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The 3 regimens of vitamin K1prophylaxis at birth: Clinical profile

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Abstract
Classical VKDB "occurs between 24 hours and 7days of life and is associated with insufficient stores at birth and delayed or insufficient feeding. The clinical presentation is often mild, with bruises, gastrointestinal blood loss or bleeding from the umbilicus and puncture sites. Blood loss can, however, be significant, and intracranial haemorrhage, although rare, has been described. Considering the smaller sample size, to avoid unequal group sizes, block randomization method was used to allocate the study participants to treatment groups. The block size used was 9, with 3 subjects randomized to each of the three treatment groups, within each block. The median cord PIVKA value on day 5 was 0.0, 0.180 and 0.4 among the intervention groups of A,B and C respectively. The difference in the median PIVKA values across the three intervention groups was statistically not significant (p value 0.346). When presented as binary variable, the proportion of subjects with abnormal PIVKA values was 0%, 3.85% and 8% respectively among intervention group A, B and C respectively.
Keywords:VKDB, PIVKA, Preterms

Introduction

A new anti-haemorrhagic factor, which is responsible for scurvy like disease in chicks was first reported by Henrik Dam in 1930 and it was named as Vitamin K by him in 1935.Vitamin K is essential, periostin and for the function of several proteins involved in blood coagulation (prothrombin, also known as factor II, factors VII, IX and X, protein C, protein S and protein Z) (osteocalcin matrix Gla protein), as well as vascular biology, cell growth and apoptosis (growth-arrest-specific gene 6 protein)[1].

All newborns have precariously low vitamin K1 stores and essentially undetectable plasma

Only a small amount of vitamin K is needed for blood coagulation inhuman beings. Therefore, deficiency of vitamin K due to diet is, extremely rare in adults and usually associated with profoundly inadequate dietary intake, intestinal disorders and malabsorption and to some extent, decreased production by normal flora (e.g. broad spectrum antibiotic) and renal failure[1].

But Vitamin K deficiency is, much more frequent in neonates, due to both endogenous and exogenous deficiency. "The former case, which is probably less clinically significant, has been attributed to insufficient intestinal colonisation by bacteria, whereas the latter case arises from poor placental transport of the vitamin and it slow concentration in breast milk. The main exogenous source of vitamin K in neonates, which is almost exclusively milk, cannot adequately compensate for deficient endogenous production, since human breastmilk contains between 1 and 4 µg/L of vitamin K1 (and a much lower concentration of vitamin K2). As in other circumstances in science and medicine,there is an apparent paradox in haemostasis in neonates, in that prolonged global coagulation tests(i.e., activated partial thromboplastin time and prothrombin time) do not translate into a particular bleeding phenotype. In fact, it is now clear that the physiology of haemostasis in childhood differs considerably from that in adults"[2].

Vitamin K deficiency may cause unexpected bleeding, the incidence of which vary from 0.25%-1.7% in the first week of life in previously healthy appearing neonates. This is labelled early VKDB (formerly known as classic hemorrhagic disease of the newborn). The efficacy of neonatal vitamin K prophylaxis (oral or Parenteral) in the prevention of early VKDB is established beyond doubt. It has been the standard of practice since theAmerican

Academy of Paediatrics recommended it in 1961[3].

Late VKDB, "a syndrome defined as unexpected bleeding attributable to severe vitamin K deficiency in infants 2 to 12 weeks of age, occurs primarily in exclusively breastfed infants who have received no or inadequate neonatal vitamin K prophylaxis. In addition, infants who have intestinal malabsorption defects (cholestatic jaundice, cystic fibrosis, etc.) may also have late VKDB. The rate of late VKDB (often manifesting as sudden central nervous system haemorrhage) ranges from 4.4 to 7.2 per 100 000 births, according to reports from Europe and Asia"[4].

In idiopathic VKDB, no cause other than breast feeding can be demonstrated. In secondary VKDB there is usually an underlying cause, such as the effect of drugs that have been given to the mother or infant or a hereditary hepatobiliary or malabsorption diseases (e.g., biliary atresia, α-1-antitrypsin deficiency, cystic fibrosis).In addition, "autosomal recessive vitamin K-dependent coagulation factor deficiencies (VKCFD), due to mutations in the gene encoding for γ-glutamyl carboxylase (VKCFD type I) and in the gene encoding for vitamin K epoxide reductase (VKCFD type II), have been reported. According to the age of onset, early VKDB presents within 24 hours of birth and is almost exclusively seen in infants of mothers taking drugs which inhibit vitamin K. These drugs include anticonvulsants (carbamazepine, phenytoin and barbiturates), anti-tuberculosis drugs (isoniazid, rifampicin), some antibiotics (cephalosporin's) and vitamin K antagonists (coumarin, warfarin). The clinical presentation is often severe with cephalohematoma and intracranial and intra-abdominal haemorrhages"[5].

Classical VKDB "occurs between 24 hours and 7days of life and is associated with insufficient stores at birth and delayed or insufficient feeding. The clinical presentation is often mild, with bruises, gastrointestinal blood loss or bleeding from the umbilicus and puncture sites. Blood loss can, however, be significant and intracranial haemorrhage, although rare, has been described". Estimates of the frequency vary from 0.25% to 1.5%in older reviews and 0-0.44% in more recent views.Late VKDB is associated with exclusive breast-feeding. "It occurs between the ages of 2 and 12 weeks. The clinical presentation is severe, with a mortality rate of 20% and intracranial haemorrhage occurring in 50%. Persistent neurological damage is frequent in survivors. In fully breast-fed infants who did not receive vitamin K at birth, the incidence is between 1/15,000 and1/20,000. Babies with

cholestasis o malabsorption syndromes are at particular risk"[6].

Methodology

Study population

Preterms (≤ 32wks) and/or with birth weight ≤1500gms.

Study setting

Neonatal intensive care unit.

Study design

Randomized controlled trial with three intervention groups.

Inclusion criteria

- All preterm babies/VLBW (≤32weeks and or ≤1.5 kg) infants delivered, during study period.

Exclusion criteria

- Major congenital malformation.
- Maternal drug treatment with known vitamin K antagonists.
- Mother diagnosed with thrombophilias and platelet disorders.
- Consent not given.
- Babes who were given vitamin K at Birth and not informed.
- Fetal intracranial haemorrhage suspected on routine antenatal ultrasound scan (18-20 weeks' gestation).

Considering the smaller sample size, to avoid unequal group sizes, block randomization method was used to allocate the study participants to treatment groups. The block size used was 9, with 3 subjects randomized to each of the three treatment groups, within each block. The sequencing of interventions, within each block was

done by simple random sampling using the random number tables in a predetermined direction. Uniform sample was maintained till the end of the 8 blocks (8X9=72, making 24 subjects in each group). Only three subjects with random sequence BCB were included in the 9th block making the final number of participants as 24, 26 and 25 in intervention groups A, B and C respectively.

Sequentially Numbered, Opaque Sealed Envelopes (SNOSE) method as described by Doig, G.S *et al*., has been used for allocation concealment in the study. The allocated intervention sequence was kept in individual, serially numbered sealed opaque covers and was kept under the custody of a senior faculty of the department but not involved in the study or patient care. The card board with the intervention name was covered with a silver foil to prevent the visibility. Each time when the participant was recruited the opaque cover was opened and the intervention was communicated to the investigator.

Results

Table 1: Comparison of antenatal and intra natal parameters among the three intervention groups

Parameter	Intervention group			P- Value
	A (N=24)	B(N=26)	C(N=25)	
Gestational age in weeks (Median ±IQR)	29.00±2.0	29.00±3.0	30.00±1.5	0.880
Antenatal steroid in frequency (%)				
Yes	16(66.7%)	21(80.8%)	20(80.0%)	0.430
No	8(33.3%)	5(19.2%)	5(20.0%)	
Singleton pregnancy in frequency (%)				
Yes	22(91.7%)	23(88.5%)	22(80.0%)	0.903
No	2(8.3%)	3(11.5%)	3(12.0%)	
Mode of delivery in frequency (%)				
Spontaneous preterm labour	12(50.0%)	13(50.0%)	12(48.0%)	0.586
LSCS	8(33.3%)	4(15.4%)	6(24.0%)	
AVD	1(4.2%)	1(3.8%)	0(0.0%)	
Induced Labour	3(12.5%)	8(30.8%)	7(28.0%)	

The median birth weight of the baby, gender distribution of the neonates, proportion of participants receiving antibiotic therapy, proportion of participants with TPN/PPN and exclusive breast milk feeding were comparable among the study groups.The minor differences in these parameters among the three intervention groups were statistically not significant.

Table 2: Comparison of post natal parameters among the three intervention groups

Parameter	Intervention group			p-Value
	A (N=24)	B(N=26)	C(N=25)	
Birth weight in kg (Median ± IQR)	1.05 ±0.289	1.10±0.251	1.15±0.250	0.862
Gender in frequency (%)				
Male	13(54.2%)	16(61.5%)	9(36.0%)	0.174
Female	11(45.8%)	10(38.5%)	16(64.0%)	
Antibiotic therapy in frequency (%)				
Yes	8(29.6%)	10(38.5%)	9 (36%)	0.931
No	16(66.7%)	16(61.5%)	16(64%)	
PPN in frequency (%)				
Yes	13(54.2%)	14(53.8%)	10(40.0%)	0.520
No	11(45.8%)	12(46.2%)	15(60.0%)	
Receiving exclusive breast milken frequency (%)				
Yes	10(41.7%)	12(46.2%)	14(56.0%)	0.522
No	14(58.3%)	14(58.3%)	11(44.0%)	

The proportion of infants with abnormal PIVKA values was 58.7% in the entire study population. The median cord PIVKA value was 3.32, 3.46 and 2.78 among the intervention groups of A,B and C respectively. The difference in the median PIVKA values across the three intervention groups was statistically not significant (p value 0.814). The proportion of subjects with abnormal PIVKA values was 45.8%, 42.3% and 36% respectively

among intervention group A, B and C respectively. The differences in these proportions were statistically not significant (P value 0.777).

Table 3: Comparison of cord PIVKA among the intervention groups

Parameter	Intervention group			p-Value
	A (N=24)	B(N=26)	C(N=25)	
Cord PIVKA Units (Median ±IQR)	3.32 ± 3.8	3.46 ± 4.25	2.78 ± 3.85	0.814
Cord PIVKA groups				
Normal	13(54.2%)	15(57.7%)	16(64.0%)	0.777
Abnormal	11(45.8%)	11(42.3%)	9(36.0%)	

Two children from intervention group B and one child from intervention group C met with mortality by day 5, hence 24 children were left in each of the intervention groups by day 5.

The median cord PIVKA value on day 5 was 0.0, 0.180 and 0.4 among the intervention groups of A,B and C respectively. The difference in the median PIVKA values across the three intervention groups was statistically not significant (p value 0.346). When presented as binary variable, the proportion of subjects with abnormal PIVKA values was 0%, 3.85% and 8% respectively among intervention group A, B and C respectively.

Discussion

Vitamin K deficiency may cause unexpected bleeding (0.25%-1.7% incidence) during the first week of life in previously healthy appearing neonates (early vitamin K deficiency bleeding [VKDB] of the newborn [formerly known as classic hemorrhagic disease of the newborn]). The efficacy of neonatal vitamin K prophylaxis (oral or parenteral) in the prevention of early VKDB is firmly established. It has been the standard of care since the American Academy of Paediatrics recommended it in 1961.

Various studies have been conducted across the globe, comparing different routes of administration of vitamin K and different dosage schedules since then. Non-carboxylated form of coagulation factors II is one of the commonly used as a marker of vitamin K deficiency and is referred to as ‘protein induced in vitamin K absence’ (PIVKA-II).In many of these studies. Presence of PIVKA-II in blood is considered as a highly specific and sensitive marker of vitamin K deficiency compared to prothrombin time (PT). Many authors have confirmed the reliability of PIVKA-II in diagnosing Vitamin K deficiency.

Sharma, R.K., *et al*., in their prospective study on 51 full term, healthy breastfed newborns "to evaluate if the injectable water soluble preparation of vitamin K (Menadione sodium Bisulfite) could be as effective. This study has tested the efficacy of 2 mg vitamin K orally, with the existing practice of 1 mg vitamin K intramuscularly and controls. Any detectable level of PIVKA II was considered as the primary outcome in the study. "PIVKA-II levels were measured in cord blood and at 72-78 hours of age. The overall PIVKA-II prevalence in cord blood was 64.7%. 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. 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. 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. Basing on these study findings the authors concluded that vitamin K prophylaxis is required for all newborns at birth and injectable vitamin K (menadione sodium bisulfite) given orally to term healthy babies is effective in preventing vitamin K deficiency state"[7].

The study included term infants andexact median PIVKA II values and the sustainability of the effect beyond 78 hours was not evaluated in this study, hence drawing comparison with present study findings is difficult. Greer, F. R., *et al*., havenew oral preparation of vitamin K1 (Konakion MM) with a standard intramuscular (IM) preparationand monitored, Prothrombin time (INR), plasma vitamin K1 and PIVKA II (undercarboxylated prothrombin) were monitored at 14, 30, and 56 days of age. PIVKA II was raised (> or = 0.1 AU/ml) in cord blood in 47% of the infants. By 14 days, only one infant in each group had a raised

PIVKA II value and both of these initially had high concentrations of PIVKA II in cord blood. At 30 days, there were no raised PIVKA II values. At 56 days, there were no raised PIVKA II values in the oral group, although three infants in the IM group had raised values. Basing on the study findings, the authors have concluded that Plasma vitamin K concentrations were at least equal or significantly higher in babies given oral vitamin K supplements compared with IM treated babies at the time points measured"[8, 9].

Cornelissen, E. A., *et al*. in their randomised clinical trial on 165 healthy breast fed infants, have compared 1 mg vitamin K1 orally with IM after birth. The infants were followed upat 2 weeks and 1month and 3 months of age. The study concluded "Although vitamin K1 concentrations were statistically significantly higher in the

intramuscular group, blood coagulability, activities of factors VII and X and PIVKA-II concentrations did not reveal any difference between the two groups. At 2 weeks of age vitamin K1 concentrations were raised compared with reported unsupplemented concentrations and no PIVKA-II was detectable. At 3 months vitamin K1 concentrations were back at unsupplemented values and PIVKA-II was detectable in 11.5% of infants. Therefore, a repeated oral prophylaxis will be necessary to completely prevent (biochemical) vitamin K deficiency beyond the age of 1 month[10]".

Conclusion

It is vital to administer appropriate dose of vitamin K, whichis efficacious and at the same time doesn't unduly increase the risk of liver dysfunction, hyperbilirubinemia and resulting brain injury.

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