Journal of Critical Care (2013) **28**, 317.e1–317.e11

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Journal of Critical Care

Consecutive thrombelastography clot strength profiles in patients with severe sepsis and their association with 28-day mortality: A prospective study☆

Sisse R. Ostrowski MD, PhD, DMSc[a,*], Nis A. Windeløv MD[b], Michael Ibsen MD, PhD[c], Nicolai Haase MD[c], Anders Perner MD, PhD[c], Pär I. Johansson MD, DMSc, MPA[a,d]

[a]*Section for Transfusion Medicine, Capital Region Blood Bank, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark*
[b]*Department of Anesthesia, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark*
[c]*Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*
[d]*Department of Surgery, Center for Translational Injury Research (CeTIR), University of Texas Medical School at Houston, TX, USA*

Keywords:
Sepsis;
Coagulopathy;
Thrombelastography;
Rotation thromboelastometry (ROTEM);
Disseminated intravascular coagulation (DIC);
Mortality;
Platelet function

Abstract

Purpose: The aim of this study was to assess associations between consecutive thrombelastography (TEG) profiles and standard coagulation tests and disease severity and mortality in patients with severe sepsis.

Materials and Methods: This was a prospective observational study of adults with severe sepsis admitted to the intensive care unit (ICU). Clinical scores/variables, infection, TEG, biochemistry, therapy, and overall mortality were recorded.

Results: Fifty patients (60% men, median age 62 years, 28-day mortality 24%) were included. At admission, 22%, 48%, and 30% had a hypocoagulable, normocoagulable, and hypercoagulable TEG clot strength (maximum amplitude [MA]), respectively. Hypocoagulable patients had higher Sequential Organ Failure Assessment and disseminated intravascular coagulation scores compared with hypercoagulable patients and higher 28-day mortality compared with normocoagulable patients (all $P < .05$). Most patients (73%-91%) displayed a TEG MA comparable with the admission profile during the initial 4 ICU days or until death/discharge. Patients progressing to hypocoagulable MA had a high early mortality (80%) and hypocoagulable MA independently predicted 28-day mortality (adjusted odds ratio, 4.29 [95% confidence interval, 1.35-13.65], $P = .014$). In hypocoagulable and hypercoagulable patients, only fibrinogen ($P = .041$ and $P < .001$, respectively) contributed independently to clot strength, whereas both platelets ($P < .001$) and fibrinogen ($P < .001$) contributed independently to clot strength in normocoagulable patients.

Conclusions: The ICU admission TEG MA remained constant for several days in patients with severe sepsis and hypocoagulable MA independently predicted 28-day mortality.

☆ Conflict of interest: The authors declare no conflict of interest.

* Corresponding author. Tel.: +45 24430464; fax: +45 35390038.
E-mail address: sisse.ostrowski@gmail.com (S.R. Ostrowski).

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http://dx.doi.org/10.1016/j.jcrc.2012.09.003

1. Introduction

Sepsis is associated with concurrent activation of coagulation and fibrinolysis and ensuing down regulation of the fibrinolytic and anticoagulant systems [1], the latter mainly due to progressive endothelial disruption and damage [2]. The vascular dysfunction and consumptive coagulopathy may ultimately progress to disseminated intravascular coagulation (DIC), multiple organ failure, and death.

Traditional coagulation tests such as activated partial thromboplastin time (APTT), prothrombin time, and international normalized ratio (INR) only report of hypocoagulability, and although platelet count, plasma fibrinogen, and D-dimer may indicate existing hypercoagulability and hyperfibrinolysis, the result of these tests is quantitative and not functional. Because hypercoagulability and hyperfibrinolysis in septic patients may be missed by traditional coagulation tests, several studies have characterized sepsis coagulopathy by viscoelastic hemostatic whole blood tests such as thrombelastography (TEG) and rotation thromboelastometry (ROTEM) [3-10]. Furthermore, experimental studies of human [11] and animal [12-14] endotoxemia report of early hypercoagulability and hyperfibrinolysis [11,12] and progressive hypocoagulability [13,14] by TEG/ROTEM.

Sepsis is a dynamic disease that may progress from normal coagulation profile to hypercoagulability, hyperfibrinolysis, and ultimately hypocoagulability with increasing disease severity [4-6], in line with the notion that especially hypocoagulability [7-9], but also hypercoagulability [7], predict a fatal outcome in these patients. Only few studies have investigated consecutive changes by TEG/ROTEM in septic patients [4,5], and these studies have not systematically reported of changes in patients stratified according to the presenting TEG/ROTEM profile, that is, normocoagulable, hypercoagulable, hyperfibrinolytic, or hypocoagulable.

Therefore, the present study investigated TEG and traditional coagulation tests, disease severity, and DIC scores and outcome in patients with severe sepsis stratified according to presenting TEG profile on ICU admission and followed daily for 4 days in ICU or until death or discharge. The primary aim was to investigate consecutive changes in TEG profiles during ICU stay and the association with traditional coagulation tests, disease severity, and outcome.

2. Materials and methods

2.1. Patients

This was a prospective observational study of patients with severe sepsis or septic shock admitted to a general intensive care unit (ICU) at a tertiary level hospital (Copenhagen University Hospital, Rigshospitalet) from January 1, 2008 to June 31, 2009. The patients were included in the study at ICU admission, if they fulfilled the criteria [15] for sepsis, severe sepsis, or septic shock, and were studied for 4 consecutive days (days 1-4) during their ICU stay.

Exclusion criteria were age below 18 years or missing admission TEG and/or laboratory data required for DIC scoring. Because Rigshospitalet has specialized ICUs for cardiology, neurosurgery, and cardiothoracic surgery, no patients from these ICUs were included in the study.

For data acquisition, admission (initial 24 hours in ICU) data; Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) scores; and focus of infection were registered along with daily (admission, days 1-4) SOFA scores, clinical variables, biochemistry, and therapy including blood products (red blood cells, fresh frozen plasma [FFP], platelet concentrate [PLT]; no patients received cryoprecipitate pool) and fluids. Vital status at days 28 and 90, total days of ventilator support, vasopressor, and renal replacement therapy were registered. All patients received thrombosis prophylaxis with subcutaneous low-molecular-weight heparin, and no patients received activated protein C.

Septic shock was diagnosed as unresponsiveness to fluid resuscitation and requirement of continuous vasopressor therapy to maintain mean arterial blood pressure above 65 mm Hg.

The study was approved by the Regional Ethics Committee (H-C-2007-0087) and the Danish Data Protection Agency and conducted in accordance with the 1964 Declaration of Helsinki. Consent was waived because all procedures were clinically indicated and, at the time point of conduct of the study, TEG was part of the daily routine analyses in septic patients admitted to the study ICU.

2.2. Blood sampling

Blood samples (Vacutainer; BD, Franklin Lakes, NJ) were drawn from an arterial line after discard of the first 5 mL of blood. Routine biochemistry were analyzed in a DS/EN ISO 15189 standardized laboratory: D-dimer and C-reactive protein (Modular P-modul; Roche, Rotkreuz, Switzerland), fibrinogen (Clauss method), and enzymatic active antithrombin (ACL TOP; Beckman Coulter, Inc, Brea, CA), APTT and INR (Q Hemostasis, Medinor, Denmark), platelet and leukocyte count (XE-2100; Sysmex, Kobe, Japan), and lactate (Radiometer ABL 725/735, Copenhagen, Denmark).

2.3. DIC score

Overt DIC was defined [16] and modified [17] according to International Society of Thrombosis and Hemostasis criteria, with the following cutoff values: (1) platelet count less than 50×10^9/L (2 points), 50 to 100×10^9/L (1 point); (2) fibrinogen less than 1 g/L (1 point); (3) D-dimer greater than 4 mg/L (3 points), 0.39 to 4.00 mg/L (2 points); and (4) INR (prothrombin time is not available at our hospital) greater than 2.3 (2 points), 1.4 to 2.3 (1 point). Overt DIC was diagnosed as a sum of 5 points or more.