Thromboelastography as a tool for monitoring blood coagulation dysfunction after adequate fluid resuscitation can predict poor outcomes in patients with septic shock

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Abstract

Background: Coagulation abnormalities are universal in patients with septic shock and likely play a key role in multiple organ dysfunction syndrome. Early diagnosis and management of sepsis-induced coagulopathy can influence the outcome. Thromboelastography (TEG) can effectively distinguish hypercoagulability and hypocoagulability in patients with septic shock. TEG may be a useful tool to objectively evaluate the degree and risk of sepsis.

Methods: A total of 76 adult patients with septic shock were enrolled and divided into four groups: patients with hypotension requiring vasopressor and serum lactate level >2 mmol/L (group A), patients with hypotension requiring vasopressor and serum lactate level ≤2 mmol/L (group B), patients with mean arterial pressure ≥65 mmHg and serum lactate level >2 mmol/L (group C), and patients with mean arterial pressure ≥65 mmHg and serum lactate level ≤2 mmol/L (group D) after adequate fluid resuscitation. TEG values were obtained at the emergency room and after 6 hours of adequate fluid resuscitation. Data on fibrinogen (FIB) levels, international normalized ratio (INR), activated partial thromboplastin time (aPTT), blood gas, platelet count, and D-dimers were also collected.

Results: The length of stay in the intensive care unit was 9.11 ± 5.36 days. Mortality rate was 6.58%. The values of reaction time, kinetics time, maximum amplitude, alpha angle, aPTT, INR, serum creatinine, FIB, and sepsis-related organ failure assessment (SOFA) score showed a significant differences. The results of the routine coagulation tests, blood gas volume, platelet count, procalcitonin level, D-dimer level, white blood cell count, creatinine level, disseminated intravascular coagulation score, SOFA score, and TEG values after adequate fluid resuscitation were significantly different between groups A and B, groups A and C, groups A and D, groups B and D, and groups C and D.

Conclusion: TEG is helpful in predicting the severity of sepsis and outcome of patients.

Keywords: Prognosis; Sepsis; Thromboelastography

1. INTRODUCTION

Sepsis is currently defined as a severe multisystem disease that is difficult to treat and has high mortality rates.[1] Sepsis is a complex condition characterized by simultaneous activation of inflammation and coagulation in response to microbial insult. These events manifest as systemic inflammatory response syndrome or sepsis symptoms due to the release of proinflammatory cytokines, procoagulants, and adhesion molecules from immune cells and/or damaged endothelium. Sepsis is associated with hemostatic abnormalities, ranging from subclinical activation of blood coagulation (hypercoagulability) to massive thrombin and fibrin formation with systemic clotting activation.[2] During the initial phase, the hypercoagulability may be associated with hypofibrinolysis, which can be considered as an attempt to compartmentalize the infectious focus. As the infection worsens, these local protective mechanisms may spread systemically, which can lead to the development of disseminated intravascular coagulation (DIC).[3,4] Thrombosis in the microcirculation may lead to different consequences depending on their possible dissolution by a mostly intact fibrinolytic system. The endpoints of routine coagulation tests occur early in the hemostatic process. Thromboelastography (TEG) measures the viscoelastic properties of blood during the process of clot formation in a whole blood assay format and may provide additional information on coagulation. TEG assesses the effect of plasmatic factors and platelets on all phases of coagulation, which allows the evaluation of clot initiation, propagation, formation, and firmness. A previous study conducted in a group of patients with septic shock showed that TEG can effectively monitor the change in coagulation in patients with sepsis and distinguish the hypercoagulable and hypocoagulable state. TEG may be a promising tool to objectively evaluate the degree and risk of septic shock.

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 674-677.

Received February 8, 2018; accepted July 17, 2019.

doi: 10.1097/JCMA.0000000000000345.

2. METHODS

2.1. Study patients

This prospective study was conducted on all patients with severe sepsis and septic shock admitted to the emergency intensive care unit (EICU) in Sir Run Run Shaw Hospital Zhengjiang University from January 2014 to September 2017. All patients agreed to the new definition of sepsis (Sepsis-3).[5] A total of 76 adult patients who developed septic shock (MAP, <65 mmHg; serum lactate level >2 mmol/L) before fluid resuscitation were enrolled in the study. Patients who have preexisting hematological disorders (congenital, malignancy, and liver dysfunction) are aged ≤18 years, who use alcohol, who are pregnant, who are on antiplatelet/anticoagulant therapy, who underwent kidney replacement, who received blood transfusion 24 hours before blood sampling were excluded from the study. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of ** University. Written informed consent was obtained from all participants.

2.2. General treatment

All patients with sepsis were monitored with a radial arterial line and a central venous line at the emergency room (ER). The septic shock treatment guideline is focused primarily on providing early goal-directed therapy (EGDT). After 6 hours of adequate fluid resuscitation,[6] patients were divided into group A (23 patients with hypotension requiring vasopressors and a serum lactate level >2 mmol/L), group B (21 patients with hypotension requiring vasopressors and a serum lactate level ≤2 mmol/L), group C (15 patients with MAP ≥65 mmHg and a serum lactate level >2 mmol/L), and group D (17 patients with MAP ≥65 mmHg and a serum lactate level ≤2 mmol/L). Selection of Surviving Sepsis Campaign Database Cohort: Hypotension was defined as an MAP <65 mmHg. Vasopressor therapy was necessary to maintain an MAP ≥65 mmHg and was considered as a binary variable. A serum lactate level >2 mmol/L after adequate fluid resuscitation is considered abnormal.[7]

2.3. Blood sampling

Patients' blood samples were obtained at the ER and after 6 hours of adequate fluid resuscitation for TEG. TEG parameters included reaction (*R*) time (time to initial fibrin formation up to 2 mm), kinetics (*K*) time (time to clot formation up to 20 mm), alpha (α) angle (speed of clot formation), and maximum amplitude (MA) (measurement of clot strength). The following laboratory parameters were also assayed: fibrinogen (FIB; g/L), international normalized ratio (INR), activated partial thromboplastin time (aPTT, seconds), blood gas, platelet count (k/μL), procalcitonin (PCT), D-dimers (μg/L), white blood cell (WBC) count (k/μL), and creatinine (μmol/L).

2.4. Data acquisition

Demographic data, source of infection, length of stay in the ICU, and 28-day mortality were recorded. The sepsis-related organ failure assessment (SOFA) score was computed upon admission at the EICU and after adequate fluid resuscitation. The SOFA score was developed to quantify the severity of illness based on the degree of organ dysfunction.[5]

2.5. Statistical analysis

Frequency tables were used to present the categorical findings. The analysis was performed using SPSS17 software (Released 2008; SPSS Statistics for Windows, Version 17.0; SPSS Inc., Chicago). Continuous variables were expressed as mean ± standard deviation, and the comparison of means was performed using a Student's *t* test. The categorical data were expressed as frequencies and percentages. A *p* value of <0.05 was considered to be statistically significant.

Table 1

Characteristics of the study population

Parameter/variable	Value
n	76
Age, y	65 ± 13
Male sex, n	42
Source of infection, n	
Lungs	29
Catheter related	3
Endocarditis	1
Abdominal	16
Soft tissue/bone	5
Urinary tract	21
Unknown/other	1
Intensive care unit	
Length of stay, d	9.11 ± 5.36
Mortality, n (%)	5 (6.58)

All values are presented as number or as mean ± SD.

3. RESULTS

3.1. Patients

Patients' characteristics are shown in Table 1. On admission to the ER and EICU, the following baseline characteristics were recorded: gender, age, type of admission (surgical), previous treatment with prophylactic antibiotics, history of antiplatelet treatments, and history of anticoagulant therapy. The mean age was 66 ± 21 years, and 42 patients (55%) were men. The following were the sources of infection (n): lungs (29), catheter-related (3), endocarditis (1), urinary tract (21), abdominal (16), soft tissue/bone (5), and unknown/other (1). Length of stay in the ICU was 9.11 ± 5.36 days. Mortality rate was 6.58%.

3.2. Routine laboratory results and thromboelastometry

Routine coagulation tests, blood gas volume, platelet count, PCT, D-dimer level, WBC count, creatinine level, and thromboelastometric variables at ER and after 6 hours adequate fluid resuscitation are presented in Table 2. There was no significant difference in prothrombin time, D-dimer levels, WBC count, PCT, PH, DIC score, and lactate levels between the two groups. However, the values of *R* time, *K* time, MA, α angle, aPTT, INR, serum creatinine, FIB, and SOFA score were significantly different between the two groups. We have also found that aPTT ($p = 0.004$), INR ($p = 0.01$), and PCT ($p = 0.032$) increased after fluid resuscitation, the α angle ($p = 0.009$) and MA ($p = 0.009$) decreased and *K* time ($p = 0.001$)/*R* time ($p = 0.014$) both increased in TEG and TEG values were significantly different between every 2 groups except for group Band group C ($p < 0.05$), while the LAC concentration was different between any 2 group. Although it may suggest that hypotension and LAC may both impact the coagulation, either lower blood pressure or higher LAC would change the coagulation system.

Routine coagulation tests, blood gas volume, platelet count, PCT, D-dimer level, WBC count, creatinine, and thromboelastometric variables in groups A, B, C, and D after adequate fluid resuscitation are presented in Table 3. The results of routine coagulation tests, blood gas volume, platelet count, PCT, D-dimer level, WBC count, creatinine level, DIC score, SOFA score, and TEG values were significantly different between groups A and B, groups A and C, groups A and D, groups B and

Table 2

Results of routine coagulation tests, DIC score, PCT, SOFA, and TEG at ER and after 6 hours of adequate fluid resuscitation

Parameter	Normal	At ER	After 6 hours adequate fluid resuscitation	*p*
aPTT, s	29.2-41.3	33.64 ± 7.37	38.42 ± 12.00	0.004*
DDI, μg/mL	0-0.5	4.04 ± 3.33	4.66 ± 3.65	0.276
DIC score (ISTH)	...	3.14 ± 1.67	3.61 ± 2.29	0.159
FIB, mg/dL	200-400	289.34 ± 19.05	278.41 ± 36.01	0.021*
INR	...	1.82 ± 0.37	2.03 ± 0.58	0.01*
pH	7.36-7.44	7.30 ± 0.03	7.29 ± 0.07	0.324
PLT (10^9)	125-350	108.38 ± 55.74	95.38 ± 67.50	0.198
PT, s	10.7-14	15.01 ± 2.3	15.69 ± 3.96	0.198
WBC count (10^9)	3.5-10	13.93 ± 3.91	15.92 ± 7.98	0.053
PCT, ng/dL	<0.5	74.8 ± 38.60	92.24 ± 58.60	0.032*
scr, μmol/mL	<110	157.2 ± 90.16	221.46 ± 130.89	0.001*
Lac, mmol/L	0.90-1.70	3.33 ± 1.27	3.12 ± 2.08	0.045
SOFA score		6.12 ± 3.55	7.62 ± 4.21	0.019*
Angle, °	47-74	56.98 ± 5.37	54.27 ± 7.10	0.009*
K, min	1-4	2.84 ± 0.76	3.47 ± 1.32	0.001*
MA, mm	54-72	56.9 ± 4.64	54.33 ± 7.00	0.009*
R, min	4-8	7.75 ± 2.56	9.07 ± 3.85	0.014*

Values are expressed as mean ± SD. Comparison of means was done by Student's *t* test.
aPTT = activated partial thromboplastin time; DDI = D-dimers; DIC = disseminated intravascular coagulation; ER = emergency room; FIB = fibrinogen; INR = international normalized ratio; Lac = serum lactate level; MA = maximum amplitude; PCT = procalcitonin; PLT = platelet; PT = prothrombin time; scr = serum creatinine; SOFA = sepsis-related organ failure assessment; TEG = thromboelastography; WBC = white blood cell.
*$p < 0.05$, after 6 hours adequate fluid resuscitation versus at ER.

D, and groups C and D. In contrast, there was no significant difference in the routine coagulation tests, blood gas volume, platelet count, PCT, D-dimer level, WBC count, creatinine level, DIC score, SOFA score, and TEG values between every 2 groups except for group B and group C ($p < 0.05$), while the LAC concentration was different between any 2 group. Although it may suggest that hypotension and LAC may both impact the coagulation, either lower blood pressure or higher LAC would change the coagulation system.

4. DISCUSSION

Coagulation abnormalities are pivotal in causing microcirculatory dysfunction and multiorgan failure in patients with sepsis.[8,9] Sepsis-induced coagulopathy ranges from a subtle activation of coagulation to a more severe condition known as DIC, which is characterized by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites.[10] Early diagnosis and management of sepsis-induced coagulopathy can influence patient's outcome. TEG can provide a comprehensive assessment of the whole coagulation process (clot initiation, propagation, and degradation).[11] TEG has been used for many years in the fields of trauma and major surgeries.[12–14] TEG is a promising tool in assessing hemostatic alterations in patients with sepsis. In our study, we observed that DIC score (ISTH) had no significant difference ($p = 0.159$), but the values of *R* time, *K* time, MA, and α angle were significantly different between the two groups (at ER and after 6 hours adequate fluid resuscitation) ($pR = 0.014$, $pK = 0.001$, pMA = 0.009, $p\alpha = 0.009$) (Table 2). Based on the above finding, TEG has shown to be a promising tool in diagnosing DIC. We found from group A to D, the severity of sepsis was much less and TEG showed the coagulation was impaired. In addition, the combination of various parameters (*R* time, MA, and α angle) improves the diagnostic value in patients with sepsis.[15,16] A scoring system for the diagnosis of DIC, using thromboelastometry, has been developed, including prolonged reaction and *K* times and decreased α angle and MA. This score was validated in patients with an underlying disease known to be associated with DIC and with an ISTH DIC[17] score of more than 5. Therefore, to date, the quality of

Table 3

Results of routine coagulation tests, DIC score, and thromboelastometry after 6 hours of adequate fluid resuscitation

Parameter	Group A	Group B	Group C	Group D	*p* A vs B	*p* A vs C	*p* A vs D	*p* B vs C	*p* B vs D	*p* C vs D
aPTT, s	52.13 ± 4.68	36.87 ± 6.85	35.12 ± 8.53	25.17 ± 6.77	0.001*	0.001*	0.001*	0.536	0.001*	0.001*
DDI, μg/mL	9.67 ± 0.57	3.66 ± 0.66	3.25 ± 1.9	0.5 ± 0.45	0.001*	0.001*	0.001*	0.469	0.001*	0.001*
DIC score (ISTH)	5.91 ± 1.08	3.64 ± 1.73	2.85 ± 1.77	1.17 ± 1.29	0.001*	0.001*	0.001*	0.211	0.001*	0.001*
FIB, mg/dL	235.96 ± 19.44	282.55 ± 17.26	287.15 ± 15.09	321.28 ± 15.42	0.001*	0.001*	0.001*	0.415	0.001*	0.001*
INR	2.71 ± 0.28	1.96 ± 0.32	1.88 ± 0.36	1.34 ± 0.19	0.001*	0.001*	0.001*	0.531	0.001*	0.001*
pH	7.22 ± 0.06	7.32 ± 0.02	7.29 ± 0.03	7.35 ± 0.04	0.001*	0.001*	0.001*	0.028	0.001*	0.001*
PLT (10^9)	33.39 ± 12.22	81.14 ± 39.74	104 ± 54.78	185.78 ± 40.83	0.001*	0.001*	0.001*	0.204	0.001*	0.001*
PT, s	20.51 ± 2.65	14.57 ± 2.16	14.51 ± 1.95	11.76 ± 1.07	0.001*	0.001*	0.001*	0.933	0.002*	0.001*
WBC count (10^9)	23.5 ± 9.3	12.7 ± 1.63	15.65 ± 7.67	10.38 ± 0.85	0.001*	0.001*	0.001*	0.195	0.001*	0.001*
PCT, ng/dL	161.17 ± 44.06	76.14 ± 23.88	66.08 ± 44.48	42.72 ± 25.5	0.001*	0.001*	0.001*	0.462	0.001*	0.001*
scr, μmol/mL	333.52 ± 149.5	198.18 ± 78.26	220.62 ± 93.36	107.33 ± 38.24	0.001*	0.001*	0.001*	0.474	0.001*	0.001*
Lac, mmol/L	5.52 ± 1.98	1.83 ± 0.27	3.19 ± 1.39	1.57 ± 0.4	0.001*	0.001*	0.001*	0.004*	0.022	0.022
ICUlos, d	15.52±4.76	7.64 ± 1.53	7.38 ± 1.98	3.94 ± 1.73	0.001*	0.001*	0.001*	0.698	0.001*	0.001*
SOFA score	11 ± 4.67	6.82 ± 2.61	6.92 ± 3.55	4.78 ± 2.71	0.001*	0.001*	0.001*	0.927	0.021	0.021
Angle, °	46.88 ± 2.32	54.55 ± 4.56	54.27 ± 4.45	63.38 ± 3.76	0.001*	0.001*	0.001*	0.857	0.001*	0.001*
K, min	4.88 ± 1.17	3.22 ± 0.5	3.34 ± 0.8	2.08 ± 0.54	0.001*	0.001*	0.001*	0.628	0.001*	0.001*
R, min	13.49 ± 2.66	8.37 ± 1.25	8.52 ± 2.71	4.6 7± 1.17	0.001*	0.001*	0.001*	0.86	0.001*	0.001*
MA, mm	47.05 ± 4.03	55.28 ± 4.17	53.83 ± 3.89	62.82 ± 3.7	0.001*	0.001*	0.001*	0.308	0.001*	0.001*

Values are expressed as mean ± SD. values of sepsis-related organ failure assessment (SOFA) score with thromboelastometric variables. In accordance with the guidelines for the treatment of septic shock, early goal-directed therapy (EGDT), the patients after 6 hours of adequate fluid resuscitation were divided into group A (23 patients hypotensive requires vasopressor, serum lactate level >2 mmol/L), group B (21 patients hypotensive requires vasopressor, serum lactate level ≤2 mmol/L), group C (15 patients hypotensive requires no vasopressor, serum lactate level >2 mmol/L), and group D (17 patients hypotensive requires no vasopressor, serum lactate level ≤2 mmol/L). Comparison of means was done by Student's *t* test.
aPTT = activated partial thromboplastin time; DDI = D-dimers; DIC = disseminated intravascular coagulation; FIB = fibrinogen; ICU = intensive care unit; INR = international normalized ratio; Lac = serum lactate level; MA = maximum amplitude; PCT = procalcitonin; PT = prothrombin time; scr = serum creatinine; WBC = white blood cell.
*$p < 0.05$: group A versus B; group A versus C; group A versus D; group B versus C; group B versus C; group C versus D.

evidence supporting the use of TEG to diagnose DIC is low, and further research is necessary.

Results of TEG measurements in sepsis vary widely across studies and show both hypocoagulability and hypercoagulability.[18–23] This is consistent with the pathophysiology of "consumption coagulopathy" during DIC.[24] The initial phase of sepsis is characterized by the formation of microvascular thrombi, and the later phase manifests as a hypocoagulant phase secondary to consumptive coagulopathy. Hence, sepsis is a dynamic process; therefore, both the timing of test and severity of sepsis can influence the results of TEG. Sivula et al in 2009 assessed the role of thromboelastometry in severe sepsis and found that patients without DIC have the tendency to develop hypercoagulability and those with overt DIC have the tendency to develop hypocoagulability.[25] The degree of hypocoagulation was found to be associated with severity of organ failure.[26] On assessment of the individual TEG values, results showed that group A patients with septic shock had lower α and MA and higher *R* and *K* times than those in groups B, C, and D. As shown in the results of the DIC score, SOFA score and TEG were significantly different between groups A and B, groups A and C, and groups A and D (Table 3). We observed that patients with septic shock had the tendency to develop hypocoagulability.

Assessment of coagulation dysfunction in patients with sepsis using TEG can be helpful in predicting the severity of sepsis and outcome of patients. These findings may be useful in the management of patients with sepsis. However, this study is just an observational study with a small sample size.

It has been found soluble lactate levels independently predicted increases in the levels of vascular endothelial growth factor (VEGF), sVEGFR1, and Ang2 in patients with DIC may have roles in the development of MODS in sepsis associated with DIC.[27] According to our study, the LAC was extremely higher in group A and group C based on the grouping, and it also showed the same tendency of TEG as previous study.

In conclusion, identification of coagulation disorders is essential in patients with sepsis as coagulopathy is a risk factor for mortality. Based on the above findings, TEG can effectively monitor the change in coagulation in patients with sepsis and distinguish the hypercoagulable and hypocoagulable states. Larger trials are needed to assess the role of TEG in predicting the severity of sepsis and outcome of patients.

ACKNOWLEDGMENTS

The study was supported by the Zhejiang Medical Science and technology project (2018KY496).

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