Original Article

Effect of oral vitamin K prophylaxis on prothrombine time and activated partial thromboplastin time: a randomized controlled comparison with an intramuscular vitamin K in infants

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Abstract

Background Low plasma concentration of vitamin K in the newborn accounts for serious bleeding in the neonatal period and early infancy. The aim of prophylactic vitamin K is to prevent bleeding. Oral prophylaxis is preferable to intramuscular (IM) administration because oral administration is less expensive and less traumatic.

Objective To compare oral vs. intramuscular vitamin K on prothrombine time (PT) and activated partial thromboplastin time (APTT) during the first 60 days of life.

Methods We randomized newborn infants to either receive oral vitamin K 2 mg at birth and repeated at 7 and 30 days of life or the 1 mg intramuscular vitamin K. PT and APTT were monitored at 0, 15, and 45 days of age. Independent *t*-test, repeated measurement, and regression analysis were used for statistical analyses and comparison of the results.

Results Fifty infants were assigned into the oral group and 50 to the IM group. All participants completed 60 days of study. Both PT and APTT decreased after administration of oral or IM vitamin K, and the values did not differ significantly at any time point and through the period of investigation. Using regression analysis it was shown that only vitamin K administration was correlated with PT and APTT with P value were 0.044 and 0.036, respectively. During 60 days of study, there was no hemorrhagic diathesis in both groups.

Conclusions Through the first 60 days of life, 3 doses of oral vitamin K maintain hemostasis by decreasing PT and APTT in infants at values equal to those achieved by the intramuscular preparation. Diathesis hemorrhagic event did not occur in both groups.[Paediatr Indones 2007;47:109-114].

Keywords: oral vitamin K, prophylaxis, PT, APTT

Vitamin K intake in newborn infants warrants special attention because the placenta is a relatively poor organ for the maternal-fetal transmission of lipid, neonatal liver is immature in term of prothrombine synthesis, and the gut is sterile during the first few days of life. Low plasma concentration of vitamin K may cause serious bleeding in the neonatal period or early infancy, which may be classified as early, classical, and late bleeding, based on the timing and type complication.[1-3]

Vitamin K deficiency can be detected by monitoring clinical manifestation of hemorrhagic diathesis and by laboratory investigation.[2] The aim of vitamin K prophylaxis is to prevent bleeding. Administration and dose of vitamin K prophylaxis vary in practice. Oral prophylaxis is preferable to parenteral prophylaxis because oral administration is as effective, less expensive, and less traumatic than intramuscular

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administration. There has been a concern that intramuscular vitamin K is associated with a doubling risk of malignant disease in children.[4,5]

The purpose of this study is to compare the effect of oral preparation of vitamin K with an intramuscular preparation on the prothrombine time (PT) and activated partial thromboplastin time (APTT) in infants during the first 60 days of life.

Methods

This was a randomized clinical trial conducted at the neonatal ward and outpatient clinic, Department of Child Health, Medical School, Udayana University, Sanglah Hospital, Denpasar from March 1 until June 30, 2005. The study was approved by the Human Study Ethical Committee of Sanglah Hospital. The nature and purpose of the study was explained to parents of all subjects and informed consent was obtained before any subject was investigated.

Infants with gestational age of 37-42 weeks, birth weight >2500 g, singleton, and Apgar score ≥7 at five minute were eligible for the study. We excluded infants with major congenital malformation or malabsorptive disorders or maternal history of anticonvulsant treatment during pregnancy.

Immediately after birth, infants who met the inclusion criteria were randomly assigned to either receive standard 1 mg intramuscular injection of vitamin K or a 2 mg oral dose of vitamin K1. Randomization was accomplished using a computer generated list, randomized in blocks of four. Because of the different methods of drug administration, subjects and clinical study personnel were not blinded to the different treatments. Intramuscular vitamin K was given according to standard hospital practice, while oral preparation was given by drawing 2 mg of medication in a teaspoon, and dispensing it to infant's mouth. The infant was observed for five minutes and if any spitting was noted, the infant was given a dose of intramuscular vitamin K and dropped from the study. The oral dose was repeated at home by parent on 7 and 30 days of age, to give a total dose of 6 mg in the 1st month of life. If an infant in the oral group dropped out before completing the eight week study, an intramuscular dose of vitamin K was given and the infant was excluded from analysis.

Venous blood specimen (2 ml) were collected at 0, 14, and 45 days of age. PT and APTT were measured with Coag-A-Mate XM (Organon Teknika). Results were expressed as seconds. Laboratory personnel were blinded to the infant's randomization.

Statistical analyses were performed using X^2 test, repeated measurement, and logistic regression. Data were analyzed using soft ware SPSS 11.5 for Windows. Data were presented as means with their 95% confidence interval (CI). $P<0.05$ was considered significant. Because it was an "on treatment analysis" one, dropouts were replaced and randomization was continued until a minimum of 50 valuable infants (completing the eight week study period) was obtained in each treatment group.

Results

One hundred infants were enrolled in the study, 50 in the oral group and 50 in the IM group. Seven infants in the oral group and 7 infants in the IM group *dropped out* before completing the eight week study period were replaced for the analysis. Mean gestational age for oral and IM group was 39.4 (SD 1.1) weeks vs. 39.1 (SD 1.15) weeks and mean birth weight was 3138.0 (SD 338.3) grams vs. 3088.4 (SD 394) grams, respectively.

No spitting or diarrhea following oral vitamin K administration were noted. None of the infants in both groups suffered from jaundice during study period. Most of the infants were breastfed during observation, 41 infants in the oral group and 42 infants in the IM group. **Table 1** depicts the baseline characteristic of the study group.

Table 1. Baseline characteristic of the study subjects in both groups

	Oral	Intramuscular
Sex, n (%)		
Boys	27 (54)	25 (50)
Gestational age (wk), mean (SD)	39.3 (1.1)	39.1 (1.1)
Birth weight (g), mean (SD)	3150.0(346.8)	3093.4(406.8)
Mode of delivery, n (%)		
Spontaneous	41 (82)	39 (78)
Cesarean section	9 (18)	11 (22)
Nutrition, n (%)		
Breast milk	41 (82)	42 (84)
Combination	9 (18)	8 (16)
Antibiotic, n (%)	7 (14)	11 (22)

Tabel 2. Mean value of PT and APTT at measurement on days 0, 15, and 45

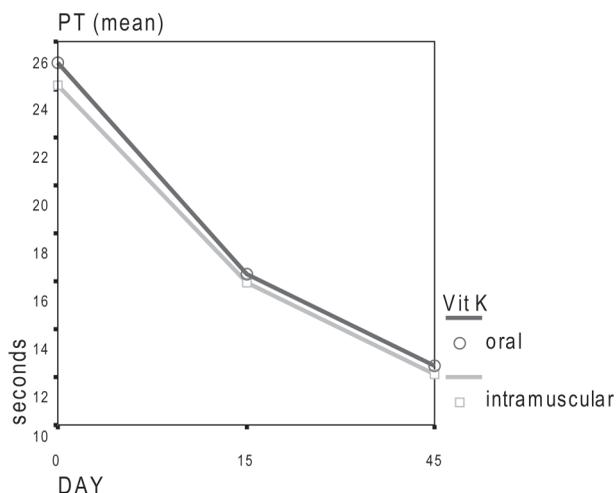|	Oral	Intramuscular	Mean	P	95% CI
PT					
Day 0	25.1(8.3)	24.1(8.2)	1.0	0.55	-2.29;4.27
Days 15	16.2(2.5)	15.9(2.6)	0.3	0.51	-0.68;1.35
Days 45	12.4(1.6)	12.1(1.5)	0.3	0.29	-0.28;0.94
APTT					
Day 0	39.3 (11.8)	36.2(7.74)	3.1	0.12	-0.83;7.07
Days 15	29.4(6.8)	26.7(5.3)	2.7	0.3	0.25;5.09
Days 45	22.6(5.6)	20.3(4.2)	2.3	0.23	0.32;4.28

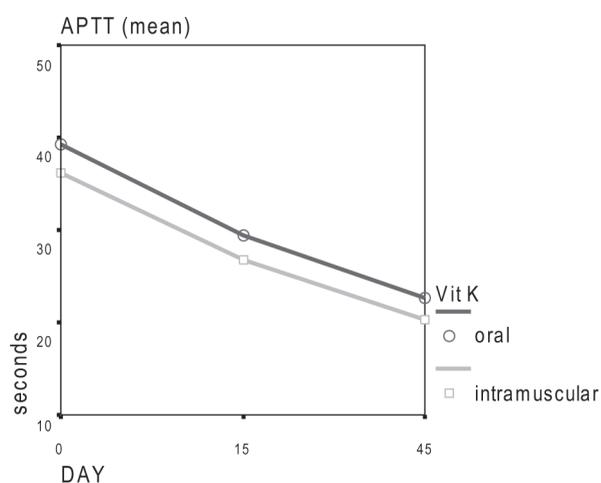**Figure 1.** Repeated measurement of PT through study period 45 days

Figure 2. Repeated measurement of APTT through study period 45 days

PT and APTT measurements

Mean value of PT decreased on day 15 and 45 after oral and IM vitamin K administration as compared to the mean values at birth. The levels in both groups did not differ significantly at any time point of measurement (**Table 2**). Similarly, the mean values of APTT levels in the both groups did not differ significantly on days 0, 15, and 45 (**Table 2**).

Analysis using repeated measurements showed that the PT value decreased after administration of oral or IM vitamin K prophylaxis, but comparison between groups did not show significant difference (**Figure 1**). APTT values also showed no statistically difference between both groups (**Figure 2**).

Multivariate analysis of factors associated with PT and APTT value

Table 3 showed multivariate analysis for PT and APTT. Multivariate analysis of independent variables such as birth weight, antibiotic administration, and type of nutrition did not show significant relationship with PT value, and only vitamin K administration showed significant relationship (P=0.04). Multivariate analysis for APTT also revealed that variable of birth weight, antibiotic administration, and type of nutrition did not show significant relationship, and only vitamin K administration showed significant relationship (P=0.03).

Adverse events

During 60 days of study period, there was no hemorrhagic diathesis event or other adverse events in any of the participants in both groups.

Table 3. Multivariate analysis for factors that influence PT value

Variables	B	SE	T	P	95%CI
Vitamin K	-0.94	0.54	-0.51	0.04	-1.87;-0.03
Birth weight	0.00	0.00	1.27	0.20	-0.001;0.007
Antibiotic	1.70	2.01	0.84	0.40	-2.30;5.70
Nutrition	-0.28	1.01	-0.28	0.77	-2.31;1.73

Table 4. Multivariate analysis for factors that influence APTT value

Variables	B	SE	T	P	95%CI
Vitamin K	-0.87	0.47	-0.54	0.03	-1.73;-0.01
Birth weight	0.002	0.00	0.77	0.44	-0.002;0.005
Antibiotic	-0.13	1.93	-0.07	0.94	-3.97;3.70
Nutrition	0.86	0.98	0.88	0.38	-1.08;2.79

Discussion

An understanding of hemostasis and unique features of the neonates in the early weeks of life is important in investigating neonate with a hemorrhagic problem. The hemostatic system is influenced by age, and the concentrations of many haemostatic proteins are dependent on both gestational and postnatal age of the infant. At birth, the concentrations of the vitamin K dependent (F II, F VII, F IX, F X) and contact factors (F XI, F XII) are reduced to about 50% of normal adult values and are further reduced in preterm infants.[6] Besides immaturity of hemostatic system, physiologic vitamin K deficiency also occur in newborn. This problems make the administration of vitamin K prophylaxis becomes important for newborn.[7]

Use of oral vitamin K1 in newborn infants has become more widespread following a report of an association between intramuscular vitamin K1 in the newborn and childhood cancer.[5,8] However, other investigators have not confirmed the association.[9] Moeslichan,[10] in 2001 made a proposal about oral vitamin K prophylaxis administration as one of the strategies to decrease infant mortality rate.

Vitamin K deficiency can be detected by laboratory investigations. Babies with vitamin K deficiency show prolongation of PT and APTT, decrease activity of vitamin K coagulation factors (F II, F VII, F IX, and F X), increase of PIVKA II concentrations, with normal platelet and fibrinogen value.[2]

This is the first study in Indonesia comparing the effect of oral and intramuscular vitamin K prophylaxis on PT and APTT. Measurement of PT and APTT were done at 0, 15, and 45 days of age. Measurement at the first day of life was used as baseline data, while at 15 and 45 days were used to monitor effect of 2nd and 3rd oral dose vitamin K administration.

Greer *et al*[11] compared directly oral mixed micellar vitamin K with intramuscular preparation. Greer concluded that three doses of oral vitamin K prophylaxis maintain hemostasis and vitamin K status in breast fed infants at values that were equal to those achieved by intramuscular preparation up to 8 weeks of life.

This study revealed that PT and APTT value was decreased significantly after administration of both oral and intramuscular vitamin K compared to value at birth. At birth, mean PT value over the normal range 10.1-15.9 seconds.[12] This findings revealed that physiologic vitamin K deficiency occur in the newborn.

PT and APTT levels of participants with oral or intramuscular vitamin K did not differ significantly at any point measurement. Using repeated measurement analysis it was also shown that PT and APTT value did not differ significantly between oral and intramuscular vitamin K (P=0.665).

Measurements of PT and APTT have some limitations; it appears that PT and APTT are not ideal screening tool for subclinical vitamin K deficiency compare to PIVKA II assay.[13] Several factors that influence the results of PT and APTT measurement include blood sampling and laboratory procedure. Blood sampling from neonate should be avoided from tissue fluids contamination because it can activate the coagulation process. Laboratory procedure should also notice temperature, water quality, pH, and sample preservation.[14] Since other laboratory investigations are not available in Denpasar, we used only PT and APTT measurement. Laboratory personnel were blinded to infant's randomization.

A regimen of multiple doses of vitamin K given orally requires further consideration. A single oral dose offers protection for only approximately 4 weeks whereas single intramuscular dose appears to be effective for at least 2 months. The period of greatest vulnerability for VKDB is between 6 and 8 weeks of age.[15]

The incidence of late VKDB after a single oral dose reported approximately 1.4 to 6.4 per 100,000 births.[16] A study using 4 oral doses of 1 mg vitamin K1 found two babies developed late VKDB in 182 000 babies given oral prophylaxis due to undiagnosed liver disease.[17] There was no bleeding episodes of any kind in infant given 3 oral doses of vitamin K.[11]

American Academy of Pediatrics (AAP) recommends vitamin K1 should be given to all newborns as a single, intramuscular dose of 0.5 to 1 mg. If an appropriate oral form is available, it should be given at birth (2.0 mg) and should be readministered at 1 to 2 weeks and at 4 weeks of age to breastfed infants. If diarrhea occurs in exclusively breastfed infants, the dose should be repeated.[4]

There was no subclinical vitamin K deficiency (monitored by PT and APTT) and hemorrhagic diathesis as well during 2 months study period.

The vitamin K concentration in breast milk is lower than those in infant formula. The amount of milk ingested is also a factor in the development of VKDB in infancy.[18-20] PIVKA II is never detectable in formula-fed infants aged 1 to 3 months as compared with up to 10% of infants of the same age who are fully breast fed.[21]

In this study, all infants tolerated the oral medication very well, no infant spat or diarrhea after administration of oral vitamin K. Multivariate analysis revealed that type of nutrition did not related with PT and APTT levels. This finding might be caused by oral vitamin K administration was sufficient for the activation of the coagulation factors.

Drugs that increase liver microsomal enzyme system include phenobarbital, chloral hydrate, meprobamate, griseofulvin, and haloperidol, will increase the excretion of vitamin K. Antibiotics like chloramphenicol, cephalosporin, and neomycin could interfere gut bacteria and inhibit endogen production of vitamin K.[22] Diseases that impair bile salt excretion like cholestatic liver disease decrease intestinal vitamin K absorption. The study showed that oral vitamin K could not prevent bleeding in cholestatic baby.[23]

All mothers of the study subjects did not receive anticonvulsant drug during pregnancy, and also most of infants did not receive antibiotics. Multivariate analysis showed that antibiotic was not associated with PT and APTT levels. This finding might be due to the short duration of antibiotic administration (5 days) which caused minimal influence to intestine bacteria. In this study we could not assess effect vitamin K on cholestatic baby since none cholestatic patient was found.

Giving three doses of vitamin K1 to infants is problematic and a public health issue because two of which should be given at home. Poor compliance in administering the subsequent doses has already been reported. By giving a complete information to the parents about the importance of vitamin K for preventing bleeding would overcome the problem and increase parent compliance.[20,21]

In this study, by giving information about vitamin K to mother in the hospital and reminding them again during their visit in outpatient clinic, all the infants had completely received three doses of oral vitamin K. There were no major adverse events attributed to both oral and intramuscular vitamin K prophylaxis in this study, at least during the first 2 months of life.

For neonates with increase bleeding tendency include prematurity, asphyxia, delayed oral nutrition, liver disorder, and maternal anticonvulsant should receive intramuscular vitamin K.[23,24]

We are aware of limitations of this study including no vitamin K concentration measurement both in the serum and milk formula, and also a relatively short period for observation that late bleeding could not be assessed.

We conclude that through the first 60 days of life, 3 doses of oral vitamin K maintain hemostasis by decreasing PT and APTT in infants at values that are equal to those achieved by intramuscular preparation.

Acknowledgments

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