Published in final edited form as:

J Stroke Cerebrovasc Dis. 2014 ; 23(10): 2914–2919. doi:10.1016/j.jstrokecerebrovasdis.2014.07.049.

A CASE CONTROL STUDY OF THE EFFECTIVENESS OF TISSUE PLASMINOGEN ACTIVATOR ON 6 MONTH PATIENT-REPORTED OUTCOMES AND HEALTHCARE UTILIZATION

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Abstract

We examined the benefit of tissue plasminogen activator (tPA), delivered as part of usual stroke management, on patient-reported outcomes and healthcare utilization. Using a case control design, patients who received tPA as part of usual stroke management were compared with patients who would have received tPA had they arrived to the hospital within the therapeutic time window. Data were collected from surveys 6 months post stroke using standardized patient-reported outcome measures and questions about healthcare utilization. Demographic and medical data were acquired from hospital records. Patients were matched on stroke severity, age, race, and gender. Matching was done with 1:2 ratio of tPA to controls. Results were compared between groups with 1-tailed tests due to directionally-specific hypothesis in favor of the tPA group.

The tPA (n = 78) and control (n = 156) groups were matched across the variables, except for stroke severity, which was better in the control group; subsequent analyses controlled for this mismatch. The tPA group reported better physical function, communication, cognitive ability, depressive symptomatology, and quality of life/participation compared to the control group. Fewer people in the tPA group reported skilled nursing facility stays, emergency department visits, and re-hospitalizations after their stroke compared to controls. Reports of other post-acute services were not different between groups. While it is known that tPA reduces disability, this is the first study to demonstrate the effectiveness of tPA in improving meaningful, patient-reported outcomes. Thus, use of tPA provides a large benefit to the daily lives of people with ischemic stroke.

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Keywords

Stroke; Patient-reported outcomes; Comparative Effectiveness; Healthcare Utilization; Tissue Plasminogen Activator; tPA; Function

INTRODUCTION

The definitive NINDS rt-PA trial showed that persons who received tissue plasminogen activator (tPA) were 30% less likely to experience disabling symptoms at 90 days post stroke compared to those who had received a placebo.(1) Economic modeling from this same dataset indicated that the increased hospitalization costs associated with tPA are offset by savings from decreased post-acute expenditures, including institutionalization.(2) Additional efforts since have refined our understanding of tPA delivery,(3-7) developed national guidelines for use of tPA,(8), and implemented national programs to increase and improve tPA use.(9-11)

Efficacy data have come primarily from clinical impairment scales, such as the NIHSS, and from brief disability scales, such as the modified Rankin Scale, at 90 days post stroke. While these scales are useful for large-scale clinical trials, they fail to capture many outcomes that are meaningful to stroke survivors.(12) Collection of outcome data at 90 days post stroke may be somewhat early, as people have just completed post-acute rehabilitation services and have yet to fully return to daily life.(12) Effectiveness data, indicating benefits of tPA as part of routine clinical care, have also been collected at 90 days post stroke and have used the same brief scales.(13-16) Thus, there are minimal data to confirm the effectiveness of routine use of tPA on patient-centered outcomes beyond 90 days post stroke. Given the resources invested at multiple levels across healthcare systems for implementation of tPA protocols, it is necessary to understand its effectiveness with respect to the daily lives of stroke survivors.

The purpose of this study was to examine the real-world benefit of tPA, delivered as part of usual stroke management, on patient-reported outcomes and healthcare utilization. This was a pragmatic comparative effectiveness study conducted at a large, academic medical center. Given the abundance of efficacy data, we hypothesized that, at 6 months post stroke, persons who received tPA would report better function across multiple domains (physical function, cognition, communication), greater return to pre-stroke activities, and lower post-acute healthcare utilization compared to people who did not receive tPA.

METHODS

This study was a retrospective case control analysis of prospectively collected data, comparing outcomes in patients who received tPA as part of usual care with patients who would have received tPA had they arrived to the hospital within the therapeutic time window, i.e. criteria other than time were met. At present, all persons with a diagnosis of stroke or transient ischemic attack (TIA) from our hospital are contacted for a follow-up survey at 6 ($\pm$ 2 weeks) months after the event. People with stroke have provided informed consent to have their data stored and used for research. Washington University Human

Research Protection Office has approved the database and studies using de-identified data. This sample includes people who received care at our hospital plus others who received tPA at a partner hospital and were transported to our facility for further care.

Data in this report were collected between February 2011 and October 2013. Follow-up surveys were completed via telephone (47% of sample), mail (33%) or email (21%). Surveys could be completed by the patient or a caregiver. If a patient experienced another stroke within the 6 month follow-up period, the survey was completed 6 months from the new stroke. No survey data were collected from deceased individuals or their caregivers. Demographic and medical data regarding the stroke were acquired from hospital records, including National Institute of Health Stroke Scale (NIHSS)(17) at time of initial presentation to the emergency department, age, gender, race, marital status, education level, insurance coverage, date of stroke, side of stroke, and pre-morbid Barthel Index.(18, 19)

Patient-reported outcomes were collected using valid, reliable, standardized questionnaires by trained personnel. Assessments administered were: the Stroke Impact Scale (SIS), a measure of self-perceived abilities in multiple domains affected by stroke(20-24); the Patient Health Questionnaire 9-item version (PHQ-9), a measure of depressive symptomatology; (25, 26) the Reintegration to Normal Living Index (RNL), a measure of satisfaction with one's abilities to engage in daily life (27, 28); and the Modified Rankin Scale, a measure of global disability.(29-31) Modified Rankin Scale scores were dichotomized to those with good outcome (scores of 0 or 1) and those with poor outcome (scores of 2 or higher). Additional items in the survey included questions about falls,(32-34) return to driving and return to work.(35)

Healthcare utilization information was collected via self-report. This was chosen over extracting data from administrative records because the utilization records of our stroke population from a large geographic area are not contained in one or only a few databases, nor did we want to limit our sample to just people covered by Medicare. Procedures to minimize self-report bias (either over- or under-reporting) were utilized as much as possible. (36) Patients reported if they had an inpatient rehabilitation facility (IRF) stay, a skilled nursing facility (SNF) stay, utilized home health services (HH), utilized outpatient rehabilitation services, the number of physician office visits, visited an emergency department, and/or were re-admitted to a hospital after discharge from the initial stroke-induced hospitalization.

tPA was administered according to hospital protocol, largely following the NINDS tPA trial and ECASS III trial inclusion/exclusion criteria.(1, 3, 37) Patients who received tPA and completed 6 month surveys were matched to patients with completed surveys who did not receive tPA. To be considered a match, the potential control had to satisfy the medical criteria (1, 3, 37) to receive tPA but arrive to the hospital outside of the therapeutic time window (beyond 4.5 hrs). Patients receiving tPA and controls were matched on initial NIHSS score (± 2 pts), age (± 5 yrs), race, and gender. Matches were only searched for within ± 12 months of date of stroke, in case any changes in hospital policies or programs had influenced care or outcomes. Matching was performed using a 1:2 ratio of tPA to controls. Personnel who collected survey data were separate and independent from

personnel who assigned matches, and each was blinded to the activities and data of the others.

Statistical analyses were performed using SAS software (Version 9.3 of the SAS System for Unix, SAS Institute, Cary, North Carolina, USA). Descriptive statistics were calculated for all variables. In order to examine how well the tPA and control groups were matched, student's t-tests were performed to compare groups for continuous variables and Chi-squared tests were used for dichotomous variables. Because the two groups were not matched for NIHSS score ($p=0.002$, control < tPA), we adjusted for this in subsequent statistical models. The differences in continuous and nominal outcome variables between groups were analyzed by general linear models (PROC GLM). Logistic regression models were used for analyses of categorical outcomes. Statistical significance was set at $p < 0.05$. One-tailed tests were used due to the directionally-specific hypotheses in favor of the tPA group.

RESULTS

The overall proportions of people completing the survey are provided in Table 1. Persons receiving tPA completed the survey at the same rate as the entire hospital stroke and TIA population ($X^2 = 4.11$, $p = 0.39$), indicating that there was no obvious selective bias in survey responders. Surveys were completed by patients themselves 91% of the time in the tPA group vs. 85% of the time in the control group ($X^2 = 1.68$, $p = 0.22$). Matched characteristics between the tPA group and the control group are shown in Table 2. Subjects were well matched on age, gender, race, pre-morbid Barthel Index and other variables. Lesion distributions were different between groups with a lower percentage of right sided lesions and a higher percentage of lesions classified as unknown in the control group. The groups were unmatched for NIHSS, with increased stroke severity, i.e. higher NIHSS scores, in the tPA group ($p = 0.002$). We therefore controlled for NIHSS in the subsequent analyses.

Six-month outcomes from patient self-report and the statistical comparisons between groups are provided in Table 3. Compared to the control group at six months, the tPA group had better physical function, cognition, communication, and quality of life/participation (SIS domains). PHQ-9 scores indicated less depressive symptomatology in the tPA group, but the difference was small. People in the tPA group had slightly more satisfaction with their abilities (RNL scores), less disability (modified Rankin Scores), and reported fewer falls. The percentage of people who reported returning to driving and working were not different between groups, in the smaller subset of people who were driving and working pre-stroke.

Self-reported healthcare utilization data and the statistical comparisons between groups are provided in Table 4. There was a trend toward fewer people in the tPA group reporting a stay in an inpatient rehabilitation facility. A larger proportion of the control group had a post-acute skilled nursing home stay. Use of home health services, outpatient rehabilitation services, and physician office visits were similar across groups. The tPA group reported fewer emergency department visits and fewer re-hospitalizations in the 6 month period after their stroke.

DISCUSSION

These data indicate the effectiveness of tPA on patient-reported outcomes and some measures of post-acute healthcare utilization at 6 months post stroke. The magnitudes of the between group differences were clinically meaningful for most outcome measures, such as a 12 point difference in physical function and a 9 point difference in quality of life/participation on the Stroke Impact Scale.(20) Utilization of the more costly healthcare services, i.e. skilled nursing facility stays, emergency department visits, and rehospitalizations, were lower in the tPA group. Our data builds upon previous reports of 90-day effectiveness (13-16, 38) to show benefit at 6 months with respect to functional domains, quality of life, and healthcare utilization that are important for daily life.

We were able to detect clinically-meaningful changes in patient-reported outcomes with a relatively small sample size. While the small sample size and single site limit generalization of results, tPA must have a powerful influence on outcomes because its benefit could be detected in patient self-report measures at 6 months post stroke. Interestingly, the patient-reported benefit spanned nearly all measured domains, such as cognition and communication, and not just physical function. Effectiveness in non-motor domains is an important finding because other tPA effectiveness data have been collected with the Modified Rankin Scale, a scale that is nearly entirely focused on disability in the motor domain.(39) Moreover, tPA in this study was delivered as a part of routine clinical care, not via a rigorously controlled research protocol. Our results therefore fully support ongoing efforts to increase access to tPA to as many eligible patients as possible.

The overall proportion of people completing the survey was low (Table 1). It was difficult to reach the more severely affected patients, particularly those permanently institutionalized. Likewise, it was difficult to reach some very mildly affected patients, as they were busy with life and often not interested in completing a survey. Because the rate of completion did not differ in the patients who received tPA compared to the overall hospital population, it is probable that any biases introduced by low response rates would have a similar effect on both groups. The low response rates limited our ability to detect a difference between groups on the questions of return to driving and return to work. These are outcomes that are highly important to patients. It is not possible to determine if the lack of differences seen here is due to a restricted sample for these questions (footnote in Table 3), individual patient choices not to return to these activities, or economic reasons, such as lack of a vehicle or job opportunities.

Self-report is an appropriate methodology for collecting longer-term functional outcomes, but is less accurate for collecting post-acute healthcare utilization.(36) An advantage of the self-report method is that data are collected regardless of the person's insurance provider and regardless of where the person receives services, e.g. the re-hospitalization is counted even if a person with private insurance provider is admitted to a different hospital. Because our facility treats patients with stroke from a 5-state catchment area with many different service and insurance providers, it would have been impossible to gather these data from administrative records. The potential for individuals to over- or under-report their healthcare utilization is high. Self-report of salient service utilization in short time periods (6 months)

appears to be the most accurate, but specific data regarding who is likely to under-vs. over-report are on which services are not clear.(40-42) The likely effect on our results therefore is that there is more noise in the healthcare utilization measures, and not a differential bias of over- or under-reporting in one group vs. the other.

Despite the potential noise in the healthcare utilization data, we saw a clear difference in utilization of some of the more costly post-acute care services. A lower utilization of services, such as skilled nursing facility stays, emergency department visits, and re-hospitalizations would likely translate to a lower cost for healthcare services, although a formal cost-effectiveness analysis is beyond the scope of this report. Our healthcare utilization findings build upon the earliest 90-day cost-effectiveness data collected in the original randomized controlled trials,(1) to show a sustained benefit of tPA use.

A final limitation to consider is that there may have been other factors that influenced stroke outcomes and could have accounted for the differences seen here. One factor may be lesion side, with slightly fewer people with right-sided lesions in the control group. Other possible factors include unmeasured variables. For example, people in the tPA group could have had stronger social support at home or better access to transportation that enabled them to arrive at the hospital in time. These same factors could also have facilitated recovery, leading to better outcomes. While we found no between-group differences in who completed the survey, marital status, education level, and insurance, these simple variables are modest proxies for the complex constructs of socioeconomic status and social support networks. Additional work is needed to determine to measure social support networks, how they change over recovery, and how they influence outcomes.

Conclusions

While it is known that tPA reduces long-term disability, this is the first study to demonstrate the effectiveness of tPA in improving meaningful, patient-reported outcomes, such as physical function, cognition, and communication. These data indicate that use of tPA provides a large benefit to the daily lives of people with ischemic stroke and is a wise use of healthcare resources.

Acknowledgments

This work was supported in part by grant #7515-55 and its supplement #7843-77 from the Barnes Jewish Hospital Foundation, and NINDS P01 NS055977. Our thanks to the staff, administrators, and data entry team of Barnes Jewish Hospital, The Rehabilitation Institute of St. Louis, and Washington University for their enthusiasm, support, and efforts on this project. Special thanks to our stroke coordinators, Jill Newgent and James Franke, for their efforts in patient allocation.

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Table 1

Proportions of survey responders and non-responders across the hospital population

	Completed	Refused	Recurrent stroke	Deceased	Unable to reach [*]
Persons receiving tPA (n = 263)	30%	22%	9%	6%	33%
All persons with stroke or TIA (n = 2901)	26%	24%	5%	13%	32%

* Unable to reach despite multiple attempts to multiple numbers over a 1 month period

Table 2

Presenting characteristics for cases and controls

	tPA group (n = 78)	Control group (n = 156)	P value
NIHSS (median [IQR])	5 [6]	3 [5]	0.002
Age (yrs, mean $\pm$ SD)	65.1 $\pm$ 12.1	64.9 $\pm$ 13.3	0.88
Gender	42% female	42% female	0.99
Race	31% Afr. American 69% Caucasian	35% Afr. American 65% Caucasian	0.66
Pre-morbid Barthel Index (mean $\pm$ SD)	99 $\pm$ 4	98 $\pm$ 6	0.32
Side of lesion*	49% Right 33% Left 10% Unknown 8% Missing	37% Right 36% Left 23% Unknown 3% Missing	0.04
Marital status	49% married/sig. other 51% single/widowed	57% married/sig. other 43% single/widowed	0.27
Education level (yrs)	13.4 $\pm$ 2.5	12.6 $\pm$ 2.3	0.07
Insurance	57% federal/state [†] 33% private 10% none	59% federal/state [†] 33% private 8% none	0.90
Current or previous smoker	21%	22%	0.96
Hypertension	53%	51%	0.95
Coronary artery disease	19%	20%	0.98
Atrial fibrillation	6%	8%	0.85
Previous myocardial infarction	5%	8%	0.65
Previous stroke or TIA	22%	28%	0.49

NIHSS: National Institutes of Health Stroke Scale; TIA: transient ischemic attack

* From clinical database

[†] Medicare or Medicaid

Table 3

Comparison of patient-reported outcome data. Values are means $\pm$ SD unless otherwise indicated.

	tPA group	Control group	P value
SIS Physical Function	80 $\pm$ 21	68 $\pm$ 26	0.0001
SIS Cognition	81 $\pm$ 21	72 $\pm$ 26	0.001
SIS Communication	87 $\pm$ 19	82 $\pm$ 23	0.008
SIS Quality of Life/Participation	71 $\pm$ 29	62 $\pm$ 31	0.0005
PHQ-9	5.3 $\pm$ 6.0	6.3 $\pm$ 6.2	0.043
RNL	76 $\pm$ 20	72 $\pm$ 20	0.001
Modified Rankin Scale (%)	0, 1 = 47% 2 = 53%	0, 1 = 30% 2 = 70%	0.001
Number of falls (%)	0 = 71% 1 = 11% 2 = 18%	0 = 56% 1 = 21% 2 = 23%	0.035
Return to driving (%) [*]	69%	62%	0.20
Return to work (%) [*]	50%	42%	0.28

SIS: Stroke Impact Scale, range 0 – 100 with 100 = normal; PHQ-9: Patient Health Questionnaire, 9-item version quantifying depressive symptomatology, range = 0 – 27, with higher scores indicating worse symptoms; RNL: Reintegration to Normal Living index, quantifying satisfaction with abilities and converted to 0 – 100%, with higher scores = greater satisfaction.

^{*} Of the 196 people (62 tPA, 134 control) driving prior to the stroke, and of the 115 people (34 tPA, 81 control) working prior to the stroke.

Table 4

Comparison of self-reported healthcare utilization data. Values are % indicated the service was used.

	tPA group	Control group	P value
IRF stay	20%	31%	0.063
SNF stay	4%	16%	0.006
Home Health services	35%	36%	0.999
Outpatient Rehabilitation services	30%	38%	0.150
Physician office visits	1 = 8% 2-3 = 34% 4 = 57%	1 = 10% 2-3 = 35% 4 = 49%	0.585
Emergency Department visits	1 = 18% 2 = 11%	1 = 26% 2 = 21%	0.001
Rehospitalization	22%	34%	.040