The Relationship of the Type of Intracerebral Hemorrhage to Early Disease Evolution and Long-Term Prognosis After r-tPA Thrombolysis

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Abstract

To investigate the relationship of different subtypes of intracerebral hemorrhage (ICH) to early disease evolution and long-term prognosis in patients with acute cerebral infarction after intravenous recombinant tissue plasminogen activator(r-tPA). Seventy ischemic stroke patients treated with intravenous r-tPA who underwent computed tomography (CT) within 24 hours after thrombolysis were divided into 4 types (hemorrhagic infarction type 1 [HI-1], HI-2, parenchymal hemorrhage type 1 [PH-1], or PH-2 which according to the size of the hematoma and the presence or absence of space-occupying effect). Early evolution of the disease was observed by the change in the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours after thrombolysis. The long-term prognosis was assessed by the modified Rankin Scale (mRS) score at the third month. There were 17 (24.3%) patients with ICH. Compared with patients in the non-ICH group, HI did not affect early neurological function or clinical outcome at the third month. PH-1 did not increase the risk of early neurological deterioration; however, PH-1 has a tendency to increase the risk of death at the third month (50% vs 11.3%, P = 0.090). PH-2 was significantly related to early neurological deterioration (66.7% vs 3.8%, P < 0.001) and mortality at the third month (50.0% vs 11.3%, P = 0.040). Patients with different subtypes of ICH after thrombolysis have different clinical outcomes. PH-2 is significantly associated with early neurological deterioration and increases mortality at the third month.

Keywords

intracerebral hemorrhage, thrombolysis, cerebral infarction, tissue plasminogen activator

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Introduction

Intracerebral hemorrhage (ICH) is one of the most common and severe complications of intravenous thrombolysis with recombinant tissue plasminogen activator (r-tPA).[1] In particular, symptomatic ICH (sICH) may aggravate the injury to the brain tissue and is proven to be associated with poor clinical outcomes.[2] Therefore, correctly assessing early disease evolution and long-term prognosis of patients with ICH after thrombolysis is a major concern for clinicians. A previous study reported that subtypes of post-thrombolytic ICH were related to the clinical outcomes of patients with acute cerebral infarction after intravenous r-tPA thrombolysis.[3] Classifying the subtypes of post-thrombolytic ICH that can contribute to clinical outcomes after thrombolysis and the management of ICH is

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necessary. To date, few large sample studies have been conducted to analyze the occurrence of ICH after intravenous r-tPA in China. The purpose of our study was to review patients treated with r-tPA for acute ischemic stroke and to investigate the relationship of different subtypes of ICH after thrombolysis to early disease evolution and long-term prognosis.

Materials and Methods

Subjects

We performed a retrospective analysis of a prospectively included cohort of 70 acute ischemic stroke patients who were treated with intravenous tPA at the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University and the First Affiliated Hospital of Wenzhou Medical University between December 2018 and February 2020. The inclusion and exclusion criteria for intravenous thrombolysis within 4.5 hours of onset were those proposed by guidelines from the American Heart Association/American Stroke Association.[4] Patients were included (1)The neurological signs should not be clearing spontaneously (2). The neurological signs should not be minor and isolated (3). Caution should be exercised in treating a patient with major deficits (4). The symptoms of stroke should not be suggestive of subarachnoid hemorrhage (5). Onset of symptoms <3 hours before beginning treatment (6). No head trauma or prior stroke in previous 3 months (7). No myocardial infarction in the previous 3 months (8). No gastrointestinal or urinary tract hemorrhage in previous 21 days (9). No major surgery in the previous 14 days (10). No arterial puncture at a noncompressible site in the previous 7 days (11). No history of previous intracranial hemorrhage (12). Blood pressure not elevated (systolic <185 mmHg and diastolic <110 mmHg) (13). No evidence of active bleeding or acute trauma (fracture) on examination (14). Not taking an oral anticoagulant or, if anticoagulant being taken, INR $\leq$ 1.7 (15). If receiving heparin in previous 48 hours, aPTT must be in normal range (16). Platelet count $\geq$100000mm3 (17). Blood glucose concentration $\geq$50mg/dL(2.7 mmol/L).[17] No seizure with postictal residual neurological impairments (18). CT does not show a multilobar infarction (hypodensity >1/3 cerebral hemisphere) (19). The patient or family members understand the potential risks and benefits from treatment. All patients or their families agreed to receive thrombolytic therapy and signed an informed consent form. The clinical inclusion criteria for patients with onset times between 4.5 to 9 hours were the same as those of patients with onset times between 0 and 4.5 hours. The radiographic inclusion and exclusion criteria were based on multimodal imaging. The radiographic inclusion criteria were as follows: (1) computed tomography (CT) perfusion imaging showing the maximum diameter of the abnormal perfusion zone >2 cm; (2) CT perfusion imaging/CT angiography showing a mismatch area $\geq$20%; and (3) CT angiography showing a thrombolysis in cerebral infarction (TICI) grade[5] of 0 or 1 (large vessel occlusion or severe stenosis). The radiographic exclusion

criteria were as follows: (1) CT showing the presence of ICH or subarachnoid hemorrhage; (2) CT angiography showing an abnormal range of >1/3 of the middle cerebral artery supply range; (3) CT perfusion imaging showing no abnormal perfusion area; and (4) any contraindication for CT examination. Included patients received intravenous r-tPA (0.9 mg/kg; 10% bolus, remainder by infusion over 1 hour). During thrombolysis and 24 hours after thrombolysis, blood pressure was maintained below 180/105 mmHg. Antiplatelet or anticoagulant therapy was initiated only if the brain CT performed 24 hours after thrombolysis showed no ICH. If headache, confusion, or neurological worsening occurred during thrombolysis, the injection was ceased, and an emergent brain CT was performed. This study was approved by the ethics committee of the hospital, and informed consent was obtained from all patients or their families (when the patients were unconscious).

Clinical Assessment

Any ICH detected by CT within 24 hours after injection was defined as post-thrombolytic ICH. In clinical practice, post-thrombolytic ICH includes symptomatic ICH and asymptomatic ICH. We defined sICH according to the definition provided by the National Institutes of Neurological Disorders (NINDS)[6] as any clinical suspicion of hemorrhage or any decline in neurological status. With respect to the radiological classification of post-thrombolytic ICH, we adopted the European Cooperative Acute Stroke Study II (ECASS II) criteria. Post-thrombolytic ICH was classified as hemorrhagic infarction (HI) or parenchymal hemorrhage (PH) according to the CT appearance. HI type 1 (HI-1) was defined as small petechiae along the margins of the infarct, and HI-2 was defined as confluent petechiae within the infarcted area without a space-occupying effect. PH type 1 (PH-1) was defined as blood clots in $\leq$30% of the infarcted area with a slight space-occupying effect, and PH-2 was defined as blood clots in >30% of the infarcted area with a mass space-occupying effect. CT scans were reviewed by a neuroradiologist with extensive experience in acute stroke who was blinded to the clinical details.

Outcome Measures

Early evolution of disease was evaluated by the change in the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours after thrombolysis. Early neurological deterioration was defined as an increase of more than 4 points in the NIHSS score 24 hours after thrombolysis compared with the baseline.The long-term prognosis was assessed by the modified Rankin Scale (mRS) score at the third month. mRS scores of 0 to 2 were considered to indicate a favorable outcome, while scores of 6 indicated death.

Statistical Analysis

All statistical analyses were performed with SPSS software version 20 (IBM Corp, Armonk, NY). Continuous variables

are described using the mean $\pm$ standard deviation and were analyzed using Student's t-tests or Kruskal-Wallis tests. Categorical variables are described as percentages and were analyzed using Pearson's chi-square or Fisher's exact tests. The NIHSS score was described using medians (ranges).

Results

Seventy patients with acute cerebral infarction who received intravenous r-tPA thrombolysis were included in our study. Seventeen of 70 patients received thrombolysis between 4.5 and 9 hours after stroke onset on the basis of multimodal imaging. The baseline characteristics are shown in Table 1. Twenty-three (32.9%) patients were treated within the 3-hour time window, whereas 17 (24.3%) patients received thrombolysis >4.5 hours after stroke onset as determined by multimodal imaging. Seventeen (24.3%) patients developed ICH after intravenous r-tPA, and sICH occurred in 6 (8.6%) patients. According to the radiological criteria, there were 3 patients with HI-1 (4.3%), 4 patients with HI-2 (5.7%), 4 patients with PH-1 (5.7%) and 6 patients with PH-2 (8.6%). CT images from these patients are presented in Figure 1. Figure 2 shows changes in the NIHSS score at 24 hours according to the presence and type of post-thrombolytic ICH. There were significant differences among the 4 groups (P = 0.002). Patients with PH-2 had a significant increase in NIHSS score at 24 hours when compared with HI (HI-1 and HI-2), PH-1, and non-ICH groups, respectively(P = 0.000, 0.014, 0.019).whereas patients with HI (HI-1 and HI-2), PH-1, or non-ICH showed unapparent changes. The mean $\pm$ standard deviation in the NIHSS score at 24 hours and the baseline scores of the 4 groups were as follows: non-ICH (-2.72 $\pm$ 5.08), HI (0.57 $\pm$ 8.08), PH-1 (-2.75 $\pm$ 4.57), and PH-2 (11.67 $\pm$ 11.59). Table 2 and Figure 3 illustrate the clinical outcomes of patients with different subtypes of post-thrombolytic ICH. HI was not associated with early deterioration of neurological function or the clinical prognosis as determined by the mRS score at the third month. PH-1 was not increased the risk of early neurological deterioration; however, PH-1 could increase the risk of death at the third month (50% vs 11.3%, P = 0.090).PH-2 significantly increased the risk of early neurological deterioration (66.7% vs 3.8%, P < 0.001) and death at 3 months (50% vs 11.3%, P = 0.040).

Discussion

The incidence of ICH after intravenous r-tPA ranged from 10.6% to 48.4% in several large-sample, randomized, double-blind, placebo-controlled trials.[6-9] The incidence of ICH in our study was 23.4%, which is higher than that in the NINDS study (10.6%) but slightly lower than that in the ECASS III study (27%).[1] In this study, we included patients who were treated between 0 and 9 hours of the onset of stroke symptoms, which may have increased the incidence of ICH. The mean time from onset to thrombolysis was 247.41 $\pm$ 104.15 minutes, which is similar to that in the ECASS III study but much higher than that in the NINDS study.[2] The median admission NIHSS score was

Table 1. Baseline Characteristics of all Patients (n = 70).

| Characteristics	Overall
Demographic datas	
Male	48 (68.6%)
Age (year)	65.44 $\pm$ 10.37
Weight (kg)	68.38 $\pm$ 7.71
Previous history	
Hypertension	50 (71.4%)
Diabetes	16 (22.9%)
Hyperlipidemia	14 (20.0%)
Transient ischemic attack	11 (15.7%)
Stroke	10 (14.3%)
Atrial fibrillation	22 (31.4%)
Myocardial infarction	12 (17.1%)
Congestive heart failure	9 (12.9%)
Smoke	23 (32.9%)
Concomitant medication 24 hours before thrombolysis	
Aspirin	7 (10.0%)
Clopidogrel	3 (4.3%)
Aspirin and clopidogrel	3 (4.3%)
Anticoagulant therapy	2 (2.9%)
Intravenous antihypertensive therapy	9 (12.9%)
Oral antihypertensive therapy	11 (15.7%)
Clinical assessment and laboratory examination	
NIHSS score	14 (4-34)
4-10	16 (22.9%)
11-15	28 (40.0%)
16-20	19 (27.1%)
>20	8 (11.4%)
Systolic blood pressure (mmHg)	150.2 $\pm$ 22.27
Diastolic blood pressure (mmHg)	85.90 $\pm$ 12.07
Blood glucose (mmol/L)	8.00 $\pm$ 3.67
Platelet ($\times 10^9$/L)	180.3 $\pm$ 65.11
INR	1.04 $\pm$ 0.16
Brain CT	
Early ischemic changes	16 (22.9%)
Hyperdense artery sign	15 (21.4%)
Insular ribbon sign	13 (18.6%)
ASPECT scores	
10	59 (84.3%)
8-9	5 (7.1%)
$\leq$7	7 (10.0%)
TOAST classification	
LAA	39 (55.7%)
CE	25 (35.7%)
LS	1 (1.4%)
Other	2 (2.9%)
Unknown	3 (4.3%)
OCSP classification	
TACI	24 (34.3%)
PACI	35 (50.0%)
POCI	10 (14.3%)
LACI	1 (1.4%)
Time (minutes)	
Time from onset to arriving at the hospital	120.07 $\pm$ 88.33
Time from arriving at the hospital to thrombolysis	125.73 $\pm$ 56.59
Time from onset to thrombolysis	247.41 $\pm$ 104.15
0-90	0
91-180	23 (32.9%)
181-270	27 (38.6%)
271-360	10 (14.3%)
>360	11 (15.7%)
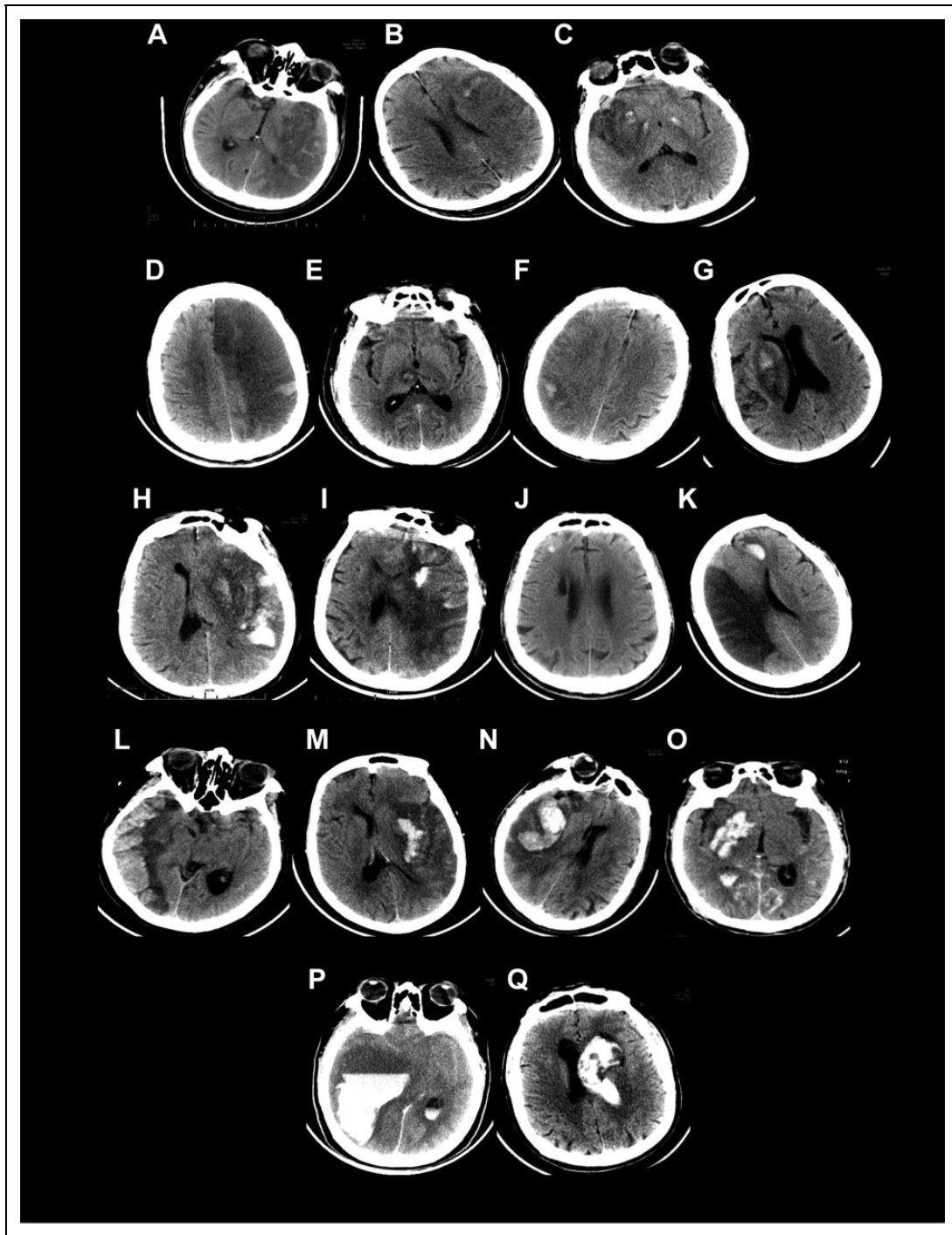
Figure 1. CT images of 17 patients with post-thrombolytic ICH. (A-C) are HI-1, (D-G) are HI-2, and (H-K) are PH-1. (H,I) Irregular and scattered hematomas are seen in the infarct area. (J) The infarcted area is located in the right basal ganglia, and the hematoma is located in the right frontal lobe, which is distant from the infarcted area. (K) The patient had a massive right cerebral infarction with a small hematoma in the left frontal lobe.(L-Q) are PH-2 and sICH. (L-O) The hematomas are located in the infarct area. (M,N) CT shows HI-2 10 hours after thrombolysis. Twenty-four hours after thrombolysis, CT shows that the hematoma has enlarged, which resulted in the deterioration of the patient's clinical symptoms. This finding suggests that some cases of PH may develop from HI. (O) The patient had a right temporal lobe infarction with hemorrhage in the infarct area breaking into the ventricle. (P) The patient had a right cerebral hemisphere infarction accompanied by a huge hematoma in the infarct area and another hematoma in the left thalamus breaking into the ventricle. (Q) The hematoma is distant from the right parietal lobe infarction, which is located in the left basal. ganglia and breaking into the ventricle.
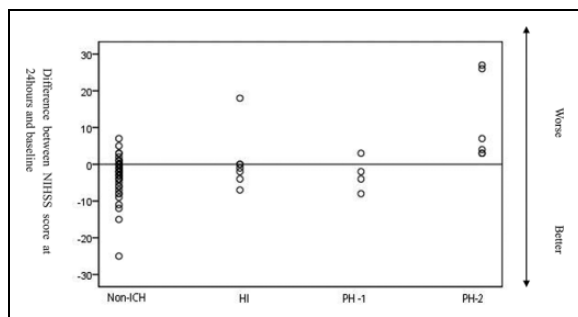
Figure 2. Changes in NIHSS score at 24 hours according to the presence and type of post-thrombolytic ICH.

Table 2. Clinical Outcomes of Patients With Different Subtypes of Post-Thrombolytic ICH.

	non-ICH (n = 53)	HI (n = 7)	PH-1 (n = 4)	PH-2 (n = 6)
Early neurological deterioration	2 (3.8)	1 (14.3)		4 (66.7) ▼
Favorable outcome at 3 months	24 (45.3)	3 (42.9)	1 (25.0)	
Disability or death at 3 months	8 (15.1)	2 (28.6)	2 (50.0)	4 (66.7)
Death at 3 months	6 (11.3)	2 (28.6)	2 (50.0)	3 (50.0) ▼

"▼" indicates that there is a statistically significance between PH-2 and non-ICH, $P < 0.05$.
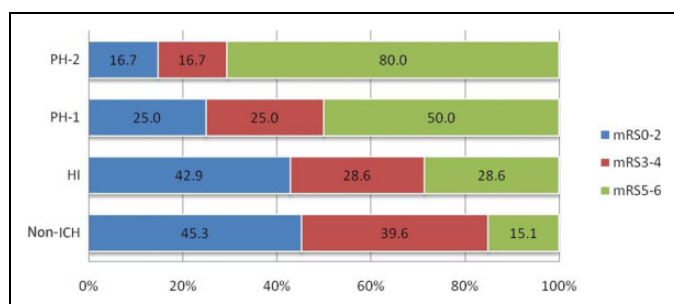

Figure 3. Distribution of mRS scores according to presence and type of post-thrombolytic ICH.

14, which is consistent with that of the NINDS study but higher than that of the ECASS III study.[6,9] The incidence of sICH in our study was 8.7%, which is close to those in the NINDS and ECASS III studies (6.4% and 7.9%, respectively). The distribution of ICH subtypes occurring within the first 36 hours after intravenous r-tPA was as follows: HI-1 was identified in 3 patients (4.3%), HI-2 in 4 (5.7%), PH-1 in 4 (5.7%), and PH-2 in 6 (8.6%). The incidences of PH-1 and PH-2 were similar to those in the ECASS II study (3.7% and 8.1%, respectively), but the incidences of HI-1 and HI-2 were relatively lower (19.6% and 15.2%, respectively). This may be because we analyzed ICH occurring within 36 hours after thrombolysis, while the ECASS II study included patients with ICH occurring within 7 days of intravenous thrombolysis.[8]

We found that patients with different subtypes of ICH identified on images after thrombolysis had different clinical outcomes. There was no significant correlation between HI and early neurological deterioration or clinical prognosis at the third month. This finding is in accordance with those of the ECASS I and ECASS II studies.[7,8] Molina et al[10] investigated the relationship between hemorrhagic transformation subtypes and thrombolytic efficacy in patients with proximal middle cerebral artery occlusion treated with intravenous r-tPA <3 hours after stroke onset. They suggested that HI represented a marker of early successful recanalization, leading to a reduced infarct size and improved clinical outcome. One pooled analysis[11] of 6 randomized placebo-controlled trials of intravenous r-tPA suggested that HI was not associated with r-tPA therapy. Overall, there is convincing evidence that HI occurs as part of the natural history of ischemic stroke and is even a potential sign of vascular recanalization.

In contrast to HI, PH was closely related to clinical outcomes. In our study, PH-1 did not increase the risk of early neurological deterioration but showed a tendency to increase the risk of death at the third month (50% vs 11.3%, P = 0.090), although there was no statistically significant difference. This result indicated that a small hematoma may have a slight or no effect on clinical outcome. Moreover, we reported that in contrast to the outcomes of other subtypes of bleeding, PH-2 was significantly associated with early neurological deterioration and increased the risk of death at the third month. Fiorelli et al[7] also reported that PH-2 had a fatal impact on early neurological course after thrombolysis (odds ratio for deterioration, 32.3; 95% confidence interval (CI), 13.4 to 77.7) and on 3-month death (odds ratio, 18.0; 95% CI, 8.05 to 40.1). Similarly, Berger et al[12] indicated that only PH-2 independently caused neurological deterioration and impaired prognosis compared with the absence of hemorrhagic transformation. This finding suggests that PH-2 is the only clinically relevant subtype of ICH after thrombolysis.

Conclusion

In conclusion, different subtypes of post-thrombolytic ICH were associated with diverse clinical prognoses. Only PH-2 was significantly associated with early neurological deterioration and increased mortality at the third month. Therefore, patients with PH-2 should be monitored intensively, and active measures should be taken.

Declaration of Conflicting Interests

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