REVIEW ARTICLE

Hemostasis Assessment in Neonates: Evaluation of Viscoelastic Properties of Blood Clots

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Abstract

In recent years, a new approach to neonatal hemostasis has been taking hold. The term "developmental hemostasis" refers to the dynamic, age-related physiological changes seen in the hemostatic system in neonates and young infants. Most conventional coagulation tests have limitations as these are focused primarily on the procoagulant factors and do not inform about platelet function and the levels/activity of von Willebrand factor (vWF), natural anticoagulants, and fibrinolytic activity. In this scheme, viscoelastic coagulation tests can rapidly provide a potentially useful, panoramic assessment of the entire coagulation process from the formation to degradation of clots, platelet function, and fibrinolysis. This is a narrative review on the use of viscoelastic tests in neonatal care; we have included information from our own clinical experience and from an extensive literature search spanning PubMed, Scopus, and Web of Science. This review is important because tests can help identify premature/critically ill infants who may be at risk of hemorrhage during routine care or after surgery and may need corrective transfusions with appropriate blood products.

Keywords: Activated partial prothrombin time, Developmental hemostasis, Fibrinogen levels, Fibrinolytic activity, Natural anticoagulants, Platelet function, Procoagulant factors, Prothrombin time, Viscoelastic coagulation tests, von Willebrand factor.

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Highlights

- In recent years, a new approach to neonatal hemostasis, called "developmental hemostasis" has been recognized. It refers to the dynamic, age-related physiological changes seen in the hemostatic system in neonates and young infants.
- Most conventional coagulation tests have limitations as these are focused primarily on the procoagulant factors and do not inform about platelet function, von Willebrand factor (vWF), natural anticoagulants, and fibrinolytic activity.
- Viscoelastic coagulation tests, such as thromboelastography (TEG) and thromboelastometry, can provide a rapid, global assessment of clotting in a graphical trace of the entire coagulation process from clot formation to clot degradation, platelet function, and fibrinolysis.
- The viscoelastic coagulation tests involve the positioning of a whole blood sample with a rotating activator in a cup with a pin at its center. A fibrin strand forms and slows down further rotation and the blood slowly coagulates.
- Preliminary studies show that viscoelastic tests may help overcome the limitations of conventional coagulation tests; there are advantages such as bedside testing, a panoramic view of the entire hemostatic process, and the need for minimal blood volumes.

Introduction

Bleeding and thrombosis are seen frequently in premature and critically ill infants. Historically, the diagnosis of coagulation disorders in neonates included platelet counts and standard coagulation tests such as the measurement of prothrombin time (PT), activated partial prothrombin time (aPTT), and fibrinogen levels. These tests measure plasma concentrations and activity of procoagulant proteins but do not provide detailed information about platelet function, concentrations of the vWF and natural anticoagulants, and fibrinolysis. In the absence of these data, we are not able to obtain a useful panoramic view of the entire hemostatic system.[1] These measurements are particularly important in infants as the hemostatic function is a dynamic system that undergoes quantitative/qualitative changes during development and postnatal age, and also gets disrupted during critical illness. Clearly, conventional coagulation tests may not be adequate to identify inherited/acquired coagulation disorders of various degrees of severity, and to guide transfusions frequently needed in premature/critically ill neonates.[2]

Viscoelastic coagulation tests, such as TEG and rotational thromboelastometry (ROTEM), may help overcome some of these limitations. These testing methods can provide a rapid, global assessment of clotting in a graphical trace of the entire coagulation process from clot formation to clot degradation, which indirectly also informs about platelet function and fibrinolysis. In this way, the tests provide a better assessment of the *in vivo* conditions than conventional coagulation tests.[3] In this article, we aim to provide an overview of current, evidence-based information on

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the clinical applications of viscoelastic testing in the context of neonatal intensive care. In these patients, rapid assessment of the coagulation systems(s) is frequently needed to determine the risk of bleeding in critical organ systems, the need for clinical and laboratory-based monitoring, and to guide blood product administration and therapy.

From "Developmental Hemostasis" to Understanding the Limits of Standard Coagulation Tests

In premature/critically ill infants in neonatal intensive care units (NICUs), there is a need to understand physiological hemostatic factors/processes and the alterations in various disease states. This information is needed not only to understand the risk of localized/systemic hemorrhage but also to guide transfusion management in these patients. The term "developmental hemostasis" was first coined by Maureen Andrews to describe the dynamic evolution of the hemostatic system during childhood.[4] The hemostatic system undergoes an age-dependent dynamic evolution during which plasma levels/isotypes of most proteins in the coagulation pathways change significantly with age. Neonates have lower plasma concentrations of vitamin K-dependent coagulation factors and contact factors than adults. During the first 6 months of life, the concentration of these coagulation factors rises gradually to reach levels seen in adults. In contrast, plasma levels of fibrinogen, factor V (FV), FVIII, FXIII, and the vWF resemble those in adults. In the natural inhibitor system, plasma concentrations of antithrombin, protein C and protein S are lower at birth and reach adult levels at about 6 months. These differences in the developmental trajectories of pro- and anticoagulant proteins are seen in both pre- and full-term infants; these changes comprise a regularly seen dynamic equilibrium in good infants.[5]

Age-related changes in clotting proteins result in corresponding changes in standard coagulation tests such as PT and aPTT. Considering the age-dependent specificity of hemostasis, the evaluation, and the interpretation of coagulation tests in newborns need to be based on appropriate reference ranges for gestational and postnatal age.[6–8] Both PT and aPTT are longer in infants than in adults, possibly due to lower levels of vitamin K-dependent factors. Consequently, these measurements are not as useful in the evaluation of acquired neonatal coagulopathies unless we have "control" results that were obtained prior to the onset of illness. Furthermore, these data do not include the effects of platelet function and the levels of vWF, natural anticoagulants, and fibrinolytic activity, without which the analysis of overall hemostasis remains incomplete.[9]

In neonates, the results of coagulation tests have been viewed as atypical/abnormal as these differ from those in adults, and have not been accurate predictors of bleeding and clinical severity of the underlying disease.[8,10–12] Therefore, routine coagulation testing is no longer performed in most NICUs at admission; most studies showed that such testing only increased the rates of transfusions without convincing evidence of benefit. Furthermore, these tests required relatively large volumes of blood (0.8–2 mL) and contributed to iatrogenic anemia, especially in very low birth weight (VLBW) infants.[13] Finally, in the context of acute, major hemorrhage the length of time required to obtain results also became an important limitation.

Viscoelastic Coagulation Tests

Given the complexity of the coagulation process and the inadequacy of standard laboratory tests, nowadays, the evaluation with viscoelastic coagulation tests is a better, rapid, panoramic assessment of hemostasis, which provides information about clot strength, dynamics, and breakdown. With information about the viscoelastic properties of the clot, these data differ from conventional coagulation tests as these also inform about the entire coagulation process, including clot development, stabilization, and dissolution; the interaction between plasma coagulation proteins; and qualitative/quantitative information about platelets and blood cells. Not surprisingly, the results are a better reflection of the situation *in vivo* than the standard tests. The interest and experience with the viscoelastic tests in neonates have been increasing over the years and its use seems promising in the diagnosis and treatment of acquired coagulopathies.[14,15] Thromboelastography (TEG) (TEG®, Haemonetics, Braintree, Massachusetts, USA) and ROTEM (TEM international, Munich, Germany) have been the main providers so far, although other similar/comparable devices are now also available.

The original TEG and ROTEM technologies involve the positioning of a whole blood sample with an activator in a cup with a pin at its center. With TEG, the cup rotates, whereas the pin moves around a circulation axis in the ROTEM. A fibrin strand forms, making the pin adhere to the wall of the cup. This slows down further rotation and the blood slowly coagulates. Blood clotting leads to the development of the TEG/ROTEM trace; the interpretations are similar, but not identical, to other different and non-interchangeable reference range parameters.[1]

Several newer cartridge-based devices have improved the viscoelastic assessment as these do not need controlled pipetting, which is subject to interuser modifications and consequent errors. One of these is the viscoelastic coagulation monitor (VCM) device (VCM™, Entegrion, Inc., Durham, North Carolina, USA), which provides an analysis of the coagulation state in approximately 1 hour with 300 μL of a fresh, whole blood sample. This device is quick and easy to use, is portable, and has the potential for more widespread clinical use in neonatal intensive care (Fig. 1).[16]

The following parameters of clot formation and lysis are evaluated as a representation of hemostasis:

- Clotting time (CT) (reaction rate (R) in minutes/CT). The time, expressed in minutes, reaches 2-mm amplitude in TEG and ROTEM, 1% above the baseline in VCM. It represents the speed of fibrin formation;
- Clot kinetics [kinetics (*K*) in seconds/clot formation time (CFT)]. Time, expressed in minutes, for clot amplitude to reach from 2 to 20 mm in TEG/ROTEM, from 1 to 10% amplitude in VCM. This time is a measure of the clot kinetics to reach a fixed level of clot strength. It correlates with fibrinogen level and, to a lesser extent, with both platelet function and values;
- Alpha angle (α). The angle formed between the midline and the tangent to the main body of the trace. Like *K*, α correlates with fibrinogen level, with platelet function and values;
- Maximum amplitude [MA/maximum clot firmness (MCF)]. The amplitude at the widest point of the trace represents the maximum clot strength as the result of the modest contribution of fibrin and the much more significant contribution of platelets;
- Fibrinolysis [clot lysis at 30 minutes after maximum clot strength (LY30)]. Reduction in amplitude 30 minutes after MA/MCF. It is expressed as a percentage of MA/MCF.[17]

One of the main advantages of viscoelastic coagulation tests is the need for smaller amounts of blood, 340 vs 800–2000 μL that was needed to perform conventional coagulation tests. Furthermore, blood samples can be obtained from a peripheral vein or artery or

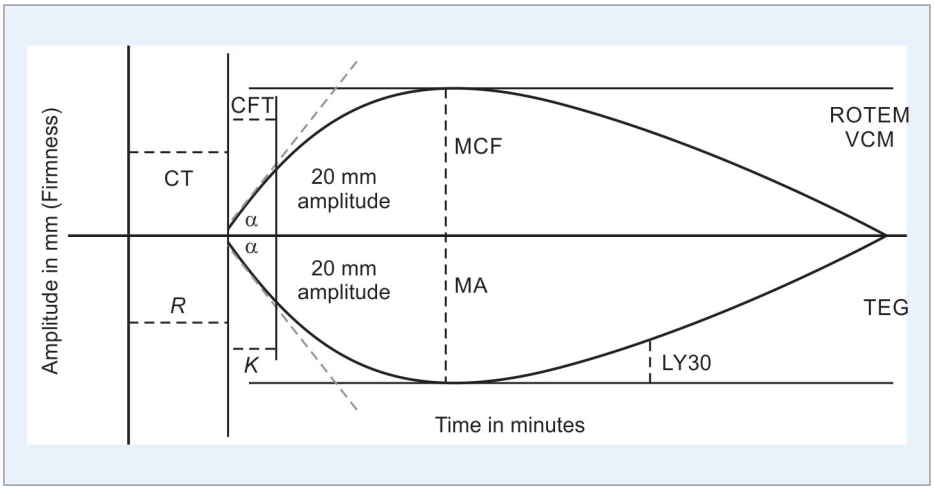


Fig. 1: Schematic representation of normal TEG/ROTEM/VCM traces

via a heel stick, maintaining both feasibility and reproducibility of the test results.[18] Another advantage of viscoelastic coagulation tests is the real-time evaluation of the hemostatic state as the results become available in just about 20 minutes, compared to the 40–90 minutes that were needed for conventional tests. Finally, these tests can be performed at the patient's bedside, allowing quick, individualized, and targeted therapeutic interventions.[9]

Reference Ranges for Viscoelastic Coagulation Tests

Many published studies are available proving the reproducibility and reliability of the viscoelastic coagulation tests to assess hemostasis in the neonatal population.[19,20] Motta et al.[21] evaluated TEG parameters in healthy preterm infants and developed reference intervals. The TEG parameters between early-preterm (<32 weeks' gestation) resembled those in moderate-/late preterm (from 32 to less than 37 weeks' gestation) neonates, suggesting that hemostatic function matures at birth even in very premature infants.[21] In another study, Sewell et al. established normative TEG ranges for blood samples from term infants obtained in tubes containing citrate or heparinase.[22] In an observational study, Ghirardello et al. performed duplicate TEG measurements on blood samples obtained from VLBW neonates and found an acceptable level of agreement between these duplicates. These data confirmed the reliability of TEG to assess hemostasis in neonates.[19]

In another study, Sokou et al. established reference ranges for peripheral arterial whole blood EXTEMROTEM® assay in pre- and full-term neonates; the two groups showed comparable results. Preterm neonates showed enhanced fibrinolytic activity as follows: Lysis at 60 minutes (LY60) values were significantly lower than full-term neonates ($p = 0.006$). There was also a significant correlation between lysis at 60 minutes (LY60) with gestational age and birth weight in preterm infants.[23]

The same author compared clot formation in neonates with small-for-gestational-age neonates' weights with those who were born appropriate-for-gestational-age weight (AGA) using EXTEM ROTEM® analysis. The two groups showed comparable results.[24]

Viscoelastic Coagulation Tests in Acquired Coagulation Disorders of Newborns

Several studies have now proved the reproducibility and reliability of the viscoelastic coagulation tests to assess hemostasis in the neonatal population by developing local, age-, analyzer-, and reagent-appropriate reference ranges. We also now have data for viscoelastic test parameters to evaluate the correlation between coagulopathy and clinical bleeding.

Radicioni et al. measured the thromboelastographic profiles of 49 premature neonates with and without intracranial hemorrhage (ICH).[15] No significant differences in TEG and standard coagulation test values between the two groups were observed at birth. Similar to traditional coagulation tests, TEG assessment failed to identify the underlying coagulopathy of preterm infants with ICH. Interestingly, newborns with ICH showed increased TEG-defined thrombin generation from birth to 21 days of life, suggesting a state of hypercoagulability. It is plausible that TEG cannot detect the bleeding risk of preterm infants, but the presence of hemorrhages such as ICH could be suggested by altered TEGs.

A retrospective study evaluated TEG parameters in healthy preterm neonates and organized the data into reference intervals. The authors also compared 24 preterm infants with active bleeding with 94 who did not have active hemorrhage; the TEG parameters were similar.[21] The bleeding group included 91.6% of preterm neonates with ICH, showing again that preterm infants with or without ICH have similar TEG parameters. In contrast, the normative ranges for citrated-modified and heparinase-modified TEG parameters in term neonates presented by Sewell et al. showed clear thresholds in TEG parameters that were associated with clinical bleeding.[22] Their bleeding group was comprised of neonates with hypoxic–ischemic encephalopathy, respiratory failure requiring extracorporeal membrane oxygenation (ECMO), critical congenital heart disease, and disseminated herpes simplex virus, and therefore, they could not exclude whether any of these illnesses could have affected the TEG parameters.

Forman et al. examined a cohort of 24 infants receiving therapeutic hypothermia for perinatal asphyxia.[25] The TEG assays were simultaneously performed at 33.5 and 37°C for comparison. Also, TEG results were affected by temperature, indicating lower temperatures impaired the coagulation pathways. The TEG parameters predicted clinical bleeding with temperature-dependent thresholds, whereas the standard coagulation tests did not. The authors concluded that TEG results should be carried out under temperature-regulated conditions for neonates undergoing therapeutic hypothermia; if so, this might be a suitable method to

assess the risk of bleeding and optimize transfusion treatment in this population.

In 1995, Stammer et al. used viscoelastography to evaluate the coagulation status of 17 neonates undergoing ECMO for severe respiratory dysfunction.[26] The TEG profiles reflected hemostatic conditions that ranged from severe disseminated intravascular coagulopathy (DIC) to hypercoagulability, identifying clotting abnormalities in 46.5% of the cases. Most were related to platelet dysfunction. The TEG profiles were normal in 73.2% of infants who did not have hemorrhages, whereas only 40% of those with hemorrhage had comparable normal values. In another study, Phillips et al. retrospectively reviewed 46 neonates with congenital diaphragmatic hernia (CDH) between 2008 and 2018 while they were being supported by (ECMO).[27] From 2015, they had implemented and standardized their anticoagulation management by including routine TEG monitoring and found that this implementation improved goal-directed blood product transfusion in neonates with CDH supported by ECMO. Thromboelastography derangements led to a significant increase in platelet transfusions, and fewer cryoprecipitate administration, but no change in the use of fresh frozen plasma (FFP). Additionally, comparing the pre-2015 and the post-2015 groups, they found a significant reduction in the incidence of hemothorax. Both these studies highlight that in neonates undergoing ECMO, the TEG assay can be a useful tool for rapid diagnosis of hemorrhagic conditions and timely administration of blood transfusion products. Peterson et al.[28] examined blood samples from 44 neonates undergoing cardiopulmonary bypass (CPB) to evaluate the heparin–protamine balance and determine its association with postoperative bleeding. They used calibrated automated thrombography, thrombin-initiated fibrin clot kinetic assay (TFCK), aPTT, anti-FXa activity, and thromboelastography. About 36% of their patients had excessive postoperative bleeding. They found that aPTT correlated strongly with TFCK but so much with the anti-FXa and ROTEM assays. This correlation between aPTT and TFCK could have been due to similarities in the measurement of fibrin formation as the endpoint for both assays. None of the coagulation tests predicted postoperative bleeding in these neonates, suggesting that hemorrhagic events were likely multifactorial.[28] In a different single-center observational study, Sokou et al.[29] compared thrombolelastometry parameters in pre- and full-term neonates with confirmed vs suspected sepsis. Septic neonates had a hypocoagulable state, not those with unconfirmed infections. This hypocoagulable profile was more evident in septic neonates with clinically evident bleeding than in those without. They also noted that EXTEM A10 was a strong predictor for bleeding events in this neonatal population.[29]

The same investigators assessed 332 critically ill pre- and full-term neonates to develop a predictive model for bleeding and then internally validated their findings.[30] They performed thromboelastometry and used the neonatal bleeding assessment tool (NeoBAT) to record hemorrhagic events occurring within 24 hours of the ROTEM testing.[31] Thromboelastometry parameters, platelet counts, and creatinine levels were identified as the most robust predictors of hemorrhage and were included in a neonatal bleeding risk (NeoBRis) index. This multivariable prediction model showed excellent performance, suggesting that, after external validation, this could help clinicians to assess the 24-hour bleeding risk and individualize the need for transfusions.

In a recent study, Raffaeli et al.[32] assessed the impact of TEG and VCM implementation on FFP transfusion of neonates undergoing surgery. They found that the TEG and VCM-based quality improvement project improved the hemostatic management of surgical newborns by reducing intraoperative FFP administration. Indeed, neonates presenting prolonged PT or aPTT and normal TEG or VCM parameters did not receive FFP transfusion; the attending physician was probably reassured by a normal viscoelastic trace.

Viscoelastic Coagulation Tests in Congenital Coagulation Disorders of Newborns

In the last few years, viscoelastic coagulation tests have been studied in the diagnosis and management of inherited bleeding disorders, including hemophilia.[33] Standard coagulation tests and factor assays have been used routinely in the diagnosis and management of hemophilia but have some limitations. Both PT and PTT only give information on the initiation of coagulation and aPTT based FVIII:C (factor VIII activity) test does not necessarily correlate with clinical severity.[34] Thus, viscoelastic coagulation tests have been studied to complement standard assays and overcome challenges in hemophilia care.

One of the main challenges in neonates with congenital bleeding disorders is monitoring for routine FVIII prophylaxis as well as a clinical response to different forms of therapy. Hawaj et al.[35] studied 8 severe hemophilia A patients with various bleeding phenotypes after receiving their standard rFVIII prophylaxis dose. Parameters including FVIII:C, TEG, and TGA were monitored over 48 hours. A significant correlation was found between FVIII:C, TEG R-time, and aPTT. At 24 hours, the TEG parameters were subtherapeutic despite the median FVIII:C of 13.0 IU/dL^{1} and lost sensitivity at 48 hours.[35]

In another study, Aghighi et al.[36] demonstrated that measurement of maximum velocity parameters by ROTEM had a 92% sensitivity and 95% specificity for diagnosing hemophilia; these findings correlated strongly with factor VIII levels.[36] Patients with hemophilia are usually classified into mild (FVIII > 5%), moderate (FVIII, 1–5%), and severe (FVIII <1%) groups.[37] One of the main issues is the differentiation of the clinical phenotype in this disease. Patients with severe hemophilia can manifest a mild clinical phenotype and, vice versa.[38] Viscoelastic testing can help differentiate the clinical phenotypes. Ramiz et al.[39] evaluated TEG analysis in patients with severe hemophilia A, who had similar levels of FVIII (<1%) but different coagulation patterns. Patients with milder phenotypes showed a shorter *R*-time and steeper α-angle as a better clot formation. They also used TEG, alongside standard coagulation tests, to monitor routine FVIII prophylaxis and to assess a variable half-life response to F VIII administrations. At 48 hours after infusion, TEG analysis showed a sufficient clotting pattern and led to a less frequent infusion schedule.[39]

In our experience, we have been using viscoelastic tests, TEG 5000 (TEG®, Haemonetics, Braintree, Massachusetts, USA) and VCM (VCM™, Entegrion, Inc., Durham, North Carolina, USA), to assess whole blood hemostasis in acquired and congenital clotting disorders. We followed up with TEG 5000 a term newborn, born by cesarean section with an antenatal diagnosis of bladder exstrophy and hemophilia A. The analysis of the chorionic villi highlighted the presence of a genetic defect in hemizygosis c.–257T>G. On the first day, factor VIII was 12%, defining mild hemophilia. On day 4, the patient underwent surgery for repair and received rFVIII prophylaxis dose. Thromboelastography tracing (Fig. 2), before receiving rFVIII, showed a long *R*- and *K*-time, and a narrow α-angle, while TEG tracing (Fig. 3), after rFVIII administration, depicted a significant

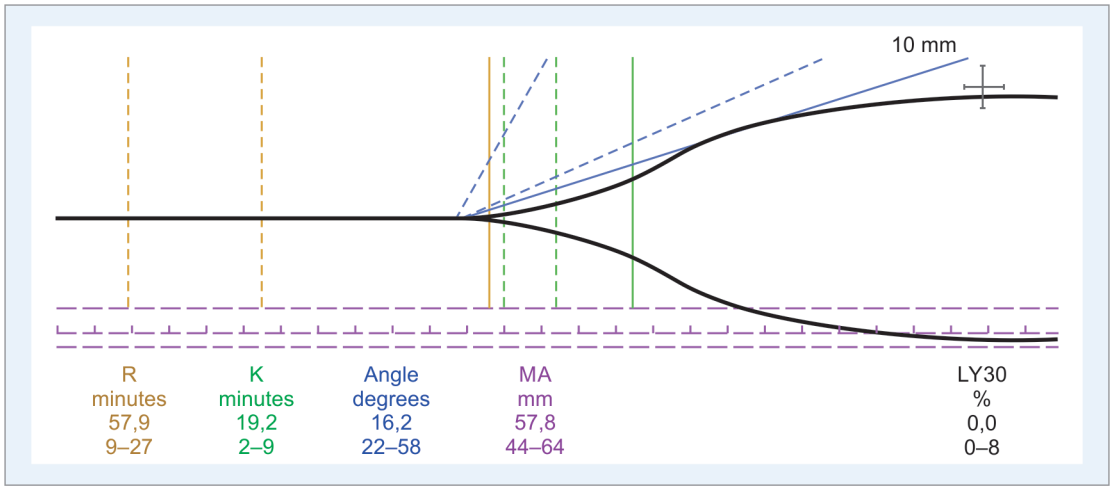


Fig. 2: The trace shows a long *R*- and *K*-time, and a narrow α-angle

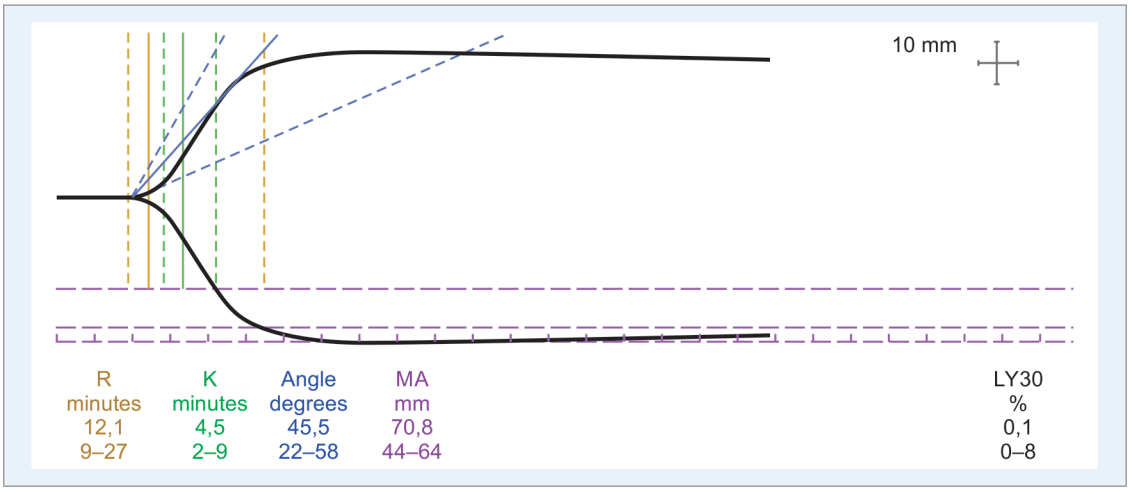


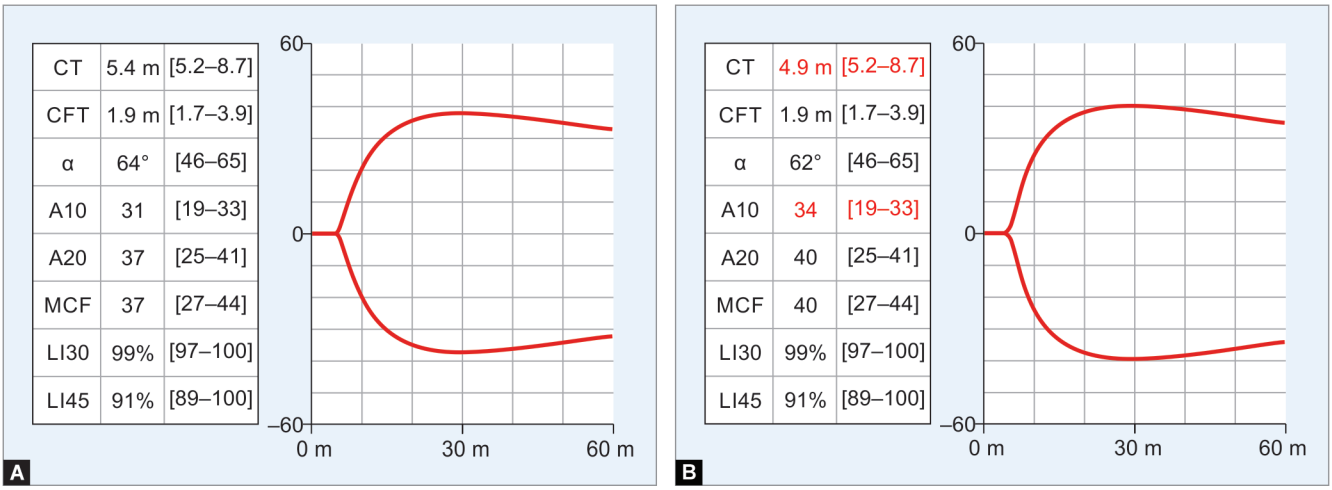
Fig. 3: The TEG tracing, obtained after rFVIII administration depicts shorter *R*- and *K*-time and a steeper α-angle

improvement of clot initiation and amplification (shorter *R*- and *K*-time and a steeper α-angle). During the postoperative period, TEG analysis together with conventional tests helps physicians understand patient hemostasis and tailor prophylactic rFVIII infusions.

Regling et al.[40] studied 160 pediatric patients aged from 2 weeks to 18 years who were evaluated for bleeding abnormalities. Seventy-eight were diagnosed with von Willebrand (VW) disease. In this subgroup, TEG parameters, such as *K*-time and maximum thrombus generation (MRTG) rate, were abnormal. Prolonged *K*-time and low MRTG were sensitive in detecting patients with VW factor activity below 30 IU/dL. The authors found the TEG test to be useful because it helped physicians in prompt identification of patients at risk of major bleeding. Furthermore, TEG assay also appeared to be beneficial in assessing the need for replacement therapy in minor acute bleeding.[40]

Rare coagulation diseases include deficiencies of coagulation factors such as fibrinogen, prothrombin, factor (F) V, FVII, FX, FXI, and FXIII, and the combined deficiency of FV + FVIII and vitamin K-dependent factors. In these patients, the clotting level activity does not always correlate with the risk of bleeding. Global coagulation tests, although not yet standardized, are believed to add information on the prediction of individual phenotypes and therefore aid the clinical management of affected patients.[41,42]

An inborn premature neonate was admitted to our NICU at 31-week gestation with a prenatally diagnosed ventriculomegaly. During follow-up, serial cranial ultrasound scans showed worsening posthemorrhagic ventricular dilatation. Due to the cerebral bleeding, standard coagulation tests were performed, and, on all occasions, a prolonged PT was noted. In addition to conventional tests, VCM™ was also used to better understand the neonate's global hemostasis (Fig. 4). Viscoelastic coagulation monitor tests consistently showed normal clot formation and lysis. However, vitamin K-dependent clotting factors II, VII, IX, and X were found to be deficient but the levels of these factors were not low enough to suggest an increased risk of spontaneous bleeding, as always demonstrated by VCM tests. Intravenous administration of vitamin K partially corrected the levels of these factors. The patient underwent surgery twice, once for ventricular reservoir placement and once for placement of a ventriculoperitoneal shunt. No bleeding complications were reported. Before surgery, the neonate was prophylactically treated with prothrombin complex concentrates and monitored for further administration with standard coagulation tests and VCM analysis. Viscoelastic traces



Figs 4A and B: The VCM trace of a premature neonate with a deficiency of vitamin K-dependent clotting factors. α, α-angle; A10, clot amplitude at 10 minutes; A20, clot amplitude at 20 minutes; CT, clotting time; CFT, clot formation time; LI30, lysis index at 30 minutes; LI45, lysis index at 45 minutes; MCF, maximum clot firmness; VCM tests showed a normal clot formation and lysis before (Fig. 4A) and after (Fig. 4B) administration of prothrombin complex concentrate

consistently demonstrated good clot formation and, together with standard coagulation tests, guided physicians in therapeutic decision making (Fig. 4) after surgery and for administration of prothrombin complex concentrate.

Conclusion

Viscoelastic coagulation tests, providing a rapid global assessment of hemostasis, appear to be useful to determine the neonatal coagulation profile, to identify neonatal patients at risk of developing postoperative bleeding and coagulation abnormalities, and therefore to guide blood product transfusions. Many neonatal units worldwide have incorporated viscoelastic testing into their practice and have been evaluating these tools in neonatology.

The promising results of preliminary studies on neonates have shown that viscoelastic tests may help overcome the limitations of conventional coagulation tests; there are advantages such as the feasibility of bedside testing, the availability of a panoramic view of the entire hemostatic process, and the need for minimal blood volumes. However, further testing is needed to support or refute the routine use of viscoelastic testing to guide hemostatic treatment compared to usual care in bleeding newborns. There is a need for larger, high-quality studies.

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