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Original Article

# Comparison of the effect of oral multiple dose with single intramuscular vitamin K1 administration on prothrombin time in term baby

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## Abstract

***Background*** Vitamin K deficiency can cause bleeding disorders in healthy breastfed infants. The efficacy of newborn intramuscular vitamin K prophylaxis for the prevention of this bleeding problem has been well established, but this is an invasive procedure. Oral vitamin K prophylaxis is more effective, less expensive, and less traumatic than intramuscular administration.

***Objective*** To compare prothrombin time (PT) after the administration of oral multiple dose vitamin $K_1$ with that after an intramuscular preparation.

***Methods*** Infants were randomised at birth into the intramuscular (IM) group (1 mg vitamin $K_1$) and the oral group (2 mg given at birth and repeated at day 3). PT was monitored before and after the administration of vitamin $K_1$.

***Results*** Thirty six of 70 infants received oral vitamin $K_1$. Mean PT (SD) before vitamin $K_1$ administration was 36.34 (SD 20.03) seconds in oral group and 31.96 (SD 25.51) seconds in IM group, PT changes after vitamin $K_1$ administration were 16.29 (SD 15.46) seconds in oral group and 11.58 (SD 10.62) seconds in IM group, it did not differ significantly (P=0.203).

***Conclusion*** Prothrombin time changes are not significantly different between oral vitamin $K_1$ and IM group. **[Paediatr Indones. 2009;49:281-5]**.

***Keywords:*** *prothrombin time, vitamin $K_1$, oral, intramuscular, term baby*

Hemorrhagic disease of the newborn due to vitamin K deficiency is potentially fatal, affecting as many as 1:100 births. It may occur as an early or late form, and is primarily a risk in breastfed babies.[1] Vitamin K deficiency may cause unexpected bleeding (0.25%-1.7% incidence in USA) during the first week of life in previously healthy-appearing neonates.[2,3] American Academy of Pediatric (AAP) recommends that vitamin $K_1$ should be given to all newborns as a single, intramuscular dose of 0.5 to 1 mg as prophylaxis.[2] The efficacy of newborn intramuscular vitamin K prophylaxis for prevention of this bleeding problem has been well established.[4-6]

Oral vitamin K prophylaxis is preferable compared to parenteral. Several studies have shown that oral administration of vitamin K is as effective, less expensive, and less traumatic than intramuscular administration.[7] Single oral dose at

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birth does not prevent the risk of late hemorrhagic disease.[1] Therefore, a repeated oral prophylaxis will be necessary.[4,8-10] However, compliance with such a regimen is difficult.[1] Croucher and Azzopardi[11] found that compliance with three-dose oral recommendation was poor. More than 10% of breastfed infants do not receive the second dose of vitamin K and less than 40% receive the third one. Ansell et al[12] found that the main reason for not following the official policy of vitamin K prophylaxis is parental refusal or insistence on an oral preparation. The purpose of our study was to compare prothrombin time between two doses of oral regimen given at day-1 and day-3 and single intramuscular vitamin $K_1$.

## Methods

This study was done at Perinatal room at Pirngadi Hospital. Inclusion criteria for infants included a gestational age of 37 weeks or ≤ 42 weeks, a birth weight > 2500 g, singleton, mothers planning to breastfeed their infants until six months of age, absence of major congenital or malabsorptive disorders, no maternal history of anticonvulsant treatment during pregnancy, and Apgar score of ≥ 7 at five minutes. We excluded infants who received antibiotic and suffered from hyperbilirubinemia. Written informed consent was obtained from all mothers and study protocol was approved by the Human Subjects Committee at the University of Sumatera Utara and Pirngadi Hospital.

Immediately after birth, infants were randomised to received either standard 1 mg intramuscular of vitamin $K_1$ or 2 mg oral dose of vitamin $K_1$ (Kaywan). Due to different methods of drug administration, subjects and clinical study personnel were not blinded to the different treatments. Oral preparation was given by dilutional powder with human milk. The infants were observed for five minutes and if any spitting was noted, they were given a dose of intramuscular vitamin K and dropped from the study. Oral dose was repeated on day three. Patient was monitored for bleeding at any site of the body (risk of vitamin K deficiency bleeding) at least six months after birth.

Blood samples from femoral vein (3 ml) were collected in EDTA coated glass tubes before being given injection or oral vitamin $K_1$ and after the second dose of oral preparation. Peripheral blood examinations (Hb, Ht, WBC, platelets) were done on day 1 using automatic cell counter (ABX Micros, France), and prothrombin time was measured at day 1 and day 4 (before and after the administration of vitamin $K_1$) using Automated Blood Coagulation Analyzer Sysmex Ca-50 (Japan). Laboratory personnels were blinded to the infant's randomization. Gestational age was based on New Ballad score. All mothers were expected to breastfeed their infants exclusively. Solid foods were not introduced. The babies who received more than one bottle of formula milk a week were excluded from the study.

Data were collected and the main result was the comparison between plasma prothrombin times in both groups. Mann Whitney and t-test were used, with value of $P<0.05$ considered as significant.

## Results

Seventy infants were enrolled in the study, 36 in oral group and 34 in IM (intramuscular) group. Four infants in oral group and two in IM group dropped out and could not be included in the data analysis due to hyperbilirubinemia (two infants), blood sample could not be analyzed (one infant), refusal to continue with blood examination follow up (PT assays after giving vitamin $K_1$). Thirty two infants in each group completed the study. Maternal and infant characteristics did not differ significantly between oral and IM groups. Characteristics of study subjects are shown in **Table 1**.

There were no major adverse events attributed to the vitamin K preparations used in this study. There were no bleeding episodes of any kind. Mean (SD) prothrombin times before vitamin $K_1$ administration was 36.34 (20.03) seconds in oral group and 31.96 (25.51) seconds in IM group (**Table 2**).

Mean prothrombin time changes in oral group were 16.29 (SD 15.46) more than IM group 11.58 (SD 10.62), but no statistical differences between the two groups ($P = 0.203$). Data were shown in **Table 3**.

**Table 1**. Characteristics of study subjects

| Characteristic | Oral (n=32) | IM (n=32) |
|---|---|---|
| Mother | | |
| Age, mean (SD) yr | 30.91 (5.62) | 31.13 (6.45) |
| Body weight, mean (SD) kg | 58.66 (5.09) | 60.31 (6.45) |
| Number of parity, mean (SD) | 2.72 (1.76) | 2.50 (1.56) |
| Infant | | |
| Male gender, n | 17 | 15 |
| Birth weight, mean (SD) g | 3,303 (377.2) | 3,281 (405.4) |
| Height, mean (SD) cm | 50.4 (1.46) | 49.8 (2.12) |
| Temperature, mean (SD) 0C | 36.7 (0.26) | 36.6 (0.39) |
| Apgar score at 1 min, mean (SD) | 7.9 (0.73) | 7.8 (1.81) |
| Apgar score at 5 min, mean (SD) | 9.2 (0.61) | 8.5 (1.34) |
| Hb, mean (SD) g/dl | 14.27 (2.11) | 14.43 (1.98) |
| Ht, mean (SD) % | 44.74 (6.90) | 44.96 (6.71) |
| RBC, mean (SD) 103/µl | 4.14 (0.59) | 4.17 (0.65) |
| Leucocyte, mean (SD) /µl | 14,56 (6.72) | 14.60 (7.06) |
| Platelet, mean (SD) 103/µl | 243.94 (74.50) | 219.531 (70.27) |

IM = Intramuscular Hb = Hemoglobin Ht = Hematocrit
RBC = Red blood cell

**Table 3**. Comparison of prothrombin time changes after vitamin $K_1$ administration between the study groups

| | Oral (n=32) Mean (SD) | IM (n=32) Mean (SD) | P |
|---|---|---|---|
| PT (second) | 16.29 (15.46) | 11.58 (10.62) | 0.203 |

PT = Prothrombin time
$D_1$ = before vitamin $K_1$ administration (days 1)
$D_4$= after vitamin $K_1$ administration (days 4)

## Discussion

In different parts of the world, various methods of vitamin K prophylaxis are practiced. The benefits of oral prophylaxis are it is easy, non-invasive, and it can also be administered by midwives.[5,10] Because parenteral vitamin K has been shown to prevent vitamin K deficiency or bleeding of the newborn and young infants, and the risks of cancer are unproven, American Academy of Pediatrics still recommends single intramuscular dose vitamin $K_1$ to all newborns.[1] Our study was done to compare the two oral doses (2 x 2 mg) of vitamin $K_1$, with the standard single intramuscular dose of 1 mg. We found that PT did not statistically differ between the two groups. Greer et al[4] concluded that plasma vitamin K concentrations were at least equal or significantly higher in babies given three oral doses vitamin $K_1$ (3 x 2 mg) compared with IM single dose at the time points measured. Multiple doses of the oral preparation maintain hemostasis in breastfed infants at least equal to that of the intramuscular preparation.[5] A single oral compared with a single intramuscular dose resulted in lower plasma vitamin K levels at two weeks and one month, whereas a 3-dose oral schedule resulted in higher plasma vitamin K levels at two weeks and at two months than did a single intramuscular dose.[4,10] There was no evidence that there was any difference between the oral and intramuscular route in effects on biochemical indices of coagulation status.[10]

Vitamin K assays are however too time consuming and expensive for routine diagnosis. Measurement of decarboxy-prothrombin (PIVKA II), which is increased in vitamin K deficiency is more specific and extremely sensitive because it is able to detect the early subclinical deficiency state.[13] Our study did not measure PIVKA because this assay is not available. Despite the sophisticated number of assays for diagnosing vitamin K deficiency, only PT is known to correlate with the risk of bleeding.[13] Cornelissen et al[14] found that blood coagulability, activities of factor VII, X, and PIVKA II concentrations did not reveal any difference after single oral or intramuscular administration, although vitamin $K_1$ concentrations were statistically significantly higher in the intramuscular group. Other study found that oral vitamin K lowers INR or PT more rapidly than subcutaneous vitamin K in asymptomatic patients who have supratherapeutic INR values in the treatment of

warfarin associated coagulopathy.[15] Our study showed that PT value changed after oral administration more than intramuscular preparation. This result suggested that multiple oral vitamin $K_1$ was more effective in maintain hemostasis.

None of the infants in our study had clinical symptoms of bleeding. A retrospective study of Wariyar et al[16] found two breastfed babies (n=182,000) who were given 1 mg vitamin K1 (four doses) developed late vitamin K deficiency bleeding (later diagnosed as $\alpha$1 antitrypsin deficiency), so 1 mg oral dose of vitamin K1 did not suffice.[16] Von Kries et al[17] concluded that new mixed micellar vitamin K (new product) do not significantly improve the efficacy of the 3 x 2 mg oral (with old cremophor) vitamin K prophylaxis schedule.[17] The intestinal absorption of mixed micellar K1 is unreliable in infants with conjugated hyperbilirubinemia. Given the strong association between cholestasis and late vitamin K deficiency bleeding, this data provides an explanation for the failure of some oral vitamin K1 prophylaxis regimens in infants with latent cholestasis.[18]

Concern with vitamin K deficiency should not affect breastfeeding promotional activities because exclusive breastfeeding is a major child survival strategy.[19]

As a conclusion, PT did not differ significantly between two oral doses (2 x 2 mg) given at birth and on day 3 and single intramuscular (1 mg) vitamin $K_1$ prophylaxis given at birth and on day 3. Further investigation with larger subjects needs to be conducted in order to prove the efficacy of this oral dose in preventing late vitamin K deficiency bleeding.

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