BRIEF COMMUNICATION

Resource Allocation: Stable Patients Remain Stable 12–24 h Post-tPA

Sheena Khan, Alexandria Soto and Elisabeth B. Marsh*

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Abstract

Background and Purpose: Stroke patients are currently monitored for neurological deterioration for 24 h following treatment with intravenous tissue plasminogen activator (IV tPA) or mechanical thrombectomy. This requires low nursing ratios and an intensive-care-like setting. As the half-life of IV tPA is short, many patients may not require such prolonged intensive monitoring and could be downgraded much earlier. We evaluate the frequency of neurological deterioration in the 0–12 and 12–24 h post-treatment windows.

Methods: Patients presenting with acute ischemic stroke treated with IV tPA and/or thrombectomy at our institution from 2016–2018 were prospectively followed per protocol for 24 h post-therapy (examinations every 15 min for 2 h, every 30 min for 6 h, and hourly thereafter). Neurological deteriorations were recorded along with interventions and complications. Frequency of deterioration within the 0–12 and 12–24 h post-treatment windows was determined, along with factors associated with decline at each time point.

Results: A total of 172 patients were treated (IV:135, IA:65, both:30). Thirty-six (21%) experienced a documented neurologic deterioration [8 due to intracerebral hemorrhage (4.7%)]. Five patients deteriorated in the 12–24 h window; all but one had experienced earlier examination changes. Elevated NIHSS was associated with a higher likelihood of deterioration overall. Early fluctuation was associated with decline after 12 h.

Conclusions: New onset of neurologic deterioration is rare 12–24 h after treatment of acute stroke. Stable patients with low NIHSS scores and no ICU needs may not require intensive monitoring greater than 12 h post-treatment.

Keywords: Stroke, Treatment, Tissue plasminogen activator, Outcomes, Cost-effectiveness, Safety

Introduction

Intravenous tissue-type plasminogen activator (IV tPA) remains the only Food and Drug Administration-approved therapy for acute ischemic stroke [1], though treatments have advanced and mechanical thrombectomy (MT) is now also considered standard of care to treat large vessel occlusions [2]. Following both interventions, patients are typically monitored in an intensive care-level setting for 24 h, allowing for frequent neurological evaluations to detect complications such as hemorrhagic transformation [3]. This resource-intensive

practice utilizes stringent protocols that require a low patient-to-nurse ratio [3]. Prior studies have shown that many patients do not otherwise require intensive care unit (ICU)-level care [4], and that the majority of symptomatic hemorrhages (sICH) occur well within the first 12 h post-treatment [5].

The objective of this study is to evaluate the frequency of neurological deterioration within the 12–24 h post-intervention window and to determine the variables that predict which patients may require prolonged frequent monitoring for hemorrhage or other complications. Determining the timing of neurological deterioration post-treatment may allow for updated monitoring protocols, allowing lower-risk patients to be downgraded earlier, opening up critical care beds, decreasing health care

*Correspondence: ebmarsh@jhmi.edu
Department of Neurology, Johns Hopkins School of Medicine, 600 North Wolfe St. Phipps 446C, Baltimore, MD 21287, USA

costs, and resulting in shorter hospital stays and emergency department boarding times.

Methods

The institutional review board at our comprehensive stroke center approved this study. Given the observational nature, informed consent was not required. We prospectively followed all patients presenting with acute ischemic stroke who were treated with IV tPA and/or MT between January 2016 and June 2018. Following treatment, patients were admitted to the Neurosciences Critical Care Unit (NCCU) per our institution's current protocol and monitored for 24 h (every 15 min $\times$ 8, every 30 min $\times$ 12, hourly thereafter). Neurological assessments were performed and documented in the electronic medical record by nursing. Assessments included an National Institutes of Health Stroke Scale (NIHSS) score based on level of consciousness, speech clarity and expression, cranial nerve assessment, and motor and sensory exams [6].

Patient demographics, medical history, stroke severity, and discharge outcomes were recorded, along with neurological fluctuations occurring within the first 24 h of treatment. A board-certified stroke neurologist (EBM) reviewed all exam changes. Neurological deterioration was defined as a change in NIHSS of 2 points or more. Notations were made regarding whether the change resulted in further action (noncontrast head computed tomography [CT]), complications (symptomatic intracerebral hemorrhage, death), and need for prolonged ICU monitoring (>48 h) due to blood pressure management, hyperosmolar therapy, mechanical ventilation, or hemicraniectomy.

Data Analysis

Statistical analyses were performed using Stata, version 14. The frequency of deterioration in neurological examination between 0–12 h and 12–24 h post-treatment was calculated. Student's *t* tests and Chi-square analyses were performed to determine factors associated with changes in exam 0–12 and 12–24 h for continuous and categorical variables, respectively. Sensitivity analyses were conducted to determine factors associated with sICH, and prolonged ICU stay, with NIHSS as the primary independent variable of interest.

Results

Frequency of Deterioration

Patient characteristics are presented in Table 1. The average change in NIHSS for all clinical deteriorations was 2.3 points. Of 172 patients, 36 (21%) had at least one documented change in exam meeting criteria for neurological deterioration over the 24-h period following treatment. Following assessment by a provider, twenty-two

underwent noncontrast head CT as a result of their exam change; eight were diagnosed with intracerebral hemorrhage (4.7%). (Fig. 1) Five patients exhibited a deterioration within the 12–24 h post-treatment period (3% of the cohort). Four of the five had experienced prior exam fluctuations in the 0–12-h period.

Factors Associated with Decline and Prolonged Critical Care Monitoring

Those experiencing a neurological deterioration at any time point in the first 24 h post-treatment were more likely to have hemorrhagic transformation and require a prolonged ICU stay, with poorer modified Rankin Scale scores on discharge and follow-up. Use of IV tPA alone (versus MT or combination therapy) was associated with lower rates of deterioration early (0–12 h post-treatment), while those with an elevated NIHSS on presentation, history of congestive heart failure, and atrial fibrillation were more likely to experience a neurological decline. Prior deterioration (in the 0–12-h window) was strongly associated with decline in the later window (OR 6.5; 95% CI 1.05–40.77), though the majority of patients (89%) stabilized and stopped fluctuating by 12 h post-intervention. Only one patient deteriorated for the first time within the 12–24-h window, and this patient was 85 years old who presented with a large right hemisphere stroke and NIHSS of 13 who ultimately required intravenous blood pressure medications and hyperosmolar therapy for cerebral edema until the family decided to withdraw care.

Fifty-one patients (30%) required >48 h of ICU monitoring post-treatment. The most common reasons for remaining in the NCCU were intravenous medications for blood pressure control and hyperosmolar therapy (Table 2). Higher NIHSS scores were associated with all reasons for prolonged stay except hemicraniectomy. NIHSS was the biggest predictor of ICU needs. An NIHSS cutoff of 12 resulted in a sensitivity and specificity of 69 and 71%, respectively, for predicting prolonged ICU needs with an AUC of 0.801; and a sensitivity and specificity of 67 and 63% with an AUC of 0.742 for sICH.

Discussion

Neurological fluctuation was not uncommon in our population in the initial hours after stroke, especially for those with high NIHSS scale scores, though it is important to consider that we chose an NIHSS change of 2 as our cutoff to maximize sensitivity, where previous trials typically reported a change of 4 or more [1]. Regardless, frequent assessment is clearly important in the acute setting. However, our data also suggest that the majority of patients, especially those who have been

Table 1 Patient characteristics

Variables	Total N = 172	Change in exam 0–12 h			Change in exam 12–24 h		
		No n = 136	Yes n = 36	p value	No n = 167	Yes n = 5	p value
Age, mean year (SD)	66.1 (17.4)	65.8 (17.2)	67.5 (18.0)	0.614	66.0 (17.4)	71.4 (16.8)	0.496
Race, % black	32.3	30.6	39.4	0.333	32.5	25.0	0.751
Sex, % women	53.8	50.7	65.7	0.113	54.2	40.0	0.530
<i>Clinical factors</i>							
Intravenous tPA (IV tPA), %	78.5	83.1	61.1	0.004	78.4	80.0	0.933
Intra-arterial thrombectomy (IA lysis), %	37.8	34.6	50.0	0.089	38.3	20.0	0.405
IV tPA and IA lysis, %	17.4	17.7	16.7	0.890	18.0	0.0	0.297
Admission NIH Stroke Scale, mean (SD)	10.0 (7.8)	9.2 (7.5)	13.1 (8.2)	0.008	10.0 (7.8)	10.0 (7.0)	0.991
Systolic blood pressure, mean mmHg (SD)	154.9 (33.0)	155.3 (31.1)	153.2 (39.9)	0.729	155.2 (33.0)	146.4 (35.0)	0.560
Hemorrhagic conversion, %	12.2	9.6	22.2	0.039	12.0	20.0	0.589
Discharge mRS, mean (SD)	3.3 (1.8)	3.1 (1.8)	4.2 (1.2)	<0.001	3.3 (1.8)	4.0 (0.7)	0.372
90-day mRS, mean (SD)	2.8 (2.0)	2.6 (1.9)	3.5 (1.8)	0.030	2.7 (2.0)	4.0 (0.0)	0.373
<i>Laboratory values,* mean (SD)</i>							
LDL mg/dL	92.5 (43.5)	93.4 (44.9)	88.6 (37.8)	0.572	92.8 (43.4)	80.3 (49.7)	0.571
A1c %	6.6 (2.2)	6.4 (2.0)	7.2 (2.9)	0.081	6.6 (2.2)	6.2 (1.4)	0.723
Platelet count K/cu mm	222.6 (74.4)	225.2 (75.3)	213.0 (71.1)	0.391	223.2 (75.1)	205.2 (49.5)	0.596
INR	1.1 (0.2)	1.1 (0.3)	1.1 (0.2)	0.654	1.1 (0.2)	1.0 (0.0)	0.373
WBC K/cu mm	9.6 (7.9)	9.1 (3.1)	11.6 (16.4)	0.100	9.7 (8.0)	7.4 (2.5)	0.526
ESR mm/h	17.9 (20.1)	17.6 (17.6)	19.2 (28.2)	0.702	18.1 (20.3)	11.6 (14.3)	0.478
Creatinine mg/dL	1.2 (1.2)	1.3 (1.3)	1.1 (0.4)	0.461	1.3 (1.2)	1.2 (0.3)	0.866
Blood glucose mg/dL	146.5 (70.4)	143.6 (68.4)	158.1 (78.1)	0.284	147.5 (71.1)	113.8 (28.4)	0.294
<i>Stroke etiology, %</i>							
Large vessel	24.7	24.2	26.5	0.220	25.5	0.0	0.416
Cardioembolic	42.6	39.0	55.9		41.4	80.0	
Lacunar	15.4	16.4	11.8		15.3	20.0	
Other	4.3	5.5	0.0		4.5	0.0	
Cryptogenic	13.0	14.8	5.9		13.4	0.0	
<i>Disposition, %</i>							
Home	40.9	46.3	20.0	0.078	42.2	0.0	0.051
Acute care facility	2.3	1.5	5.7		1.8	20.0	
Other health care facility	37.4	33.8	51.4		36.8	60.0	
Hospice	5.3	5.2	5.7		4.8	20.0	
Expired	1.8	1.5	3.0		1.8	0.0	
<i>Medical history, %</i>							
Atrial fibrillation	24.4	20.6	38.9	0.023	23.4	60.0	0.060
Coronary artery disease	28.2	30.4	20.0	0.225	28.5	20.0	0.678
Carotid disease	3.7	3.1	5.9	0.444	3.8	0.0	0.657
Depression	11.0	12.3	5.9	0.286	10.7	20.0	0.512
Diabetes mellitus	27.7	25.9	34.3	0.324	27.9	20.0	0.698
Drug use	9.2	7.8	14.7	0.212	8.9	20.0	0.396
Hyperlipidemia	38.0	40.4	28.6	0.197	38.0	40.0	0.926
Congestive heart failure	13.5	10.0	26.5	0.013	13.3	20.0	0.666
Hypertension	72.5	71.3	77.1	0.492	72.3	80.0	0.704
Obesity	16.5	16.2	17.7	0.834	16.4	20.0	0.829
Prior stroke	19.3	21.3	11.4	0.186	19.3	20.0	0.968
Valve replacement	0.6	0.0	2.9	0.051	0.6	0.0	0.858
Obstructive sleep apnea	3.1	3.9	0.0	0.245	3.1	0.0	0.687
Smoking	24.1	23.7	25.7	0.804	24.9	0.0	0.201

Table 1 (continued)

Bold values are statistically significant ($p < 0.05$)

A1c hemoglobin A1c, ESR erythrocyte sedimentation rate, IA Intra-arterial, INR international normalized ratio, IV tPA Intravenous tissue-type plasminogen activator, LDL low-density lipoprotein, mRS modified Rankin Scale, NIH National Institutes of Health, WBC white blood cell count

Fig. 1 Neurological deteriorations and complications post-treatment**Table 2 Critical care outcomes**

Variable	N (%)	Mean NIHSS (+)*	Mean NIHSS (–)*	p value
Extended ICU stay	51 (29.7%)	15.9 (7.9)	7.5 (6.3)	<0.001
Hyperosmolar therapy	24 (14.1%)	15.0 (8.0)	9.1 (7.5)	<0.001
Hemicraniectomy	4 (2.3%)	12.5 (4.0)	10.0 (7.9)	0.521
IV blood pressure medications	38 (22.1%)	12.2 (7.3)	9.4 (7.8)	0.049
Mechanical ventilator	12 (7.0%)	17.5 (9.6)	9.5 (7.4)	<0.001
Symptomatic ICH	21 (12.2%)	15.0 (6.3)	9.3 (7.7)	0.001
Death	24 (14.0%)	18.4 (8.4)	8.7 (6.8)	<0.001

Extended ICU stay—greater than 48 h; hyperosmolar—mannitol or 2–3% saline

Bold values are statistically significant ($p < 0.05$)

ICH intracerebral hemorrhage, ICU intensive care unit, IV Intravenous, NIHSS National Institutes of Health Stroke Scale

*(+) variable present, (–) variable absent

neurologically stable, do not experience significant exam changes 12–24 h following treatment. Not surprisingly, patients presenting with more severe strokes and higher NIHSS scores were more likely to experience a neurological deterioration in the acute setting and need interventions days after infarct. This may be due to the fact that those with larger strokes are at higher risk for both hemorrhagic transformation and malignant edema [7]. Similarly, those with atrial fibrillation or congestive heart failure were also more likely to deteriorate, likely because cardioembolic strokes tend to be larger. Patients treated with IV tPA alone, rather than intra-arterial lysis or combination therapy, were less likely to have neurological decline, likely given that large vessel occlusions are typically treated with intra-arterial lysis or combination therapy while IV tPA alone can be used to treat smaller infarcts.

When considering the 12–24 h post-treatment window, prior change is most predictive of neurological deterioration, and an NIHSS of 12 or more is associated with sICH and extended ICU requirement. Conversely, new deterioration after 12 h appears to be rare. Those with an elevated NIHSS may not be good candidates for early downgrade; however, we believe that we have identified an important group of patients who present with lower NIHSS scores, are neurologically stable during the first 12 h post-treatment, and do not require the ICU for other reasons such as monitoring for cerebral edema. This group is unlikely to have significant exam changes due to treatment complications or stroke evolution after 12 h and likely does not require continued intensive neurological monitoring. Given our aggressive NIHSS scale cutoff of 2, not all patients who had change underwent subsequent repeat imaging after physician assessment ($n=14$). This leads to the possibility that the rate of hemorrhagic transformation may be higher; however, the number is relatively small and these patients had good outcomes without extended ICU needs.

By transferring patients determined to be “low risk” to a lower level of care, costly intensive monitoring can be reduced, producing a great financial benefit and critical resources including hospital beds, and staffing would become available for sicker or more critically ill patients. In addition, transferring patients out of the NCCU may prevent known ICU complications such as delirium, allowing for a faster transition toward home and rehabilitation. Our results suggest that many patients with lower NIHSS scores of less than 12 who remain stable

for the first 12 h post-intervention likely could continue to receive adequate care with no adverse impact on outcome, in a less-resource-intensive setting. Given the limitations of a single-center study, further studies are needed; however, these results illustrate the need to critically assess our current monitoring protocols.

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Conflicts of interest

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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