Brief Report

Shorter Intensive Care Unit Stays?

The Majority of Post-Intravenous tPA (Tissue-Type Plasminogen Activator) Symptomatic Hemorrhages Occur Within 12 Hours of Treatment

Adam Chang; Edward J. Llinas; Karen Chen, BA; Rafael H. Llinas, MD; Elisabeth B. Marsh, MD

Background and Purpose—Symptomatic intracranial hemorrhage (sICH) is a life-threatening complication after treatment with intravenous tPA (tissue-type plasminogen activator) for acute stroke. Currently, patients are monitored for sICH in a neurocritical care unit or intensive care unit-like setting for 24 hours post-treatment—a costly and resource intensive practice. Because the half-life of tPA is much shorter than 24 hours, it is possible that the majority of patients do not require such intensive monitoring. In this study, we evaluate the time period of the highest risk for sICH post-tPA.

Methods—All patients receiving intravenous tPA for acute stroke between 2004 and 2017 at our institution were prospectively followed for sICH for 36 hours after treatment. The mean time from tPA administration to hemorrhage was calculated. Additional data were collected regarding: patient demographics, medical variables, and stroke characteristics. Variables significant in univariate analysis were entered into multivariable logistic regression models to determine factors associated with symptomatic hemorrhage.

Results—Three hundred eighty-five patients were administered intravenous tPA. Twenty-one (5.5%) developed sICH. The mean time from administration to hemorrhage was 8.5 hours. Greater than 80% of sICHs occurred before 12 hours post-treatment. The only variable significantly associated with sICH was combination therapy (intravenous tPA and intra-arterial thrombectomy).

Conclusions—sICH associated with the administration of intravenous tPA typically occurs within the first 12 hours of treatment. Longer monitoring in an intensive care unit-like setting may be unnecessary for most individuals. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021398.)**

Key Words: cerebral hemorrhage ■ demography ■ half-life ■ humans ■ stroke ■ therapeutics

Despite intra-arterial thrombectomy revolutionizing treatment of acute stroke, administration of intravenous tPA (tissue-type plasminogen activator) remains the first-line treatment.[1–3] However, intravenous tPA also carries risk of symptomatic intracranial hemorrhage (sICH).[1,4] As such, patients treated with intravenous tPA are currently observed in a neurocritical care unit or intensive care unit (ICU)-like setting, capable of frequent monitoring, for 24 hours post-treatment.[5] This is useful for evaluation of neurological status; however, many patients may not require such intensive monitoring.[6] Intravenous tPA results in a transient coagulopathy that peaks 1 to 4 hours after administration.[7] We posit that patients' highest risk of sICH is actually within the first 12 hours of treatment and that the majority do not require 24 hours of intense monitoring. In this study, we evaluate the time period of the highest risk for sICH in a prospectively collected cohort of patients administered intravenous tPA for acute stroke.

Methods

This study was approved by the Johns Hopkins Institutional Review Board. Data supporting our findings are available from the corresponding author on request. We prospectively followed all adult patients presenting to the Johns Hopkins Bayview Medical Center with acute stroke who received intravenous tPA between October 2004 and July 2017. After treatment, patients were admitted to our Neuro Critical Care Unit. As per our institution's tPA protocol, follow-up neuroimaging (in most cases, noncontrast head computed tomography) was performed for all patients ≈24 hours after tPA administration or earlier if concerned for sICH.

All neuroimaging performed ≤48 hours post-tPA was reviewed for presence of hemorrhage by 2 abstractors (25% overlap). sICH was defined based on ECASS (European Cooperative Acute Stroke Study) criteria, maximizing the sensitivity by defining sICH as any neurological decline with associated intracranial bleeding on neuroimaging.[8] A sICH was considered related to tPA if it occurred within 36 hours of treatment. Time from tPA to hemorrhage was calculated along with time to hemorrhage from last known well for all sICH. Patient demographics, medical variables, stroke characteristics,[9,10] concurrent treatment with intra-arterial thrombectomy,

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Table 1. Patient Characteristics

Variables	Total Population n=385	No sICH n=364	sICH n=21	*P* Value
Age, mean y (SD)	66.9 (16.2)	66.7 (16.2)	68.8 (16.4)	0.57
Race: black, %	29.6	29.7	28.6	0.915
Sex: women, %	53.0	52.8	57.1	0.695
NIH stroke scale score at admission, mean points (SD)	10.4 (6.7)	10.4 (6.7)	11.9 (5.6)	0.332
Stroke pathogenesis, %				
Large vessel	24.4	25.0	14.3	0.066
Cardioembolic	41.3	39.8	66.7	
Lacunar	12.0	12.6	0	
Other	7.0	7.4	0	
Undetermined	15.3	15.1	19.1	
Stroke volume, mean cc (SD)	42.3 (81.2)	40.2 (78.7)	82.1 (117.1)	0.051
Time from last known well to treatment, mean min (SD)	151.3 (56.7)	151.2 (57.3)	153.3 (46.2)	0.887
Microbleeds, %	19.0	18.2	35.71	0.102
CHS score, %				
1	23.6	24.2	13.3	0.172
2	30.4	30.5	26.7	
3	14.4	14.4	13.3	
4	5.4	5.7	0	
5	6.7	7.1	0	
6	4.8	4.4	13.3	
7	5.4	5.4	6.7	
8	9.3	8.4	26.7	
Combination therapy (IV tPA/IA thrombectomy), %	7.0	6.0	23.8	0.002*
SBP at admission, mean mm Hg (SD)	157.5 (28.1)	157.6 (27.5)	156.6 (37.8)	0.880
Peak SBP in 24 h, mean mm Hg (SD)	182.4 (80.1)	182.0 (82.0)	189.2 (35.4)	0.687
Creatinine, mean mg/dL (SD)	1.3 (1.2)	1.3 (1.2)	1.1 (0.6)	0.427
Platelets, mean×10^3/mm^3 (SD)	242.9 (84.0)	243.6 (84.1)	230.3 (83.2)	0.480
LDL, mean mg/dL (SD)	101.0 (40.4)	101.2 (40.5)	96.2 (37.5)	0.610
INR, mean (SD)	1.1 (0.5)	1.1 (0.5)	1.1 (0.1)	0.810
Atrial fibrillation, %	24.7	24.2	33.3	0.344
Diabetes mellitus, %	28.8	28.3	38.1	0.335
Medication use on admission, %				
Antiplatelet	37.4	37.1	44.4	0.528
Anticoagulant	8.0	8.5	0	0.198

CHS indicates Cardiovascular Health Study; IA, intra-arterial; INR, international normalized ratio; IV, intravenous; LDL, low density lipoprotein; NIH, National Institutes of Health; SBP, systolic blood pressure; sICH, symptomatic intracranial hemorrhage; and tPA, tissue-type plasminogen activator.
*Statistically significant ($P<0.05$).

past medical history, and home medications were also recorded (Table 1). Data were entered into the Get With The Guidelines National Database for use in quality assurance, and informed consent was not required.

Analyses were performed using Stata, version 14. Our primary outcome of interest, mean time from tPA to hemorrhage, was calculated for all patients with sICH. To adjust for potential confounders and ensure our population was similar to that of others, Student *t* tests and χ^2 analysis were used to compare those with sICH to those without. Factors significant in univariate analysis ($P<0.1$) were entered into multivariable logistic regression models.

Results

The baseline characteristics of the population are displayed in Table 1. Sixty-one patients (15.8%) had some evidence

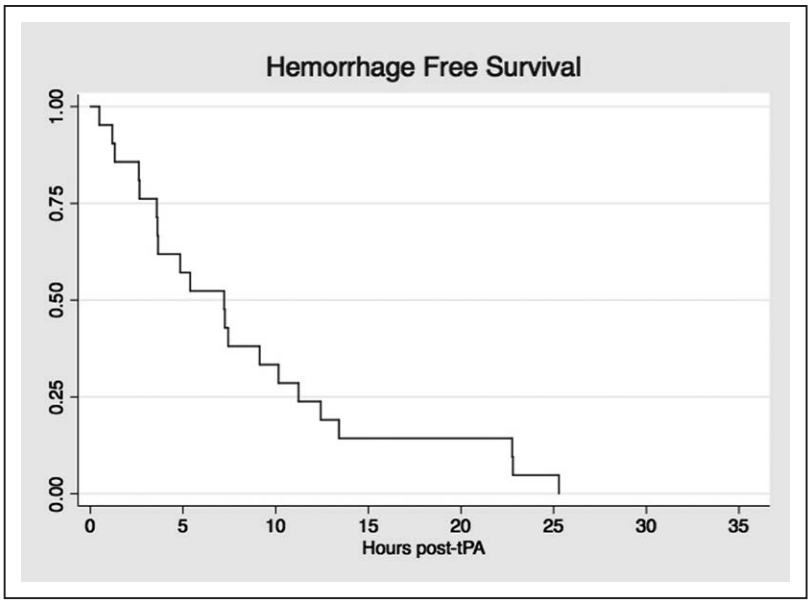

Figure. Timing of symptomatic hemorrhage after intravenous tPA (tissue-type plasminogen activator).

of hemorrhagic transformation on follow-up neuroimaging (symptomatic or incidentally found) within 36 hours of treatment. Twenty-one of the 385 patients (5.5%) met criteria for sICH. The mean length of time from tPA administration to bleed detection for those with sICH was 8.5 hours (Figure). The mean time from last known well to sICH was 10.5 hours.

Only 4 patients experienced a sICH that occurred >12 hours after administration (1 at 13 hours and 3 between 23 and 25 hours). Two of these patients were found to have cerebral amyloid angiopathy and bled both into and outside their stroke bed (at 13 and 25 hours). The 2 additional patients appeared worse on examination at the time of the 24-hour follow-up scan, and magnetic resonance imaging revealed blood within the area of infarct; however, the precise timing of their sICH was less clear.

Factors associated with sICH are displayed in Table 1. Patients with more severe strokes (those with larger stroke volumes [P=0.051] because of a cardioembolic source [P=0.066]) had increased likelihood of sICH, along with those who had undergone intra-arterial thrombectomy in combination with intravenous tPA (P=0.002). In multivariable models, combination therapy remained statistically significant (Table 2).

Discussion

Our findings suggest that the majority of sICHs associated with intravenous tPA occur within the first few hours of treatment. This implies that most patients do not require the standard 24 hours of ICU monitoring to evaluate for neurological worsening because of sICH. This would enable a patient administered intravenous tPA in the afternoon to be downgraded the following morning rather than later in the day, significantly decreasing the length of time a patient spends in an ICU-like setting.

It is important to consider that 20% of patients with sICH in our cohort bled outside of the 12-hour window. However, this was only 4/385 (1%) of our entire population receiving intravenous tPA, indicating that the overall number of patients is low. In addition, 2 of our patients likely developed sICH before the time of their diagnosis. Stroke severity factors, such as pathogenesis, and volume were most significantly associated with hemorrhage, and one possible explanation that combination intravenous tPA/intra-arterial thrombectomy was also associated with sICH is that these infarcts were also larger and more severe. This is an important consideration as we increase the number of mechanical thrombectomy cases. Patients with thrombectomy may be a group that would benefit from extended ICU times. Conversely, it is also important to consider whether any patient requires ICU-level monitoring after treatment with tPA given the lack of strong evidence for surgical intervention for sICH or even the utility of 24-hour post-tPA neuroimaging. Our cohort was similar to many urban stroke center populations, with a sICH rate of 5.5%,[1] allowing for generalization of our findings; however, a larger meta-analysis, or study incorporating the national Get With The Guidelines Database, would be helpful to determine risk factors important for delayed sICH after 12 hours and evaluate the utility of our current practice standards.

Our findings are consistent with prior studies evaluating ICU needs in tPA patients,[6] but along with identifying risk factors, we also evaluate the timing of sICH. We acknowledge that data are from a single, urban, comprehensive stroke center and rely on documentation of the clinical team to adjudicate sICH. Despite these relative weaknesses, our results illustrate that the majority of patients do not require extended

Table 2. Logistic Regression Models Predicting Hemorrhage

	sICH	
Variables	Odds Ratio	95% Confidence Interval
Cardioembolic pathogenesis	1.133	0.775–1.657
Stroke volume	1.004	0.999–1.008
Combination therapy (IV tPA/IA thrombectomy)	8.293*	2.474–27.795*

IA indicates intra-arterial; IV, intravenous; sICH, symptomatic intracranial hemorrhage; and tPA, tissue-type plasminogen activator.

*Statistically significant (P<0.05).

monitoring for sICH and may be transferred to the floor after 12 hours of ICU-intensity monitoring.

Conclusions

sICH associated with the administration of intravenous tPA occurs rarely and predominantly within the first 12 hours of treatment for most individuals. Longer monitoring in an ICU-like setting may be unnecessary.

Disclosures

None.

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