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Original Article / Оригинални рад

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Late vitamin K deficiency bleeding despite intramuscular prophylaxis at birth – is there a need for additional supplementation?

Касни облик крварења услед дефицита витамина К упркос примени интрамускуларне профилаксе на рођењу – да ли је потребна додатна надокнада?

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Касни облик крварења услед дефицита витамина К упркос примени интрамускуларне профилаксе на рођењу – да ли је потребна додатна надокнада?

SUMMARY

Introduction/Objective Vitamin K deficiency is common in newborn infants and without prophylaxis there is a risk of vitamin K deficiency bleeding (VKDB). The most frequent prophylactic approach is an intramuscular (IM) injection of vitamin K1 immediately after birth. Its efficiency to prevent late VKDB has been recently questioned by several reports.

Based on our experience, we discuss the need for additional vitamin K1 supplementation after its IM administration at birth.

Methods We present retrospective review of 12 infants, 11 with confirmed and one with probable late VKDB despite intramuscular prophylaxis at birth who were treated during 15 years.

Results All patients were exclusively breast fed. In 11 patients daily weight gain was normal or increased and one patient had failure to gain weight. Six infants were previously healthy, three infants received antibiotics prior to bleeding and in two diarrhea and cholestasis, respectively, existed previously. An intracranial bleeding was documented in 9 infants, 4 of them died.

Conclusion Low content of phythomenadione in human milk occasionally could be attributed to late VKDB despite postnatal IM injection of vitamin K1 in otherwise healthy, exclusively breast fed infants. This might be aggravated by transient disturbance of vitamin K turnover due to antibiotic use, acute diarrhea or transient cholestasis. We suggest that an additional vitamin K1 supplementation after postnatal IM prophylaxis could be justified in exclusively breast fed infants.

Keyword: Vitamin K; late vitamin K deficiency bleeding; intramuscular prophylaxis

САЖЕТАК

Увод/Циљ Без одговарајуће профилаксе, недостатак витамина К код новорођене деце и одојчади може довести до хеморагијског синдрома познатог под називом крварење услед дефицита витамина К (ВКДК). Најчешћа профилакса ВКДК је интрамускуларна (ИМ) инјекција вит. K_1 одмах по рођењу. Новији извештаји о појави касног облика ВКДК упркос интамускуларној профилакси по рођењу, довели су у питање уверење у потпуну поузданост овог приступа.

Циљ рада је да изнесе сопствена искустава и предлоге за надокнаду вит. К после ИМ примене на рођењу.

Методе рада Ретроспективно је анализано 12 новорођенчади и одојчади, лечених протеклих 15 година, 11 са доказаним и једно са вероватним касним обликом ВКДК упркос ИМ профилакси витамином К1 на рођењу.

Резултати Сви болесници су били искључиво на природној исхрани. Пораст телесне масе код 11 је био је нормалан или повећан и код једаног недовољан. Пре појаве кВКДБ 6 болесника је било здраво, 3 су претходно добијали антибиотике, један је имао акутни пролив и један холестазу. Интракранијално крварење доказано је код девет болесника, од којих су четири умрла.

Закључак Снижен садржај фитоменадиона у хуманом млеку може понекад резултирати ВКДК код ексклузивно дојене здраве новорођенчади и младе одојчади. Пролазном недостатку витамина К додатно доприноси примена антибиотика, акутни пролив или холестаза. Зато је оправдано после профилаксе витамином K_1 на рођењу, код искључиво дојене деце, настави додатни унос препарата фитоменадиона током прва три месеца.

Кључне речи: новорођенче; витамин К; крварење услед недостатка витамина К; профилакса

INTRODUCTION

Newborn infants are deficient in vitamin K due to its poor transplacental transport, delayed intestinal synthesis and low content in human milk [1, 2]. Therefore, vitamin K dependent clotting factors (F II,VII,IX,X) express no more than 50% of activity attained in later life, and both prothrombin time (PT) and activated partial thrombin time (aPTT) are prolonged in comparison to adult values [3]. In some infants "physiological hypoprothrombinaemia" leads to spontaneous or iatrogenic bleeding formerly known as hemorrhagic disease of the newborn (HDN), and lately more appropriately named vitamin K deficiency bleeding (VKDB). VKDB presents in three different forms – early, classic and late VKDB. Early VKDB is very rare and its occurrence with severe bleeding

immediately after birth is mostly related to maternal intake of certain medications (anticonvulssive, antitubercular and anticoagulant drugs). Without prophylaxis classic form has incidence of 0.25–1.7% of all newborn, potentially presenting the most common acquired pediatric haemostatic disorder. Fortunately, in majority of cases there is only mild to moderate gastrointestinal, skin or bleeding from umbilicus typically occurring during first week of life. Late VKDB presents between 2 and 26 weeks of life (peak is between 3 and 8 weeks), and without prophylaxis incidence in western world range from 4–7 cases per 100.000 deliveries. Primary, or idiopathic late VKDB occurs in exclusively breast fed, otherwise healthy infants, while secondary form is a consequence of some pathological conditions which steadily disturb intestinal synthesis and/or absorption of vitamin K (biliary atresia, cystic fibrosis, celiac disease, alfa-1 antitrypsin deficiency, chronic diarrhea etc.). Up to 60–80% infants with the late VKDB have an intracranial hemorrhage with a mortality rate between 14–24%, and nearly 50% of survivors had a permanent neurological impairment [1,2].

Initially, prevention of classic VKDB, intramuscular (IM) administration of vitamin K_1 (phytomenadione) to all newborn infants immediately after birth has been introduced in the US more than 50 years ago [4]. Over time this practice was adopted almost worldwide. Routine IM injection of vitamin K_1 (1 mg IM for all term newborn infants / 0.5 mg for preterm infants) was recommended in Serbia in 1995 [5]. Vitamin K prophylaxis at birth via IM route is obligatory, except in cases of parental refusal or their alternative choice of an oral mode. Both decisions should be stated in a written form.

Because of presumed, but unproven association between intramuscular prophylaxis and later greater risk of cancer, in the 1990' a shift from IM towards oral prophylaxis in some countries was accepted. However, it soon became evident that despite its efficiency against early and classic forms, a single oral dose of vitamin K_1 does not prevent late VKDB. Therefore, in order to increase efficiency of oral regiment, several distinct strategies of prolonged oral supplementation of vitamin K have been implemented [6–9].

Unlike oral policy, a single IM injection of vitamin K_1 at birth has long been considered as a "gold standard" and as a reliable way to eradicate all forms of VKDB [2]. However, several reports of late VKDB occurring after intramuscular prophylaxis, brought into doubt traditional belief in the superiority of such approach. Beside few sporadic single cases [10–12], case series of otherwise healthy infants with failure of postnatal IM injection of vitamin K_1 to prevent late VKDB, have recently been reported from Turkey [13–16], Egypt, India [17, 18] and Albania [19]. Whilst these papers focused on an intracranial hemorrhage as the main consequence of the late VKDB, at the moment we present the largest European group of patients with the late VKDB, despite IM administration of vitamin K_1 at birth.

The aim of this study is to retrospectively review cases of late VKDB occurrence despite IM prophylaxis with vitamin K_1 given at birth. Based on our experience, we discuss a need and possible

regimes of an additional vitamin K supplementation for the exclusively breast fed infants during early infancy.

METHODS

Hospital files of patients with diagnoses HDN/VKDB or other unspecified neonatal hemorrhagic conditions (ICD-9 codes 776.0 / 776.3 and 269.0, respectively; ICD-10 code P53) treated between the 2000 and 2015 in two largest tertiary care pediatric hospitals in Serbia: Mother and Child Health Institute of Serbia (New Belgrade) and Univesity Childrens' Hospital (Belgrade) were retrospectively reviewed. Confirmed case of late VKDB is defined respecting following criteria: a) spontaneous or iatrogenic hemorrhage in an infant aged 2 to 26 weeks; b) PT prolonged ≥ 4 times over normal values, aPTT > 60 sec. and/or international normalized ratio (INR) > 4 control values; c) cessation of hemorrhage and normalization of PT and aPTT and/ or INR after administration of vitamin K; d) normal both platelet count and fibrinogen levels. If criterion "c" is not satisfied, the case is classified as "probable" late VKDB. Coagulation was investigated on admission and 6–12 hours thereafter. Intracranial hemorrhage is documented by CT scan and/or NMR imaging. All patients were emergently treated with vitamin K_1 1 mg/kg intravenously. Fresh frozen plasma (10–15 ml/kg) was administered to patients with life treating bleeding.

RESULTS

Our research revealed 16 patients with diagnosis of HDN/VKDB, treated in pediatric intensive care units of our hospitals during the previous 15 years. Of those, 4 patients who didn't receive vitamin K at birth were excluded from the final presentation: one newborn with a classic VKDB whose parents refused vitamin K injection, and 3 patients with a late form who were born in neighboring countries without reliable data on postnatal prophylaxis. In the remaining 12 patients (10 males; 2 females), an IM injection of 1 mg vitamin K_1 was administered and recorded in the discharge list from the maternity ward.

According to the data shown in the Table 1, there were 10 male and 2 female infants, aging from 21 to 51 days (median age was 35 days). All our patients had a significantly prolonged PT and aPTT, as well as abnormal INR. The normalization of these tests after the vitamin K administration was documented in 11 cases. A patient 12 died soon after admission and there wasn't possible to check coagulation tests after administration of vitamin K, so he was classified as probable case. Except for the patient number 3 who was born at 34^{th} gestational week with body weight 1950 g, all others were born at term. There was a history of previous antibiotic use in 3 cases (patients 3, 4, 6), while the patient 8 had a history of two-day diarrhea before the bleeding. A female infant aged 49 days (patient 5) had a prolonged indirect jaundice with a rise of total serum bilirubin level during the first month of life up to 204.0 μmol/l (direct fraction 23.0 μmol/l). Upon hospital admission, conversion to direct hyperbilirubinemia indicating cholestasis was noted (total serum bilirubin level

Table 1. Relevant laboratory and clinical data of infants with late vitamin K deficiency bleeding despite intramuscular prophylaxis.

Patient Gender	Age (days)	PT (sec)		aPTT (sec)		INR		Localization of bleeding Outcome	Remarks
		(1)	(2)	(1)	(2)	(1)	(2)		
1 M	31	did not cloth	11.6	did not cloth	25.1	NC	0.8	Intracranial Recovery	-
2 M	35	74.0	11.4	63.0	24.6	4.1	0.9	Intracranial Recovery	-
3 M	34	98.7	14.5	70.7	28.1	10.6	1.1	Intracranial Died	Preterm, 15 days antibiotic use
4 M	45	> 200	11.6	83.9	25.1	NC	0.9	Intracranial Died	2 days antibiotic use
5 F	49	77.1	16.5	66.2	35.7	7.34	1.3	Intracranial Died	Prolonged jaundice with mild cholestasis
6 M	51	>300	10.8	>300	23.3	NC	0.9	Intracranial Recovery	15 days antibiotic use
7 F	42	did not cloth	14.8	>300	28.2	NC	1.3	Haematoma after venepunction Recovery	Intrauterine growth restriction
8 M	21	did not cloth	14.9	did not cloth	32.4	NC	1.3	Large haematoma after vaccination. Recovery	2 days antibiotic use
9 M	39	did not cloth	11.4	did not cloth	30.0	NC	0.9	Large haematoma after vaccination. Recovery	-
10 M	37	119	10.6	139	30.2	14.6	1.0	Intracranial Recovery	-
11 M	36	>200	9.7	83.9	28.7	NC	0.9	Intracranial Recovery	-
12 M	35	did not cloth	ND	>300	ND	NC	ND	Intracranial Died	Probable case of late VKDB

M – male; F – female; (1) results before and (2) after therapy with vitamin K; NC – not calculated; ND – not done; VKDB – vitamin K deficiency bleeding.

was 127.0 μmol/l; direct fraction was 43.6 μmol/l). Both the mother and the child had the same blood type, and there were no signs of hemolysis.

The platelet count, fibrinogen levels, as well as liver enzymes were within normal range in all our patients. It was documented in all cases that both FV and FVII expressed normal or increased clotting activity upon admission.

All our patients were solely breast-fed. Their daily weight gain, was calculated by dividing the difference between infants weight on admission and birth weight, with age in days. In 11 patients, including one born prematurely, and the one with intrauterine growth restriction, daily weight gain was in the range 16.8–46.5 g (mean 32.5 g; SD 11,2 g). Only in one case (patient 10), daily weight gain was unsatisfactory, 8.1 g. The intracranial bleeding was documented in 9 infants (75% of patients). Four infants in study group died, making an overall mortality of 25%.

DISCUSSION

The international definition of a confirmed late VKDB was fulfilled in 11 of our patients. An infant with extremely prolonged PT and APTT, who died immediately after admission, without the possibility to check the laboratory testing, was classified as a probable case of the late VKDB [10,20, 21]. Congenital, as well as clotting disorders due to liver impairment were excluded in all cases.

Exclusive breast feeding was the common factor for all our patients and the most of previously published cases of late VKDB occurring after intramuscular prophylaxis with vitamin K at birth. The human milk contains 0.5–4 μg/l of phytomenadione, while the minimal daily requirements for vitamin K in infants from birth up to 6 months are 1.5 μg/l [1,2,21,22]. Assuming the daily amounts of

suckled milk of 0.5-0.8 l, the daily intake of vitamin K would be between 0.25 and 3.2 μg. Therefore, in the best case, exclusively breast fed infants, weighing 3–6 kg, which corresponds to the first 6 months of life, would not satisfy their total daily needs of ≈ 5–10 μg of phytomenadione.

Elaify and al. documented that in infants given IM injection of vitamin K at birth those suffering from intracranial bleeding due late VKDB, had significantly lower serum levels of phylloquinone than matched control group. They also showed that babies who bled more frequently used antibiotics or had acute diarrhoea [17]. The large prospective British study revealed the patients with association of biliary atresia and a severe late VKDB despite an intramuscular administration of vitamin K at birth [10]. All aforementioned disorders interfere with intestinal synthesis and/or absorption of vitamin K, but without adverse effect on activity of IM given vitamin K. This fact indirectly proves that effective prevention of late VKDB requires additional supply of phytomenadione from gastrointestinal tract. Hence, besides IM prophylaxis at birth, in healthy, solely breast fed infants some oral supplementation of vitamin K is required thereafter. The US Nutritional Board of National Institute of Health estimates that if prophylactic dose of vitamin K was given IM at birth, 2 μg of vitamin K is an adequate daily intake during the first 6 months of life [23]. According to the previously calculated daily allowance of phytomenadione by human milk (0,25–3,2 μg), there are some exclusively breast fed healthy infants with possible insufficient vitamin K supply (<2 μg per day) and consecutive risk of the late VKDB in spite of previous IM prophylaxis.

Normal or even excessive weight gain [24] was recorded in 11 of 12 cases, so insufficient milk intake as a cause of lack of vitamin K could be excluded.

Six of our patients were healthy infants without any predisposing factor to the late VKDB. Out of the remaining five, three were treated with antibiotics during 2–15 days, while one had the acute diarrhea. A seven-week old infant with a transition of prolonged unconjugated hyperbilirubinemia to the cholestatic jaundice, which preceded a lethal intracranial hemorrhage, confirms that neonatal jaundice lasting more than 2–3 weeks justifies the “yellow alert” [10]. We observed that beside to secondary late VKDB due to the serious pathological conditions, there is a subgroup of otherwise healthy exclusively breast fed infants with some transient risk factors which further deteriorate the vitamin K deficiency and increase the risk of late VKDB.

Male infants have accounted for a large majority of our patients, corresponding to reported twofold-to-sevenfold male predominance [13-15, 25]. Although this striking gender discrepancy is not yet clarified, results of previously reported investigation, suggest that male infants may require more dietary phytomenadion than females with the same body weight [26].

Our hospitals, as tertiary referring pediatric institutions, cover a gravitating area with approximately 40.000 deliveries per year. For the entire period of 15 years the total amounts to nearly 600.000 live births. Accordingly, 12 patients give an estimate of the rate of late VKDB of 1 case per 50.000 live births (2 per 100.000 live births). Possible explanations for 2 to 3-fold higher incidence

than in developed countries [10] could be inadequate maternal diet with low intake of vitamins, and less critical use of antibiotics in infants [27–29].

Frequent occurrence of intracranial bleeding and a high mortality rate in our patients correspond with reported severity of late VKDB [1, 2]. A single case of failure of IM prophylaxis to prevent the late VKDB, initiated the Italian Society of Neonatology to recommend 25 μg of vitamin K per day orally during the first three months of life for all breast fed infants, previously given an IM injection of vitamin K at birth [2, 11]. Up to date, no adverse effects even of higher intake of vitamin K by standard milk formula containing 50–60 μg/l were reported [1, 2, 21, 22]. Unlike weekly "pharmacological" regime, the daily oral supplementation with low doses of phythomenadione is considered to be "physiological" because such approach maintains a constant serum level and efficiently compensates inadequate intake of vitamin K [30]. Therefore, after immediate postnatal IM dose, we recommend prolonged oral prophylaxis for all exclusively breast fed infants with daily intake of 25 μg of phythomenadione from 2 to 12 weeks of life. Prolonged oral prophylaxis, even with higher doses of phytomenadione is strongly advised if parents instead of IM mode choose oral route as a way of prophylactic use of vitamin K at birth.

Except in cases of cholestasis, an oral intake of 25 μg of vitamin K efficiently prevented the late VKDB [7,8,23]. The presence of cholestatic jaundice requires a more individualized approach. One option may be an increase of oral dose up to 150 μg of phythomenadione per day, which is recommended in Holland as a routine three-month policy after an initial oral prophylaxis at birth [8]. Some authors consider an additional intramuscular dose of vitamin K [17]. The Danish regime of a three-month weekly oral supplementation with 1 mg of vitamin K is effective even in infants with biliary atresia [9]. In our country, there isn´t commercial oral vitamin K preparation containing the required dose. Off label use of vitamin K glass ampules may be an alternative, but it is connected with problems such as parental resistance because of uncomfortable use. On the other hand, the professional assistance makes the weekly oral doses a costly alternative [10]. Therefore, we consider that in the cases of transient disturbance of vitamin K intestinal turnover, an additional parenteral dose of 1 mg should be given in infants on daily oral intake of 25 μg of vitamin K. Such approach seems particularly justified if there is prolonged jaundice with any sign of cholestasis.

Like in the number of other cases, our recommendation is also an experts' opinion based on personal experience with severe and highly lethal late VKDB [6-9]. According to the facts that "oral vitamin K ….has not been tested in randomized trials for its effect on either classic or late VKDB" [29] and that "the results regarding late HDN and prolonged oral prophylaxis are still inconclusive… due to lack of scientific evidence" [31] we suggest this recommendation despite its low level of evidence.

CONCLUSION

We hope that our experience will increase the awareness that despite an IM dose of vitamin K at birth there is still a risk of serious, potentially lethal late VKDB. At the moment, its occurrence could be attributed to an occasional extremely low content of phythomenadione in human milk. Therefore, three-month additional daily oral supplementation with low doses of phytomenadione could be justified in solely breast fed infants in our country. In the cases of transient disturbance of vitamin K turnover due to antibiotic use, acute diarrhea, or transient cholestasis, a more individualized approach, including additional parenteral dose of vitamin K could be considered.

Final decision about vitamin K prophylaxis policy should be based on thorough assessment of overall circumstances, including incidence of late VKDB, availability and cost of vitamin K preparations.

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