



Evaluation of hemostasis with thromboelastometry during the diagnosis and at 24th hours in sepsis

Sepsis tanılı hastaların yatış ve 24. saatte tromboelastometri ile hemostazının değerlendirilmesi

Using rotem in the sepsis's first hours and 24th hours

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Öz

Amaç: Tromboelastometri yöntemi konvansiyonel tekniklerin yerine, hemostaz aksını tek başına gösterebilen bir tekniktir. Gereç ve Yöntem: Çalışma için yoğun bakım ünitesinde sepsis tanısı almış 50 hasta ve yerel popülasyon içerisinde yaşayan sağlıklı 50 gönüllü çalışmaya dahil edildi. Çalışma grubu Grup S ve Grup C olarak 2 gruba ayrıldı. Yoğun bakım ünitesinde sepsis tanısı almış hastalar Grup S, yerel popülasyonda yaşayıp koagülasyon profilini değiştirebileceği bilinen bir hastalığı olmayan gönüllüler Grup C olarak adlandırıldı. Tüm gruplara tromboelastometri yöntemi uygulandı. Bulgular: Grup S de Grup C'ye kıyasla PT ve PTT değerlerinde anlamlı bir yükselme görülürken, platelet düzeylerinde anlamlı bir azalma görülmüştür. Tromboelastometri parametreleri değerlendirildiğinde INTEM testinin tüm parametrelerinde, EXTEM testinin ise CT parametresi hariç tüm parametrelerinde gruplar arasında anlamlı bir farklılık görülmüştür. EXTEM testinin CT parametresinde ise gruplar arasında herhangi bir farklılık görülmemiştir. Grup S'de tanı sırasında ve 24. saatte bakılan konvansiyonel testler ve tromboelastometri testleri arasında herhangi bir farklılık görülmemiştir. Tartışma: Sonuçlarımız göstermiştir ki sepsis intrensek yolak üzerinde daha çok etkindir. Tromboelastometri yöntemi sepsis tanısında kullanım için uygun bir teknik iken sepsis takibinde anlamlı bir sonuç göstermemiştir. Sepsis tanısı için tromboelastometri kullanılmasını önermekteyiz.

Anahtar Kelimeler

Tromboelastometri; Koagülasyon; Kan Koagülasyon Testleri; Sepsis; Yoğun Bakım Ünitesi

Abstract

Aim: Thromboelastometry shows the monitorization of the hemostasis axis with the use of a single method instead of conventional techniques. Material and Method: This study was conducted on 50 patients who were admitted to the intensive care unit and diagnosed with sepsis together with 50 healthy volunteers from the local population. The patients were divided into two groups. Group S consisted of patients who were diagnosed with sepsis in the intensive care unit. Group C consisted of healthy volunteers who were selected from the local population and had no impairments of their coagulation profile. Thromboelastometry measurements were performed for both groups. Results: While elongation was observed in PT and aPTT between Group C and Group S, a decrease was observed in platelet counts ($p<0.05$). When analyzing thromboelastometry parameters, significant differences were seen between groups ($p<0.05$) in all parameters in INTEM and all parameters except CT in EXTEM. There was no significant differences in the CT parameter of the EXTEM measurement between groups ($p>0.05$). Within Group S, when the results from the time of diagnosis and the 24th hour were compared, no significant difference was observed in PT, aPTT, platelet count, or in all INTEM and EXTEM parameters examined. Discussion: Our results revealed that sepsis was clinically more disruptive of the intrinsic pathway. Thromboelastometry was a suitable technique for use in the diagnosis of sepsis, but did not show a significant effect in the follow-up of sepsis. We recommend using thromboelastometry for the diagnosis of sepsis.

Keywords

Thromboelastometry; Coagulation; Blood Coagulation Tests; Sepsis; Intensive Care Unit

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Introduction

Sepsis, defined as the systemic inflammatory response to infection, is created by a hereditary response of the individual against infection. [1-3]. An extremely severe response of the host against infection leads to sepsis. This may be followed by severe clinical sepsis, which is accompanied by hypotension that is unresponsive to fluid resuscitation [4]. In sepsis, the coagulation system is exposed to injury by systemic activation of multiple intermediate pathways involving a complement system and cytokine network, resulting in a complex relationship between the host and infectious agent [5]. An irregular hemostasis axis is formed in sepsis by the simultaneous activation of the anticoagulant and fibrinolytic systems. While progressive coagulopathy, disseminated intravascular coagulation, multiple organ failure, and death may occur, extensive bleeding diathesis as a result of hypocoagulation may also be seen in clinical sepsis [6].

Rotational thromboelastometry is an evaluation method of the coagulation process that shows all of the steps from the beginning of hemostasis to the fibrin degradation process with whole blood. It displays the dynamic interactions among platelets, coagulation and fibrinolytic factors, activators, and inhibitors within the coagulation process [7]. In terms of coagulation parameters, more significant determinations can be made for rapid results and the selection of the proper blood components to replace by using the thromboelastometry method instead of conventional laboratory data to determine factors such as activated partial thromboplastin time (aPTT), prothrombin time (PT), and platelet (Plt) counts [8].

The rotational thromboelastometry method, which assesses the coagulation profile and monitors hemostasis as a whole, may show the monitorization of the hemostasis mechanism by a single method instead of conventional techniques that investigate the coagulation process part by part. We aimed to evaluate the coagulation profiles of patients with sepsis and compare them with healthy individuals, using the rotational thromboelastometry method.

Material and Method

Study Design and Population Group

Following approval of the Atatürk University Clinical Research Center Ethics Committee, this study was conducted on 50 patients who were diagnosed with sepsis and admitted to the Atatürk University Medical Faculty Hospital, Intensive Care Unit between December 2012 and December 2013. Another group of 50 healthy volunteers, workers at the hospital, who were without any impairments of their coagulation profile, also signed informed consent forms. The total study population of 100 was divided into two groups. Group S (n = 50; Sepsis) consisted of patients in intensive care units who were diagnosed with sepsis. Group C (n = 50; Control) was comprised of individuals chosen from healthy volunteers who were from the general population and had no impairments of their coagulation profile. The diagnosis of sepsis was based on the consensus criteria of the International Working Party Consensus Definitions for Sepsis and Septic Shock [3].

Exclusion Criteria

Patients excluded from this study were those with a medical history of bleeding diathesis, or current usage of a drug or food that can impair the coagulation cascade, and individuals under 18 years or over 65 years of age.

Demographic datas, such as age and gender, of patients with sepsis and the healthy volunteers were obtained and recorded. After patients had given their written informed consent, blood was obtained in 10 cc volumes in both groups to study all parameters in each sample. In Group S, blood samples were obtained through the arterial system on the day sepsis was diagnosed and on the following day, at hour 24, with the first option being the radial artery. In Group C, samples were obtained through the venous system only on day one, with the first option being the antecubital system [9]. Blood samples were placed into test tubes for analysis of platelet count, PT, aPTT, and for study in the rotational thromboelastometry device (ROTEM® delta, Tem International GmbH, Munich, Germany). The tubes were gently turned upside down four to five times to prevent clotting. These blood samples were sent to the related laboratory unit within 30 minutes. The blood samples were placed into citrated blood test tubes (BD Vacutainer, UK, REF 363048). Following the notification that ROTEM measurements could be launched, equipment referred to as "cup" and "pin pro" were placed as described by the manufacturer, the device was brought to the "completely ready to run" position, and the thromboelastometry device was started. In our study, we performed measurements of intrinsic activation of thromboelastometry (INTEM) and extrinsic activation of thromboelastometry (EXTEM), which are the two basic measurements used in thromboelastometry analyses [10]. In circumstances in which heparin was used, heparinase was added to the INTEM reagent to prevent any probable differences in the results [11]. We also used heparinase in our INTEM measurements for patients in our intensive care unit in order to prevent the likely effects of low molecular weight heparin (LMWH). Test samples were prepared in 20 seconds and measurements were initiated.

Rotational Thromboelastometry

With regard to rotational thromboelastometry measurements, there are some parameters specific to the measurements. One of these parameters is the clotting time (CT, s), which continues until the occurrence of thrombin formation, platelet aggregation, and the initiation of polymerization. Another parameter is the clot formation time (CFT, s) in which the initiation of platelet aggregation is observed in a gross view, fibrin polymerization and platelet aggregation are accelerated, stabilization is enhanced by factor XIII, and this parameter continues until platelet aggregation occurs to a size of 20 mm in diameter. The angle created by the curve of the line, drawn from the starting point of the CFT parameter and tangential to the ascending slope of the curve, is called α ($^\circ$). If the platelet functions are powerful, the degree of the angle increases; alternatively, if the functions are weak, it is reduced. The value of the clot width at the end of the first 10 minutes of the platelet plug formation process was named A10 (mm x 100), and the value of the clot width at the end of the first 20 minutes was named A20 (mm x 100). The maximum value of the clot width was named maximum clot formation, (MCF, mm x 100) [12].

Statistical Analysis

In the power analysis for this study, which was performed to determine the sampling adequacy, the power of the study was 0.99 and the effect size was 1.75 for the Mann-Whitney U test with 50 people in both groups at the 0.05 significance level and 95% confidence interval. This figure showed that sampling of the study was sufficient [13, 14]. All statistical calculations were performed by SPSS 17.0 (Statistical Program for the Social Science) statistical software. The Shapiro-Wilk test was used to determine the distribution of data, and to compare data the Wilcoxon sign-rank test and the Mann-Whitney U test were used. In all statistical analyses, results were considered significant when P values were < 0.05 and highly significant when < 0.001.

Results

There were no significant differences ($P > 0.05$) in the demographic data for gender and age between the two groups in our study. The patients' demographic data are shown in Table 1.

The conventional coagulation tests, such as platelet count, PT, and aPTT values for both groups, showed highly significant differences between Groups C and S ($P < 0.001$) (Table 2).

By using thromboplastin-phospholipid in the INTEM measurement, the intrinsic pathway was initiated with the aim of controlling the process through the intrinsic pathway. When analyzing the INTEM parameters, highly significant differences were seen between groups in the CT, CFT, and MCF parameters. In addition, significant differences were seen in the α , A10, and A20 parameters of the INTEM measurement between groups. By using the tissue factor in the EXTEM measurement, the extrinsic pathway was initiated with the aim of controlling the process through the extrinsic pathway. When analyzed, the EXTEM parameters showed highly significant differences between groups in the CFT, α , A20, and MCF parameters. In addition, significant differences were seen in the A10 parameters of EX-

TEM measurement between groups. There were no significant differences in the CT parameter of the EXTEM measurement between groups. Laboratory data of the groups are shown in Table 3.

The comparisons of the first and second day Plt, PT, and aPTT values for Group S are shown in Table 4. According to these figures, in conventional coagulation measurements in the patients with sepsis, there were no significant differences between the INTEM and EXTEM parameters (Table 4).

The comparison of the first and second day (hour 24) INTEM and EXTEM parameters of Group S are shown in Table 3. According to these findings, in the INTEM and EXTEM measurements of Group S by the thromboelastometry method, there were no significant differences between any of the INTEM and EXTEM parameters (Table 5).

Discussion

Excessive activation of coagulation in sepsis results with increased coagulation system consumption. As a consequence of this consumption, during the acute period augmentation of coagulation and during the following hours, deficiency in coagulation is seen. Consumption of the coagulation system is increased following severe activation of coagulation in sepsis. At the end of the consumption, while there is an increase in the acute period of coagulation, when the coagulation system is evaluated by thromboelastometry in sepsis, the exaggerated increase of the ML parameter shows that hyperfibrinolysis and hypocoagulation can occur with an increase of CT, CFT, α , A10, A20, and MCF parameters.

The early detection of disorders in the coagulation profile, which is developed through the mediators of the coagulation system not only alerts physicians to the need for a resuscitation procedure for the coagulation system, but also an important step in the treatment of sepsis. In our study, by using thromboelastometry with control and sepsis groups, and by evaluating CT, CFT, α , A10, A20, and MCF parameters of INTEM and EXTEM measurements, highly significant differences were determined between the sepsis and healthy control groups. These differences suggest that, by using thromboelastometry, significant improvements can be made in the diagnosis.

Durilla et al. showed that measurements performed by a thromboelastography (TEG) device were faster and more effective in planning treatments directed at the cause of the basic problem when compared to using laboratory test results, such as PT, aPTT, INR, etc. [15]. In our study, we also determined that a more rapid evaluation of the coagulation profile on the first and second days could be made by thromboelastometry in the sepsis group. We obtained the results for the CT, CFT, and α parameters with the thromboelastometry device in short periods of 10 minutes, unlike the longer durations required to determine PT, aPTT, and INR using conventional techniques.

In the study by Nates et al., endotoxemic sepsis was created in pigs by lipopolysaccharide induction [16]. In their TEG test, they determined an increase in the k parameter, which corresponds to the CT parameter in thromboelastometry. They also determined reductions in the α and MA parameters in the TEG test, which are the same parameters determined in thromboelastometry. Sucker et al. evaluated the thromboelastometry results

Table 1. Demographics Data of Patients

Characteristics of 50 Patients with Sepsis and 50 Healthy Volunteers		
Variables	Group S	Group C
Age*	50.61 ± 5.54	50.94 ± 6.03
Gender *(Male/Female)	20 / 30	22 / 28
Procalcitonin	16.06±27.78	-
C-reactive Protein	121.60±67.21	-
Day of Diagnosed Sepsis	3.14±3.76	-
Apache II Score	22.66±6.70	-
Pulmonary disease	15 (%30)	-
Postoperative patient	12 (%24)	-
Neurologic disease	10 (%20)	-
Trauma (Without operation)	6 (%12)	-
Post-CPR patient	7 (%14)	-

* P > 0.05

Table2. The comparison of Laboratory Data for the 1st Days Between Group S and Group C*

	Plt($\times 10^9$)	PT	aPTT
Group S	207.0(111.0)**	16.6(6.8)**	37.7(16.0)**
Group C	327.3(33.6)	12.7(0.65)	29.4(0.98)

(Plt : platelet; PT : Prothrombin time ; aPTT : activated partial thromboplastin time ; * denote data presented as mean (SD), ** denotes $p < 0.001$.)

Table 3. The comparison of 1st day ROTEM parameters between Group S and Group C*

	Groups	CT(secs)	CFT(secs)	MCF(mm)	α (°)	A10(secs)	A20(secs)
INTEM	Group S	170.3(53.6)***	107.4(57.8) ***	63.1(15.4) ***	70.3(14.7)**	54.6(16.8)**	60.6(16.0)**
	Group C	206.2(12.5)	102.9(33.9)	58.5(3.7)	70.3(5.89)	50.1(5.3)	56.6(4.2)
EXTEM	Group S	123.2(69.9)	142.7(51.2)***	65.1(13.3)***	71.2(14.7)***	56.2(16.3)**	62.6(14.9)***
	Group C	117.3(13.1)	123.6(32.0)	59.1(3.7)	66.0(5.5)	49.5(7.1)	57.2(4.6)

INTEM : intrinsic activation of thromboelastometry ; EXTEM : extrinsic activation of thromboelastometry ; CT : Clotting time ; CFT : Clot formation time ; MCF : Maximum clot firmness ; A10 : The value of clot width at the end of the first 10 minutes ; A20 : The value of clot width at the end of the first 20 minutes). * denote data presented as mean (SD), ** denotes $p < 0.05$; *** denotes $p < 0.001$.

Table 4. The comparison of Laboratory Data for the 1st and 2nd Days in the Group S*

	Plt($\times 10^9$)	PT	aPTT
1 st day	207.0(111.0)	16.6(6.8)	37.7(16.0)
2 nd day	192.7(101.3)	17.18(7.16)	38.18(16.55)

(Plt : platelet; PT : Prothrombin time ; aPTT : activated partial thromboplastin time ; * denote data presented as mean (SD)

that they performed in sepsis models created by induction with lipoteichoic acid (LTA) under in vitro conditions. As a result, they concluded that endotoxemia induced by LTA affected CT, but had no effect on other parameters including CFT, MCF, and α as determined by thromboelastometry [17]. Daudel et al. performed thromboelastometry on 30 patients with sepsis who were treated in the intensive care unit and reported the results of the CT, CFT, α , and MCF parameters of the INTEM, EXTEM and the heparinase-modified thromboelastometry (HEPTEM) tests. While no significant changes were found in patients with sepsis, increases in the CT and CFT parameters, together with a reduction in MCF, were determined in EXTEM tests in severe sepsis patients when normal target ranges for each parameter were compared [11]. In the study conducted by Velik et al. on pigs administered an Escherichia coli endotoxin, a reduction in platelet levels after the endotoxin infusion was observed; however, no changes were observed in PT and aPTT values. When the thromboelastometry values were examined, a reduction was observed in the CT value in INTEM analysis, but there was no change in the CT value in EXTEM analysis. Furthermore, an increase in CFT values and decreases in α and MCF values were observed in both INTEM and EXTEM analyses. As a result of this study, it was demonstrated that use of the thromboelastometry method can provide for more positive outcomes in the early period in the evaluation of an early-period coagulation profile compared to conventional methods [18]. Intrinsic pathway activity that could not be specified by conventional techniques in the early period could be determined by thromboelastometry. In the present study, we partially determined the elongation by conventional methods in the intrinsic pathway and observed a decrease in the CT parameter of INTEM analyses [18].

Andersen et al. studied severe sepsis and septic shock patients and found that platelet counts decreased over time and PT

values decreased during the early period followed by a later increase. Furthermore, an elongation was observed in aPTT values, and, parallel to the conventional tests, the elongation was observed in the CT parameter in INTEM and EXTEM analyses. When the literature was examined, we observed that, parallel to this study, a rapid activation in the intrinsic pathway during the early periods of sepsis increased in the forthcoming days as shown by the CT parameter in the INTEM analysis, which was parallel with aPTT values. Similarly, the CT reductions were dependent on rapid consumption in the intrinsic pathway during the early period via thromboelastometry. However, since the present study examined the early period, during the diagnosis and at 24th hours, it could not reveal this elongation that would be expected in the forthcoming days; this would transfer the patient to the disseminated intravascular coagulation (DIC) picture and would show a rapid consumption and would cause an increase in the INTEM CT value [19]. When our results were taken into consideration, except for the CT parameter of the EXTEM measurement, all thromboelastometry parameters were significantly affected. This was concluded to be related to a thrombocytopenia reduction in factors of intrinsic pathway levels, which were caused by an uncontrolled consumption occurring in clinical sepsis. Furthermore, when CT parameters in EXTEM and INTEM measurements were considered, significant differences were found in INTEM measurements, which showed the intrinsic pathway, while the EXTEM measurements, showing the extrinsic pathway, did not reveal any significant difference. This result revealed that sepsis was clinically more disruptive of the intrinsic pathway. Although the definitive distinction of the intrinsic and extrinsic pathways of the coagulation system has not been achieved yet, our results suggest that sepsis-induced coagulation disorders do not initiate through the tissue factor-induced pathway. This result was explained by the reduction of a special factor (or factors) of the intrinsic pathway, which was analyzed together with conventional tests. In a study by Yaşar et al., increases in the CT parameter and reductions in the MCF parameter of INTEM and EXTEM tests were detected in patients with Behçet's disease and compared to a control group consisting of healthy volunteers [20]. Although their etiologies are different, Behçet's disease and sepsis cause similar clinical

Table 5. The comparison of 1st and 2nd day ROTEM parameters in the Group S*INTEM : intrinsic activation of thromboelastometry ; EXTEM : extrinsic activation of thromboelastometry ; CT : Clotting time ; CFT : Clot formation time ; MCF : Maximum clot firmness ; A10 : The value of clot width at the end of the first 10 minutes ; A20: The value of clot width at the end of the first 20 minutes). * denote data presented as mean (SD)

	Day	Groups	CT(secs)	CFT(secs)	MCF(mm)	α (°)	A10(secs)	A20(secs)
INTEM	1.Day	Group S	170.3(53.6)	107.4(57.8)	63.1(15.4)	70.3(14.7)	54.6(16.8)	60.6(16.0)
	2.Day	Group S	159.4(40.3)	102.2(54.3)	65.0(11.6)	73.1(10.7)	56.7(13.8)	62.7(12.7)
EXTEM	1.Day	Group S	123.2(69.9)	142.7(51.2)	65.1(13.3)	71.2(14.7)	56.2(16.3)	62.6(14.9)
	2.Day	Group S	116.2(54.2)	149.4(52.4)	65.0(12.8)	69.2(16.1)	54.8(16.3)	61.8(14.9)

outcomes since both have clinical courses involving features of vasculitis. In our study, we also obtained similar thromboelastometry results.

In conclusion, the rotational thromboelastometry method, with its rapid diagnosis and point-detection properties, seems to be one step ahead in the identification of impairments developing in the coagulation system when compared to other methods. We suggest that the probability of error might be higher in conventional methods, which evaluate coagulation profiles part by part, compared with thromboelastometric/thromboelastographic methods, which enable in vitro evaluations and evaluate the coagulation profile as a whole. Considering the results of previous studies together with our results, we suggest that the rotational thromboelastometry method is useful in evaluating the coagulation profile and predicting a sepsis prognosis.

Competing interests

The authors declare that they have no competing interests.

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