CME

Coagulopathy in Children With Liver Disease

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ABSTRACT

It was thought that a high international normalized ratio predicted bleeding in patients with chronic liver disease (CLD) and patients were ''autoanticoagulated.'' Contrary to this belief, while patients with CLD experienced bleeding, they also developed thromboses. In the last decade, the prevailing literature challenged the idea that an elevated international normalized ratio increased bleeding risk. The global assays of coagulation such as thromboelastography (TEG)/rotational thromboelastometry and thrombin generation assays provide additional insight into coagulation processes. It has become apparent that a parallel reduction of procoagulant and anticoagulant factors leave patients in a new ''balanced'' state, albeit a fragile one, where the balance can be easily disrupted. The inherent differences in coagulation between children and adults such as differences in levels of procoagulant and anticoagulant factors, underlying liver disease, and the paucity of studies in children make extrapolation of these findings to the pediatric population problematic. Ultimately, this is an area that requires further investigation to avoid inappropriate use of blood products and medication.

Key Words: coagulation, international normalized ratio, pediatric, thrombin, viscoelastic

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What Is Known

- In adults with chronic liver disease, the belief that those with elevated values on coagulation tests, specifically (prothrombin time, international normalized ratio, activated partial thromboplastin time) are ''autoanticoagulated'' has been refuted. These tests do not predict risk of bleeding or thrombosis in this patient population.
- Lack of procoagulant and anticoagulant factors create a new ''balanced'' state of coagulation.
- There is a paucity of similar data in the pediatric population with liver disease.

What Is New

- Thrombin generation assays and viscoelastic tests assess global hemostasis. These tests may provide better estimates of hemostasis compared to standard tests.

In the past decade, our understanding of the coagulation system in adults with chronic liver disease (CLD) has undergone a paradigm shift. No longer are adult patients with CLD with abnormal hemostatic tests, specifically an increased prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT), believed to be ''autoanticoagulated'' with an increased risk of bleeding, but instead are considered in a ''rebalanced'' state. Similar studies are lacking in the pediatric population with CLD, and the potential implications are unknown. We will review the pathophysiology, diagnostic, and therapeutic considerations of the rebalanced hemostatic system focusing on implications in children with CLD.

REBALANCED HEMOSTATIC SYSTEM IN LIVER DISEASE

The belief that a high INR equates to an elevated bleeding risk has been refuted. Tripodi et al (1) compared thrombin generation and factor assays in 44 cirrhotic adult patients with abnormal PT to healthy controls. Despite the cirrhotic patients having lower levels of the procoagulant factor II and anticoagulant protein C, the cirrhotic group generated similar amounts of thrombin compared to controls. Indeed, patients with cirrhosis have lower procoagulant levels of factors II, V, VII, IX, X, XI, and XIII and fibrinogen but also lower activity levels of inhibitors of coagulation, protein C and antithrombin (AT) (1–3). With increasing severity of cirrhosis, factors II and V, AT, and protein C decreases but factor VIII increases. High levels of factor VIII and low levels of protein C are thought to confer hypercoagulability and may potentially explain why some patients develop thromboses (2). High levels of factor VIII have been reported in primary extrahepatic portal vein obstruction, with and without cirrhosis, compared to healthy controls (4). Von Willebrand factor antigen levels are increased and ristocetin cofactor activity is decreased in cirrhosis (5). The overall equilibrium of procoagulants and anticoagulants contribute to a ''rebalanced'' state, albeit fragile, one that can be easily tipped toward thrombosis or bleeding (6–8).

There is a paucity of literature in pediatric liver disease addressing this rebalanced state. Developmental differences in normal levels of procoagulants and anticoagulants make it difficult to apply adult data to the pediatric group. In addition, differences in etiologies of liver disease between adult and children make

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extrapolation of this knowledge problematic (9). It is clear more pediatric data are required.

WHY STANDARD HEMOSTATIC TESTS DO NOT PREDICT BLEEDING IN LIVER DISEASE

Standard hemostatic tests, PT, INR, and aPTT, only measure the effect of procoagulants and do not take into account the effect of in vivo inhibitors, contribution of platelets, or other cellular components (10). They are plasma-based assays that measure clotting with the fibrin clot forming quickly when only 5% of total thrombin is generated (11). The endpoint of these tests coincides with the beginning of the propagation phase; therefore, these tests do not provide information on the remaining 95% of thrombin generated and fibrin formation, nor do they inform on clot lysis.

The INR is a commonly used test in patients with liver disease yet numerous studies have questioned its accuracy and its applicability in CLD (12–14). The INR was initially developed by the World Health Organization (WHO) as a means to standardize PT between laboratories. The formula for calculation of the INR is $(PT_{patient}/PT_{mean\text{-}normal})^{ISI}$ where ISI stands for international sensitivity index. The reproducibility of INR is poor with laboratories reporting different INR values on the same blood samples taken from patients listed for liver transplantation (13). Furthermore, the ISI was derived specifically for patients on oral anticoagulant therapy and not validated for patients with liver disease. Applying ISIs developed specifically for CLD improved standardization and reduced variability in the INR (14).

There are concerns that abnormal hemostatic tests suggest a propensity for hemorrhage in patients with CLD particularly with invasive procedures. For example, bleeding complications after percutaneous liver biopsy in adults has been reported to be low at 0.35% to 0.83% (15–17) with similar rates in those with CLD 0.6% (18). Although other studies have reported higher postbiopsy bleeding rates of 2.4% to 31% in CLD especially those with platelet counts $<75{,}000/\mu L$ (16,18,19). In children undergoing liver biopsy, hemorrhagic complications are reported to be 0.91% to 4.2% and coagulopathy did not predict bleeding complications (20,21). Overall standard hemostatic tests have been inconsistent in predicting risk of bleeding complications after liver biopsy.

Esophageal variceal hemorrhage is a significant cause of mortality in patients with CLD (22,23). Factors such as Child-Pugh score, variceal size, red wale markings, hepatic venous pressure gradient (HVPG) and presence of gastric varices in the cardia are better predictors of increased risk of bleeding (24–26). Neither serum fibrinogen, prothrombin activity, aPTT, or platelet count have been shown to predict bleeding risk in adults with esophageal varices (27,28).

Patients with CLD can also develop thrombosis, despite an elevated INR. In an adult Danish study, the relative risk of venous thromboembolism in cirrhotic liver disease was 1.74, nearly twice that of controls (29). A prospective, multicenter randomized trial of 1243 cirrhotic adult patients demonstrated 1- and 5-year cumulative portal vein thrombosis (PVT) incidence rates of 4.6% and 10.7% (30). In a pediatric study, 10% of patients with end-stage liver disease developed PVT (31). Northup et al (32) found the INR and platelet count did not predict risk of venous thromboembolism, whereas serum albumin did (32). The role of anticoagulation in CLD was examined in a nonblinded, single-center randomized study in which adult patients with CLD received either enoxaparin prophylaxis for 1 year or no treatment. None of the patients with cirrhosis on enoxaparin developed PVT in contrast to 17% of the controls (33). In addition, those who received enoxaparin experienced less decompensation compared to controls suggesting anticoagulation may influence the rate of disease progression.

THE CENTRAL ROLE OF THROMBIN IN CLOT FORMATION

Understanding the role of thrombin in coagulation is essential to appreciate the limitations of the INR as a test. A comprehensive review of coagulation is beyond the scope of this review. Instead, the cell-based model will be briefly described with a focus on thrombin.

The coagulation cascade is a well known and accepted model of hemostasis, but has been superseded by a cell-based model of hemostasis. The cell-based model focuses on components of the cell surface and incorporates complexities that improve understanding of clinical observations (34). In this model, hemostasis is not a cascade but consists of 3 overlapping phases; initiation, amplification, and propagation. Thrombin plays an important role in all 3 phases.

Tissue factor (TF) is essential to the initiation of coagulation and is present in the adventitia of blood vessels and in extravascular tissues (35). Disruption of the vasculature exposes TF to blood and platelets. The initiation phase begins when plasma factor VII binds to TF on TF bearing cells to form an activated complex. The factor VIIa/TF complex then activates factor IX and factor X. Activated factor X subsequently activates factor V to form prothrombinase on TF-bearing cells, which then generates thrombin but in small amounts (36). In the following amplification phase, platelets bind to the preformed matrix complex resulting in their partial activation. The initial thrombin activates platelets and factors V, VIII, and XI. In addition, thrombin releases von Willebrand factor complexed to factor VIII, activating factor VIII, and freeing von Willebrand factor to participate in platelet adhesion and aggregation (36). At the end of the amplification phase, factor V and VIII are activated on the platelet cell surfaces to act as the foundation for further complex formation. In the propagation phase, activated factor VIII binds activated factor IX to form the ''tenase'' complex. The tenase subsequently activates factor X, which binds to activated factor V to form the ''prothrombinase'' complex on the platelet surface. The prothrombinase generates large amounts of thrombin resulting in fibrin polymerization and formation of the fibrin clot.

Thrombin prevents thrombosis by self-regulation. Thrombin forms a complex with thrombomodulin on endothelial cells and activates protein C. Activated protein C forms a complex with protein S, leading to inactivation of FVIIIa and FVa, which are required for the tenase and prothrombinase complexes and subsequent thrombin production (34). The effects of activated protein C and other anticoagulants are limited to the site of injury thus preventing propagation of thrombus beyond the disrupted endothelium. Thrombin is also regulated by tissue factor plasma inhibitor and AT (11).

Overall, the balance between procoagulant and anticoagulant factors regulates thrombin generation, the final step before formation of the fibrin clot. Tight control of this system is paramount to prevent excess thrombin generation.

THROMBIN GENERATION IN CHRONIC LIVER DISEASE

Global hemostatic assays inform on clot formation and dissolution. One such measure is the thrombin generation assay (TGA), which determines the amount of thrombin generated (37). The data from these assays are expressed in thrombin generation curves or thrombograms. Thrombograms provide data on clot formation and lysis, and therefore measuring both procoagulation and anticoagulation. The assay is based on concept that, ''The more thrombin the more thrombosis and the less bleeding; the less thrombin the more bleeding and less thrombosis'' (38) TGAs have provided insight into hemostasis in cirrhotics by demonstrating that

they have normal thrombin generation compared to controls (1). A correlation between the INR and amount of thrombin generated has not been found (10). Patients with cirrhosis with similar INRs demonstrate wide variability of thrombin generation with severe thrombocytopenia contributing to reduced thrombin generation in these patients (39,40).

There has been 1 study examining TGAs in children with CLD (41). In this study, 8 of 63 patients had altered coagulation profiles (abnormal INR, aPTT, or fibrinogen). This group also had lower levels of procoagulants and inhibitors of coagulation; higher levels of factor VIII and von Willebrand ristocetin cofactor compared to controls, consistent with adult data (1,2,5). Of note, thrombin generation was reduced compared to controls, indicating an increased bleeding risk or hypocoagulable state although thrombomodulin was not added. Only 1 out of 8 children bled from esophageal varices. In the remaining 55 children with CLD with normal coagulation profile, there was no difference in thrombin generation when compared to controls. Notably, the present study included only a small number of children with an abnormal coagulation profile indicating more studies are needed to accurately define the concept.

VISCOELASTIC ASSAYS

Other global tests include the viscoelastic tests, thromboelastography (TEG), and rotational thromboelastometry (ROTEM). TEG was developed in the late 1940s, but it was not until the mid-1980s before it was used in the setting of liver transplantation (42,43). Both TEG and ROTEM use whole blood samples and measure the shear elasticity of the clot (44). In brief, a sample of whole blood is placed into a cylindrical cup with a pin suspended in it. In TEG, the cup oscillates around a stationary pin and as the clot forms with increasing viscoelasticity, an electromagnetic transducer produces a trace. In ROTEM, the pin oscillates within a stationary cup and as the clot forms the impedance to rotation of the pin is detected optically creating a trace. In both tests, data on clot formation and lysis are obtained providing a global assessment of hemostasis.

Studies using TEG provide further insight on the global state of coagulation in CLD. TEG parameters in patients with stable cirrhosis without thrombocytopenia were within the normal range (8). Those with thrombocytopenia showed a decreased maximum amplitude or clot strength, which is determined by platelet activation and fibrinogen and is consistent with a hypocoagulable state. In a subset of patients with decompensated cirrhosis (INR $\geq$1.5), 2 of the TEG parameters, maximum amplitude and α-angle (measures rate of fibrin formation), were below the reference range reflecting lower platelet counts and fibrinogen levels. Similarly, ROTEM studies conducted by Kleinegris et al (45) showed increasing severity of cirrhosis was associated with decreased clot strength and delayed clot formation. With worsening cirrhosis, endogenous thrombin, however, increased, suggesting a heightened procoagulant state. Ben-Ari et al (46) demonstrated that 22% of patients with primary biliary cirrhosis and 30% with primary sclerosing cholangitis were hypercoagulable on TEG despite abnormal median PT and platelet count. Overall, the current adult data are inconsistent and it is difficult to draw firm conclusions, whereas there are currently inadequate studies evaluating the use of viscoelastometric studies in children with CLD.

THE PEDIATRIC HEMOSTATIC SYSTEM IS DIFFERENT THAN ADULTS

Age-specific differences in procoagulants and inhibitors of coagulation exist from the neonatal period and throughout childhood in healthy children (47). Factors II, VII, IX, and X have levels that are at least half that of adults in the neonatal period and gradually increase to adult values over the first 6 months of life (48,49). Factor VIII has been reported to have levels that are higher in childhood compared to adults (50); increased on day 1 of life then falling in the newborn period before rising in childhood to adult levels (49). Levels of von Willebrand factor are similar to adults, although some children have elevated levels (47). The levels of the inhibitors of coagulation also differ; levels of protein C and protein S are low in the neonate and increase throughout childhood (48).

There are also differences between children and adults in standard hemostatic tests and global tests of coagulation. The INR is statistically higher in neonates, although within the normal range, and normalizes by 1 month of age (49). Thrombin generation in healthy children less than 1 year of age is half the adult value and increases throughout childhood (49). Kaolin-activated TEG demonstrated no differences between parameters between adult and children (51), whereas celite-activated TEG parameters suggested a hypercoagulable state in children 12 months and younger (52). Similarly, ROTEM parameters demonstrated children ages 0 to 3 months were hypercoagulable despite elevated PT and aPTT (53). It is evident that healthy children have different levels of coagulation factors and thrombin generation compared to adults.

THERAPEUTIC IMPLICATIONS

Although there is evidence of a rebalanced system in adult patients with CLD, many patients routinely receive blood products for high INRs. In a 2012 survey of blood product use, adult patients with cirrhosis accounted for 7.7% (13/168) of the total number of patients transfused; and the patients received 32% of the plasma units and 13% of platelet units (54). Of these, 3 were transfused for bleeding and the remainder were transfused prophylactically.

In a split retrospective-prospective study of adult patients with CLD and coagulopathy, the mean PT improved with 2 to 6 units of fresh frozen plasma (FFP), but only 12.5% in the retrospective group and 10% in the prospective group were deemed to have corrected their PT, defined as PT within 3 seconds of control PT (55). To correct an INR of 2 in a cirrhotic adult patient, it is estimated that 1.5 L of FFP is required. This amount of volume is predicted to increase portal pressure by 15.5 mmHg (56). Correcting an INR of 4 is expected to require 2.5 L of FFP with an estimated rise in portal pressure of 25.8 mmHg. This is particularly significant in cirrhosis because HVPG (which assesses portal pressure) of $>$12 mmHg increases the risk for first episode of esophageal variceal bleeding (25) and $>$20 mmHg predicts risk of recurrent bleeding (27). Aggressively treating abnormal INRs with large volumes of FFP in these patients may be to their detriment. In patients with cirrhosis with thrombocytopenia undergoing variceal ligation, administering 1 unit of platelets produced only a small rise in platelet count with no significant effect on thrombin generation or thromboelastometry (57). Therefore, the value of significantly correcting laboratory values in patients who are not bleeding with blood products is questionable and patients may be exposed to more harm. Viscoelastic-guided blood product transfusions maybe the future. In 2016, De Pietri et al (58) randomized 60 patients with cirrhotic liver disease with an INR $>$1.8 and/or platelets $<50 \times 10^9$/L who were undergoing an invasive procedure to either a TEG-guided transfusion protocol or standard of care with 30 patients in both groups. All those randomized to standard of care received blood products compared to 5 in the TEG-guided transfusion group (100% vs 16.7%, $P < 0.0001$), with bleeding occurring in 1 patient after large volume paracentesis (standard of care arm). Those with coagulopathy did not experience an increased procedure-related bleeding risk (58). This novel study suggests viscoelastic whole blood studies potentially have a role in guiding transfusion practice

in patients with CLD. Unfortunately, there are not any similar studies of blood product transfusion practices in pediatric CLD.

THE IMPORTANCE OF UNDERSTANDING HEMOSTASIS IN LIVER DISEASE

Understanding the hemostatic system in CLD is important as it may also contribute to knowledge of liver disease progression in CLD. As mentioned above, in a small randomized control trial of cirrhotic adults, enoxaparin prevented PVT, improved liver function, and reduced decompensation (33). It is hypothesized that anticoagulation with enoxaparin in the presence of portal hypertension may lead to removal of microthrombi from the intestinal microcirculation leading to enhanced blood flow. This could protect enterocytes from ischemic injury and avert microbial translocation associated with disease progression. Understanding the processes involved has considerable implications for pediatrics. In pediatric patients with end-stage liver disease, the ability to slow progression of disease is an important consideration while awaiting liver transplantation. An analysis of the UNOS database demonstrated patients who are $\leq$5 kg have inferior outcomes with 1-year graft survival of 71% and 5-year graft survival of 64% with a waitlist mortality of 18.2%. Altering the course of disease could give pediatric patients the opportunity to obtain a higher body weight and experience better outcomes (59).

CONCLUSIONS

There is evidence supporting the concept of a balanced coagulation in adults with CLD; however, similar pediatric studies are lacking. Inherent differences between adults and children make it difficult to extrapolate the data. Ultimately, global assays may provide a more accurate assessment of the hemostasis. Further studies are required to characterize the coagulopathy of liver disease in children.

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