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Trauma induced hypercoagulablity in pediatric patients☆,☆☆,★,★★

Mark L. Ryan [a], Robert M. Van Haren [a], Chad M. Thorson [a], David M. Andrews [b], Eduardo A. Perez [c], Holly L. Neville [c], Juan E. Sola [c], Kenneth G. Proctor [a,*]

[a] Dewitt-Daughtry Department of Surgery, Divisions of Trauma and Surgical Critical Care, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[b] Department of Pathology, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[c] Dewitt-Daughtry Department of Surgery, Division of Pediatric Surgery, University of Miami Miller School of Medicine, Miami, FL 33136, USA

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ABSTRACT

Purpose: Coagulation changes in pediatric trauma patients are not well defined. To fill this gap, we tested the hypothesis that trauma evokes a hypercoagulable response.
Methods: A prospective observational study was conducted in hospitalized patients (age 8 months to 14 years) admitted for trauma or elective surgery. Informed consent was obtained from the parents and informed assent was obtained in patients 7 years of age or older. Coagulation changes were evaluated on fresh whole blood using thromboelastography (TEG) and on stored plasma using assays for special clotting factors.
Results: Forty three patients (22 trauma, median injury severity score = 9; and 21 uninjured controls) were evaluated. For trauma vs control, prothrombin time (PT) was higher by about 10% ($p < 0.001$), but activated partial thromboplastin time was not altered. TEG clotting time (R;$p = 0.005$) and fibrin cross-linking were markedly accelerated (K time, alpha angle; $p < 0.001$) relative to the control patients. D-Dimer, Prothrombin Fragment 1 + 2, and Plasminogen Activator Inhibitor-1 were all elevated, whereas Protein S activity was reduced (all $p < 0.01$). Importantly, a large fraction of TEG values and clotting factor assays in the pediatric control group were outside the published reference ranges for adults.
Conclusion: A hypercoagulable state is associated with minor trauma in children. More work is needed to determine the functional significance of these changes and to establish normal pediatric reference ranges.

Hemorrhage is a primary cause of potentially preventable trauma death in both adults and children [1,2]. Hypercoagulability is a homeostatic compensatory response to traumatic hemorrhage, and most patients manifest this condition on arrival to the emergency department. However, the opposite response is common, and is associated with hypothermia and acidosis in those who are the most severely injured [3–5]. Goal directed blood product therapy is probably most beneficial in these patients [6].

Traditionally, the coagulation status of a trauma patient is assessed using prothrombin time (PT), international normalized ratio (INR), and/or partial thromboplastin time (PTT). However, these standard tests do not routinely assess platelet function, fibrinolysis, or a hypercoagulable state, and these results do not necessarily correlate with who is actually bleeding [6,7]. Furthermore, findings in adult trauma patients cannot always be extrapolated to the pediatric population because there are age-related quantitative differences in the plasma concentrations of clotting factors [8,9]. In fact, pediatric reference ranges for many coagulation factors are not well defined [10–12].

Thromboelastography (TEG) is a rapid, point-of-care test that can assess the entire coagulation cascade. In pediatric patients, TEG has been used in cardiac surgery [13,14], massive transfusion [15], and in those with clotting factor deficiencies [16], but to our knowledge, there has been only one other study in pediatric trauma patients.

Vogel et al. retrospectively reviewed 86 severely injured patients (age < 14 years) and compared admission rapid thromboelastography (rTEG) to conventional coagulation tests and to early life-saving

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* Corresponding author at: Divisions of Trauma and Surgical Critical Care, Daughtry Family Department of Surgery, University of Miami School of Medicine Ryder Trauma Center, 1800 NW 10th Ave. Miami, FL 33136. Tel.: +1 305 585 1178; fax: +1 305 326 7065.
E-mail address: kproctor@miami.edu (K.G. Proctor).

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interventions [17]. They observed that rTEG activated clotting time (ACT), k-time, and α-angle were strongly correlated to PTT, and that maximum amplitude (MA) was correlated to platelet count. When controlling for age, gender, and injury severity score (ISS), ACT, r-value, k-time, α-angle, and MA all predicted transfusion requirements [17]. There have been no other prospective studies on the subject. Therefore, we prospectively evaluated the hypothesis that pediatric trauma patients exhibit a hypercoagulable response similar to that in adults.

1. Materials and methods

This study protocol was approved by the Institutional Review Board (IRB) of the University of Miami and the Clinical Trials Office of Jackson Memorial Hospital (UM Protocol #20090816). Informed consent was obtained from the parents and informed assent was obtained in patients 7 years of age or older. This prospective, observational study included patients <15 years who were admitted to the Ryder Trauma Center at Jackson Memorial Hospital via ambulance or air rescue services between December 2009 and March 2011. Exclusion criteria were patients with burns, who were incarcerated, pregnant, suffering from a psychiatric condition, or had a history of coagulopathy or bleeding disorder.

Blood samples were obtained from the intravenous cannula placed at the time of admission using a "two-syringe technique" [18]. Three mL was drawn into the first syringe in order to prevent contamination with tissue thromboplastin. Three mL of blood was then drawn into a second syringe and transferred to 2 vacuum-sealed tubes containing 3.2% (0.105 M) sodium citrate. Samples stored in sodium citrate may be run within 4 h of blood draw, according to the manufacturer.

Previous studies in adult trauma patients have utilized either nothing, kaolin or tissue factor activating reagents in the vacuum sealed tubes. The use of activating reagents shortens the total analysis time. In this study, many of the pediatric trauma patients arrived at nights or on weekends. We chose sodium citrate to allow us enough time to come from home and run the sample of a new trauma patient. We chose to run the sample at exactly 60 min from the time of blood draw using a TEG 5000 Thromboelastograph Hemostasis System (Haemoscope Corporation, Niles, IL). Citrated whole blood (340 μL) was recalcified using 20 μL of 0.2 M calcium chloride prior to initiation of the test. The sample was run for 90 min to allow ample time to evaluate fibrinolysis. Data were interpreted using TEG™ Analytical Software Ver. 4.2.3. The remaining tube was centrifuged for 10 min at 3000 rotations per minute, at which point the plasma was extracted and stored at −70 °C for clotting factor analysis.

Sample size was estimated based on the probability of finding a 30% difference between trauma and control patients using a power and sample size calculator. A sample size of 20 with a 30% difference in R value (2 vs 2.6) yielded a significant difference with a power of 0.8. Once all samples had been collected from trauma patients, data were collected from age and sex matched patients who were uninjured, to account for the lack of reference range in the pediatric population. These patients were being seen in the pediatric surgery clinic prior to undergoing an elective operation or had presented to the emergency room with no evidence of systemic infection or trauma.

TEG parameters included: reaction time (R), k-time (K), alpha angle (α), maximum amplitude (MA), G-value (G), and coagulation index (CI) (Fig. 1). R is the time between initiation of test and initial fibrin formation, and represents the enzymatic portion of coagulation. K is the time needed to reach 20-mm clot strength, and represents clot kinetics. α is the measure of the TEG tracing's slope, and represents fibrin cross-linking. MA is the measure of overall clot strength, and represents platelet aggregation. Coagulation Index (CI) is derived using the R, K, α, and MA of native whole blood using the equation: $CI = -0.2454R + 0.0184\,K + 0.1655MA - 0.0241\alpha - 5.0220$. The adult reference range for CI is −3.0 to 3.0. Values greater than 5.0 are associated with hypercoagulable conditions such as cancer and deep vein thrombosis [19].

The shear elastic modulus strength (G) reflects clot strength, is measured in dyn/cm^2, and is calculated using the formula G =

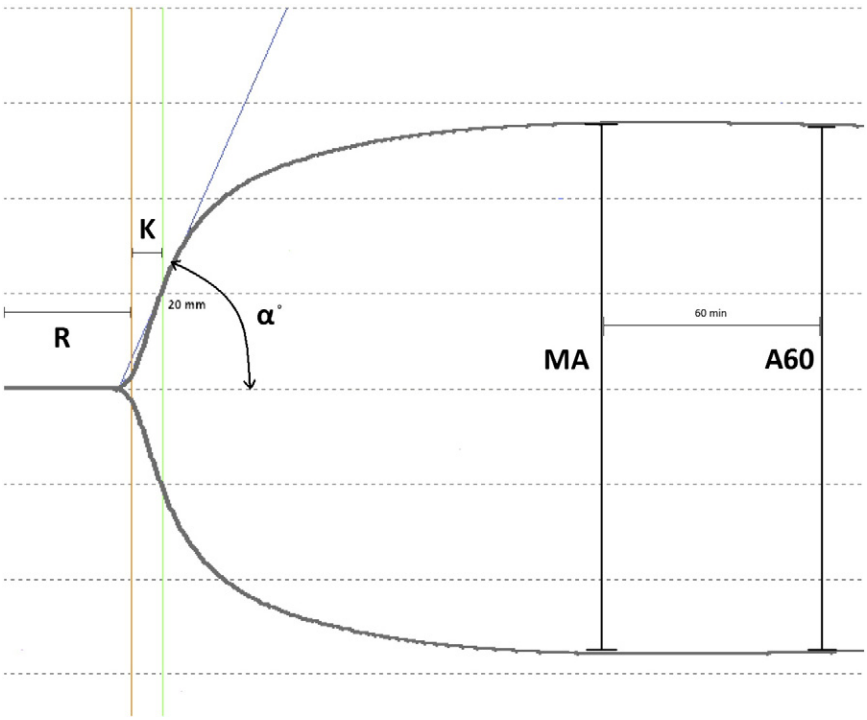

Fig. 1. A TEG tracing illustrating the measured clotting parameters. R, reaction time; K, time to firmness of 20 mm; α°, alpha angle; MA, maximum amplitude; A60, amplitude 60 min after measurement of MA.