

# EFFECT OF ORAL WATER SOLUBLE VITAMIN K ON PIVKA-II LEVELS IN NEWBORNS

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## ABSTRACT

*Intramuscular administration of vitamin K for prophylaxis against hemorrhagic disease of the newborn has the disadvantage of increased cost, pain, anxiety to parents and risk of transmission of infection. Oral route is a better alternative. Oral absorption of vitamin K has been shown to be equally good using special oral preparations. However, this preparation is not available in India. A prospective study was carried out on 51 full term, healthy breastfed newborns to evaluate if the injectable water soluble preparation of vitamin K (menadione sodium bisulphite) could be as effective. Fourteen babies received 1 mg vitamin K intramuscularly, 24 received 2 mg vitamin K orally while 13 controls did not receive vitamin K at birth. PIVKA-II levels were measured in cord blood and at 72-78 hours of age in all babies as a marker of vitamin K deficiency. The overall PIVKA-II prevalence in cord blood was 647%. At 72-78 hours, PIVKA-II was present in 50% of babies in IM group, 58.3% of babies in oral group and in 76.9% of babies in 'no vitamin K' group ( $p > 0.05$ ). The PIVKA-II levels decreased or did not change at 72-78 hours in 91.6% of babies in oral group versus 92.8% of babies in IM group ( $p > 0.05$ ). On the other hand, PIVKA-II levels increased in 30.7% of babies who did not receive vitamin K as against in 7.8% of babies receiving vitamin K in either form ( $p < 0.05$ ). Hence, vitamin K prophylaxis is required for all newborns at birth and injectable vitamin K (menadione sodium bisulphite) given orally to term healthy babies*

Hemorrhagic disease of newborn (HDN) is a serious disorder of blood coagulation resulting from vitamin K deficiency in the first few days of life. Absence of bacterial flora in the gut, their low storage-capacity for vitamin K and deficient state of vitamin K in breastmilk, predispose a newborn to this disorder. Its approximate incidence is 1 per 1000 live births(1). With increased emphasis on breastfeeding all over the world and especially in developing countries, the newborns may be more prone for developing HDN.

The American Academy of Pediatrics has recommended that prophylaxis be given to all newborn infants using vitamin K 0.5-1 mg intramuscularly (IM) or 2 mg orally(2). This recommendation is being followed in many countries. Because of the ease of administration, less cost, no pain, or risk of transmission of infections, oral route will be preferable, especially at the community level. Usefulness of this route has been studied using special oral vitamin K preparation in the West(3). This preparation is not

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*is effective in preventing vitamin K deficiency state.*

**Keywords:** *Vitamin K, Protein induced in vitamin K absence (PIVKA-II), Hemorrhagic disease of newborn (HDN).*

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available in India. Water soluble vitamin K preparation used for IM injection has been used orally and shown to be useful by measuring prothrombin time as the end point(4,5). Some coagulation factors are present in reduced quantity during the newborn period(6,7). The low level of prothrombin activity in newborns may be due to reduced synthesis of the protein in the liver or to impaired gamma-carboxylation of the prothrombin precursor because of vitamin K deficiency. These two mechanisms are not distinguished by the prothrombin time test(8). Vitamin K deficiency can be diagnosed more reliably by measuring the level of a circulating prothrombin precursor, a protein induced by vitamin K absence (PIVKA-II)(9-11). This study was conducted to evaluate the effectiveness of orally administered water soluble vitamin K by measuring blood PIVKA-II levels.

#### Material and Methods

Seventy five full term appropriately grown babies with normal Apgar scores born consecutively in the Labor Room of PGIMER from August to December '93 were randomized to three groups. Group A babies received injection Vitamin K (menadione sodium bisulphite) 1 mg IM within one hour of delivery, as is the current practice in the unit. Group B babies received the same preparation of vitamin K, 2 mg orally. Group C babies did not receive vitamin K at birth but were given 1 mg vitamin K, IM after drawing samples for PIVKA-II at 72 hours of age. All the babies were exclusively breastfed. Babies with perinatal complications like maternal hypertension, maternal drugs, *e.g.*, aspirin, luminal *etc.* or babies receiving antibio-

tics were not included. The study was approved by the Hospital Ethics Committee.

Cord and venous blood samples were drawn soon after birth and at 72-78 hours of age, respectively. 1.8 ml of blood was obtained and added to 0.2 ml sodium citrate in a precalibrated tube. The tubes containing the sample were spun for 15 minutes at 1500 rpm soon after collection and plasma separated and stored at -70°C until the time of analysis. PIVKA-II was assayed by modified method of Megura and Yamada(12). Citrated test plasma was absorbed with aluminium hydroxide to remove normal carboxylated prothrombin. The abnormal prothrombin (PIVKA-II) remained in the supernatant. Radial immunodiffusion technique with anti human prothrombin antibody (Boehring) was used to quantitate levels of total prothrombin antigen (before absorption) and PIVKA-II (after absorption). An unabsorbed standard control for calculation of a curve (100%, 50%, 25% and 12.5%) was prepared with pooled adult plasma with neat at 100%. The sensitivity of this method was 0.125 AU/ml (arbitrary units).

#### Results

There were 25 babies in each group. Blood samples of 3 babies in Group A and 5 in Group C could not be processed because of technical problems. The second blood sample for PIVKA-II could not be drawn at the predecided age of 72-78 hours in 8 babies in Group A, 1 in Group B and 7 in Group C due to early discharge from hospital. These babies were excluded from analysis. The 7 babies in 'no vitamin K' group were how-

ever, given 1 mg vitamin K before discharge. Hence, there were 14, 24 and 13 babies available in groups A, B and C, respectively for analysis.

The mean birth weights of babies in Groups A, B and C were 2.85 ( $\pm 0.31$ ), 2.77 ( $\pm 2.1$ ) and 2.84 ( $\pm 0.33$ ) kg, respectively. The sex distribution and age at sampling were also similar. PIVKA-II was present in 64.7% of all the cord samples with 64.2%, 67% and 61.5% in Groups A, B and C respectively which were comparable ( $p > 0.05$ ). PIVKA-II was present in 50% of babies in IM group, 58.3% of oral group and 76.9% of 'no vitamin K' group at 3 days of age ( $p > 0.05$ ) (*fig. 1*). The changes in PIVKA-II levels at 72-78 hours of age in the 3 groups are shown in *Table I*. A total of 92.8% of the babies who received IM vi-

tamin K showed a fall or no change in PIVKA-II levels at 3 days as against 91.6% of oral group ( $p > 0.05$ ). The number of babies showing a rise in PIVKA-II levels at 3 days was not different in the groups receiving JM or oral vitamin K (7.1% vs 8.3%;  $p > 0.05$ ). PIVKA-II levels increased in 30.7% of the babies who did not receive vitamin K as against 7.8% of those who received vitamin K in either form ( $p < 0.05$ ). The levels decreased or did not change in 92.1% of babies who received vitamin K in either form as against 69.3% of babies who did not receive vitamin K ( $p < 0.05$ ).

None of the babies studied suffered from any bleeding till one month follow up and none of the babies required phototherapy for hyperbilirubinemia.

**Discussion**

The prevalence of PIVKA-II positivity in cord blood has varied from 0 to 89%(6,12-15). The wide differences in the prevalence rates are due to the differences in population groups and variations in the method of estimation of PIVKA-II. Methods such as radio-immunoassay or enzyme linked immunoabsorbent assay have a greater

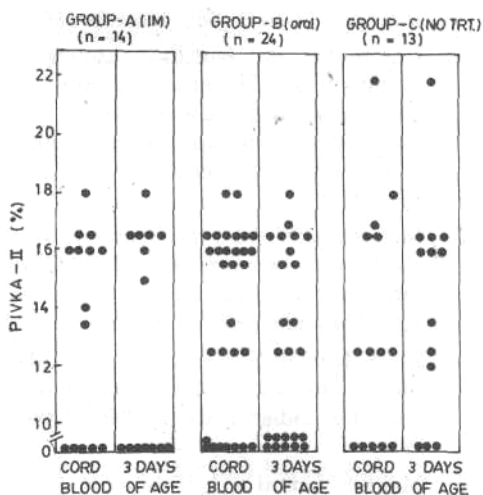


Fig. 1. PIVKA-II levels in cord blood and blood obtained at 3 days of age.

TABLE I- Changes in PIVKA-II Levels at 72-78 Hours

Change	IM Vit. K (n=14)	Oral Vit. K (n=24)	No. Vit. K (n=13)
Fall	3 (21.4)	6 (25)	1 (7.6)
No change	10 (71.5)	16 (65.7)	8 (61.3)
Rise	1 (7.1)	2 (8.3)	4 (30.7)

Figures in parentheses indicate percentages.

sensitivity than methods that use crossed immunoelectrophoresis or immunoelectrophoresis(16). All the available studies are from western population. No data is available for our population. The high prevalence of 64.7% in our study is possibly because of the poor nutritional status of our mothers.

Motohara(8) has shown that number of babies who were PIVKA-II positive at birth fell from 19.6% to 18.5% at 3 days of age, following administration of 5 mg oral vitamin K1. This further fell to 11.4% at 5 days of age. Since oral preparation of vitamin K is not available to us, we used the injectable watersoluble vitamin K analogue (menadione sodium bisulphite) orally. With this, we found a fall in PIVKA-II positive babies from 67% to 58.3% at 3 days of age in babies given oral vitamin K. This fall was similar to that seen in IM group. As half life of PIVKA-II may extend upto 70 hours, the fall is likely to be more with increasing age(16). There was no significant difference in the number of babies showing a fall or no change, or rise in PIVKA-II levels at 3 days in the oral and IM groups. These findings suggest that oral water soluble vitamin K is as effective as intramuscular vitamin K in preventing vitamin K deficiency in, term, well breastfed babies.

Fears have been expressed of hemolysis and neonatal hyperbilirubinaemia with administration of large doses of water soluble vitamin K analogues(2). However, we did not find any increase in incidence of hyperbilirubinemia requiring phototherapy or exchange transfusion in babies receiving 2 mg oral watersoluble vitamin K.

PIVKA-II positivity of 64.7% in cord blood suggests widespread vitamin K deficiency state in our newborns. Though statistically not significant, PIVKA-II positivity increased to 76.9% in the 'no vitamin K' group while it decreased to 50% and 58.3% in IM and oral groups, respectively at 3 days of age. This and the further increase in PIVKA-II levels in significant number of babies who did not receive vitamin K against those who received vitamin K (30.7% vs 7.8%;  $p < 0.05$ ) implies that this deficiency state is worsened by non administration of vitamin K.

In conclusion, oral water soluble vitamin K can be safely given and is as effective as IM administration for correcting vitamin K deficiency state in term, healthy newborns. All newborns should be given vitamin K prophylaxis in either oral or IM form at birth to correct the deficiency state and prevent HDN.

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