Review Article

VITAMIN K PROPHYLAXIS IN THE NEWBORN

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ABSTRACT

Bleeding in newborn from vitamin K deficiency is still a major concern in Pediatrics. Intramuscular vitamin K prevents bleeding in newborn even those who are exclusively breast fed and thus at greatest risk for bleeding. Human milk vitamin K content is very low compared with standard infant formulas. Oral prophylactic vitamin K currently used in some countries, following the association found in a single report between childhood cancer and intramuscular vitamin K has produced controversial results. The role of vitamin K in preventing intraventricular hemorrhage in premature infants has not been sufficiently demonstrated.

Key Words: Bleeding disorders, Newborn, Vitamin K.

INTRODUCTION

Vitamin K given to infants to prevent vitamin K deficiency bleeding has been a controversy since time in memorial. The first large series of infants with bleeding disorders was published a century ago and it was speculated that the disease was of an infectious origin and thus fresh cows milk was therapeutic for the infants in this report (1). Description of vitamin K deficiency in chicks by Henrink Dam appeared in 1929 and by 1936 it was known that this deficiency state was associated with a decrease in plasma concentration of prothrombin (2,3). Later it was shown that vitamin K played a major role in the synthesis of prothrombin and other coagulation factors. Studies published in 1950s concluded that newborn hypoprothrombinemia secondary to vitamin K deficiency occurred primarily in breast fed infants in the first few days of life and giving vitamin K to the mother prior to delivery or to the infant after birth could prevent it (4).

In most third world countries prophylactic vitamin K in the newborn is still an uncommon practice and there is little information on bleeding disorders in the newborn in these countries. However countries like Canada and USA where intramuscular vitamin K is recommended, bleeding disorders in the newborn is not a major concern. In some western countries that have recommended oral vitamin K over the traditional intramuscular route, bleeding disorders in the newborn has become a major problem once again (5,6).

Hemorrhagic Disease of the Newborn

Three types of hemorrhagic disease of the newborn have been described. The first one, the classical hemorrhagic disease occurs in newborn babies who are exclusively breast fed and have not received prophylactic vitamin K. It occurs between second and third day of life and the manifestations are usually generalized echymoses, gastrointestinal bleeding, bleeding from the umbilical stump or circumcision site. Intracranial bleeding is rare. Inactive prothrombin molecules have been found in plasma of some newborn but they disappear after administration of vitamin K, hence parenteral vitamin K can treat this disease (7).

The second type of hemorrhagic disease of the newborn, so called the late hemorrhagic disease of the newborn is not benign and it occurs exclusively in breast fed infants who have not received prophylactic vitamin K or have gastrointestinal disorders associated with significant fat malabsorption (cystic fibrosis, biliary atresia, alpha-1-antitrypsin deficiency). This is the most common disorder and leaves devastating sequelae(8).

The third type of hemorrhagic disease is associated with maternal administration of medication such as warfarin, hydantoin or barbiturates which reduce the vitamin K dependent factors. In rare cases no

contributing factor is found. Bleeding occurs within 24 hours and may occur at any site. It can be prevented by administration of vitamin K prior to delivery (9,10).

Vitamin K Requirements

The US RDA (Recommended Dietary Allowance) committee recommendation of vitamin K intake during the first 6 months and the second 6 months of life is 5ug/day and 10ug/day respectively (11). This is close to the amount recommended for all ages (1ug/kg/day). Infants feeding exclusively on human milk receive much less than this, whereas those fed on standard formulas greatly exceed this daily requirement. The published values for vitamin K (phylloquinone) concentration of human milk ranges from 1 to 2 ug/ml (12,13). Hence for a 5 kg infant to receive a RDA of 1ug/kg/day the daily breast milk intake would be in the range of 2500ml to 5000ml. As with other fat soluble vitamins the vitamin K content of colostrum is much lower than mature milk. Due to the variation of dietary intake by mothers, human milk phylloquinone concentration shows individual daily variation. However in some published studies, the average phylloquinone content of mature human milk varied little through the first 6 months of lactation.(13). In these reports the vitamin K intake of breast fed infants through the first 26 weeks of lactation ranged from 0.554 ug/day to 0.774 ug/day (0.075 to 0.125 ug/kg/day) or about 10 times of the RDA. Contrary to this, formula fed infants in this same population had phylloquinone intake of 45.4 to 55.3 ug/day (7.0 to 9.3 ug/kg/day) greatly exceeding the recommendation of the RDA committee. Formula fed infants thus exceed breast fed infants by nearly 100 times. Therefore breast-fed infants are thus of special concern with regard to the risk of hemorrhagic diseases.

Vitamin K (Phylloquinone) Assay

There are two types of vitamin K. Vitamin K phylloquinone found in plants and menaquinone synthesized by bacteria including those that colonize human intestine (14). A quantitative assay of vitamin K was first described in 1982 and further modification occurred later on (15). This technology allowed measurement of vitamin K phylloquinone in infants plasma, stool, and liver as well as in human milk. Serial phylloquinone concentration in a group of exclusively breast fed infants through the first 6 months of life has been reported (13). The serum phylloquinone concentration of these infants was found to be very low (less than 0.3ng/ml compared to greater than 0.5ng/ml in normal adults). None of these infants showed any signs of vitamin K deficiency. The plasma prothrombin time in human milk fed infants was higher as compared to formula fed infants (4). Measurements of prothrombin times and plasma phylloquinone concentration is thus not sensitive in the diagnosis of vitamin K deficiency. Recent technological development in diagnosing vitamin K deficiency was the description of an abnormal prothrombin protein, (protein induced in vitamin K absence) PIVKA-II. (4). This abnormal prothrombin lacks its biological activity and it was shown to be due to the inability to bind to calcium ions (16). The precursor of prothrombin, or abnormal prothrombin is a relatively small molecule containing 10 "glu" residues, which, in the presence of vitamin K are carboxylated to "gla" residues. Vitamin K was shown to be the necessary co-factor for the activity of microsomal enzymes-glutamyl carboxylase, which is required in the creation of effective calcium binding sites. Four methods have been described to measure PIVKA-II in the newborn and have been reviewed in details elsewhere (17). One of these methods, the specific antibody detection is in widespread use at the moment. The principle of this method is the preparation of a murine monoclonal antibody to PIVKA-II that is subsequently utilized in an ELIS A.A number of such antibodies have been described (18,19). Oral vitamin K supplements in infants did not significantly alter PIVKA-II detection rate in Japanese infants at 4 to 6 weeks of life whether the infants are breast fed or formula fed (20, 21). Other studies in Netherlands in exdusively breast fed infants who received vitamin K at birth PIVKA-II is detected in 4 of 262 at 4 weeks and in 15 of 131 infants at 12 weeks of life (22). When oral vitamin K was given daily or weekly in this same population, PIVKA-II was not detected in exclusively breast fed infants at 4 and 12 weeks (23,24). Some of these confusions in literature in studies using specific antibodies may be secondary to the cut-off levels used for the normal values which have included values of 0.13,1.3 and 4 AU per 1ml.. Comparison between these reports is thus difficult depending on what normal cut off levels were used.

Prophylactic Vitamin For Neonates

The most serious controversy which encouraged the use of oral rather than parenteral prophylactic vitamin K in neonates was precipitated in 1992 by publicity given to reports by Golding et al that intramuscular vitamin K was associated with the doubling of the risk of malignant disease in childhood (25,26). There is considerable doubts whether the association is causal but there is no other obvious explanation.. Reports from Sweden and Denmark, where the vitamin K preparation used was the same as that used in Britain suggest that the risk if any cannot be as high as Golding et al reported (27,28). In another study, a retrospective analysis using data collected from collaborative perinatal projects in the USA, no association was found between exposure to intramuscular vitamin K and increased risk of any childhood cancer (29). After Golding's report reassessment of the need of prophylactic vitamin K

was made in most developed countries and in fact countries like Britain, Germany and Australia recommended the use of oral vitamin K in place of intramuscular vitamin K, even though no licensed oral preparation was available. Unfortunately this lead to an increase in the incidence of late hemorrhagic disease of the newborn in these countries (5,6). The use of oral prophylactic vitamin K has produced widespread concern and in fact it was shown that the blood levels of phylloquinone after oral administration was much lower than that after intramuscular route. There is also much variability on availability and efficiency of intestinal absorption of phylloquinone from the available oil-based preparation (30). A single 1-mg dose of intramuscular vitamin K produces peak plasma levels of vitamin K in neonates that may exceed normal adult physiologic level by a factor of 1000, whereas in other reports it has been shown that a single 1-mg oral dose of vitamin K produces serum levels of about 90ng/ml to undetectable levels (31). If oral doses are ever to be used then repeated doses will be necessary in the first 2 months of life in exclusively breast fed infants or infants at risk (liver diseases, chronic diarrhea) in order to prevent late hemorrhagic disease (32). Oral vitamin K leads to compliance problems as appeared in recent reports(33). This did not occur with the intramuscular route. Cases of late hemorrhagic disease increased after the introduction of oral prophylaxis as it is reported in several studies and indeed The Pediatric Society of Australia has recommended the return to the intramuscular route (4). To prevent hemorrhagic disease of the newborn the Committee of Fetus and Newborn of the American Academy of Pediatrics has recently reaffirmed its recommendation that all infants receive prophylactic vitamin K at birth and that the preferred route is the parenteral one (32). If oral prophylaxis is to be used then it should be given at birth (2.0mg) and administered again at 1 to 2 weeks and at four weeks of life in breast fed infants (32). An oral preparation, Konakion -MM (La Roche, Basel, Switzerland) is available in Europe. In this preparation vitamin K is prepared with a bile acid (glycocholic acid) and phospholipid lecithin. This "mixed-micellar" solution has greater reliability of absorption following oral administration in infants and children with cholestasis (34). There is one published study in normal neonates with regard to this preparation which showed the blood levels at 24hrs and 4 days to be the same after both oral and parenteral administration of Konakion, however the level dropped at 23 days after the oral administration, but not below the normal adults reference range (0.2-0.7ng/ml) Maternal administration of vitamin K provides another method of vitamin K prophylaxis in the newborn. It has been shown that maternal supplementation of 2.5mg/day of vitamin K significantly increases the vitamin K content of human milk (35). In this study the aim was to increase the vitamin K concentration of human milk such that the viamin K intake of breast fed infant would approach that of formula fed infants. In another study breast fed infants' mothers receiving 5mg oral vitamin K daily had intake of vitamin K that approached the formula fed infants (36).

Intraventricular Hemorrhage (IVH) in Premature Infants. Role of Vitamin K

The role of vitamin K in IVH is questionable. The pathogenesis of IVH is believed to be multifactorial.(4). One of the postulated factors is the hepatic dysfunction due to immaturity leading to inability of the liver to synthesize coagulation factors even in the presence of vitamin K. Because IVH occurs shortly after birth, most studies have looked at the administration of vitamin K to mothers during premature labor. Seven such studies in literature have looked at the effects of maternal antenatal vitamin K administration on coagulation studies in premature infants (37-43). In only one of these studies maternal vitamin K administration was found to significantly decrease PT and PTT in premature infants as compared to controls (40).

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