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The effect of 3 regimens (0.3mg Vs0.5mg vs 1mg.I.M.) of vitamin K1prophylaxis at birth on vitamin k status in preterm And/Or VLBW infants

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Abstract

Vitamin K deficiency of the newborn has the potential risk of Vitamin K deficiency-related bleeding (VKDB) between birth and up to six months.Vitamin K deficiency may cause unexpected bleeding during the first week of life in previously healthy appearing neonates (early vitamin K deficiency bleeding [VKDB] of the newborn. 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 proportion neonates, who had Necrotizing Enterocolitis (NEC) (≥ Stage 3 by Modified Bell staging) was 4.2%, 11.5% and 8.0% in intervention group A, B and C respectively. The difference in this proportion was statistically not significant (P value 0.631). The proportion neonates, who had pulmonary hemorrhage was 0.0%, 7.7% and 4.0% in intervention group A, B and C respectively. The difference in these proportion was statistically not significant (P value 0.382).

Keywords: Vitamin K1prophylaxis, preterm, VLBW infants

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 concentrations. Neonates are especially prone for vitamin K deficiency at birth. The reasons are many, there is little transplacental transfer of vitamin K. After birth, they are preferentially fed maternal milk, which contains low concentrations of vitamin K1.

Premature infants are even at higher risk of vitamin K deficiency as they have additional risk factors like delayed enteral feeding, retarded micro floral gut colonization and delayed endogenous synthesis of menaquinones (vitamin K2). In addition, they frequently receive drugs such as antibiotics that antagonize vitamin K directly or reduce its availability[2].

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Vitamin K deficiency of the newborn has the potential risk of Vitamin K deficiency-related bleeding (VKDB) between birth and up to six months.Vitamin K deficiency may cause unexpected bleeding during the first week of life in previously healthy appearing neonates (early vitamin K deficiency bleeding [VKDB] of the newborn [formerly known as classic haemorrhagic disease of the newborn]). The reported incidence of classic haemorrhagic disease of the new born in between 0.25%-1.7% across the globe. 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. 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[3].

Even though the practice of administering Vitamin K prophylaxis has been in vogue for the last few decades, there is still no national or international level consensus on the appropriate dose, route and schedule of the vitamin K which is safe and efficacious. Routine prophylaxis with either IM or oral administration after birth with variable route of administration is quite variable across different nations. In the United States, the AAP recommended standard is IM administration of 0.5 mg for birth weight <1,500 g and 1 mg for newborns ≥1,500 g within the first six hours after birth.Oral dosing of 1 mg weekly for the first three months likely provides the same protection as the single IM dose at birth[4].

There is an underlying concern that high vitamin K dosing could cause detrimental effects like hyperbilirubinemia,kernicterus,hemolytic jaundice' and lower dosing could still lead to VKDB. Preterm infants with higher susceptibility to develop VKDB. Many premature infants receive doses even as high as 5 mg for various reasons and with their immature hepatic function, very preterm infants may be especially susceptible to any adverse consequences of large vitamin K doses. Considering the possible serious adverse consequences of both under dosing and excessive dosing, aadministering appropriate dose of vitamin K is even more important in premature infants[5].

Few studies exist regarding dosage of prophylactic Vitamin K in preterm infants and evidence is conflicting and there is wide variation in dose, route and formulation of vitamin K used for preterm infants. Extensive literature search showed only one RCT on vitamin K prophylaxis in preterm infants. Clarke *et al*. showed that even a dose of 0.2mg is as effective as 0.5 mg in infants <32 weeks & prevents hepatic overload of vitamin K metabolite (vitamin K2,3 epoxide) which is seen in babies receiving 0.5mg IM. Considering the small sample size in a forementioned study, thequantity of evidence is also very limited in this vital area. There are practically no studies conducted on Indian premature infants in this subject. Hence there is still lack of national and international consensus on ideal dose and route of administration of vitamin K to achieve the desired goal of provision of adequate protection against VKDB while avoiding unnecessary overload[6].

Methodology

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[58].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

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prevent the visibility. Each time when the participant was recruited the opaque cover was opened and the intervention was communicated to the investigator.

Ethics approval was obtained from institute Human Ethics Committee. Informed written consent was sought from all the parents, after thoroughly explaining the study objectives, nature of the intervention, risks and benefits of the intervention to the participants. Complete voluntary nature of participation in the study was explained and no undue pressure or coercion was exerted on the parents. Parents were informed that, they are free to withdraw their child from the study at any point during the course of the trial. Confidentiality of the study participants was maintained throughout the conduction, analysis and reporting of the study findings.

The vitamin K (Kenadion), containing Phytomenadione (0.5mg/mL), a synthetic form of vitamin K1was used in the study. The product was stored at room temperature away from excess heat, light and moisture.

The ingredients in Kenadion with no preservatives include

- 1 mg of Vitamin K1, a fat-soluble vitamin derived from plants.
- 10 mg of Polysorbate 80, which helps Vitamin K1 (a fat-soluble Vitamin) dissolve in liquid for the injection. Polysorbate 80 is made from natural sorbitol and plant-based oleic acid, is used in a wide variety of foods, medicines and vitamin supplements, and is included in the Handbook of Green Chemicals.
- 10.4 mg of Propylene glycol, which helps absorb extra water and maintain moisture in certain medicines. Propylene glycol has been recognized as safe by the FDA for use in food products.
- 0.17 mg of Sodium acetate anhydrous, a mixture of salt and bicarbonate that is used to adjust the pH of the injection.
- 0.00002 mL of Glacial acetic acid, also known as vinegar that is used to adjust the pH of the injection.

Informed written consentwas obtained beforehand, in case of the anticipated preterm delivery or after the delivery in the unanticipated cases. Each consented participant was allotted a serial number. The investigator contacted the faculty member with the randomization sequence, for the treatment code for each participant and the appropriate dosing regimen was obtained. As per the instructions of the investigator, the physician attendant/staff nurse, prepared the drug and administered it to the infant intra muscularly using 1cc syringe along with 26 and half gauge needle on anterolateral aspect of right thigh (left thigh if contraindicated on right for any reason) and was documented. As per the unit policy, the infants were evaluated by cranial ultrasonography on day 1, 3 and 7 in extreme preterm (weight < 1000 gms) and day 3 and7in moderate preterm babies (weight ≥1000 gms). Any infant showing abnormal finding in the initial scans were followed up by weekly ultrasounds.The USG grading was done according to PAPILE'S staging.

During the entire study period, all the participants were closely monitored for nay bleeding. Any participant showing clinical signs of bleeding, as a measure of safety, a single additional

dose of 0.2mg IM of vitamin K was immediately administered, and PT and PIVKA levels were seen to see if bleeding was due to VKDB.Any babies on antibiotic were given Vitamin K 0.2mg twice weekly[59, 60].

For all these infants serum samples were immediately sent for PIVKA II levels and prothrombin time. Cord blood of the infant was obtained at delivery and peripheral venous blood samples for serum PIVKA II after 5 days and day 28. Blood volume required for test is very low (0.5ml) and was least likely to cause any adverse effects. As preterm require regular investigations like serum bilirubin, electrolytes, CBC, especially sick preterm, blood samples were collected forthese investigations and separate prick to collect samples for the purpose of the study was not needed. Blood samples were protected from light and immediately

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transported for centrifugation and serum stored at -20°C until analysis.
For each infant completing the study, absolute vitamin K intake was assessed at 28 days of life. This was calculated from the sum amounts received from allocated prophylaxis dose, any extra bolus dose, enteral feeds, and total or partial parenteral nutrition (TPN) or PPN.As per our unit policy we use lipids rarely and no Vitamin K is present in amino acids and multivitamin we use. We followed aggressive enteral nutrition and PPN was stopped as early as possible.

Results

Table 1: Comparison of post intervention PIVKA on day 5 among the intervention groups

Parameter	Intervention group			p-Value
	A (N=24)	B (N=26)	C (N=25)	
PIVKA Units AU/ml i(Median ±IQR)	0	0.18 ± 0.9	0.41 ± 1.42	0.346
PIVKA groups				
Normal	24 (100%)	23 (88.46%)	22 (88%)	*
Abnormal	0 (0%)	1 (3.85%)	2 (8%)	
Death	0 (0%)	2 (7.69%)	1 (4%)	

Total of 5 children were lost to follow up and 4 children met with mortality by day 28, hence the number of children left were 21, 23 and 22 respectively in intervention group A, Band C respectively. The median cord PIVKA value on day 28 was 0.0, 0.0 and 0.516 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 (pvalue 0.130). When presented as binary variable the proportion of subjects with abnormal PIVKA values was 0%, 0% and 8% respectively among intervention group A, B and C respectively.

Table 2: Comparison of post intervention PIVKA on day 28 among the intervention groups

Parameter	Intervention group			p-Value
	A (N=24)	B(N=26)	C(N=25)	
D28 PIVKA AU/ml (Median ±IQR)	0	0	0.516±1.79	0.13
D 28PIVKA groups				
Normal	21 (87.5%)	23 (88.46%)	20 (80%)	*
Abnormal	0 (0%)	0 (0%)	2 (8%)	
Lost to follow-up	2 (8.33%)	1 (3.85%)	2 (8%)	
Death	1 (4.17%)	2 (7.69%)	1 (4%)	

The proportion of children with abnormal USG findings was 0%, 7.7% and 4% among the three intervention groups of A, B and C respectively. The difference in these proportion was statistically not significant (P value 0.382). In all theinfants, who had abnormal USG findings, the prothrombin time and PIVKAIIlevels were normal, hence the abnormal USG findings were not attributable to vitamin K deficiency bleeding.

Table 3: Comparison of ultrasonography findings among the intervention groups

Parameter	Intervention group			p-Value
	A (N=24)	B(N=26)	C(N=25)	
USG < 72 hours infrequency (%)				
Normal	24(100.0%)	24(100.0%)	24(100.0%)	0. 382
Abnormal (≥ Stage II according PAPILE'S staging)	0(0.0%)	2(7.7%)	1(4.0%)	

The proportion of neonates, who received phototherapy was 95.8%, 96.25 and 100% in intervention group A, B and C respectively.The difference in these proportion was

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statistically not significant (P value 0.597). The median duration of phototherapy in hours was higher in intervention group A(80.00±32.0), compared to group B and C (48.000±12.0).This difference in the duration of phototherapy was statistically significant (P value 0.005).

Table 4: Comparison of phototherapy status among the intervention groups

Parameter	Intervention group			p-Value
	A (N=24)	B(N=26)	C(N=25)	
Phototherapy received in frequency(%)				
Yes	23(95.8%)	25(96.2%)	25(100.0%)	0.597
No	1(4.2%)	1(3.8%)	0 (0.0%)	
Duration of phototherapy (Median ±IQR)	80.00±32.0	48.00±12.0	48.000±12.0	0.005

Comparison of Vitamin K1 total dose showed no statistically significant difference in the median dose of vitamin K1 received among the three intervention groups intervention groups.

Table 5: Comparison of Vitamin K1 total dose received among the intervention groups

Parameter	Intervention group			p-Value
	A (N=25)	B(N=24)	C(N=26)	
K1 Total (Mean ± IQR)	156±47.25	138±342	168±344	0.618

Comparison of highest bilirubin showed higher levels of values in intervention group A, when compared to the other two intervention groups.Highest bilirubin (mg/dl) showed gradual increasing trend from intervention group C (8.30±0.85)o intervention group A (10.68±2.43).

Table 6: Comparison of highest bilirubin among the intervention groups

Parameter	Intervention group			p-Value
	A (N=25)	B(N=24)	C(N=26)	
Highest bilirubin (Mean ± IQR)	10.68±2.43	8.83±1.93	8.30±0.85	<0.001

The proportion neonates, who had Necrotizing Enterocolitis (NEC) (≥ Stage 3 by Modified Bell staging) was 4.2%, 11.5% and 8.0% in intervention group A, B and C respectively. The difference in this proportion was statistically not significant (P value 0.631). The proportion neonates, who had pulmonary hemorrhage was 0.0%, 7.7% and 4.0% in intervention group A, B and C respectively. The difference in these proportion was statistically not significant (P value 0.382).

None of these infants had abnormal PIVKA or PT and was attributed to Prematurity.

Table 7: Comparison of other relevant parameters among intervention groups

Parameter	Intervention group			p-Value
	A (N=24)	B(N=26)	C(N=25)	
NEC (frequency (%))				
Yes	1(4.2%)	3(11.5%)	2(8.0%)	0.631
No	23(95.8%)	23(88.5%)	23(92.0%)	
Pulmonary hemorrhage (frequency (%))				
Yes	0(0.0%)	2(7.7%)	1(4.0%)	0.382
No	24(100.0%)	24(92.3%)	24(96.0%)	

Discussion

Many other similar studies by Rossi R *et al.*[7], Hansen KN *et al.*[8], Chawla, D., *et al.*[9]compared the efficacy of different formulations, dosage schedules and route of administration of vitamin K in preventing VKDB, with varied clinical and laboratory

outcomes.

But none of the above mentioned studies have studied the optimum dose of Vitamin K in premature infants, which is the primary objective of the current study. Very few studies by Clarke, P., *et al*.,[10],Costakos, D.T., *et al*.[11]and Kumar, D., *et al*.[12]have addressed the issue of optimum dose in premature infants. Higher susceptibility of premature infants to develop VKDB and also to develop adverse toxicity to higher doses of vitamin K including liver dysfunction, hyperbilirubinemia and kernicterus, administering appropriate dose of vitamin K is even more important in premature infants. There are practically no studies conducted on Indian premature infants in this subject, addressing the issue of appropriate dose of vitamin K.

The current study in an attempt to fill in this vital gap in the knowledge, has studied compared the efficacy of 0.3 mg IM dose of vitamin K 1, with the earlier suggested doses of 0.5 mg and 1 mg IM doses. Serum PIVKAII value was taken as the primary outcome measure indicating vitamin K deficiency.

In the current study, the proportion of infants with abnormal cord PIVKA values was 58.7% in the entire study population. (Need to be compared with other studies). The prevalence of PIVKA-II positivity in cord blood has varied from 0 to 89%. In the study by Sharma, R. K., *et al*., The overall PIVKA-II prevalence in cord blood was 64.7%[13].Von Kries, R. *et al*., have reported abnormal PIVKA II values in 49.47% of the infants[14].Motohara, *et al*. (11) used a cutoff value of abnormally elevated PIVKA-II as a level more than 0.1 AU (Arbitrary Unit)/mL. They detected PIVKA-II in 21.5% of cord blood samples. In their study of 170 infants, Chawla D *et al*., have considered PIVKA-II level of >2 ng/mL was considered as 'detectable' and have found that PIVKA-II levels were >2 ng/mL in 48.2% (41/85) babies in Group I (phytomenadione) and 44.7% (38/85) babies in Group II (Menadione)[9].

In the current study, the median cord PIVKA II value on day 5 after the intervention was 0.0, 0.180 and 0.410 among the intervention groups with 1 mg, (A) 0.5 mg (B) and 0.3 mg (C) doses respectively. The proportion of subjects with PIVKA II levels above the critical value of >0.5 Au/ml was 0%, 3.85% and 8.0% respectively among intervention group A, B and C respectively. On day 28, the median PIVKA values were 0.0, 0.0 and 0.516 among the intervention groupsof A,B and C respectively. The proportion of subjects with PIVKA II levels above the critical value of >0.5 Au/ml was 0%, 0% and 8% respectively among intervention group A, B and C respectively. Clarke, P., *et al*., have compared the PIVKA II values among the three intervention groups receiving, Vitamin K1 0.5 mgintra muscular dose (control) or 0.2 mg intramuscular or 0.2 mg intravenous doses as the secondary outcome. On day 5, the median PIVKA II values reported in the study were 0.62, 0.51 and 0.36 among the three intervention groups. The proportion of infants with PIVKA II values above 0.5 Au/ml was 7%, 9% and 14% respectively on day 5. On day 25 the median PIVKA II values reported were 0.20, 0.36 and 0.25 respectively in three intervention groups. The proportion of infants with PIVKA II values above 0.2Au/ml was 4% in all the intervention groups on day 28.

But the primary outcome in the study conducted by Clarke, P., *et al*., were serum vitamin K1, its epoxide metabolite (vitamin K1 2,3-epoxide) and undercarboxylated prothrombin assessed at birth, 5 days and after 2 weeks of full enteral feeds. The study results showed "On day 5, serum vitamin K1 concentrations in the 3 groups ranged widely (2.9-388.0 ng/mL) but were consistently higher than the adult range (0.15-1.55 ng/mL). Presence of vitamin K1 2,3-epoxide on day 5 was strongly associated with higher vitamin K1 bolus doses. Vitamin K1 2,3-epoxide was detected in 7 of 29 and 4 of 29 infants from the groups that received 0.5 mg intramuscularly and 0.2 mg intravenously, respectively, but in none of 32 infants from group that received 0.2 mg intramuscularly. After 2 weeks of full enteral feeding, serum vitamin K1 was lower in the infants who received 0.2 mg intravenously compared with the infants in the control group. Three infants from the 0.2-mg groups had undetectable serum vitamin K1 as early as the third postnatal week but without any evidence of even mild functional deficiency, as shown by their normal undercarboxylated prothrombin concentrations". The study has

concluded that, to protect against late vitamin K1 deficiency bleeding, breastfed preterm infants given a 0.2-mg dose of prophylaxis should receive additional supplementation when feeding has been established".

In another study, by Costakos*et al*., preterm neonates who were given 0.5 to 1 mg vitamin K prophylaxis also showed vitamin K levels that were 1,900 to 2,600 times higher (2 days afterwards) and 550 to 600 times higher (10 days afterwards) than normal adult plasma values (0.5 ng/mL). Basing on their study findings, the authors have concluded that "0.5 mg as the initial dose of vitamin K intramuscularly or intravenously would likely be more than adequate to prevent hemorrhagic disease of the newborn, and that 0.3 mg/per kg may be used for babies with birth weights below 1000g".Even though the primary outcome measure in the current study is different, the findings of the study strongly substantiates the comparable efficacy of lower doses of vitamin K 1 as documented in studies by Clarke, P., *et al*.[14]and Costakos*et al.* [11].

Even though concerns have been raised about the possible risks of supraphysiologic vitamin K1 doses used for preterm infants and many authors suggesting "it would be appropriate to give less vitamin K to preterm babies till we thoroughly understand the physiological role ofall vitamin K-dependent proteins not many studies have directly documented the adverse effects. In the current study, comparison of highest bilirubin showed higher levels of values in intervention group A (1 mg group), when compared to the other two intervention groups (0.5 mg and 0.3 mg groups). Highest bilirubin showed gradual increasing trend from intervention group C (8.30±0.85)o intervention group A (10.68±2.43).

In the randomized controlled trial by Clarke, P., *et al*., "Vitamin K1 prophylaxis with 0.2 mg administered intramuscularly maintained adequate vitamin K status of preterm infants until a median age of 25 postnatal days and did not cause early vitamin K1 2,3-epoxide accumulation. In contrast, 0.2 mg administered intravenously and 0.5 mg administered intramuscularly led to vitamin K1 2,3-epoxide accumulation, possibly indicating overload of the immature liver."[10] But he other studies by Costakos, D. T., *et al*.[11]and Kumar, D., *et al*.[12]conducted on premature infants have not made any explicit mention of hepatic injury or any other adverse effects on vitamin K1 administration.

So it can be concluded that, it is vital to administer appropriate dose of vitamin K, which is efficacious and at the same time doesn't unduly increase the risk of liver dysfunction, hyperbilirubinemia and resulting brain injury. The dose of 0.5 mg and 1 mg doses, even though highly efficacious may put the premature infant at undue risk of hepatic injury and the resulting hyperbilirubinemia remote possibility of resulting brain injury, which may need long term follow up and monitoring of the infant. Hence we conclude that the 0.3 mg vitamin K administered through IM route at birth may be sufficient to prevent the VKDB in premature infants and has the better safety profile, compared to the higher doses.

Conclusion

- There was no statistically significant difference in the serum PIVK levels among the three intervention groups, hence it can be concluded that 0.3mg of IM vitamin K is as efficacious as the higher doses of 0.5 mg IM and 1 mg IM doses of vitamin K, in premature infants.(≤ 32weeks and/or ≤ 1500g).
- The average highest bilirubin value has shown gradually increasing trend with increasing dose of vitamin K. Hence it can be concluded that lower (0.3 mg IM) vitamin K dose is safer in premature infants.(≤ 32weeks and/or ≤ 1500g).

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