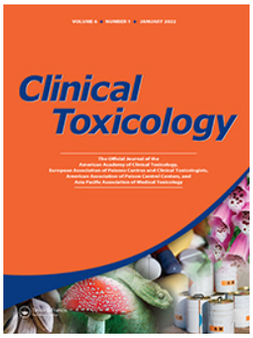

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SHORT COMMUNICATION

Thromboelastography in the setting of acetaminophen-induced hepatotoxicity

Sanjay Mohan[a], Christian Koziatek[b], Jordan Swartz[b], Mary Ann Howland[a,c] and Mark K. Su[a]

[a]Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, NYU Grossman School of Medicine, New York, NY, USA; [b]Ronald O. Perelman Department of Emergency Medicine, NYU Grossman School of Medicine, New York, NY, USA; [c]College of Pharmacy and Health Sciences, St. John's University, Queens, NY, USA

ABSTRACT

Background: Severe acetaminophen (APAP) poisoning can result in fulminant hepatic failure and abnormal tests of coagulation. Although the international normalized ratio (INR) may be elevated, the actual hemostatic status of patients with APAP-induced hepatotoxicity is unknown. Few studies exist investigating the clinical use of thromboelastography (TEG) to evaluate the hemostatic status in the setting of APAP-induced hepatotoxicity.

Methods: We performed a retrospective review of patients who were admitted for APAP toxicity and received TEG testing at a single transplant center.

Results: Nine patients had detectable APAP concentrations and exhibited elevated aspartate and alanine aminotransferase activities. Seven had thrombocytopenia. TEG revealed a decreased median alpha angle and maximum amplitude but other values were within the normal reference range.

Discussion: Based on our study of APAP-induced hepatotoxicity, TEG showed a decreased rate of fibrin formation and cross-linking, as well as reduced clot strength. These findings suggest that patients with APAP-induced hepatotoxicity and thrombocytopenia have a theoretically increased bleeding risk as demonstrated by both elevated INR and abnormal TEG values. However, these TEG findings are more likely related to thrombocytopenia rather than directly to APAP-induced hepatotoxicity. Further studies should be performed to elucidate the potential role of TEG in various stages of APAP-induced hepatotoxicity.

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KEYWORDS
Liver; paracetamol; GI

Background

Severe acetaminophen (APAP) poisoning can result in fulminant hepatic failure and cause an elevated prothrombin time (PT) or International Normalized Ratio (INR) [1]. An INR greater than 6.5 or (PT > 100 s) is a component of the King's College criteria and a poor prognostic marker in APAP toxicity [2]. Although the INR may be elevated, the actual coagulation status of patients with APAP-induced hepatotoxicity is unknown.

Thromboelastography (TEG) is a laboratory technique that measures anticoagulation via a different method than PT/INR [3]. It has become increasingly popular to use TEG to evaluate and treat patients with potential coagulopathy [4,5]. The role of TEG in the setting of APAP-induced hepatotoxicity is not well-established. In a single swine model of APAP-induced liver failure, TEG results vary depending on the stage of APAP toxicity [6]. Few studies exist investigating the clinical use of TEG in the setting of APAP-induced hepatotoxicity. Here we provide preliminary data regarding TEG use in this setting.

Methods

We performed an IRB-approved retrospective review of medical records of clinical data at a single academic transplant center between January 1, 2016 and March 1, 2021. We searched the electronic medical record for patients who were admitted for APAP toxicity and received TEG testing. Inclusion criteria were: adult patients 18 years and older who ingested supratherapeutic amounts of APAP and manifested hepatotoxicity (i.e., increase in aspartate and alanine aminotransferase activities >1000 IU/L). Other than peak APAP concentrations, all laboratory data were obtained simultaneously at the time of TEG testing.

Thromboelastography was performed using the TEG® 5000 Hemostasis Analyzer System (Haemonetics®, Boston, MA). TEG consists of five components (See Figure 1). The TEG components that best correlate with INR are R-time (reaction time) and K-time (kinetic time) since these are dependent upon clotting factors. Abnormal TEG values were defined as an R or K time above the upper limit of normal, or an alpha angle or maximum amplitude below the lower laboratory limit which are similar to other series [8]. Descriptive statistics were used to characterize the data.

Results

Nine patients met inclusion criteria during the study period. Four had acute ingestions and five had repeated supratherapeutic ingestions. All nine patients had elevated AST activities, with five having activities >7400 IU/L. Median ALT activity was 7040 IU/L

CONTACT Sanjay Mohan sanjay.mohan@nyumc.org Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, NYU Grossman School of Medicine, 455 First Avenue, Room 124, New York, NY 10016, USA

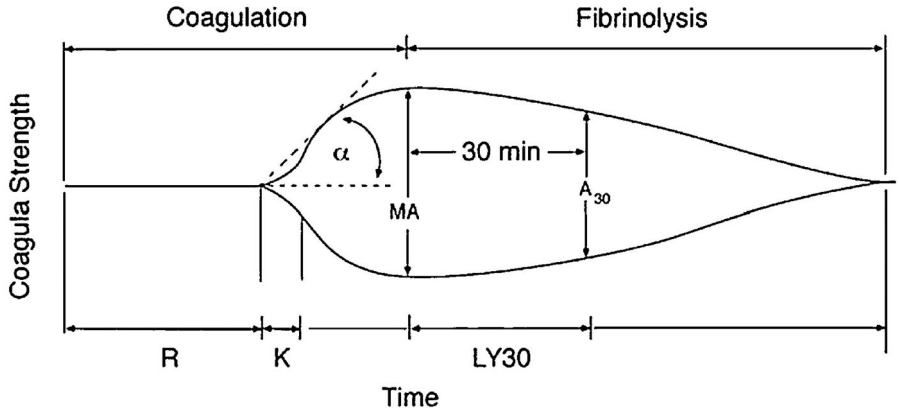

Figure 1. Thromboelastography. R-time: latency of clot formation; K-time: time until clot reaches a fixed strength; Alpha Angle: speed of fibrin accumulation; Max Amplitude (Ma): maximal clot strength; Lysis at 30 min (Ly30): clot dissolution 30 min after reaching maximum amplitude. Reproduced from Saeveraas et al. with permission [7].

Table 1. Demographic, laboratory data, and thromboelastography.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Reference normals
Age (years)	33	67	43	44	18	26	35	29	46	
Sex	Male	Male	Female	Male	Female	Female	Female	Female	Female	
BMI	31	29	28	25	21	21	27	18	33	
Race	White	White	Hispanic	Hispanic	White	White	White	Hispanic	Asian	
Type of ingestion	Acute	RSTI	RSTI	RSTI	Acute	RSTI	Acute	RSTI	Acute	
APAP (ug/mL)	337	5	8	200	116	30	64	128	73	<30
AST (IU/L)	2855	>7400	>7400	>7400	>7400	>7400	3154	5854	6035	5–34
ALT (IU/L)	1866	8457	4603	5212	9677	7040	4725	7451	7443	0–37
Creatinine (mg/dL)	0.6	4.5	0.75	3	2.3	0.65	4.5	1.1	3.3	0.6–1.1
pH	7.35	7.28	7.36	7.36	7.2	7.39	7.32	7.45	7.29	7.30–7.40
Lactate (mmol/L)	2.5	11	3.7	3.5	11.6	2.3	2.2	1.1	4.6	0–1.9
Phosphate (mg/dL)	1.4	7	2	5.2	2.7	1.3	3.9	2.2	3.9	2.3–4.7
INR	5.2	3.1	7.5	4.6	5.4	8.3	2.6	2	3.9	0.9–1.2
PT (s)	58.9	35	84.8	55.8	59.5	92.1	29.9	23.3	46.5	9.3–12.7
PTT (s)	41.6	57	38.2	35.3	58.2	36.8	30.9	26.4	31.2	27–39
Platelets ($\times 10^3/\mu L$)	7	25	67	122	149	48	191	180	110	150–400
Reaction time (min)	7.7	20.5	9.7	7.2	5.3	9.8	3.9	2.3	4.8	5–10
K-time (min)	N/A	N/A	3.1	3.4	4.3	4.7	1.1	1.5	1.6	1–3.1
Alpha angle (degrees)	28.6	7.6	51.5	50.2	47.5	44.2	73.7	70.6	69.7	53–72
Ma (mm)	18.3	11.5	48.6	48.8	43.3	34.7	67.7	57.4	57.9	50–70
Ly30 (%)	0	0	0	0	0	0	0.1	1.2	0	0–12

RSTI: Repeated Supratherapeutic Ingestion; BMI: Body Mass Index; APAP: Acetaminophen; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; INR: International Normalized Ratio; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; Ma: Maximum Amplitude; K-time: Kinetic Time; Ly30: Lysis at 30 min.
Note: AST, ALT, PT, PTT, INR, and Lactate are peak values. Platelet counts are nadirs.

(Range: 1866–9677); median INR, PT, and PTT were 4.6 (Range: 2–8.3), 55.8 s (Range: 23.3–92.1), and 36.8 s (Range: 26.4–58.2), respectively. The median platelet count was 110×10^3/uL of blood (Range: 7–191 $\times 10^3/\mu L$). Seven patients had thrombocytopenia (platelet count $< 150 \times 10^3/\mu L$). The rest of the laboratory data are summarized in Table1.

Thromboelastography results are summarized in Table 1. Median R-times and K-times were 7.2 min (Range: 2.3–20.5 min) and 3.1 min (Range: 1.1–4.7 min) respectively, both of which were within the normal laboratory reference ranges. The median alpha angle was 50.2 (Range: 7.6–73.7°) and maximum amplitude was 48.6 mm (Range: 11.5–67.7 mm), both of which were below the normal laboratory reference ranges. Lysis at 30 min (Ly30) was within the normal reference range for all patients.

Regarding patient outcomes, one received a liver transplant (Patient 1), two died (Patients 2 and 7), and six were discharged after resolution of hepatic dysfunction.

Discussion

The purpose of this study was to examine TEG in the setting of APAP-induced hepatotoxicity. All nine patients in this study had either acute or repeated supratherapeutic ingestion of APAP, had detectable APAP concentrations, and had hepatotoxicity. Furthermore, all patients demonstrated an elevated INR. While patients with acute severe APAP toxicity typically have an increased INR, our clinical experience suggests that bleeding rarely occurs. Furthermore, in patients with acute liver failure/injury, in general, TEG reveals normal clotting despite elevations in INR [9].

In this study, both the median R- and K-times were within the normal reference range – thus reflecting a normal latency of activation of the coagulation cascade and a normal rate of initial clot formation. In contrast, the median alpha angle and maximum amplitude were below the normal

reference range. The alpha angle describes the rate of fibrin formation and cross-linking and is dependent on platelet counts – which in this cohort were reduced. Maximum amplitude indicates maximal clot strength and is reflective of the culmination of all the constituents of the clotting cascade.

Based on the TEG results in this cohort, we found a decreased rate of fibrin formation and cross-linking, as well as reduced clot strength. These findings suggest that patients with APAP-induced hepatotoxicity have a theoretically increased bleeding risk as demonstrated by both elevated INR and abnormal TEG values. Additionally, bleeding risk may be exacerbated by dose-dependent APAP inhibition of platelet cyclooxygenase [10]. However, most of our patients had thrombocytopenia, a finding commonly seen in hepatotoxicity regardless of etiology, and this finding likely explains the abnormal TEG results seen in our study [11]. Thus, it appears that TEG does not provide any further information regarding potential bleeding diathesis in these patients with elevated INRs and may not be useful as part of routine management in APAP poisoning.

There are several limitations to this study. The retrospective nature and small sample size make it difficult to formulate definitive conclusions about the utility of thromboelastography in this setting. Moreover, our cohort of patients contained a combination of both acute and repeated supratherapeutic APAP ingestions rather than purely acute overdoses. We also do not know the indication for TEG testing or whether patients had TEG testing based on the results of any abnormal coagulation tests. Furthermore, given that n-acetylcysteine artificially increases the INR, this might account for some abnormal INR elevations seen in our cohort and distorts the correlation between INR and TEG [12]. Lastly, only one TEG was obtained for each patient and TEG testing was not protocolized. Future direction should include prospective studies that obtain serial TEGs to better understand its potential role in APAP-induced hepatotoxicity.

Disclosure statement

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ORCID

Jordan Swartz http://orcid.org/0000-0001-6482-9545
Mark K. Su http://orcid.org/0000-0001-5211-5334

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