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Thromboelastography in the evaluation of coagulation disorders in patients with sepsis

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Aim: Unbalanced hemostasis and disseminated intravenous coagulopathy serve as key participants in organ dysfunction and disability. In this study we evaluated the coagulation profiles of patients diagnosed with systemic inflammatory syndrome (SIRS)-sepsis and multiple organ dysfunction syndrome. We also researched coagulation in sepsis by comparing thromboelastography (TEG) data with those of nonsepsis patients to determine the usefulness of the TEG device.

Materials and methods: Data were collected from 55 anesthesiology and surgery intensive care unit (ICU) patients: 21 with SIRS-sepsis (Group S) and 34 patients without SIRS-sepsis (Group C). Blood samples were taken upon admission to the ICU (t1) and on day 3 of the ICU stay (t2). TEG data (R = reaction time, K = coagulation time, α = alpha angle, and MA = maximum amplitude) were recorded. TEG parameters were compared with routine coagulation and hemogram studies.

Results: The mean R value in Group C was higher than that of Group S at both t1 and t2. Group S had a significantly lower K value and higher alpha angle at t1 compared to Group C ($P < 0.05$).

Conclusion: Hypercoagulability was observed in SIRS-sepsis patients in the ICU, as measured with TEG. We believe that TEG will be a useful tool in the evaluation of coagulation disorders developing in septic critically ill patients.

Key words: Sepsis, coagulation, thromboelastography

1. Introduction

Sepsis involves the invasion of blood and body tissues by microorganisms and/or their toxins and the reactions of the body against this invasion (1). During the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, sepsis was defined as a systemic inflammatory response syndrome (SIRS) caused by infection (2).

In sepsis, interactions among inflammation, coagulation, and fibrinolysis, including disseminated intravenous coagulopathy (DIC), create organ dysfunction; these areas have also been the focus of new treatment strategies in recent years (1,3). The initiating event in sepsis is thought to be direct or indirect damage of the endothelium by a microorganism or its toxin(s) (1-3). Subendothelial tissues are then affected and collagenase is released. In sepsis, activation of the extrinsic coagulation cascade begins first, and then the intrinsic pathway increases coagulation even more (1). The activation of both extrinsic and intrinsic pathways results in increased availability of thrombin. As a result, consumption coagulopathy (DIC) may develop and spontaneous hemorrhages may occur.

However, severe hemorrhage diathesis is not common (<3%) in critical patients (1).

Thromboelastography (TEG) uses full blood as its test material and evaluates the whole coagulation system with multiple parameters. TEG can determine the stability, endurance, and kinetics of the coagulation system. Stability and endurance reflect hemostasis and clot formation; its kinetic parameters reveal whether factors are sufficient enough in quantitative terms that clot formation will occur (4,5).

In this study, TEG was examined for its usefulness in the evaluation of coagulation disorders in patients with sepsis.

2. Materials and methods

The study protocol was approved by the university's board of ethics. After obtaining informed consent, a suitable group of patients admitted to the Anesthesiology and Surgery Intensive Care Unit (ICU) between December 2009 and November 2010 were included in the study in a prospective fashion.

The patients were assigned to 2 groups. Group S (n = 21; sepsis) included the patients diagnosed with

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SIRS-sepsis and Group C (n = 34; control) included patients admitted to the ICU without SIRS findings (2). Exclusion criteria were age under 18 years, preexistent hematological disorders, current oral anticoagulants, or therapy to inhibit platelet aggregation. Demographic and clinical characteristics of patients were recorded, including vital signs, diagnoses, DIC, APACHE II score, length of hospital stay, and use of mechanical ventilation, blood or blood products, vasopressors, and anticoagulant and antiplatelet agents. Diagnosis of DIC was proven when prolongation in prothrombin time (PT) and activated partial thromboplastin time (aPTT), low platelet and fibrinogen levels, and an increase in D-dimer and other fibrin split products were observed.

Blood samples were taken upon admission to the ICU (baseline, t1) and at the end of the third day (t2). TEG analysis was done by an anesthesiologist blinded to the study group of the patient using a Thrombelastograph 5000 coagulation analyzer (Haemonetics Corp., Braintree, MA, USA). The TEG device was adjusted to measure at 37 °C. First, 1 mL was taken from the citrated blood sample and mixed in a kaolin tube by gentle shaking. Next, 340 µL of blood was taken from this blood sample with an automatic pipette and put into the TEG tube, and then 20 µL of calcium was added to the tube to eliminate the effect of citrate. A disposable piston covered with plastic was placed into the blood sample by a wire. The TEG tool was started and the following standard TEG data were recorded: reaction time (R, normally 3–8 min), coagulation time (K, normally 1–3 min), alpha angle (α , normally 55–78°), and maximum amplitude (MA, normally 51–69 mm). Results from coagulated samples and systematic errors were excluded from data analysis. In addition, routine

coagulation tests [PT, aPTT, and international normalized ratio (INR)], hemoglobin, hematocrit, platelet (PLT) count, white blood cell (WBC) count, and procalcitonin (PCT) levels were measured on admission to the ICU and on day 3.

2.1. Statistical analysis

Measured TEG parameters were compared with the bleeding profile of patients in the sepsis and control groups. Power analysis revealed that a minimum sample size of 20 patients was required to achieve a power (β) of 0.80, with a significance level of 95% ($\alpha = 0.05$). All statistical calculations were performed with SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA). Means \pm standard deviations (SDs) were calculated for continuous variables. Chi-square and Mann–Whitney U tests were used to compare TEG and routine coagulation parameter results. Findings were considered statistically significant if the P-value was less than 0.05.

3. Results

During the study period, 21 patients with SIRS-sepsis (Group S, mean age of 57 ± 18 years) and 34 control patients without SIRS-sepsis (Group C, mean age of 58 ± 16 years) were included. The groups were not significantly different in age, weight, or sex. APACHE II scores were significantly higher in Group S patients (Table 1). Within 28 days of admission to the ICU, 9 (48%) patients in Group S and 2 (5.88%) patients in Group C died.

While the majority (52%) of Group S patients were postoperative patients, 19% were trauma patients, 14% were infectious disease patients, 10% were postcardiopulmonary resuscitation (post-CPR) patients, and 5% were suffering

Table 1. Demographic data of patients.

	Group S (n = 21)	Group C (n = 34)	P-value
Age (years)	57.47 \pm 17.63	58.17 \pm 15.67	0.96
Sex (M/F)	10 / 11	15 / 19	0.804
Weight (kg)	86.61 \pm 17.12	78.44 \pm 18.0	0.13
APACHE II	23.61 \pm 10.14	7.97 \pm 3.22	0.0001
Diagnosis of patients			
Postoperative patient	11 (52%)	22	
Trauma	4 (19%)	5	
Infectious disease	3 (14%)	-	0.252
Post-CPR patient	2 (10%)	3	
Pulmonary disease	1 (5%)	2	
Intoxication	-	2	

Data are reported as mean \pm SD. S: sepsis patients, C: control patients, M: male, F: female, APACHE II: Acute Pathophysiology and Chronic Health Evaluation II score.

from pulmonary diseases. The majority (65%) of Group C patients were also postoperative patients. The distribution of diagnoses in the 2 groups was not significantly different ($P = 0.252$).

Use of medications affecting the hemostatic system was similar in the 2 groups, and DIC occurred in only 1 patient from Group S ($P = 0.199$). Use of mechanical ventilation and length of hospital stay were greater in Group S patients ($P = 0.003$). Use of blood and blood products ($P = 0.004$), vasopressors ($P = 0.0001$), and total parenteral nutrition ($P = 0.003$) was also considerably higher in Group S (Table 2). The first 28-day mortality rates were 47.6% (9 patients) and 5.88% (2 patients) in Group S and Group C, respectively ($P = 0.004$).

When Group C and Group S were compared with regard to basic SIRS criteria, significant differences were found in all criteria ($P < 0.05$). At t1, significant differences between the 2 groups were found in hemoglobin, hematocrit, WBC, PLT, PT, aPTT, INR, and PCT values (Table 3). At t2, hemoglobin, hematocrit, and aPTT values were not significantly different ($P > 0.05$) (Table 3).

No significant differences were found between Group S and Group C in diastolic blood pressure (DBP), mean arterial pressure (MAP), or central venous pressure (CVP) at t1 ($P > 0.05$) (Table 4). However, mean systolic blood pressure (SBP) and $\text{PaO}_2/\text{FiO}_2$ rates in the 2 groups at t1 were significantly different ($P < 0.05$, Table 4).

The R value in Group S was lower than that of Group C at t1 and t2 ($P < 0.05$), the K value was lower in Group S at t1 ($P < 0.05$), and the alpha value was higher in Group S at t1 ($P < 0.05$, Table 5).

4. Discussion

Early diagnosis of coagulation disorders, one of the most important causes of mortality in sepsis, is a critical aspect of sepsis treatment. In this study, we investigated the efficacy of TEG as a diagnosis method in evaluating the coagulation disorders of patients with sepsis. When

patients with sepsis were evaluated with TEG, we observed hypercoagulability variations and saw that TEG is effective in diagnosing coagulation disorders.

Sepsis affects many systems and causes hemodynamic changes, which can progress to shock, organ dysfunction, and organ failure (2). Despite advances in treatment, sepsis maintains its importance because of its high morbidity and mortality (6,7). Its incidence has increased in recent years due to more widespread use of immunosuppressive medications, more invasive therapies, and an overall longer lifespan, which means more elderly patients who have chronic diseases (6,8). Mortality rates resulting from sepsis in various series have been reported to be between 20% and 60%, which are comparable to our results (48% died within 28 days) (9–12).

Hematological dysfunction (as in DIC) occurring within the first 24 h of sepsis treatment is associated with a high rate of organ failure and death. In the early stages, only prolongation of PT and aPTT may be seen. Eventually, as a result of consumption of coagulation factors, sepsis coagulopathy will occur (13). Early diagnosis is very important so that treatment can be started promptly. In our study, significant differences between Groups S and C in PT, aPTT, and INR values were identified at t1; however, by t2, differences remained only in PT and INR values. In the multicenter Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis study (14), 93% of patients with sepsis had a prolonged PT and 63% of patients with sepsis had a prolonged aPTT. The degree of coagulation test abnormalities correlated with the intensity of the disease (15). DIC is characterized by intravenous fibrin formation, which results in the thrombotic obstruction of small- and medium-sized vessels. In acute DIC, prolongation in PT and aPTT, low platelet and fibrinogen levels, and an increase in D-dimer and other fibrin split products are observed (16,17).

TEG analyzes the hemostatic system by evaluating the viscoelastic and mechanical characteristics of the

Table 2. Clinical characteristics of patients within the first 3 days.

	Group S (n = 21)	Group C (n = 34)	P-value
Length of hospital stay (days)	23 ± 14.16	62.11 ± 68.35	0.003
Use of blood products	18 (85.7)	16 (47.1)	0.004
Presence of DIC	1 (4.8)	-	0.199
Medications affecting the hemostatic system	10 (47.6)	15 (44.1)	0.34
Use of vasopressor	10 (47.6)	1 (2.9)	0.0001
Mechanical ventilation support	16 (76.2)	12 (35.3)	0.003
Implementation of total parenteral nutrition	11 (52.4)	5 (14.7)	0.003

Data are reported as n (%), S: sepsis patients, C: control patients, DIC: disseminated intravenous coagulopathy.

Table 3. Laboratory data of patients.

		Group S (n = 21)	Group C (n = 34)	P-value
Hemoglobin (g/dL)	t1	10.72 ± 1.6	12.01 ± 1.89	0.003
	t2	10.8 ± 51.4	11.25 ± 1.96	0.621
Hematocrit (%)	t1	31.19 ± 4.52	35.64 ± 6.04	0.0001
	t2	31.9 ± 4.27	33.06 ± 6.16	0.709
WBC (cell/mm ³)	t1	16.76 ± 8.14	11.26 ± 3.49	0.004
	t2	14.99 ± 7.83	11.63 ± 5.38	0.057
PT (s)	t1	17.35 ± 3.37	13.2 ± 2.22	0.0001
	t2	15.25 ± 2.91	13.35 ± 1.94	0.006
aPTT (s)	t1	36.41 ± 6.39	27.5 ± 3.44	0.0001
	t2	31.62 ± 10.47	28.62 ± 4.83	0.066
PLT (×10 ³)	t1	135.14 ± 68.06	223.52 ± 94.96	0.0001
	t2	155.04 ± 103.11	221.73 ± 77.64	0.009
INR	t1	1.1 ± 0.28	1.06 ± 0.19	0.0001
	t2	1.26 ± 0.82	1.06 ± 0.28	0.008
PCT (ng/mL)	t1	30.51 ± 48.86	0.36 ± 0.46	0.001
	t2	27.50 ± 53.23	0.23 ± 0.82	0.004

Data are reported as mean ± SD. S: sepsis patients, C: control patients, t1: day of admission, t2: third day, WBC: white blood cell count, PT: prothrombin time, aPTT: activated partial thromboplastin time, PLT: platelet count, INR: international normalized ratio, PCT: procalcitonin.

Table 4. Hemodynamic and respiratory parameters of patients at t1.

	Group S (n = 21)	Group C (n = 34)	P-value
SBP (mmHg)	104.8 ± 31.3	121.76 ± 17.64	0.01
DBP (mmHg)	60.66 ± 14.82	66.47 ± 11.29	0.083
MAP (mmHg)	76.47 ± 20.84	84.55 ± 11.29	0.074
CVP (mmHg)	9.56 ± 5.75	8.57 ± 3.74	0.920
PaO ₂ /FiO ₂	193.62 ± 63.44	334.98 ± 106.10	0.0001

Data are reported as mean ± SD. t1: day of admission, S: sepsis patients, C: control patients, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, CVP: central venous pressure, PaO₂/FiO₂: partial pressure of oxygen in arterial blood/fraction of inspired oxygen.

clot, a full dynamic process that differs from conventional coagulation tests (18). TEG can identify a hypercoagulable state quickly and is preferred in the postoperative evaluation of coagulation (19). In our study, significant differences in Groups S and C were found between the TEG values (R, K, α angle, and MA) at t1 and t2, indicating that TEG will better identify abnormal coagulation in the septic patient.

In a study of 28 patients with sepsis (DIC also in 12) and 10 control patients, TEG correctly identified hypocoagulation in all who developed DIC and hypercoagulation in all septic patients who did not develop DIC (20). Accordingly, it was stated that TEG was a suitable and efficient technique that easily demonstrated the coagulation capacity of all patients with sepsis (20). In a study of 30 patients with sepsis using rotation

Table 5. Thromboelastography parameters of patients.

		Group S (n = 21)	Group C (n = 34)	P-value
R (min)	t1	3.37 ± 1.65	5.05 ± 1.55	0.0001
	t2	3.76 ± 1.91	5.12 ± 1.95	0.015
K (min)	t1	1.6 ± 0.9	2.33 ± 1.42	0.041
	t2	1.88 ± 1.73	2.10 ± 1.27	0.538
Alpha angle (°)	t1	72.97 ± 7.01	67.77 ± 8.88	0.027
	t2	70.68 ± 8.71	68.34 ± 8.78	0.341
MA (mm)	t1	67.11 ± 1.31	63.81 ± 9.996	0.262
	t2	64.52 ± 14.84	63.41 ± 10.61	0.748

Data are reported as mean ± SD. t1: day of admission, t2: third day, S: sepsis patients, C: control patients, R: reaction time, K: coagulation time; MA: maximum amplitude.

thromboelastography (ROTEM), a modified form of TEG, ROTEM values changed significantly with the intensity of sepsis and subsequent appearance (or not) of organ dysfunction (21). The advantage of TEG is that it measures the entire coagulation process from the beginning of fibrin formation to clot lysis with minimal delays. In contrast, routine coagulation tests measure the in vitro static state of hemostasis and must be interpreted by correlating their results with the clinical condition of the patients (22).

Spiel et al. (23) produced experimental endotoxemia by giving lipid polysaccharide infusion to 16 volunteers and evaluated ROTEM parameters. ROTEM demonstrated not only changes related to coagulation but also changes related to fibrinolysis (23). In a study by Collins et al. (24), hemostasis disorder patients were evaluated with both ROTEM and routine coagulation tests. Routine coagulations tests were found to be inadequate to predict thrombosis and multiorgan failure, but ROTEM demonstrated the disorders of hemostasis more clearly (24).

In a study of newborns with sepsis, TEG had 96% sensitivity and 96% specificity in the diagnosis of coagulation disorders; the authors stated that it should be accepted as a simple, quick, and sensitive diagnostic method (25). Reikvam et al. (26) showed the efficiency of TEG in the diagnosis of coagulation disorders and stated

that the main advantage of TEG was in its ability to quickly evaluate the hemostatic system of patients in a global fashion.

Gonano et al. (27) investigated the coagulation profile of septic patients before and during antithrombin treatment (AT); they found pretreatment hypercoagulability in all sepsis patients using TEG. Despite high antithrombin plasma levels when receiving AT, the hypercoagulable state did not normalize, as measured by both TEG and standard coagulation tests (27). Just as we found, many others have found TEG to be very sensitive in detecting hypercoagulability (28–30).

Sepsis has a high mortality rate and should be diagnosed early and treated without delay. Coagulation disorders are among the most important causes of death in sepsis, and thus early identification of a coagulation disorder may be critical in prompting a clinician to initiate treatment. Thromboelastography can rapidly give the clinician an overview of the hemostatic condition of a patient. We believe that TEG is very useful in the diagnosis of coagulation disorders in sepsis.

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