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A 36-Year-Old Woman with Acute Liver Failure Following Acetaminophen Overdose, Raised INR of 8.7, and Normal Blood Viscosity Measured by Rotational Thromboelastometry (ROTEM)

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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None declared

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Patient: Female, 36-year-old
Final Diagnosis: Liver failure
Symptoms: Coagulopathy
Medication: —
Clinical Procedure: —
Specialty: Anesthesiology

Objective: Unusual clinical course


Background: Fulminant hepatic failure (FHF) is commonly associated with elevated prothrombin time (PT) and international normalized ratio (INR). There is a commensurate decline in pro- and anti-hemostatic factors, and hemostatic function is rebalanced, not reflected in INR. This report presents the case of a 36-year-old woman with FHF following acetaminophen overdose, an increased INR above 8.7, and normal blood viscosity measured by rotational thromboelastometry (ROTEM).

Case Report: A 36-year-old woman presented with FHF following an acetaminophen overdose. On arrival, she was lethargic but arousable and followed commands. Her King's College Criteria for acetaminophen toxicity was 2 and her MELD score was 36. Her INR was unmeasurably high (>8.7). To evaluate whole-blood coagulation, a ROTEM analysis was performed. All parameters (CT, CFT, alpha-angle, A10, MCF) of the NATEM were within reference range. Despite the normal ROTEM, spontaneous bleeding was a concern. The patient received 5 units of cryoprecipitate and 9 units of FFP prior to a central venous line placement. She was started on molecular adsorbent recirculating system and continuous veno-venous hemodialysis, but died on day 7.

Conclusions: Patients with FHF can have normal whole-blood coagulation based on ROTEM even if INR levels are unmeasurably high. Viscoelastic tests such as ROTEM, which assesses whole-blood coagulation properties, are preferable for coagulation monitoring in these patients. Blood product transfusion to correct coagulation abnormality, like FFP and cryoprecipitate, may be used based on the result of viscoelastic testing over conventional coagulation testing.


Keywords: Blood Coagulation • Liver Transplantation

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Background

Acetaminophen hepatotoxicity accounts for more than 50% of overdose-related acute liver failure cases and approximately 20% of liver transplant cases [1]. Metabolism primarily occurs through glucuronidation and sulfuration in the liver. In an overdose, these pathways are saturated, thereby forming the noxious NAPQI metabolite. NAPQI is a toxic substance that causes irreversible hepatic necrosis [2,3]. Current management of acetaminophen overdose involves administering intravenous or oral acetylcysteine. Previous systematic reviews have indicated that treatment with acetylcysteine can decrease morbidity and mortality [4].

Fulminant hepatic failure (FHF) can occur from acetaminophen hepatotoxicity and is commonly associated with elevated prothrombin time (PT) and international normalized ratio (INR). There is a commensurate decline in pro- and anti-hemostatic factors, and hemostatic function is rebalanced. This is not reflected in INR [5], which is derived from PT. It is calculated as a ratio of the patient's PT to a control PT standardized for the potency of the thromboplastin reagent. This was developed by the World Health Organization (WHO) using the following formula: $INR = \frac{\text{Patient PT}}{\text{Control PT}}$ [6]. The reference values for INR consider PT measurement in device-related variations, type of reagents used, and sensitivity differences in the tissue factor (TF) activator. At our institution, the reference value for INR is 0.82-1.13.

PT/INR can be prolonged in liver dysfunction, vitamin K deficiency, malnutrition, disseminated intravascular coagulation, factor deficiency, drug interactions, anemia, sepsis, advanced-stage cancer, end-stage renal disease, or laboratory errors. The viscoelastic test of whole-blood hemostasis was first developed by Hartert in 1948 [7]. TEG was introduced by Kang et al in 1985 in liver transplantation [8]. The ROTEM® (Instrumentation Laboratory, Bedford, MA, USA) system is a development of the classic TEG and has been used widely in liver transplantation, cardiovascular surgery and trauma, and other clinical settings for coagulation management [9-11]. The system records the kinetic changes during the interaction of platelets with the coagulation factors from initial platelet-fibrin interaction through platelet aggregation, clot strengthening, and fibrin cross-linking to eventual clot lysis [12].

At our institution, the conventional coagulation testing laboratory and the ROTEM® laboratory are in full compliance with the College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) regulations and certified by CLIA and the Department of Health.

To address the risk of bleeding in FHF patients with an elevated INR, fresh frozen plasma (FFP) is commonly transfused prior

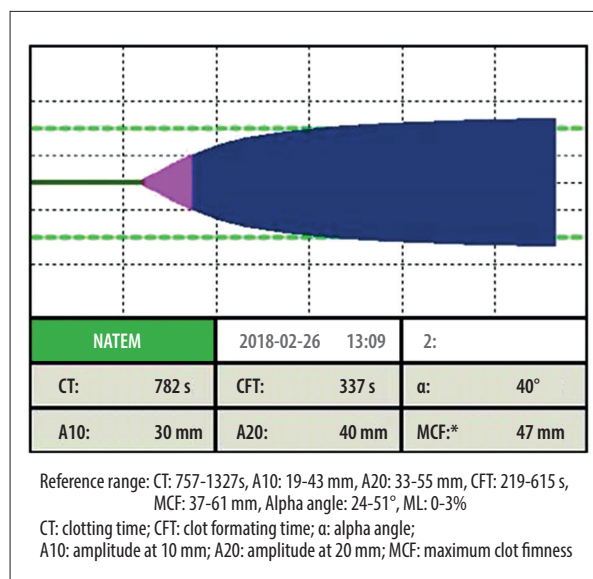


Figure 1. Patient's perioperative ROTEM analysis for liver transplantation evaluation.

to an invasive procedure. However, PT/INR is a poor indicator of hemostatic function in acute liver disease, and recent evidence has shown that ROTEM is a better tool for whole-blood coagulation monitoring [13,14]. This report presents the case of a 36-year-old woman with FHF following acetaminophen overdose, an increased INR of 8.7, and normal blood viscosity measured by ROTEM.

Case Report

A 36-year-old woman was admitted for FHF due to acetaminophen overdose. On arrival, she was lethargic but arousable and followed commands. Her vital signs were stable. There was no evidence of focal neurological deficits, and both cardiopulmonary examinations were unremarkable. The patient's medical history included depression, remote history of polysubstance abuse, and suicide attempts. Her home medications were cetirizine-pseudoephedrine, famotidine, fluticasone, and paroxetine. The patient had ingested up to 80 pills of acetaminophen in the past few days and had a serum acetaminophen (APAP) level of 110 mcg/mL (<25 mcg/mL) with AST: 1900 IU/L (7-35 IU/L), ALT 1900 IU/L (<30 IU/L). Her Model for End-Stage Liver Disease (MELD) score was 36 [Na⁺: 141 mmol/L (135-146 mmol/L), creatinine: 0.9 mg/dL (0.7-1.4 mg/dL), INR >8.71 (0.82-1.13), bilirubin: 3.6 mg/dL (0.1-0.9 mg/dL)]. Her King's College Criteria for Acetaminophen Toxicity was 2 [INR > 6.5, grade IV hepatic encephalopathy]. Her other labs were hemoglobin 11 g/dL (12.5-15 g/dL); hematocrit 33% (36-46%); platelets 156 000 (140-400 B/L); fibrinogen 116 mg/dL (204-462 mg/dL); PT >100 s (8.9-13.1 s); partial thromboplastin time (PTT) 30 s; factor V activity 7% (normal 50-150%); D-dimer: 10658 ng/ml

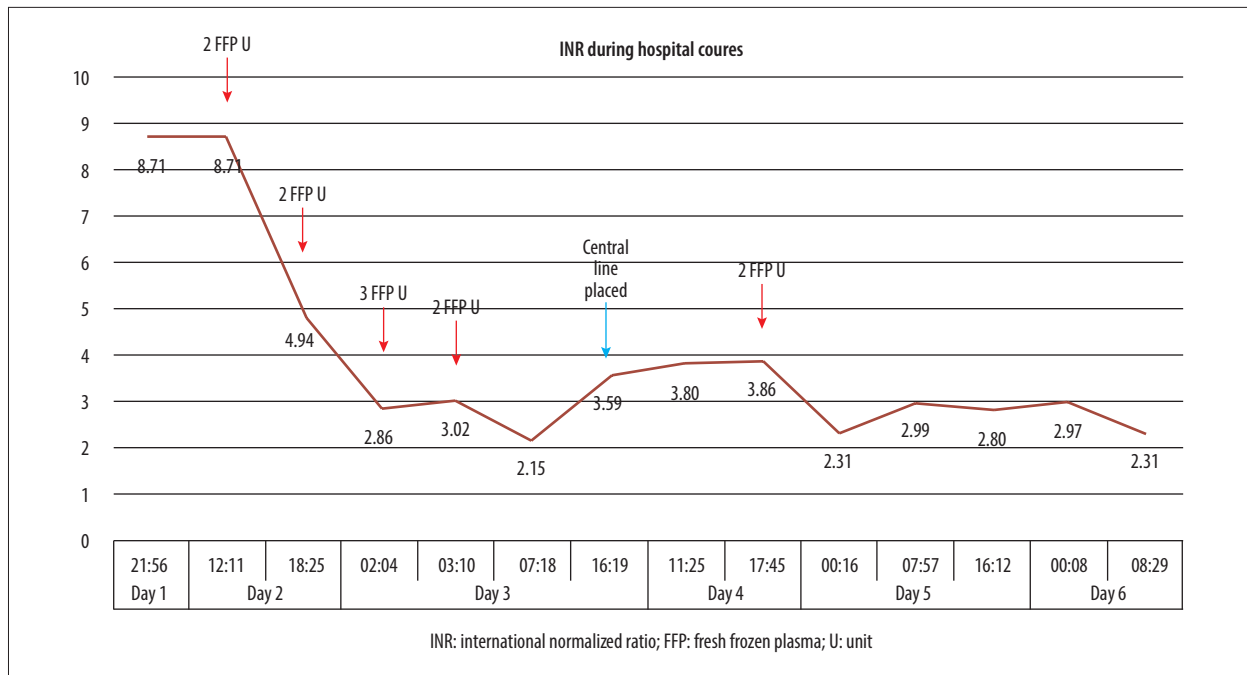


Figure 2. INR trend and blood product transfusion over hospital course.

Table 1. Conventional coagulation testing values and viscoelastic coagulation testing values during patient's hospital stay.

	Ref. range	Day 1 21: 56	Day 2 12: 11	Day 2 18: 25	Day 3 02: 04	Day 3 03: 10	Day 3 07: 18	Day 3 16: 19
PT	8.9-13.1 sec	>100.0	>100.0	56.1	32.1	34.0	24.0	40.5
INR	0.81-1.19	>8.71	>8.71	4.94	2.86	3.02	2.15	3.59
PTT	24-35 sec	30	35	32	28	29	26	35
D-Dimer	<204 ng/mL	10658	10515	7649	5772	5979	6207	21797
Fibrinogen	204-462 mg/dL	116	94	120	218	198	231	138
Notes			ROTEM 2FFP	2FFP 2CRYO	3FFP 3CRYO	2FFP		Central line placed
	Ref. range	Day 4 11: 25	Day 4 17: 45	Day 5 00: 16	Day 5 07: 57	Day 5 16: 12	Day 6 00: 08	Day 6 08: 29
PT	8.9-13.1 sec	43.0	43.7	25.9	33.6	31.5	33.4	25.8
INR	0.81-1.19	3.80	3.86	2.31	2.99	2.80	2.97	2.31
PTT	24-35 sec	34	35	33	35	35	42	37
D-Dimer	<204 ng/mL	18442	16097	>69000	66681	49010	>69000	65573
Fibrinogen	204-462 mg/dL	108	96	118	69	134	40	118
Notes			2FFP 3CRYO		2 CRYO		2 CRYO	

PT – prothrombin time; PTT – partial thromboplastin time; INR – international normalized ratio; ROTEM – rotational thromboelastometry; CRYO – cryoprecipitate.

(<204 ng/ml). To rule out laboratory errors, INR was repeated within 4 h of the initial result, showing INR >8.7 and PT >100 s. Her clinical history, physical exam, and other lab results did not reveal any other cause for the high INR.

Upon admission, a liver transplantation anesthesiologist was consulted to evaluate the patient for possible liver transplantation. A viscoelastic test was performed with ROTEM®-Delta due to the elevated PT/INR and concern for spontaneous bleeding. The NATEM test was used. Clotting Time (CT), Clot Formation Time (CFT), alpha-angle, Clot Amplitude at 10 min (A10) and 20 min (A20), and Maximum Clot Firmness (MCF) were all within reference range (Figure 1).

The patient became hypoglycemic and tachypneic with shallow breathing and had developed significant encephalopathy. She became lethargic, minimally responsive, and was intubated within 24 h of admission. On admission day 2, despite the normal ROTEM analysis, the hepatologist was concerned about the patient's severe coagulopathy, and 9 units of FFP and 5 units of cryoprecipitate were given before a central line placement for molecular adsorbent recirculating system (MARS). No bleeding-related complications or post-procedure hematoma occurred after femoral vein central line insertion. No transfusion reaction was noted. MARS continued for 5 days. During this time, the patient developed acute kidney injury and showed signs of fluid overload and pulmonary edema on a chest X-ray, which was treated with continuous veno-venous hemodialysis (CVVHD). Unfortunately, the patient was not deemed a suitable candidate for liver transplantation due to her history of multiple drug overdosing attempts without obtaining treatment and minimal social support available after transplantation. Despite full medical care, her clinical status deteriorated with worsening neurological exam, abdominal distension, rapid rise in lactate, progressive sinus tachycardia, and acidemia consistent with sepsis. She was started on empiric antibiotics and norepinephrine infusion, without improvement. Her poor prognosis was communicated to the family, and the patient died on hospital admission day 7. During the hospital stay, despite the elevated PT/INR, no signs of clinical bleeding were observed. The INR trend is shown in Figure 2 and Table 1.

Discussion

The primary finding in this case is that, despite an unmeasurably high INR (>8.7), the patient's whole-blood coagulation was still normal based on ROTEM analysis. The literature reports patients with acetaminophen toxicity and hepatic failure resulting in elevated INR [15,16]. However, the focus in those case reports was not coagulation monitoring, and viscoelastic testing was not performed.

An elevated PT/INR in FHF reflects a dysfunction or decreased production of the coagulation factors but is not necessarily a bleeding risk. This is especially true for factor VII, which has the shortest half-life of all the procoagulant factors (approximately 3-6 h) [17]. A dysfunction of coagulation factors does not translate to a dysfunction of hemostasis since adequate hemostasis does not require 100% of coagulation factors [18]. While FHF patients may have lower coagulation factors, they also have decreased anticoagulant protein C [19]. As a result, FHF patients can have normal clotting potential despite an elevated PT/INR.

Recent evidence has suggested that viscoelastic tests of coagulation, such as ROTEM, offer better clinical utility in assessing hemostatic function in patients with liver disease, including FHF [20]. This is because while PT/INR is analyzed from isolated plasma and its value is generated at the initiation of fibrin polymerization, ROTEM is analyzed from whole-blood samples and evaluates the kinetics and coagulation from clot initiation, propagation, stabilization, and lysis. This reflects a much more comprehensive picture of coagulation status, capturing the importance of plasma, blood cells, and platelets during hemostasis. Secondly, ROTEM considers the levels of pro- and anticoagulants, which are both decreased in FHF, and therefore the coagulation balance is maintained. In contrast, PT/INR only considers procoagulant levels, especially factor VII.

Most liver transplantation anesthesiologists understand that PT/INR is not reflective of the patient's whole-blood coagulation status and is not an indication to transfuse FFP. However, an INR of >8.71 is rarely seen and would generally lead physicians to transfuse FFP prior to an invasive procedure, mainly due to a fear of spontaneous bleeding or continuous bleeding from the procedure site. However, in FHF, the risk of spontaneous bleeding related to coagulation defects is unlikely. Munoz et al analyzed more than 1000 FHF cases and found minor gastrointestinal bleeding in only 6.6% of cases, with no significant difference in PT/INR between patients who bled versus those who did not [21]. Stravitz et al studied 1770 FHF cases and reported bleeding complications in 11% of cases, with no difference in PT/INR between FHF patients who bled versus those who did not [22]. Further, Fisher and Mutimer found no major vascular complications attributed to an elevated INR in a prospective audit of 580 central line placements in liver disease patients with an INR >1.5 [23].

According to the 2015 Practice Guidelines for Perioperative Blood Management from the American Society of Anesthesiologists, prophylactic blood products are not indicated if there is no bleeding, regardless of laboratory results [24]. There is also no clear evidence that prophylactic administration of FFP and cryoprecipitate improves outcomes when used solely to correct PT/INR in FHF patients based on conventional coagulation

testing. One small randomized trial showed that prophylactic administration of FFP had no influence on mortality in patients with FHF with abnormal PT/INR and no active bleeding [25]. FFP used to correct coagulopathy in FHF has a high potential to cause volume-overload acute lung injury, hypersensitivity reactions, and nosocomial infections [26,27]. The main cause is the large volume needed, which is about 15 to 20 mL of FFP per kilogram of body weight to achieve any hemostatic effect [28]. To avoid large-volume transfusion, PCC has been studied as an alternative in liver transplantation. A retrospective review from Kirchner et al found that ROTEM-guided first line hemostatic therapy with fibrinogen concentrate and PCC did not appear to increase the risk of thrombotic, thromboembolic, or ischemic events in liver transplant patients [29].

In this case, the patient received FFP and cryoprecipitate based on conventional coagulation tests and under the assumption that it would correct whole-blood coagulation abnormalities. However, physicians should be encouraged to utilize viscoelastic testing over conventional coagulation testing to assess bleeding risk and guide FFP transfusions. Dotsch et al reported that ROTEM was a better predictor of postoperative bleeding than plasma fibrinogen concentration [30]. Multiple studies found that thromboelastography-guided transfusion decreased FFP

transfusions and intraoperative blood loss and was superior to conventional coagulation tests [31-34]. The International Liver Transplantation Society (ILTS) ERAS4OLT.org Consensus

Conference on Enhanced Recovery for Liver Transplantation recommends viscoelastic tests over conventional coagulation tests to guide transfusion management [35].

Conclusions

Patients with FHF can have normal whole-blood coagulation based on ROTEM, even if INR levels are unmeasurably high. Viscoelastic tests such as ROTEM, which assesses whole-blood coagulation properties, are preferable for coagulation monitoring in these patients. Transfusion with blood products like FFP and cryoprecipitate can be used based on the result of viscoelastic testing over conventional coagulation testing.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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