Published in final edited form as:

J Stroke Cerebrovasc Dis. 2014 ; 23(10): 2527–2532. doi:10.1016/j.jstrokecerebrovasdis.2014.03.020.

Determinants of Early Outcomes in Patients with Acute Ischemic Stroke and Proximal Artery Occlusion

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Abstract

Background—Proximal artery occlusions (PAO) recanalize in only a small percentage of acute ischemic stroke (AIS) patients treated with intravenous tPA (IV tPA) alone, yet the benefits of adjunctive or substitutive intra-arterial therapy (IAT) in this patient subgroup are not well-established. We evaluated early post-stroke outcomes in a cohort of AIS patients with PAO categorized as "likely to benefit" from IAT using pre-specified criteria.

Methods and Results—Using a pre-specified protocol, 193 patients from our institutional stroke database admitted between 01/01/2007–12/31/11 were prospectively deemed LTB from IAT. Logistic regression was used to determine independent predictors of favorable (discharge to home or acute rehab) *versus* unfavorable (discharge to skilled nursing facility, hospice, or in-hospital mortality) outcome. Of the patients included, 29.5% received IV tPA only, 11.4% underwent IAT only, and 37.8% had both. Overall in-hospital mortality was 19.2%. In a univariate analysis, age (OR 0.95, 95% CI 0.93–0.98), IV tPA (OR 2.3, 95% CI 1.2–4.3), and history of atrial fibrillation (OR 0.5, 95% CI 0.28–0.97) were associated with outcome. Effect of IAT was not statistically significant (OR 1.3, 95% CI 0.7–2.3; $p=0.4$). In multivariate analysis, the only independent predictor of favorable outcome was IV tPA administration (OR 2.4, 95% CI 1.2–5.0). The odds of favorable post-stroke outcome were significantly lowered (OR 0.3, 95% CI 0.1–0.6; $p=0.0006$) in those receiving neither IV tPA nor IAT.

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Conflict(s) of Interest/Disclosures:

Dr. Jamie LaBuzetta, Dr. Syed Ali, Ms. Kaitlin Fitzpatrick, and Dr. Thabele Leslie-Mazwi have nothing to disclose.

Dr. Albert Yoo receives research support from Penumbra Inc and NIH/NINDS.

Dr. Joshua Hirsch is a shareholder in Intratech.

Dr. Lee Schwamm is on the CoAxia Advisory Board, the Lundbeck DIAS 4 Intl Steering Committee, and is a Medtronic advisor on device design. He has been involved with RTI Health for economic models of imaging in thrombolysis. He is a stroke systems consultant for the Massachusetts Department of Public Health.

Dr. Natalia Rost receives research support from the NIH/NINDS (K23 NS064052 and R01NS082285) and Genzyme Co.

Conclusions—In AIS patients with PAO thought most likely to benefit from IAT, IV tPA independently predicted favorable outcomes. These data reinforce the recommendation to provide early IV tPA to all eligible patients.

Keywords

stroke; tPA; endovascular treatment; outcome; proximal artery occlusion

Introduction

Current recommendations for acute ischemic stroke (AIS) therapy are based on the premise that reperfusion of at-risk brain tissue is essential for favorable clinical outcomes. Intravenous (IV) tissue plasminogen activator (tPA) has a proven benefit in patients suffering from acute ischemic stroke (AIS) ^(1,2), and is the only FDA-approved treatment available in the acute setting. The beneficial clinical effects of revascularization with IV tPA are sustained across various AIS populations ^(3–8). However, individual response to IV tPA varies depending on factors that include the location, size, and composition (fibrin-rich versus platelet-rich) of the clot ^(9–12).

While overall reported rates of recanalization in IV thrombolysis may reach 66% ⁽¹³⁾, these are significantly lower in the presence of proximal artery occlusion (PAO), ranging from 9–13% for internal carotid artery (ICA) ^(14–16) versus 12.5–47% for middle cerebral artery (MCA) ^(10,14,17–19). Given the importance of recanalization and time to clot dissolution for clinical outcome ^(13,17), therapies that improve the rate of recanalization in these proximal vessels are under intense investigation.

Among these therapies, intra-arterial therapy (IAT) such as mechanical thrombectomy and intra-arterial thrombolysis has been used by itself or as an adjunctive treatment in AIS with evidence of PAO. These endovascular procedures target occluded vessels, aiming to restore the blood flow, salvage cerebral tissue, and ultimately, improve clinical outcomes.

Rates of recanalization are significantly higher in patients undergoing IAT as compared to IV thrombolysis ⁽³⁾, with up to 66.7% and 74.1% revascularization rates for ICA and MCA respectively ⁽²⁰⁾. Although adjunctive IAT may be a cost-effective treatment option ⁽²¹⁾, the clinical benefits of IAT in patients with PAO are not well-established ⁽²²⁾. Even though patients who achieve reperfusion sooner have better outcomes ⁽²³⁾, the proportion of patients who achieve functional *independence* is similar between those treated with IV tPA and IAT only ^(24,25). This is particularly true in elderly patients ⁽²⁶⁾. Failure to select patients appropriately for IAT is commonly cited as a possible explanation for the lack of IAT association with favorable clinical outcomes.

In this study, we sought to assess predictors of early post-stroke outcomes in a thoroughly ascertained cohort of AIS patients with PAO prospectively deemed likely to benefit (LTB) from IAT based on pre-specified institutional criteria ⁽²⁷⁾.

Materials and Methods

Patient characteristics and categorization

This is a retrospective analysis of prospectively collected data. Consecutive AIS patients recorded from January 2007 to December 2011 in our institutional GWTG-Stroke database were reviewed. All AIS patients were considered for IAT based on a previously published institutional protocol ⁽²⁷⁾.

Patient characteristics on admission including demographics (age; gender), past medical history, details of clinical presentation (last seen well (LSW) time; stroke severity (NIHSS)), and neuroimaging characteristics were prospectively recorded. A vascular neurologist evaluated each patient. All patients underwent diagnostic parenchymal and vessel neuroimaging with CT and/or MR modalities upon arrival to the Emergency Department. Patients were deemed LTB from IAT if they presented with 1) NIHSS ≥ 8 , 2) evidence of a PAO (ICA, MCA M1, or proximal M2 segment) on CT or MR angiogram, 3) infarct size $<1/3$ territory (by head CT) or $<100\text{cc}$ (on MRI DWI sequence), and 4) if imaging was completed within 6 hours of LSW time. The institutional protocol does not contain an age cut-off. Patients in whom *all* criteria were met were defined as LTB.

Neuroimaging analysis and medical record review

For each subject considered LTB based on the IAT protocol criteria, additional medical record review was completed to elucidate other potential relationships between patient characteristics, clinical variables, therapy, and primary outcome. Total acute infarct volumes used in initial decision-making regarding IAT were calculated retrospectively using ABC/2 measurements ⁽²⁸⁾ on the MR DWI by a single investigator (JNL) blinded to clinical outcome data. All MR imaging was obtained with a 1.5T, whole-body MR scanner. Diffusion-weighted trace sequences had a 5mm thickness.

In addition, medical records were abstracted to identify the reasons for withholding IAT. Reasons for non-treatment were categorized as “family refusal” (patients were IAT candidates, but family or patient declined intervention), “technical challenge” (as determined by the endovascular team), “carotid dissection”, “clot burden” (as determined by endovascular team), “trial enrollment” (patient was enrolled in therapeutic trial and randomized to non-intervention), “advanced age” (older age cited as a significant contributor to deciding against IAT), “advanced directive” (IAT not compatible with previously expressed wishes), “rapid improvement” (an improvement in NIHSS to less than LTB cut-off of eight prior to intervention), “limited tissue at risk” (no determined mismatch between the actual and expected clinical exams; the stroke was felt to have been completed), “hemorrhagic conversion,” or “unclear/ unrecorded”. In many cases, multiple reasons were given for not pursuing IAT, and each reason was included.

Lastly, the treating vascular neurologist was abstracted from the data when available. For the purpose of this analysis, a level of experience based on the number of years in practice was assigned to each vascular neurologist as follows: level 1 (<4 years of experience), level 2 (4–8 years of experience) or level 3 (>8 years of experience).

Statistical analysis

The primary outcome was discharge destination. The secondary outcome was in-hospital mortality. Univariate and multivariate logistic regression analyses were used to determine independent predictors of “favorable discharge” (discharge to home or acute rehabilitation facility if the subject was deemed to have rehabilitation potential by the multi-disciplinary stroke team) *versus* “unfavorable discharge” (discharge to skilled nursing facility, hospice, or in-hospital mortality). Predictors of mortality were also analyzed separately. Of note, age was treated as a continuous variable.

The level of significance was set at $p < 0.05$ for all statistical analyses. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Ethics—All aspects of this study were approved by the local Institutional Review Board. The final decision to proceed with IAT required informed patient or health care proxy consent.

Results

Of 988 AIS patients arriving within 6 hours of LSW time to our ED from January 2007 until December 2011, 193 (19.5%) were considered LTB from IAT. Patient characteristics are presented in Table 1. Mean age of the cohort was 71.5 years (SD 15.3), and 54.4% of patients were female. Median NIHSS at the time of first evaluation was 16 (IQR 13–19). Median stroke duration at the time of presentation was 184 minutes (IQR 95–245). Medical co-morbidities included atrial fibrillation (33.7%), hypertension (65.8%), coronary artery disease (26.9%), hyperlipidemia (40.4%), diabetes mellitus (16.6%), and tobacco use (9.8%). Thirteen (6.7%) had suffered from a previous stroke. At baseline, 151 (78.2%) of LTB patients were ambulatory.

Median acute infarct volume (measured on DWI series) was 17.0cc (IQR 9.12–39.4). Only 154 patients were able to undergo MRI evaluation due to medical contraindications (e.g. pacemaker). Of these, 150 patients (97.4%) had DWI volume 70cc; 36 (23.4%) had DWI volume >40cc (range 1.26–138.2cc).

Treatment Modalities

Of the 193 patients considered LTB from IAT, 130 (67.3%) received IV tPA, and 95 (49.2%) underwent IAT. The median time from LSW to IV tPA was 1hour 37minutes (IQR 1h 15min – 2h 23min). Of the data available for IAT, median time from LSW to IAT was 5hours 18minutes (IQR 3h 37min – 6h 54min; n=83). In total, 29.5% of patients received IV tPA only, 11.4% underwent IAT only; 37.8% had both.

Outcomes and Predictors of Outcome in Patients LTB from IAT

Favorable primary outcome was achieved in 129 patients (66.8%). Overall, in-hospital mortality was 19.2%. Fourteen percent of LTB patients ambulated independently on discharge and went directly home.

In a univariate analysis, the odds of favorable outcome were greater in those who received IV tPA (OR 2.3, 95%CI 1.23–4.34), and lower in older individuals (OR 0.95, 95%CI 0.93–0.98) and those with atrial fibrillation (OR 0.52, 95%CI 0.23–0.97). The odds of in-hospital mortality were similarly greater with increasing age (OR 1.04, 95%CI 1.01–1.07) and a history of atrial fibrillation (OR 2.20, 95%CI 1.06–4.56). No association was found between outcome measures and acute infarct volume, IAT, or level of staff experience (Table 2).

The odds of favorable post-stroke outcome were significantly lowered (OR 0.3, 95%CI 0.1–0.6; $p=0.0006$) in those receiving neither IV tPA nor IAT.

In multivariate analysis, IV tPA administration independently increased the odds of favorable outcome (OR 2.42, 95%CI 1.19–4.95), while increasing age lowered these odds (OR 0.96, 95%CI 0.93–0.98) (Table 3). Neither age (OR 1.03, 95%CI 0.99–1.06) nor history of atrial fibrillation (OR 1.54, 95%CI 0.68–3.44) affected in-hospital mortality in a multivariate analysis (Table 4).

Attending level of experience

Thirteen patients (8.1%) were cared for by attending physicians with fewer than four years of stroke care experience; 92 patients (57.5%) by stroke attendings with four to eight years of experience; and 55 patients (34.4%) by stroke attendings with greater than eight years of experience. There was no effect of attending experience on outcome ($p>0.05$).

Reasons for non-treatment

There were 87 patients who were deemed LTB from IAT but did not undergo IAT. Descriptively, the reasons for not performing IAT in the LTB group were: neuroimaging features of limited tissue at risk (18.4%), family refusal (16.1%), late presentation or concerns about reliability of the reported LSW time (13.8%), rapid improvement (12.6%), extensive clot burden (10.3%), technical challenge (8.0%), reason unclear/unrecorded (6.9%), advanced age (5.7%), advanced directive (5.7%), carotid dissection (2.3%), hemorrhagic conversion (2.3%), and trial enrollment (2.3%).

In addition to these categories, six patients were initially felt not to be candidates based on prospective preliminary review of MRI DWI size. However, these patients met strict criteria for LTB with DWI size $<100\text{cc}$ (not necessarily DWI size $<1/3$ territory) at the time of retrospective review. The first patient had a DWI lesion size of 65cc and clot in the proximal M2 superior division. However, it was not clear that revascularization would have offered substantial benefit, and there was a higher risk of hemorrhage given the time lapse between tPA and IAT decision-making. Patients two and three had—respectively—85cc and 60cc lesions on MRI DWI, and did not have clear contraindications or reasons for not pursuing IAT. The fourth patient's lesion was 96cc, and IAT was not compatible with goals of care. Patient five had multifocal DWI changes consistent with embolic clot with further propagation, and also had signs of petechial hemorrhage on MRI. The sixth patient had several strokes of varying ages in bilateral hemispheres, but the largest stroke did not have clear evidence on neuroimaging for tissue at risk.

Discussion

In our evaluation of 193 patients deemed LTB from IAT, the only independent predictors of early post-stroke outcomes were age and administration of IV tPA. Given that IV tPA was the only modifiable predictor between the two, these findings reinforce the recommendation to provide early, rapid IV tPA to all eligible patients. IV tPA can be given quickly in many clinical settings—especially compared with IAT—and our data show that even in proximal, large artery occlusions, IV tPA should be first-line therapy despite literature showing lower recanalization rates when compared with IAT^(14,20).

We have selected discharge destination as the primary outcome in this analysis. This choice has several advantages, despite its limitations. Firstly, discharge destination is an easily understood, objective outcome measure. Secondly, this value can be systematically collected. In a large academic medical center, there are many outside hospital transfers for acute-stroke-level care. In these patients—many of whom were discharged back to their home regions—long-term follow-up measures are impractical to obtain. However, even in these patients, discharge destination is known. Thirdly, this is a measure that can be easily compared between institutions. Moreover, Quinn et al.⁽²⁹⁾ note that home-time assessment correlates with modified Rankin Score (mRS) at 90-day follow-up. Furthermore, discharge destination has a high predictive value for outcome at 3 months post-stroke⁽³⁰⁾. Nevertheless, other factors such as social support, cultural beliefs and financial resources can influence discharge destination⁽³⁰⁾. Therefore, the number of patients achieving a favorable outcome may be falsely elevated. Our mortality rate of 19.2% is comparable to other mortality rates reported in the literature for IV tPA and IAT^(5,7,22).

Previous studies indicated that early PAO recanalization is an important predictor of improved clinical outcomes⁽²³⁾. As a limitation of retrospective study design, recanalization rates were not evaluated in this analysis, as these data were not available for all patients. Since other studies do not usually supply recanalization rates from IV tPA alone, potential confounding may stem from adjustment for recanalization rates in the IAT arm only in the studies of post-stroke outcomes. Nevertheless, our time-to-treatment data highlight the importance of expediting attempts to recanalize the affected vessels. The data here demonstrate that in AIS patients with PAO, IV tPA—alone or with adjunct IAT—is an independent predictor of favorable early post-stroke outcomes; one mechanism through which this improvement may be achieved is a greater recanalization potential than previously suggested for IV tPA^(14–17,19).

The design of this study does not allow us to draw definitive conclusions regarding the efficacy of IAT; instead, it validates the use of IV tPA in all AIS patients, including those with PAO. Lack of significant effect of IAT on outcome in this analysis may in part be explained by a relatively small sample size and, consequently, insufficient statistical power to detect an effect of IAT. Other possibilities include residual confounding, unaccounted selection bias, or an interaction between the IV tPA and IAT. In spite of this, our data do not contradict the findings of the Interventional Management of Stroke III trial⁽²²⁾, where there was no significant effect of IAT on outcome at 90-day follow-up when comparing IV tPA and IV tPA *plus* IAT despite good recanalization rates⁽²⁶⁾.

Further clinical trials are necessary to explore the potential role for IAT in stroke therapy. For instance, the utility of IAT in patients who are ineligible to receive IV tPA is not yet defined. Furthermore, the role of stent retrievers needs to be better elucidated. None of the patients in this cohort were treated with these newest-generation devices. However, Leker et al. ⁽³¹⁾ showed improved functional outcome using the Solitaire device compared with IV tPA. Although it would have been worthwhile to expand our data set to include some of these newer devices in the analysis, a significant change in our institutional approach to the IAT process in 2012 prevented a meaningful direct comparison between the data included here and more contemporary data. Future randomized clinical trials will be best positioned to answer the questions with regard to the outcome related to treatment using a specific device or technique.

To reduce confounding introduced by different practice patterns in patient selection for IAT, we used an institutionally-defined protocol that has been shown to increase the rates of appropriate referral for endovascular treatment for AIS patients deemed LTB from it ⁽²⁷⁾. This uniform approach to a patient-selection strategy for IAT is validated in current analysis, as no significant effect of acute stroke staff involved in decision-making regarding IAT was demonstrated.

Our data review revealed two patients who were initially not deemed LTB, but in whom retrospective strict application of the criteria and lack of other precluding factors would have changed their categorization to LTB. In these two patients, it was felt that the volume of infarcted territory was $>1/3$, and this factor was used to argue against them being LTB. However, measurement of DWI size using the ABC/2 method revealed volumes $<100\text{cc}$. These findings are instructive. First, a uniform and objective, volumetric radiographic criteria must be used going forward. Secondly, the variability in acute infarct size measurement should be considered. Prior reports demonstrated the importance of acute stroke volume measured on DWI to be a critical predictor of outcomes after IAT ^(32,33). In general, the importance of using final DWI lesion versus recanalization rate when evaluating outcome measures ^(32,34) should be considered. In our analysis, acute DWI volume was not independently associated with post-stroke outcomes. This might be in part explained by the generally small infarct size among the study subjects.

In conclusion, early, rapid IV tPA is critical in eligible patients, and should be the first-line intervention even for PAO. These results are applicable to clinical practice, quality of care, and patient outcomes. Future studies of IAT are warranted by the current state of equipoise between treatment options in acute cerebral ischemia following IV tPA or outside of the IV thrombolysis window in a carefully selected patient population.

Acknowledgments

This study was supported by the National Institute of Neurological Disorders and Stroke (NINDS), the American Heart Association Get With The Guidelines-Stroke (GWTG-Stroke).

Sources of Funding:

Natalia Rost is supported by the National Institute of Neurological Disorders and Stroke (K23NS064052 and R01NS082285).

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Table 1

Clinical characteristics of patients designated as likely to benefit from intra-arterial therapy (n=193)

Variable	
Age (<i>years</i>)	71.5(SD 15.27)
Stroke Duration (<i>minutes</i>)	184(IQR 95–245)
NIHSS (<i>points</i>)	16(IQR 13–19)
DWI Volume (<i>cc</i>)	17.0(IQR 9.12–39.4)
	N (%)
Gender (<i>female</i>)	105(54.4)
Atrial Fibrillation	65(33.7)
Coronary Artery Disease	52(26.9)
Diabetes	32(16.6)
Dyslipidemia	78(40.4)
Hypertension	127(65.8)
Prior Ambulation	151(78.2)
Prior Stroke	13(6.7)
Tobacco Use	19(9.8)
DWI volume ≤70cc	150(97.4)*
DWI volume >40cc	36(23.4)*

Abbreviations: DWI = diffusion weight imaging; NIHSS = National Institutes of Health Stroke Scale

* The number of MRI images available for analysis was fewer than the total number of patients (n=154)

Table 2

Univariate predictors of outcomes in patients likely to benefit from intra-arterial therapy

Variables	Favorable Discharge [†]		Mortality	
	OR	95%CI	OR	95%CI
Age	0.95	0.93–0.98*	1.04	1.01–1.07*
Stroke Duration	0.08	0.001–7.29	0.58	0.003–114.7
NIHSS	0.95	0.89–1.01	1.06	0.98–1.14
DWI Volume	1.00	0.99–1.02	1.01	0.99–1.03
Intra-arterial tPA	1.3	0.7–2.3	1.67	0.81–3.45
Intravenous tPA	2.32	1.23–4.34*	0.75	0.36–1.59
Gender	0.81	0.44–1.49	1.71	0.81–3.6
Diabetes	0.58	0.27–1.26	1.52	0.62–3.72
Dyslipidemia	0.99	0.54–1.82	1.01	0.49–2.09
Coronary Artery Disease	0.92	0.47–1.79	1.89	0.89–4.04
Tobacco Use	1.97	0.63–6.21	0.21	0.03–1.65
Atrial Fibrillation	0.52	0.28–0.97*	2.20	1.06–4.56*
Prior Stroke	1.13	0.33–3.80	0.001	0.001–999.9

Abbreviations: DWI = diffusion weight imaging; NIHSS = National Institutes of Health Stroke Scale; tPA = tissue plasminogen activator

* p-value <0.05

[†] defined as discharge to acute care rehab or home

Table 3

Multivariate predictors of favorable discharge

Variables	Favorable Discharge [†]	
	OR	95%CI
Intravenous tPA	2.42	1.19–4.95*
NIHSS	0.94	0.87–1.01
Age	0.96	0.93–0.98*
Atrial Fibrillation	1.00	0.48–2.06
Diabetes	0.58	0.26–1.32

Abbreviations: NIHSS = National Institutes of Health Stroke Scale; tPA = tissue plasminogen activator

* p-value <0.05

[†] defined as discharge to acute care rehab or home

Table 4

Multivariate predictors of in-hospital mortality

Variables	Mortality	
	OR	95%CI
Intra-arterial tPA	1.90	0.87–4.15
NIHSS	1.05	0.96–1.13
Age	1.03	0.99–1.06
Gender	1.69	0.76–3.74
Coronary Artery Disease	1.83	0.81–4.10
Tobacco Use	0.38	0.05–3.15
Atrial Fibrillation	1.54	0.68–3.44

Abbreviations: NIHSS = National Institutes of Health Stroke Scale; tPA = tissue plasminogen activator

*
p-value <0.05