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Use of intravenous recombinant tissue plasminogen activator in patients with borderline elevation of international normalized ratio

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Abstract

Objective: To determine the rates of symptomatic intracerebral hemorrhages (sICH), parenchymal hematoma type 2 (PH2), and favorable outcomes in patients with borderline elevation of international normalized ratio (INR) or recent anticoagulation use prior to treatment with intravenous recombinant tissue plasminogen activator (IV rt-PA) for acute ischemic stroke.

Methods: Consecutive patients with acute ischemic stroke that received IV rt-PA were identified. History of recent use of anticoagulation and the INR at presentation and after use of thrombolytics, up to 72 h was recorded. Neuroimaging and clinical charts were reviewed for evidence of sICH. Outcomes were recorded at the time of discharge and on follow-up up to 6 months using the modified Rankin scale (mRS).

Results: A total of 106 patients (mean age was 65.95 ± 15.29 years and 55.67% were men) were identified. Of these, 12 (11.3%) patients had initial INR elevation (1.2–1.7) and 12 (11.3%) patients that had recently received oral anticoagulation. The rate of PH2 was higher in patients on anticoagulation or with elevated initial INR compared to patients with normal INR and no history of anticoagulation (15.79% versus 2.30%, $P = 0.023$). In subgroup analyses, elevation of INR during the first 24 h and history of recent use of anticoagulation in a different analysis inversely correlated with favorable outcomes at discharge and at follow-up.

Conclusion: Borderline elevation in INR or recent use of anticoagulation before thrombolytic use can increase the rate of ICH in patients treated with IV rt-PA for acute ischemic stroke. These patients should cautiously receive thrombolytics for acute ischemic stroke as per the AHA/ASA Stroke Council guidelines.

Keywords

acute ischemic stroke; warfarin; thrombolytics; International Normalized Ratio; hemorrhagic transformation

Introduction

Although intravenous (IV) recombinant tissue plasminogen activator (rt-PA) is the only approved treatment shown to improve outcomes in acute ischemic stroke [1], associated symptomatic intracerebral hemorrhage (sICH) can occur in up to 3.6–11.3% of treated patients [2]. Several studies have attempted to identify the risk factors that are associated with an increased risk of sICH which have helped develop the current American Heart Association/American Stroke Association (AHA/ASA) guidelines [3–5]. The current guidelines recommend that patients who are on anticoagulation can only receive IV rt-PA if the initial international normalized ratio (INR) is ≤1.7 even if they meet the other criteria [5]. At most laboratories, INR in the range of 1.2 and 1.7 is considered a borderline elevation [6,7] and may be associated with an increase in risk of bleeding with or without thrombolytic use [8,9]. Due to these concerns, the European Cooperative Acute Stroke Study III (ECASS III) study, IV rt-PA was administered only to patients for acute ischemic stroke between 3 and 4.5 h from the time of onset of symptoms [10], who did not use any anticoagulants in the last 24 h.

Warfarin use is common among patients with acute ischemic stroke and atrial fibrillation, seen in up to 32%

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of the patients [11]. Currently, the rate of sICH and overall outcomes in patients with borderline elevated INR (i.e., INR ≤ 1.7 s) and patients with recent use of anticoagulation who receive IV rt-PA for acute ischemic stroke are not fully understood. The controversy has been highlighted by one recent study [12] that observed an increased risk of sICH following administration of IV rt-PA in patients with ischemic stroke who were on warfarin. We hypothesize that administration of IV rt-PA in patients with recent use of anticoagulants and an elevated INR, results in a higher rates of sICH and poor outcomes. Any delayed elevation of INR up to 72 h, possibly due to prolonged effects of warfarin taken before thrombolytic use, might also affect these outcomes. We assessed the frequency of sICH and poor outcomes among rt-PA-treated patients with recent warfarin use and borderline elevation of INR.

Methods

Patients presenting to a comprehensive stroke center between April 30, 2005 and December 31, 2009 with acute ischemic stroke who received IV rt-PA were identified based on a prospective database maintained at our stroke research center supplemented by chart review. Patients with no INR measurement prior to rt-PA administration were excluded from the study. IV rt-PA was administered in a dose of 0.9 mg/kg, to a maximum of 90 mg, 10% of which was administered as a bolus in the first 1 to 2 min and the rest over an hour, as specified by the AHA/ASA guidelines [4]. Patients were also excluded from the study, if there was any deviation in the rt-PA administration dosage protocol.

Baseline demographic and clinical characteristics for patients included in the study were collected from the documentation provided in the medical records. These items included: age, gender, race/ethnicity as specified by patients on admission, vascular risk factors (history of cigarette smoking, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, congestive heart failure (CHF), coronary artery disease (CAD), previous history of stroke or transient ischemic attack (TIA), recent use of antiplatelets or anticoagulation, and history of liver disease.

Patients admission systolic blood pressure, laboratory values (INR, partial thromboplastin time [PTT], blood glucose, platelet counts, liver function tests), baseline National Institutes for Health Stroke Scale (NIHSS) score [13,14] and time interval between symptom onset and administration of IV rt-PA were also recorded. Infrequently, NIHSS score was estimated based on the neurological examination documented. Use of endovascular therapies for vessel recanalization and recanalization status defined as reduction in ≥1 grade on the Qureshi grading scale [15] on comparison of pre- and immediately post-treatment cerebral angiograms, in the acute phase, was also recorded. Laboratory INR values, if available, were recorded for the first 72 h. The etiology of the patients' stroke based on the Trial of ORG 10172 in Acute Stroke Treatment criteria was also recorded [16]. Any deterioration in NIHSS score during the hospitalization and the cause if known was also recorded.

The patients' functional status was estimated based on modified Rankin scale (mRS) at the time of discharge and at the 1–3 month and 3–6 month follow-up appointments [17]. If the mRS was not documented in the chart, it was estimated based on physician and rehabilitation team assessments. If the patient did not follow-up in the clinic after discharge, the last known mRS was carried forward. Vital status was ascertained using social security index if follow-up was missing. Favorable outcomes were defined as mRS score of 0 or 1 at any time.

All neuroimaging studies obtained within 36 h after administration of IV rt-PA was reviewed by one of the investigators (HA) for all patients for any evidence of hemorrhagic complications without knowledge of clinical history, findings, and laboratory results. Hemorrhagic transformations (HTs) were classified according to clinical and radiological criteria defined previously [17]. In brief, HI1 (hemorrhagic infarction) was defined as a small petechiae along the margins of the infarct; HI2, as confluent petechiae within the infarcted area but no space-occupying effect; PH1 (parenchymal hemorrhages), as blood clots in 30% of the infarcted area with some slight space-occupying effect; PH2, as blood clots in >30% of the infarcted area with a substantial space-occupying effect; and symptomatic intracerbral hemorrhage (sICH) if the patient had clinical deterioration causing an increase in the NIHSS score of ≥4 points and if the hemorrhage was likely to be the cause of the clinical deterioration. However, in case of doubt regarding whether edema or hemorrhage was the leading pathology, an association of the ICH with the deterioration was assumed [18]. Neuroimaging done in the 36–72-h period after thrombolytic administration was similarly reviewed and ICHs were classified as above. Contrast extravasation was defined as a new hyperdensity exhibited on a noncontrast computed tomography (CT) scan immediately after an endovascular procedure, with a maximal HU measurement higher than 90 and/or disappearance of the hyperdensity on a repeat CT within 24 h [19].

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Statistical analysis

Descriptive statistics were expressed as means with standard deviation, medians with intraquartile range and frequency (percentages). Patients were divided into two groups based on borderline elevated INR values and history of warfarin use, and their baseline characteristics and outcomes were compared with the rest of the study population (Tables 1 and 2). Univariate analysis was performed using t-tests, Welch test, Pearson chi-square test, Fisher's exact test, and Wilcoxon (Mann-Whitney) test as appropriate. Results were considered significant if the two-sided probability values were $P < 0.05$ for the whole study. Adjusting for multiple comparisons using the Bonferroni correction, P values<0.025 were considered significant for individual tests.

Baseline characteristics (independent variables) that reached a statistical significance of $P < 0.1$ in the two groups ($P < 0.05$ after Bonferroni correction) and characteristics that could possibly act as confounding variables were chosen for multivariate logistic regression analysis. All multivariate models were tested for possible multicollinearity. All statistical analyses were performed using the JMP statistical package version 8.0.2.2 (SAS Institute Inc., Cary, NC).

Results

There were 178 patient identified with acute ischemic stroke that received IV rt-PA and presented between April 30, 2005 and December 31, 2009. Of these, 69 patients were excluded because a baseline INR before IV rt-PA administration was not available, and 67 of these patients received IV rt-PA at an outside facility, before being transferred to our hospital. Another 3 patients were excluded because they were only given a partial dose of IV rt-PA than the recommended dose. The remaining $n = 106$ patients form the sample population of this study.

Of the 106 patients in our study, 55.67% were men. Mean age was 65.95 ± 15.29 years. Of these, 50% were white and 24.5% were African-American. The median initial NIHSS score was 11 (IQR:6–17). Mean and median time to treatment with IV rt-PA was 2.11 ± 0.77 h and 2 h (IQR: 2–3 h), respectively. Eleven patients had ICH in the first 36 h, of which 4 ICHs were symptomatic; 5 ICHs were classified as PH2. No new ICHs were seen on neuroimaging in the 36–72-h period. Favorable outcomes were seen among 34.90% of patients at any time in the first 6 months and 20.75% patients died at any time in the first 6 months. In hospital death rate, however, was 10.37% (11 patients). Only 63.2% of patients followed up in the first 3 months and 46.62% in the 3–6-month period. Median discharge mRS was 4 (IQR: 2–5); at 3 months 3 (IQR: 1–5) and at 6 months 3(IQR: 1–5).

All patients included in the study had their INR checked before thrombolytic administration. Only 58.49% (62 of 106) of patients had their INR checked in the first 24 h of receiving IV rt-PA. INR in the first 24 h was elevated in 26.4% (28 of 106) of patients. Median INR value was 1.1 (IQR: 1.1–1.25). The INR after the first 24 h but up to 72 h was measured in 33.02% of patients and was elevated in 16.98% (18 of 106) of patients. Median INR value was 1.2 (IQR: 1.1–1.3). A total of 12 patients (11.32%) were identified to have recently used warfarin. Relationship between elevated INR at various times and warfarin use is shown in Table 3.

The results of the univariate analyses comparing baseline characteristics of patients with elevated INR value or history of warfarin use prior to receiving thrombolytics are available in Tables 1 and 2, respectively. There were no significant differences between various groups in regards to baseline characteristics except for increased incidence of atrial fibrillation in the group with recent use of warfarin. Rates of any ICH or sICH in the elevated INR before administration of thrombolytics group (any ICH RR = 1.74; 95% CI: 0.42–7.12; $P = 0.61$ and sICH RR = 0; 95% CI: 0–1/0; $P = 1.00$) and in the recent use of warfarin group (any ICH RR = 1.74; 95% CI :0.42–7.12; $P = 0.61$ and sICH RR = 2.61; 95% CI: 0.29–23.14; $P = 0.39$) were not statistically significantly different from the controls. In both these groups, these patients were more likely to have statistically significant higher mRS scores on follow-up and higher rates of overall death compared to controls.

Multivariate regression analysis was preformed to adjust for age, NIHSS score, use of endovascular treatment initially, history of atrial fibrillation, and congestive heart failure. History of baseline warfarin use or elevated INR prior to IV rt-PA did not have any statistically significant correlation with any of the outcomes (mRS on discharge and follow-up, favorable outcomes, in hospital death, death at any time, any ICH, sICH, PH2 hemorrhages) after adjusting for the above confounders. When recent history of warfarin use was nested with initial INR before thrombolytic use and vice versa or crossed, no new statistically significant results were obtained. In a different multivariate logistic regression analysis, patients on anticoagulation or with elevated initial INR were more likely to have higher rates of PH2 hemorrhages as a group compared to patients with normal INR

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Table 1.

Baseline characteristics and outcomes in patients with initial elevated INR before administration of rt-PA

Variables	Normal initial INR	Initially elevated INR	Univariate analysis results (*P*-values)
Total patients (*n* = 106)	94 (88.68%)	12 (11.32%)	
Mean age (y, SD)	65.59 ± 15.40	68.8 ± 14.8	0.4911
Men	51 (54.26%)	8 (66.7%)	0.5424
Demographics			0.7720**
White	48 (51.06%)	5 (41.67%)	
African-American	23 (24.47%)	3 (25.0%)	
Other	23 (24.47%)	4 (33.33%)	
Median initial NIHSS (IQR)	11 (5–16)	14 (7.5–17.75)	0.3904
Use of endovascular recanalization methods(Any)	25 (26.60%)	5 (41.7%)	0.3137
IA thrombolytics	21 (22.34%)	3 (25.0%)	1.0000
Mechanical thrombectomy or angioplasty	16 (17.02%)	5 (41.67%)	0.0584
Etiology of stroke			0.5733**
Large vessel	17 (18.09%)	3 (25.00%)	
Cardioembolic	35 (37.23%)	6 (50.00%)	
Small vessel	6 (6.38%)	0 (0.00%)	
Other	36 (38.30%)	3 (25.00%)	
Mean time to rt-PA from symptom onset (hours)	1.93 ± 0.79	2.04 ± 0.54	0.6371
INR			
Initial INR (median, IQR)	1 (1–1.1)	1.2 (1.2–1.3)	<0.0001****
Elevated INR in first 24 h INR (median, IQR)	1.1 (1–1.2)	1.4 (1.2–1.6)	0.0004****
Elevated INR after the first 24 h up to 72 h (median, IQR)	1.1 (1.1–1.2)	1.35 (1.15–1.83)	0.0726
Causes of INR elevation (any known)	18 (19.15%)	7 (58.33%)	0.0065****
Use of baseline anticoagulant	7 (7.45%)	5 (41.67%)	0.0040****
Liver disease or elevated AST or ALT	12 (12.77%)	4 (33.33%)	0.0814
Use of baseline antiplatelet agents	36 (38.30%)	7 (58.33%)	0.2199
Elevated PTT >39	4 (4.26%)	0 (0.00%)	1.000
Low platelets (<150,000)	11 (11.70%)	1 (8.33%)	1.000
SBP before rt-PA administration (mean mm Hg, SD)	148.91 ± 22.90	135.11 ± 18.70	0.0858
Blood glucose >200 mg/dl before rt-PA administration	7 (7.45%)	1 (8.33%)	1.0000
Incidence of vascular risk factors			
Cigarette smoking history	33 (35.11%)	4 (33.33%)	1.0000
Hypertension	68 (72.34%)	10 (83.33%)	0.5104
Diabetes mellitus	32 (34.04%)	5 (41.67%)	0.7491
Hyperlipidemia (LDL cholesterol>100 mg/dl)	66 (70.21%)	7 (58.33%)	0.5094
Coronary artery disease	17 (18.09%)	3 (25.00%)	0.6943
Atrial fibrillation	33 (35.11%)	7 (58.33%)	0.2040
Congestive heart failure	16 (17.02%)	5 (41.67%)	0.0584
History of previous ischemic stroke/TIA	19 (20.21%)	4 (33.33%)	0.2872
Incidence of ICH (any)	9 (9.57%)	2 (16.67%)	0.6097
NINDS rt-PA trial classification of ICH (1)			0.2664**
Asymptomatic ICH	5 (5.32%)	2 (16.67%)	
Symptomatic ICH	4 (4.26%)	0 (0.00%)	1.000
ECASS criterion for ICH (17)			0.1776**
Hemorrhagic infarction 1 (HI1)	0 (0.00%)	0 (0.00%)	
Hemorrhagic infarction 2 (HI2)	2 (2.13%)	0 (0.00%)	
Parenchymal hemorrhage (PH1)	4 (4.26%)	0 (0.00%)	
Parenchymal hemorrhage (PH2)	3 (3.19%)	2 (16.67%)	
Outcomes			
Median mRS at discharge (IQR)	4 (2–5)	5 (3.25–5)	0.0804
Median mRS at 1–3 months (IQR)	3 (1–5)	5.5 (1.75–6)	0.0179****
Median mRS at 3–6 months (IQR)	3 (0.75–5)	5.5 (1.75–6)	0.0204****
Favorable outcomes at any time (mRS <2)	34 (36.17%)	3 (25.00%)	0.5354
In hospital deaths	9 (9.57%)	2 (16.67%)	0.6097
Death at any time	16 (17.02%)	6 (50.00%)	0.0165****
Follow-up			
Patients who followed up between 1 and 3 months	47 (50.00%)	4 (33.33%)	0.3632
Patients who followed up between 3 and 6 months	30 (31.91%)	2 (16.67%)	0.3400

* **Chi-square suspect, more than 20% expected values are <5.**

** ***P* < 0.025 is significant.**

Table 2.

Baseline characteristics and outcomes in the cohort, grouped by warfarin use

Variables	No warfarin use	Warfarin use	Univariate analysis results (*P*-values)
Total patients (*n* = 106)	94 (88.68%)	12 (11.32%)	
Mean age (y, SD)	65.18 ± 15.03	72.00 ± 16.66	0.1467
Men	53 (56.38%)	6 (50.00%)	0.7622
Demographics			0.3419**
White	49 (52.13%)	4 (33.33%)	
African-American	23 (24.47%)	3 (25.0%)	
Other	22 (23.40%)	5 (41.67%)	
Median initial NIHSS (IQR)	11 (5.5–16.5)	14 (10.0–18.75)	0.2177
Use of endovascular recanalization methods(any)	26 (27.66%)	4 (33.33%)	0.7372
IA thrombolytics	21 (22.34%)	3 (25.0%)	1.0000
Mechanical thrombectomy or angioplasty	18 (19.15%)	3 (25.00%)	0.7014
Etiology of stroke			0.1904**
Large vessel	20 (21.28%)	0 (0.00%)	
Cardioembolic	34 (36.17%)	7 (58.33%)	
Small vessel	6 (6.38%)	0 (0.00%)	
Other	34 (36.17%)	5 (41.67%)	
Mean time to rt-PA from symptom onset (hours)	2.10 ± 0.79	2.20 ± 0.63	0.7064
INR			
Initial INR (median, IQR)	1 (1–1.1)	1.1 (1.025–1.275)	0.0005****
Elevated INR in the first 24-h INR (median, IQR)	1.1 (1.075–1.2)	1.2 (1.1–1.4)	0.2660
Elevated INR after the first 24 h up to 72 h (median, IQR)	1.2 (1.1–1.25)	1.15 (1.075–1.45)	0.8662
Use of baseline antiplatelet agents	40 (42.55%)	3 (25.00%)	0.3526
Elevated PTT >39	3 (3.19%)	1 (8.33%)	0.3861
Low platelets (<150,000)	13 (13.83%)	0 (0.00%)	0.3535
SBP before rt-PA administration (mean mm Hg, SD)	146.86 ± 22.38	152.67 ± 26.99	0.4727
Blood glucose >200 mg/dl before rt-PA administration	8 (8.51%)	0 (0.00%)	0.5927
LDL<60	19 (20.21%)	3 (25.00%)	0.7102
Incidence of vascular risk factors			
Cigarette smoking history	35 (37.23%)	2 (16.67%)	0.2087
Hypertension	69 (73.40%)	9 (75.00%)	1.000
Diabetes mellitus	32 (34.04%)	5 (41.67%)	0.7491
Hyperlipidemia (LDL cholesterol >100 mg/dl)	65 (69.15%)	8 (66.67%)	1.000
Coronary artery disease	18 (19.15%)	2 (16.67%)	1.000
Atrial fibrillation	29 (30.85%)	11 (91.67%)	<0.0001****
Congestive heart failure	16 (17.02%)	5 (41.67%)	0.0584
History of previous ischemic stroke/TIA	18 (19.15%)	5 (41.67%)	0.1285
Incidence of ICH (any)	9 (9.57%)	2 (16.67%)	0.6097
NINDS rt-PA trial classification of ICH (1)			0.6484**
Asymptomatic ICH	6 (6.38%)	1 (8.33%)	
Symptomatic ICH	3 (3.19%)	1 (8.33%)	0.3861
ECASS criterion for ICH (17)			0.2696**
Hemorrhagic infarction 1 (HI1)	0 (0.00%)	0 (0.00%)	
Hemorrhagic infarction 2 (HI2)	1 (1.06%)	1 (8.33%)	
Parenchymal hemorrhage (PH1)	4 (4.26%)	0 (0.00%)	
Parenchymal hemorrhage (PH2)	4 (4.26%)	1 (8.33%)	
Outcomes			
Median mRS at discharge (IQR)	4 (2–5)	5 (3.25–5.75)	0.0523
Median mRS at 1–3 months (IQR)	3 (1–5)	5 (2.5–6)	0.0189****
Median mRS at 3–6 months (IQR)	3 (1–5)	5.5 (1.75–6)	0.0327
Favorable outcomes at any time (mRS <2)	34 (36.17%)	3 (25.00%)	0.5354
In hospital deaths	8 (8.51%)	3 (25.00%)	0.1088
Death at any time	16 (17.02%)	6 (50.00%)	0.0165****
Follow-up			
Patients who followed up between 1 and 3 months	48 (51.06%)	3 (25.00%)	0.1262
Patients who followed up between 3 and 6 months	29 (30.85%)	3 (25.00%)	1.000

* **Chi-square suspect, more than 20% expected values are <5.**

** ***P* < 0.025 is significant.**

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Table 3.

Relationship between elevated INR at various times and warfarin use

Variables: *n*- and (*P*-values)	Elevated INR before IV thrombolytic administration	Elevated INR in the first 24 h	Elevated INR after the first 24 h, up to 72 h	Warfarin use 24 h before IV thrombolytic administration
Elevated INR before IV thrombolytic administration (12 patients)	NA	9 patients (75%), *P* = 0.003**	5 patients (41.67%), *P* = 0.1774	5 patients (41.67%), *P* = 0.0040**
Elevated INR in the first 24 h (28 patients)	9 patients (32.14%), *P* = 0.003**	NA	12 patients (40.00%), *P* = 0.0253**	5 patients (17.86%), *P* = 0.4486
Elevated INR after the first 24 h, up to 72 h (18 patients)	5 patients (27.78%), *P* = 0.1774	12 patients (80.00%), *P* = 0.0253**	NA	5 patients (27.78%), *P* = 1.0000
Warfarin use 24 h before IV thrombolytic administration (12 patients)	5 patients (41.67%), *P* = 0.0040**	5 patients (41.67%), *P* = 0.4486	5 patients (41.67%), *P* = 1.0000	NA

* ***P* < 0.05 is significant.**

and no history of anticoagulation (15.79% versus 2.30%, *P* = 0.023).

When a similar analysis was done only including patients (*n* = 62) who had an INR checked within 24 h after administration of thrombolytics, elevated INR during this time correlated with lower frequency of good outcomes and higher mRS scores on discharge and follow-up. Adjustment for elevation of INR beyond this time point, up to 72 h produced no new results. To evaluate the above results in a more comprehensive manner various multivariate stratified models with elevated INR defined as a value of 1.4 or more were created, but failed to produce any statistically significant results. No multicollinearity was present in any of the above models.

In the patients (*n* = 30) that underwent endovascular recanalization procedures in the acute state, the rates of recanalization during the procedure were similar in patients with elevated initial INR (60% vs 72%; *P* = 0.62) or history of recent use of warfarin (100% vs 65.4%; *P* = 0.2874) compared to controls. Patients with successful recanalization irrespective of their INR values and history of warfarin use, in the acute phase had overall statistically significant better outcomes on discharge and follow-up than those that did not recanalize. In this multivariate model (similar to the main cohort), history of recent warfarin use correlated with statistically significant poorer outcomes and higher mRS scores after adjustment for vessel recanalization status. There was no statistically significant correlation between elevated initial INR and outcomes in this model.

Discussion

Our study demonstrates similar rates of sICH and any ICH among patients treated with IV rt-PA for acute ischemic stroke with borderline elevated INR or use of anticoagulation within the last 24 h compared to patients without and higher rates of PH2 hemorrhages when the groups are merged. In a subset analysis, any elevation of INR in the first 24 h after administration of rt-PA and history of recent use of anticoagulation in a different analysis correlated with a lower frequency of good functional outcomes and higher mRS on discharge and at follow-up. None of the variables of interest had any affect on in hospital death rates or the overall death rate for the first 6 months after adjusting for confounding variables.

Currently, based on the AHA/ASA guidelines for management of acute ischemic stroke, patients on anticoagulants with INR≤ 1.7 can receive thrombolytics for acute ischemic stroke [5]. Patients with elevated INR or with recent use of warfarin who receive thrombolytics may experience augmentation of the thrombolytic properties of IV rt-PA, resulting in higher early recanalization rates with better outcomes and also perhaps higher late vessel recanalization rates [20–22]. However, higher rates of recanalization and impaired clotting mechanisms may increase the incidence of sICH in these patients [2,20–23]. On the other hand, borderline elevation in INR might not be sufficient to cause higher rates of late recanalization and produce enough coagulopathy to increase the rates of hemorrhagic transformation [8,9]. In our study, there were no increases in rates of early recanalization from endovascular recanalization procedures in patients with elevated initial INR or warfarin use suggesting no effect on early recanalization in these patients. It remains unclear if this indifference in recanalization rates is limited to patients that underwent endovascular procedures with or without elevated INR, or history of warfarin use, or can be extended to the other patients in the study, who only received IV thrombolytics.

Our results were slightly different from the recent study of Prabhakaran *et al* [12] who compared patients with and without recent use of warfarin, who presented for acute ischemic stroke and received IV thrombolytics. They found that patients with recent use of anticoagula-

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tion were at higher risk for sICH and any ICH following IV rt-PA treatment. Our study failed to show such a difference, possibly due to the low rate of sICH among our patient population (Type II error). On the other hand, our study did show that the rate of PH2 hemorrhages, which have been shown to correlate with sICH [24], was higher among patients on anticoagulation or with elevated initial INR as a group when compared to patients with normal INR and no history of anticoagulation.

INR is not always a very reliable measure of anticoagulation in the subtherapeutic range due to daily fluctuations [25]. Furthermore, the accuracy of the INR test is ±0.2, which makes it hard to differentiate between normal INR values (0.9–1.14) with borderline elevated values (1.15–1.34) [25]. Warfarin use alone can be used to determine the eligibility of thrombolytics in acute ischemic stroke but this lacks the quantitative value the INR provides. The complex pharmacokinetics of warfarin, using the time interval between the last dose of warfarin and presentation may exclude several patients unnecessarily due to suspected anticoagulant status. Patients are often unable to provide their medication history due to neurological deficits from the stroke and last use of warfarin might be unavailable in the chart. To analyze the issue in a comprehensive manner, we assessed the risk in various strata based on INR values and history or warfarin use, which did not show any statistically significant difference in outcomes. It remains unclear if the outcomes seen in patients with elevated INR at various times have any correlation with the quantitative INR value or not.

Several patients in our study had elevated INR values up to 72 h after thrombolytic use. This elevation could be secondary to baseline warfarin use. The similar outcomes seen in patients with history of baseline warfarin use and elevation of INR in the first 24 h, after thrombolytic administration, suggests an association between the two variables. In our study, no statistically significant association was observed between elevated INR values in the first 24 h and history of recent warfarin use suggesting possible inaccuracy in the history of warfarin use obtained initially in the emergency department. This might have also been a reason for the difference in the results between our study and the study by Prabhakaran *et al* [12].

Our study had several limitations. This is a retrospective study and there is variability in ascertainment of confounding factors and INR values (excluding the baseline value) in the first 72 h. All our patients did not undergo tests to determine if they had vessel recanalization, which limits our ability to comment on the effect of anticoagulation and rt-PA on recanalization rates. The sample study is small and therefore the rates of ICH are small in each group preventing us from reaching any conclusions about risk of ICH in patients with an elevated INR or history of recent warfarin use without merging the two groups. Lastly, our study was conducted at one hospital only and these results might not hold true for other hospitals or patient populations.

Conclusion

Patients presenting with an acute ischemic stroke with borderline elevation of INR (INR $\leq$ 1.7 s) or recent use of anticoagulation who received IV rt-PA had a higher incidence of PH2 but not sICH when compared to controls. Patients with elevation of INR within the first 24 h of IV rt-PA administration or patients with recent anticoagulation use were less likely to have favorable outcomes and had higher mRS on discharge and follow-up. The current data does not completely refute the AHA/ASA guidelines for acute stroke management and these patients should be treated with thrombolytics for acute stroke. The cause for the elevation of INR in the first 24 h and the accuracy of initial history of recent anticoagulation use obtained in emergency department needs to be examined further.

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