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Effect of antiplatelet pretreatment on platelet aggregation and clinical outcomes in acute ischemic stroke patients treated with recombinant tissue-type plasminogen activator

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Early administration of antiplatelet agents in acute ischemic stroke patients (AIS) receiving intravenous thrombolysis (IVT) is a potential therapeutic strategy, however, safety and efficacy are not well established. We hypothesize that antiplatelet pretreatment (AP) before IVT have a similarly role as initiation of AP within the first 24 hours following IVT. We aimed to explore the effect of AP on platelet aggregation and clinical outcomes in thrombolysis-treated AIS patients. We enrolled AIS patients treated with IVT at the Neurology Department of the Nanjing First Hospital from January 2016 to June 2018. Prior use of antiplatelet agent was recorded. Light transmittance aggregometry was used to estimate the maximum platelet aggregation (MPA). Linear regression model was performed to investigate the factors associated with MPA. Multivariate logistic regression was used to analyse the association between AP and clinical outcomes. A total of 59 patients were included; 23 (38.9 %) were taking antiplatelet agent before stroke. Prior AP (β=-20.209, SE mean=6.574; P=0.004) was significantly lower the arachidonic acid-induced MPA at the time point of 3h after thrombolysis. AP did not increase of the risk for sICH (OR=3.41, 95%CI 0.16-7.20, p=0.436) or mortality (OR=3.55, 95%CI 0.39-8.52, p=0.260). There were no associations between AP and improved clinical outcomes (all P>0.05). In thrombolysis-treated AIS patients, AP was associated with lower MPA after thrombolysis. AP is safe in these patients, however, further studies are required to confirm the efficacy.

1. Introduction

For patients with acute ischemic stroke (AIS), intravenous thrombolysis (IVT) with rt-PA (recombinant tissue-type plasminogen activator) remains the most effective treatment shown to improve outcomes (Powers et al. 2018). However, as a result of endothelial injuries and platelet-mediated thrombotic mechanism, early reocclusion is an inevitable complication that occurs in 14-34% of AIS patients receiving IVT (Alexandrov et al. 2002; Saqqur et al. 2007), resulting in neurologic deterioration and in-hospital mortality. Therefore, early inhibition of platelet aggregation might be a potential therapeutic strategy for treatment of AIS patients following rt-PA.

Antiplatelet therapy in Combination With rt-PA thrombolysis in ischemic stroke (ARTIS) study is a randomized, placebo-controlled, multicenter trial that firstly investigated the effect of aspirin therapy on safety and efficacy outcomes following IVT (Zinkstok et al. 2002). However, the conclusion demonstrated that aspirin administration immediately after thrombolysis increased the risk of symptomatic intracranial hemorrhage (sICH), and did not improve follow-up functional outcome (Zinkstok et al. 2002). The results of this trial do not support a change of the clinical guidelines (Jauch et al. 2013), which advise to start antiplatelet therapy 24h after rt-PA. However, a previous study has shown that clinical deterioration following IVT was less frequent in AIS patients with antiplatelet pretreatment (AP) (Grotta et al. 2001). This phenomenon may be explained by that prior use of AP was associated with a higher rate of early recanalization in thrombolysis-treated AIS patients (Saňák et al. 2012). There has been conflicting conclusions drawn between studies that investigated the effect of AP prior to IVT. Some studies indicated that prior AP increased the risk for sICH in AIS patients receiving rt-PA (Zinkstok et al. 2002; Dorado et al. 2010; Xian et al. 2010), but with no increase of good outcome after thrombolysis (Zinkstok et al. 2002; Diedler et al. 2010; Ibrahim et al. 2010). Other studies demonstrated that prior AP was safe (Grotta et al. 2001; Saňák et al. 2012; Bravo et al. 2008; Diedler et al. 2010; Ibrahim et al. 2010) and had better outcome (Saňák et al. 2012; Xian et al. 2010) compared to patients not receiving AP therapy. To date, little was known about the role of AP on maximum platelet aggregation (MPA) at different time points within 24h after thrombolysis and the association with clinical outcomes.

We hypothesize that AP before rt-PA have a similarly role as AP combined with rt-PA. In this study, we aimed to explore the effect of AP on MPA at different time points following rt-PA, and to investigate the association of AP with clinical outcomes in thrombolysis-treated AIS patients.

2. Investigations and results

2.1. Baseline characteristics of the patients

A total of 110 AIS patients treated with intravenous rt-PA were identified. Of them, 35 patients did not agree with participation, 9 were excluded due to incomplete blood samples, and 7 were lost

Table 1: Demographic and clinical characteristics of ischemic stroke patients with and without antiplatelet pretreatment

Characteristics	Non-AP (n = 36)	AP (n = 23)	p value
Age, yrs	68.8 ± 10.6	74.5 ± 7.7	0.046
Male,%	26 (72.2)	15 (65.2)	0.569
Hypertension,%	26 (72.2)	20 (87.0)	0.183
Diabetes mellitus,%	9 (25.0)	7 (30.4)	0.647
Hyperlipidaemia,%	4 (11.1)	0(0.0)	0.098
Coronary heart disease,%	4 (11.1)	10 (43.5)	0.004
Atrial fibrillation,%	4 (11.1)	10 (43.5)	0.004
Previous cerebral infarction,%	3 (8.3)	7 (30.4)	0.027
Smoking,%	7 (19.4)	2(8.7)	0.263
Systolic blood pressure, mmHg	152.1 ± 20.2	137.8 ± 24.2	0.020
Diastolic blood pressure, mmHg	87.1 ± 10.0	82.8 ± 16.3	0.234
Platelet count, $\times 10^9$/L	200.0 ± 68.5	171.5 ± 43.4	0.149
Fasting blood-glucose, mmol/L	6.2 ± 1.8	6.6 ± 2.1	0.608
Total cholesterol, mmol/L	4.4 ± 1.1	3.9 ± 1.0	0.032
Triacylglycerol, mmol/L	1.6 ± 0.9	1.4 ± 0.6	0.974
LDL, mmol/L	3.1 ± 1.1	2.3 ± 1.0	0.004
TOAST classification,%			
Large-artery atherosclerosis	13 (36.1)	4 (17.4)	0.135
Cardioembolism	10 (27.8)	13 (56.5)	
Small-artery occlusion Lacunar	12 (33.3)	6 (26.1)	
Others	1 (2.8)	0(0.0)	
OCSP,%			
Total anterior circulation infarct	6 (16.7)	8 (34.8)	0.228
Partial anterior circulation infarct	22 (61.1)	10 (43.5)	
Posterior circulation infarct	6 (16.7)	2 (8.7)	
Lacunar infarct	2 (5.6)	3 (13.0)	
Time from onset to thrombolysis, min	170.1 ± 58.1	177.9 ± 56.7	0.514
NIHSS, median(IQR)	7 (4-13)	8 (4-11)	0.651

TOAST=Trial of Org 10172 in Acute Stroke Treatment; OCSP=Oxfordshire Community Stroke Project; NIHSS=National Institutes of Health Stroke Scale; LDL=Low-density lipoprotein cholesterol; IQR=interquartile range; AP=antiplatelet pretreatment

to follow-up. Finally, 59 participants were included in the study. The mean age was 71.0±9.9 years, 41 (69.5%) patients were male. Prior AP was recorded in 23 (38.9%) patients. Table 1 provides the characteristics of patients with and without AP. Compared to patients without prior antiplatelet agent, AP users were older (74.5 vs 68.8 years; p = 0.046), accompanied by a higher rate of coronary heart disease (43.5% vs 11.1%; p = 0.004), atrial fibrillation (43.5% vs 11.1%; p = 0.004) and previous cerebral infraction (30.4% vs 8.3%; p = 0.027). Moreover, systolic blood pressure (137.8 vs 152.1 mmHg; p = 0.020), total cholesterol (3.9 vs 4.4 mmol/L; p = 0.032) and low-density lipoprotein cholesterol (2.3 vs 3.1 mmol/L; p = 0.004) were significant difference between the two groups.

2.2. Assessment of clinical factors associated with platelet aggregation

Table 2 shows the results of AA-induced MPA measured within 24 h after thrombolysis. Compared to patients without AP, AA-induced MPA was significantly lower on admission (18.7 vs 41.5; p = 0.029), and the following measurement points of 3 h (16.6 vs

Table 2: Maximum platelet aggregations induced by arachidonic acid within 24 h after thrombolysis in patients with acute ischemic stroke

MPA	Non-AP (n = 36)	AP (n = 23)	p value
On admission	41.5 ± 21.7	18.7 ± 17.7	0.029
3 h	40.1 ± 23.0	16.6 ± 19.6	0.0001
6 h	44.4 ± 22.8	24.2 ± 19.9	0.004
12 h	45.9 ± 22.5	19.1 ± 19.2	0.0001
18 h	42.4 ± 24.2	26.9 ± 21.7	0.025

MPA=maximum platelet aggregation; AP=antiplatelet pretreatment

Table 3: Multivariate liner regression analysis for clinical factors associated with arachidonic acid-induced maximum platelet aggregation at 3 h after thrombolysis

Independent variable	β Coefficient		p value
	Value	SE	
AP	-20.209	6.574	0.004
Age	0.102	0.332	0.759
Previous cerebral infarction	0.531	8.633	0.951
Platelet count	0.105	0.050	0.042
Total cholesterol	4.114	2.954	0.171

AP=antiplatelet pretreatment; SE= standard error

Table 4: Association between antiplatelet pretreatment and clinical outcomes in multivariate logistic regression

Outcomes	Non-AP (n = 36)	AP (n = 23)	OR(95% CI)	p value
NFI at 24h, %	22 (61.1)	15 (65.2)	0.84(0.28-2.49)	0.750
NFI at 7d, %	26 (72.2)	17 (73.9)	0.92(0.28-2.99)	0.887
mRS (0-2) at 1m, %	23 (63.9)	12 (52.2)	1.62(0.56-4.70)	0.372
mRS (0-2) at 3m, %	23 (63.9)	12 (52.2)	1.62(0.56-4.70)	0.372
mRS (0-2) at 6m, %	25 (69.3)	14 (60.9)	1.46(0.49-4.38)	0.497
sICH,%	2 (5.6)	0 (0.0)	3.41(0.16-7.20)	0.436
Death,%	5(13.9)	1 (4.3)	3.55(0.39-8.52)	0.260

Adjusted for age, National Institutes of Health Stroke Scale, maximum platelet aggregation and variables with P<0.1 in univariate analysis. NFI=neurological function improvement; mRS=modified Rankin Scale score; sICH=symptomatic intracranial hemorrhage

40.1; $p = 0.0001$), 6h (24.2 vs 44.4; $p = 0.004$), 12h (19.1 vs 45.9; $p = 0.0001$) and 18 h (26.9 vs 42.3; $p = 0.025$) in patients received prior AP. The distribution of AA-induced MPA at different time points is shown in the Fig. When clinical factors associated with platelet aggregation in multivariate linear regression were investigated, it was found that only platelet count and AP were significantly associated with AA-induced MPA on admission ($p = 0.007$; $p = 0.042$, respectively) and 3h after thrombolysis ($p = 0.042$; $p = 0.004$, shown in Table 3).

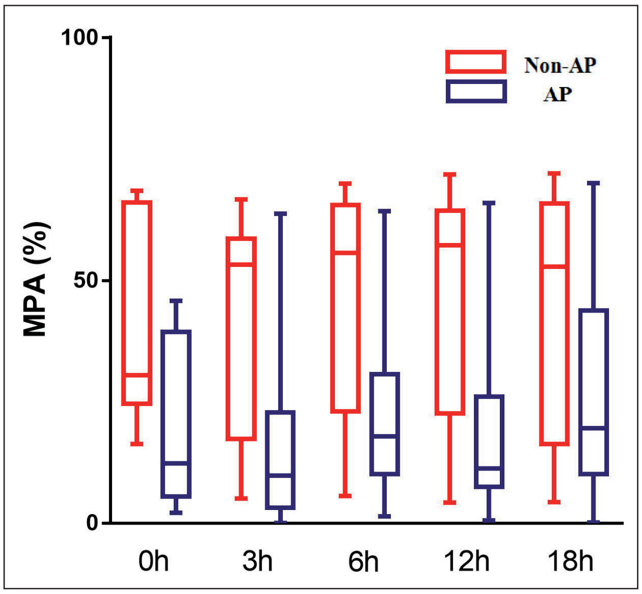

Fig.: Arachidonic acid-induced maximum platelet aggregations within 24 h after thrombolysis in patients with and without antiplatelet pre-treatment.

2.3. *Association of prior AP use with clinical outcomes*

Table 4 shows the association between prior AP and clinical outcomes in thrombolysis-treated AIS patients. After adjustment for potential confounders in the logistic regression model, the result indicated AP did not associated with NFI or good functional outcome at different follow-up points (all P>0.05), nor increase of the risk for sICH (OR=3.41, 95%CI 0.16-7.20, p=0.436) or mortality (OR=3.55, 95%CI 0.39-8.52, p=0.260).

3. Discussion

To the best of our knowledge, this is the first study to investigate the effect of prior AP on MPA in thrombolysis-treated AIS patients. We showed that pre-stroke oral antiplatelet agent was associated with lower AA-induced MPA at 3 h after thrombolysis, which suggested that prior AP may reduce the risk of early reocclusion. However, the effect of AP on MPA does not improve the early NFI or functional outcome at follow-up. Our results demonstrated that AP before stroke is safe in patients receiving rt-PA, while the efficacy needs further studies to confirm.

AIS patients presented with prior AP before rt-PA are frequent in the clinical settings. A previous study reported that more than half of the patients were under antiplatelet therapy at stroke onset (Sandercock et al. 2016). The AHA/ASA Scientific Statement recommends intravenous rt-PA treatment for patients taking antiplatelet drug before stroke on the basis of evidence that the benefit of alteplase outweighs a possible risk of sICH (Demaerschalk et al. 2016). In this study, pre-stroke antiplatelet agent therapy was recorded in 23 (38.9%) patients when they were treated with rt-PA. These patients were accompanied with vascular risk factors such as coronary heart disease, atrial fibrillation and previous cerebral infraction. We confirmed that AP had an important role on MPA in thrombolysis-treated AIS patients. This effect was obviously measured at the time point of 3 h following rt-PA treatment. Based on the hypothesis that prior AP before rt-PA has a similarly role as AP combined with rt-PA, this finding suggested that early inhibition of platelet aggregation is a potential therapeutic strategy to prevent the artery reocclusion. However, the administration of antiplatelet agents was considered as contraindicated during the first 24 h after treatment with intravenous rt-PA in the 2013 AHA/ASA guideline (Jauch et al. 2013). The restriction is mainly based on the protocol used in the NINDS trial (John et al. 1995) and the results of the ARTIS trial (Zinkstok et al. 2002). In addition to aspirin, some studies also investigated the adjunctive therapy of other antiplatelet agent (The II b/III a glycoprotein antagonist) in AIS patients receiving rt-PA in recent years. In a preliminary study reporting safety and efficacy of early tirofiban treatment, the authors selected thrombolysis-treated AIS patients for tirofiban therapy by multimodal images. They concluded that intravenous tirofiban immediately after alteplase seems to be safe and potentially more effective than alteplase alone (Li et al. 2016). Moreover, a cohort study further investigated the efficacy of tirofiban administered at different time points after IVT in AIS patients (Liu et al. 2019). Eligible patients were randomly divided into four groups (within 2 h, 2-12 h and 12-24 h group after thrombolysis, and a control group only receiving standard rt-PA), and the results reflected that tirofiban combined with rt-PA is safe and effective, and particularly beneficial when administered at 2 h and 2-12 h after IVT in AIS patients (Liu et al. 2019). Nevertheless, these studies did not estimate MPA before tirofiban therapy, so we could not make a direct comparison with our study. Besides, the updated 2018 AHA/ASA guideline indicated that the efficacy of intravenous tirofiban is not well established (Powers et al. 2018). Therefore, more studies are needed to confirm these findings.

Our study found that prior AP is safe, with no significant increase of the risk for sICH and mortality in thrombolysis-treated AIS patients. In addition, the results also suggested that no correlations were found between AP and improved clinical outcomes. Previous studies have drawn the same conclusion that prior AP use did not lead to significant improved outcomes in AIS patients receiving rt-PA therapy (Pan et al. 2015; Luo et al. 2016). However, compared to those without pre-stroke antiplatelet therapy, prior AP may be associated with greater risks of developing sICH after IVT (Pan et al. 2015; Luo et al. 2016), especially in patients receiving dual AP therapy before stroke (Pan et al. 2015). In the present article with a small sample size, 23 (38.9%) patients with prior AP were mono therapy, which may explain the partial heterogeneity between studies.

Several limitations should be considered in our study. First, the sample size was relatively small and we failed to perform subgroup analyses to estimate the effect of different antiplatelet agents on MPA; hence, potential heterogeneity may exist. Secondly, the study population was limited to the Chinese population, and most studies reported early administration of tirofiban were performed in Asian patients (Li et al. 2016; Liu et al. 2019;Guo et al. 2019), due to the common etiology caused by large artery atherosclerosis (Guo et al. 2019). Because of these limitations, the results of the current study should be explained with caution.

4. Experimental

4.1. *Study population*

We performed a single-center, prospective observational cohort at the Neurology Department, Nanjing First Hospital of Nanjing Medical University between January 2016 and June 2018. Included were AIS patients receiving intravenous rt-PA according to the clinical guideline (Jauch et al. 2013). The diagnosis of AIS was assessed by professional neurologists. The exclusion criteria were platelet count < 100 × 10^9/L, severe renal or hepatic disorder, hematologic disorder, active malignancy, body mass index (BMI) < 18.5 or > 40 kg/m^2, prior treatment with glycoprotein IIb/IIIa inhibitors during the 10 days, under anticoagulant therapy before stroke onset. Patient baseline information regards to AP was carefully collected before the decision making for rt-PA therapy. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethics committee of Nanjing First Hospital. All patients signed their written informed consent to study participation and blood sampling for MPA assays before the study.

4.2. *Patient characteristics and clinical outcomes*

Baseline data were extracted from the database of Nanjing First Hospital Stroke Registry, as described elsewhere (Shi et al. 2016). Stroke subtypes were classified by TOAST (Trial of Org 10 172 in acute stroke treatment) and OCSP (Oxfordshire

Community Stroke Project) classification. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) by neurologists on admission, 24 h and 7 d after rt-PA. The primary outcomes were: (1) neurological function improvement (NFI), defined as a ≥4 points reduction in NIHSS score at 24 h and 7 d following rt-PA; (2) good functional outcome, defined as modified Rankin Scale score (mRS) of 0-2 at follow up. The secondary outcomes were: (1) sICH according to the ECASS II (European Cooperative Acute Stroke Study) criteria (Hacke et al. 2008), defined as intracerebral hemorrhage on CT and an increase of 4 points or more in the NIHSS score within the first 36 h, (2) mortality in the hospital or follow-up.

4.3. Blood sampling collection and testing

Blood sample collections were taken at the time of admission before rt-PA, and 3 h, 6 h, 12 h, 18 h after rt-PA. At least 3 ml samples for each time were collected in tubes containing 3.8% sodium-citrate (NanGeer Biomedical Co., Ltd, Sichuan, China). Blood samples for platelet aggregation testing were processed within 2 h of blood collection. Light transmittance aggregometry (LTA) is a gold standard for the determination of platelet aggregation. MPA was measured by LTA in platelet-rich plasma (PRP) after stimulation with arachidonic acid (AA) using a four-channel aggregometer (PuLiSheng, Beijing, China). The PRP was prepared by centrifugation of citrated venous blood at 150 g for 15 min, and platelet-poor plasma (PPP) by centrifugation at 1,500 g for 20 min. PRP was adjusted to 200-250×10^9 platelets/L by dilution with autologous PPP. Aggregation results were expressed as a percentage of maximal light transmission using PPP from the same patient as the reference (100% transmission). *Ex vivo* platelet aggregation testing was performed as described previously (Zou et al. 2013).

4.4. Statistical analysis

Continuous variables were presented with mean±standard deviations (SD) and compared using the unpaired two-tailed t-test if normally distributed, whereas continuous variables with a non-Gaussian distribution were compared using the Mann–Whitney U test. Categorical variables were shown as number (percentage) with the chi-square or Fisher's exact test. Multivariate linear regression was performed to detect the correlation between potential factors and MPA. Multivariate logistic regression was used to investigate the association between potential factors and clinical outcomes. Independent variables whose $p < 0.1$ without multi-collinearity, and identified variables (age, MPA and NIHSS on admission) were forced into the logistic regression model. Statistically significant was considered as $p < 0.05$. All statistical analysis was performed with SPSS 22.0 (SPSS Inc, Chicago, IL, USA).

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