

The Comparison Effect of Oral and Intramuscular Injection vitamin K on PT and APTT in Neonates

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ABSTRACT

The aim of this study was to determine the effect of oral versus intramuscular vitamin K on PT (Prothrombin time) and APTT (Activated partial thromboplastin time) in neonates.

Ninety five healthy term live born neonates with birth weight more than 2500 grams who delivered in Mashhad Emmamreza hospital since 6 feb 2006 were elected. They were divided in two groups. The injection group(n=45) that received 1 mg vitamin K (Phytonadion) intramuscularly and oral group (n=50) 2 mg vitamin K Per oral in first 6 hours of age. PT and APTT was measured 12 hours after vitamin K administration.

PT and APTT was measured at 24.78 ± 9.95 hours after vitamin K injection and 22.16 ± 7.4 hours in oral groups (P=0.14). Mean PT in injection group was 16.77 ± 4 second and in oral group was 16.39 ± 2.98 second (P=0.38). Mean APTT in injection and oral group were 37.73 ± 22.25 second and 34.95 ± 7.73 second respectively (P=0.69).

As classic form of hemorrhagic disease of the newborn is prevented with vitamin K.

This study showed that there were not significant differences in PT and APTT between two groups. Therefore both oral and intramuscular vitamin K can prevent classic hemorrhagic disease of the newborn , but for showing prevention effect of oral vitamin K in late onset vitamin K further study is needed for targeting of newborns.

Key Words: Vitamin K deficiency, Newborn, PT, APTT

ÖZET

Yenidoğanda Oral ve İntramuskuler Vitamin K'nın PT ve APTT Üzerine Etkilerinin Karşılaştırılması

Bu çalışmanın amacı, yenidoğanda oral ve intramuskuler K vitamininin PT (protrombin zamanı) ve APTT (aktive parsiyel tromboplastin zamanı) üzerine etkisini karşılaştırmaktır. İmam Rıza Hastanesinde 6 Şubat 2006'dan itibaren doğan 95 sağlıklı ve doğum ağırlığı 2500 gramın üzerinde olan bebekler çalışmaya alınmıştır. Yenidoğanlar iki gruba ayrılmıştır. Doğumdan sonraki ilk 6 saatte enjeksiyon grubuna (n=45) 1 mg vitamin K (Phytonadion) intramuskuler olarak yapılmış ve oral gruba (n=50) 2 mg vitamin K oral yolla verilmiştir. PT ve APTT değerleri vitamin K verilmesinden 12 saat sonra ölçülmüştür.

PT ve APTT değerleri vitamin K enjeksiyonundan 24.78 ± 9.95 saat ve oral grupta 22.16 ± 7.4 saat sonra ölçülmüştür ($P=0.14$). Ortalama PT enjeksiyon grubunda 16.77 ± 4 saniye ve oral grupta 16.39 ± 2.98 saniye olarak ölçülmüştür ($P=0.38$). Ortalama APTT enjeksiyon ve oral gruplarda sırasıyla 37.73 ± 22.25 ve 34.95 ± 7.73 saniye bulunmuştur ($P=0.69$)

Yeni doğanın klasik hemorajik hastalığı, vitamin K ile önlenmiştir. Bu çalışma PT ve APTT değerleri açısından gruplar arasında önemli fark göstermemiştir. Bu nedenle, hem oral hem de intramuskuler vitamin K yeni doğanın klasik hemorajik hastalığını önleyebilir. Ancak, geç dönem sonuçlarının aydınlatılması için ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Vitamin K eksikliği, Yenidoğan, PT, APTT

INTRODUCTION

The classic hemorrhagic disease of the newborn or vitamin K deficiency bleeding (VKDB) occurs between the second and fifth day of life. It is a rare unpredictable and life-threatening hemorrhage, therefore vit K prophylaxis is necessary. Although intramuscular form of vitamin K is most effective, but unfortunately has disadvantages such as trauma to nerve and vessels, pain, osteomyelitis, Abscesses, poor acceptance by parents and potential risk due to very high vitamin K levels (1,2).

Despite the effectiveness of intramuscular vitamin K as prophylaxis is proved, there have been concerns about the need and safety of this method. Indeed a problem that remain to be solved is the effect of prophylactic vitamin K on late onset vitamin K deficiency in newborns.

However, routine vitamin K administration have been used in different methods such as a single intramuscular dose of 1mg vitamin K or an oral dose at birth and repeated at two or four weekly for six to eight weeks. All of these methods are effective in preventing classic form of VKDB but for knowing the effect of vitamin K on late VKDB further study is needed.

Oral vitamin K has not disadvantages of intramuscular one but parents may refuse to use it for prolonged time.

PATIENTS AND METHODS

In a randomized clinical trial all term newborns delivered in Emamreza hospital belong to research center were elected since 6 Feb 2006.

After consent of parents, babies were randomly divided in two groups, first group (injection) were re-

ceived 1 mg vitamin K (phytonadion) intramuscularly and second group (oral) a single dose of 2 mg vitamin K orally in first six hours of age.

Twelve hours after vitamin K, coagulative tests, PT (prothrombin time) and APTT (activated partial thromboplastin time) were measured.

Sample size was estimated 45 in each group by result of pilot study in independent t-test testing ($\alpha = 0.05$, $\beta = 0.2$). Finally we considered 50 cases in each group for unpredictable problems. Random allocation has been considered in this research (5 cases of injection group excluded during the study).

Including criteria were healthy term newborn with birth weight more than 2500 grams and excluding criteria were prematurity, ill baby, mothers with history of bleeding disorders usage of drugs such as warfarin and anticonvulsant. PT and APTT were determined in the morning. Baby's blood sample mixed with trisodic citrate in 9:1, two hours after sampling plasma separated and PT, APTT were tested.

Each test was done two times by Sysmex CA-50 coagulometer. Thromboplastin reagent for PT also cephalin kaolin reagent for APTT was belong to France Biobabo Company. International sensitivity index for PT reagent (ISI) was 1.65. Ratio was calculated from patient PT to control PT.

International Normalized Ratio (INR) for each sample was calculated from ISI and ratio ($INR = \frac{[Ratio]}{ISI}$)

Data was analyzed by SPSS by using t-test and mann-whitney test, P value less than 0.05 was considered significant.

The protocol of the study was approved by the local ethical committee of Mashhad University of Medical Science.

Table 1. Demographic pattern of babies with interamuscular and oral vitamin K

P value	IM group (n= 45)	Oral group (n= 50)	Factor
T= 1.48 , df = 93, P= 0.14	24.78 ± 9.95	22.16 ± 7.21	Time of sampling after vitamin K (hour)
Z* =-0.9 , P= 0.36	2	3	Parity (Median)
Chi ² = 0.001, P= 0.57	43.2%	42%	Male sex (%)
T= 2.24 , P=0.03	3196 ± 385	3018 ± 400	Birthweight (g)

* Mann Whitney U-test

Statistical Analysis

Descriptive statistics such as central and variation tendency were done. chi-square test were used for statistical analysis of qualitative variables. Student's t-test was used for comparing the means of birth weight, time of coagulating tests after treatment by vitamin K. Mann whitney U-test were used for comparing of median of PT, APTT, INR, birth rank as well. The significance level was set at $p < 0.05$. Data analysed using SPSS version 11.5.

RESULTS

From 95 newborn babies 45 were in Injection group and 50 in oral group. There were no significant differences between two groups in sex ($P=0.57$) birth weight ($P=0.05$) and parity ($P=0.36$) Table 1. PT and APTT were measured at 24.78 ± 9.95 hours (Min 12 hours, max 56 hours) in Injection group and 22.16 ± 7.21 hours (Min 13 and Max 41 hours) in oral group after vitamin K prescription ($T=1.48$, $p=0.14$).

Mean PT in Injection and oral groups were 16.77 ± 4.0 and 16.39 ± 2.98 second respectively ($Z=-0.87$, $p=0.038$).

Mean APTT in Injection group was 37.73 ± 22.25 second and in oral group was 34.93 ± 7.73 second ($Z= -0.4$, $P= 0.69$).

Mean INR in Injection and oral groups were 1.59 ± 0.74 , 1.58 ± 0.401 respectively ($Z= -1.25$, $P= 0.22$).

Mann-whitny test showed no significant difference between two groups in PT ($Z=0.87$, $P=0.38$), APTT ($T=-0.4$, $P=0.69$) and INR ($Z=1.32$, $P= 0.22$) (Figure 1).

DISCUSSION

Hemorrhagic disease of the newborn was first describe one decade ago by Townsend (3). This disease characterized by gastrointestinal bleeding, echimosis and sometime intracranial hemorrhage.

Nearly in all newborns 48-72 hours after delivery vitamin K related factors (II, VII, IX, X) decrease and between 7-10 days they return to normal level. This transient deficiency of vitamin K related factors is probably due to absence of free vitamin K in mothers and intestinal bacterial flora in newborns.

Rarly in term neonates but more in preterm infants this deficiency exist till 2-7 days post partum and results instantaneous prolong hemorrhage.

In 1961, in order to prevent this problem the Committee on Nutrition of the American Academy of Pediatrics (AAP) recommended administration of 0.5-1 mg vitamin K intramuscularly to all newborns shortly after birth (4).

In 1988 because of some report of cancer in children that received intramuscular vitamin K, the Canadian Paediatric Society recommended 2 mg vitamin K orally in first 6 hours of birth (5-7).

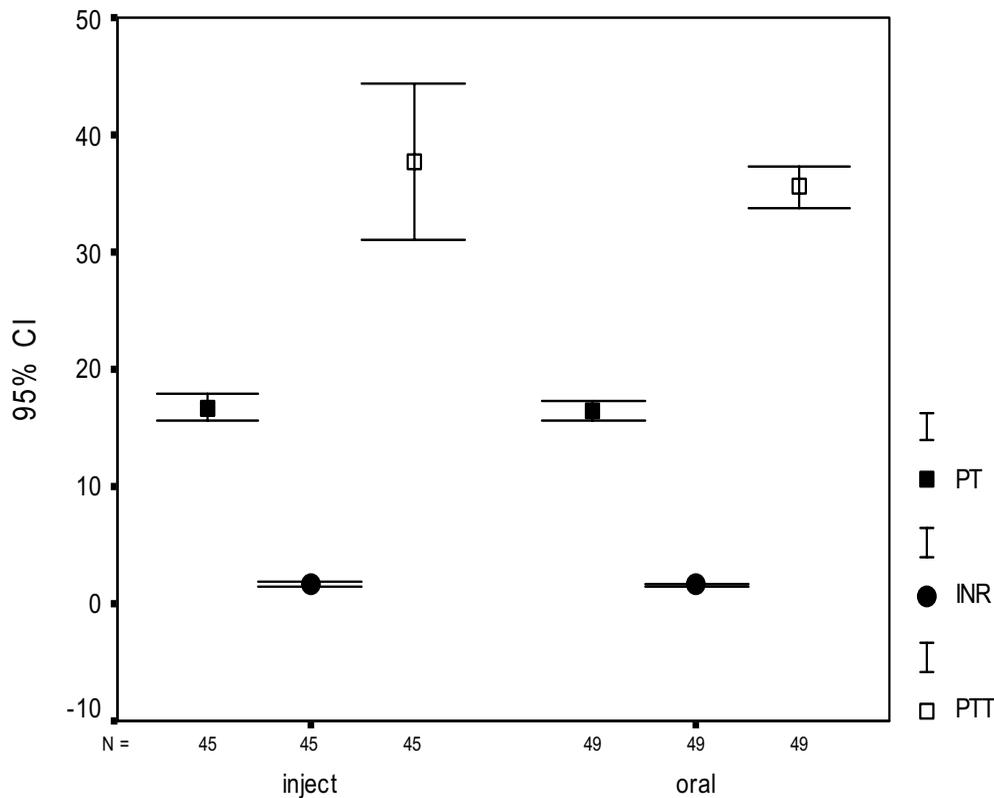


Figure 1. The mean PT , APTT , INR levels of two groups

Although other countries joined to Canadian protocol, but because oral form of vitamin K wasn't approved the American Academy of Pediatrics recommended injectable form (8).

In full term neonates injection of vitamin K after birth prevents the decreasing of vitamin K related factors while in preterm infants hasn't such effect as full terms.

There are many protocols for oral vitamin K such as 1-2 mg after birth, at discharge and 3-4 weeks after birth, or every other weeks for 3 times or weekly until 3 months.

Although these protocols decreased the incidence of late form of hemorrhagic disease of the newborn but didn't eliminate it (10-17).

Sutor showed that oral vitamin K (2 mg is better than 1 mg) protect neonates but he wasn't sure that it can prevent the hemorrhage caused by vitamin K deficiency. It seems that using lower doses, daily

or weekly oral vitamin K has prophylactic effect on hemorrhage without harm of injection form (1). Zipursky believed that at birth vitamin K deficiency is not so severe that cause hemorrhage but in severe form in breast fed infants severe vitamin K deficiency can cause classic form in first week or late form in first month after birth, these two forms can be so severe that cause brain damage and death (15).

This study showed that oral or injectable form of vitamin K have the same effect on correction of vitamin K related factors.

So we think that in addition of giving oral vitamin K, knowing the signs and symptoms of the disease and emergency management can reduce the danger of classic form of hemorrhage but for protective effect on late form of the disease, as already Sutor recommended, knowing the predisposing factors in neonates is pooled for choosing the route of giving vitamin K prophylaxis for targeting of them.

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