace or precede endovascular treatment that was already available for such patients. Suzuki et al [30] documented that most of the US population has access to interventional neuroradiologic expertise for acute stroke treatment (in 200-mile radius, 99% of total US population have access within 6 hrs, and within 65-mile radius, 82% within 3 hrs). To address that, we performed an exploratory analysis to compare outcomes between patients treated with IV rt-PA and those treated with endovascular treatment in comparable time frames. The rates of sICH and favorable outcome at discharge and 3-month follow-up appeared similar among patients treated with IV rt-PA and those treated with primary endovascular treatment.

The frequency of favorable outcomes is higher in the 3-4.5 hrs group compared to the endovascular treatment group, although statistically insignificant. It is not clear if there could have been a selection bias in the endovascular treatment group in which prior to IV rt-PA window expansion, milder strokes were not treated and only severe strokes were treated with endovascular techniques in the 3-4.5 hrs window, but since the time window expansion, milder strokes are being treated with IV rt-PA. The fact that the median NIHSS score being slightly higher in the endovascular treated patients compared to those treated with IV rt-PA in 3-4.5 hr window group may partly explain the above observation.

Conclusion

Delayed hospital presentation is one of the main reasons for rt-PA ineligibility, and an expanded window will certainly increase the number of patients who can receive treatment. It is reassuring to observe that patient outcome is not adversely affected by this shift of patients from primary endovascular treatment to an expanded IV rt-PA treatment window. We recommend a larger scale assessment of the implementation of IV rt-PA treatment in the expanded time window.

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