

Review article

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Disorders in Hemostasis

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Neonatal bleeding is a common problem encountered in nursery rooms or neonatal intensive care units, especially among premature infants. Furthermore, owing to recent remarkable improvement of neonatology, survival rates of preterm neonates have increased; hence, neonatal bleeding cannot be emphasized enough. Since the total blood volume of neonates is small, bleeding can be one of the causes of morbidities and mortalities. Therefore, rapid diagnosis and immediate therapy is urgently needed. The patient's medical history including a familial history of a bleeding disorder or of a previously affected infant who suffered from bleeding along with maternal and neonatal drugs can provide important diagnostic clues. Presence of bleeding with or without petechiae and ecchymoses in a healthy term or late preterm infant with thrombocytopenia but normal prothrombin time and activated partial thromboplastin time strongly suggests a congenital bleeding disorder. For a sick infant who is bleeding from multiple sites, an acquired disorder such as disseminated intravascular coagulation is suspected. Intracranial hemorrhage in term or late preterm infants without a history of birth trauma is highly suggestive of coagulation disorders. The purpose of this review is to summarize recent advances in diagnostic methods as well as basic concepts of neonatal hemostatic disorders. First, an outline of background information will be presented followed by a discussion of primary and secondary hemostatic disorders as well as inherited and acquired disorders.

Key Words: Hemostasis, Newborn, Hemorrhage, Congenital bleeding disorder, Acquired bleeding disorder

Introduction

Neonatal bleeding is one of the common problems encountered in nursery rooms or neonatal intensive care unit (NICU), especially among premature infants. Neonatal thrombocytopenia is usually the most common cause of bleeding; however, coagulation problems also occur frequently, and these two conditions can co-exist¹⁻³⁾. Thrombocytopenia develops in 1-5% of newborns at birth and in 22-35% of all babies admitted to NICU, 20% of those patients undergo severe thrombocytopenic episodes³⁾. Since the blood volume of a neonate is small, bleeding can be one of the causes of morbidities and mortalities. Thus, a

rapid diagnosis and immediate therapy is urgently needed. Furthermore, owing to recent remarkable improvements of neonatology, survival rates of preterm neonates have increased and neonatal bleeding cannot be emphasized enough. The purpose of this review is to summarize recent advances as well as basic concepts of neonatal hemostatic disorders.

Definition of hemostasis and neonatal coagulation system

Hemostasis is a process regulating the formation and dissolution of fibrin clots to preserve vascular integrity. This

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is maintained by a balance between coagulation mechanisms, and fibrinolysis. Imbalances between these two factors make neonate susceptible to both hemorrhagic as well as thrombotic complications.

Neonatal coagulation system is unique and reflects a highly complex process. It is influenced by age, and the concentrations of the various coagulation systems components in neonates differ from those of adults^{1, 4-6}. In the neonate, plasma concentrations of vitamin K dependent coagulation factors (II, VII, IX, X) and contact factors (XI, XII, prekallikrein and high molecular weight kininogen) are about 50% of adult values^{3, 7}. Similarly, concentrations of naturally occurring anticoagulants, antithrombin, protein C, and protein S, are low at birth. Thus, the capacity of newborns to generate thrombin, a process dependent upon plasma concentrations of procoagulants, is reduced^{3, 4}. These are delicately balanced by the protective effects of physiological deficiencies of the inhibitors of coagulations, as well as the decreased fibrinolytic capacity found in infants^{8, 9}.

Approaches to diagnosing and treating bleeding neonates

While the presence of bleeding in a healthy term or near term infants, especially ones with normal platelet counts, is strongly suggestive of a congenital bleeding disorder or immune mediated thrombocytopenia, acquired disorders most often present in sick term or preterm infants^{1, 2}. The

presence of a family history of a bleeding disorder or of a previously affected infant together with a history of maternal and neonatal drugs can also be an important diagnostic clue^{1, 3}. Common presentations of congenital bleeding disorders are oozing from the umbilical stump, excessive bleeding from peripheral venipuncture or heel stick sites, large caput succedaneum and cephalohatomas without a history of significant birth trauma, and prolonged bleeding following circumcision, Hemarthrosis, usually seen in a child with hemophilia is rarely observed during the neonatal period. Intracranial hemorrhage in a term or late preterm infant without a history of birth trauma is highly suggestive of coagulation disorders^{2, 3}. When bleeding disorders are suspected, a stepwise approach including initial screening is required (Fig. 1). Initial screening test are a complete blood count with platelet number, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels⁴. When further investigations are required including factor assays, age-adjusted values must be used for correct interpretation^{2, 4-6}.

Disorders in primary hemostasis

Primary hemostasis is a process characterized by vessel contractions and platelet plug formation at the bleeding site. Neonates with primary hemostasis disorders apparently look healthy with normal PT and aPTT value but have decreased platelet counts. Disorders in primary hemostasis

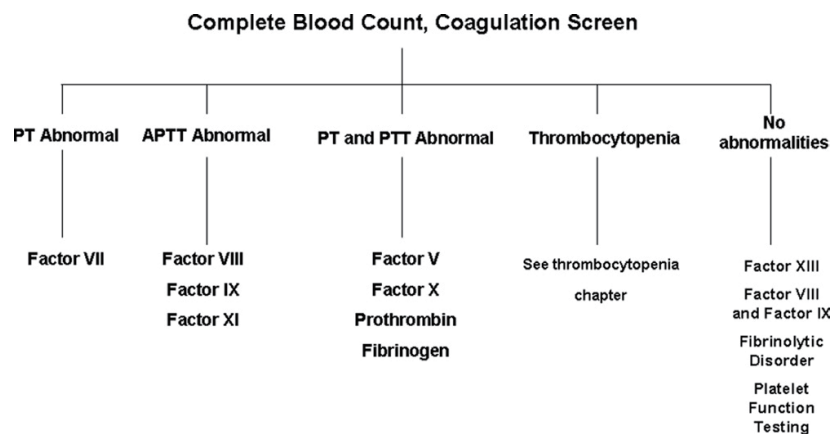


Fig. 1. Evaluation for suspected congenital bleeding disorders². Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; PTT, partial thromboplastin time.

in neonates include the following.

1. Neonatal alloimmune thrombocytopenia

Neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of severe neonatal thrombocytopenia and a life-threatening bleeding disorder. It is caused by maternal sensitization to paternally-derived antigens on fetal platelets that cross the placenta. These maternal IgG alloantibodies (antiplatelet antibodies) cross the placenta into the fetal circulation and lead to the destruction of fetal platelets, resulting in severe thrombocytopenia^{9,10}. This process is somewhat similar to hemolytic disease of the newborn by Rh (-) incompatibility in newborns¹¹. Unlike hemolytic disease, severe NAIT occurs during the first pregnancy in 40–50% of cases. Furthermore, if a newborn is affected with NAIT, the next child in the family will likely be more severely affected³. There are three platelet surface antigens; human leukocyte antigen (HLA) class I, human platelet antigen (HPA), and ABO antigen. The frequency of platelet antigen expression is different among ethnic groups. Immunization against HPA-1a and HPA-5b are responsible for up to 95% of cases of NAIT in the white population^{8,11,12}. However, HLA antigen is most frequently found platelet-associated antigen among Asians, including Koreans, instead of the HPA-1a antigen¹³. NAIT is usually suspected in neonates with bleeding or severe, unexplained thrombocytopenia. Intracranial hemorrhage (ICH) is the major cause of mortality and long-term morbidity in NAIT. Although there is a risk of hemorrhage due to severe thrombocytopenia at the time of delivery, it is reported that 80% of ICH associated with NAIT occurs in utero, with 14% occurring before 20 weeks and an additional 28% occurring before 30 weeks¹⁰. Any newborn infant with a low platelet count (usually $<50,000/\mu\text{L}$) is more likely to have NAIT. The diagnosis is based on detection and identification of the maternal HPA antibody and determination of the HPA genotype of both parents⁹. Differential diagnosis of severe thrombocytopenia includes congenital infections such as toxoplasmosis, rubella and cytomegalovirus; congenital heart disease, maternal immune thrombocytopenia, and

disseminated intravascular coagulation¹⁰. NAIT is primarily treated by random donor platelet transfusion. It is recommended to transfuse platelets if the count is less than $30,000/\mu\text{L}$. Maternal platelets are preferable because of their certain compatibility availability, and safety. Maternal platelets must be washed and centrifuged to remove maternal alloantibodies and irradiated to prevent graft-versus-host disease¹². Although antenatal treatment remains controversial, transfusion in utero immediately before delivery and maternal administration of intravenous immunoglobulin (IVIg) are seemed to be effective¹¹. Recently, Bussel et al. summarized appropriate protocols for managing newborns with NAIT and their mother^{14,15}.

2. Autoimmune thrombocytopenia

Transplacental passage of maternal platelet autoantibodies in mothers with autoimmune disorders such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, lymphoproliferative disorders, and hyperthyroidism may cause autoimmune thrombocytopenia (AIT)^{3,12}. The overall incidence of thrombocytopenia in the offspring of mothers with idiopathic thrombocytopenic purpura (ITP) is about 15–45% and severe thrombocytopenia is found in about 5–15% of newborns with affected mothers¹⁶. Newborns with thrombocytopenia secondary to maternal autoimmune disorders undergo a milder clinical course than ones with NAIT¹¹. Intracranial hemorrhage may occur in 3% in infants born to mothers with ITP. Maternal disease severity and/or platelet count during pregnancy can be used to predict the neonatal platelet count in most cases^{3,16}. The platelet count nadir in neonates born to mothers with ITP occurs not at birth but a few days after birth. Therefore, in thrombocytopenic neonates, the platelet count should be monitored daily at least for the first week of life³. Since newborns with AIT appear healthy, this condition is predominantly diagnosed by the clinical presentation of mother and infant as well as the exclusion of other known causes of thrombocytopenia^{3,16}. Treatment is recommended for any neonates with severe thrombocytopenia (platelets $<30,000/\mu\text{L}$) with IVIg regardless of whether or

not there is evidence of bleeding¹⁷⁾.

Disorders in secondary hemostasis

Secondary hemostasis is a process characterized by sequential activation of circulating coagulation factors by intrinsic and extrinsic pathways to form a final stable fibrin clot. Coagulation factors are not transferred through placenta from mothers to the fetus; thus, the values in the newborn reflect their ability to synthesize these factors. Since the coagulation factors are main component of this process, hence it is called as 'coagulation factor disorders'. Disorders in secondary hemostasis in neonates include the following.

1. Inherited diseases

1) Hemophilia

This is the most common congenital bleeding disorder presenting in the newborn period¹⁸⁾. Hemophilia is an X-linked, recessive disorder caused by a deficiency in the coagulation factor VIII (hemophilia A) and factor IX (hemophilia B). It occurs in 1/5000 male births, with approximately 80–85% of cases accounting for hemophilia A and 15–20% for hemophilia B^{12, 19)}. Recent wide surveillance studies by the United States Hemophilia Treatment Center network and the Universal Data Collection reported that out of 864 male infants aged 0–2 years with hemophilia patients, 633 (73%) were diagnosed within 1 month of birth. The reasons for diagnosis were carrier mothers (47.2%), familial history (23.2%), and bleeding events (28.8%)⁸⁾. Basis on the factor levels, hemophilia are classified as severe (<1% of the normal level), moderate (1–5%), or mild (5–40%). Severe hemophilia is the most common hereditary coagulation defect that manifests during the newborn period¹²⁾. A retrospective review evaluated bleeding episodes in 349 newborns with hemophilia; intracranial bleeding accounted for 27% of cases, bleeding from circumcision for 30%, and bleeding following heel puncture blood sampling for 16%¹⁹⁾. Any bleeding neonates with isolated aPTT prolongation with or without a family history should be evaluated for he-

mophilia. If hemophilia is suspected, specific factor assays, factor VIII and IX should be obtained. Because aPTT is somewhat prolonged in term and preterm infants during the first few weeks of life and those with mild forms of hemophilia, aPTT values may be normal value, and specific factor assays should be performed to confirm^{3, 19)}. The Medical and Scientific Advisory Council of the National Hemophilia Foundation in the United States recommends that factor VIII and factor IX activity levels should be evaluated in all term and late preterm neonates with ICH, even in the presence of normal screening coagulation results^{3, 20)}. Early genetic diagnosis can be made by chorionic villus sampling at 11 to 13 weeks of gestation or by amniocentesis around 16 weeks¹²⁾. Recommended treatment for hemophilia A or B is administration of factor VIII or factor IX concentrate, respectively. Fresh frozen plasma (FFP) may be used for patients with severe bleeding pending factor assay results^{6, 19, 20)}.

2) von Willebrand disease

Although this is the most common hereditary bleeding disorder, found in up to 1% of the general population, it is rarely seen during the neonatal period. This is because healthy neonates have elevated levels of von Willebrand Factor activity (vWF) with an increased proportion of high-molecular-weight vWF multimers compared to adults²¹⁾. Thus, type III von Willebrand disease (vWD) (the severe form, complete factor deficiency) can be diagnosed in neonatal period, whereas other mild type I or qualitative deficiencies (type II) are rarely diagnosed²²⁾. Rare clinical presentations reported in newborn are intracranial hemorrhage, thrombocytopenia, and soft tissue bleeds in vWD type III²³⁾. The optimal treatment for vWD is critically dependent on accurate diagnosis and sub-classification. Nonreplacement therapies including DDAVP nasal spray and antifibrinolytic agents, such as Amicar (Immunex Corporation, Seattle, WA, USA) after dental procedures are currently recommended treatment²⁴⁾.

3) Others

Most bleeding problems in neonates are acquired. Severe

congenital deficiencies in factor II, VII, IX, X, VIII, or XIII can present in the neonatal period⁸⁾. Clinical presentations of a severe factor deficiency include spontaneous bleeding or excessive bleeding following minor trauma in otherwise healthy infants⁸⁾. Following screening tests, evaluation of specific factor levels should be performed to make the correct diagnosis³⁾. Once confirmed, specific treatment is important to reduce complications and unnecessary side effects. Several cases of newborns and children have been reported in South Korea including: three cases of factor XII deficiency²⁵⁾, factor VII deficiency with hydrocephalus and intraventricular hemorrhage²⁶⁾, a case of factor V and VIII deficiency²⁷⁾.

2. Acquired diseases

1) Vitamin K deficiency

At first, the term “Haemorrhagic disease of the newborn”

(HDN) was coined by Charles Townsend in 1894 to describe bleeding in the early days of life which was not caused by traumatic delivery or hemophilia²⁸⁾. The link between vitamin K deficiency and spontaneous hemorrhage was first reported in 1929²⁹⁾. In 1999, Sutor et al.³⁰⁾ suggested to replace the term HDN to vitamin K deficiency bleeding (VKDB) since the former entity included any neonatal bleeding not associated with vitamin K. In general, VKDB is defined as bleeding due to inadequate activities of vitamin K-dependent coagulation factors (II, VII, IX, and X), corrected with vitamin K replacement. Newborns are at particular risk of vitamin K deficiency state, as placental transfer is limited and concentration of vitamin K in breast milk is poor. Vitamin K is a cofactor for γ -glutamyl carboxylase which is responsible for post-translational modification of some glutamate side chains to γ -carboxyglutamate (G1a; Fig. 2). Since G1a-containing proteins include the vitamin K dependent coagulation factors such as

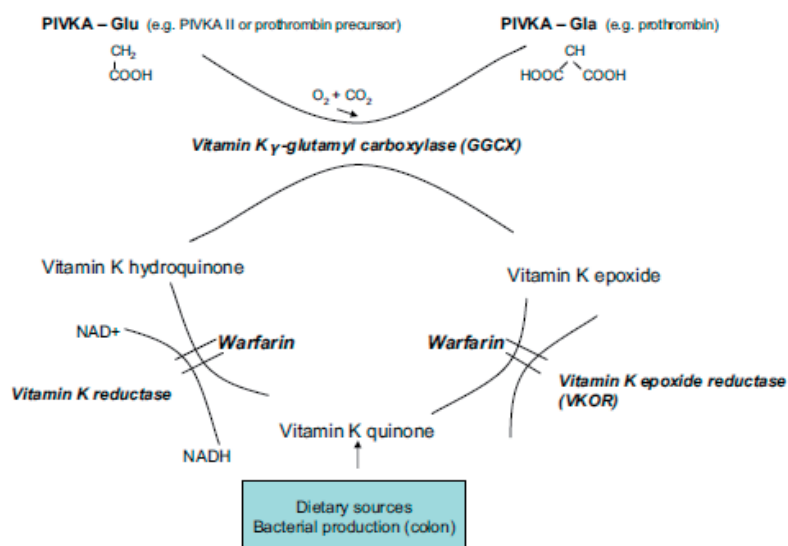


Fig. 2. The vitamin K cycle³¹⁾.

Table 1. Summary of the Available Recommendations about Vitamin K Administration in Neonates

Organization	Vitamin K dosage
American Academy of Pediatrics	Single intramuscular dose of 0.5 to 1 mg
Canadian Paediatric Society, Committee on Child and Adolescent Health, College of Family Physicians of Canada.	Single intramuscular dose of 0.5 mg (birth weight=1,500 g) or 1.0 mg (birth weight >1,500 g) within the first 6 h after birth
UK Department of Health in 1998	Single intramuscular or oral dose of 400 μ g/kg babies <2.5 kg) or 1 mg (babies >2.5 kg)
Italian Society of Neonatology (two alternatives)	Single intramuscular dose of 0.5 mg at birth, followed by 25 μ g/die orally from the 2 to the 14 week.

Adapted from Lippi and Franchini³⁹⁾

II, VII, IX, and X along with protein C, and protein S, bleeding occurs in vitamin K deficient states³¹. Vitamin K deficiency leads to the synthesis of undercarboxylated proteins that are unable to bind calcium and are hence inactive. Consequently, undercarboxylated forms of vitamin K-dependent coagulation proteins (proteins induced by vitamin K absence (PIVKA)) are released^{31, 32}. Clinical presentation of VKDB is classified into three forms by etiology and age of onset. Early VKDB presents within the first 24 hours of life and is seen in infants of mothers taking drugs which inhibit vitamin K. These drugs include anticonvulsants (carbamazepin, phenytoin, and barbiturates), antibiotics (cephalosporins), tuberculostatic agents (rifampicin and isoniazid), and vitamin K antagonists (coumarin and warfarin)³¹. Clinical presentation is often severe with cephalic hematoma and intracranial and intra-abdominal hemorrhage. Classic VKDB manifests on days 2 to 7 of life in breast-fed infants with delayed or insufficient feeding. VKDB rarely occurs in formula-fed infants because formula has a higher content of vitamin K (>50 µg/L) than that of breast milk (<5 µg/L)^{12, 33}. Clinical presentation is often mild, with bruises, gastrointestinal blood loss or bleeding from umbilical stump and puncture sites. Intracranial bleeding is infrequent in cases of classic VKDB. Without vitamin K supplementation, incidence in older reviews is estimated to be 0.25–1.7%³² whereas more recent reviews show lower rates of 0.01–0.44%³⁰. Late VKDB occurs between the ages of 2 and 12 weeks and is associated with exclusive breast-feeding. It is mostly secondary to disorders that compromise the supply of vitamin K, such as biliary atresia or other hepatobiliary diseases²⁹. Clinical presentation is severe, with a mortality rate of 20% and intracranial hemorrhage occurring in 50% of patients with this condition³⁰. The incidence is between 4.4/100,000 and 10.5/100,000 births³⁴. This disease is diagnosed by prolonged PT (international normalized ratio >3.5) in the presence of normal fibrinogen concentrations and platelet counts. Further confirmation is given by rapid (within 2 hours) normalization of coagulation tests results after vitamin K administration³⁰. PIVKA is a marker of

subclinical VKDB and can be measured after vitamin K therapy owing to its long half-life up to 70 hours³³. When VKDB is suspected, vitamin K should be immediately administered pending laboratory confirmation. Vitamin K should not be given intramuscularly to infants with VKDB, because large hematomas may form at the injection site. The safest and most effective route is subcutaneous³⁴. Several studies have demonstrated that prophylactic administration of vitamin K to newborns is effective for reducing VKDB. Although routine prophylaxis with 1 mg vitamin K at birth was adopted as a universal measure, methods for prophylaxis of vitamin K deficiency vary in different parts of the world (Table 1)^{35–39}. Oral prophylaxis with repeated doses is used in the Netherlands and in Germany³¹. The American Academy of Pediatrics (AAP) recommends that all infants receive 1.0 mg of intramuscular vitamin K on the first day of life³². Any oral vitamin K preparations are not licensed in the USA. Although no evidence-based recommendations for the appropriate dose are available for all premature infants, the first dose of vitamin K often is given as intravenously and current empirical dosages by AAP are as follows: 0.3 mg for infants <1,000 g and 0.5 mg for infants >1,000 g but <32 weeks of gestation³².

2) Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) may be the most common acquired disorder that occurs in a wide variety of clinical conditions in NICU. Several factors such as low plasma reserves in pro- and anticoagulant coagulation factors, intravascular volume contraction after birth, and a high incidence of hypoxia and sepsis in critically ill newborns rapidly lead to decompensation of the coagulation system^{40, 41}. It is not a primary diagnosis but a secondary process related to a variety of primary disease states. It is characterized by the widespread activation of coagulation, which results in the intravascular formation of fibrin and ultimately thrombotic occlusion^{40, 42}. The consumption of platelets and coagulation factors may in turn cause severe, diffuse hemorrhage^{41, 42}. Common etiologic disorders observed during the neonatal period include asphyxia,

respiratory distress syndrome, necrotizing enterocolitis, shock, infection, and meconium aspiration syndrome⁴³. Clinical presentations depend upon degree and duration of the hemostatic system activation, extent of impaired blood flow, and liver function. Affected infants, especially preterm babies, usually present with multiorgan failure and/or bleeding from multiple sites. However, some newborns with laboratory evidence of DIC may show few or no clinical signs. There is no single laboratory test or clear-cut diagnostic criteria that can confirm or rule out the diagnosis of DIC in newborns. However, in general, a diagnosis of DIC is made in ill neonates with thrombocytopenia, prolonged PT and aPTT, reduced fibrinogen, and increased D-dimers^{42, 43}. Morbidity and the risk of mortality vary depending on underlying clinical conditions and the severity of the coagulation disorder. The primary treatment strategy is to reverse the trigger of DIC by treating underlying disorders such as sepsis, hypoxia, and acidosis, as well as promoting general support of circulation, oxygenation, and blood pressure^{42, 43}. Additional therapeutic interventions include administration of FFP, cryoprecipitate, factor concentrates, and anticoagulants, and exchange transfusions. Recombinant factor VIIa has been used successfully to treat life-threatening bleeding in babies with DIC^{41, 43}. Another treatment option is the use of heparin to inhibit activation of the coagulation system and subsequently reduce the generation of excess thrombin in the early stages of DIC^{41, 44}. However, to date, no evidence is available to support the use of heparin to infants with DIC. Likewise, the use of anti-thrombin and protein C concentrates are still under investigation for its safety and efficacy^{45, 46}.

3) Liver disease

Acute liver disease or failure is rarely observed in the neonatal period. Coagulopathies of liver disease in newborn are similar to those in adults and reflect the failure of hepatic synthetic functions along with physiologic immaturity, activation of coagulation and fibrinolytic systems, poor clearance of activated coagulation factors, loss of hemostatic proteins into ascetic fluid, and splenic sequestration of

platelets¹². Common etiologies occurring hepatic dysfunction in newborns are viral hepatitis, hypoxia, total parenteral nutrition, biliary atresia, congenital heart disease with low cardiac output, inherited metabolic disorders, shock, and fetal hydrops¹². Clinical presentations are variable including ecchymosis, petechiae, mucous membrane bleeding, hemorrhage from gastrointestinal varices or into the abdomen, and ICH. Laboratory findings with liver diseases are elevated liver enzymes, direct hyperbilirubinemia, elevated ammonia concentrations, prolongation of PT and aPTT, thrombocytopenia, prolonged bleeding time, decreased plasminogen, increased fibrin degradation products, and D-dimer³. Neonates with bleeding may temporarily benefit from replacement of coagulation proteins with FFP, cryoprecipitate, platelet transfusion, recombinant factor VIIa, and vitamin K³. However, without recovery of hepatic function, replacement therapy is futile.

4) Heparin induced thrombocytopenia

Unfractionated heparin (UFH) is frequently used in NICU for the prophylaxis and treatment of thromboembolic events⁴⁷. HIT is a kind of drug-induced immune-mediated thrombocytopenic disorder. It is frequently complicated by thrombosis in adults who are exposed to UFH, and more rarely in those exposed to low-molecular-weight heparin⁴⁷. Mild to moderate thrombocytopenia (platelet count 40,000–100,000/L) usually occurs 5–14 days after the commencement of heparin therapy. Until now, the exact incidence of this condition in infants and children has been unknown. Diagnosis of heparin induced thrombocytopenia (HIT) is complicated by the lack of a definitive diagnostic test to confirm the presence of an immune reaction to UFH. HIT should be suspected in patients with thrombocytopenia (platelet nadir 20,000–100,000/L) who have been exposed to heparin and without any other identifiable causes⁴⁸. Other diagnostic tests include the platelet factor IV assay and heparin-induced platelet aggregation. Treatments include heparin withdrawal of heparin exposure along with non-heparinoid anticoagulation infusion^{47, 49}.

Conclusions

In summary, neonatal bleeding is a common problem encountered in nursery rooms or NICU. Since the survival rate of premature infant has increased tremendously owing to recent advances in neonatology, a number of different coagulation disorders may manifest during the neonatal period. When first evaluating neonates with bleeding, it is critical to recognize that the infant is term or preterm and looks healthy or sick. While bleeding in a healthy term or near term infant, especially in an infant with a normal platelet count, is strongly suggestive of a congenital bleeding disorder or immune mediated thrombocytopenia, acquired disorders are most often observed in sick term or preterm infants. Then, a stepwise approach including initial screening (complete blood count, PT, and aPTT) is needed followed by further investigations including factor assays. Early recognition of abnormal bleeding with immediate diagnosis in neonates is important and appropriate treatment for these neonates is required.

한글요약

신생아 출혈은 신생아실에서 흔하게 경험하는 증상 중 하나이며 신생아중환자실에서는 특히 미숙아에게 종종 발생하므로 신속한 진단 및 즉각적인 치료가 필수적이다. 신생아 출혈은 이 환율과 사망률의 중요한 원인이 되며 심한 경우 생명을 위협할 수 있다. 특히 최근 들어 비약적인 신생아학의 발달로 인해 초극 소저체중출생아를 포함한 미숙아들의 생존율이 높아지고 있어 혈액응고질환의 진단 및 치료의 중요성은 날로 높아져 간다고 하겠다. 출혈이 의심되는 신생아의 정확한 진단을 위해서는 출혈의 가족력, 산모의 병력, 과거 임신력, 신생아 및 산모의 약물 복용여부를 포함한 자세한 병력청취가 무엇보다 주의 깊게 시행되어야 하고 특정부위에 국한되어 증상을 보이는지 아니면 광범위한 출혈인지 감별을 해야 한다. 혈소판감소증만 단독으로 보이는 신생아의 경우 자반증(petechiae)과 반상출혈(ecchymoses), 점막출혈 등이 동반될 수 있으나 대부분은 건강해 보이며 비타민 K 결핍출혈, 혈우병 같은 선천성 응고장애를 의심해 볼 수 있으며, 아파 보이는 신생아에서 폐, 위장관, 비

뇨생식기계, 천자부위 등에서 출혈이 일어나는 경우는 파종성 혈관내응고증후군을 포함한 후천성 응고이상을 의심해 볼 수 있다. 특별히 외상의 흔적이거나 난산의 병력이 없는 만삭아나 준미숙아 등에서 두개 내 출혈이 보이는 경우에도 반드시 혈액응고이상 질환을 의심해 봐야 한다. 저자는 본 종설을 통해 신생아 출혈을 유발하는 혈액응고질환에 대해 임상유형 및 발생기전에 따라 대해 1차성 및 2차성 응고이상질환으로 나누어 알아보고 이를 다시 선천성 응고장애질환과 후천성 응고장애질환으로 나뉘 각각에 대해 최신지견을 토대로 자세히 살펴보고자 한다.

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