Viscoelastic coagulation testing in Neonatal Intensive Care Units: advantages and pitfalls in clinical practice

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The expression "developmental hemostasis" indicates the age-related physiological changes occurring during the maturational process of the hemostatic system. Despite the quantitative and qualitative alterations, the neonatal hemostatic system is competent and well-balanced. Conventional coagulation tests do not provide reliable information as they only explore the procoagulants during the neonatal period. In contrast, viscoelastic coagulation tests (VCTs), such as viscoelastic coagulation monitoring (VCM), thromboelastography (TEG or ClotPro), and rotational thromboelastometry (ROTEM), are point-of-care assays that provide a quick, dynamic and global view of the hemostatic process, allowing prompt and individualized therapeutic intervention when necessary. Their use in neonatal care is on the increase and they could help monitor patients at risk of hemostatic derangement. In addition, they are crucial for anticoagulation monitoring during extracorporeal membrane oxygenation. Moreover, implementing VCT-based monitoring could optimize blood product use.

Keywords: *neonatal, developmental hemostasis, viscoelastic test, point-of-care tests.*

INTRODUCTION

The expression "developmental hemostasis" was coined by Andrew in the late 1980s to indicate the age-related physiological changes occurring during the maturation of the hemostatic system in the early months of life[1-3].

Hemostasis is a dynamic process that develops in utero, evolves throughout life, and involves multiple interlinked steps to prevent bleeding or thrombosis. The initial injury to the vascular endothelium causes vasoconstriction and platelet plug formation. The presentation of tissue factor at the damaged site then activates the coagulation cascade that culminates with the conversion of fibrinogen to fibrin to form the fibrin clot.

Term and premature newborns have low plasma levels of most procoagulant clotting factors compared to older individuals[4]. However, the whole system is compensated by a concurrent deficit of anticoagulants: antithrombin, protein C, and protein S[4]. Similarly, many factors that promote platelet/vessel wall interactions counteract neonatal platelet hypofunction, such as higher hematocrit, higher mean corpuscular volume, and increased von Willebrand Factor (vWF) concentration[5,6]. The differences between neonatal and adult hemostatic systems appear to be also qualitative; for example, a predominance of

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high molecular weight vWF multimers, with enhanced adhesive activity, is detected at birth, as well as a "fetal" form of fibrinogen with an increased sialic acid content, which is responsible for a particular mechanism of clot polymerization[6-8]. All these findings, in addition to strong evidence of adequate hemostasis in vivo and sufficient thrombin generation, suggest that the neonatal hemostatic system is competent and well-balanced[4,9-12] (**Figure 1**). It is also worthy of note that preterm neonates display a procoagulant imbalance, as evidenced by the increased thrombin generation assay[13].

An understanding of this concept, together with the establishment of postnatal and gestational age-related ranges, are needed to ensure optimal prevention, diagnosis, and treatment of hemostatic disturbances in newborns[11,14].

STANDARD COAGULATION TESTS *VS* VISCOELASTIC TESTS

When evaluating the coagulation status of patients, conventional coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (APTT), are routine clinical practice. They are plasmatic in vitro tests that selectively explore the procoagulants without evaluating the role of anticoagulants and cellular contributors in hemostasis. Both PT and APT are prolonged in the neonatal period, reflecting the lower levels of vitamin K-dependent coagulation and contact factors, and therefore they are not suitable for evaluating acquired neonatal coagulopathy[10,15]. Polycythemia may further contribute to an artificial prolongation of coagulation time, especially PT, as a consequence of the incorrect ratio of citrate to whole blood due to the reduced plasma volume in the blood collection tube[16,17]. Consistent with the concept of developmental hemostasis, the correct interpretation of coagulation tests requires appropriate age-related, as well as reagent and analyzer reference ranges[18].

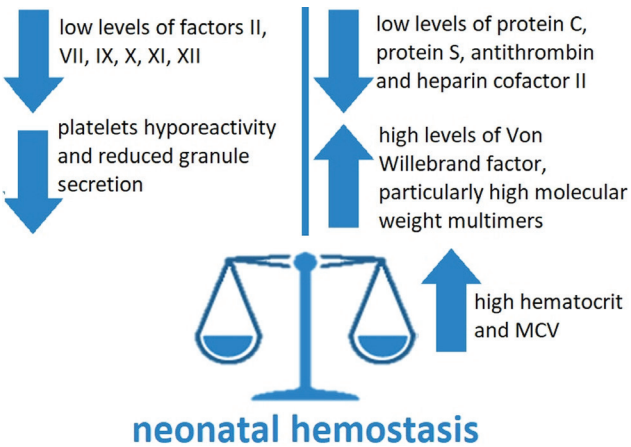

Figure 1 - Neonatal hemostasis: a well-balanced system
MCV: mean corpuscular volume.

Based on previous considerations, mild to moderate PT and APTT prolongation is of poor predictive value of bleeding risk in neonates. Therefore, their use for routine coagulation screening on admission to the neonatal intensive care unit (NICU) should be avoided since it can lead to an increased transfusion rate without any clinically relevant benefit[16,19]. However, abnormal coagulation tests are still one of the main indications for fresh frozen plasma (FFP) administration, and the reduction in coagulation testing is reported to have led to a decrease in the number of FFP transfusions[20].

Another disadvantage of these tests is that they require relatively large volumes of blood (0.8-2 mL), and this can be highly challenging in neonates, especially for those with a very low birth weight (VLBW), who are at significant risk of iatrogenic anemia[21]. Furthermore, the technical difficulties inherent to collecting samples through venepuncture can make it difficult to completely fill the collection tube, resulting in an imbalance of the normal citrate-to-blood ratio (1: 9) or early activation of coagulation. In addition, blood sampling from central venous access may be contaminated with heparin and therefore a significant initial blood volume has to be discarded to avoid inaccurate coagulation results[1]. Moreover, as these tests are performed at a standardized temperature of 37°C, they cannot detect hypothermia-induced coagulopathy[15].

Viscoelastic coagulation tests (VCTs), such as viscoelastic coagulation monitoring (VCM™) (Entegrion Inc., Durham, NC, USA), thromboelastography (TEG or ClotPro) (TEG®, Haemonetics, Braintree, MA, USA; ClotPro®, enicor GmbH, Munich, Germany), and rotational thromboelastometry (ROTEM) (ROTEM®, TEM International, Munich, Germany) may be able to overcome some of these limitations.

These point-of-care (POC) devices provide a dynamic and global view of the hemostatic process, derived from the

interaction of platelets, plasma pro- and anticoagulation factors, and fibrinolytic protein, reflecting the cell-based model of coagulation[22]. Specifically, they measure the time until initial clot formation, clot kinetics, clot strength, and stability over time in whole blood[15].

The neonatal hemostatic system exhibits a faster initiation and propagation of coagulation than older individuals when evaluated with VCTs[23].

The main advantage of VCTs is their potential to provide a real-time assessment (in approximately 20 minutes *vs* 40-90 minutes as required by conventional tests) of the hemostatic status with a simple procedure performed directly at the patient's bedside, thus allowing individualized goal-directed therapeutic interventions when necessary[15,24]. The need for a relatively small sample volume (340 *vs* 800-2000 µL as required by conventional tests) is another advantage in the NICU setting. However, consistent with the developmental hemostasis paradigm, specific gestational and postnatal age-related reference ranges should be used to avoid misdiagnosis[25].

It has been demonstrated that VCTs are reliable tests to predict bleeding, and for hemostatic monitoring and treatment[15,26]. At the same time, like many test procedures, VCTs are operator-dependent and as such are prone to preanalytical errors related to sample handling and processing. Nevertheless, the reproducibility of TEG in VLBW is high (coefficient of variation <10%) and provides reassuring data regarding its use in the NICU[27]. In addition, introducing automated analyzer systems should help further reduce preanalytical variability: the ClotPro system eliminates reagent handling with automatic pipettes with dried reagents contained in a small sponge in the tip[28]. Furthermore, defects in platelet adhesion or vWF deficiency are not identified by standard TEG analysis; therefore, modified TEG Platelet Mapping (TEG-PM) and ROTEM with a multiple-electrode aggregometry analyzer have been introduced to study platelet function[29].

VISCOELASTIC COAGULATION TEST TECHNOLOGY

TEG and ROTEM assess clotting kinetics by measuring the amount of a constantly applied rotational force that is generated and transmitted to an electromechanical transduction system by the developing clot. In both methods, 340 µL of whole blood is contained in a cylindric cup, and a pin is submerged in the sample. The pin is connected to a torsion wire or an optical detector in the TEG or ROTEM system. After the start of the analysis, the cup (in TEG) or pin (in ROTEM) begins to oscillate

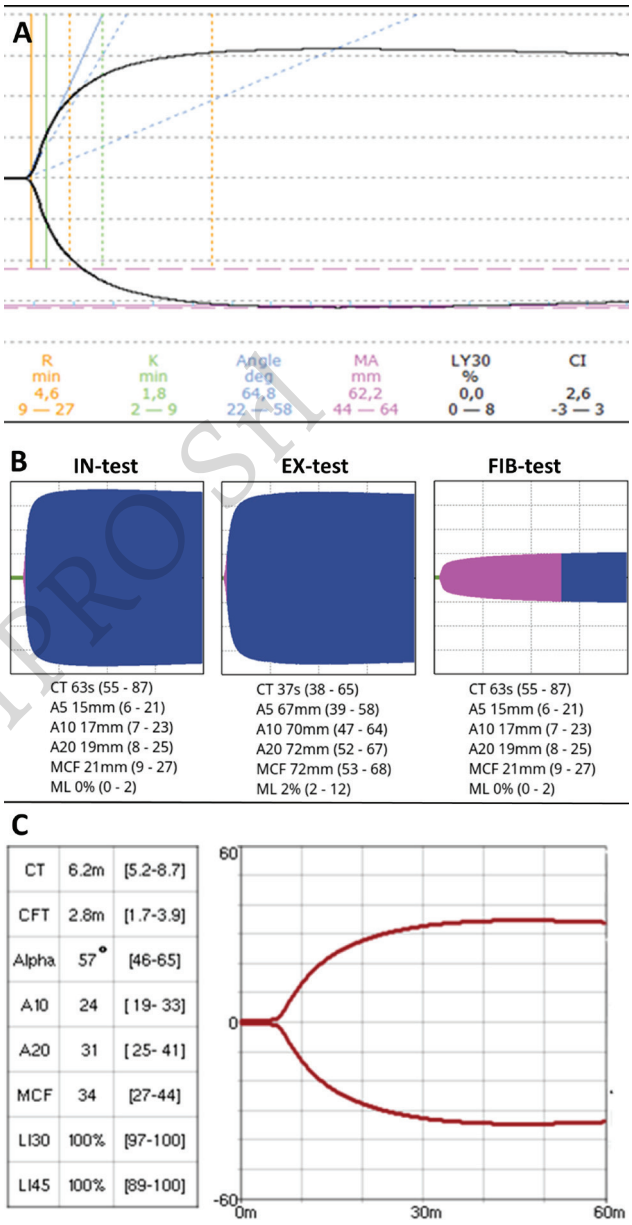

Figure 2 - Representative viscoelastic coagulation reading
(**A**) Thromboelastography (TEG) tracing (citrated whole blood) of a healthy term newborn on the first day of life. (**B**) ClotPro reading using EX-test, IN-test, and FIB-test in a one-month-old term newborn. (**C**) Viscoelastic coagulation monitoring of a healthy term newborn on the seventh day. A5: clot amplitude at 5 minutes; A10: clot amplitude at 10 minutes; A20: clot amplitude at 20 minutes; CFT: clot formation time; CI: coagulation index; CT: clotting time; K: kinetics time; LI30 or LY30: lysis index at 30 minutes; LI45: lysis index at 45 minutes; MA: maximum amplitude; MCF: maximum clot firmness; ML: maximum lysis; R: reaction time.

according to a definite angle. As coagulation occurs, the pin adheres to the clot, and rotation is transmitted to the torsion wire, detected by an electromagnetic transducer, and converted into electrical signals[30]. The amplitude decreases with the onset of fibrinolysis until the pin dissociates from the cup. The complete process gives a digital reading of clot formation and subsequent lysis generated by the integrated software (see **Figure 2A**).

TEG analysis can be performed with non-anticoagulated blood and can be processed immediately after sampling, because of its limited stability, or with citrated blood, which remains stable for between 30 minutes and 2 hours after sampling and needs to be recalcified before testing[31]. Over time, technical improvements have increased the performance of VCTs, such as reduced susceptibility to vibrations and automated pipetting[30].

The addition of different reagents allows different processes of coagulation to be investigated. For example, adding kaolin activates the contact pathway of coagulation and provides the same kind of information as the APTT. Likewise, adding heparinase neutralizes unfractionated heparin (UFH) in patients exposed to anticoagulants, such as those on extracorporeal membrane oxygenation (ECMO) or cardiac bypass. Finally, platelet inhibitors (such as abciximab or cytochalasin D) allow a qualitative analysis of the fibrinogen contribution to clot strength (**Figure 3A**)[30].

ClotPro is a newly developed viscoelastometric assay that uses elastic motion thromboelastography to assess blood coagulation[28]. The process begins when citrated whole blood is pipetted to an active-tip containing dried reagents. Blood mixed with reagents is subsequently

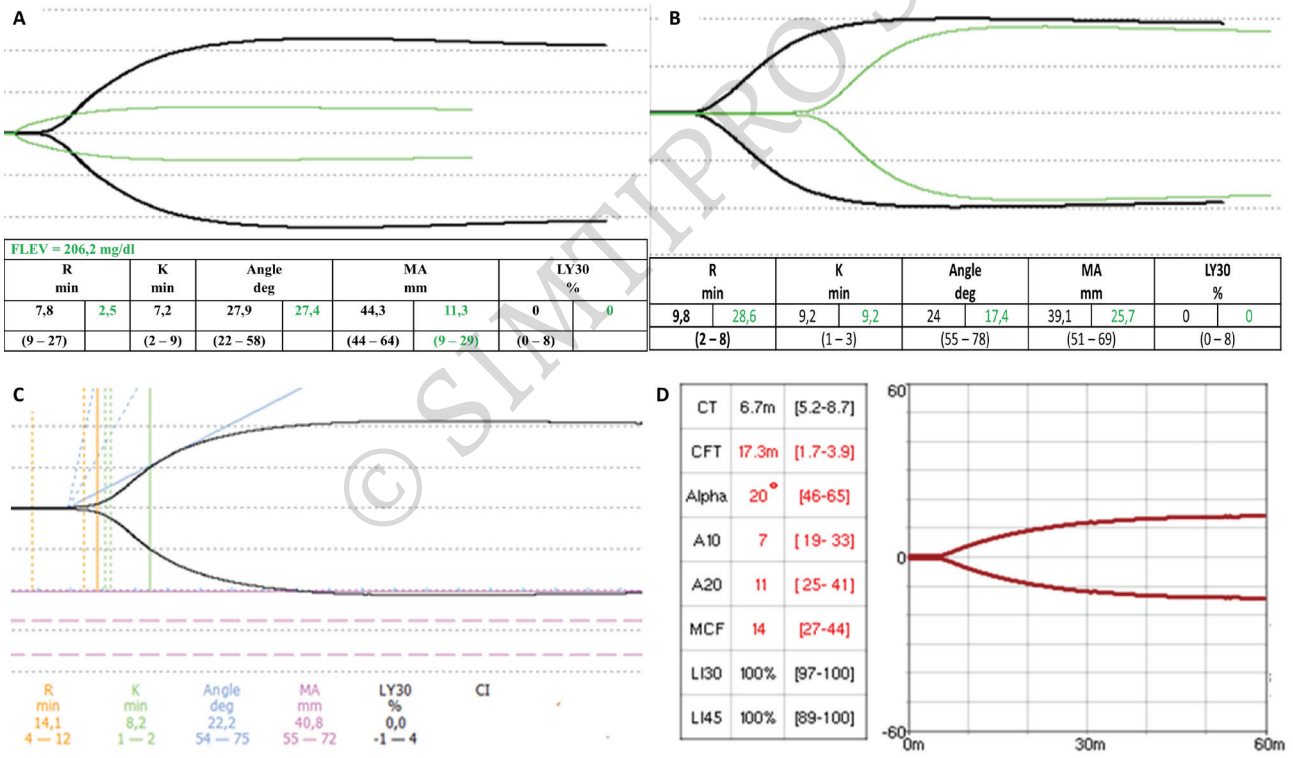

Figure 3 - Representative viscoelastic coagulation trace in specific conditions
(**A**) Comparison of thromboelastography (TEG) functional fibrinogen assay (FLEV-TEG) (green tracing) with citrated whole blood sample (black lines). (**B**) TEG during extracorporeal membrane oxygenation (ECMO). Effect of heparin on TEG testing during neonatal ECMO: the green lines represent kaolin activation without heparinase; the black lines indicate kaolin activation with heparinase. (**C**) TEG reading of thrombocytopenia in a preterm newborn (31 weeks of gestational age) on the 47th day of life. The blood count showed thrombocytopenia (24×10^9/L platelets). (**D**) Viscoelastic coagulation monitoring of thrombocytopenia in a preterm newborn (31 weeks of gestational age) on the first day of life. The blood count showed thrombocytopenia (platelets 44×10^9/L). A10: clot amplitude at 10 minutes; A20: clot amplitude at 20 minutes; CFT: clot formation time; CI: coagulation index; CI: coagulation index; CT: clotting time; FLEV: functional fibrinogen level; K: kinetics time; LI45: lysis index at 45 minutes; LY30 or LI30: lysis index at 30 minutes; MA: maximum amplitude; MCF: maximum clot firmness; R: reaction time.

transferred into the cup, which rotates using an elasticated system while the pin remains stationary[32].

ClotPro allows simultaneous analysis of up to 6 assays[28,33,34]. Examples of ClotPro traces using extrinsic coagulation test (EX-test), intrinsic coagulation test (IN-test), and fibrinogen test (FIB-test) in a term newborn are represented in **Figure 2B**. The main TEG, ROTEM, and ClotPro assays are summarized in **Table I**.

Recently, a small, portable VCM device has been developed that has several advantages, including the ability to perform an automated analysis in about one hour with only 300 microliters of non-anticoagulated blood. Blood is directly transferred from the syringe to the VCM cartridge after sampling without manipulation or the addition of activators[35]. A recent study has shown that VCM analysis can be performed in newborns using non-anticoagulated blood obtained by a heel prick. (A consolidated blood sampling technique in neonates, especially premature babies[36]).

VCM is extremely easy to use, making it a promising tool for assessing hemostasis in NICU[37]. An example of a normal VCM reading of a healthy term newborn is shown in **Figure 2C**.

The different assays share similar clinical applications and measure the same parameters using different terminology, as reported in **Table II**, but the results are not interchangeable.

Table I - *Summary of the main TEG, ROTEM, and ClotPro assays*

Description	TEG	ROTEM	ClotPro
Non-anticoagulated whole blood analysis	Native	NATEM	
Explores contact pathway of coagulation	Kaolin	INTEM	IN-test
Activates coagulation through tissue factor		EXTEM	EX-test
Activates coagulation through tissue factor and contact pathway	RapidTEG		
Contains heparinase that neutralizes UFH	HTEG	HEPTEM	HI-test
Blocks platelets and provides qualitative analysis of fibrinogen contribution to clot strength	Functional fibrinogen (FLEV-TEG)	FIBTEM	FIB-test
Contains aprotinin, an inhibitor of fibrinolysis		APTEM	AP-test

TEG: thromboelastography; ROTEM: rotational thromboelastometry; UFH: unfractionated heparin.

REFERENCE RANGES FOR VISCOELASTIC COAGULATION TESTING DEVICES

The establishment of neonatal TEG/ROTEM reference ranges has been problematic for many reasons, and are probably due to preanalytical variables, such as differences in sample timing and collection site (umbilical cord vs peripheral venous or arterial blood) and the anticoagulant used[23]. In addition, the correct

Table II - *A comparison of the main viscoelastic coagulation testing variables*[35]

TEG	ROTEM	ClotPro	VCM	Definition	Unit	Interpretation	Clotting process
R	**CT**	**CT**	**CT**	Time to reach a certain amplitude (2 mm in TEG/ROTEM, 1% above the baseline in VCM)	Minutes	Initiation of clotting	Clotting factors
K	**CFT**	**CFT**	**CFT**	Time necessary for clot amplitude to increase (from 2 to 20 mm in TEG/ ROTEM, from 1 to 10% in VCM)	Minutes	Kinetics of clot formation	Fibrinogen, platelets, Factor XIII
α	**α**	**α**	**α**	Angle of tangent line from R/CT to the slope of the curve	Degrees (°)	Rate of clot formation	
MA	**MCF**	**MCF**	**MCF**	Peak amplitude of the clot		Clot strength	Fibrin – platelets interaction, Factor XIII
LY30, LY60	**LY30 LY60**	**CLI30 CLI45 CLI60**	**LY30 LY45**	Amplitude of the clot at 30 or 45, or 60 minutes expressed as a percentage of MA/MCF	%	Clot stability and fibrinolysis	Antifibrinolytic activity
		ML		Maximum lysis in relation to MCF at any time point of measurement			

α: alpha angle; CFT: clot formation time; CLI: clot lysis index; CT: clotting time; LY: clot lysis; MA: maximum amplitude; MCF: maximum clot firmness; ML: maximum lysis; R: reaction time; VCM: viscoelastic coagulation monitor.

interpretation of VCTs requires age-specific reference ranges. In the past, evaluation of neonatal hemostasis was mainly based on cord blood samples, which are easily obtainable[38-42]. However, it has recently been demonstrated that placental blood samples are not suitable for measuring TEG/ROTEM parameters since they are not strongly correlated with hemostasis in newborns[43]. Therefore, other studies have established neonatal reference ranges using non-anticoagulated blood from preterm or term newborns[44-49].

VISCOELASTIC COAGULATION TESTS IN NEONATAL INTENSIVE CARE UNITS

The first clinical application of VCTs was reported in liver transplantation and cardiac surgery to guide blood transfusions and reduce bleeding. However, over the past few years, they have become more widely used in several clinical settings, such as polytrauma, obstetrics, and NICUs[23,24].

Preterm and critically ill neonates are at risk of hemostatic derangement, which can be multifactorial. Around 25% of all neonates admitted to an NICU experience at least one episode of bleeding, 11% of which are classified as major/severe[23].

Common neonatal clinical conditions, such as sepsis or asphyxia, may impair clotting[50,51]. Similarly, drugs such as ibuprofen/indomethacin or therapeutic hypothermia may impact neonatal hemostasis[52,53].

The risk of coagulopathy is further increased in neonates requiring ECMO, where coagulation alterations are among the main contributors to morbidity and mortality[54]. The exposure of the blood to the non-endothelial surface causes activation and subsequent consumption of both platelets and coagulation factors, and during ECMO, systemic anticoagulation is required to limit clotting within the circuit[15,55,56].

MONITORING OF PATIENTS AT RISK OF DEVELOPING A COAGULOPATHY

Neonatal sepsis

Sepsis still represents one of the major causes of mortality among NICU patients[57,58]. However, diagnosis in newborns is complicated by difficult to discern clinical signs, making sepsis indistinguishable from other non-infectious conditions[58]. In addition, coagulopathy frequently complicates sepsis, so early identification can allow prompt treatment before disseminated intravascular coagulopathy becomes clinically evident, possibly resulting in a poor outcome[50].

The diagnostic and prognostic role of VCTs has been extensively studied in septic adults. The ROTEM-derived lysis index is reported to be a more reliable marker of severe sepsis than IL-6, procalcitonin, and C reactive protein[15,59].

In neonates, VCTs appear to be promising assays in the detection of hemostatic disorder early in sepsis[59]. However, unlike adults, who show a hypercoagulable TEG/ROTEM pattern during the initial phase of sepsis followed by a "consumption coagulopathy", hypocoagulability has been observed as an early finding in neonates[59,60]. Notably, neonates with suspected sepsis tend to present hyper- rather than hypocoagulability, as indicated by increased alpha angle and clot formation time (CFT), with an increasing trend for maximal clot firmness (MCF)[59]. Furthermore, a possible correlation between disease severity and the degree of hypocoagulability has been reported, especially in cases of hemorrhagic diathesis[59]. A recent study investigated the role of the fibrinolytic system in neonatal sepsis through the ROTEM assay showing a fibrinolytic shutdown in septic newborns, which can be considered an index of severity; however, ROTEM-derived fibrinolytic parameters could not effectively discriminate septic neonates (**Figures 4A-C**)[61].

Intraventricular hemorrhage

Intraventricular hemorrhage (IVH) is one of the most devastating complications of prematurity which, in the first weeks of life, affects up to one in 4 infants born under 28 weeks gestational age, with an important long-term neurodevelopmental impact[23]. Hence, neonatologists have tried to identify predictors of IVH in premature babies[62]. Radicioni et al. compared the TEG profiles of 49 premature neonates with or without IVH in the first three weeks of life and found no significant difference between the two groups at birth. Surprisingly, newborns who developed IVH showed a hyper- rather than hypo-coagulant phenotype at TEG assay (shorter reaction [R] time and increased maximal amplitude [MA]) from birth onwards. Therefore, although TEG cannot predict the onset of IVH, thromboelastographic changes may aid in diagnosing severe occult bleeding[63].

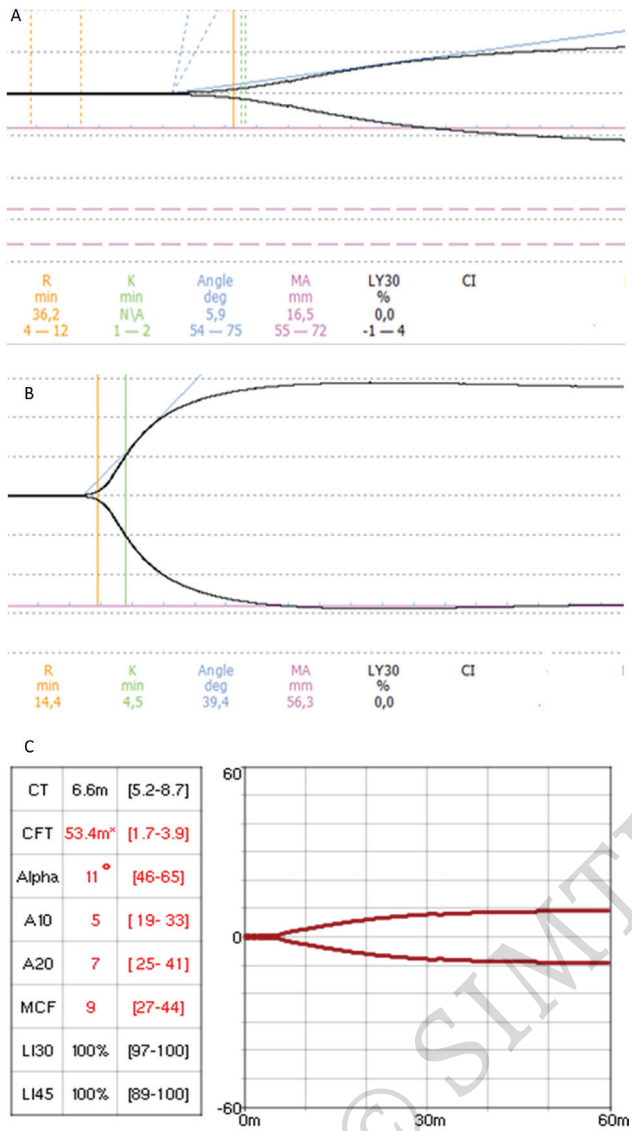

Figure 4 - Septic shock and disseminated intravascular coagulation

(**A**) Thromboelastography (TEG) of a term newborn who presented disseminated intravascular coagulation on the second day of life due to Klebsiella Pneumoniae ESBL + sepsis. Thrombocytopenia and coagulopathy were confirmed at blood count (26×10^9/L platelets, PT ratio 2.46, PTT ratio 2.11). (**B**) TEG was performed in the same patient after platelet transfusion (89×10^9/L platelets). (**C**) Viscoelastic coagulation monitoring of a very early preterm newborn (24 weeks of gestational age) who experienced a septic shock complicated by disseminated intravascular coagulation at six weeks of life. The blood count showed severe thrombocytopenia (2×10^9/L), hypofibrinogenemia (97 mg/dL), and prolonged PT (86 s) and APTT (91.4 s). Blood culture was positive for coagulase-negative Staphylococcus (Staphylococcus epidermidis). A10: clot amplitude at 10 minutes; A20: clot amplitude at 20 minutes; CFT: clot formation time; CI: coagulation index; CT: clotting time; K: kinetics time; LY30 or LI30: lysis index at 30 minutes; LI45: lysis index at 45 minutes; MA: maximum amplitude; MCF: maximum clot firmness; R: reaction time.

Perinatal asphyxia and therapeutic hypothermia

Birth asphyxia induces coagulopathy due to acidosis and hypoxia, with a systemic effect, including a direct insult to the liver and bone marrow. ROTEM has proven to be a reliable device in investigating the degree of coagulation abnormalities of asphyxiated neonates, who show a hypocoagulable extrinsic coagulation test (EXTEM) profile with a prolonged clotting time (CT) and CFT, and reduced α-angle and MCF when compared to healthy newborns[51].

This hemostatic derangement can worsen in neonates undergoing therapeutic hypothermia, the current standard of care to treat moderate-to-severe hypoxic-ischemic encephalopathy. Indeed, hypothermia can impair platelet function and reduce pro- and anticoagulant enzymatic activity. However, monitoring the thermic effects on hemostasis is challenging because standard coagulation tests are performed at 37°C, so they do not mirror the in vivo condition of a patient with a core temperature of 33.5°C[15,18,64]. VCTs could be the method of choice for hemostatic assessment in cooled patients since the analysis can be calibrated to the patient's temperature[65]. All TEG variables are altered under hypothermia, particularly kinetics (K) time and α-angle, reflecting the impaired clotting factor activity[64-66]. Although an association between TEG parameters and clinical bleeding in newborns undergoing therapeutic hypothermia has been reported, this should be further investigated in larger cohorts[65].

ANTICOAGULATION MONITORING

The role of TEG/ROTEM in anticoagulation monitoring has been explored in recent years, and a correlation between TEG R-time/ROTEM CT-time and heparin levels has been reported[26,67,68]. Hemostatic monitoring with VCTs during ECMO can be taken as an illustrative example.

Coagulopathy is one of the most common complications in neonatal ECMO and plays a large part in morbidity and mortality in critically ill neonates[69]. Indeed, the exposure of circulating blood to the non-endothelial surface of the circuit activates coagulation and inflammation resulting in a systemic inflammatory response syndrome[70]. In addition, platelet activation is further enhanced by the high shear stress within the ECMO circuit[55,56,70,71].

Systemic anticoagulation with UFH remains the standard of care to counterbalance this procoagulant state, but

it can lead to bleeding complications[70]. The particular characteristics of the neonatal hemostatic system further complicates the issue. Therefore, real-time and close anticoagulation monitoring during ECMO is crucial in order to reduce morbidity and mortality. Several tests are currently used for this purpose, with great variability across centers, each of which measures different functional and quantitative hemostatic variables. For example, APTT and anti-factor Xa tests are plasma-based, while activated clotting time (ACT) and VCTs are point-of-care whole-blood tests. In ECMO patients, paired VCTs tests with and without adding heparinase allow both the titration of UFH and the timely diagnosis of a patient's underlying coagulopathy in the presence of UFH, thus supporting the administration of blood products[72]. UFH responsiveness can be evaluated by comparing the difference in R or CT between the heparin reading and that of kaolin (**Figure 3B**)[73]. Standardized TEG/ROTEM-based algorithms to assess hemostasis during neonatal ECMO might provide information regarding which phase of the coagulation cascade is impaired and allow guided intervention, thus optimizing blood product use and patient outcome[74,75]. Recently, Henderson et al. established the specific threshold for the R-TEG parameter for predicting thrombotic events in neonates supported with ECMO[72]. However, further studies should focus on the role of VCTs as markers of bleeding and clotting complications during ECMO.

OPTIMIZING BLOOD PRODUCT USE

Packed red blood cell transfusions

Packed red blood cells (PRBC) are the most commonly transfused blood products in preterms[76]. Indeed, more than 60% of ELBW neonates require at least one PRBC transfusion even when a restrictive threshold is applied[76,77]. In these patients, transfusions can be a life-saving procedure, although they are associated with adverse outcomes, including retinopathy of prematurity, intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, and abnormal neurodevelopment[76,78]. Use of VCTs could reduce blood transfusion rates. For example, one randomized controlled trial has demonstrated that a ROTEM-based algorithm leads to early hemostatic intervention, thus reducing postoperative blood loss and the subsequent need for PRBC transfusions after pediatric cardiac surgery[79].

Platelet transfusion

Thrombocytopenia, defined as a platelet count <150×10^9/L, affects around 18-35% of newborns in NICUs, and up to 70% of EBLW neonates[80].

In non-bleeding patients, a low platelet count is the main indicator for prophylactic platelet transfusion. However, the platelet count threshold greatly varies depending on gestational and postnatal age, clinical conditions, the need to perform invasive procedures, and individual clinical experience. In addition to the degree of thrombocytopenia, other factors contribute to determining the bleeding risk, such as the use of some drugs that alter platelet function, cardiovascular stability, or some comorbidities (such as sepsis, patent ductus arteriosus, and pulmonary hypertension)[81].

Platelet transfusions are not without risk, and a restrictive platelet threshold has proved to be less harmful in premature infants. Platelets have a key role in hemostasis, but they also play a role in angiogenesis, inflammation, and immunity. Therefore, the transfusion of adult-derived platelets may have a detrimental effect on the neonatal hemostatic system, causing a pro-inflammatory state[23].

Therefore, it is essential to assess the whole hemostatic process with an essay that evaluates the contribution of both platelet count and function. In a recent case report, a pair of preterm twins with a May-Hegglin anomaly and severe thrombocytopenia at birth were managed with close clinical and hemostatic monitoring through VCM. Although the low platelet count was under the restrictive threshold for premature newborns, their hemostatic system was found to be competent, thus avoiding the need for platelet transfusions (**Figure 3C** and **D**)[82].

Fresh frozen plasma transfusions

Up to 15% of NICU patients receive fresh frozen plasma (FFP) transfusions, with a peak of 24% if preterm infants born under 27 weeks gestational age are included[83,84]. However, the benefit of FFP when used only to prevent bleeding (as reported in 42-63% of cases[16]) is still unconfirmed.

Current guidelines are based on poor-quality evidence resulting in a wide variability of neonatal care. It has been reported that FFP transfusion practice in NICUs is not compliant with the recommendation in around 26% of cases[19,84]. In addition, isolated prolongation of PT and APTT in neonates, in the absence of hemorrhages, is not a predictor of bleeding, and it should not be an indication

for FFP transfusion[19]. The decision as to whether to transfuse neonates should consider age-related changes in coagulation proteins[18].

Indeed, FFP transfusions are not free of collateral effects: they can cause infection or other severe and potentially fatal complications, such as transfusion-related acute lung injury (TRALI) or transfusion-associated circulatory overload (TACO)[83,85]. In addition, an association between early FFP transfusions (in the first 5 days of life) and venous thrombosis has also been reported[83]. Hence there is an urgent need to establish evidence-based guidelines for FFP administration in the neonatal setting.

As global hemostatic tests, VCTs can help provide tailored treatment and reduce inappropriate blood transfusions and the associated risks and cost, while potentially improving short- and long-term outcomes. The quick turnaround time (15-20 vs 45-60 minutes as in conventional coagulation tests) makes VCTs a promising procedure in the emergency care setting. At the same time, their global assessment may help guide the timely selection of blood products in case of bleeding[23,30]. It has already been shown that a project to improve quality of care based on TEG, staff training, and a shared transfusion algorithm can reduce FFP intraoperative transfusion rates in neonates undergoing surgery[86]. Therefore, implementing a TEG-based algorithm for FFP administration should be encouraged in order to standardize hemostatic management in NICUs.

FUTURE PERSPECTIVES

In recent years, our understanding of neonatal hemostasis has widened. However, some gaps in knowledge still persist; the role of vascular endothelium, for example, is often overlooked, even though evidence of its importance as a regulator of several processes is emerging[87].

Interpretation of neonatal coagulation assays may be challenging. In addition, technical difficulties in neonatal blood sampling, pre- and analytical errors, and the need for age-, analyzer- and reagent-related reference ranges complicate the diagnosis and management of hemostatic diseases in newborns. Therefore, the development of techniques that minimize sample handling and perform automated analysis should be encouraged to overcome these limitations.

Further studies should focus on defining normal ranges based on gestational and postnatal age. These should then be used to design randomized controlled trials aimed at confirming the beneficial role of VCTs as a hemostatic marker for acquired neonatal coagulopathy in terms of patient outcomes.

In this context, the role of PT and APTT remains paramount in congenital coagulation factor deficiencies[23].

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AUTHORSHIP CONTRIBUTIONS

FMa, GR, GSA, IA, VC, SGu, GCe, AT, MC, AA, SGh, and GCa contributed to study conception and design. FMa, GR, GSA, IA, SGu, VC, SGh, and GCa contributed to study methodology, investigation, and data management. FMa, GR, GSA, IA, SGu, VC, SGh, and GC wrote the first draft. GCe, AT, MC, AA, SGh, GCa, and FMo provided extensive critical revision. All Authors critically revised, read, and approved the final version for submission.

The Authors declare no conflict of interest.

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