Severe Hemorrhagic Transformation after Thrombolysis for Acute Ischemic Stroke Prevents Early Neurological Improvement

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Background: Intravenous thrombolysis can improve neurological outcomes after acute ischemic stroke (AIS), but hemorrhagic transformation (HT) of the infarct remains a risk. Current definitions for symptomatic intracerebral hemorrhage (ICH) all entail that there be some degree of associated neurological deterioration. However, early deleterious effects of secondary ICH might also be manifested as reduced neurological improvement. This study aims to investigate whether there are any independent associations between different radiological subtypes of HT and the degree of neurological improvement 24 hours after thrombolysis. *Methods:* This study is a retrospective analysis of a single-center database of consecutive thrombolysis cases for AIS. Multivariate regression analysis was undertaken to explore the relationship between different subtypes of HT with changes in National Institutes of Health Stroke Scale (NIHSS) score 24 hours after thrombolysis, after adjusting for potential confounders. *Results:* As compared to cases with no HT, occurrence of the parenchymal hematoma 2 (PH2) subtype of secondary ICH was independently associated with reduced improvement or worsening in the NIHSS score, with an average effect size of 7 points (95% confidence interval −10 to −4, $P < .001$). In the absence of PH2, thrombolysis for AIS was generally associated with an improvement in the neurological status at 24 hours. *Conclusions:* The PH2 subtype of HT is associated with reduced neurological improvement or deterioration 24 hours after thrombolysis for AIS. **Key Words:** Intracerebral hemorrhage—hemorrhagic transformation—ischemic stroke—rtPA—thrombolysis—stroke subtype.
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Introduction

The timely and appropriate administration of intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) can improve neurological outcomes, reduce mortality, and lead to higher rates of independent ambulation after acute ischemic stroke (AIS).[1-6] However, an increased incidence of hemorrhagic transformation (HT) of the infarct remains the main safety concern after IVT and has been shown to occur in approximately 27% of the patients treated,[1] although neurological deterioration is seen in only 2.2%-8.8%.[1-6]

HT can be divided into hemorrhagic infarction and parenchymal hematoma (PH). Hemorrhagic infarction pertains to a heterogeneous hyperdensity occupying a portion of an ischemic infarct zone on neuroimaging. In contrast, PH describes a more homogenous, dense hematoma with mass effect. These can be subdivided into 2 further subtypes (Box 1).[6]

We aimed to investigate whether there are any associations between the various radiological subtypes of post-thrombolysis HT and the degree of neurological improvement at 24 hours following the administration of IVT, independent of potential confounders.

Methods

Population

This was a retrospective single-center observational study. All patients were transferred to a hyperacute stroke unit at Imperial College Healthcare NHS Trust (ICHNT, London, United Kingdom) and subsequently thrombolysed for presumed AIS between October 1, 2011, and June 30, 2015, inclusive. Patients subsequently treated with mechanical thrombectomy, patients who were later confirmed to have nonstroke diagnoses (following review of neuroimaging and clinical characteristics by 1 or more consultant stroke physicians), and patients that died within 24 hours were excluded from the present study.

Box 1 *Radiological definitions of the hemorrhagic transformation subtypes[6]*

Hemorrhagic infarction type 1 (HI1): small dense petechiae
Hemorrhagic infarction type 2 (HI2): a confluent hyperdensity throughout the infarct zone
Parenchymal hematoma type 1 (PH1): homogenous hyperdensity occupying less than 30% of the infarct zone with some mass effect
Parenchyal hematoma type 2 (PH2): homogenous hyperdensity occupying over 30% of the infarct zone with significant mass effect

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Clinical Criteria

The following clinical characteristics were analyzed in the patient cohort: duration elapsed from symptom onset to administration of rtPA (minutes), systolic blood pressure (SBP, millimeter of mercury) and capillary blood glucose (millimole per liter) upon admission, National Institutes of Health Stroke Scale (NIHSS) score at admission and 24 hours following rtPA, and incidence and subtype of post-thrombolysis HT.

Radiological Criteria

Radiological criteria to define and subtype HTs were as previously described by the European Cooperative Acute Stroke Study (see Box 1).[5,6] All routine follow-up neuroimaging examinations performed 22-36 hours after thrombolysis for included patients were considered and were independently reviewed by 2 trained investigators; any discrepancy was resolved by discussion.

Statistical Analysis

Statistical analysis was performed using Stata 14 (StataCorp LP, College Station, TX). Summary statistics are offered as percentages, medians, and interquartile ranges. Multivariate regression analysis was used to explore the relationship between different subtypes of HT (categorical predictor variable) and reduction in NIHSS score 24 hours after thrombolysis (dependent variable). This model was adjusted for other important independent variables that have previously been demonstrated to predict outcomes after thrombolysis for AIS: SBP on thrombolysis, blood glucose on thrombolysis, NIHSS score on thrombolysis, and the time to thrombolysis after symptom onset.[7] Age was not considered to be a confounding variable as previous studies have demonstrated that tissue plasminogen activator is as effective in those over 80 years compared to those under.[8] Coefficients and confidence intervals were used as indicators of effect size; P values with a cutoff less than .05 were used as indicators of statistical significance.

Ethical Review

Only anonymized data already acquired for service evaluation purposes were used in this work. The study proposal was reviewed and approved locally, and further ethical evaluation was not deemed necessary.

Results

Between October 1, 2011, and June 30, 2015, inclusive, a total of 535 patients were consecutively treated with intravenous thrombolytic therapy for AIS at ICHNT. Of these, 46 patients who proceeded to be treated with mechanical thrombectomy, 50 patients later confirmed to have a nonstroke diagnosis, and 4 patients who died within