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In-depth analysis of clotting dynamics in burn patients

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ABSTRACT

Background: Studies associating coagulopathic changes with burn injury have relied on limited tests such as partial thromboplastin time (PTT) and international normalized ratio (INR). Understanding the clotting dynamics and associated risk factors after burn injury could influence management. This work aimed to identify real-time changes in coagulation after burn injury not indicated by PTT or INR alone.

Materials and methods: Nine burn-injured patients at a regional burn center were enrolled for blood collection at admission and set intervals over 96 h. Patient demographics, management, and laboratory data (PTT and INR) were collected. Plasma assays determined factors II, V, VII, VIII, IX, X, XI, antithrombin, and protein C functional activity as well as PAP, D-Dimer, fibrin monomer, TFPI, IL-1b, IL-6, IL-10, IL-12p.70, and TNF-α concentrations.

Results: Overall, five patients died. These patients had higher mortality scores and were more acidotic. All patients had normal coagulation studies (INR < 1.5, PTT < 45 s) within 24 h of admission, and only two were abnormal after. Increased factor VIII and IX activity were identified in seven patients at admission. Decreased antithrombin and protein C activity were seen in all patients. Patients had increased PAP, D-Dimer, and fibrin monomer concentrations throughout their hospital course. At admission, increased fold changes were seen in IL-6 (2.5–117) and IL-10 (2.4–32), whereas IL-1b and TNF-α levels were depressed in all patients.

Conclusions: Extensive changes not identified by PTT or INR were seen after burn injury that may explain perturbed coagulation in these patients. This approach further characterizes the impact thermal injury has on coagulation.

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Introduction

Major homeostatic changes in coagulation have been described in the trauma literature after a multifactorial process initiated by hemorrhagic shock, endothelial injury, factor consumption, hypothermia, acidosis, and more [1]. These processes impair the interactions of procoagulants, anticoagulants, and fibrinolytic components that are crucial for proper hemostasis [2]. The acute traumatic coagulopathy (ATC) that can occur after injury results in increased transfusion requirements, injury severity scores, organ dysfunction, and overall mortality [2–4]. Data from the Center for Disease Control noted that of 180,000 deaths in 2010, most fatal sequelae of traumatic injury were attributed to hemorrhagic shock and multiple organ failure [5]. Treatment strategies to manage ATC and improve outcomes have since developed. US military studies, for example, have shown improved outcomes with administration of fresh whole blood or plasma compared to the usage of red cell concentrates [6].

A growing body of literature has similarly identified coagulopathic changes in patients after burn injury. Although sometimes considered a subset of the trauma population, burn injury is inherently different. In trauma patients, severe tissue injury and systemic hypoperfusion due to hemorrhage are major contributors to ATC. Burn-injured patients in comparison do not experience the significant hemorrhagic injuries or massive blood transfusions that often characterize the trauma population [7]. Clinical metrics such as burn size, temperature, number of procedures, inhalation injury, and mechanical ventilation are all thought to factor proportionally into coagulation behavior [7–12]. Molecular changes, such as inflammatory system activation, and clinical management with burn wound excision can extend or worsen the negative impact on the coagulation system [13]. Septic complications can even further drive thrombosis, leading to cellular hypoperfusion, multisystem organ failure, or even death [13].

Current routine measures of coagulation include laboratory assessments such as prothrombin time, partial thromboplastin time (PTT), and the international normalized ratio (INR) [1]. The ubiquity and availability of these tests allow clinicians to assess the integrity of the intrinsic and extrinsic coagulation pathways in these patients. However, it takes some time for these tests to be performed and they only provide a limited snapshot of a patient's overall coagulation profile [14]. For example, these tests are insensitive to alterations in both the status of the protein C system and the fibrinolytic system. Systemic anticoagulation via protein C activation has been proposed as a mechanism of ATC as a hyperfibrinolytic state [2]. Further changes in coagulation can manifest later due to factor consumption, dilution, or delayed fibrinolysis and may be missed by standard laboratory testing. Continued clinical intervention in burned patients, such as central venous access, mechanical ventilator management, or fluid administration can similarly cause delayed coagulation changes [15,16]. This can significantly delay identification and treatment of coagulopathy in a thermally injured patient.

Coagulopathy has been identified as a risk factor for increased morbidity and mortality [17]. Understanding the pathophysiology and timing behind coagulopathy in burn-injured patients has major implications and could lead to better transfusion and blood loss management at admission, later in the hospital course, and after burn wound excision. Previous studies examining coagulation changes in thermally injured patients are typically retrospective in nature and rely on routine measures of coagulation. Measurements are usually infrequent and do not account for the rapid and dynamic nature of coagulation itself after injury. If coagulation abnormalities after thermal injury could be better characterized, the potential for new or improved therapeutic intervention could arise.

The aim of this study was to develop a real-time assessment model to examine and characterize acute changes and associated risk factors in the coagulation profile of thermally injured patients and compare those changes to established routine measures of coagulation.

Methods

Setting

The Burn Center at MedStar Washington Hospital Center is a regional urban burn center providing total burn care to the Washington metropolitan area, serving Washington, D.C., southern Maryland, northern Virginia, and eastern West Virginia. MedStar Washington Hospital Center is a 926-bed level I trauma center. The Burn Center is equipped with an 18-bed burn rehabilitation and intermediate care unit and a dedicated burn intensive care unit and operating suite.

Patients

After institutional review board approval, nine thermally injured patients with a total body surface area (TBSA) burn size of $\geq$25% were identified on presentation to the trauma bay between 2013 and 2014 and enrolled for study after informed consent. Patients who presented with chemical burn injuries, were aged under 18 y, actively taking anticoagulants, not fluent in either English or Spanish, presented more than 4 h after injury, or were otherwise thought not fit for inclusion based on preexisting conditions were not included for study.

Study design

After consent, standardized time points for blood collection were scheduled at admission and at hours 2, 4, 8, 12, 24, and every 12 h after until 96 h (4 d) after admission. Samples were collected in SCAT-144 tubes (500 μM of AEBSF, 20 μM of elastinal, 10 μM of GGACK, 4.5 mM of EDTA, 5 μM of E64, 1 μM of Repastin A, 300 KIU/mL of aprotinin; Haematologic Technologies, Inc, Essex Junction, VT) and citrated tubes for further analysis. Plasma obtained from these samples was then used to determine clotting factor activity, natural anticoagulant activity, and fibrinolytic and cytokine concentrations for all time points. Routine measures of coagulation, including PTT and the INR, were obtained at the discretion of the managing clinical team. Patients were grouped by burn size and mortality to identify trends and differences. Burn size was