REVIEW ARTICLE

Approach to the Management of a Bleeding Neonate

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Abstract

Introduction*: Neonatal bleeding disorders are common in clinical practice but the laboratory tests required for making the diagnoses are often sophisticated, expensive and so, largely unavailable in the developing world. Thus, a simple clinical approach to the diagnoses and management of neonatal bleeding is desirable in the developing world.*

Methodology: *A review of literature was done using Medline search, texts on the topic were reviewed. The treatment modalities for each of the common causes of neonatal bleed as well as the limitations encountered in the developing world are also highlighted.*

Results: *Various methods are available for the evaluation of the bleeding neonate, clinical and laboratory with variable sensitivity. For ease of diagnosis in the face of limited laboratory facilities, bleeding babies can be divided into two broad groups: well babies with and without thrombocytopaenia as well as sick babies with and without thrombocytopaenia.*

Conclusion: *Using the parameters like the platelets count, prothrombin time, partial thromboplastin time, assays of fibrin degradation products and the clinical condition of the newborns, a large number of commonly encountered causes of neonatal bleeding disorders can be diagnosed to a fair extent.*

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Introduction

Neonatal bleeding is common in clinical practice and its importance lies in the associated morbidities and mortality. It is associated with such catastrophes because of the relatively small total blood volume of newborn infants as well as the tendency to be concealed in some cases. [1] Bleeding disorders had been reported to be a contributor to newborn morbidity and mortality in various centres in different parts of the developing world. For instance, haemophilia was reported to be common among Egyptian children. [2] However, there is a dearth of indexed literature on the epidemiology and burden of newborn bleeding disorders in Nigeria. A few Nigerian studies have shown that neonatal bleeding disorders occurred among 0.3% of babies in Calabar, [3] among 26.5% of out-born babies in Ibadan [4] and constituted 1.5% of newborn mortality in Sagamu. [5]

Paradoxically, it is in this resource-poor part of the globe that facilities for diagnosing and treating neonatal bleeding disorders are sparse. The use of blood and blood products in the developing world is fraught with many problems prominent among which are poorly stocked blood banks, the paucity of screening facilities for infections and the attendant risk of transmitting such infections as well as the lack of facilities to harvest the constituents of blood. [6] Therefore, it is imperative that physicians practicing in the developing world be familiar with a simple clinical approach to diagnosing neonatal bleeding disorder. This may improve case management and prevent unnecessary interventions which may not be totally innocuous after all.

Physiological peculiarities of neonatal haemostasis

Although, the platelets count is the same for adults as well as preterm and term babies (150 400 × 10^9/l), preterm babies are more prone to bleeding due to easy bruising arising mainly from increased fragility of their blood vessels. [7] The plasma levels of fibrinogen and clotting factors V and VIII in newborns are also near adult levels while those of factors II, VII, IX, X, XI, XII and XIII are very depressed in newborn infants. [7] These deficiencies are worse in preterm infants because hepatic synthesis of clotting factors ordinarily increase with gestation. [8] Anti-coagulation factors like anti-thrombin III, plasminogen and Proteins C and S are also remarkably low at birth. These deficiencies in the anti-coagulation factors protect neonates against abnormal bleeding despite the physiologic deficiencies in the clotting factors. [7]

Therefore, laboratory values of these parameters in the neonatal period should be interpreted with consideration for the maturity and age of the patient.

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Evaluation of Neonatal Bleeding

Bleeding disorder may arise *de novo* and it raises a lot of concern particularly when the site is unusual, when it is excessive or prolonged and when it involves multiple sites at the same time. Such episodes of bleeding may be due to illnesses causing platelets disorders (qualitative and quantitative), congenital defects of clotting factors or exaggeration of naturally occurring deficiencies in coagulation mechanisms.[1]

The first essential step in the evaluation of a bleeding neonate is to establish whether the bleeding infant is sick or not. This is important because the causes of bleeding among sick and well infants are quite different. An ill baby may have fever, hypothermia, lethargy or irritability, feed refusal, feed intolerance, poor colour or abnormal cry. Features of abnormal bleeding may include spontaneous umbilical oozing, oozing from injection and venepuncture sites, cephalohaematoma and subgaleal haematoma, petechiae, purpura, easy bruising and ecchymosis. Other manifestations include post-circumcision bleeding, bleeding into muscles and joints, mucosal bleeding like malaena, haematochezia, heamatemesis and haematuria. It may also be concealed in the cranium (usually within the ventricles, cerebral tissues or in the subarachnoid spaces) and manifest with features of raised intracranial pressure like seizures and altered sensorium.

A detailed history and complete physical examination is, therefore, essential in establishing the aetiology and severity of bleeding.

History:

Bleeding occurring soon after birth may be due to neonatal thrombocytopaenia (autoimmune or alloimmune), disseminated intravascular coagulopathy (DIC) or haemophilia. von Willebrand disease and other inherited clotting factor disorders very rarely occur in the neonatal period except in the presence of co-existing vascular abnormalities. [9] Classic vitamin K deficiency bleeding (VKDB) occurs typically between the 2nd and 5th days of life while the late form occurs between the 4th and 12th weeks of life. Babies who are exclusively breastfed or babies on *nil per oris* and prolonged antibiotic therapy are particularly prone to late onset VKDB especially if they are not given prophylactic vitamin K soon after birth.

Maternal febrile illnesses associated with exanthema or jaundice during pregnancy may suggest intrauterine TORCHES (toxoplasmosis, rubella, cytomegalovirus, herpes, Epstein Barr virus and syphilis) infection. Such intrauterine infections cause neonatal thrombocytopaenia.[10]Previous bleeding episodes in the mother may suggest autoimmune thrombocytopaenia following Immune Thrombocytopaenia (ITP) and systemic lupus erythematosus (SLE). [10] History of perinatal events like abruptio placentae and asphyxia are also usual in neonatal bleeding due to DIC. DIC occurs commonly in neonatal intensive care units as a complication of neonatal sepsis.[11]

Maternal ingestion of drugs like phenytoin, isoniazid and non-steroidal anti-inflammatory agents may increase the hepatic metabolism of vitamin K and predispose to VKDB. Quinine and sulphonamides therapy may also cause immune-mediated maternal and neonatal thrombocytopaenia.

History of previous neonatal bleeding and recurrent neonatal deaths may suggest neonatal alloimmune thrombocytopaenia (NAIT) although this may occur in the first pregnancy in about 40 to 50% of cases. [10] Similarly, family history of bleeding may suggest inherited disorders particularly haemophilias, von Willebrand disease and clotting factor deficiencies. Parental consanguinity may also predispose to disorders of platelet functions like Bernard-Soulier syndrome.[12]

Physical findings:

Apart from the tell-tale signs of bleeding (uncontrolled oozing, purpura, petechiae, ecchymosis, pallor and features of circulatory collapse), other aetiology - specific signs include the following:

Microcepahly, chorioretinitis, cataract and hepatosplenomegaly occur in TORCHES infection.
Prolonged jaundice and hepatomegaly may occur in hepatic diseases.

Seizures and apnea as well as severe respiratory distress may occur in severe cases of intracranial and pulmonary bleeding respectively.

Congenital hydrocephalus may occur from intra-uterine intracranial haemorrhage occurring in NAIT. Most bleeding in NAIT had been reported to occur *in-utero.*[13]
Rapidly-enlarging haemangioma may result in Kasabach-Merritt syndrome.[14]

Limb deformity especially absent radii occur in TAR (thrombocytopaenia, absent radii) which is a cause of inadequate platelet production

The differential diagnoses and steps in the laboratory evaluation of neonatal bleeding disorders are summarised in Figures 1 and 2.

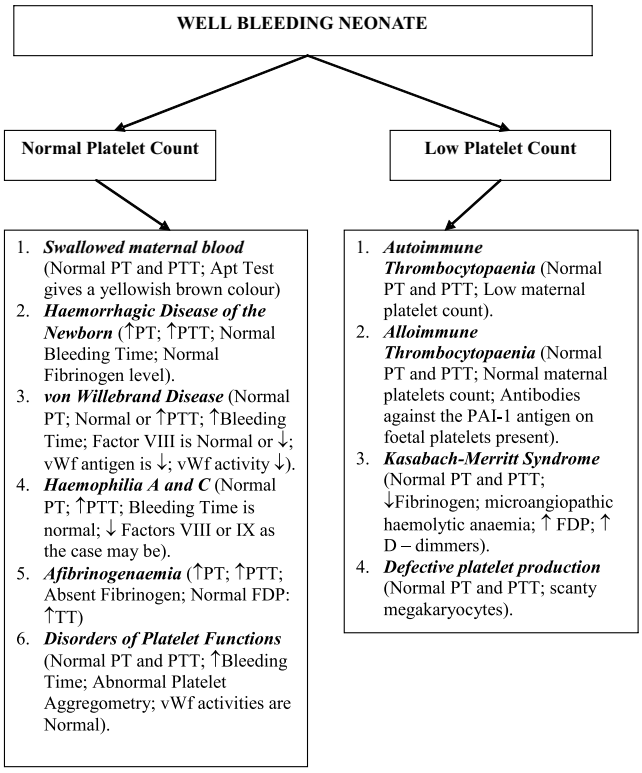

Figure 1: Evaluation of a well bleeding neonate

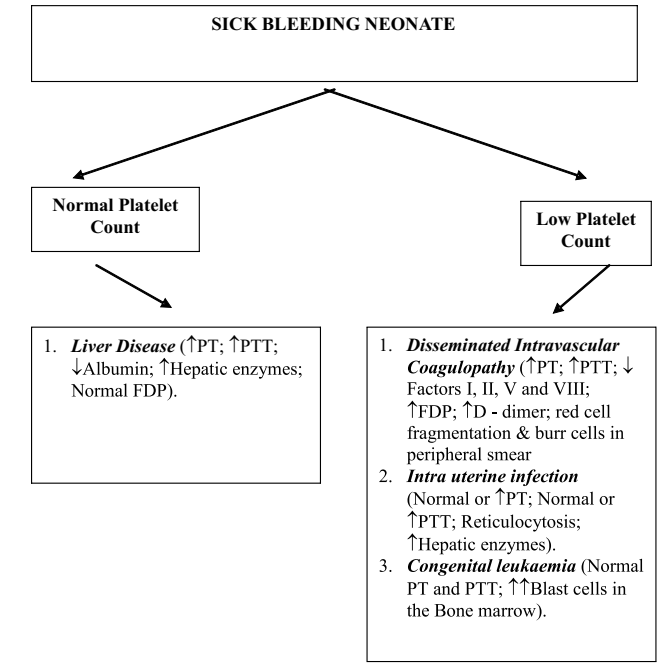

Figure 2: Evaluation of a sick bleeding neonate

Laboratory Investigations:

Complete blood count (CBC): The haematocrit may be abnormally low (<0.45) following severe blood loss and in the presence of TORCHES infection. The leucocytes are usually normal except in some cases of NAIT when neutropaenia may occur. The platelets count is very helpful in establishing the aetiology of neonatal bleed. Thrombocytopaenia is associated with DIC, septicaemia, TORCHES infection, NAIT, maternal immune thrombocytopaenia, Kasabach-Merritt syndrome and congenital disorders like TAR, Trisomy 18, Fanconi anaemia and Wiskott Aldrich syndrome. For congenital thrombocytopaenia, maternal platelets count must also be monitored. This is usually significantly reduced in autoimmune cases while it is within normal limits in alloimmune cases. In the latter condition, the mother is usually negative for the platelet antigen PAI-1a while the baby is positive for PAI-1a. Instructively, the PAI-1a platelet antigen is the commonest. On the other hand, VKDB, liver disease, haemophilia, vonWillebrand disease and disorders of platelet function like Glanzmann thrombastenia are associated with normal platelets count.

Blood film appearance: Fragmented erythrocytes and burr cells typically occur in DIC and Kasabach-Merritt syndrome. Reticulocytes and nucleated cells are increased in TORCHES infection. Giant platelets occur in maternal immune thrombocytopaenia, NAIT and Kasabach-Merritt syndrome while the platelets appear dysplastic in TAR and Bernard-Soulier syndrome.

Fibrin degradation products (FDP) and D-dimer: These are increased in situations of increased cell fragmentation like DIC and Kasabach-Merritt syndrome.

Apt test: This simple, cheap and reliable test helps to differentiate between neonatal gastrointestinal haemorrhage and swallowed maternal blood syndrome when neonates present with maleana or pseudohaemorrhage of the gastrointestinal system soon after birth. [15] It is based on the susceptibility of adult haemoglobin to denaturation by alkaline and the resistance of foetal haemoglobin to alkaline.

Bone marrow examination: This is relevant in cases of bleeding secondary to inadequate platelet production as it may occur in congenital leukaemia and Wiskott Aldrich syndrome where excessive blast cells and dysplastic megakaryocytes respectively are typical.

Liver function tests: Hyperbilirubinaemia, decreased serum albumin and deranged hepatic enzymes (Aspartate transaminase, Alanine transaminase and Alkaline transferase) characterize TORCHES infection and liver diseases generally.

Coagulation profile: Prothrombin Time (PT) measures the components of the extrinsic coagulation pathway and the normal value varies between 11 and 15 seconds. Partial Thromboplastin Time (PTT) measures the components of the intrinsic pathway and

the normal value ranges between 30 and 40 seconds. Thrombin Time (TT) measures the final pathway in fibrin formation. The normal value ranges between 11 and 15 seconds. Bleeding time (BT) assesses the platelets count or function and their interaction with vascular walls. The normal value ranges between 4 and 8 minutes but it is mostly determined by individual laboratories.[16]

Prolonged PT and PTT in the presence of reduced plasma fibrinogen characterize DIC, TORCHES infection, Kasabach-Merritt syndrome and liver impairment. PT and PTT are also prolonged but with normal fibrinogen level in VKDB. However, PT and PTT are normal in maternal immune thrombocytopaenias, NAIT, conditions of inadequate platelets production like congenital leukaemia, TAR, Trisomy -18 and Wiskott Aldrich syndrome. They may also be normal or marginally prolonged in vonWillebrand disease. TT is normal in VKDB and haemophilia but may be prolonged in DIC, liver disease and TORCHES infection. Only PTT is prolonged in haemophiliacs while PT is usually normal. Bleeding time is typically prolonged in thrombocytopaenia and in situations of poor platelets function like von Willebrand disease, Bernard Soulier syndrome and Glanzmann thrombasthenia.

Plasma clotting factors profile: This measures the plasma levels of the various clotting factor using individual factor-deficient plasmas. However, with the exception of afibrinogenaemia and haemophilia most clotting factor deficiencies are uncommon in the neonatal age.

Mixing study is used to determine the cause of prolonged PT or PTT. For example in haemophilia, the mixture of normal plasma and suspected haemophiliac plasma in 1:1 ratio typically corrects the prolonged PTT and establishes the diagnosis of Factor VIII or IX deficiency. This is based on the fact that 50% level of a clotting factor is adequate to produce normal coagulation, hence the correction of prolonged PTT or PT.

Platelet aggregometry: Activation of platelet-rich plasma from a suspected case of platelet dysfunction with a platelet aggregation agonist like adrenaline or collagen corrects the dysfunction. Reduced platelets aggregation characterizes conditions of platelets dysfunction like Bernard Soulier syndrome and Glanzmann thrombasthenia.

Imaging Studies: Transfontanelle cranial ultrasonography, computerized tomographic scan (CT scan) and magnetic resonance imaging (MRI) are important for the exclusion of intracranial haemorrhage. ICH is a common complication of neonatal intensive care and it may be asymptomatic ("silent") or severely symptomatic. It is commoner among preterms; more than 50% of preterm babies have intraventricular bleeding.[17] Although, the exact role of haemostatic disorders in the pathogenesis of ICH in preterm infants is undefined, conditions like VKDB, NAIT and DIC have been associated with ICH,[18, 19] hence, the need to conduct imaging studies in affected babies. Prompt intervention may limit the extent of damage and so, the degree of neurologic sequelae thereof. Unfortunately, such imaging facilities are not available for routine use in most parts of the developing world.

Management Guidelines

Although, the main goal of the management of bleeding disorders is the correction of deficient coagulation factors, the treatment depends on the aetiology and severity of the bleeding. This is best done in consultation with experienced paediatric haematologists. Sometimes, rapid expansion of the intravascular compartment with 20mL/kg of either whole blood or plasma prevents or combats life-threatening shock particularly, when bleeding is severe. The products used in the management of coagulopathies include (i) fresh frozen plasma (FFP) containing all clotting factors (10-20ml/kg), (ii) cryoprecipitate containing fibrinogen, Factors VIII and XIII and vonWillebrand factor, (iii) Factor VIII concentrate (25-50u/kg) and (iv) platelet concentrate (1-2u/5kg).[20] However, clinical practice in the developing world is compounded with lack of the facilities to produce these concentrates, hence, the over-reliance on fresh whole blood and fresh plasma transfusion in the management of neonatal bleeding. In the face of poor screening facilities for antigens and infections, the use of blood is obviously fraught with various immunologic and infectious risks.[6]

The treatment modalities for some common causes of neonatal bleeding are as follows:

Vitamin K Deficiency: Prophylactic management with intramuscular Vitamin K_1 (0.5 mg to 1 mg for term babies and 0.5 mg for preterm babies) soon after birth is recommended. It may also be given orally at 2 mg per dose soon after birth, between days 3 and 5 of life and at 2 weeks of age.[7] When bleeding is established, 1-3 mg Vitamin K_1 is given intravenously as intramuscular injection poses the risk of intramuscular haematoma. This drug acts within a few hours of administration. The use of FFP is, however, recommended when bleeding is severe.

DIC: The primary condition must be treated. Replacement therapy with platelets concentrate, cryoprecipitate and FFP is helpful. Plasma fibrinogen level must be raised to about 100mg/dl. When bleeding is severe, double-volume exchange blood transfusion with 160mL/kg of fresh whole blood may be helpful. Interestingly, anticoagulant therapy for DIC has not been shown to be helpful among neonates. Therefore, refractory cases must be jointly managed with experienced paediatric haematologists.

TORCHES infection and Liver diseases: Treatment of the underlying aetiology coupled with replacement therapy with platelets concentrate, cryoprecipitate and FFP.

Thrombocytopaenias: The goal of treatment is to raise platelet count above 100,000/mm^3 in a bleeding infant. Transfusion with one unit of platelets concentrate would raise the platelets count by 50 × 10^9 per 5kg body weight in the absence of peripheral destruction of the cells. The treatment guidelines stipulate that platelet transfusion is recommended if the platelets count is < 30 × 10^9/L with or without bleeding, at the count of 30 - 49× 10^9 /L if any bleeding occurs and at the count of 50 - 99 × 10^9/L if any major bleeding occurs. When the platelets count is >99× 10^9/ L, platelets transfusion is unnecessary. [21] Although, the details of platelets transfusion are beyond the scope of this literature, it is important to note that there is preference for HLA-matched, irradiated and rhesus-negative platelets to minimise the problem of alloantibody formation, Graft-Versus-Host-Disease and rhesus isoimmunization respectively. These conditions may be difficult to meet in most centres in the developing world due to lack of facilities and infrastructural supports. In addition to platelets concentrate, intravenous Immunoglobulin 1-2g/kg and short-course high dose hydrocortisone therapy may also be given in cases of autoimmune and alloimmune thrombocytopaenia. [10]Prenatal administration of IV Immunoglobulin had also been shown to reduce the postnatal occurrence of NAIT in the infant. [22] The first baby affected by NAIT in a family is usually delivered undiagnosed but elective caesarean section may be needed for subsequent pregnancies to reduce the risk of spontaneous bleeding, particularly, ICH.

Haemophilia: Replacement therapy with lyophilized concentrate of Factor VIII or IX is recommended depending on the severity of bleeding. The target of this therapy is achievement of 100% activity of Factor VIII or 100u/dl plasma level. However, recombinant DNA forms of Factors VIII and IX are preferred because of the eliminated risk of transmission of infections. For mild bleeding, 10-25u/kg of Factor VIII and 15-30u/kg of Factor IX are administered bolus intravenously. When bleeding is life threatening, 50u/kg of Factor VIII is given bolus IV and it is maintained with 8-10u/kg/hour by infusion; Factor IX is given as 75-100u/kg bolus IV and it is maintained with 5u/kg/hour infusion. [7] Often, physicians are faced with extreme difficulties in harvesting and preserving these blood products due to dearth of appropriate laboratory facilities and supportive infrastructure.

Conclusion

Using the parameters like the platelets count, prothrombin time, partial thromboplastin time, assays of fibrin degradation products and the clinical condition of the newborns, a large number of commonly encountered causes of neonatal bleeding disorders can be diagnosed to a fair extent. The facilities for measuring these few parameters are available in most centres which offer specialist neonatal services in the developing world. Therefore, with the diagnosis made, appropriate treatment modalities can be worked out in conjunction with experienced paediatric haematologists using appropriate technologies.

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