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PATIENT REFUSAL OF THROMBOLYTIC THERAPY FOR SUSPECTED ACUTE ISCHEMIC STROKE

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Abstract

Objective—To determine factors associated with patients refusing IV t-PA for suspected acute ischemic stroke (AIS), and to compare the outcomes of patients who refused t-PA (RT) with those treated with t-PA.

Methods—Patients who were treated with and refused t-PA at our stroke center were identified retrospectively. Demographics, clinical presentation, and outcome measures were collected and compared. Clinical outcome was defined as excellent (mRS: 0–1), good (mRS: 0–2), and poor (mRS: 3–6).

Results—Over 7.5 years, thirty (4.2%) patients refused t-PA. There were no demographic differences between the treated and RT groups. The rate of RT decreased over time (OR 0.63, 95% CI 0.50 – 0.79). Factors associated with refusal included a later symptom onset to emergency department presentation time (OR 1.02, 95% CI 1.01 – 1.03), lower NIHSS (OR 1.11, 95% CI 1.03 – 1.18), a higher proportion of stroke mimics (OR 17.61, 95% CI 6.20 – 50.02) and shorter hospital stay (OR 1.32, 95% CI 1.09 – 1.61). Among patients who were subsequently diagnosed with ischemic stroke, only length of stay was significantly shorter for refusal patients (OR 1.37, 95% CI 1.06 – 1.78). After controlling for mild strokes and stroke mimics, clinical outcome was not different between the groups (OR 1.61, 95% CI 0.69 – 3.73).

Conclusion—The incidence of patients refusing t-PA has decreased over time, yet it may be a cause for t-PA under-utilization. Patients with milder symptoms were more likely to refuse t-PA. Refusal patients presented later to the hospital and had shorter hospital stays. One out six refusal patients (16.6%) had a stroke mimic.

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INTRODUCTION

Stroke remains the leading cause of adult long-term disability and morbidity¹. Early revascularization of salvageable brain tissue with intravenous tissue plasminogen activator (IV t-PA / t-PA) is the single, FDA approved therapy to improve outcomes in patients with AIS. National stroke registries show that only 4% to 7%² of AIS patients receive t-PA. Various factors account for its low utilization rate³. One of the most widely acknowledged barriers is the short time window for maximizing the beneficial effects of t-PA⁴⁻⁷. Other reasons include lack of public awareness about stroke symptoms, skepticism and concern of emergency physicians to utilize thrombolytic therapy in AIS, a high percentage of mild strokes, and a lack of or poor availability of services^{8,9}.

Another factor that may contribute to low t-PA rates is patient refusal, which has not been formally studied. Refusal adds a layer of complexity to the already multifaceted process of selecting optimal patients who would benefit from t-PA. The American Heart Association (AHA) guidelines state: "Although written consent is not necessary before administration of rtPA for treatment of stroke, a full discussion of the potential risks and benefits of treatment with rtPA with the family and the patient if possible is recommended." The verbal consent process provides an opportunity for the patient and/or caregivers to refuse t-PA even in the absence of any other contraindications. Our objective was to identify factors associated with patients refusing t-PA. We characterized the incidence, demographics, severity, and outcome of patients who were eligible yet refused IV t-PA for suspected AIS. We tested whether any of the demographics, clinical presentation and outcome of patients with suspected AIS who refuse IV t-PA would differ from those who receive it. Initiating an investigational process for patient refusal of t-PA might identify reasons for refusal to standard of care treatment and lead to the implementation of measures to maximize the utility of proven therapies for AIS.

METHODS

Our stroke service maintains a registry of all suspected stroke patients evaluated at our center. An initial query was designed to identify all patients who presented to our hospital within three hours of symptom onset between January 1st 2004 and March 31st 2011. Patients for whom the only reason for not being treated with IV t-PA was registered as refusal were classified as the RT group. For comparison, all patients were chosen during the same time period who were treated with IV t-PA at our center within 3 hours of symptom onset. Further data were obtained by re-abstraction of clinical information from electronic medical records. Data were evaluated for quality by re-abstraction of key variables. We collected demographics, baseline National Institute of Health Stroke Scale (NIHSS) scores and discharge outcomes.

At our hospital, all patients presenting to emergency department (ED) having suspected acute stroke symptoms are evaluated by a fellow in vascular neurology or a stroke faculty member. Patients meeting criteria for treatment based on FDA and AHA guidelines are verbally consented for IV t-PA. The consent entails explanation of potential risks and benefits of thrombolytic therapy. Though there is no written script for consent within the 3

hour window, we rehearse how to obtain consent together as a group. For the purpose of this investigation, we included those patients in the RT group who had presented to our ED, were evaluated within three hours of symptom onset, and were suspected to have acute focal cerebral ischemia. They fulfilled treatment criteria based on AHA guidelines, were offered treatment, but the only reason for not receiving t-PA was patient and / or family's refusal. All patients who initially reported to other hospitals before transfer to our center and those who presented beyond three hours of symptom onset were not included in analyses.

For patients whose neurological deficit prevents them from agreeing to treatment, verbal consent is usually obtained from a legally authorized representative (LAR) either in person or on the phone. If family members are not immediately available, treatment is instituted by the physician using best clinical judgment and documented. University of Texas Institutional Review Board and the Memorial Hermann Hospital at Texas Medical Center ethics committee approved the study.

STATISTICAL METHODS

All statistical analyses were done using STATA version 11¹⁰. Univariate descriptive analyses were performed to determine the differences in demographic characteristics, severity of stroke at presentation, and outcome parameters between the RT and the treatment groups. NIHSS scores were dichotomized for further analyses and mild strokes were defined as presentation NIHSS score of ≤ 4 . Modified Rankin Scale (mRS) scores were classified into excellent outcome (mRS: 0–1), good outcome (mRS: 0–2) and poor outcome (mRS: 3–6). The normality of the continuous variables was assessed using histograms and Shapiro – Wilk test. Based on the shape and scale of measurements, appropriate measures of central tendency were used. Two sample t tests or Wilcoxon rank-sum tests were used to compare groups. Logistic regression models were fitted to identify factors associated with refusing t-PA. Factors that were clinically relevant or statistically significant at 20% level in the univariate analysis were considered for multivariate modeling. Likelihood ratio test was performed to assess for significance of a parsimonious model vs. the full model. Regression diagnostics were performed on the final model along with testing for the fit of the model using Hosmer and Lemeshow goodness of fit test.

The crude association between refusal and excellent outcome was evaluated for the effect of potential confounders. Initial assessment was performed by stratifying the data on potential confounders and testing for homogeneity of the odds ratios across strata. Factors deemed as confounders were controlled for in the final logistic regression model. Level of significance for all hypotheses testing was set at 0.05.

Results

We identified 30 patients who refused t-PA treatment as per our inclusion criteria. Based on equivalent inclusion criteria, we identified 683 patients who were treated with IV t-PA during the same period of investigation. This translated into a refusal rate of 4.2% (i.e., one t-PA refusal for every 23 eligible patients). There was a decline in frequency of refusal over

the period of our inquiry (OR 0.63, 95% CI 0.50 – 0.79), the average being four refusals per year (Fig 1).

Demographics of refusal and treated groups

There were no significant gender differences between the RT and treated groups. Likewise, no statistically significant differences between the two groups were observed for other demographic characteristics (Table 1).

Clinical presentation and Outcome

Significant differences were observed in clinical presentation and outcome parameters for the two groups. Median onset to door time was 81.5 minutes for the RT group and 63.0 minutes for the treated group. The median NIHSS score at presentation was significantly lower in the RT group as compared with the treated group (7.5 vs. 12.0). Furthermore, 7 out of 30 patients in the refusal group had mild deficits (defined as presentation NIHSS $\leq$ 4); this proportion was significantly higher when compared to the proportion of mild deficits in the treated group (23.3% vs. 11.2%). The proportion of patients presenting with aphasia or neglect was significantly higher in the treatment group as compared with the RT group. Eight patients (26.6%) had aphasia at presentation in the RT group, whereas 335 out of 683 (46.9%) had aphasia in the treated group ($p = 0.02$). Likewise, 5 patients (16.6%) had neglect in the refusal group as compared to 266 patients (39.0%) in the treated group ($p = 0.01$).

The median discharge modified Rankin Scale (mRS) score for RT was 2.5 and was statistically different ($p = 0.008$) from that of the treated group's discharge mRS of 3.0. Among patients who refused t-PA, 43.3% had an excellent outcome, whereas 22.5% of treated patients had an excellent outcome (OR 2.63, 95 CI 1.25 – 5.54). This difference however was not significant when adjusted for baseline NIHSS and non-stroke diagnoses. The difference between the two groups for good and poor outcome was not statistically significant.

Subgroup analysis for patients having a stroke diagnosis

Of the 30 patients who refused IV-tPA, 18 (60.0%) had a clinical and / or radiological diagnosis of stroke, 7 had a transient ischemic attack (TIA), and 5 were discharged with non-stroke diagnoses (stroke mimics). The five stroke mimics were discharged with the diagnoses of seizure, urinary tract infection, encephalitis, complicated migraine, and non-specific musculoskeletal symptoms. The proportion of stroke mimics was significantly higher in the RT group as compared with the treated group (16.0% vs. 3.9%, OR 15.59, 95% CI 6.18 – 37.84). The median presentation NIHSS for refusal patients with a diagnosis of stroke was 9 and not statistically different from the median NIHSS score of 12 for patients who were diagnosed with stroke in the treated group. Sub group analysis for patients diagnosed with stroke in the RT and the treated group found no difference in discharge mRS - a 3 for both groups. The proportion of ischemic stroke patients having excellent outcome in the RT group (33.3%) was not statistically different from that of the treated group. Likewise the proportion of patients with a poor outcome was also similar in the RT and treated groups (61.1% vs. 64.3%). These results are summarized in (Table 2).

Multivariate analysis for factors associated with patient refusal

We analyzed factors associated with refusal using logistic regression based multivariate analysis. Our final parsimonious multivariate model indicates that RT patients have significantly longer onset to door time, they have greater odds of being a stroke mimic, their length of stay in the hospital is significantly shorter and with each increasing year there are lesser odds of observing a refusal patient (Table 3). Though presentation NIHSS score was significantly lower for the RT group in univariate analysis, it was no longer significant in the final model. However, based on the final model, we observed that the probability of refusing t-PA decreases as the presentation NIHSS score increases (Figure 2).

Modeling for comparison of outcomes between the RT and treated groups

The unadjusted odds ratio for excellent outcome in the RT group was 2.63 (95% CI 1.25 – 5.54). We evaluated mild strokes (NIHSS = 4) and stroke mimics as possible confounders in the refusal – excellent outcome relationship. Stratification based on stroke mimics and mild strokes generated odds ratios different from the crude and the test for homogeneity did not reveal significant differences in odds ratios of the strata. Therefore, in our final model, we adjusted for mild strokes as well as stroke mimics. After this adjustment, the odds ratio for excellent outcome was not statistically significant (Table 4).

DISCUSSION

To our knowledge, this is the first study to investigate patient refusal of IV t-PA in the setting of suspected acute ischemic stroke. We found that at our center one patient with suspected AIS refuses t-PA for every 23 patients treated. Such high numbers underscore the importance of studying the phenomenon of patient refusal in greater detail. Given the high incidence of stroke with 25% presenting to treatment centers within less than 2 hours of onset, a refusal rate of around 5% would translate into 8,750 patients refusing treatment annually¹¹. There was a diminishing trend in refusal over a period of 7 years and this decline may be attributable to the increasing awareness among the general public about the warning signs of AIS, the need for treatment, and proven benefit of t-PA.

The patients who refused IV t-PA in our study had a significantly higher proportion of stroke mimics with milder deficits captured on the NIHSS. Consequently, this group had an overall improved outcome as compared to the treated group and their duration of hospital stay was shorter. Improved outcomes in stroke mimics treated with IV t-PA as compared to AIS patients have been previously reported¹². The outcomes in our patient cohorts were not statistically different when we compared refusals and treated patients who ultimately were diagnosed with ischemic stroke. The refusal patients still had milder strokes and later presentations to the hospital even when controlling for non – stroke diagnoses.

It is possible that patients presenting with mild deficits did not perceive their symptoms to be grave enough to warrant treatment with t-PA and did not want to accept the risk of hemorrhage. Based on our modeling, late presentation time did not seem to confound the relationship of mild stroke and t-PA refusal. Furthermore we investigated patients who were well within the time window of treatment. This leads us to believe that both mild strokes and

later presentation time may independently be associated with refusal. We determined that the treated patients had a higher proportion presenting with aphasia and neglect as compared to the patients who refused treatment. Therefore, it is unlikely that refusal was due to an under-appreciation of stroke severity or inability to communicate to RT patients since they had less neglect and less language deficits.

Since a number of the refusal patients had a stroke mimic, it is possible that the treating physician may have suspected an alternate diagnosis and, therefore, gave a more ominous rather than favorable interpretation of the risks vs. benefits of t-PA. Patients likely show marked differences in reaction to the variation in tone, style, and presentation of the treating physician. In fact, we appreciate the effect of variation in physicians' approach to patients as one possible factor that has led to a decline in t-PA refusal over years. It could be that there is change in behavior of our physicians, who have become more persuasive over time, particularly so in cases of mimics and mild strokes. Our stroke fellows and attending faculty initially may not have been very excited about treating presumed stroke mimics and mild strokes but several recent studies have reported the safety of t-PA in these groups¹²⁻¹⁴.

In cases where patients were not competent to consent and no legally authorized representative was available, the treating physician at our center instituted thrombolytic therapy using their best clinical judgment. It is possible that some of these patients may not have wanted to consent for treatment and accordingly the actual incidence of refusal could be higher.

The ethics of refusing standard of care has been examined in the past^{15, 16}. Authors have stated that physicians harbor a moral responsibility to address competence of refusing patients and then make an attempt to rectify patient's false beliefs. Despite adequate efforts, a competent patient persistently refusing a treatment should only receive coercive intervention if their refusal would result in harm to any other individual or the society at large. Though there are mixed opinions on the paternalistic model of medical care, most investigators tend to agree that establishing competence, applying the principle of liberty, and judging harm to other individuals or society is where the physician's role ends. The above-described model holds greater relevance in non-acute settings. Since time from onset of stroke symptoms to treatment is a predictor of favorable outcome, we feel that the need to make quick decisions is imperative. Consequently, it is important to develop practical and applicable guidelines for physicians to follow in cases of t-PA refusal. We recommend assessment of patients' competence in cases of refusal. If not competent or the patient cannot provide consent, a legally authorized representative should be sought immediately to make a decision.

Although we found a low refusal rate, at a population level refusal may be a significant and under-studied factor in treatment decisions to use IV t-PA for AIS. While our data did not show significantly different outcomes for refusal patients compared with treated patients, the favorable outcome of these patients is likely directly related to the mild severity of their deficits.

The major limitation of this study is that it is a historic retrospective chart review. Paucity of the past electronic medical records did not afford us an opportunity to ascertain if patients or their caregivers made the refusals. Moreover, the retrospective nature of our study design only allows us to report the observed differences as mere associations. Nevertheless, we have reasonably established that refusal of IV t-PA therapy has continued to be a recurring theme over the span of several years.

In conclusion, our analysis reveals a low and declining incidence of t-PA refusal over the period of the last seven years. The refusal rate is significant enough to warrant further investigation as a cause contributing to low utilization of t-PA therapy for AIS. There is a need to study refusal in the behavioral, cultural, social, psychological, and ethical context. We suggest creating a standardized approach to non-competent patients refusing t-PA in the setting of suspected AIS.

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Figure 1.
Rate of patient refusal of IV t-PA per year

Figure 2.
Probability of refusal as a function of presentation NIHSS

TABLE 1

Demographic characteristics of patients in the RT and treated groups

Demographic Characteristics	RT (n = 30)	Treated Group (n = 683)	OR	95% CI
<i>Gender</i>				
<i>Female</i>	19 (63.3%)	328 (48%)	1.86	0.87 – 3.98
<i>Race</i>				
<i>White</i> *	14 (46.6%)	327 (47.9%)		
<i>Black</i>	12 (40.0%)	241 (35.3%)	1.16	0.52 – 2.55
<i>Hispanic</i>	3 (10.0%)	101 (14.8%)	0.69	0.19 – 2.46
<i>Others</i>	1 (3.3%)	13 (1.9%)	1.79	0.22 – 14.71
<i>Age – median years (IQR)</i>				
	65.5 (55 – 77)	66 (51 – 74)	1	0.97 – 1.02

* White has been used as reference category for race

TABLE 2

Comparison of the RT and treated groups with respect to clinical presentation and outcomes: Univariate analysis

Comparison of all diagnoses (infarct, TIA, & stroke mimics)				
	RT (n = 30)	Treated Group (n = 683)	OR	95% CI
Clinical Presentation and Outcome Parameters				
<i>Onset to Presentation time – median minutes (IQR)</i>	81.5 (50 – 125)	63 (47 – 84)	1.02	1.01 – 1.04
<i>NIHSS at presentation – median</i>	7.5	12	1.11	1.03 – 1.18
<i>Mild Strokes (NIHSS ≤ 4)</i>	7 (23.3%)	76 (11.1%)	2.42	1.01 – 5.83
<i>Length of Stay (days) – median</i>	3	5	1.32	1.09 – 1.61
<i>Discharge mRS – median</i>	2.5	3	1.32	1.07 – 1.64
<i>Excellent Outcome (mRS 0 – 1)</i>	13 (43.3%)	153 (22.5%)	2.63	1.25 – 5.54
<i>Good Outcome (mRS 0 – 2)</i>	15 (50.0%)	251 (36.9%)	1.71	0.82 – 3.55
<i>Poor Outcome (mRS 3 – 6)</i>	15 (50.0%)	429 (63.0%)	0.58	0.28 – 1.21
Sub Group Analysis for patients with discharge diagnosis of stroke				
	RT (n = 18)	Treated Group (n = 655)	OR	95% CI
Clinical Presentation and Outcome Parameters				
<i>Onset to Presentation time – median minutes (IQR)</i>	71.5 (49 – 124)	63 (47 – 84)	1.02	1.01 – 1.03
<i>NIHSS at presentation – median</i>	9 (6 – 11)	12 (7 – 18)	1.05	0.97 – 1.13
<i>Mild Strokes (NIHSS ≤ 4)</i>	2 (11.1%)	71 (10.8%)	1.02	0.23 – 4.54
<i>Length of Stay (days) – median</i>	3.5 (2 – 5)	5 (4 – 8)	1.37	1.06 – 1.78
<i>Discharge mRS – median</i>	3 (1 – 4)	3 (2 – 4)	1.15	0.88 – 1.51
<i>Excellent Outcome (mRS 0 – 1)</i>	6 (33.3%)	140 (21.4%)	1.83	0.67 – 4.96
<i>Good Outcome (mRS 0 – 2)</i>	7 (38.8%)	233 (35.6%)	1.14	0.43 – 2.99
<i>Poor Outcome (mRS 3–6)</i>	11 (61.1%)	421 (64.4%)	0.86	0.33 – 2.27

TABLE 3

Factors associated with t-PA refusal: Multivariate Analysis

Factors associated with t-PA Refusal	OR	95% Confidence Limits	
Non Stroke Diagnosis (Stroke Mimics)	17.61	6.20	50.02
Longer Onset to Door Time	1.02	1.01	1.03
Year of presentation	0.63	0.50	0.79
Longer Length of stay (days)	0.83	0.63	0.98

TABLE 4

Logistic regression model fitted for odds of excellent outcome in refusal patients

Model Characteristics	OR	95% Confidence Limits	
Refusal	1.61	0.69	3.73
Stroke Mimics	2.99	1.46	6.08
Mild Strokes	2.89	1.78	4.69