Safety of Intravenous Thrombolysis in Chronic Intracranial Hemorrhage: A Five-Year Multicenter Study

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Introduction: Although the recently updated U.S. alteplase label removed "history of intracranial hemorrhage (ICH)" as a contraindication, there are very limited data on the safety of intravenous thrombolysis (IVT) in acute ischemic stroke (AIS) patients with chronic ICH. We sought to evaluate IVT safety in AIS patients with a history of ICH. *Methods:* We analyzed consecutive AIS patients treated with IVT at 3 tertiary stroke centers during a 5-year period. We identified AIS treated with IVT with clinical history and neuroimaging confirmation of prior ICH. The safety measure was symptomatic ICH (sICH) defined according to European Cooperative Acute Stroke Study-III criteria combined with the clinical deterioration of 4 points or higher in the National Institutes of Health Stroke Scale (NIHSS) or death. *Results:* Of the 1212 AIS patients treated with IVT, 7 (.6%) (mean age 72 ± 11 years, 57% men, median NIHSS: 5 points, interquartile range: 2-8) had a history of ICH (hematoma volume: 1-21 cm^3, elapsed time between previous ICH and AIS: 1.5-12 years, 5 located in basal ganglia and 2 in periventricular white matter). Patients with previous ICH did not differ in terms of demographics and admission stroke severity in comparison with the rest. The 2 groups had similar rates of sICH (0% [0/7] versus 3.6%, $P = .61$) and in-hospital mortality (0% [0/7] versus 6.0%, $P = .50$). *Conclusion:* Our study indicates that IVT might be safe among AIS patients with a history of chronic ICH. Further research with a larger sample size is required to confirm our finding and define the shortest time interval between the hemorrhagic and ischemic events that can be associated with the safe administration of IVT. **Key Words:** Intracerebral hemorrhage—thrombolysis—ischemic stroke—hemorrhagic transformation.

Introduction

Although the recently updated alteplase U.S. Food and Drug Administration package insert[1] removed history of intracranial hemorrhage (ICH) as a contraindication for intravenous thrombolysis (IVT) for acute ischemic stroke (AIS), there are scarce data on the safety of IVT in AIS patients with a history of chronic ICH. The recent American Heart Association/American Stroke Association guideline[2] still considers IVT in stroke patients with a history of ICH as "potentially harmful."

The Food and Drug Administration's Physician Labeling Rule used to determine that drug contraindications require evidence of harm for exclusion criteria; this led

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to the removal of chronic ICH along with numerous other unsupported items, many of which were remnants of clinical trials.[3] Presently, the literature only reveals a handful of cases describing outcomes of AIS in patients with chronic ICH who received treatment with IVT. Meretoja et al[4] found no sign of post-IVT symptomatic ICH (sICH) in 3 stroke patients. One patient had a history of previous spontaneous ICH, and 2 other patients had a subarachnoid hemorrhage with no required surgical intervention. Kvistad et al[5] studied 265 patients who had received IVT for ischemic stroke. Of those patients, 135 had contraindications for IVT and 130 had no contraindications. In the group of patients with contraindications for IVT, 3 had a history of ICH. Of those 3 patients, 1 (age >80 years) developed sICH. However, the rates of sICH for both groups were similar. Lyerly et al,[6] in a retrospective study, did not observe any significantly increased risk of ICH among patients with IVT protocol violations compared with patients without violations. Interestingly, 3 patients who inadvertently received IVT in that study had a history of ICH. However, no data about the possible development of sICH among those patients are available.

In view of the former considerations, we sought to evaluate the safety of IVT among AIS patients with a history of chronic ICH who were inadvertently treated with IVT.

Methods

We evaluated consecutive patients who received IVT for stroke-like symptoms at 3 tertiary stroke centers (2 in the southeastern United States, 1 in Greece) during a 5-year period (2010-2014). Thrombolysis protocols were similar in all 3 centers. Magnetic resonance imaging (MRI) is routinely considered for all patients in each center. Baseline characteristics of patients were obtained and included age, race, gender, and medical history of hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, cigarette smoking, and other clinical presentations. Pretreatment National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale scores at discharge were obtained per institutional protocol. The standard dosage for IV alteplase was .9 mg/kg body weight, with a maximum dose of 90 mg at all centers. Details regarding definitions of demographic characteristics, vascular risk factors, and outcomes in our international collaborative group have been previously reported.[7-9] Outcome measures in our study included (1) sICH as defined by the European Cooperative Acute Stroke Study (ECASS) criteria combined with a clinical deterioration of 4 points or higher in the NIHSS[10-12] or (2) death.

We reviewed T1-weighted, T2 fluid-attenuated inversion recovery (FLAIR), and T2*-weighted (gradient echo [GRE]) sequences for any signs of chronic ICH. We defined chronic ICH as hypointensity on T1-weighted and FLAIR imaging with marked susceptibility on GRE.[13] Patients who had MRI findings consistent with a chronic ICH but denied the incidence and did not have any previous confirmatory imaging or clinical documentation were excluded from the study. We also excluded patients who reported a previous incidence of intracerebral hemorrhage but did not have imaging confirmation. Post-thrombolysis head computed tomography was evaluated for the presence and burden of hemorrhagic transformation according to European Cooperative Acute Stroke Study criteria.

Statistical Analyses

Continuous variables are presented as mean ± standard deviation (normal distribution) and as median ± interquartile range (skewed distribution). Statistical comparisons were performed among different groups using the $\chi 2$ test, Fisher's exact test, the unpaired *t*-test, and the Mann–Whitney *U*-test as indicated for dichotomous or continuous variables. Statistical significance was achieved with a P value of <.05. The Statistical Package for Social Sciences (SPSS 22.0, SPSS Inc., Chicago, IL, USA) (SPSS Inc., version 22 for Windows [Microsoft Corporation, Redmond, WA]) was used for statistical analysis.

Results

Of the 1212 AIS patients treated with IVT, 7 (.6%) (mean age: 72 ± 11 years, 57% men, median NIHSS score: 5 points, IQR: 2-8) had a history of ICH (hematoma volume: 1-21 cm^3, mean elapsed time between previous ICH and AIS: 5.7 years, range: 1.5-12years). A total of 3 patients were excluded from our study. Two patients reported the history of possible chronic ICH, but we could not confirm their claim with old or new neuroimaging. One patient had MRI findings consistent with a chronic ICH, but he denied any history, and we were not able to confirm the diagnosis based on old imaging or clinical documentation. None of these 3 patients were complicated with sICH following treatment with IVT.

Baseline characteristics of the study population are presented in Table 1. The diagnostic workup of the 7 AIS patients with chronic ICH did not disclose any underlying vascular abnormality. Previous ICH was located in basal ganglia and in periventricular white matter in 5 and 2 cases, respectively. The etiology of previous ICH was hypertension in 6 cases, while in the remaining patient the underlying pathogenic mechanism could not be determined. All 7 cases received full-dose intravenous alteplase. Patients with previous ICH did not differ in terms of demographics and admission stroke severity in comparison with the rest. The 2 groups had similar rates of sICH (0% [0/7] versus 3.6%, P = .61) and in-hospital mortality (0% [0/7] versus 6.0%, P = .50). The rate of asymptomatic ICH was 14% (n = 1, small petechial hemorrhage consistent with hemorrhagic infarction type I on follow-up computed tomography). One patient had