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Comparison of point-of-care hemostatic assays, routine coagulation tests, and outcome scores in critically ill patients

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ABSTRACT

Purpose: The purposes of the study are to compare point-of-care (POC) hemostatic devices in critically ill patients with routine laboratory tests and intensive care unit (ICU) outcome scoring assessments and to describe the time course of these variables in relation to mortality rate.
Materials and methods: Patients admitted to the ICU with a prognosis of more than 3 days of stay were included. The POC devices, Multiplate platelet aggregometry, rotational thromboelastometry, and ReoRox viscoelastic tests, were used. All variables were compared between survivors and nonsurvivors. Point-of-care results were compared to prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen concentration, and Sequential Organ Failure Assessment score and Simplified Acute Physiology Score 3.
Results: Blood was sampled on days 0 to 1, 2 to 3, and 4 to 10 from 114 patients with mixed diagnoses during 237 sampling events. Nonsurvivors showed POC and laboratory signs of hypocoagulation and decreased fibrinolysis over time compared to survivors. ReoRox detected differences between survivors and nonsurvivors better than ROTEM and Multiplate.
Conclusions: All POC and routine laboratory tests showed a hypocoagulative response in nonsurvivors compared to survivors. ReoRox was better than ROTEM and Multiplate at detecting differences between surviving and nonsurviving ICU patients. However, Simplified Acute Physiology Score 3 showed the best association to mortality outcome.

1. Introduction

Patients admitted to the intensive care unit (ICU) often experience hemostatic disorders. Many factors contribute to these disorders, including trauma with acute coagulopathy of trauma shock, sepsis with disseminated intravascular coagulopathy (DIC), bleeding, transfusion of blood components, crystalloid/colloid fluid therapy (dilutional coagulopathy), and decreased synthesis of coagulation factors and platelets (and platelet dysfunction). In sepsis and trauma, 1 contributing factor for hemostatic disorders is endothelial damage resulting in the activation of the coagulation system and fibrinolysis in parallel [1,2], followed by a later phase with fibrinolytic shutdown and an increase in fibrinogen as a part of the acute phase response. Both hypocoagulation and hypercoagulation and a decrease in platelet count (PLC) are associated with increased organ failure, longer stays in the ICU, and increased mortality [3,4].

Activated partial thromboplastin time (aPTT) and prothrombin time (PT) are coagulation tests routinely used to measure a patient's initial coagulation status but are not fully adequate to detect coagulopathy [5] or predict massive bleeding [6]. Hyperfibrinolysis and hypercoagulability cannot be identified by these routine tests; neither can decreased fibrinolysis, which is shown to be a predictor of organ failure and mortality [7]. These limitations have contributed to the introduction of different point-of-care (POC) methods in the intensive care and perioperative settings such as the viscoelastic hemostatic assays (VHAs), including rotational thromboelastometry (ROTEM) and thromboelastography (TEG). Sonoclot and the recently introduced free-oscillating rheometry (FOR; ReoRox) are VHA alternatives. Another POC method is multiple electrode aggregometry (MEA; Multiplate). Viscoelastic hemostatic assay measures coagulation and platelet function in terms of clotting time (CT) and clot structure (clot strength), whereas Multiplate assesses platelet function by evaluating platelet aggregation [8]. Viscoelastic hemostatic assay is currently regarded as the best option when monitoring coagulation in perioperative patients [9]. Both ROTEM and TEG can be used to monitor bleeding and guide transfusion therapy, which reduce bleeding [10] and transfusion requirements [11]. However, their association with mortality is still unclear [10,12].

There are different scoring systems commonly used to assess the prognosis and severity of the disease and to predict a patient's outcome in the ICU. The Simplified Acute Physiology Score 3 (SAPS3) provides an

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estimate on the degree of affecting diseases upon admission to ICU [13]. The expected mortality rate (EMR) is calculated from the SAPS3. The Sequential Organ Failure Assessment (SOFA) score was developed to better describe the progression of organ failure with a simple scoring system [14] and is calculated daily. The SOFA is used to estimate the degree of organ dysfunction. The aim of this prospective observational study was to monitor coagulation and platelet function with 3 POC hemostasis devices and to compare these tests with routine coagulation tests and ICU scoring systems in critically ill patients with mixed diagnoses. Furthermore, the time courses of these variables in relation to mortality were also assessed. Our hypothesis was that POC devices would show a better association with mortality than routine coagulation tests in critically ill patients.

2. Materials and methods

2.1. Study subjects and sampling

Patients who had been admitted to the ICU at Skåne University Hospital in Lund were included in the study. The study was approved by the Regional Ethical Review Board (Lund, Protocol DNR 2010/482 and DNR 2014/916). Only patients who had routine coagulation analyses (PT with international normalized ratio [PT-INR] and aPTT), PLC, and fibrinogen concentrations taken at the discretion of the treating physician were included. Informed and signed consent was obtained from all patients or their next of kin.

2.2. Blood sampling

Arterial blood was sampled from indwelling radial arterial catheters with a continuous flush system. The samples were collected in Vacutainer tubes with citrate (0.129 mol/L) as the anticoagulant (Becton Dickinson, Plymouth, UK) for TEG and FOR analysis and in a 3.0-mL Hirudin tube (Roche Diagnostics GmbH, Mannheim, Germany) for aggregometry with multiple electrode aggregometry. Samples were obtained 0 to 10 days after admission to the ICU. The median time to the first sampling occasion was 1 day. When all sampling occasions were included, the samplings occurred at median of 2 days after admission. Of the patients, 65% had their first sample taken at days 0 to 1; 22%, at days 2 to 3; and the remainder, at days 4 to 10. The only significant difference between diagnosis groups was between cardiac arrest patients and patients with trauma where all cardiac arrest patients had their first sampling occasion on days 0 to 1, whereas for trauma patients, most had their first sample taken at days 2 to 3.

In total, 17% of the patients had a follow-up sample taken at days 2 to 3, and 20%, at days 4 to 10. For the sepsis patients, 14% had a follow-up sample on days 2 to 3, and 41%, on days 4 to 10. None of the trauma patients had a follow-up sample on days 2 to 3, but 22%, on days 4 to 10. Of the medical patients, 27% had a follow-up sample analyzed on days 2 to 3, and 15%, on days 4 to 10. For surgery patients, 10% had follow-up sample on days 2 to 3, and 10%, on days 4 to 10. Of the cardiac arrest patients, 40% had a follow-up sample on days 2 to 3, and 10%, on days 4 to 10.

2.3. Routine coagulation analyses and cell counting

Routine coagulation analyses that included PT-INR and aPTT, PLC, and fibrinogen concentrations were determined according to the accredited methods at the Department of Clinical Chemistry at the University Hospital in Lund. The results from these tests were retrieved from the clinical information system used in the ICU.

2.4. Multiple electrode aggregometry

Platelet aggregometry was assessed by impedance technology using Multiplate (Roche Diagnostics), which measures platelet adhesion to the electrodes in the test cuvette after stimulation of the platelets with a platelet agonist. This method produces a change in the electric resistance between the electrodes that can be detected.

Next, 300 μL of prewarmed 9 mg/mL NaCl (B.Braun, Melsungen, Germany) was added to the test cuvette, followed by 300 μL of hirudin anticoagulated blood. The blood and buffer were incubated under constant stirring for 3 minutes. This was followed by the addition of 20 μL of a platelet agonist (ADPtest, COLtest, or TRAPtest; Roche Diagnostics). Aggregation followed for 6 minutes at 37°C under constant stirring. The final concentrations of the agonists were 32 μmol/L for TRAPtest, 6.5 μmol/L for ADPtest, and 3.2 μg/mL for COLtest. The area under the curve (AUC) was determined and used as a measure of aggregation. All samples were analyzed within 0.5 to 3 hours from blood collection as recommended by the manufacturer in the ICU laboratory. The median time to analysis was 40 minutes, and it was similar for the different diagnosis groups.

2.5. Viscoelastic coagulation analysis

Clot formation and clot elasticity were studied using TEG (ROTEM; Pentapharm, Munich, Germany) and FOR (ReoRox G2; Medirox, Nyköping, Sweden).

ROTEM has a fixed sample cup with a pin suspended in the blood sample. The pin oscillates, and the movement is registered in the coagulating sample [15]. The analysis of coagulation with ROTEM gives rise to a curve from which several variables can be obtained, including the CT, maximum clot firmness (MCF; the maximum strength/stiffness of the clot), and maximum clot lysis (ML) (Fig. 1) [15]. All samples were analyzed within 2 hours of blood collection (median, 10 minutes) at 37°C in the ICU laboratory. After the addition of 20 μL of 0.2 mol/L $CaCl_2$ (StartTEM) to 300 μL of blood, coagulation was initiated by thromboplastin alone (ExTEM) in the presence of cytochalasin D (FibTEM). Cytochalasin D inhibits platelet function; therefore, FibTEM provides information of the functional fibrinogen concentration and fibrin stability of the clot. Clot time and MCF variables were determined from the ExTEM tracings, and MCF, from FibTEM tracings. Maximum clot lysis was determined in 173 ExTEM samples.

Free-oscillating rheometry was assessed with the ReoRox G_2. The sample is added to a reaction chamber, which consists of a gold-coated sample cup with a gold-coated cylinder (bob) suspended in the blood sample [16]. The sample cup oscillates, and the change in the frequency and damping of the oscillation in the coagulating sample is registered. The change damping is displayed as a viscosity, whereas the frequency is an elasticity curve (Fig. 1). Several variables can be obtained, including the coagulation time (COT), which represents the time when the clot is fully formed and the elasticity starts to develop and is comparable to CT in ROTEM analysis. Other variables include the maximum elasticity (G'max: the maximum strength/stiffness of the clot) and clot strength reduction (Clot SR: representing the fibrinolytic process). All samples were analyzed within 0.5 hours of blood collection (median, 10 minutes) at 37°C in the ICU laboratory. After the addition of 25 μL of 0.5 mol/L $CaCl_2$ (MediRox AB) to 1000 μL of blood, coagulation was initiated with thromboplastin alone (FibScreen1 and MediRox AB) and in the presence of abciximab (FibScreen2 [Fib2]). Abciximab inhibits platelet function, and Fib2 provides information regarding the functional fibrinogen concentration and fibrin stability of the clot. Coagulation time and G'max were determined from the FibScreen1 (Fib1) tracings, whereas G'max was obtained from Fib2. The Clot SR was determined from the Fib1 assay of 166 samples. Twelve samples reached the detection limit for FOR elasticity (4500 Pa) and were, therefore, not assessed for Clot SR; the G'max for these samples was set to 4500 Pa.

2.6. Intensive care unit scores

Patient mortality statistics 30 days after admission to the ICU and SOFA score and SAPS3 were retrieved from the regular patient administrative system (PASIVA).