Brief Reports

Prevention of Subclinical Vitamin K Deficiency Based on PIVKA-II Levels: Oral Versus Intramuscular Route

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Classical hemorrhagic disease of newborn (HDNB) was first described in 1894(1). Clinically manifest classical HDNB is relatively uncommon with incidence of 1-2/1000 live births. Exclusively breastfed babies are predisposed to develop HDNB because of absence of bacterial flora in the gut, lack of stores of vitamin K and low vitamin K levels in breastmilk(2,3). In the absence of vitamin K, its precursor non-carboxylated proteins called Proteins Induced in Vitamin K Absence (PIVKA) are elevated. Levels of PIVKA-II (Precursor Protein of Factor II) are more specific than Pro-thrombin Time (PT) because the former does not get elevated in states of decreased synthesis of coagulation factors as occurs in hepatitis(4). The American Academy of Pediatrics (AAP) recommends prophylactic administration of intramuscular (IM) vitamin K for all newborn babies at birth(5) whereas in India, there is lack of consensus and (IM) vitamin K is given only to high risk babies in many centers. Intramuscular vitamin K is associated with the potential risks of transmission of viral infections, lymphoreticular malignancies in later childhood and excessive cost. Oral administration of vitamin K is thus preferable because of safety and cost effectiveness. The present study was conducted to look for sub-clinical evidence of vitamin K deficiency in exclusively breastfed term neonates and evaluate the efficacy of orally and intramuscularly administered water soluble vitamin K in them.

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Subjects and Methods

The present pilot study was conducted in two phases.

Phase I Trial: Thirty five appropriate for date term babies with normal Apgar score, born at AIIMS and exclusively breastfed were enrolled to look for sub-clinical vitamin K deficiency based on PIVKA-II levels and prothrombin time (PT).

Phase II Trial: Fifty four term appropriate-for-dates neonates with normal Apgar score, born at AIIMS were block randomized in two groups. Group A received 1.0 mg vitamin K IM while Group B received 2.0 mg vitamin K orally under supervision, as soon as possible after birth (within 4 hours). All the babies were exclusively breastfed. Babies born to mothers with complications like hypertension, maternal ingestion of drugs like phenobarbitone, anticoagulants, antitubercular agents and newborn babies with congenital malformations, and those receiving intravenous fluids were excluded from the study. Blood samples were collected for PT and PIVKA-II at 72 ± 12 hours age. The serum was separated and stored at-20° C until analysis. PIVKA-II was estimated by ELISA technique in batches along with control samples. A value of PT more than 1.5 times of control was taken prolonged while a value of PIVKA-II above 2 ng/ml was considered as suggestive of vitamin K deficiency. All the babies enrolled in the study were kept under observation for first seven days of life for any bleeding manifestations. The data were analysed using Chi square test (with yates correction), unpaired Y test and Fischer's exact test.

Results

Phase I Trial: Babies in Phase I trial were of mean birth weight 2.8 kg (SD ± 0.3) and gestation 38.5 wk (SD ± 1.2). Of the 35 babies enrolled, PIVKA-II and PT could be done in 31 babies. Four babies were excluded because they received supplemental formula feed. PIVKA-II and PT levels were raised in 25 (80.6%) and 15 babies (48.4%), respectively. No baby developed any overt bleeding manifestations and also no baby developed pathological jaundice.

Phase II Trial: The baseline characteristics of babies of Phase II trial are shown in *Table I.* Of the 54 babies enrolled 2 subjects were excluded because they received top milk. Thus 27 were randomized to Group A (IM group) while 25 babies to Group B (oral group). The birth weight and gestation were comparable in two groups. PIVKA II levels were not detectable in 85.2% and 84% of the babies in Group A and B, respectively and the difference between the

TABLE I-*Baseline Characteristics of Study Group (Phase II)*

Characteristic	Group A (n=27)	Group B (n=27)
Birth weight (kg)	2.8 ± 0.3	2.9 ± 0.2
Gestation (weeks)	38.7±1.3	38.8±1.0
Male: Female	16:11	15:12
Apgar Scores at 1 min > 6	27	27

None of the differences between the two groups were significant.

two groups was not significant *(Table II).* No baby in either group had a prolonged prothrombin time.

No significant difference in the morbidity in two groups was noticed. None of the babies suffered from any bleeding manifestations on follow up for seven days. Two babies in Group B developed pathological jaundice requiring phototherapy. However, jaundice was possibly attributed to ABO incompatibility in one and the excessive use of oxytocin in the mother in the other baby.

Discussion

Classical HDNB is a rare clinical entity affecting 1-2/1000 live born babies. The American Academy of Pediatrics recommends routine administration of IM vitamin K to all babies at birth. This may not be feasible in most developing countries because of constraints of non-availability of safe vitamin K preparation and logistics of giving IM vitamin K under aseptic conditions particularly to babies born at home. In recent years, fear has been raised that IM vitamin K may be associated with increased risk of cancer in children (6, 7). However, there have been several studies which have refuted this risk(8, 9). Hence there is a need to evaluate the efficacy and safety of oral vitamin K for prevention of HDNB.

TABLE II- *PIVKA II Levels After Vitamin K Administration.*

	Group A (n=27)	Group B* (n=25)
Abnormal PIVKA-II	4	4
Normal or decreased PIVKA-II	23	21

The differences between the two groups were not significant.
*Two babies were excluded due to administration of top milk.

The present study, first of its kind from India, using PIVKA-II as a marker of sub-clinical vitamin K deficiency showed that sub-clinical vitamin K deficiency does occur in 80.6% of exclusively breastfed term neonates (Phase I trial). The water soluble preparation of vitamin K given orally or intramuscularly to neonates resulted in decreased PIVKA II levels in majority of babies and normal PT in all, at 3 to 4 days. There was no significant difference in the efficacy of oral versus IM vitamin K. Earlier studies from India have reported improvement in PT by oral administration of water soluble vitamin K(10). As PT may not be specific to pick up vitamin K deficiency, PIVKA-II levels were also estimated in the present study.

Following administration of water soluble vitamin K in high doses, neonatal hyperbilirubinemia may occur. However, we did not find any pathological jaundice in babies attributable to the use of vitamin K.

In conclusion, oral water soluble vitamin K can be safely given and it is as effective as IM vitamin K for correcting sub-clinical vitamin K deficient state (based on PIVKA II levels) in exclusively breastfed term neonates. A larger prospective randomized trial is required to document efficacy of oral water soluble vitamin K in high risk neonates.

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NOTES AND NEWS

SECOND AIIMS WORKSHOP ON NEONATAL VENTILATION

The Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, is organizing a Workshop on Neonatal Ventilation from February 3-5, 1997. It will focus on practical aspects of assisted ventilation of newborn infants. Overseas faculty will consist of Dr. Vinod Bhutani, Dr. D. McMillan and Dr. Nalini Singhal. The format of the Workshop will be skill-oriented with emphasis on group work in tutorials and on problem-solving. If interested, please write to the undersigned along with registration fee of Rs 750/-(by cheque/DD in favor of CME in Neonatology AIIMS by 31st Dec, 19%. The number of participants will be restricted to 30, on the 'first come, first served basis'. Please contact: Dr. V.K. Paul, Additional Professor, Department of Pediatrics, AIIMS, Ansari Nagar, New Delhi-110 029. Ph.: 6594372 (O); 6868849 (R); Fax: 686 2663