

Study on the Guidance of Platelet Inhibition Rate Detected with Thrombelastogram in Antiplatelet Therapy for Acute Non-Cardiogenic Stroke

Yong Liu*, Xuemei Feng, Juan Wang

Department of Neurology in the Fourth People's Hospital of Yibin, Yibin 644000, Sichuan Province, China

*Corresponding author: Yong Liu, 1041956786@qq.com

Copyright: © 2022 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract: *Objective:* To investigate the application value of thrombelastogram (TEG) in the detection of platelet inhibition rate for antiplatelet therapy for acute non-cardiogenic stroke. *Methods:* A total of 100 patients with ischemic non-cardiogenic stroke were selected for this study from September 2020 to October 2021. Patients were randomly divided into experimental group and control group, with 50 cases for each group. Before and after 1 week of antiplatelet drug treatment, the platelet inhibition rate in the experimental group was measured with arachidonic acid (AA) and adenosine diphosphate (ADP) by TEG; no platelet inhibition rates detection was conducted for the control group. The dose and type of drugs were adjusted for the experimental group according to the platelet functions and medication based on the clinical experience conducted for the control group. The neurological deficits of the discharged patients were scored with NIHSS score, mRS score, stroke recurrence, hemorrhage, and other events were followed up at the 3rd month of discharge. *Results:* In the experimental group, the inhibition rates of AA and ADP were significantly higher than those before treatment (both $P < 0.05$). After treatment, the inhibition rates of AA and ADP in dual antiplatelet patients were higher than those of monoclonal antiplatelets (both $P < 0.05$). The NIHSS score at discharge and the mRS score at the 3rd-month-follow-up in the experimental group were lower than those in the control group (both $P < 0.05$). The incidences of stroke recurrence and hemorrhage events in the experimental group were lower than those in the control group ($P < 0.05$). *Conclusion:* The application of a thrombelastogram in the detection of platelet inhibition rate to guide antiplatelet therapy in patients with acute non-cardiogenic stroke reduces the recurrences of cerebral infarction and the risk of hemorrhage and improves patients' clinical prognosis.

Keywords: Thrombelastogram; Platelet inhibition rate; Ischemic stroke; Antiplatelet therapy

Online publication: September 15, 2022

1. Introduction

Data from the Global Burden of Disease (GBD) study show that stroke has become the first cause of death among Chinese residents. The annual recurrence rate of ischemic stroke in China is as high as 17.7%^[1,2]. Although antiplatelet drugs such as aspirin and clopidogrel still play an important role in clinical practice, in reality, due to the difference in drug resistance and drug compliance, it may lead to stroke recurrence as well as bleeding events due to excessive antiplatelet therapy affecting blood coagulation. The use of the TEG method to evaluate the therapeutic effect of antiplatelet drugs has clinical value and effectiveness^[3]. Through the rapid and effective detection of the efficacy of antiplatelet drugs, it can provide a basis for individual treatment of antiplatelet drugs in patients with ischemic stroke. This study was to explore the application of TEG in the detection of platelet inhibition rate, combined with clinical prognosis and end

events, to determine the application value of antiplatelet therapy in acute non-cardiogenic stroke.

2. Data and methods

2.1. General data

100 patients with acute non-cardiogenic stroke diagnosed in our hospital from September 2020 to October 2021 were divided into experimental group (n = 50) and control group (n = 50) according to TEG detection. The experimental group was tested by TEG, while TEG was not conducted in the control group. Inclusion criteria: 1 acute non-cardiogenic stroke, 2 no contraindications to aspirin and clopidogrel. Exclusion criteria: 1 cardiogenic cerebral embolism; 2 hematopathy or bleeding tendency; 3 active peptic ulcers; 4 platelet count $< 100 \times 10^9/L$.

2.2. Methods

2.2.1 Antiplatelet therapy

Antiplatelet drugs were selected according to Chinese guidelines for secondary prevention of ischemic stroke and transient ischemic attack (TIA) in 2015 after admission. Drugs include: aspirin (100mg/ tablets, Bayer Pharmaceutical Company of Germany), clopidogrel (75mg/ tablets, Hangzhou Sanofi Co., Ltd., trade name Polivir), used alone or in combination, all drugs are used continuously.

2.2.2. Detection of platelet inhibition rate

Blood samples were collected after admission in the experimental group, and then corresponding antiplatelet drugs were administrated. Blood samples were collected again at least one week after treatment. Chongqing Dingrun (DRNX- type III) thrombus elastography and its supporting reagents were used to detect AA inhibition rate in patients with aspirin and ADP inhibition rate in patients with clopidogrel.

2.3. Observation indicators

Before and after the treatment of clopidogrel, the test data were compared: The inhibition rate of ADP after clopidogrel treatment was 30% and 90% was considered as normal, more than 90% excessive inhibition, and less than 30% was considered as hyporeactivity or drug resistance. After aspirin treatment, the AA inhibition rate of 50% to 90% was considered as normal, more than 90% was considered as over inhibition, and less than 50% was hyporeactivity or drug resistance. If the inhibition rate was in the normal range, the drug will remain unchanged, and if the inhibition rate was more than 90%, the drug dose should be controlled and the signs of bleeding were observed closely; if the inhibition rate was lower than the normal lower limit, the dosage were increased or it was switched to other antiplatelet drugs.

2.4. Evaluation of efficacy and safety

All patients were evaluated with NIHSS score at discharge, mRS score at 3 months follow-ups, and the occurrence of end-point events (stroke recurrence, bleeding, death, etc.).

2.5. Statistical methods

SPSS22.0 software was used to analyze the data, the measurement data were expressed by $\bar{x} \pm s$, t-test, counting data were expressed by n (%), χ^2 test was used, and the difference was statistically significant.

3. Results

There was no significant difference in age, sex, time of onset, hypertension, diabetes, hyperlipidemia, and NIHSS score at admission between the two groups.

3.1. Comparison of the inhibition rates of AA or ADP

After treatment, the inhibition rates of AA and ADP in the experimental group were significantly higher than those before treatment, and the inhibition rates of AA and ADP in patients with double antibodies were higher than those of AA and ADP in patients with monoclonal antibodies after treatment.

3.2. Efficacy and adverse events

The patients were followed up for 3 months. 3 cases in the test group and 5 cases in the control group lost follow-up. The NIHSS score at discharge and the mRS score at 3 months of follow-up in the test group were lower than those in the control group, and the incidence of stroke recurrence and bleeding in the test group were lower than those in the control group. (See **Tables 1** and **2**).

Table 1. Comparison of neurological deficits and clinical outcomes in the test and control groups [$\bar{x} \pm s$, score]

Group	n	Discharge NIHSS score	mRS score
Experimental group	50	3.12±1.46	1.20±0.34
Control group	50	5.28±2.34	2.10±1.01
t value		5.538	5.972
P value		<0.001	<0.001

Table 2. Comparison of good functional outcomes (mRS score 0 to 2), endpoint events at follow-up in the trial and control groups [n (%)]

Group	n	Good Function Ending	Stroke recurrence	Bleeding incidents
Experimental group	47*	44 (93.62)	2 (4.26)	1 (2.13)
Control group	45*	34 (75.56)	9 (20.00)	8 (17.78)
χ^2 value		5.813	5.414	4.730
P value		0.016	0.020	0.030

Note: *represents 3 lost cases in the trial group and 5 lost cases in the control group

4. Discussion

The global prevalence of stroke is increasing year by year [4]. Stroke not only has a high incidence but also has a very high mortality, recurrence rate, disability rate, and high economic burden on families and the society. In clinical work, aspirin and clopidogrel are the most commonly used antiplatelet drugs recommended by relevant guidelines at home and abroad [5]. However, 10% to 20% of patients still have a recurrent stroke after regular antiplatelet drug treatment, indicating that the response of antiplatelet drugs is low, which is called antiplatelet drug resistance [6]. Some scholars also call it antiplatelet drug non-response [7]. When two or more drugs are used at the same time or when the dose is increased for a long period of time, the risk of hemorrhagic transformation increases, and even leads to severe gastrointestinal or intracranial hemorrhage. At present, some progress has been made in the clinical research on the relationship between aspirin and clopidogrel gene polymorphism and drug resistance, especially the CYP2C19 gene mutation related to clopidogrel resistance [8]. However, due to the differences in medical equipment, personnel, and other conditions, gene detection is difficult to be widely used in the clinic.

In this study, the changes in platelet inhibition rate and drug adjustment before and after antiplatelet drug treatment with TEG were analyzed, and the functional recovery and prognosis were evaluated. The

results showed that the inhibition rates of AA and ADP were significantly higher than those before treatment. After treatment, the inhibition rates of AA and ADP in patients with double antibodies were higher than those in patients with monoclonal antibodies (all $P < 0.05$). It is suggested that aspirin and clopidogrel have a synergistic effect, which may be the result of mutual promotion when the two pathways inhibit platelet aggregation at the same time. Qiu Shi ^[9] analyzed the antiplatelet effect of aspirin, clopidogrel, and the combination of aspirin and clopidogrel by meta-analysis. 5 case-control studies were included in the study. It is suggested that the conventional dose of aspirin and clopidogrel combined with antiplatelet therapy has a synergistic effect, which is consistent with the results of this study. The NIHSS score at discharge and the mRS score during the follow-up period in the test group were lower than those in the control group. The incidence of stroke recurrence and bleeding in the test group was lower than that in the control group ($P < 0.05$). Rowe et al. found that TEG can not only dynamically monitor the efficacy of drugs, but also improve the clinical prognosis of stroke patients in the individualized antiplatelet therapy of acute ischemic stroke ^[10]. Of course, it may be more comprehensive for those with conditions to combine genotyping screening at the same time to choose medication options. Some studies have found that the serological concentration of clopidogrel active metabolites in patients with 1 or 2 CYP2C19 inactivation alleles (* 2) is significantly lower. The results of the latest CHANCE-2 study showed that in Chinese patients with mild ischemic stroke (NIHSS score ≤ 3) or TIA with CYP2C19 functional deletion allele, the efficacy of aspirin combined with Ticagrelor Tablets in preventing stroke recurrence was better than that of clopidogrel combined with aspirin, and the stroke recurrence rate within 90 days of the former was 23% lower than that of the latter ^[11].

5. Conclusion

In conclusion, thromboelastogram detection of platelet inhibition rate can guide antiplatelet therapy in patients with acute non-cardiogenic stroke, through efficacy evaluation and risk stratification, reduce bleeding events caused by recurrence and adverse drug reactions, and improve the clinical prognosis of patients. Hence, it is worth popularizing in clinical work.

Disclosure statement

The authors declare no conflict of interest.

References

- [1] GBD 2019 Stroke Collaborators, 2021, Global, Regional, and National Burden of Stroke and its Risk Factors, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *The Lancet Neurology*, 20(10): 795–820. [https://www.doi.org/10.1016/S1474-4422\(21\)00252-0](https://www.doi.org/10.1016/S1474-4422(21)00252-0)
- [2] Wang Y, Xu J, Zhao X, et al., 2013, Association of Hypertension with Stroke Recurrence Depends on Ischemic Stroke Subtype. *Stroke*, 2013, 44(5): 1232–1237. <https://www.doi.org/10.1161/STROKEAHA.111.000302>
- [3] Cao J, Liu L, Fan L, et al., 2012, The Prevalence, Risk Factors, And Prognosis of Aspirin Resistance in Elderly Male Patients with Cardiovascular Disease. *The Aging Male: The Official Journal of the International Society for the Study of the Aging Male*, 15(3): 140–147. <https://www.doi.org/10.3109/13685538.2012.666584>
- [4] Gan Y, Yang T, Liu J, et al., 2019, Research Progress on Epidemic Trend and Influencing Factors of Stroke at Home and Abroad. *Chinese Journal of Preventive Medicine*, 20(02): 139–144. <https://www.doi.org/10.16506/j.1009-6639.2019.02.013>
- [5] Shulga O, Bornstein N, 2011, Antiplatelets in Secondary Stroke Prevention. *Frontiers in Neurology*, 2:

36. <https://www.doi.org/10.3389/fneur.2011.00036>
- [6] Greer DM, 2010, Aspirin and Antiplatelet Agent Resistance: Implications for Prevention of Secondary Stroke. *CNS Drugs*, 24(12): 1027–1040. <https://www.doi.org/10.2165/11539160-0000000000-00000>
- [7] Depta JP, Fowler J, Novak E, et al., 2012, Clinical Outcomes Using a Platelet Function-Guided Approach for Secondary Prevention in Patients with Ischemic Stroke or Transient Ischemic Attack. *Stroke*, 43(9): 2376–2381. <https://www.doi.org/10.1161/STROKEAHA.112.655084>
- [8] Jia D–M, Chen Z-B, Zhang M-J, et al., 2013, CYP2C19 Polymorphisms and Antiplatelet Effects of Clopidogrel in Acute Ischemic Stroke in China. *Stroke*, 44(6): 1717–1719. <https://www.doi.org/10.1161/STROKEAHA.113.000823>
- [9] Qiu S, Miao F, Wu T, et al., 2014, Meta-Analysis of Antiplatelet Effect of Aspirin and Clopidogrel. *Shandong Medicine*, 54(22): 40–43.
- [10] Shaun Rowe A, Greene CL, Snider CC, et al., Thromboelastographic Changes in Patients Experiencing an Acute Ischemic Stroke and Receiving Alteplase. *Journal of Stroke and Cerebrovascular Diseases*, 23(6): 1307–1311.
- [11] Wang Y, Meng X, Wang A, et al., 2021, Ticagrelor Versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA. *The New England Journal of Medicine*, 385(27): 2520–2530 <https://www.doi.org/10.1111/2530.10.1056/NEJMoa2111749>

Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.