Comparison of Time to Treatment Between Intravenous and Endovascular Thrombolytic Treatments for Acute Ischemic Stroke

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Abstract

Background: Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) is used to treat acute ischemic stroke (AIS) within 4.5 hours of symptom onset. Endovascular treatment (ET) may provide higher rates of recanalization, but longer time to treatment may limit comparative clinical benefit and widespread applicability.

Objective: This retrospective study compares symptom onset to treatment times in patients who received both IV rt-PA and ET for AIS and its effect on clinical outcome.

Methods: AIS patients presenting to our facility who received both IV rt-PA and ET were reviewed using them as case and control to match other factors contributing to time to treatment. Good outcome was defined as modified Rankin Scale score 0 to 2 at discharge.

Results: Fifty patients received both treatments with significantly shorter mean symptom onset to time to IV rt-PA compared with symptom onset to time to ET (96.8 ± 39.3 minutes versus 255.3 ± 92.2 minutes, $p < 0.001$). Patients receiving ET in less time than the mean time had a higher rate of favorable outcome at discharge (45.5% versus 11.8%, $p = 0.017$) and a significantly lower rate of mortality at three months (15.2% versus 52.9%, $p = 0.017$) than those receiving it after the mean time. The symptom onset to times to ET was significantly longer in transferred patients compared to primary emergency department patients (299.3 minutes versus 230.5 minutes, $p = 0.01$)

Conclusion: A considerable difference in symptom onset to treatment times between IV and ET was observed among patients with AIS, especially those who were transferred from another facility. Reducing the time to treatment for ET has the potential to improve outcomes among ischemic stroke patients.

Key words: Cerebrovascular diseases, combined therapy, endovascular treatment, intravenous treatment, ischemic stroke, time to treatment, tissue plasminogen activator.

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Background

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) has been recommended for patients who are found to have acute ischemic strokes (AIS) within 4.5 hours of symptom onset.1 Despite an increase in incidence of symptomatic intracerebral hemorrhage among those treated with IV rt-PA, the utilization of IV thrombolysis has improved clinical outcome. These patients are 30% more likely to have minimal or no disability at three months.1,2 The use of IV rt-PA alone does not result in favorable outcomes in approximately 57% of the treated patients, and in particular, patients with proximal occlusions.3 Endovascular therapies (intra-arterial thrombolysis or mechanical embolectomy) may be required in addition to or in place of IV rt-PA (in those who are not candidates for IV rt-PA) to accomplish successful recanalization of the occluded cerebral arteries.4 This mode of therapy is especially useful for areas such as the carotid terminus, the basilar artery, the proximal middle cerebral artery,5 and those with significant clinical deficits, as defined by the National Institutes of Health Stroke Scale (NIHSS) score of 10 or greater.6

The benefits of IV thrombolysis with or without endovascular treatment (ET) are dependent on time to treatment.7,8 The time to treatment is expected to be longer among patients undergoing ET compared with those being treated with IV rt-PA treatment due to the additional requirements of an angiographic suite, equipment, and personnel. A comparative analysis has not been performed

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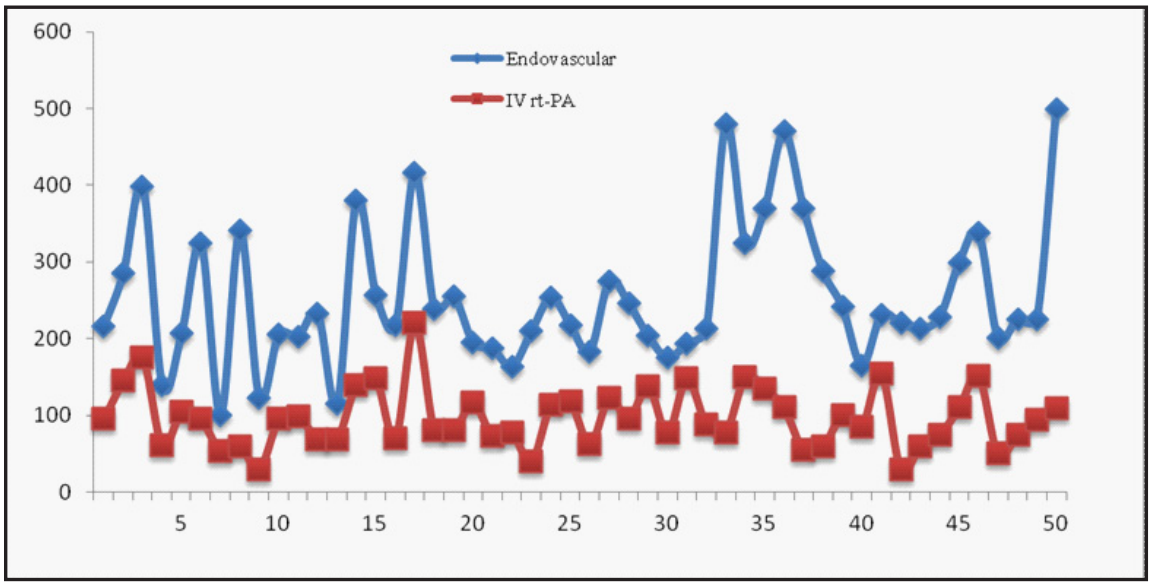
Table 1: Demographic and clinical characteristics of patients who received IV rt-PA followed by endovascular treatment.

	Time to IV			Time to endovascular			Time from IV to endovascular		
	‹mean Time (96.8 min)	›mean Time (96.8 min)	P value	‹mean Time (255.3 min)	›mean Time (255.3 min)	P value	‹mean Time (158.5 min)	›mean Time (158.5 min)	P value
No. of patients	29	21		33	17		31	19	
Men	9 (31.0%)	14 (66.7%)	0.013	13 (39.4%)	10 (58.8%)	0.192	14 (45.2%)	9 (47.4%)	0.879
Age (years ± SD)	69.47 ±13.26	70.95 ±13.25	0.694	68.61 ±12.56	73.94 ±14.17	0.274	69.39 ±12.18	71.21 ±13.25	0.639
Mean initial NIHSS score	15.28±8.08	17.48±5.55	0.288	15.61±5.85	17.35±9.27	0.419	16.35±5.39	15.95±9.52	0.847
Transferred from outside ED	10 (34.5%)	8 (38.1%)	0.793	9 (27.3%)	9 (52.9%)	0.073	8 (25.8%)	10 (52.6%)	0.055
Primary ED presentation	19 (65.5%)	13 (61.9%)		24 (72.7%)	8 (47.1%)		23 (74.2%)	9 (47.4%)	
Hypertension	20 (69.0%)	16 (76.2%)	0.574	24 (72.7%)	12 (70.6%)	0.873	22 (71.0%)	14 (73.7%)	0.836
Diabetes mellitus	5 (17.2%)	4 (19.0%)	0.870	6 (18.2%)	3 (17.6%)	0.963	7 (22.6%)	2 (10.5%)	0.282
Atrial Fibrillation	10 (34.5%)	10 (47.6%)	0.349	13 (39.4%)	7 (41.2%)	0.903	13 (41.9%)	7 (36.8%)	0.721
Coronary artery Disease	8 (27.6%)	6 (28.6%)	0.939	8 (24.2%)	6 (35.3%)	0.410	8 (25.8%)	6 (31.6%)	0.659
Dyslipidemia	7 (24.1%)	10 (47.6%)	0.084	10 (30.3%)	7 (41.2%)	0.442	11 (35.5%)	6 (31.6%)	0.777
Congestive Heart Failure	6 (20.7%)	8 (38.1%)	0.176	4 (12.1%)	10 (58.8%)	0.001	6 (19.4%)	8 (42.1%)	0.082
Cigarette smoking	6 (20.7%)	8 (38.1 %)	0.176	8 (24.2%)	6 (35.3 %)	0.410	8 (25.8%)	6 (31.6 %)	0.659
Previous stroke/ TIA	4 (13.8%)	5 (23.8%)	0.363	4 (12.1%)	5 (29.4%)	0.132	5 (16.1%)	4 (21.1%)	0.715
Intracerebral hemorrhage*	10 (34.5%)	10 (47.6%)	0.277	12 (36.4%)	8 (47.1%)	0.362	12 (38.7%)	8 (42.1 %)	0.884
mRS 0-2 at discharge	12 (41.4%)	5 (23.8%)	0.196	15 (45.5%)	2 (11.8%)	0.017	12 (38.7%)	5 (26.3%)	0.369
mRS 0-2 at 3 months#	13 (44.8%)	6 (28.6%)	0.233	14 (42.4%)	5 (29.4%)	0.121	12 (38.7%)	7 (36.8%)	0.397
Mortality at 3 months#	6 (20.7%)	8 (38.1%)	0.142	5 (15.2%)	9 (52.9%)	0.017	5 (16.1%)	9 (47.4%)	0.058

Key: IV = intravenous; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack. * = 3 symptomatic hemorrhages; # = 9 patients were lost to follow up.

Figure 1: Time (minutes) from symptom onset to treatment for IV rt-PA and endovascular treatment in patients who received IV rt-PA followed by endovascular treatment.



to determine the magnitude of difference in time to treatment between the two treatments and whether the delay with ET can obscure the comparative benefit with higher recanalization. Such comparative studies have not been possible due to difference in characteristics among those receiving IV rt-PA and those receiving ET. The patients who receive both IV rt-PA and ET represent a unique population by using its control and avoid confounding by patient-related factors. The focus of our study was to compare time to treatment between IV rt-PA and ET in patients with AIS who received both treatments and identify any effects on clinical outcome.

Methods

AIS patients presenting to our facilities who received IV rt-PA from 2005 until 2009 were identified from a prospective database collected at our facilities supplemented by retrospective chart review. The details of the database have been provided in a previous publication.9 The infrastructure of our program has been described in a previous publication.10 Briefly, the neurology residents, vascular neurology fellows, endovascular fellows, and stroke and endovascular staff form the acute response team at our comprehensive stroke centers. When emergency medical services or emergency department (ED) staff activates a "Stroke Code," all parties are paged (modeled after an alert system that is established for patients suffering from acute myocardial infarctions requiring coronary reperfusion). Radiology is also notified to prepare a room for an urgent computed tomography (CT) scan of the head. During regular weekday business hours, all parties are in-house. On nights and weekends, residents are in-house with fellows and staff on home call. Notifying all parties of a "Stroke Code" initially offers a unique advantage in preventing potential delays in time sensitive therapies.

We reviewed the charts to collect risk factors information including hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, dyslipidemia, congestive heart failure, cigarette smoking, and prior stroke or transient ischemic attack (Table 1). The severity of deficit in a patient with AIS was determined by utilizing the NIHSS score. A comparative analysis was performed with patients who had received both IV rt-PA and ET using the same patients as case and control. Outcome from treatment was assessed by use of the modified Rankin Scale (mRS) ascertained at the time of discharge. Good outcome was defined as mRS score of 0 to 2 at time of discharge and at three months follow up. The rate of mortality at three months was also measured. For patients who were lost to follow up, the Social Security Death Index was used to assess vital status post-hospitalization. Patients who suffered mortality during admission were carried forward as mortality at three months follow up.

Complications were defined as asymptomatic or symptomatic intracerebral hemorrhages (ICH) within 24 hours of treatment ascertained by a review of all CT scans routinely performed at 24 hours in all patients by one of the investigators (GA). Symptomatic ICH was based on the presence of concurrent neurological deterioration defined as an increase in the NIHSS score of 4 or greater.

Statistical analysis was performed using SAS 9.1 software (SAS Institute Inc., Cary, NC). Descriptive statistics were expressed as means with standard deviation, medians with intra-quartile range, and frequency (percentages). Continuous and categorical variables were compared using

Table 2: Characteristics of patients based on location of presentation..

	Outside ED presentation	Primary ED presentation	P value
No. of patients	18	32	
Age (years ± SD)	71.56 ± 15.6	69.25 ± 11.7	0.556
Admission NIHSS score (mean ± SD)	16 ± 7.8	16.3 ± 6.9	0.916
Time (min) to IV (mean ± SD)	93.5 ± 37.3	98.7 ± 40.9	0.657
Time (min) to endovascular (mean ± SD)	299.3 ± 102.8	230.5 ± 76.7	0.010
Time (min) from IV to endovascular (mean ± SD)	205.8 ± 98.7	131.8 ± 57.8	0.002
mRS 0-2 at discharge	7 (38.9%)	10 (31.3%)	0.7568
mRS 0-2 at 3 months#	6 (37.5%)	12 (48%)	0.5396
Mortality at 3 months#	7 (43.8%)	7 (28%)	0.3322

Key: ED= emergency department;IV = intravenous; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack. # = 9 patients were lost to follow up.

ANOVA and chi-square tests, respectively.

Table 3: Characteristics of patients based on time of day of presentation..

	Presentation during working hours (8a-5p, Mon-Fri)	Presentation on nights and weekends	P value
No. of patients	23	27	
Age (years ± SD)	69.57 ± 13.4	70.52 ± 13.1	0.801
Admission NIHSS score (mean ± SD)	15.78 ± 8.4	16.56 ± 6.1	0.707
Time (min) to IV (mean ± SD)	82.96 ± 31.2	108.67 ± 42.1	0.020
Time (min) to endovascular (mean ± SD)	252.83 ± 110.1	257.41 ± 75.8	0.863
Time (min) from IV to endovascular (mean ± SD)	169.87 ± 100.8	148.74 ± 62.9	0.371
mRS 0-2 at discharge	8 (34.8%)	9 (33.3%)	0.914
mRS 0-2 at 3 months#	10 (43.5%)	9 (33.3%)	0.647
Mortality at 3 months#	7 (30.4%)	7 (25.9%)	0.910

Key: IV = intravenous; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack. # = 9 patients were lost to

Results

There were 179 patients who received IV rt-PA between 2005 and 2009; 50 patients (mean age 73 years, 44% men [n = 22]) received additional ET (Figure 1). The mean symptom onset to treatment times for IV rt-PA (MOTI) was significantly shorter compared with mean symptom onset to treatment times for endovascular treatment (MOTE) (96.8 ± 39.3 minutes versus 255.3 ± 92.2 minutes, $p < 0.001$) among these 50 patients.

There were 29 patients who received treatment in lesser time than the MOTI of 96.8 minutes (Table 1). There was a trend in difference in rates of good outcome at discharge when comparing patients receiving treatment in lesser or greater than MOTI ($p = 0.196$). There was no statistical significance between the two groups when comparing mRS at discharge, mRS at three months follow up, and mortality at three months.

The MOTE was 255.3 minutes. There were 33 patients who received treatment in less time than the MOTE. Patients receiving ET in lesser time than the mean time had a higher rate of favorable outcome at discharge than those receiving it after the mean time (45.5% versus 11.8%, $p = 0.017$). There was also a significantly lower rate of mortality at three months (20% versus 56.3%, $p = 0.017$) among these patients as well. The mean time interval between initiation of IV rt-PA and ET was 158.5 minutes. Lower time interval between IV rt-PA and ET than the mean time yielded lower rates of mortality at three months ($p = 0.058$).

Of the 50 patients, 18 patients (mean age 73 years, 50% men [n = 9]) were transferred from an outside facility, and 32 patients (mean age 70 years; 44% men [n = 14]) presented to the ED of our comprehensive stroke centers (Table 2). Nine of the 18 patients had IV rt-PA initiated at an outside facility (drip-and-ship paradigm). The MOTI for transferred and primary ED patients was similar (93.5 minutes versus 98.7 minutes, $p = 0.657$). The MOTE was significantly longer in transferred patients compared to primary ED arrival patients (299.3 minutes versus 230.5 minutes, $p = 0.01$). There was no significant trend in outcome when comparing the time of day during which patients present (Table 3). Of the 50 patients, there were 23 patients who presented within Monday through Friday between the business hours of 8:00 AM and 5:00 PM; the other 27 patients presented either afterhours or on weekends. While there was a significant difference in time to IV thrombolytic treatment (82.96 ± 31.2 minutes versus 108.67 ± 42.1 minutes, $p = 0.020$) favoring quicker treatment times for patients who presented during business hours, there was no significance in time to ET or time from IV to ET in strata defined by presenting time and day.

Discussion

As both IV rt-PA and ET are time dependent, the effect of factors that delay time from symptom onset to treatment must be minimized. Patients who live alone, present to the hospital by private vehicle rather than ambulance, and seeking medical attention from a primary care provider first rather than presenting to an ED have delays in time to thrombolytic treatment.[11-13] There has been suggestion that patients living in a large catchment area also may experience a delay in treatment.[13] Stroke education in the community may help play a role in potentially reducing time to thrombolytic treatment in eligible patients.[12] In-hospital delay also exists as there is a potential delay in treatment when patients wait to be evaluated by a physician or to be taken to CT scan.[13] Another cause for delay to treatment is presentation to a facility without a stroke protocol or with physicians not familiar or comfortable administering IV rt-PA.[14-16] Access to a comprehensive stroke center by either telephone or video consultation can be beneficial in aiding physicians at these outside facilities in starting IV rt-PA prior to transfer to stroke centers.[14] Therefore, patients presenting to outside centers who are eligible for both IV and ET should be started on IV rt-PA without delay prior to transferring to a center that provides endovascular therapies. Increasing communication between a comprehensive stroke center and its referring hospitals can encourage quicker treatment times.

The time of day and weekend presentation can also impact the time interval from symptom onset to treatment. Interestingly, there was a significant difference in time to IV rt-PA in our study based on time of day, but no significant difference to time to endovascular therapy. The finding appeared paradoxical because we expected the treatment time for IV rt-PA to not be affected significantly by time of day, but rather the time to ET may be prolonged due to the availability of personnel and equipment. It remains unclear why such a discrepancy exists, but one possibility is the experience and level of comfort of the residents on call during the evenings and weekends.

The goal for this study was to compare symptom onset to treatment times for IV rt-PA and ET in patients with AIS and identify any effect on outcome related to delay in treatment. We found that the MOTI was significantly shorter compared with the MOTE (96.8 ± 39.3 minutes versus 255.3 ± 92.2 minutes, $p < 0.001$) among a group of patients with essentially similar baseline demographic and clinical characteristics. While the finding is not surprising, the magnitude of difference (two folds greater) between the symptom onset to treatment times between the two modalities was concerning. Furthermore, the delay in initiating ET was associated with higher rates of death and disability among the treated patients. The larger delays in symptom onset to treatment times for ET but not IV rt-PA treatment raise concerns about transfers for primary ET among patients with AIS.[17]

Over the last ten years, a substantial effort has been directed towards improving the technology and

technique of ET for AIS. Substantial emphasis has been placed on achieving recanalization in AIS. Hussein et al. suggested that despite successful recanalization, some patients do not improve due to irreversible ischemic injury that was not evident on the initial CT scan; this led to the idea of futile recanalization.18 However, the "time to microcatheter" remains an unaddressed area in improving outcomes following ET. Due to a wide variability in "time to microcatheter" among facilities, there is a need to standardize treatment time measurements before making it a quality parameter for comprehensive stroke centers.19

ET for AIS patients has been proven to be effective in reperfusion of occluded arteries, especially large arterial occlusions that are somewhat resistant to IV therapy.4-6,20 However, this should not be used as primary treatment as it can delay time to treatment; rather it should be used as a supplement to IV thrombolysis. IV rt-PA is still the only approved treatment for AIS. There is not enough data about the effectiveness of ET in comparison with IV rt-PA; therefore, it has not been used as a core metric but rather a supplemental metric for comprehensive stroke centers per American Heart Association/American Stroke Association (AHA/ASA) Stroke Council guidelines. The AHA/ASA recommendations for defining metrics for comprehensive stroke centers also identifies the time to treatment as a potential measure to be ascertained within a comprehensive stroke center.21 Once there is enough evidence for the efficacy of ET, data can then be used to establish a treatment window for time to ET. A "time to microcatheter" parameter can then be implemented at all comprehensive stroke centers.

Limitations of our study include retrospective design with a small sample size, which decreases the power to detect differences among subgroups of patients for endpoints such as mortality and good outcome.

Conclusions

Our study suggests that reducing the time to treatment for ET, when used as a supplement to the rapid use of IV rt-PA, has the potential to improve outcomes among AIS patients. A considerable difference in symptom onset to treatment times between IV and ET was observed among patients with AIS, and in particular those who were transferred from another facility.

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