REVIEW ARTICLE

Coagulation Reference Values and Indications for the Use of Plasma Derivatives in Neonates: A Narrative Review

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Abstract

Normal levels of coagulation factors in neonates are generally lower, which lead to prolonged clotting times, namely prothrombin time and activated partial thromboplastin time. These tests are frequently requested in neonatal intensive care units, and altered values are commonly found. However, these coagulation factor deficiencies are physiologic. Developmental hemostasis is a process that leads to the progressive increase of coagulation factor levels from birth to adulthood. It is crucial to define appropriate reference values for activated partial thromboplastin time, prothrombin time, and fibrinogen levels to avoid unnecessary transfusions. Physicians tend to prophylactically transfuse neonates in the presence of abnormal test results in an attempt to correct these deficiencies and decrease bleeding risk. As these changes are not associated with an increased risk of bleeding, namely intraventricular hemorrhage, most neonates do not require the transfusion of plasma products. In fact, transfusion of blood products has risks, and transfusion recipients should be carefully selected. This review aimed to determine the reference range values for fibrinogen and clotting times (prothrombin time and activated partial thromboplastin time) in neonates. Moreover, it was attempted to identify the specific indications for the transfusion of plasma derivatives. This review emphasizes the need for evidence-based reference ranges for coagulation tests (activated partial thromboplastin time, prothrombin time, fibrinogen), in preterm and full-term infants, as well as the importance of establishing universal guidelines for the transfusions of plasma products to ensure a standard clinical approach to this subject.

Keywords: Blood Coagulation Factors/administration & dosage; Blood Coagulation Tests; Blood Component Transfusion; Blood Coagulation Disorders/therapy; Infant, Newborn; Reference Values

Keypoints

What is known:

- Normal levels of coagulation factors in neonates are lower and lead to prolonged prothrombin time and activated partial thromboplastin time. These findings are physiologic but can be misinterpreted.
- Previous studies attempted to establish reference range values for coagulation tests to avoid unnecessary transfusions of plasma products.

What is added:

- Review of developmental hemostasis and reference range values for fibrinogen, prothrombin time and activated partial thromboplastin time in preterm and full-term neonates.
- Summary of current indications for plasma derivative transfusions and analysis of available products (fresh frozen plasma, cryoprecipitate, fibrinogen).

Introduction

Newborns, mainly very premature infants, have decreased levels of coagulation factors, which lead to prolonged clotting times, namely prothrombin time (PT) and activated partial thromboplastin time (aPTT).[1] These infants are at risk of bleeding complications, such as intraventricular hemorrhage, which can lead to severe neurologic sequelae, including cerebral palsy.[2] Several factors increase the risk of intraventricular hemorrhage, namely the inherent fragility of the germinal matrix and cerebral blood flow fluctuations. This risk is naturally increased by the presence of platelet or coagulation disorders which impair homeostasis mechanisms.[3] Nevertheless, the association between prolonged clotting times and intraventricular hemorrhage has never been proved, and gestational age continues to be the most important clinical predictor of a brain hemorrhage.[2,4]

Unnecessary routine screening of coagulation on admission to the neonatal intensive care unit contributes

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to neonatal anemia and often leads to the detection of prolonged clotting times and excessive use of plasma transfusion in the absence of bleeding in an attempt to correct these deficiencies, thereby decreasing this theoretical bleeding risk.[1,5]

Nonetheless, it seems that there are other factors in neonatal blood (high levels of von Willebrand factor, high hematocrit, reduced levels of natural anticoagulants) that compensate for these deficits and promote a well-balanced neonatal hemostatic system.[1] The establishment of normal coagulation values for preterm and term neonates is crucial to avoid futile transfusions. This review aimed to determine the reference range values for fibrinogen and clotting times (prothrombin time and activated partial thromboplastin time) in neonates. Moreover, it was attempted to identify the specific indications for the transfusion of plasma derivatives.

Methods

This narrative review is based on a thorough literature search of the Medical Subject Headings (MeSH) terms, including hemostasis or plasma or blood coagulation disorders and infant or newborn in PubMed / Medline and Cochrane database during the last 10 years. It should be mentioned that the articles written in English, Spanish, and Portuguese were retrieved in this study.

Furthermore, guidelines, systematic and narrative reviews, observational studies, and medical books together with other relevant sources were included, followed by the exclusion of incomplete / redundant papers. When applicable, references from the selected articles were also included. The abstracts of identified articles were assessed for relevance, along with screening of their references for further relevant publications. After this literature search, we included a total of 48 articles in the final review.

Neonatal hemostasis

The classical coagulation cascade model involves the interaction of clotting factors, followed by a series of enzymatic reactions via the contact activation (intrinsic) and tissue factor (extrinsic) pathways leading to a common pathway that results in thrombin formation.[1] The hemostatic system continuously evolves and matures from fetal to adult life, especially during the first months of life.[6] Maternal coagulation factors cannot cross the placental barrier due to their size. However, the clotting factor synthesis in the fetus begins during the fifth week of gestation, and at week 11, the blood becomes clottable.[6,7] Fetal coagulation factors increase with gestational age. In addition, at weeks 19-23 and 30-38 of gestational age, coagulation factors reach 10%-30% and 10%-50% of adult values, respectively.[8] At birth, the coagulation factors plasma levels of full-term infants are around half of those in adults.[6] This explains the lower levels of procoagulant and anticoagulant factors in preterm infants, compared to full-term infants, and full-term neonates, compared to older children and adults.[1] The vitamin K-dependent coagulant factors (II, VII, IX, and X), contact factors (XI, XII, and prekallikrein), and high-molecular-weight kininogen are approximately 50% of the adult values at birth.[7] The activity of vitamin

Table 1. Coagulation test recommended upper and lower limits

Post-natal age	Fibrinogen (mg/dL) Lower limit	PT Upper limit	aPTT Upper limit
Gestational age < 28 weeks			
-	71	21	64
Gestational age 28-34 weeks			
-	87	21	57
Gestational age 30-36 weeks			
Day 5	160	15	74
Day 30	150	14	62
Day 90	150	15	51
Full-term infant			
Day 5	162	15	60
Day 30	162	14	55
Day 90	150	14	50

aPTT - activated partial thromboplastin time; PT - prothrombin time.
Adapted from: Andrew M, et al. Development of the human coagulation system in the healthy premature infant. Blood 1988;72:1651-7,[10] Christensen RD, et al. Reference intervals for common coagulation tests of preterm infants (CME). Transfusion 2014;54:627-32,[15] and Andrew M, et al. Maturation of the hemostatic system during childhood. Blood 1992;80:1998-2005.[16]

K-dependent factors is further reduced in preterm infants to approximately 30% before 30 weeks of gestation.[1] Inhibitors, such as antithrombin, protein C, and protein S are also decreased in preterm and term infants.[2,9-11] Contrastingly, factors V, VIII, XIII, von Willebrand factor, alfa-1-antitrypsin, alfa-2-antiplasmin, alfa-2-macroglobulin, as well as C1 esterase inhibitor are within the adult range in the neonates.[1,7,9-11] According to some authors, the neonates can tend to have elevated levels of von Willebrand factor.[1] Hemostasis during the neonatal period has been summarized in both preterm and full-term newborns.[9,10] These authors were the first to explore developmental hemostasis in a series of articles describing reference values for coagulation parameters in healthy preterm and term infants from birth to 6 months of age.[9,10] More specifically, PT tends to normalize to adult levels by 1 month of age, while aPTT normalizes by 6 months of age. Adult levels of coagulation factors are mostly reached by 6 months of age although some factors only reach adult levels at 16 years of age.[11] The differences between preterm and term infants tend to be small, and by 6 months of age, both preterm and full-term infants have the same levels of factors of the coagulation system, apart from factor VIII, plasminogen, antithrombin, and heparin cofactor II.[10,11]

These studies reported that coagulation screening tests at birth were prolonged, and coagulation factor levels were low. These changes were correlated with the gestational age and postnatal age of the infant.[9,10] It appears that anticoagulant and procoagulant factors, as well as fibrinolytic protein levels, are changed not only with gestational age but also with birth weight.[6,12] It is believed that these changes might be part of a protective mechanism for neonates, as they may decrease the risk of thrombosis and/or bleeding in this age group. The understanding of the development of hemostasis is critical to ensure adequate detection, prevention, and treatment of thrombotic and hemorrhagic diseases in neonates. It is essential to effectively define gestational and post-natal age-dependent reference ranges for the components of the coagulation system of the newborn.[6]

Normal values

Given the uncertain and broad reference ranges of PT and aPTT in neonates, it is difficult to define coagulopathy in the newborn infant. In adults, it is defined as a PT or aPTT greater than 1.5 times the mid-point of the normal range.[13] Coagulation values, such as PT, aPTT, and fibrinogen, are frequently measured in preterm neonates.[1] An attempt was made to establish reference values of known coagulation factors and inhibitors in preterm and full-term infants from birth until 6 months of infant age.[9,10] Since then, other studies supported these findings through the analysis of different population of patients in various technical conditions. It was found only slight differences between the coagulation systems of healthy premature infants between 30-36 weeks of gestational age and full-term infants.[9,10] Thus, the period between 30-40 weeks of gestational age does not seem to be a time of rapid changes in the coagulation system.[14] Reference ranges (using 5th-95th percentile values) for infants under 34 weeks of gestational age were published. This study was conducted on a sample of 175 preterm neonates and measured fibrinogen, PT, and aPTT.[15]

A sample of 116 neonates under 30 weeks of gestational age whose blood was drawn at birth on days one and three, as well as fortnightly until 30 weeks corrected gestational age was studied. Prothrombin time, aPTT, and fibrinogen levels were measured.[2] The study estimated the median values (5th-95th percentile) of day one for different parameters for preterm (n = 106) and full-term infants (n = 15, control samples) at PT 17.5 seconds (12.7-26.6 seconds), aPTT 78.7 seconds (48.7-134.3 seconds), and fibrinogen 140 mg/dL (72-380 mg/dL). The same study did a serial analysis in preterm infants (n = 106) who did not receive plasma, and the results revealed a reduction of median values (10th-90th percentile) of PT and aPTT from day one to week two (Table 2).[2]

Other authors also tried to define the coagulation values of PT and aPTT for extremely premature neonates and described values of PT, aPTT, and fibrinogen which were obtained on day one of life of a retrospective cohort of 183 premature infants born under 27 weeks of gestational age.[17] In this cohort, the median values

Table 2. Coagulation test values on different post-natal ages

	Day 1	Day 3	Second week of life
PT	17.1 seconds (13.2-20.5 seconds)	13.7 seconds (11.6-16.2 seconds)	12.0 seconds (11.2-16.2 seconds)
aPTT	74.7 seconds (53.8-97.9 seconds)	49.3 seconds (35.3-68.3 seconds)	47.4 seconds (31.9-68 seconds)

aPTT - activated partial thromboplastin time; PT - prothrombin time.
Adapted from: Neary E, et al. Coagulation indices in very preterm infants from cord blood and postnatal samples. J Thromb Haemost 2015;13:2021-30.[2]

of PT, aPTT, and fibrinogen were estimated at 20.2 seconds (14.4-36.7 seconds), 67.4 seconds (34.9-191.6 seconds), and 140 mg/dL (50-480 mg/dL), respectively. These values were higher than those reported by other authors,[15] which could possibly be due to the use of distinct reagents and the source of the blood (cord blood *versus* neonatal blood).[17] All these studies support the hypothesis that upper limits for both PT and aPTT values are higher among healthy extremely preterm neonates than moderately preterm or term infants, which is in accordance with the previously mentioned concept of developmental hemostasis. However, both PT and aPTT decrease rapidly in the first few days after birth with significantly lower levels noted on day three of life, compared to day one of life in extremely preterm neonates.[2,14,15,17] There were other studies conducted on extremely preterm infants, however, with smaller sample sizes.[18,19] It was also confirmed that in 21 infants born at 24-27 weeks of gestational age, coagulation factors II, V, VII, and X had the lowest activity.[14,19]

A retrospective study that included 132 extremely preterm infants born at completed 23 to 27 weeks of gestational age and confirmed that the levels of activity of vitamin K-dependent clotting factors II, VII, and X were gestational age-dependent (their activity rises with increasing gestational age).[13] Yet, factors V and VIII were higher than those of vitamin K-dependent factors in these infants.[13] Some studies have proposed reference ranges for coagulation factors at birth in extremely low birth weight infants.[12,14]

These findings stress the importance of defining reference ranges for coagulation tests. However, other neonatal intensive care unit practices should be changed as well. It is important to stress that routine coagulation screening of neonates admitted to neonatal intensive care units should be avoided. It is known that PT and aPTT do not reflect *in vivo* hemostasis. Therefore, the use of these tests to routinely assess hemostasis in nonbleeding patients is questionable.[20] Coagulation screening should therefore be only performed on the selected neonates with evidence of bleeding or at high risk of disseminated intravascular coagulation (those with necrotizing enterocolitis or severe sepsis).[13] The above-mentioned reference values should be utilized with diligence, as the physician must bear in mind that the laboratory uses analyzer (reagents and equipment) and population-specific reference ranges. Ideally, laboratories should use the direct approach to define their own reference values.[21] However, establishing pediatric reference intervals is a complex and extremely difficult process (due to ethical limitations related to blood drawing in neonates), and laboratories tend to apply an indirect approach using appropriate statistical techniques to determine reference intervals in this specific population.[22] The choice of an appropriate method for this calculation depends on the many biological and technical factors connected with populations and laboratory equipment differences.[21]

Illness and decreased coagulation factors

Acquired and congenital hemostatic disorders in neonates are more difficult to diagnose due to the particularities of the coagulation system. Several conditions, such as prematurity, birth asphyxia, hypoxia, and intrauterine growth retardation, have been associated with hemostatic abnormalities.[14] Prothrombin time-international normalized ratio (PT-INR), aPTT, and D-dimer are all affected by placental abruption, birth asphyxia, and intraventricular hemorrhage.[23]

Asphyxiated preterm infants have decreased mean activities of coagulation factors favoring bleeding tendencies.[14] Additionally, these neonates develop thrombocytopenia, decreased platelet survival and function, and an increased risk for disseminated intravascular coagulation.[24] Septic neonates may develop thrombocytopenia and coagulopathy secondary to liver failure and/or disseminated intravascular coagulation.[24]

Hemostatic irregularities in the neonate can be due to a variety of etiologies that present more frequently within the neonatal intensive care unit such inborn errors of hemostasis, acquired thrombotic or hemorrhagic states, and imbalances of hemostasis secondary to another disease process or medical intervention (Table 3).[25]

Acquired diseases include disseminated intravascular coagulation, vitamin K deficiency, and liver coagulopathy:

- Disseminated intravascular coagulation leads to the formation of micro clots in the peripheral vasculature, which consumes the body clotting factors and precipitates bleeding. Neonates have a greater risk of developing disseminated intravascular coagulation, specifically when additional body systems have been compromised by a primary disease.[27] While sepsis remains the most

Table 3. Coagulopathies of the neonate that increase the risk of bleeding

Hereditary coagulopathy	Acquired coagulopathy
Haemophilia A and B	Vitamin K deficiency
Other factor deficiencies	Disseminated intravascular coagulation
	Liver coagulopathy
	Asphyxia

Adapted from: Revel-Vilk S. Neonatal haemostasis. Impact on bleeding and thrombosis. Hamostaseologie 2016;36:261-4,[24] and Eberl W. Diagnostic challenges in newborns and infants with coagulation disorders. Hämostaseologie 2020;40:84-7.[26]

common cause, many other disease processes may lead to disseminated intravascular coagulation (hypoxia-induced encephalopathy, necrotizing enterocolitis).[25] It is important to measure coagulation parameters in ill neonates with perinatal risk factors for disseminated intravascular coagulation as the presence of coagulopathy, thrombocytopenia, low fibrinogen, and elevated D-dimer suggests the diagnosis.[23] Treatment of causative agent of disease is vital.

- Vitamin K deficiency is considered rare due to the successful implementation of near-universal prophylactic treatment of newborns with vitamin K. However, this condition may still occur in the setting of limited prenatal care or following maternal medication use (anticonvulsants, rifampin, and isoniazid).[25]
- Coagulopathy of liver disease presents a complex set of problems that include both bleeding and thrombosis risks. Although there are significant hemostatic abnormalities due to impaired synthetic function, as well as defects in platelet number and function, procoagulant function, and regulation of fibrinolysis, these changes appear to be balanced by substantially elevated levels of factor VIII and von Willebrand factor.[28]

Some inherited diseases can manifest in the neonatal period including:

- Congenital protein C / protein S deficiency can manifest as *purpura fulminans* with necrosis of the skin, severe coagulopathy (disseminated intravascular coagulation), as well as arterial and venous thrombosis.[29]
- Hemophilia A (congenital factor VIII deficiency) and B (congenital factor IX deficiency) are commonly diagnosed during the neonatal period.[25]

Although many conditions can lead to increased bleeding risk due to the relative lack of anticoagulant factors, it has generally been accepted that neonates have a higher risk for acquired thrombotic states, particularly in the setting of extensive medical intervention.[25]

Indications for transfusion

Fresh frozen plasma

Fresh frozen plasma (FFP) is a human donor plasma frozen that is stored at -30°C eight hours after collection.[5] Fresh frozen plasma contains fibrinogen (400-900 mg/unit), albumin, protein C, protein S, antithrombin, and tissue factor pathway inhibitor. Each unit contains 250 mL and can be used as volume replacement in resuscitation.[30]

Fresh frozen plasma is often administered to neonates, and 5%-12% of all neonatal intensive care unit admissions receive at least one fresh frozen plasma transfusion.[31-33] Furthermore, FFP has been most frequently given to non-bleeding neonates (specifically critically ill newborns) in order to prevent bleeding and/or volume expansion in an infant with a massive capillary leak.[20] It was revealed in a study that the most common determining factor for the use of fresh frozen plasma was an association with a finding of an abnormal PT/aPTT which was misinterpreted as half of these neonates actually had normal coagulation tests for gestational age.[31] In another study, FFP was used in nonbleeding patients to correct abnormal coagulation parameters in an assumption that it would limit the risk of bleeding.[20] Other authors also conclude that 62% of infants who received FFP did not have signs of clinical bleeding and 14% had no coagulation tests prior to fresh frozen plasma administration.[34] A rate of 63% of fresh frozen plasma transfusions given for prophylaxis is indicated.[35]

These findings suggest that FFP is used inappropriately in many occasions. Recent studies have shown that fresh frozen plasma has little effect in correcting mild to moderate abnormalities of PT in non-bleeding neonates.[5,20] So far, there is no evidence to support the routine use of FFP for the correction of abnormal clotting tests, volume expansion, or prevention of intracranial haemorrhage.[13,33,36] Partial exchange transfusion for polycythemia or reversal of coagulopathy without bleeding due to warfarin toxicity are no longer indications for fresh frozen plasma.[33]

There are two main indications for FFP administration: to prevent bleeding and stop bleeding.[5] Fresh frozen plasma may be beneficial in neonates who have coagulopathy (PT and aPTT above normal limits or fibrinogen levels below the lower limit for the neonate gestational age and postnatal age) and one of the following[13,36]:

Table 4. Fibrinogen dosing according to the product available

RiaSTAP® / Haemocomplettan P®	Fibryga® / Octafibrin®	Clottafact® / FibCLOT®
Dose (mg/kg body weight) = [Target level (mg/dL) - measured level (mg/dL)] / 1.7 (mg/dL per mg/kg)	Dose (mg/kg body weight) = [Target level (mg/dL) - measured level (mg/dL)] / 1.8 (mg/dL per mg/kg)	Dose (mg) = [Target level (mg/dL) - baseline level (mg/dL)] x 1 / recovery (mg/dL) / (mg/kg) x body weight (kg) When 1 / recovery unknown: 53 mg/kg for < 40 kg 43 mg/kg for ≥ 40 kg

Adapted from: Huisman EJ, et al Pediatric fibrinogen part I. Pitfalls in fibrinogen evaluation and use of fibrinogen replacement products in children. Front Pediatr 2021;9:617500.[42]

- The neonate will undergo an invasive procedure that has a risk of significant bleeding.
- The neonate with clinically significant bleeding (including massive blood loss).

Neonates with sepsis, hypotension, hypoxia, or liver disease with a significant coagulopathy and bleeding or if they are at risk of bleeding from an invasive procedure should receive fresh frozen plasma (10-20 mL/kg and a dose of vitamin K). The response should be monitored clinically and by coagulation tests.[37]

There are other possible indications for FFP administration:

- Major bleeding in neonates with vitamin K deficiency: urgent treatment may be required and although four-factor prothrombin complex concentrate is preferable, FFP is an alternative therapy. Yet, every newborn should receive vitamin K.[13,38]
- Congenital deficiencies of single clotting factors for which no factor-specific concentrate is available.[36] Fresh frozen plasma is appropriate for the early management of severe hereditary protein S deficiency and protein C deficiency (if protein C concentrate is not available).[13] A symptomatic neonate can be treated with FFP every six to 12 hours until the newborn is stable and protein C activity remains above 10 IU/dL.[25] The treatment of hemophilia A and B is based on the replacement of the missing factors. However, fresh frozen plasma can also be administered.[25]
- Multiple coagulation factor deficiencies secondary to disseminated intravascular coagulation. Data on blood product support in children with disseminated intravascular coagulation are limited, and there are no guidelines for pediatric practice. Fresh frozen plasma contains all the coagulation factors and fibrinogen. Therefore, it is used in the first instance for disseminated intravascular coagulation with bleeding, reserving cryoprecipitate, or fibrinogen for persistent hypofibrinogenemia despite FFP.[23,25] Fresh frozen plasma may be beneficial in children with disseminated intravascular coagulation who have a significant coagulopathy associated with clinically significant bleeding or prior to an invasive procedure.[13] A recent Japanese study that included 985 neonates admitted to the neonatal intensive care unit found that the combination of recombinant human soluble thrombomodulin with FFP therapy was effective for neonatal disseminated intravascular coagulation at birth.[23]
- Coagulopathy due to liver disease may be associated with a variable degree of coagulopathy. However, recent evidence shows that the hemostatic system is reset with an accompanying reduction in the natural anticoagulants associated with an increased risk of thrombosis. There is no formal recommendation for fresh frozen plasma or cryoprecipitate transfusion in this setting. Standard coagulation tests may be misleading and do not reflect bleeding risk.[13]

Fresh frozen plasma is typically administered (10-20 mL/kg) over 30 minutes.[5,36,39] The fresh frozen plasma must be ABO compatible and safe (quarantined or subjected to pathogen inactivation).[36] The absence of viable leukocytes in FFP makes graft-*versus*-host disease and cytomegalovirus transmission impossible.[30] Screening and pathogen inactivation has reduced transmission rates of human immunodeficiency virus, as well as hepatitis B and C viruses.[30]

Regarding the success rate of FFP transfusion, which is defined as the normalization of neonatal clotting times, studies have found dose-dependent success rates of 40%-60%. This rate increased to 59%-68% if neonatal reference ranges for coagulation factors were considered.[1,30] The degree of correction is unpredictable. Therefore, clotting tests should be repeated after transfusion.[39]

Despite increased knowledge and evidenced-based indications for fresh frozen plasma use, a significant number of neonates continue to receive FFP outside recommendations.[33,39] Current guidelines for FFP administration in neonates are mainly based on poor-quality evidence, and this contributes to the high level of inappropriate fresh frozen plasma use. In addition, the age-related changes of coagulation proteins during infancy make it difficult to correctly diagnose coagulopathy in neonates and subsequently determine when FFP should be used.[39]

Fibrinogen

Fibrinogen is currently available as a plasma-derivative. However, there is insufficient experience with its use in the neonatal period.[36] Although fibrinogen concentrate is widely used instead of other sources of fibrinogen, such as FFP and cryoprecipitate, there is a lack of adequate knowledge that supports this approach. There is no evidence to support the use of fibrinogen over the other two products, as a recent Cochrane review revealed weak evidence to support fibrinogen concentrate in patients with bleeding.[40]

Although the theoretical benefit of fibrinogen supplementation to treat hypofibrinogenemia appears obvious, there is scarce evidence to support this practice, and it is unknown what the optimal fibrinogen replacement product is in the neonate. When cryoprecipitate is not available, fibrinogen concentrate is sometimes used to treat acquired hypofibrinogenemia.

However, there is no consensus on fibrinogen concentrate indications, thresholds, and doses for this product in the European statements or guidelines.[41] In some neonatal intensive care units in Portugal, where cryoprecipitate is not available, fibrinogen has been used as replacement therapy for hypofibrinogenemia with satisfying results.

Fibrinogen concentrate use in neonates seems to have several advantages, compared to cryoprecipitate, it can be administered more quickly, there is a smaller infusion of volume (1-3.5 mL/kg, compared to 5-10 mL/kg for cryoprecipitate), it has a superior pathogen safety profile, and low rates of adverse effects. Moreover, it only requires refrigeration for storage.[42] Regarding dosing recommendations, it depends on the fibrinogen concentrates on the market, and it is therefore recommended to consult the individual product information for specific dosing advice.[41]

Cryoprecipitate

Cryoprecipitate is used as a more concentrated source of fibrinogen than fresh frozen plasma and is primarily indicated when the fibrinogen levels are low. Transfusion is usually performed for fibrinogen levels < 80-150 mg/dL (depending on reference values for gestational and postnatal age).[13,43] There are several recommended dosages of cryoprecipitate transfusion that range from 2 mL/kg to 15 mL/kg.[43] Neonatal hypofibrinogenemia is most likely to be acquired due to disseminated intravascular coagulation or liver dysfunction. However, severe congenital hypofibrinogenemia may also occur.[13]

Although some authors believe that cryoprecipitate should be administered in the presence of isolated hypofibrinogenemia,[43,44] neonates tend to have lower fibrinogen levels without an increased bleeding risk. Therefore, most guidelines do not advise the correction of asymptomatic hypofibrinogenemia.[42] Transfusions seem to be acceptable in the presence of hypofibrinogenemia and bleeding or hypofibrinogenemia before major surgery (*eg* neonatal cardiac surgery).[13,36] When there is an acquired and severe hypofibrinogenemia, and there is a high risk of bleeding, transfusion can also be considered.[42] The optimal fibrinogen replacement product in neonates is still unknown, and Table 5 compares the two possible products that can be administered in this clinical scenario.

Consequences of prolonged coagulation times

Neonates, especially those born preterm, are at high risk of bleeding. Intraventricular hemorrhage is a serious complication that has a multifactorial etiology.[47] It has been suggested that coagulation disorders may play a role. The study of the level of factor VIIa and its effects on thrombin in preterm and full-term children concluded that the effects of factor VIIa on factor II in preterm infants could lead to an increased risk of bleeding.[48] In another study with a cohort of 195 neonates, no abnormal coagulation value, either alone or in combination, was able to predict hemorrhage

Table 5. Comparison between cryoprecipitate and fibrinogen

	Fibrinogen	Cryoprecipitate
Composition	Fibrinogen: 20 g/L. Each vial (50 mL) of fibrinogen contains 1.0 g (range = 0.9-1.3 g) >> Standardized fibrinogen content Purified fibrinogen - Human albumin - Arginine hydrochloride	Fibrinogen (varies widely): 3-30 g/L per unit. Varies 120-796 mg/15 mL Non-purified product Other components: - Fibronectin - Platelet microparticles - Coagulation factors VIII, XIII - von Willebrand factor
Storage	Lyophilized can be stored at room temperature >> allowing for easy storage, reconstitution, and administration	Frozen state >> maintained and shipped in a frozen state and then thawed and pooled before administration
Administration	Reconstitution in minutes can be rapidly administered to patient afterward	Kept frozen at -20ºC Thawed in 30-45 minutes Can be rapidly administered to the patient afterward
Total volume	50 mL for 1 g vial	70-120 mL for a 10 unit pool
Shelf-life	≤ 24 hours after reconstitution (less wastage)	< 4-6 hours after thawing (more wastage)
Safety	Virally inactivated (pasteurization) Pooled plasma from thousands of donations, a higher number of donor exposure	Does not undergo pasteurization or viral inactivation Multiple single donor units of cryoprecipitate (typically 5-6 units) are combined into a single pooled unit

Adapted from: Huisman EJ, et al Pediatric fibrinogen part I. Pitfalls in fibrinogen evaluation and use of fibrinogen replacement products in children. Front Pediatr 2021;9:617500,[42] Callum J, et al. Effect of fibrinogen concentrate vs cryoprecipitate on blood component transfusion after cardiac surgery. JAMA 2019;322:1966,[45] and Novak A, et al. Do we still need cryoprecipitate? Cryoprecipitate and fibrinogen concentrate as treatments for major hemorrhage - how do they compare? Expert Rev Hematol 2018;11:351-60.[46]

(intraventricular, gastrointestinal, or pulmonary) during the first week of life.[15] It was found that day one aPTT and PT values of 160 preterm infants were not associated with intraventricular hemorrhage.[2] This link remains debatable, and there is uncertainty about the role of specific coagulation factors in the etiology of intraventricular hemorrhage persists.[14]

Conclusions

Neonatal intensive care units should use evidence-based reference ranges for coagulation tests (aPTT, PT, fibrinogen) for preterm and full-term infants taking into account gestational and postnatal age and establishing evidence-based guidelines for transfusion to minimize the adverse effects and product wastage. Indications for transfusion should be clear. Although the indications for fresh frozen plasma usage are well established, there is still debate regarding the product of choice when treating hypofibrinogenemia. Routine coagulation testing on neonatal intensive care unit admission should be avoided as it could lead to increased plasma derivative administration without evidence of benefit. Further studies should be conducted to better define reference ranges and indications for transfusion.

Author Contribuitions

STBC participated in the study conception or design. STBC participated in acquisition of data. STBC participated in the analysis or interpretation of data. STBC participated in the drafting of the manuscript. MJP and AMG participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

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The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Valores de Referência de Coagulação e Indicações de Uso de Derivados de Plasma em Recém-Nascidos: Revisão Narrativa

Resumo:
Os níveis normais de fatores de coagulação em recém-nascidos são em geral inferiores, o que leva a tempos de coagulação prolongados, nomeadamente o tempo de protrombina e o tempo de tromboplastina parcial ativada. Estes exames são pedidos frequentemente nas unidades de cuidados intensivos neonatais e é comum estarem alterados. No entanto, estas deficiências nos fatores de coagulação são fisiológicas. A hemostasia do desenvolvimento é um processo que leva a um aumento progressivo dos níveis de fator de coagulação desde o nascimento até a idade adulta. É fundamental definir valores de referência apropriados para o tempo de tromboplastina parcial ativada, tempo de protrombina e níveis de fibrinogénio para evitar transfusões desnecessárias. Os médicos tendem a transfundir recém-nascidos profilaticamente na presença de resultados alterados nos testes na tentativa de corrigir essas deficiências e diminuir o risco de hemorragia. Como essas alterações não estão associadas a um risco aumentado de hemorragia, nomeadamente de hemorragia intraventricular, a maioria dos recém-nascidos não necessita de transfusão de produtos plasmáticos. Na realidade, a transfusão de hemoderivados tem riscos, e os recetores de transfusões devem ser cuidadosamente selecionados. Esta revisão tem como objetivo determinar os valores do intervalo de referência para o fibrinogénio e os tempos de coagulação (tempo de protrombina e tempo de tromboplastina parcial ativada) em recém-nascidos. Além disso, procurou-se identificar as indicações específicas para a transfusão de derivados do plasma. Esta revisão salienta a necessidade de intervalos de referência baseados em evidência para testes de coagulação (tempo de tromboplastina parcial ativado, tempo de protrombina, fibrinogénio), de prematuros e nascidos de termo, bem como a importância de estabelecer orientações universais para as transfusões de produtos plasmáticos para garantir uma abordagem clínica uniforme.

Palavras-Chave: Alterações da Coagulação Sanguínea/tratamento; Fatores de Coagulação Sanguínea/administração & dosagem; Recém-Nascido; Transfusão de Componentes Sanguíneos; Testes de Coagulação Sanguínea; Valores de Referência