Post-IV thrombolytic headache and hemorrhagic transformation risk in acute ischemic stroke

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Abstract

Background: Headache during or soon after administration of IV tissue plasminogen activator (tPA) in patients with acute ischemic stroke (AIS) is a concern for hemorrhagic transformation (HT). However, no data are available regarding the incidence of HT in these patients or the prognostic indication of these headaches. We examine the importance of tPA-associated headaches among AIS patients in terms of HT rates and clinical outcomes. **Methods:** AIS patients treated with IV tPA at a comprehensive stroke center between January 2007 and November 2012 were retrospectively reviewed for documented tPA-associated headache in the first 24 hours post-tPA. We compared the headache and nonheadache groups for differences in various clinical and radiologic outcomes.

Results: Of the 193 patients, 63 (32.6%) had tPA-associated headache. Headache patients (HP) were younger than nonheadache patients (NHP) (mean $\pm$ SD, 59.5 ± 17.4 years vs 69.9 ± 15.5 years, $p < 0.0001$), and 53% of HP were men, compared to 49.2% of NHP ($p = 0.537$). Comorbid conditions did not differ between the 2 groups. There were no statistical differences between HP and NHP in admission NIH Stroke Scale (NIHSS) score (11.2 ± 5.7 vs 11.5 ± 5.5 , $p = 0.646$), NIHSS score at 24 hours (6.5 ± 5.7 vs 7.4 ± 6.9 , $p = 0.466$), NIHSS score at discharge (6.7 ± 10.1 vs 8.1 ± 11.6 , $p = 0.448$), HT (12.7% vs 18.4%, $p = 0.3$), cervical artery dissection (4.7% vs 5.38%, $p = 0.764$), length of hospitalization (6.29 ± 5 days vs 6.35 ± 4.7 days, $p = 0.935$), and disposition. **Conclusion:** tPA-associated headache does not predict increased risk of HT and has no other prognostic importance in patients with AIS. Prospective studies with a larger cohort may be needed to further explore this relationship. *Neurol Clin Pract* 2016;6:22-28

IV tissue plasminogen activator (tPA) was approved by the US Food and Drug Administration for acute ischemic stroke (AIS) in 1995, and the rate of thrombolytic therapy has been on the rise since.¹⁻³ Intracerebral hemorrhage (ICH) is an infrequent but feared complication associated with thrombolytic therapy that can result in neurologic

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deterioration and mortality. Development or worsening of headache during or soon after IV tPA administration in patients with AIS can be a concern for hemorrhagic transformation (HT). In some clinical settings, this concern may result in either interruption or discontinuation of thrombolytic treatment, which nullifies its benefit. However, to date no sufficient data explore this association. The purpose of this study is to evaluate the relationship and prognostic importance of headache and adverse events, in particular HT risk, in AIS patients treated with IV tPA.

METHODS

Patients who received IV tPA at a comprehensive stroke center between January 2007 and November 2012 were identified from a prospectively maintained database for AIS patients. Basic demographic information (age, sex, and race/ethnicity) and data regarding stroke risk factors present before onset of stroke symptoms (e.g., hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, previous stroke/TIA, congestive heart failure, and coronary artery disease) were collected from hospital records. Stroke severity on admission was assessed by the NIH Stroke Scale (NIHSS) score. IV tPA was administered using standard dosing protocol and a follow-up noncontrast head CT or brain MRI was obtained in all patients at 24 hours to rule out intracranial hemorrhage. Neurology house staff evaluated each patient before and after treatment, and a follow-up neurologic examination including NIHSS was performed daily. NIHSS data from admission, 24 hours posttreatment, and discharge were collected. Occurrence of ICH was determined from the radiologic studies, including CT head or special brain

Figure Graphical presentation of age of patients with/without headache receiving IV tissue plasminogen activator (tPA) for ischemic stroke

Table 1 Baseline demographics and clinical characteristics among ischemic stroke patients treated with IV tPA with or without headache

	IV tPA without headache	IV tPA with headache	p Value
No. of patients	130	63	
Men	64 (49.2)	34 (53.9)	0.537
Age, y, mean $\pm$ SD	69.9 $\pm$ 15.5	59.5 $\pm$ 17.4	<0.0001
Age strata, y			0.001
<50	16 (12.3)	21 (33.3)	
50-59	17 (13.1)	14 (22.2)	
60-69	28 (21.5)	10 (15.8)	
70-79	25 (19.2)	7 (11.1)	
≥ 80	44 (33.8)	11 (17.5)	
Initial NIHSS score strata			0.992
<10	57 (43.8)	28 (44.4)	
10-19	59 (45.4)	28 (44.4)	
≥ 20	14 (10.7)	7 (11.1)	
Underlying mechanism of stroke ^a			0.833
Large vessel	29 (23.2)	17 (28.8)	
Cardioembolic	51 (40.8)	19 (32.2)	
Lacunar infarct	17 (13.6)	8 (13.6)	
Cryptogenic	10 (8.0)	5 (8.5)	
Unclassified	18 (14.4)	10 (16.9)	
Dissection	5 (3.8)	3 (4.7)	0.765
Length of hospital stay, d, mean $\pm$ SD	6.35 $\pm$ 4.7	6.29 $\pm$ 5.0	0.935
Comorbid conditions			
Hypertension	75 (58.1)	35 (55.5)	0.734
Diabetes mellitus	24 (18.4)	12 (19.0)	0.922
Atrial fibrillation	32 (24.6)	8 (12.7)	0.056
Coronary artery disease	21 (16.1)	11 (17.4)	0.819
Congestive heart failure	14 (10.7)	6 (9.5)	0.790
Previous stroke/TIA	27 (20.7)	8 (12.7)	0.172
Peripheral vascular disease	4 (3.1)	0	0.159
NIHSS score at 24 h ^b			0.837
NIHSS worsening	16 (14.6)	7 (13.5)	
NIHSS improvement or no change	93 (85.3)	45 (86.5)	
NIHSS score at discharge ^c			0.598
NIHSS worsening	19 (16.7)	7 (13.5)	
NIHSS improvement or no change	95 (83.3)	45 (86.5)	
Intracranial hemorrhage secondary to IV tPA	24 (18.4)	8 (12.7)	0.313

Continued

Table 1 Continued

	IV tPA without headache	IV tPA with headache	p Value
Discharge outcome			0.100
Home	56 (43.1)	34 (53.9)	
Inpatient/subacute rehabilitation	52 (40.0)	25 (39.6)	
Nursing facility and hospital mortality	22 (16.9)	4 (6.4)	
Discharge outcome			0.560
Alive at discharge	121 (93.1)	60 (95.3)	
In-hospital mortality	9 (9.6)	3 (4.7)	
Abbreviations: NIHSS = NIH Stroke Scale; tPA = tissue plasminogen activator.			
Data are n (%) unless otherwise indicated.			
^a Information missing in 26 patients.			
^b Information missing in 32 patients.			
^c Information missing in 27 patients.			

MRI sequences, hospital course notes, and/or discharge summary. Vascular imaging (Doppler ultrasound, CT or magnetic resonance angiogram) reports were reviewed and data collected for rate of cervical artery dissection. Data regarding headache were obtained for all patients by review of medical records for documentation of subjective headaches. tPA-associated headache was defined as new headache or worsening of pretreatment headache during the first 24 hours post-tPA. Favorable outcome in our analysis was defined as (1) independent discharge to home, (2) discharge NIHSS score improvement of ≥ 4 points, or (3) NIHSS of 0 at 24 hours post-tPA.

Standard protocol approvals, registrations, and patient consents

We obtained approval from an ethical standards committee before review of medical records. Waiver of informed consent was obtained from our institutional review board. Disclosure (consent-to-disclose) of any recognizable person in photographs, videos, and registration with clinical trials registry is not applicable to this study because of the retrospective nature of chart review.

Statistical analysis

We divided the patient population into 2 groups based on presence or absence of tPA-associated headache after thrombolytic treatment. All data were descriptively presented using mean $\pm$ SD for continuous variables and frequencies for categorical variables. Statistical association was assessed with analysis of variance and χ^2 test for categorical variables between 2 groups. Clinical outcomes, including ICH, in-hospital mortality, and independent discharge to home, were compared between the 2 groups by univariate and multivariate analysis. We performed logistic regression models adjusting for age to evaluate the effect of headache on the outcomes. We used SAS 9.1 software (SAS Institute Inc., Cary, NC) for statistical analyses and a probability value less than 0.05 was considered statistically significant.

RESULTS

The mean age of the study population was 66.6 ± 16.9 years, with 50.8% men. The mean initial NIHSS score was 11.5 ± 5.6 . The underlying mechanisms of stroke were large vessel in 31.1%, cardioembolic in 41.9%, cryptogenic in 10.2%, and unclassified in 16.8%. Of 193 AIS patients treated with IV tPA, 63 (32.6%) had associated headache. Patients with headache were younger (59.5 ± 17.4 years vs 69.9 ± 15.5 years, $p < 0.0001$) (figure). Basic

The clinical implication of headache at onset in patients with AIS is controversial and reported data are limited by small sample sizes.

demographic data and clinical characteristics were similar in the 2 groups (table 1). There was no statistical difference between the 2 groups in admission NIHSS score (11.2 ± 5.7 vs 11.5 ± 5.5 , $p = 0.646$), NIHSS score at 24 hours (6.5 ± 5.7 vs 7.4 ± 6.9 , $p = 0.466$), or NIHSS score at discharge (6.7 ± 10.1 vs 8.1 ± 11.6 , $p = 0.448$). There was no difference between the 2 groups for underlying mechanism ($p = 0.686$) (table 1).

The rate of NIHSS improvement by ≥ 4 points at 24 hours was not different in patients with or without headache (86.5% vs 85.3%, $p = 0.830$). There was also no significant difference in the rates of ICH, independent discharge to home, and in-hospital mortality between the 2 groups (table 2). In the multivariate logistic regression adjusted for age, headache was not a predictor of ICH development (odds ratio [OR] 0.55, 95% confidence interval [CI] 0.22–1.36) or death (OR 0.93, 95% CI 0.23–3.75). We performed a subset analysis to evaluate the difference in the outcome based on any change in NIHSS score and found similar results between the 2 groups.

DISCUSSION

Our retrospective analysis suggests that AIS patients who report headache after IV tPA are not at increased risk of adverse outcomes or ICH. A number of hypotheses have been proposed regarding the mechanism of headache after AIS, including changes in flow dynamics of heavily innervated pain-sensitive meningeal vessels, vasodilatation of arteries akin to migraines, and release of vasoactive substances such as serotonin and prostaglandins from activated platelets.^{4–6} Alternatively, headaches can be postulated to be secondary to reperfusion or hyperperfusion injury, implying successful recanalization. This phenomenon is well described after carotid revascularization, in which cerebral hyperperfusion syndrome can occur after both carotid endarterectomy and carotid artery stent placement.⁷ Reperfusion injury can be characterized by throbbing ipsilateral or diffuse headache, focal motor seizures with frequent secondary generalization, focal neurologic deficits, and intracerebral or subarachnoid hemorrhage. Finally, there may also be an intrinsic property of tPA inducing such headaches, although no data exist to examine this theory.

In our study, patients treated with IV tPA had a headache incidence of 32.6%, which is consistent with previous reports of headache incidence in AIS patients (8%–43%).^{4,8–16} In addition, we found that patients who developed headaches after tPA administration were younger, which is consistent with a previous observation.¹⁷ One previous study reported a higher incidence of headache in cardioembolic infarcts than in TIAs, lacunar infarcts, or thrombotic infarcts.¹⁴ Female sex and lower mean NIHSS score on admission were associated with headache in another study.¹⁸ We did not observe such differences between the 2 groups.

The clinical implication of headache at onset in patients with AIS is controversial and reported data are limited by small sample sizes. One study reported no difference in functional outcome between patients with and without headache on presentation.^{19,20} In contrast, 2 studies suggest that stroke patients with headache have lower frequencies of symptom-free rate on discharge than those without headache.^{21,22} We tried to evaluate the influence of onset of headache in the setting of thrombolytic treatment on clinical outcomes. Although post-thrombolytic headache may be an indicator of possible complications, especially when associated with neurologic worsening, in our study the presence of headache alone was not associated with worse outcomes or with increased risk of HT. In fact, some studies suggest that AIS patients presenting with headache at the time of stroke have better outcomes at 6

Table 2 Results of multivariate logistic regression evaluating the effect of headache on discharge outcomes in acute ischemic stroke patients treated with IV tPA

	Unadjusted		Adjusted for age	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Discharge home	1.54 (0.84–2.84)	0.156	1.22 (0.64–2.32)	0.541
ICH secondary to thrombolytic treatment	0.64 (0.27–1.52)	0.315	0.55 (0.22–1.36)	0.199
Inpatient mortality	0.67 (0.18–2.57)	0.562	0.93 (0.23–3.75)	0.921

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; OR = odds ratio; tPA = tissue plasminogen activator.

months.¹⁸ Although the difference was not significant, our headache population showed potential toward a better outcome compared to the nonheadache cohort. This tendency was observed in univariate analysis only and may be attributed to the difference in age between the 2 groups.

The results of our study should be interpreted with caution. Our study should be seen as hypothesis-generating rather than hypothesis-testing because it has several limitations, including the retrospective collection of data, lack of consistent headache documentation, and limited ability to correlate the intensity and character of the headaches as well as previous history of headaches or migraines with the incidence of hemorrhage. Another important theoretical factor is hypertensive headaches, but in our study data were not documented consistently.

In conclusion, we found that IV tPA–related headache is not associated with HT of AIS or worse clinical outcome. The study adds to the limited pool of data that suggest headache is relatively frequent after thrombolytic therapy and can be hypothesized to be secondary to mild perfusion injury with minimal clinical correlation. This study calls for additional prospective studies with a larger cohort to further investigate the clinical implication of our findings. Meanwhile, we suggest that in the absence of neurologic worsening IV tPA infusion not be interrupted prematurely in AIS patients who report headache alone during the infusion.

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AUTHOR CONTRIBUTIONS

Saqib A. Chaudhry: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, statistical analysis, study supervision. Soo Young Kwon: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Hillary Kneale: analysis or interpretation of data, acquisition of data. Ammar Al Jajeh: drafting/revising the manuscript, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis. Syed Hussain: study concept or design, analysis or interpretation of data, study supervision. Anmar Razak: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision.

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