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Research Article

Right Hemisphere Ischemia is more likely to Cause Falsely "Mild" Symptoms and Poor Outcomes without Thrombolysis

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Abstract

Background: Rapidly improving or mild symptoms is the most common reason that acute stroke patients arriving within the approved time window are not treated with intravenous tissue-type plasminogen activator (IV tPA). We reviewed outcomes at discharge for patients excluded from IV tPA because of rapidly improving or mild symptoms, with the aim of being better able to identify patients who may benefit from thrombolysis.

Methods: All patients between April 2006 and June 2010 from our center who did not receive IV tPA with "rapidly improving or mild symptoms" as the reason for exclusion were identified. Poor outcome was defined as hospital discharge to location other than home or inability to ambulate independently at discharge.

Results: There were 66 patients excluded from tPA treatment because of rapidly improving or mild symptoms. Eleven patients (16.7%) had poor outcomes. In 6 patients (9%), poor outcome was due to neurologic deficit. All 6 patients with neurologic deficits had right hemisphere strokes, and one also had cerebellar infarcts.

Conclusions: Patients presenting with rapidly improving or mild symptoms do not universally have good outcomes. This may be particularly true in the case of right hemispheric ischemia where deficits are not fully reflected by NIHSS score. If a patient with a low NIHSS score is otherwise a candidate for tPA, a more detailed exam is warranted to better identify potentially disabling deficits that might benefit from thrombolysis.

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ABBREVIATIONS

IV tPA: Intravenous recombinant tissue plasminogen activator; **GWTG**: Get with the Guidelines database; **NIHSS**: National Institutes of Health Stroke Scales

INTRODUCTION

Intravenous recombinant tissue plasminogen activator (IV tPA) remains the only approved treatment for acute ischemic stroke. Despite its approval for use in stroke for 15 years, only 3.4% to 5.2% of patients with acute stroke receive tPA [1]. The most common reason patients are excluded from treatment, when they arrive within the approved time window, is "rapid improvement or stroke severity too mild." [2-5]. It has previously been found that patients excluded from IV thrombolysis for mild or rapidly improving symptoms do not universally have a benign course [6-9]. As many as 20-32% have a poor outcome at discharge.

We reviewed outcomes of consecutive patients from a single center who did not receive thrombolytic therapy with "rapidly improving or minor symptoms" as the reason for exclusion from treatment, with the aim of being better able to identify patients in this group who may benefit from thrombolysis.

METHODS

We used the AHA/ASA "Get with the Guidelines" (GWTG) database to identify consecutive acute ischemic stroke patients between April 2006 and June 2010 from University of Maryland Medical Center who did not receive IV tPA. The GWTG data in combination with the medical record were reviewed to identify those patients with "rapid improvement or stroke severity too mild" as the only reason documented by the treating vascular neurologist for exclusion from thrombolytic therapy. If the documentation indicated fluctuation of symptoms, with more severe symptoms prior to time of thrombolytic

treatment decision, patients were considered to be in the "rapid improvement" subset. Demographic data, stroke risk factors, baseline National Institutes of Health Stroke Scale (NIHSS) scores, discharge location and ambulatory status were recorded prospectively in the GWTG database and extracted for this study. The medical records of patients with poor outcome were reviewed retrospectively to determine details of hospital course, infarct location, and reasons for poor outcome. Poor outcome was defined as hospital discharge to location other than home or inability to ambulate independently at discharge. Patients were considered to have a non-neurologic reason for poor outcome if hospital notes documented no or only very minor residual neurological deficits and other medical or social reasons as the primary factors in patient not being discharged to home.

Differences between the groups were assessed using the two-tailed Fisher exact test for dichotomous variables and the unpaired t-test for continuous variables with the InStat 3 program (version 3.1a; Graph Pad Software).

RESULTS AND DISCUSSION

During the study period, 1036 patients with acute ischemic stroke were admitted to our center. Of those, 168 patients (16%) were treated with IV tPA. There were 66 patients excluded from treatment with IV tPA for "rapid improvement or stroke severity too mild". Eleven (16.7%) of those patients had poor outcomes. Patients with poor outcomes were significantly older in comparison to patients with good outcomes (mean age 72.4 years vs. 63 years; p=0.0021), but there were no other significant differences in baseline characteristics (Table 1).

Of the 11 patients with poor outcome, 5 were attributed to deconditioning and poor general medical condition and 6 to continued neurologic deficits (Table 2). All six patients with continued neurologic deficit and poor outcome had right hemisphere infarcts. Patient 6 had a right frontal lobe infarct and also a left superior cerebellar infarct, which required a posterior craniotomy and decompression to treat malignant cerebellar edema.

Of the 6 patients with poor outcome due to continued neurologic deficit, 4 had improving deficits and 2 had consistently mild deficits, whereas all 5 of the patients with non-neurologic reason for poor outcome had consistently mild deficits from onset to the time of evaluation for thrombolytic therapy. This trend toward patients with poor outcome being more likely to have improving rather than consistently mild deficits was not statistically significant due to small numbers. Possible reasons for this trend toward worse outcome in the "rapidly improving" group include: overly optimistic interpretation of the degree of improvement or assumption that improvement seen would continue rather than plateau, or patients with more severe deficits at some point being more prone to worsen back to prior deficit severity. We were unable to explore this further due to lack of detailed documentation of serial examinations.

The predominance of right hemisphere infarcts in our patients with poor outcomes due to neurologic deficit is striking. Known predictors of poor outcome at discharge in patients excluded from thrombolysis for improving or mild symptoms include: an initial NIHSS ≥10 with rapid improvement, and a persistent large vessel occlusion [7,8]. We know of no previous studies reporting right hemisphere localization as a possible predictor of poor outcome in this patient population. It has been shown that the NIHSS assigns more points for equal volume infarcts of left hemisphere compared to the right [10,11]. Therefore, a low NIHSS may conceal a large right hemisphere stroke burden that could result in poor outcome if not treated. A study comparing baseline NIHSS score and long term outcome showed this may also be true for posterior circulation strokes, as patients had a

Table 1: Patient Characteristics.

	Total	Good	Poor	p
n (%)	66	55 (83.3)	11 (16.7)	
Age (y)	63	61	72.4	0.0021
Male Gender	29 (43.9%)	26 (47.2%)	3 (27.3%)	0.323
Ethnicity				
White	34 (51.5%)	30 (54.5%)	4 (36.4%)	0.333
Non-White	27 (40.9%)	25 (45.5%)	7 (63.6%)	
Time to Presentation (min)	93.4	96.4	78.4	0.2521
NIHSS (mean)	2.7	2.6	3.1	0.6543
Rapid Improvement	24 (36.4%)	20 (36.4%)	4 (36.4%)	1.000
Hypertension	49 (74.2%)	40 (72.7%)	9 (81.8%)	0.713
Hyperlipidemia	28 (42.4%)	25 (45.5%)	3 (27.3%)	0.331
Diabetes Mellitus Type 2	15 (22.7%)	11 (20.0%)	4 (36.4%)	0.254
Smoker	24 (36.4%)	18 (32.7%)	6 (54.5%)	0.189
Coronary Artery Disease	17 (25.8%)	14 (25.5%)	3 (27.3%)	1.000
Atrial Fibrillation	9 (13.6%)	7 (12.7%)	2 (18.2%)	0.638
CHF	1 (1.5%)	1 (1.8%)	0	1.000
Prior stroke	18 (27.3%)	13 (23.6%)	5 (45.5%)	0.155

Abbreviations: **NIHSS**: National Institutes of Health Stroke Scales; **CHF:** Congestive Heart Failure.

Table 2: Patients with Poor Outcome.

Pt.	Age	Sex	NIHSS	Rapidly Improving	Discharge Location	Location of Stroke	Reason for Poor Outcome
1	70	M	5: 2 gaze 1 LUE 2 LLE	Yes	Acute Rehab	Right MCA	Continued Neurologic Deficit
2	74	F	7: 2 LOC 2 VF 2 face 1 dysarthria	Yes	Acute Rehab	Presumed Right MCA	Continued Neurologic Deficit
3	80	F	2: 1 face 1 neglect	Yes	Acute Rehab	Right parietal lobe	Continued Neurologic Deficit
4	68	F	5: 1 face 1 LUE 2 RUE 1 sensory	Yes	Home with assistance	Right Corona Radiata and External Capsule	Continued Neurologic Deficit
5	67	F	5: 1 RUE, 1 RLE 1 LUE, 1 LLE 1 neglect	No	Acute Rehab	Right thalamus and posterior limb of internal capsule	Continued Neurologic Deficit
6	54	M	2: 1 sensory 1 dysarthriaa	No	Acute Rehab	L Superior Cerebellum R Frontal Lobe	Worsening of neurologic deficits; posterior craniotomy
7	79	F	1: 1 face	No	Acute Rehab	Right MCA	Deconditioning
8	73	F	2: 1 face 1 dysarthria	No	Acute Rehab	TIA	Deconditioning
9	79	M	2: 2 gaze	No	Acute Rehab	Right Frontal Lobe	Deconditioning
10	87	F	3: 1 face 1 RUE 1 RLE	No	Home with assistance	Left Thalamus	Deconditioning Family declined rehab
11	79	F	0	No	Acute Rehab	TIA	Deconditioning

Abbreviations: **NIHSS**: National Institutes of Health Stroke Scales; **L(R)UE**: left (right) upper extremity; **L(R)LE**: left (right) lower extremity; **LOC:** level of consciousness, **VF:** visual fields; **TIA:** transient ischemic attack.

higher probability of an unfavorable outcome with relatively low NIHSS scores in the posterior circulation compared to anterior [12].

Age was the only baseline characteristic with a significant difference between patients with good vs. poor outcome. This may represent a bias against giving IV tPA in elderly patients. Or it could reflect the poorer baseline medical status in the elderly, with older patients generally doing worse regardless of the intervention. This is supported by our finding that in five of the 11 patients with poor outcome it was due to general deconditioning rather than specific new neurologic deficits.

In agreement with prior reports, we found rapidly improving patients and patients with continuously mild symptoms may not be at equal risk for poor outcomes [7,8]. At the time when the patients in this study were entered into the Get with the Guidelines database, the "mild" and "rapidly improving" reasons for not treating with tPA were combined into one data point. Since then, they have been separated into two different categories. So, outcomes in these patients can be more easily tracked going forward to confirm this finding. Limitations of our study include the use of a retrospective chart review and small numbers.

CONCLUSION

Our findings support the practice of not using a strict NIHSS threshold when making treatment decisions, especially for patients who present with non-dominant hemisphere symptoms. Before the decision is made to withhold thrombolytics because the symptoms are "mild" or "rapidly improving", a more detailed exam may be warranted to better assess for deficits that are not picked up on the initial NIHSS but may still contribute to disability. Treatment with tPA for patients with mild stroke has been found to be safe, supporting more liberal treatment in this patient population [13,14]. Recent analysis estimated that about 2000 patients per year would not be disabled (with a savings of $200 million/year) if patients with NIHSS less than 5, and otherwise eligible, were treated with tPA [15]. More research is needed to help guide treatment in this large group of stroke patients.

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