Causes, Predictors, and Timing of Early Neurological Deterioration and Symptomatic Intracranial Hemorrhage After Administration of IV tPA

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Abstract

Background: Acute ischemic stroke (AIS) is a major contributor toward healthcare-associated costs and services. Symptomatic intracranial hemorrhage (sICH) and early neurologic decline (END), defined as a National Health Institute Stroke Scale score decline of ≥ 4 within 24 h (with or without sICH), remain major concerns when administering intravenous tissue plasminogen activator (IV tPA) despite improved functional neurologic outcomes with its use. Given these risks, current guidelines recommend comprehensive stroke care (most often in an intensive care unit setting) for 24 h posttreatment. However, a number of patients may remain stable after IV tPA and thus not require such intensive resources. We sought to determine causes of END, along with timing and predictors of both sICH and END, to identify patients at lower risk of neurological deterioration and those suitable for earlier transition to a lower level of care.

Methods: This present study analyzed patients with AIS that presented within 4.5 h of being last seen well and received IV tPA. Baseline demographic, clinical, and radiographic findings were collected. Outcomes included END from any cause, parenchymal hemorrhage (PH1 or PH2), sICH, and mortality at 90 days.

Results: A total of 1238 patients with AIS without acute treatment of large vessel occlusion received IV tPA. 9.4% (116) had presence of any degree of ICH on noncontrast computed tomography head and 7.4% (91) experienced END. 2.7% (33) of patients experienced sICH, while 6.7% (83) experienced asymptomatic ICH. Of the patients with END, 63.7% did not have ICH. Predictive factors at presentation for END included an older age (72.6 ± 16.1 vs. 69.1 ± 14.8, p = 0.03), history of tobacco use (odds ratio [OR] 2.1 [1.1–4.3], p = 0.04), and hyperlipidemia (OR 1.7 [1.1–2.8], p = 0.02), along with the presence of an untreated large vessel occlusion (OR 2.1 [1.4–3.1], p = 0.02).

Most END occurred within a mean time of 242 ± 251 min (4 ± 4 h). Because of the small proportion of patients suffering from sICH (33), predictors could not be determined; however, for patients with any ICH, predictive factors included an older age (74.6 ± 12.4 vs. 68.8 ± 15.1, p = 0.001), higher baseline National Health Institute Stroke Scale score (14.6 ± 7.3 vs. 10.8 ± 7.9, p = 0.002), and higher baseline glucose levels (155.1 ± 87.5 vs. 140.4 ± 70.5, p = 0.04).

Conclusions: In this study, only a small proportion suffered from either sICH and/or END, typically within 12 h of tPA administration. These findings may support earlier deescalation of higher acuity monitoring in clinically stable post-IV tPA patients without large vessel occlusion.

Keywords: Stroke, Thrombolytic therapy, Intracranial hemorrhage, Ischemia
**Introduction**

Stroke is a major source of worldwide disability and mortality accounting for nearly 6.5 million deaths each year, the majority of which, are acute ischemic (AIS) in nature. In the United States alone, approximately 795,000 individuals will experience a stroke, resulting in more than $34 billion in annual costs toward medications, missed work, and health services such as intensive care unit (ICU) recovery [1].

Twenty-five years ago, the pivotal National Institute of Neurological Disorders and Stroke trial showed that intravenous tissue plasminogen activator (IV tPA) therapy, when given within 3 h of AIS onset, improved functional neurologic outcomes at 3 months [2]. This became the first established and proven treatment for AIS. Thirteen years later, the ECASS III trial expanded the thrombolytic window to 4.5 h in patients with moderately severe symptoms [3].

Despite improved functional neurologic outcomes, IV tPA must be administered with caution given its thrombolytic profile. Its use in cerebral vessel recanalization can lead to symptomatic intracranial hemorrhage (sICH), defined as hemorrhage contributing to an increase in National Health Institute Stroke Scale (NIHSS) score by 4 points or more than baseline or the otherwise lowest value in past 7 days [2, 4]. Spontaneous hemorrhagic conversion post-IV tPA is particularly common in those with clinically severe ischemic presentation (i.e., hemiplegia with eye deviation, impaired consciousness, early hypodensity on computed tomography [CT]) and has been shown to increase risk of persistent deficit or even death [4]. For patients who experience an NIHSS decline of ≥4 within 24 h of tPA administration, they are defined as having early neurologic decline (END). This may occur in the presence of sICH or without.

Given the potential of END (irrespective of the cause) and its associated clinical consequences, current guidelines recommend that AIS patients treated with IV tPA be observed in a setting that specializes in comprehensive stroke care (most often, an ICU setting) for 24 h posttreatment [5]. This ensures that any clinical decline is promptly identified and managed accordingly. Reassuringly, a number of patients remain stable after IV tPA administration and may not require the time and labor intensive resource of the current 24 h monitoring paradigm [6]. Furthermore, the factors associated with and the timing at which patients experience sICH and/or END remain unclear.

We sought to determine the causes of END (hemorrhagic and nonhemorrhagic) along with the timing and predictors of sICH and END. Based on this data, we identified patients who were at a lower risk of developing neurological deterioration and could safely be transitioned to a lower level of care/monitoring prior to 24 h of post-IV tPA administration.

**Methods**

After institutional review board approval, we performed a retrospective analysis of a prospectively maintained database of AIS receiving IV tPA between 01/2013 and 06/2019. Demographic characteristics, treatment information, and clinical and radiological data were extracted and analyzed. Data used to prepare this article may be made available on reasonable request.

**Patient Selection**

We analyzed AIS patients who presented directly to our comprehensive stroke centers (CSC) and received IV tPA or who were transferred to our CSCs after receiving IV tPA at one of our referring hospitals during the study period. Patients included those who presented within 4.5 h of last seen well (LSW) and received IV tPA based on American Heart Association/American Stroke Association guidelines. Additionally, noninvasive angiographic imaging was performed to detect large vessel occlusion (LVO), defined as internal carotid artery (ICA), middle cerebral artery (segment 1 [M1]), posterior cerebral artery (segment 1 [P1]), and basilar artery. Patients who did not undergo acute intervention for LVO were included in the study.

**Baseline Characteristics**

Baseline demographic (age, sex), clinical (presenting NIHSS, LSW, risk factor profile, baseline modified Rankin Scale [mRS], pre-tPA blood pressure, weight, tPA dose), and laboratory (pre-tPA glucose, platelets, International normalized ratio (INR)) information were collected and analyzed by a vascular neurologist blinded to patient characteristics. Post-IV tPA CT head (CTH) was routinely obtained 24 h after administration of IV tPA per guidelines. CTH imaging obtained prior to 24 h was in response to adverse patient clinical change per the discretion of the treating team. For the subgroup of patients who had an NIHSS ≥4-point worsening of NIHSS at 24 h or who had presence of any hemorrhage on the 24 h scan, the following additional clinical and radiographic data were abstracted: NIHSS at all prespecified intervals within 24 h of IV tPA administration, pretreatment Alberta Stroke Program Early CT Score (ASPECTS), post-IV tPA CTH findings, post-IV tPA magnetic resonance imagining findings, and presence and location of LVO.
Outcomes
Outcomes included early neurological deterioration (≥ 4-point worsening of NIHSS at 24 h) from any cause, parenchymal hemorrhage (PH1 or PH2), symptomatic intracranial hemorrhage (sICH; ≥ 4-point NIHSS worsening with presence of any type of hemorrhage), and mortality at 90 days.

Statistical Analyses
Continuous variables are reported as mean ± standard deviation or median with interquartile range (as appropriate), and categorical variables are reported as proportions. Between-groups comparison for continuous variables was performed using Student’s t-test and for categorical variables using χ² test or Fisher exact test, as appropriate. Multivariate stepwise logistic regression was performed to identify independent predictors. Significance was defined as p ≤ 0.05. Statistical analysis was performed using IBM SPSS Statistics 23 (IBM-Armonk, NY, USA).

Results
A total of 1238 patients with AIS without acute treatment of LVO received IV tPA during the study time period (Fig. 1). Mean age was 69.5 ± 14.9 years, and 49% (606) of patients were women. The remaining baseline characteristics are outlined in Table 1. Median NIHSS score was 9 (5–16). Stroke etiologies were as follows: large vessel (31.5%), small vessel (10.2%), cardioembolic (31.7%), other (5%), and cryptogenic (21.4%). Of this population, 9.4% (116) had presence of any degree of ICH on noncontrast CTH, and 7.4% (91) experienced an increase in NIHSS score ≥ 4 within 24 h of IV tPA administration (END). Reasons for END were the following: ICH (36%), undetermined (30%), metabolic/respiratory (18.5%), infarct expansion/cerebral edema (11%), and seizures (5.5%). Of all patients, 2.7% (33) experienced sICH, while 6.7% (83) patients experienced asymptomatic ICH. Of the patients with END, 63.7% (58) did not have ICH within 24 h of IV tPA (neurological deterioration without ICH). 34.7% (430) patients harbored an LVO but were not deemed candidates for endovascular therapy due to a variety of reasons, including improved examination, large core upon arrival to thrombectomy center, proximal vessel recanalized on initial angiographic run and occlusion subsequently too distal for retrieval, or poor baseline mRS. Location of vessel occlusion included ICA (22.6%), M1 (30.4%), M2 or distal (32.7%), P1 (12.2%), and vertebrobasilar system (2.1%). Data regarding tandem occlusion were not available.
Table 1 Baseline characteristics

|                     | Overall \((n = 1238)\) | Overall \((n = 1238)\) | Groups based on ICH \((n = 116)\) | Groups based on END \((n = 91)\) | Groups based on sICH \((n = 33)\) | Groups based on sICH \((n = 1,205)\) | \(p\) value |
|---------------------|------------------------|------------------------|-----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------|
| **Age**             | 69 ±15                 | 75±12                  | 69±15                             | 0.001                            | 72 ±16                            | 69 ±15                            | 0.012     |
| Male sex            | 51%                    | 60%                    | 50%                               | 0.060                            | 55%                                | 51%                               | 0.441     |
| NIHSS score         | 9 (6–15)               | 15 (8–20)              | 5.5 (5–15)                        | **0.001**                         | 9 (6–15)                           | 9 (6–17)                           | 0.810     |
| ASPECTS             | 10 (6–10)              | 10 (9–10)              | 0.98                             | 0.001                            | 10 (9–10)                          | 10 (9–10)                          | 0.992     |
| Mean body weight (kg) | 81.2±9.1               | 77.1±10                | 81.4±8.9                         | **<0.01**                         | 78.8 ±12                           | 81.6 ±9                            | **0.005** |
| Baseline mRS 0–2    | 80% (990)              | 77% (89)               | 80% (901)                        | 0.351                            | 78% (71)                           | 80% (919)                          | 0.624     |
| HTN                 | 74%                    | 82%                    | 73%                               | **0.033**                         | 70%                                | 74%                               | 0.531     |
| HLD                 | 48%                    | 46%                    | 48%                               | 0.624                            | 35%                                | 49%                               | **0.011** |
| Prior stroke        | 25%                    | 32%                    | 24%                               | 0.090                            | 23%                                | 25%                               | 0.702     |
| Smoking             | 23%                    | 16%                    | 23%                               | 0.061                            | 12%                                | 24%                               | 0.014     |
| Atrial fibrillation | 19%                    | 33%                    | 18%                               | **0.001**                         | 18%                                | 20%                               | 0.680     |
| Diabetes            | 30%                    | 28%                    | 30%                               | 0.677                            | 31%                                | 29%                               | 0.081     |
| Systolic BP         | 162 ±30                | 166±28                 | 161 ±30                           | 0.122                            | 166 ±30                            | 162 ±30                            | 0.223     |
| Diastolic BP        | 86 ±19                 | 86±20                  | 86 ±19                            | 0.890                            | 87 ±23                             | 86 ±19                            | 0.750     |
| Serum glucose       | 142 ±72                | 155±18                 | 140 ±71                           | **0.04**                          | 156 ±85                            | 141 ±72                            | **0.04**  |
| INR                 | 1.2 ±0.1               | 1.1±0.1                | 1.2 ±0.1                          | **<0.001**                        | 1.4 ±0.3                           | 1.2 ±0.1                          | **<0.001** |
| Platelet            | 213,000 ±45,000        | 216,000±58,000         | 212,000 ±44,000                   | 0.361                            | 212,000 ±61,000                    | 213,000 ±43,000                    | 0.830     |

Statistically significant values (\(p < 0.05\)) are given in bold.

ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; END, early neurologic decline; HLD, hyperlipidemia; HTN, hypertension; ICH, intracranial hemorrhage; INR, international normalized ratio; NIHSS, National Health Institute Stroke Scale; mRS, Modified Rankin Scale; sICH, symptomatic intracranial hemorrhage.
ICH
116 patients were observed to have any degree of ICH. Mean age was 74.6 ± 12.5, 59.5% (69) were men, and median NIHSS score was 15 (8–20). Mean LSW to IV tPA was 148 ± 48 min.

Timing of ICH
Mean and median time from IV tPA administration to observation of any degree of ICH on CTH was 1073 ± 549 min (17.8 ± 9.2 h) and 1,440 (430–1440) minutes (24 [7–24] hours), respectively. 30% of patients had ICH within 12 h of IV tPA administration, 59.5% of patients had ICH 21 h after IV tPA administration. 90-day mortality for patients with ICH was 49% vs. 14% compared to those without ICH (\(p=0.001\)).

Predictors of ICH
Univariate analysis demonstrated that patients with ICH compared to those without were significantly older (74.6 ± 12.4 vs. 68.8 ± 15.1, \(p=0.001\)), had a higher NIHSS score (14.6 ± 7.3 vs. 10.8 ± 7.9, \(p=0.001\)), had a higher serum glucose on presentation (155.1 ± 87.5 vs. 140.4 ± 70.5, \(p=0.040\)), and had a higher proportion of history of hypertension (81.9% vs. 72.6%, \(p=0.035\)) and atrial fibrillation (32.8% vs. 17.8%, \(p=0.001\)). In the multivariate analysis, patients who were men, had higher presentation NIHSS, and higher presentation glucose levels were more likely to develop ICH (\(p=0.023\), \(p=0.011\), and \(p=0.021\), respectively). Other factors, including baseline mRS (\(p=0.702\)), IV tPA dose (\(p=0.330\)), INR (\(p=0.291\)), platelet count (\(p=0.280\)), pretreatment ASPECTS (\(p=0.460\)), and pretreatment systolic blood pressure (\(p=0.772\)), were not predictive of development of ICH.

END
91 (7.4%) patients were observed to have an increase in NIHSS score ≥ 4 points. Mean age was 72.6 ± 16.1 years, 56% (51) were men, and median NIHSS score was 9 (6–15.5). Mean LSW to IV tPA was 157 ± 51 min.

Timing of END
Mean and median time from IV tPA administration to observation of NIHSS score ≥ 4 points was 242 ± 251 min (4 ± 4 h) and 180 (60–300) minutes (3 [1–5] hours), respectively. 82% of patients had END within 12 h of IV tPA administration. Figure 2 is a column graph of proportion of patients having END across cumulatively increasing time periods. 90-day mortality for patients with END was 47% vs. 15% compared to those without END (\(p=0.001\)).

Predictors of END
Univariate analysis revealed that patients with END were significantly older (72.6 ± 16.1 vs. 69.1 ± 14.8 years, \(p=0.03\)) and included a greater proportion of those with history of tobacco use (23.6% vs. 11%, \(p=0.001\)) compared to those without END. Multivariate analysis indicated history of tobacco use (odds ratio [OR] 2.1 [1.1–4.3], \(p=0.04\)), hyperlipidemia (OR 1.7 [1.1–2.8] \(p=0.02\)), and presence of LVO (OR 2.1 [1.4–3.1], \(p=0.02\)) as predictors of END. Other factors, including baseline mRS (\(p=0.45\)), pretreatment NIHSS score (\(p=0.22\)), patient’s weight (\(p=0.77\)), IV tPA dose (\(p=0.40\)), INR (\(p=0.28\)), platelet count (\(p=0.30\)), pretreatment ASPECTS (\(p=0.21\)), and pretreatment systolic blood pressure (\(p=0.30\)), were not predictive of development of ICH. For patients who experienced delayed END (≥ 12 h), only the presence of LVO (OR 2.8 [1.9–4.0], \(p=0.001\)) was an independent predictor of END.
sICH
Thirty-three (2.7%) patients were observed to have sICH. Mean age was 76.8 ± 13.4 years, 63.6% (21) were men, and median NIHSS score was 9 (7–18). Mean LSW to IV tPA was 148 ± 55 min. Mean and median time from IV tPA administration to observation of sICH was 206 ± 204 min (3.4 ± 3.4 h) and 150 (30–360) minutes (2.5 [0.5–6] hours), respectively. 90-day mortality for patients with sICH was 66% vs. 16% compared to those without sICH ($p = 0.001$).

Discussion
Our study demonstrates a relatively small proportion of patients suffering sICH, END, or both in patients receiving IV tPA per standard guidelines. The Association/American Stroke Association recommends monitoring key physiologic variables, including blood pressure, glucose, thermoregulation, and clinical neurologic status using frequent standardized NIHSS assessments during the first 24 h after IV tPA administration [7]. These systematic examinations ensure prompt identification of examination changes, especially if meeting criteria for END. A commonly feared etiology of END is a hemorrhagic event due to thrombolytic administration, which occurs in 2–7% of treated patients [2, 8, 9]. Rates of END can vary widely, with reports as high as 40%, which are attributable to causes outside of hemorrhage. This can be multifactorial in nature, but the more commonly reported reasons include arterial reocclusion, extension of ischemic territory, and cerebral edema [8, 10–13].

Predictive factors at presentation for END are even more numerous, including, but not limited to, higher NIHSS, older age, lower ASPECTS, LVO, hyperglycemia, or history of diabetes mellitus [8, 11, 12, 14, 15]. In this study, older patients, those with history of tobacco use, and history of hyperlipidemia were predictive of END along with the presence of an untreated LVO.

Despite the abundant contributing factors to END, there does appear to be a temporal relationship dictating when the majority of deteriorating events occur. Median time worsening from both hemorrhagic and nonhemorrhagic causes have been shown to be between 7 and 12 h [15, 16]. Patients with relatively milder deficits, specifically NIHSS < 10, have sICH rates of 3% compared to 17% for those with NIHSS > 20 [17]. Furthermore, contemporary evidence suggests that close monitoring for adverse events may only be necessary in lower risk patients up to 12 h after IV tPA administration [18]. Even when incorporating the more sensitive threshold of NIHSS change of 2, END was infrequently seen within 12 h in patients with NIHSS < 12 [6]. We observed similar findings: patients who experienced END did so within a mean time of < 5 h from tPA administration.

Analogous to END, predictors of sICH have been widely reported, including but not limited to higher NIHSS on presentation, older age, history of hypertension, and hyperglycemia [19–21]. Because of our small proportion of patients suffering from sICH, predictors could not be determined; however, for patients that had any ICH, we found similar findings: older age, more severe baseline NIHSS, and higher presentation glucose levels. Notably, a proportion of our patients (59.5%) harbored ICH 21 h after IV tPA administration, which reflects the timing whereby routine CTH were obtained by the treating team. The slight variability from 24 h is possibly related to the practical timing when the patients were able to travel for their scan (i.e., CT scan availability, nursing availability, transport team availability, etc.).

Overall, a small proportion of our patient population experienced clinically relevant change (END and/or sICH) after IV tPA administration. The overwhelming majority of these occurred within 12 h, thus many patients may not require higher acuity ICU level monitoring beyond this time. Lower intensity monitoring in stable post-IV tPA patients has demonstrated feasibility in a recent study [22]. Transferring patients to a lower level of care along with reduced frequency of neurological checks in this subset of patients carries several potential benefits, especially in the COVID-19 era. Specifically, these patients would decompress ICUs, and healthcare providers would be protected from repeated unnecessary exposures. This could also lower overall length of stay and, by extension, reduce hospital costs. Notably, while most of our patients experienced END ≤ 12 h, there was still nearly ~ 20% of patients that had this event occur between 12 and 24 h. Lower intensity monitoring may still be feasible, but there remains a potential of clinical deterioration for a proportion of patients. Prospective studies are warranted to elucidate the ideal population suited for early deescalation of monitoring.

While our data do demonstrate promise for potential process changes regarding post-IV tPA monitoring, there are limitations to our study, such as those inherent to its retrospective design. Specifically, data regarding stroke mimic diagnoses and magnetic resonance imaging confirmed infarct on imaging was incomplete, limiting detailed analyses. Additionally, we obtained detailed NIHSS breakdown only on patients who were screened to have a worsening NIHSS ≥ 4 at 24 h. It is possible that we did not capture worsening NIHSS ≥ 4 in a group of patients who improved by the 24-h mark. These patients would not have had ICH present on any follow-up scan (as we accounted for those patients), thus we believe this transient worsening may not have had any notable clinical impact. Furthermore, we excluded LVO patients undergoing interventional therapy, as we aimed to focus
on intravenous thrombolytic therapy alone; however, we acknowledge this introduces bias in our study population. Additionally, intervention performed on medium vessel occlusions (i.e., M2, A2, P2, and distal) would have also removed patients from our study population, which may not reflect practice patterns around the country.

Conclusions
In our patient population who received IV tPA within 4.5 h of LSW, a relatively small proportion suffered either sICH, END, or both. Of those that did experience any of these complications, a large proportion occurred within 12 h of tPA administration. These findings may support earlier deescalation of higher acuity monitoring for clinically stable post-IV tPA patients who do not harbor an LVO. Further prospective studies may be warranted to further elucidate this proposed practice change.

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Author Contributions
All authors have contributed substantively to the conception, design, analysis, and interpretation of the data, contributed substantively to the drafting of the manuscript or critical revision for important intellectual content; have given final approval of the version, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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