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Comparison of Thrombelastography (TEG) in Patients with Acute Cerebral Hemorrhage and Cerebral Infarction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCF **Zongbao Liu**
ADEG **Erqing Chai**
BCE **Hecheng Chen**
ADF **Hongzhi Huo**
BD **Fei Tian**

Cerebrovascular Disease Center, Gansu Provincial Hospital, Lanzhou, Gansu, P.R. China

Corresponding Author: Erqing Chai, e-mail: happybirds@126.com

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Background: The aim of this study was to analyze the changing role of thrombelastography (TEG) by detecting the indexes of TEG in patients with acute cerebral hemorrhage and cerebral infarction, combined with pathogenesis, and to find objective laboratory indexes for the diagnosis and treatment of cerebrovascular diseases.


Material/Methods: Data from 150 patients were collected, including 69 cases identified as the cerebral infarction group and 81 cases identified as the cerebral hemorrhage group. In addition, 50 healthy adults were selected as a control group. The cerebral hemorrhage group was divided into 3 subgroups according to the amount of bleeding: small hemorrhage group, moderate hemorrhage group, and large hemorrhage group. The diagnosis for each participant was mainly based on computed tomography (CT) and magnetic resonance imaging (MRI). TEG indexes [R value (coagulation reaction time), K value (coagulation time), Angle (reflecting the formation rate of blood clot and the function of fibrinogen), MA (maximum thrombus amplitude), CI (coagulation index)] were measured by TEG YZ5000 instrument.

Results: The cerebral infarction group had lower R and K values and higher Angle and CI ($P < 0.05$). The cerebral hemorrhage group had higher K value; the Angle and MA were lower in the moderate hemorrhage group and in the large hemorrhage groups ($P < 0.05$). In the cerebral hemorrhage group, Angle and MA were negatively correlated with the amount of cerebral hemorrhage ($r = -0.475, -0.394$ respectively, $P < 0.05$), and the K value was positively correlated with the amount of cerebral hemorrhage ($r = 0.337, P < 0.05$), while the R value had no significant correlation with the amount of cerebral hemorrhage ($r = 0.251, P > 0.05$). R and K values in the cerebral infarction group were significantly lower, while Angle, MA, and CI were significantly higher in the cerebral hemorrhage group.

Conclusions: K value, Angle, and MA may be of value in the assessment of the amount of cerebral hemorrhage.

MeSH Keywords: **Cerebral Hemorrhage • Cerebral Infarction • Thrombelastography**

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Background

Cerebrovascular disease is one of the 3 major killers of human life and health [1,2]. It has the characteristics of high incidence, disability, mortality, and recurrence rates. Among cerebrovascular diseases, acute cerebral infarction has the highest incidence rate (50% to 80%), and its disability rate can be as high as 50% to 70% [3,4]. The incidence rate of acute cerebral hemorrhage is second only to that of cerebral infarction, and accounts for 20% to 30% of all cerebrovascular diseases, but its mortality rate is much higher than that of acute cerebral infarction, ranking first in cerebrovascular diseases [5].

Previous studies have shown that coagulation indexes, such as D-dimer, fibrinogen (FIB), and platelet agglutination (PAG), are correlated with the severity of cerebral hemorrhage and cerebral infarction, and can be used as important indexes for evaluating the patient's condition and judging prognosis [3,4,6]. A study in China, and other countries, showed that the level of plasma D-dimer in patients with cerebrovascular diseases was significantly higher than that in a normal control group, and the level of plasma D-dimer in the acute stage of ischemic cerebrovascular disease was significantly higher than that in the convalescent stage [6]. In patients with cerebral hemorrhage, it was found that the higher the plasma level of D-dimer, the greater the amount of cerebral hemorrhage and the severer the condition. A clinical study has shown that elevated FIB is an independent risk factor for ischemic cerebrovascular disease [7]. The increase of FIB level indicates an increase in the risk of cerebrovascular disease, which can guide the prognosis of cerebrovascular disease. PAG mainly reflects the aggregation function of platelets, and can have a guiding role in treatment with antiplatelet aggregation drugs [8,9].

Thrombelastography (TEG) can be used to monitor the whole process, from initiation of internal and external coagulation systems and the formation of fibrin, to blood clot dissolution. It can aid in qualitative and quantitative diagnosis of coagulation function by synthesizing various parameters [10]. The purpose of this study was to investigate the effectiveness of TEG in the diagnosis, curative effect evaluation, and prognosis judgment of cerebrovascular diseases in patients with acute cerebral infarction and patients with cerebral hemorrhage with different amounts of bleeding.

Material and Methods

Study participants

A total of 150 patients with acute cerebral hemorrhage or cerebral infarction who were admitted to the Cerebrovascular Disease Center, Gansu Provincial Hospital from October 2016

to December 2017, and 50 healthy volunteers from a physical examination center, were enrolled in this study. There were 69 patients in the acute cerebral infarction group, including 38 males and 31 females, aged 32–79 years old, and 81 patients in the acute cerebral hemorrhage group, including 44 males and 37 females, aged 31–69 years old. In the healthy control group, there were 30 males and 20 females, aged 28–70 years old. Study inclusion criteria included: 1) patients with cerebral hemorrhage or cerebral infarction confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI), which were in line with the relevant diagnostic criteria; 2) patients aged 18–80 years old who were receiving medical treatment within 48 hours after onset; and 3) in the control group, no patient had basic disease, especially vascular disease. Signed written informed consent was obtained from all participants before the study. This study was approved by the ethics committee of Cerebrovascular Disease Center, Gansu Provincial Hospital.

Methods

Calculation of the amount of cerebral hemorrhage

The patients with acute cerebral hemorrhage received brain CT scans immediately after admission and the hemorrhage volume was calculated according to the Tada formula [11] as follows: hemorrhage volume (mL) = long axis (cm) × short axis (cm) × thickness (cm) × $\pi/6$. The longest diameter of the largest plane of the hematoma area was taken as the long axis and the widest plane diameter was taken as the short axis. Brain CT was reexamined within 24 hours, and if hematoma was found enlarged, the hemorrhage volume was calculated with the enlarged values.

Determination of main parameters of TEG and their significance

A 2 mL sample of venous whole blood was extracted from each patient within 6 hours after admission and placed in an ethylenediaminetetraacetic acid (EDTA)-K2 vacuum tube. TEG images and reference values were measured by TEG YZ5000 elastic instrument (Beijing Zhongxing, Beijing, China). R value (coagulation reaction time), which is equivalent to the time of production of thromboplastin, mainly reflects the comprehensive effects of blood coagulation factors, and its reference value is 4–8 minutes. K value (coagulation time) is an index to reflect the formation speed of blood clots and assess the strength of blood clots, which mainly reflects the function and level of FIB, and its reference value is 1–3 minutes. Angle reflects the formation rate of a blood clot and the function of FIB, and its reference value is 53–72°. MA (maximum thrombus amplitude) mainly reflects the function of platelets, and its reference value is 50–70 mm. CI (coagulation index) is calculated from the synthesis of the aforementioned 4 parameters, which reflects

Table 1. Basic characteristics of included patients.

	n (Male/Female)	Age (y)	Hypertension (%)	Diabetes (%)
Normal control group	50 (30/20)	44.96±8.17	12 (24.00)	14 (28.00)
Cerebral hemorrhage group	81 (44/37)	49.04±6.35	27 (33.33)	25 (30.86)
Cerebral infarction group	69 (38/31)	53.82±7.26	18 (26.09)	19 (27.54)
F/ χ^2	0.229	3.587	0.326	0.532
P	0.054	0.125	0.416	0.227

Table 2. Comparison of TEG between cerebral infarction group and normal control group.

	n	R (min)	K (min)	Angle (deg)	MA (mm)	CI
Normal control group	50	5.52±1.26	1.64±0.32	67.95±8.27	61.90±5.26	1.41±0.33
Cerebral infarction group	69	2.87±1.64*	1.28±0.19*	75.65±7.85*	72.83±5.82	2.81±0.78*
t		4.389	3.114	3.146	5.832	7.094
P		0.032	0.029	0.030	0.128	0.014

* $P < 0.05$ in comparison with normal control group.

the comprehensive state of the blood coagulation of the sample under various conditions, and its reference value is $-3 \sim +3$.

Statistical analysis

All statistics were performed using statistical product and service solutions (SPSS) 20.0 software (Armonk, NY, USA). Quantitative data were expressed as ($\bar{x} \pm s$), and *t*-test or variance analysis was used to compare differences between groups. Enumeration data were compared by chi-square test. Grade data were compared by Spearman rank correlation analysis. $P < 0.05$ suggested that the difference was statistically significant.

Results

Comparisons of general data among the cerebral hemorrhage group, the cerebral infarction group, and the control group

The results of comparisons of general data among the cerebral hemorrhage group, the cerebral infarction group, and the normal control group showed that there were no statistically significant differences in sex, age, and concomitant disease among groups ($P > 0.05$, Table 1).

Abnormal changes of TEG in patients with cerebral infarction

The R value (coagulation reaction time) in 69 patients with cerebral infarction was significantly lower than the R value

in the normal control group (2.87±1.64 min versus 5.52±1.26 min, $P < 0.05$, Table 2). The K value (coagulation time) in the cerebral infarction group was lower than in the normal control group (1.28±0.19 min versus 1.64±0.32 min, $P < 0.05$, Table 2). The Angle measurement in the cerebral infarction group was 75.65±7.85°, and in the normal control group it was 67.95±8.27°; the difference was statistically significant ($P < 0.05$, Table 2). The CI in the cerebral infarction group was significantly higher compared to the normal control group (2.81±0.78 versus 1.41±0.33, $P < 0.05$, Table 2).

Abnormal changes of TEG in patients with cerebral hemorrhage

The K value (coagulation time) in 81 patients with cerebral hemorrhage was 3.23±1.26 min, and in the normal control group it was 1.64±0.32 min; the difference was statistically significant ($P < 0.05$, Table 3). The Angle measurement in the cerebral hemorrhage group was significantly lower compared to the normal control group (57.14±5.35° versus 67.95±8.27°, $P < 0.05$, Table 3). The MA in the cerebral hemorrhage group was significantly lower compared to the normal control group (55.81±3.68 mm versus 61.90±5.26 mm, $P < 0.05$, Table 3).

Different TEG performances among patients with different amount of cerebral hemorrhage

The K value (coagulation time) of 27 patients in the small hemorrhage group was 2.44±0.87 min, for the 39 patients in the moderate hemorrhage group, it was 3.69±1.35 min, for the 15 patients in the large hemorrhage group it was 4.41±1.58

Table 3. Comparison of TEG between cerebral hemorrhage group and normal control group.

	n	R (min)	K (min)	Angle (deg)	MA (mm)	CI
Normal control group	50	5.52±1.26	1.64±0.32	67.95±8.27	61.90±5.26	1.41±0.33
Cerebral hemorrhage group	81	5.98±1.77	3.23±1.26*	57.14±5.35*	55.81±3.68*	1.32±0.39
t		2.132	5.147	6.238	4.015	1.693
P		0.225	0.037	0.028	0.021	0.463

* $P < 0.05$ in comparison with normal control group.

Table 4. Comparison of TEG among patients with different amount of cerebral hemorrhage.

	n	R (min)	K (min)	Angle (deg)	MA (mm)	CI
Normal control group	50	5.52±1.26	1.64±0.32	67.95±8.27	61.90±5.26	1.41±0.33
<10 mL group	27	5.58±1.59	2.44±0.87*	68.73±7.54	60.15±5.07	1.52±0.55
10–30 mL group	39	5.93±1.38	3.69±1.35*	53.44±3.26*	57.12±3.02*	1.24±0.38
>30 mL group	15	6.74±2.52*	4.41±1.58*	48.92±5.43*	48.14±4.61*	1.19±0.27
r		0.337	0.596	-0.475	-0.394	0.468
P		0.525	0.016	0.021	0.043	0.374

* $P < 0.05$ in comparison with normal control group.

Table 5. Comparison of TEG between cerebral hemorrhage group and cerebral infarction group.

	n	R (min)	K (min)	Angle (deg)	MA (mm)	CI
Cerebral hemorrhage group	81	5.98±1.77	3.23±1.26	57.14±5.35	55.81±3.68	1.32±0.39
Cerebral infarction group	69	2.87±1.64*	1.28±0.19*	75.65±7.85*	72.83±5.82	2.81±0.78*
t		8.226	7.659	9.563	11.175	7.837
P		0.024	0.032	0.022	0.037	0.019

* $P < 0.05$ in comparison with cerebral hemorrhage group.

min, and in the healthy control group it was 1.64±0.32 min; the differences were statistically significant ($P < 0.05$, Table 4). The Angle measurement in the small hemorrhage group was 68.73±7.54°, in the moderate hemorrhage group it was 53.44±3.26°, in the large hemorrhage group it was 48.92±5.43°, and in the healthy control group it was 67.95±8.27° ($P < 0.05$, Table 4). The MA in the small hemorrhage group was 60.15±5.07 mm, in the moderate hemorrhage group it was 57.12±3.02 mm, in the large hemorrhage group it was 48.14±4.61 mm, and in the control group it was 61.90±5.26 mm; the differences were statistically significant ($P < 0.05$, Table 4). Spearman rank correlation analysis showed that there were significant correlations of K value, Angle, and MA with the amount of cerebral hemorrhage ($r = 0.596$, $r = -0.475$, and $r = -0.394$ respectively, $P < 0.05$, Table 4), while R value had no significant correlation with the amount of cerebral hemorrhage ($r = 0.337$, $P > 0.05$, Table 4).

Difference TEG performances between the cerebral hemorrhage group and the cerebral infarction group

Compared with those in the cerebral hemorrhage group, the R value and K value in the cerebral infarction group were significantly shortened, while the Angle, MA, and CI were significantly increased; the differences were statistically significant ($P < 0.05$, Table 5).

Discussion

In this study, the R and K values of patients in the cerebral infarction group were lower than those in the healthy control group, suggesting that the activities of blood coagulation factors, FIB, and platelets of patients in the cerebral infarction group were increased, and the patients were in a

hypercoagulable state. This state has been associated with vascular endothelial damage, enhanced platelet adhesion, and aggregation function. Due to long-term effects of hypertension, diabetes, atherosclerosis, and other risk factors in patients with cerebral infarction, the local accumulation of platelets activates coagulation factors, which can result in FIB decomposition and crosslinking to cause increased fibrin [3,4]. The Angle in the cerebral infarction group was higher compared to the control group. This suggests that the levels or activities of plasma FIB and platelets were increased [12]. As an independent risk factor for cerebrovascular disease, FIB is an effective index to evaluate the condition of cerebral infarction [7]. K value and Angle reflect the function and level of FIB. Therefore, it is believed that the increased K value and Angle can reflect the severity of cerebral infarction in patients. It is worth mentioning here that Angle and K value also reflect the quality and quantity of platelets and FIB. However, Angle is not affected by the extremely low coagulation state. Therefore, Angle is considered to be a more objective index than K value. CI in the cerebral infarction group was higher than CI in the control group, suggesting that the whole coagulation function of patients in the cerebral infarction group was in a hypercoagulable state. However, CI cannot reflect the abnormality of a specific process of coagulation or the absence of quality or quantity of a component, so it is mainly used for judging the coagulation function and evaluating the patient's condition. For targeted therapies for correcting the coagulation state (such as the use of anti-platelet aggregation and anticoagulant drugs), other indexes that reflect specific links of coagulation are recommended [3,4,10]. In summary, we believe that the severity and prognosis of patients with cerebral infarction can be evaluated by dynamic examination of R value, K value, Angle, and CI of TEG, so as to guide the anticoagulant and anti-aggregation therapies for patients with cerebral infarction. The common TEG used in this study can only indicate the platelet function and level. Further TEG platelet graphs can accurately reflect the degree of platelet activation, so as to achieve the purpose of individualized treatment.

After the rupture of blood vessels in patients with cerebral infarction, tissue factors are released to activate the extrinsic coagulation pathway. Vascular endothelial damage activates the endogenous coagulation pathway and platelet aggregation, so as to form a thrombus to achieve the effect of hemostasis. At the same time, there may be hypercoagulant changes similar to cerebral infarction during cerebral ischemia under compression of peripheral tissues of the bleeding foci or intracranial hypertension. The increased coagulation function and thrombus formation also activate the fibrinolytic system, which consumes a large number of clotting substances, and presents in a low-coagulation state [5,6,13]. As a result, the degree of coagulation disorders in the cerebral hemorrhage group will be quite different. In this study, compared with those in the control

group, the cerebral hemorrhage group had low Angle and MA, and increased K value, suggesting that patients with cerebral hemorrhage had a relatively low coagulation state. Studies have shown that the coagulation and fibrinolytic systems are activated in patients with cerebral hemorrhage, during which FIB is consumed in large quantities, resulting in thrombosis and secondary hyperfibrinolysis. D-dimer is an important index for judging the severity and prognosis of cerebral hemorrhage [9,10]. As K value is the coagulation time, it is mainly related to the function and level of FIB. We speculate that there is a certain correlation between K value and D-dimer, and K value can also indicate the degree of risk of cerebral hemorrhage.

Further subgroup analyses based on the amount of bleeding in the cerebral hemorrhage group showed that there were significant correlations with the K value, Angle and MA with the amount of cerebral hemorrhage, thus suggesting that these 3 indexes may reflect the severity and prognosis of cerebral hemorrhage [14]. In the moderate hemorrhage group and the large hemorrhage group, MA and Angle were negatively correlated with the amount of bleeding, while K value was positively correlated with the amount of bleeding. It is speculated that for patients with cerebral hemorrhage, the larger the amount of bleeding, the more active the coagulation and fibrinolysis systems, the more clotting substances consumed, and the more the body is in a hypo-coagulable state, the aforementioned changes of K value, Angle, and MA occur [15]. Similarly, Angle and MA largely overlapped with reference value ranges, and in view of the small size of the 3 subgroups and the more complicated mechanism of changes in the coagulation function of cerebral hemorrhage, large-sample size research is needed to further clarify the relationship between these two measures.

Compared with those in the cerebral hemorrhage group, the values of R and K in the cerebral infarction group were obviously shortened, while Angle, MA and CI were obviously expanded. These results suggested that the activities of blood coagulation factors, platelets, and FIB in the cerebral infarction group were elevated, showing an overall hypercoagulable state [12]. In contrast, the cerebral hemorrhage group was in a relatively hypo-coagulable state. WE found in this study that the TEG indexes of the cerebral hemorrhage group generally indicated a relatively hypo-coagulable state. However, results of TEG in some individuals indicate a hypercoagulable state, which has been speculated to be related to the different activation levels of coagulation and fibrinolysis systems after cerebral hemorrhage [10,12–15]. This phenomenon reflects that the disorder of coagulation function in cerebral hemorrhage is more complicated than that in cerebral infarction, which needs larger research with larger sample size, and more detailed grouping and stratification, to explore the regularity of the disorder.

Conclusions

As the blood of patients with acute cerebral infarction is in a relatively hypercoagulable state, the treatment and evaluation of patients with acute cerebral infarction can be guided by monitoring values of R, K, CI, and Angle. Angle is more meaningful for the treatment of anti-platelet aggregation in cerebral infarction due to its reflection of the quality and quantity of platelets. As patients with acute cerebral hemorrhage

have coagulation disorders and are in a relatively low coagulation state, Angle, MA, and K values may be of a certain significance for the evaluation of the patient's condition and prognosis of cerebral hemorrhage.

Conflict of interest

None.

References:

1. Engelhardt E: Apoplexy, cerebrovascular disease, and stroke: Historical evolution of terms and definitions. *Dement Neuropsychol*, 2017; 11: 449–53
2. Crawford KM, Gallego-Fabrega C, Kourkoulis C et al: Cerebrovascular disease knowledge portal: An Open-Access data resource to accelerate genomic discoveries in stroke. *Stroke*, 2018; 49: 470–75
3. Ono H, Nishijima Y, Ohta S et al: Hydrogen gas inhalation treatment in acute cerebral infarction: A randomized controlled clinical study on safety and neuroprotection. *J Stroke Cerebrovasc Dis*, 2017; 26: 2587–94
4. Wang S, Ma T, Wang L et al: Effect of acupuncture on cerebrovascular reserve in patients with acute cerebral infarction: Protocol for a randomized controlled pilot study. *Trials*, 2017; 18: 292
5. Chan E, Anderson CS, Wang X et al: Significance of intraventricular hemorrhage in acute intracerebral hemorrhage: Intensive blood pressure reduction in acute cerebral hemorrhage trial results. *Stroke*, 2015; 46: 653–58
6. Liu J, Yang H, Yu B: The correlation between blood calcium level, hematoma volume, stroke severity and prognosis in patients with acute cerebral hemorrhage. *Eur Rev Med Pharmacol Sci*, 2016; 20: 4119–23
7. Beg M, Nizami A, Singhal KC et al: Role of serum fibrinogen in patients of ischemic cerebrovascular disease. *Nepal Med Coll J*, 2007; 9: 88–92
8. Cabrera N, Moret A, Caunedo P et al: Comparison of a new chemiluminescent immunoassay for von Willebrand factor activity with the ristocetin cofactor-induced platelet agglutination method. *Haemophilia*, 2013; 19: 920–25
9. Matsui T, Hori A, Hamako J et al: Mutant botrocetin-2 inhibits von Willebrand factor-induced platelet agglutination. *J Thromb Haemost*, 2017; 15: 538–48
10. McDonald MM, Almaghrabi TS, Saenz DM et al: Dual antiplatelet therapy is associated with coagulopathy detectable by thrombelastography in acute stroke. *J Intensive Care Med*, 2017 [Epub ahead of print]
11. Xu X, Chen X, Zhang J et al: Comparison of the Tada formula with software slicer: precise and low-cost method for volume assessment of intracerebral hematoma. *STROKE*, 2014; 45: 3433–3435.
12. Solbeck S, Jensen AS, Maschmann C et al: The anticoagulant effect of therapeutic levels of dabigatran in atrial fibrillation evaluated by thrombelastography (TEG((R))), Hemoclot Thrombin Inhibitor (HTI) assay and Ecarin Clotting Time (ECT). *Scand J Clin Lab Invest*, 2018; 78(1–2): 25–30
13. Laursen TH, Meyer M, Meyer A et al: Thrombelastography early amplitudes in bleeding and coagulopathic trauma patients: Results from a multicenter study. *J Trauma Acute Care Surg*, 2018; 84: 334–41
14. Da LL, Nascimento B, Rizoli S: Thrombelastography (TEG(R)): Practical considerations on its clinical use in trauma resuscitation. *Scand J Trauma Resusc Emerg Med*, 2013; 21: 29
15. Bliden KP, Chaudhary R, Mohammed N et al: Determination of non-vitamin K oral anticoagulant (NOAC) effects using a new-generation thrombelastography TEG 6s system. *J Thromb Thrombolysis*, 2017; 43: 437–45