CONTINUING MEDICAL EDUCATION

AN APPROACH TO DISORDERS OF HEMOSTASIS IN THE NEWBORN

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Hemostasis is the complex process by which blood vessels, platelets and coagulation proteins interact sequentially to prevent excessive hemorrhage following tissue injury(1).

A rational diagnostic and therapeutic approach to the bleeding neonate requires basic understanding of the hemostatic mechanisms that are unique to the fetus and neonate. These normal 'physiologic' variables that differ from those of older children and adults include impaired platelet function, diminished activity of certain clotting proteins and suboptimal humoral and cellular mechanisms of defence against excessive blood coagulation. In instances of severe infection, hypoxemia, hypovolemia, or acidosis, serious and often fatal hemorrhage may occur. In the following review a summary of normal hemostatic mechanism in the newborn is followed by clinical approach, laboratory investigation and management of a bleeding neonate.

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1. Hemostasis in the Neonate

Blood Vessels and Platelets

Capillary fragility is increased, particularly in the premature neonate(2). The mean platelet count in the term newborn infants is about $250 \pm 70 \times 10^9$/L. Although a slightly lower value is seen in normal preterm infants, *i.e.*, $223 \pm 80 \times 10^9$/L, a platelet count of less than 150×10^9/L indicates thrombocytopenia regardless of the gestational age(3). Even though the platelet count may near normal adult range, the neonatal platelets have diminished aggregation due to low molar ADP, 1-adrenaline, collagen, thrombin, and arachidonic acid. Aggregation to restocetin is, however, normal(4). Inspite of these observations, the bleeding time in normal term and preterm infants is the same as in older children and adults(5).

Coagulation Proteins

The major hemostatic defect in normal newborns is a reduction in activity of various clotting factors. Besides the deficiency of Vitamin K dependent factors II, VII, IX and X, there is also deficiency of contact factors XI, XII prekallikrein and high molecular weight kininogen(6,7). Factors V, VIII and XIII are present in concentrations approaching those of adults. Vitamin K-dependent factors are decreased to levels of 10-60% at birth(8). In the absence of Vitamin K, the levels drop to half of the

initial level by day two to three and then gradually improve over the next few days. The mean levels of these factors appear to be dependent on gestational age.

Fibrinolysis and Inhibitors of Blood Coagulation

Inspite of levels of plasminogen ranging from 50% in term infants to 25% in premature infants, the newborn infant displays an increased overall firbrinolytic activity which lasts for several hours. This activity does not correlate with gestational age(9), and plaminogen reaches adult levels by about 2 weeks. Decreased levels of antithrombin III (AT III) in normal full term and premature infants has been reported(10), preterm infants show a progressive increase of AT III from 28% at 28-32 weeks gestation to 60% at term, and adult levels are reached by about 6 months of age. Protein C levels are also decreased in the neonate, term infants displaying levels of 18-57%(11).

Hemostasis in the Fetus and Premature Infant

Visible evidence of clotting of fetal blood occurs at approximately 12 weeks gestation(12). Fibrinogen is measurable at this age and platelets can be seen on the blood smear, these platelets aggregate poorly and prolonged bleeding from puncture wounds is seen(13,14).

As discussed earlier the premature infant displays moderate deficiencies of the Vitamin K dependent factors, the contact factors, plasminogen and AT III. Interestingly, other procoagulants necessary for normal hemostasis are within the adult normal range even in the extremely premature infant, *i.e.,* factor VIII, V, fibrinogen, and platelets. Therefore, it is not surprising that 'thriving' premature infants show no bleeding tendency even when subjected to major surgery. Thus healthy premature infants do not bleed excessively but have limited reserve to compensate for decreased procoagulants, but sick preterms bleed excessively due to many pathologic conditions that may complicate their early lives(15).

2. Clinical Approach to the Bleeding Neonate

Hemorrhage in the newborn infant requires accurate diagnosis and prompt therapy. As with older children, a careful history and physical examination are of utmost importance and provide more information than a battery of tests(16).

The history should include a family history of excessive bleeding, focusing particularly on the mother. A chronic disease (*e.g.,* idiopathic thrombocytopenic purpura) in the mother prior to or during the pregnancy, an intrauterine infection, and serious complications of labor and delivery all may have adverse effects on hemostasis in the newborn. Pregnant women who are taking anticonvulsants (particularly Diphenyl hydantoin) may give birth to neonates with Vitamin K deficiency(17) and recent aspirin ingestion by the mother has been associated with postnatal hemorrhage in the infant(18). Records should be reviewed regarding details of the birth history, Vitamin K prophylaxis, and the clinical course of the infant in the nursery prior to the onset of bleeding, particularly with reference to the presence of factors predisposing to DIC.

Physical examination is directed towards identifying underlying diseases as well as determining the site and extent of

hemorrhage. It is found that the characterization of the infant as 'sick' or 'well' is useful(19). The differential diagnosis of bleeding disorders differs greatly in these two easily separable clinical circumstances. Most bleeding neonates are 'sick' with a serious non-hematologic disease, they are generally of a low birth weight and have clinical or laboratory evidence of congenital or acquired infection, hypoxemia or shock. Often the bleeding symptoms are overshadowed by other life threatening complications. Mechanical platelets consumption and/or intravascular coagulation and localized hemorrhage in the brain are the most common types of bleeding in these infants. 'A well-appearing' full term baby is, however, likely to have either immune thrombocytopenia, a hereditary bleeding disorder or Vitamin K deficiency(20).

Presence of petechiae usually represents a platelet deficiency or fragile vasculature. Localized petechiae are, however, often seen on the presenting part and are usually not indicative of generalized impairment of hemostasis(21). However, diffuse petechiae should always raise concern about the presence of moderate to severe thrombocytopenia. A deficiency of platelets may also cause easy bruising and mucosal or internal hemorrhage. Petechiae are not seen in coagulation disorders because primary hemostasis is normal in such circumstances. The severity of hemorrhage should be ascertained, because it determines the need for therapy. Most infants who are not bleeding but who have laboratory measurements reflecting impaired hemostasis do not require specific treatment.

3. Laboratory Tests

Tests *(Table I)* to screen for hemostatic defects should be readily available, accurate, specific and easy to perform on small quantities of blood(22).

TABLE I—*Screening Laboratory Tests to Evaluate Bleeding Disorders in the Neonate*

Test	Normal Values (Upper limits)			
	Adult and older children	Term infant (Vit. K not given)	Preterm infant (1500-2000 g)	Preterm (<1500 g)
Prothrombin time (PT-sec)	10-14 (14)	11-15 (15)	12-16 (17)	13-18 (18)
Partial thromboplastin time (PTT-sec)	25-35 (50)	30-40 (84)	30-50 (120)	80-108 (150)
Thrombin time (sec)	10-20 (20)	15-20 (20)	17-25 (25)	17-25 (25)
Fibrinogen (mg/dl)	175-400	175-350	150-325	–
Fibrin split products (μg/ml)	<10	<10	<10	–
Platelet count (per mm^3)	150-400,000	150-400,000	150-400,000	150-400,000

In most instances a platelet count, accompanied by careful review of the peripheral blood smear, PT, PTT and fibrinogen measurement suffice as screening tests(23). Unfortunately, problems may arise in obtaining specimens and in interpreting results of blood coagulation tests in neonates(24-26). Although blood for clotting tests is preferably drawn by venepunctre from a peripheral vein, adequate samples for necessary serial coagulation studies not only are difficult to obtain but also deplete these tiny babies of much of their blood volume. To attempt to remedy these problems, micro-methods have been described but they are not widely available.

A major barrier preventing easy interpretation of results of the PT and PTT is the wide range of normal values for these screening tests, especially in premature infants(27). Term infants who have received Vitamin K should not have values much greater than the upper limit of normal for older children, that is, 14 to 15 seconds for the PT and 35 to 45 seconds for the PTT (28,29). It is much more difficult to generalize about premature infants, but in general a PT greater than 15 seconds should be considered abnormal. The markedly reduced levels of contact factors in premature infants result in the PTT, being of little importance in the screening of these babies. Even strikingly prolonged PTT values are not associated with bleeding diathesis(30,31).

The values for normal newborns are essentially the same as adult values for the platelet count, bleeding time, and fibrinogen. In practice, premature infants within a clinical setting suggesting an acquired hemostatic defect (DIC, heparin contamination, liver disease, Vitamin K deficiency) are screened with a platelet count, fibrinogen level, PT, TT and FDP using the latex agglutination test. In the term infant, the bleeding time and KPTT are added to this battery. The accurate performance of coagulation tests in the newborn requires adherence to several technical details:

(*a*) Since newborns may be polycythemic, the amount of anticoagulant used should be decreased proportionately to the increased hematocrit value.

(*b*) Avoid tissue 'juice' contamination of blood samples by assuring free flow of blood from vessel or capillaries.

(*c*) If heparin is used to flush catheters used for blood samples at least 4 ml of blood should be withdrawn before obtaining the sample for coagulation studies in order to avoid heparin contamination.

(*d*) Blood for FDP determinations should always be collected in a tube containing fibrinolytic inhibitors in order to prevent *in vitro* fibrinolysis.

4. Management of Hemostatic Defects

The modalities of therapy of hemostatic defects include platelets, plasma, plasma concentrate replacements, exchange transfusions, Vitamin K, and anticoagulant or fibrinolytic therapy for thrombosis or consumption coagulopathy. The minimal hemostatic levels in a neonate who is otherwise well are as follows:

Fibrinogen 100 mg/dl, Vitamin K dependent factors: 20-30%; Factors V and VIII: 30-40%; Factor XIII 25%; and platelets 30-50 $\times$ 10^6/L. With the possible exception of Factor XI, the contact factors are not necessary for hemostasis. By and large, therapy is aimed at achieving these levels. However, infants may display bleeding tendencies at these levels due either to altered platelet function or abnormal anticoagulant effect of FDP.

Replacement Transfusions

Replacement therapy consists of repeated doses of fresh frozen plasma (10-15 ml/kg) or platelet concentrate packs to achieve clinical hemostasis and keep the platelet count above 25 × 10^9/L, fibrinogen level above 100 mg/dl and the PT shorter than 18-20 seconds (*Table II*). Correction of the PTT with fresh frozen plasma is difficult to achieve(32). With the exception of cryoprecipitates (to replace fibrinogen or treat hemophilia A), plasma concentrates are usually not used in the neonatal period, in particular, prothrombin concentrates may produce a tendency to thrombosis in the newborn infant with physiological deficits of AT III and protein C.

Exchange Transfusion

Although exchange transfusion has been reported to achieve hemostasis in infants with DIC(33,34), erythroblastosis fetalis(35,36), and severe liver disease in infancy(37), only a few controlled studies of the efficacy of the procedure have been done. Exchange transfusion could be recommended for correction of those hemostatic defects that would appear to respond poorly to replacement transfu-

TABLE II—*Guidelines for Dosage Requirements in Neonatal Hemostatic Disorders*

Disorder	Transfusion material	Dosage	*In-vivo* half life
Thrombocytopenia	Platelet concentrates	10 ml/kg	1-3 days
Hemorrhagic disease of newborn	FFP+	10-15 ml/kg	Variable
Consumption coagulopathy	FFP, Platelet concentrate	10-15 ml/kg	Variable
Afibrinogenemia	Cryoprecipitates	1 pack/3 kg infant	4-6 days
Factor II deficiency	Prothrombin complex, Concentrates of FFP	FFP 10-15 ml/kg	3-4 days
Factor VII deficiency			4-6 days
Factor X defiency			48-60 hours
Factor IX deficiency			20 hours
Factor VIII deficiency	Cryoprecipitates VIII concentrates	1 cryoprecipitate = 80 units*	12 hours
Factor V deficiency	FFP	10-15 ml /kg	15-24 hours
Factor XI deficiency	FFP	10-15 ml /kg	60 hours
Factor XIII deficiency	FFP	10 ml/ kg	6 days
von Willebrand's disease	Cryoprecipitates	1 pack/3 kg infant	4 hours

Adapted from Hathaway WE(14).

* A unit of the factor is the equivalent clotting activity in 1 ml of fresh normal plasma.

+ FFP = Fresh Frozen Plasma.

sions or in which volume overload is a significant clinical problem, *e.g.,* in patient with severe DIC and/or liver disease.

Heparinisation

The usual indication for heparin use in the neonate is treatment of large vessel thrombosis. Heparinisation is achieved by giving a bolus of 50 μ/kg followed by 25-30 μ/hour of heparin infusion(38).

Treatment of DIC and Thrombosis

The mainstay of therapy of DIC is removal or control of the triggering event. If the triggering event is successfully treated and the coagulation changes are not severe, the DIC resolves spontaneously. If the coagulation chances are severe, replacement therapy is advised. Infants with massive thrombotic disease and those with purpura fulminans should be suspected of homozygous protein C deficiency. These infants may respond better to replacement therapy with FFP (10 ml/kg) every 12 hour followed by Warfarin rather than heparinization(39).

Neonatal Thrombocytopenias

The management depends on the etiology of thrombocytopenia(40) and has not been discussed in the present article.

Ascertainment of the cause of excessive hemorrhage during the newborn period is usually not difficult. The history and physical examination provide information regarding whether the baby is 'well' or 'sick'. Infants in the former category usually have immune thrombocytopenia, Vitamin K deficiency(41), a congenital bleeding disorder, or hemorrhage from a local anatomical lesion. Infants in the latter group most frequently have disseminated intravascular coagulation, or consumptive thrombocytopenia(42). Easy to perform and widely available laboratory tests assist with the diagnosis and treatment. Therapy is directed at the underlying disease and is based on the location and severity of hemorrhage, not just on the presence of laboratory abnormalities.

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EMERGENCY TIPS

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Doppler Ultrasonography in Tortion of the Testes

Urgent treatment for torsion of the testes is necessary if the testes are to be preserved. The inaccuracy of clinical diagnosis is now well recognized, but an aggressive surgical approach has resulted in an 18-65% unnecessary operation rate. What is the value of Doppler ultrasonography is the diagnosis of testicular torsion? Bickerstaff *et al.*(1) report the use of Doppler ultrasonogrphy in 41 patients who underwent an emergency exploration of the scrotum because of suspected testicular torsion.

The final operative diagnoses were testicular torsion in 18 patients, epididymitis in 15 patients, and torsion of a testicular appendage in 8 patients. The sensitivity and specificity of the test for the diagnosis of testicular torsion were 67 and 83% respectively, and the predictive value of either a positive or negative result was 100. The precise technique of the Doppler examination is of critical importance if misdiagnosis is to be avoided. Most of the reported cases of misdiagnosis can probably be attributed to faulty technique. Testicular torsion can be diagnosed incorrectly as epididymitis if a pulsatile signal, originating from either the inflamed scrotal skin or the testicular artery proximal to the torsion is

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