Review Article

VITAMIN 'K' DEFICIENCY HAEMORRHAGIC DISEASE OF NEW-BORN AND PRESENT CONTROVERSIES

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ABSTRACT

Vitamin K deficiency haemorrhagic disease of newborn (HDN) is a well known entity and presents in 3 different clinical forms - early, classical and late. The coagulopathy is due to deficiency of vitamin K dependent procoagulant factors II, VII, IX, X. In the event of vitamin K deficiency Protein Induced in Vitamin K Absence (PIVKA) are in excess and its estimation is very helpful in diagnosis even after starting the treatment. The bleeding defects are usually corrected within few hours after administration of vitamin K. All newborn babies require vitamin K prophylaxis. Oral route is effective like parenteral route but require higher and more doses. Intra muscular route is safe and does not increase the risk of childhood cancer. All breast fed babies with diarrhoea, malabsorption require another dose of vitamin K in postneonatal period to prevent late vitamin K deficiency bleeding.

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KEYWORDS : Haemorrhagic disease of newborn (HDN); PIVKA; Vitamin K.

Introduction

Vitamin K has been a subject of great fascination and interest for pediatricians, hematologists, and clinicians.

In 1894, Townsend first described the term haemorrhagic disease of the new born and reported 50 infants with bleeding. This haemorrhagic disease of the new born is believed to be the first documented bleeding state. Dam in 1927 discovered vitamin K, for which he was awarded Nobel prize in medicine. Vitamin K derived its name from the first letter of German word Koagulation vitamin (Vitamin K). In 1939 it was discovered that haemorrhagic disease of new born was due to low level of prothrombin [1]. In 1961 committee on Nutrition of the American Academy of Pediatrics recommended the prophylactic administration of vitamin K parenterally to all new born babies [2]. Vitamin K is required for the modification and activation of a number of proteins like coagulation factors and anticoagulant factors like protein C and S. The coagulopathy of haemorrhagic disease of newborn is due to deficiency of the vitamin K dependent procoagulant factors II, VII, IX, X.

In the event of vitamin K deficiency, the non carboxylated forms of these proteins, PIVKA (protein induced in vitamin K absence) are detected in circulation. This can be estimated by HPLC (High pressure liquid chromatography), Enzyme Linked Immunosor-

bant Assay, or crossed immuno-electrophoresis. Presence of any amount of PIVKA is abnormal and is indicative of vitamin K deficiency. It remains in circulation for 48 to 72 hours after administration of vitamin K. So measurement of PIVKA even after treatment of acute bleeding episode will be helpful in making a diagnosis of vitamin K deficiency [3].

In clinical practice 3 states of vitamin K deficiency are known. (a) Early haemorrhagic disease of new born (b) Classical haemorrhagic disease of new born (c) Late haemorrhagic disease (or) Late vitamin K deficiency bleeding (VKDB).

Early haemorrhagic disease of new born (Early HDN)

In early HDN bleeding occurs either in utero, during delivery, or during first 24 hours of life. The causes of bleeding are idiopathic and maternal intake of drugs that effect the metabolism of vitamin K like warfarin, phenobarbitone, phenytoin, rifampicin, INH, salicylates and broad spectrum antibiotics. The extent of bleeding varies from skin bruising, subcutaneous haemorrhage, ecchymoses, umbilical bleeding to wide spread fatal intracranial, intra thoracic, intra abdominal bleeding but site of bleeding is usually concealed inside body cavities.

Classical Haemorrhagic Disease of New Born

Classical HDN typically occurs at 2nd to 5th day

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and its incidence is reported to be 0.25 to 0.5 per cent [4]. It is due to physiological deficiency of vitamin K and its dependent procoagulants. These procoagulant levels in new born baby are 30-60 per cent of adult value and gradually increase to adult value by 6 weeks of age. New born babies are also deficient of vitamin K because of poor placental transfer, poor hepatic storage (one fifth of adult), delay in colonization of the gut by the flora known to synthesize vitamins, and mostly babies are breast fed and breast milk is relatively deficient in vitamin K. All these factors contribute in causing classical HDN. Affected infants are normal at birth but subsequently develop generalised ecchymoses, gastro-intestinal bleeding, nasal bleeding, bleeding after circumcision or bleeding from umbilical stump. The manifestations are not very severe and the disease can readily be managed with administration of vitamin K. Classical HDN is virtually non existent in infants given a parenteral dose of vitamin K at birth.

Late Haemorrhagic Disease of New Born

Late onset vitamin K deficiency bleeding or late HDN is seen between 4-8 weeks in healthy breast fed infants. Vitamin K deficiency bleeding is an important cause of morbidity and mortality in infants older than 1 month [5]. This occurs in healthy breast fed infants and infants with underlying malabsorption like chronic diarrhoea, prolonged administration of antibiotics, hepatic cholestasis, biliary atresia, mucoviscidosis and it may be idiopathic [6]. Most of these infants present with acute intra cranial haemorrhage as the initial features and sometimes bleeding at puncture sites, ecchymoses and nodular purpuras.

Diagnosis

Age of onset of bleeding and relative healthy state of the infants usually gives a clue to the diagnosis. HDN infant does not look ill, toxic like septicemia and DIC. The clotting time (CT), prothrombin time (PT), partial thromboplastin time (PTT) and thrombo test are all prolonged while the thrombin time (TT) is normal.

Other tests like estimation of PIVKA II level, coagulation factors II, VII, IX, X and estimation of native prothrombin antigen using monoclonal antibody is helpful in diagnosis of vitamin K deficiency bleeding.

Treatment

Vitamin K is available in 3 forms - Vitamin K1, K2 and K3. Vitamin K1 a phyloquinone derivative, is widely distributed in plants, natural in origin, fat soluble and in substantial doses reduces prothrombin

time to normal in 6 to 12 hours time. Vitamin K2, naphthoquinone derivative, naturally occurring, fat soluble and synthesized in alimentary tract by bacteria. K1 and K2 are rapid in action and nontoxic in high doses. Vitamin K3 is a synthetic sodium bisulfite and tetrasodium salt of menadione derivative, water soluble, takes 24 hours to act and has longer duration of action. In larger doses produces haemolytic anaemia, hyperbilirubinemia and kernicterus. Parenteral preparations are available (ampules containing 10 mg of vitamin K, Oral preparations as tablets containing 10 mg of acetomenophane).

In infants 1-2 mg of vitamin K is adequate enough to correct even a severe vitamin K deficiency bleeding. The bleeding defect is usually corrected within few hours after parenteral administration of vitamin K. When the deficiency is severe it is advisable to administer vitamin K intravenous (IV) route because intramuscular (IM) route takes longer time for correction and may produce local haematoma.

For life threatening haemorrhages alongwith IV administration of vitamin K, 10-20 ml per kg body weight fresh frozen plasma should be administered. If the blood loss is more than 20 per cent and there is evidence of shock, immediate blood transfusion is essential for life saving [4].

Prevention

Haemorrhagic diseases of new born are preventable by administration of vitamin K. Infants predisposed to manifest early HDN as evidenced by maternal intake of drugs should receive vitamin K, 1 mg IV at birth and they may be delivered by cesarean section to avoid the trauma due to vaginal delivery [4]. Even for its prevention high risk mothers may be administered vitamin K orally 7-10 days before delivery [7].

American Academy of Pediatrics (AAP) (Vitamin K task force U.S.A. 1993) has recommended : - [8]

(a) Vitamin K should be given to all new born babies in a single IM dose of 0.5 to 1 mg.

(b) Oral regimen should have 2 mg dose at birth which should be repeated at 2 and 4 weeks.

(c) A repeat dose should be given to breast fed infants with diarrhoea.

Current Controversies

Do all new born require prophylaxis ?

As on today all clinical and biochemical evidence support the use of vitamin K prophylaxis to all babies and AAP recommends vitamin K prophylaxis to all new born babies [8].

Will an oral dose be sufficient? or IM Injection necessary?

Both the routes have their own merits and demerits. Studies have shown that oral vitamin K is sufficient to prevent classical HDN like IM route. But single oral dose in breast fed infants is not as efficient as a single parenteral dose in preventing late HDN [9,10]. IM vitamin K have lower incidence of failure because of more reliable absorption but it has its hazards of injection whereas oral route has better acceptance, administration is better suited in developing countries, less complicated but there may be a chance that medicine may be vomited, absorption may vary and not easily available in India.

Is vitamin K required in post-neonatal period?

Late vitamin K deficiency bleeding in infants in post-neonatal period is well known established entity. To prevent this it is recommended for all breast fed babies with diarrhoea or malabsorption another dose of vitamin K in post neonatal period.

Does IM vitamin K injection cause cancer?

The publication of the article by Jean Golding from UK in 1992, linking IM administration of vitamin K with increased risk of childhood cancer has generated a great deal of discussion in this subject [11]. But however Klebannof et al (U.S.A) in 1993 found no association between perinatal IM vitamin K administration and risk of childhood cancer [12]. Other reports from Sweden [13], Denmark [14], and Britain [15] are also not agreeing with the report of Golding. USA study involved more than 3 times as many children as British study and was better designed, it should be considered the final word that the vitamin K injection is safe. Considering the life threatening potential of vitamin K deficiency and the risk of cancer yet unproven, it is perhaps unjustifiable at this time to abandon IM prophylaxis atleast until more effective studies are available.

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