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Postthrombolytic Antiplatelet Use for Patients with Intercerebral Hemorrhage without Extensive Parenchymal Involvement Does Not Worsen Outcome

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Background and Purpose It is unclear whether postthrombolytic antiplatelet (AP) therapy after thrombolytic-related hemorrhage without extensive parenchymal involvement (THEPI) affects the clinical outcome. This study explored whether AP administration in patients with THEPI affects short- and long-term outcomes.

Methods All of the data for this study were collected from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) registry. Patients with THEPI were assigned to either the AP (AP therapy should be commenced 24 h after intravenous thrombolysis) or AP-naïve groups. THEPI was defined according to European-Australasian Acute Stroke Study II criteria. The 90-day functional outcome, 7-day National Institutes of Health Stroke Scale (NIHSS) score, and 7-day and 90-day mortalities were compared between the AP and AP-naïve groups. Logistic regression analysis was used to evaluate the effects of AP therapy on the short- and long-term clinical outcomes.

Results Of the 928 patients enrolled from those in the TIMS-China registry (n=1,440), 89 (9.6%) had nonsymptomatic intracerebral hemorrhage (ICH) within 24−36 h after thrombolysis; 33 (37%) of these patients were given AP therapy (AP group) and 56 (63%) were not (AP-naïve group). No significant differences were found for the risk of 7-day aggravated ICH (p=0.998), 7-day NIHSS score (p=0.5491), 7-day mortality [odds ratio (OR)=3.427; 95% confidence interval (95% CI)=0.344−34.160; p=0.294], 90-day mortality (OR=0.788, 95% CI=0.154−4.040, p=0.775), or modified Rankin score 5 or 6 at 90-days (OR=1.108, 95% CI=0.249−4.928, p=0.893) between the AP and AP-naïve groups after THEPI.

Conclusions Early administration of postthrombolytic AP therapy after THEPI does not worsen either the short- or long-term outcome. AP therapy may be a reasonable treatment option for patients with THEPI to reduce the risk of ischemic stroke recurrence.

Key Words ischemic stroke, thrombolytic-related hemorrhage, antiplatelet therapy, outcome.

INTRODUCTION

Intravenous thrombolysis with alteplase [a recombinant tissue plasminogen activator (rt-PA)] is the only approved treatment for acute ischemic stroke.[1,2] However, the potential increased risk of postthrombolytic hemorrhagic transformation (HT), including thrombolytic-related hemorrhage without extensive parenchymal involvement (THEPI), limits its application.[3-6] The early administration of AP therapy after THEPI is neither recommended nor discouraged by the guidelines. The guidelines of the American Heart Association/American Stroke Association suggest that HT within an ischemic stroke may have a different course and natural history from intracerebral hemorrhage (ICH).[7] However, many cli-

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nicians are still reluctant to continue AP therapy after THEPI. Several controversial findings regarding THEPI may influence the clinical outcome.[8-10] The administration of AP therapy for THEPI remains a matter of debate. The findings of one retrospective study[11] suggest that the early administration of antithrombotics is not associated with aggravation of HT and poor short-term outcome. However, in the current study HT was defined according to cranial magnetic resonance imaging (MRI) series, and thrombolysis was administered to some of the patients (46.7%). There have been few studies of the effects of early administration of AP therapy on the long-term outcome for patients with THEPI based on cranial computed tomography (CT).

The relationship between postthrombolytic AP therapy and clinical prognosis was assessed in patients with THEPI from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) registry. The hypothesis that early AP therapy worsens the outcome of postthrombolytic hemorrhage without extensive parenchymal involvement was tested.

METHODS

Subjects

The data for this study were collected from the TIMS-China registry,[12] which is a national prospective stroke registry of thrombolytic therapy with intravenous rt-PA in patients with acute ischemic stroke in China. Nationwide, 67 centers participated in this stroke registry between May 2007 and April 2012. The demographics, clinical characteristics, cranial CT scans, medical therapies, and thrombolysis data were collected, and all of the patients were followed up for 3 months. All patients or their caregivers were interviewed at the clinic or by telephone. The physicians performed the data collection during the follow-up period. Eligible patients received thrombolysis within a 4.5-h poststroke time window. Patients with a National Institutes of Health Stroke Scale (NIHSS) score of ≥25 were excluded. Treatment information regarding the use of aspirin (ASA), clopidogrel (CLP), and other AP therapies commenced 24 h after thrombolysis was recorded in the TIMS-China case-report form. Patients with postthrombolytic nonsymptomatic ICH (non-sICH) were assigned to the AP group (AP therapy should have commenced within 24 h after intravenous thrombolysis) or the AP-naïve group (AP therapy should not have commenced within 14 days after thrombolysis and hemorrhage disappeared on CT scan). Those on ASA only (21 cases), CLP only (10 cases), or dual AP therapy (2 cases) were not analyzed separately due to the smallness of the sample. The TIMS-China registry was approved by ethics committee of Beijing Tian Tan Hospital in 2006. The data from the TIMS-China registry was anonymized before access and analysis by all researchers, who were blind to the patient treatment assignation. All patients or his/her legal representatives provided written informed consent to participation before being entered in the registry.

Outcome analysis

Follow-up CT scans were collected at 24−36 h and 7 days. All follow-up CT scans demonstrating HT were rated according to European Cooperative Acute Stroke Study II (ECASS II) classification,[2] as follows: HI1, small petechiae; HI2, confluent petechiae; PH1, hematoma in <30% of the infarcted area, with a mild space-occupying effect; and PH2, hematoma in >30% of the infarcted area, with a significant space-occupying effect. HT was also often divided into symptomatic ICH (sICH) and hemorrhage without extensive parenchymal involvement based on the deterioration in neurologic status. According to ECASS II criteria, sICH was defined as an increase in NIHSS score of ≥4 points from baseline for neurological status in the first 24 h after thrombolysis and the presence of HT on the follow-up CT scan at 24−36 h.[2,13,14] Patients with sICH were excluded from the present study. The remaining patients with thrombolysis-related HTs were labeled as having thrombolytic-related hemorrhage without extensive parenchymal involvement. Aggravation of HT was defined as either enlargement of the original HT or newly developed HT within the infarcted area. All scans were interpreted independently by two experienced neuroradiologists who were blinded to the clinical data. In cases of discrepancy between the two raters, the scans were reviewed simultaneously by a central radiological adjudication committee. The primary outcome measures included functional outcome at 90 days [functional independence was defined as a modified Rankin Scale (mRS) score of 0−6], NIHSS score at 7 days, and mortality at 7 and 90 days.

Statistical analysis

Data are presented as mean±SD values, or as frequencies for categorical variables. Pearson's chi-square (χ^2) test was used for comparisons of categorical variables. Continuous variables were analyzed using the *t*-test or Mann-Whitney U test. Percentage proportions of outcome events were calculated by dividing the number of events by the total number of patients. A separate multivariable logistic regression was performed for each outcome variable. Odds ratios with 95% confidence intervals were calculated using the AP-naïve group after thrombolytic-related hemorrhage without extensive parenchymal involvement as the reference group. The threshold for statistical significance was set at $p<0.05$. All statistical analyses were performed using SAS software

version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Of the 1,440 patients enrolled on the TIMS-China registry at 67 centers across China, the data of 928 patients were included in the data analysis; of these, 89 patients had THEPI within 24–36 h. It has been reported that 9.6% of thrombolysis patients in China transform to asymptomatic hemorrhage. In the present study, 33 of the 89 THEPI patients (37%) who were administered AP therapy 24–36 h, and the remaining 56 without AP therapy (63%) transformed to asymptomatic hemorrhage (Fig. 1). The baseline characteristics of the patients with asymptomatic HT postthrombolytic therapy with or without AP drugs are given in Table 1. The findings demonstrate that more male asymptomatic patients with HT were administered postthrombolytic AP agents than their female counterparts. There were 38, 30, 15, and 6 patients who transformed to the HI2, HI1, PH1, and PH2 subtypes of asymptomatic hemorrhage, respectively, after thrombolytic therapy, of which 13, 15, 3, and 2 with the HI1 received AP drugs. The bleeding ratio of patients with asymptomatic HT after thrombolysis in the AP group was 9.09% (*n*=3), while that of patients in the AP-naïve group was 7.14% (*n*=4). Furthermore, two of the AP-naïve patients with the PH2 subtype suffered hematoma expansion, while only one of the AP-group patients with the PH2 subtype suffered hematoma enlargement (Figs. 2 and 3). Follow-up after 7 days revealed NIHSS scores of 9.19±7.86 and 10.45±8.49 in the AP and AP-naïve groups,

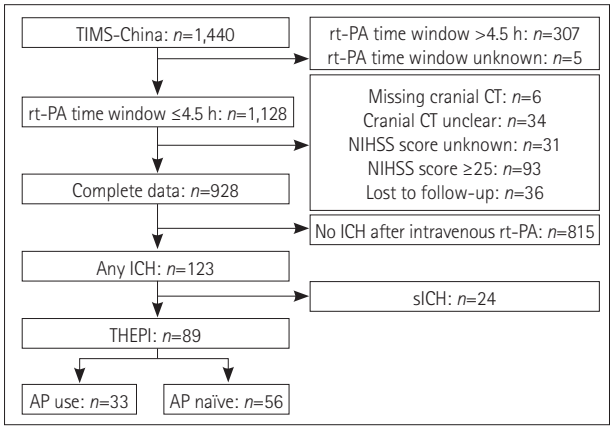

Fig. 1. Numbers of eligible study patients in the TIMS-China registry. AP: antiplatelet, ICH: intracerebral hemorrhage, NIHSS: National Institutes of Health Stroke Scale, rt-PA: recombinant tissue plasminogen activator, sICH: symptomatic ICH, TIMS-China: Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China.

Table 1. Baseline characteristics of THEPI patients with (AP group) and without (AP-naïve group) AP therapy

	AP group (*n*=33)	AP-naïve group (*n*=56)	*p*
Gender (male)	10 (30.30)	30 (53.57)	0.033
Age (years)	65.12±9.82	66.70±9.72	0.427
History of hypertension	17 (51.52)	32 (57.14)	0.606
History of diabetes	3 (9.09)	9 (16.07)	0.542
History of atrial fibrillation	11 (33.33)	20 (35.71)	0.812
History of smoking	12 (36.36)	13 (23.21)	0.182
Postthrombolytic AP use	5 (15.15)	7 (12.50)	0.974
Time rt-PA administered after symptom onset (hours)	3.06±0.81	2.72±0.68	0.451
Serum glucose (mmol/L)	6.84±1.21	7.34±2.85	0.590
Systolic blood pressure (mm Hg)	140.06±24.11	151.95±22.04	0.126
Dystolic blood pressure (mm Hg)	81.00±12.42	87.54±13.80	0.204
History of hyperlipidemia	2 (6.06)	2 (3.57)	0.986
TOAST stroke type			
Atherothrombotic	22 (66.67)	28 (50.00)	0.303
Cardioembolic	9 (27.27)	22 (39.29)	
Other/unknown	2 (6.06)	6 (10.71)	
Dose of rt-PA (mg/kg)	0.85±0.08	0.87±0.12	0.265
NIHSS score before thrombolysis	14.42±5.86	16.23±6.98	0.220
History of mRS	3 (3.37)	33 (4.06)	0.637
History of TIA	0 (0.00)	3 (5.36)	0.456
History of stroke	4 (12.12)	11 (19.64)	0.360
Occlusion of total ICA	5 (16.67)	3 (6.12)	0.261
Occlusion of proximal MCA	5 (16.67)	3 (6.12)	0.261

The data are mean±SD or *n* (%) values.
AP: antiplatelet, ICA: internal carotid artery, MCA: middle cerebral artery, rt-PA: recombinant tissue plasminogen activator, THEPI: thrombolytic-related hemorrhage without extensive parenchymal involvement, TIA: transient ischemic attack, TOAST: Trial of Org 10172 in Acute Stroke Treatment.

respectively (p=0.549).

Analysis of the data without adjustment for covariates revealed that administration of postthrombolytic AP therapy improved the clinical outcomes at 90 days of follow-up (i.e., 90-day mortality, mRS score 0–2, and mRS score 5 or 6) in patients with THEPI. After adjustment for age, sex, baseline NIHSS score, and dose of rt-PA using a logistic regression model, the use of postthrombolytic AP therapy still exhibited a favorable trend, although not a statistically significant one (Table 2), and there was no increase in mortality or in the mRS score 5 or 6 ratio. Subgroup analysis of THEPI revealed that postthrombolytic AP therapy did not adversely affect the clinical outcomes of patients with the HI1, HI2, or PH1 subtypes (Table 3).

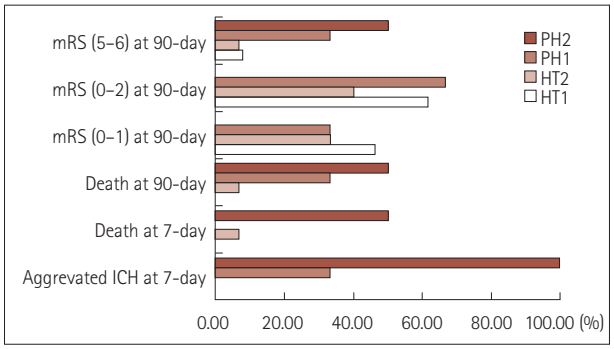

Fig. 2. Comparison of function in different types of THEPI in the AP group at the 7- and 90-day follow-ups in patients from TIMS-China. AP: antiplatelet, ICH: intracerebral hemorrhage, mRS: modified Rankin Scale, THEPI: thrombolytic-related hemorrhage without extensive parenchymal involvement, TIMS-China: Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China.

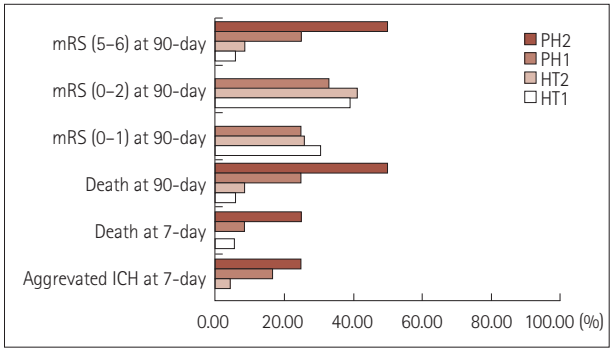

Fig. 3. Comparison of function in different types of THEPI in the AP-naïve group at the 7- and 90-day follow-ups in patients from TIMS-China. AP: antiplatelet, ICH: intracerebral hemorrhage, mRS: modified Rankin Scale, THEPI: thrombolytic-related hemorrhage without extensive parenchymal involvement, TIMS-China: Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China.

DISCUSSION

While the use of AP therapy after THEPI has not been recommended in any studies, the present study showed that postthrombolytic AP therapy in such patients did not worsen the short- or long-term prognosis, and that the early use of AP therapy after THEPI might thus be relatively safe for patients enrolled in the TIMS-China registry. In addition, although aggravation of HT was observed more frequently in patients with PH2 than in those with the other subtypes, the administration of AP therapy after THEPI was not associated with neurological deterioration. Therefore, the results of the present study suggest that the use of AP therapy after THEPI-especially the HI1, HI2, and PH1 subgroups-might be reasonable for the prevention of subsequent ischemic stroke.

THEPI in China

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study found remarkably low rates of nonsymptomatic HT (4.5%),[1] as did a large observational study of intravenous thrombolysis, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST; 9.6%).[13] In TIMS-China, this figure was 9.5%. However, there were higher rates of asymptomatic hemorrhage (39.6%) in ECASS II.[2] Earlier initiation of thrombolysis may be the reason for the lower asymptomatic hemorrhage rates in NINDS, SITS-MOST, and TIMS-China compared to ECASS II. Direct comparison of the non-sICH rates among the different studies may also be hampered by variability in definitions and differences in the timing of imaging.[15-19]

Table 2. Functional outcomes for THEPI with and without postthrombolysis AP therapy

Outcome	Postthrombolysis AP therapy		Unadjusted OR		Adjusted OR	
	Yes (n=33; 37%)	No (n=56; 63%)	OR (95% CI)	p	OR (95% CI)	p
Mortality at 7-day follow-up	2 (6.06)	3 (5.36)	1.185 (0.049–1.696)	0.113	3.427 (0.344–34.160)	0.294
Mortality at 90-day follow-up	3 (9.09)	8 (14.29)	0.690 (0.086–0.818)	0.036	0.788 (0.154–4.040)	0.775
mRS score 0–1 at 90-day follow-up	12 (36.36)	15 (26.79)	1.191 (1.089–3.409)	0.055	1.461 (0.532–4.011)	0.462
mRS score 0–2 at 90-day follow-up	15 (45.45)	19 (33.93)	1.253 (10.153–4.416)	0.021	1.568 (0.609–4.039)	0.351
mRS score 5 or 6 at 90-day follow-up	4 (12.12)	8 (14.29)	0.720 (0.547–0.929)	0.014	1.108 (0.249–4.928)	0.893

Adjusted covariates (logistic regression model): age, sex, baseline NIHSS score, and dose of rt-PA.
AP: antiplatelet, CI: confidence interval, NIHSS: National Institutes of Health Stroke Scale, OR: odds ratio, rt-PA: recombinant tissue plasminogen activator, THEPI: thrombolytic-related hemorrhage without extensive parenchymal involvement.

Table 3. Functional outcomes for THEPI subgroups (HT1+HT2+PH1) with and without AP therapy after thrombolysis

Outcome	Postthrombolysis AP therapy		Unadjusted OR		Adjusted OR	
	Yes (*n*=31; 37%)	No (*n*=52; 63%)	OR (95% CI)	*p*	OR (95% CI)	*p*
Mortality at 7-day follow-up	1 (3.33)	2 (3.85)	0.690 (0.060–7.973)	0.766	1.251 (0.0860–18.297)	0.870
Mortality at 90-day follow-up	2 (6.67)	4 (7.69)	0.679 (0.116–3.969)	0.667	0.429 (0.068–2.717)	0.370
mRS score at 90-day follow-up						
0 or 1	11 (35.48)	13 (25.00)	1.291 (0.480–3.474)	0.612	1.597 (0.563–4.528)	0.379
0–2	14 (45.16)	17 (32.69)	1.287 (0.500–3.313)	0.601	1.724 (0.236–3.706)	0.275
5 or 6	3 (9.68)	4 (7.69)	1.056 (0.218–5.105)	0.946	0.693 (0.139–3.453)	0.654

Except where stated otherwise, data are *n* (%) values. Adjusted covariates (logistic regression model): age, sex, baseline NIHSS score, and dose of rt-PA.

AP: antiplatelet, CI: confidence interval, NIHSS: National Institutes of Health Stroke Scale, OR: odds ratio, rt-PA: recombinant tissue plasminogen activator, THEPI: thrombolytic-related hemorrhage without extensive parenchymal involvement.

AP therapy after THEPI

Kim et al.[11] found that the use of AP therapy was reduced to about 73% in patients who had hemorrhagic infarction and noncardioembolic stroke. In the present study, only about 37% of Chinese patients were administered AP therapy after THEPI, suggesting that physicians in China were cautious about using AP therapy in such patients. The probable explanation for this reluctance was that the physicians worried that HT would aggravate the clinical outcome. The increase, however, may also be attributable to the increase in the number of medical disputes in China.[20] The retrospective study of Kim et al.[11] suggested that the early administration of antithrombotics was not related to the aggravation of HT and poor short-term outcome. However, in that study HT was defined according to cranial MRI series, and the long-term clinical outcome was not assessed. In the present study, HT, defined as cranial CT and THEPI, was defined clinically (worsening of the NIHSS score by <4 points from the baseline NIHSS score). We attempted to ascertain whether postthrombolytic AP therapy in patients with THEPI was associated with a worse outcome. However, the present findings are in agreement with that of Kim et al.[11]—AP therapy after THEPI does not lead to a worse clinical outcome.

The assumption was made at the start of this study that the risks of early administration of AP therapy after THEPI would outweigh the benefits. However, the study showed that postthrombolytic AP therapy for patients with THEPI does not worsen either the short- or long-term clinical outcome. Given the differences in proportions of patients taking AP therapy between the subtypes of THEPI, and the tendency toward a reduction in AP therapy among those with the PH2 subtype, the data were reanalyzed with only data from the HI1, HI2, and PH1 subgroups, with similar findings. The increased risk of aggravated HT at 7 days found for those with the PH2 type of THEPI who were treated with early AP therapy must be interpreted with caution, since the effect was measured in a relatively small number of patients. However, this finding perhaps indicates that physicians should be more circumspect when considering postthrombolytic APs therapy in PH2-type patients.

Study limitations

This study was subject to some limitations. The sample was relatively small, which may have had a subtle effect (either positive or negative) on the outcome of THEPI. It should be noted that the application of AP therapy did not follow the randomized, double-blind principles of clinical study, which may have resulted in different proportions of patients being given AP therapy between the various subtypes, possibly affecting the observed tendency to decline AP therapy in the PH2 subtype. This might explain the favorable trend of an mRS score 0 or 1 or an mRS score 0–2 outcome in the AP group. However, in the subgroup (HI1+HI2+PH1) analysis, the early use of AP therapy for THEPI still does not still worsen either the short- or long-term clinical outcome. A double-blinded, placebo-controlled design would have prevented this bias.

In summary, notwithstanding the aforementioned study limitations, the present results suggest that AP therapy in patients with THEPI in China does have not a negative effect on the clinical prognosis. Evidence was found that early administration of postthrombolytic AP therapy after THEPI does not worsen either the short- or long-term clinical outcome. AP therapy in patients with THEPI, and especially the HI1, HI2, and PH1 subgroups, may be a safe intervention for stroke recurrence.

Conflicts of Interest

The authors have no financial conflicts of interest.

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