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 a retrospective review of 12 infants, 11 with confirmed and one with probable late VKDB despite IM prophylaxis at birth, who were treated in the two largest tertiary care pediatric hospitals in Serbia during the last 15 years.

Results All the patients were exclusively breastfed. 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 nine infants, four of whom died.

Conclusion Low content of phytomenadione in human milk could occasionally be attributed to late VKDB despite postnatal IM injection of vitamin K₁ in otherwise healthy, exclusively breastfed 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 breastfed infants.

Keywords: vitamin K; late vitamin K deficiency bleeding; intramuscular prophylaxis

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 hypoprothrombinemia” 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 (anticonvulsive, antituberculcar, and anticoagulant drugs). Without prophylaxis, classic form has incidence of 0.25–1.7% of all newborns, potentially presenting the most common acquired pediatric hemostatic disorder. Fortunately, in majority of cases there is only mild to moderate gastrointestinal, skin, or bleeding from umbilicus typically occurring during the first week of life. Late VKDB presents between the second and 26th week of life (the peak is between three and eight weeks), and without prophylaxis, incidence in the western world ranges from four to seven cases per 100,000 deliveries. Primary, or idiopathic late VKDB occurs in exclusively breastfed, 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% of infants with the late VKDB have an intracranial hemorrhage, with a mortality rate of 14–24%, and nearly 50% of survivors have a permanent neurological impairment [1, 2].

Initially, prevention of classic VKDB, intramuscular (IM) administration of vitamin K₁ (phytomenadione) to all newborn infants immediately after birth was introduced in the US more than 50 years ago [4]. Over time, this practice was adopted almost worldwide. Routine IM injection of vitamin K₁ (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 IM prophylaxis and later greater risk of cancer, in the 1990s 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 K₁ does not prevent late VKDB. Therefore, in order to increase the efficiency of oral regimen, several distinct strategies of prolonged oral supplementation of vitamin K have been implemented [6–9].

Unlike oral policy, a single IM injection of vitamin K₁ at birth has long been considered a “gold standard” and a reliable way to eradicate all forms of VKDB [2]. However, several reports of late VKDB occurring after IM prophylaxis called into question the traditional belief in the superiority of such an approach. In addition to some sporadic single cases [10, 11, 12], a case series of otherwise healthy infants with failure of postnatal IM injection of vitamin K₁ to prevent late VKDB has recently been reported from Turkey, Egypt, India and Albania [13–19]. Whilst these papers focus on intracranial hemorrhage as the main consequence of the late VKDB, we present the largest European group of patients with the late VKDB despite IM administration of vitamin K₁ at birth.

The aim of this study is to retrospectively review cases of late VKDB occurrence despite IM prophylaxis with vitamin K₁ given at birth. Based on our experience, we discuss a need and possible regimes of an additional vitamin K₁ supplementation for exclusively breastfed infants during early infancy.

METHODS

Hospital files of patients with HDN/VKDB diagnoses or other unspecified neonatal hemorrhagic conditions (ICD-9 codes 776.0/776.3 and 269.0, respectively; ICD-10 code P53) treated between 2000 and 2015 in two largest tertiary care pediatric hospitals in Serbia – the Institute for Mother and Child Healthcare of Serbia (New Belgrade) and University Children’s Hospital (Belgrade) – were retrospectively reviewed. A confirmed case of late VKDB is defined by the following criteria: a) spontaneous or iatrogenic hemorrhage in an infant aged two 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 the administration of vitamin K₁; 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 a computed tomography scan and/or nuclear magnetic resonance spectroscopy (NMR) imaging. All the patients were emergently treated with 1 mg/kg of vitamin K₁ intravenously. Fresh frozen plasma (10–15 ml/kg) was administered to patients with life-threatening bleeding.

RESULTS

Our research revealed 16 patients with a diagnosis of HDN/VKDB, treated in pediatric intensive care units of our hospitals during the previous 15 years. Of those, four 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 three patients with a late form, who were born in neighboring countries, without reliable data on postnatal prophylaxis. In the remaining 12 patients (10 males; two females), an IM injection of 1 mg of vitamin K₁ was administered and recorded in the discharge list from the maternity ward.

According to the data shown in Table 1, there were 10 male and two 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 K₁ administration was documented in 11 cases. Patient No. 12 died soon after admission; as it was not possible to check coagulation tests after the administration of vitamin K₁, he was classified as a probable case. Except for patient No. 3, who was born at the 34th gestational week with body weight of 1,950 g, all others were born at term. There was a history of previous antibiotic use in three cases (patients No. 3, 4, and 6), while patient No. 8 had a history of two-day diarrhea before the bleeding. A female infant aged 49 days (patient No. 5) had prolonged indirect jaundice with a rise of total serum bilirubin level during the first month of life up to 204 µmol/l (direct fraction of 23 µmol/l). Upon hospital admission, conversion to direct hyperbilirubinemia indicating cholestasis was noted (total serum bilirubin level was 127 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 breastfed. 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 one with intrauterine growth restriction, daily weight gain was in the 16.8–46.5 g range (mean 32.5 g; SD 11.2 g). In only one case (patient No. 10), daily weight gain was unsatisfactory, reaching 8.1 g. The intracranial bleeding was documented in nine infants (75% of patients). Four infants in the 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 breastfeeding was the common factor for all our patients and the most of previously published cases of late VKDB occurring after IM prophylaxis with vitamin K at birth. Human milk contains 0.5–4 μg/l of phytomenadione, while the minimal daily requirements for vitamin K in infants from birth up to six 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 μg and 3.2 μg. Therefore, exclusively breastfed infants weighing 3–6 kg, which corresponds to the first six months of life, would not satisfy their total daily needs of ≈ 5–10 μg of phytomenadione even in the best case scenario.

Elaiify et al. [17] documented that in infants given IM injection of vitamin K at birth, those suffering from intracranial bleeding due to 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 diarrhea [17]. A large prospective British study revealed patients with association of biliary atresia and a severe late VKDB despite an IM administration of vitamin K at birth [10]. All aforementioned disorders interfere with intestinal synthesis and/or absorption of vitamin K, but without an adverse effect on the activity of vitamin K IM injection. 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 breastfed 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 as an IM injection at birth, 2 μg of vitamin K is an adequate daily intake during the first six 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 breastfed healthy infants with possible insufficient vitamin K supply (< 2 μg per day) and consecutive risk of late VKDB in spite of previous IM prophylaxis.

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

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 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 for more than two to three weeks justifies the “yellow alert” [10]. We observed that in addition to secondary late VKDB due to serious pathological conditions, there is a subgroup of otherwise healthy exclusively breastfed infants with some transient risk factors which further deteriorate the vitamin K deficiency and increase the risk of late VKDB.

Male infants accounted for a large majority of our patients, corresponding to reported twofold-to-sevenfold

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>PT (sec)</th>
<th>aPTT (sec)</th>
<th>INR</th>
<th>Localization of bleeding</th>
<th>Remarks</th>
</tr>
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<td>1 M</td>
<td>31</td>
<td>did not clot</td>
<td>11.6</td>
<td>did not clot</td>
<td>25.1</td>
<td>NC 0.8</td>
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<tr>
<td>2 M</td>
<td>35</td>
<td>74.0</td>
<td>11.4</td>
<td>63.0</td>
<td>24.6</td>
<td>4.1 0.9</td>
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<tr>
<td>3 M</td>
<td>34</td>
<td>98.7</td>
<td>14.5</td>
<td>70.7</td>
<td>28.1</td>
<td>10.6 1.1</td>
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<tr>
<td>4 M</td>
<td>45</td>
<td>&gt; 200</td>
<td>11.6</td>
<td>83.9</td>
<td>25.1</td>
<td>NC 0.9</td>
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<tr>
<td>5 F</td>
<td>49</td>
<td>77.1</td>
<td>16.5</td>
<td>66.2</td>
<td>35.7</td>
<td>7.34 1.3</td>
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<td>6 M</td>
<td>51</td>
<td>&gt; 300</td>
<td>10.8</td>
<td>&gt; 300</td>
<td>23.3</td>
<td>NC 0.9</td>
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<tr>
<td>7 F</td>
<td>42</td>
<td>did not clot</td>
<td>14.8</td>
<td>&gt; 300</td>
<td>28.2</td>
<td>NC 1.3</td>
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<tr>
<td>8 M</td>
<td>21</td>
<td>did not clot</td>
<td>14.9</td>
<td>did not clot</td>
<td>32.4</td>
<td>NC 1.3</td>
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<tr>
<td>9 M</td>
<td>39</td>
<td>did not clot</td>
<td>11.4</td>
<td>did not clot</td>
<td>30.0</td>
<td>NC 0.9</td>
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<tr>
<td>10 M</td>
<td>37</td>
<td>119</td>
<td>10.6</td>
<td>139</td>
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<td>14.6 1.0</td>
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<tr>
<td>11 M</td>
<td>36</td>
<td>&gt; 200</td>
<td>9.7</td>
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<tr>
<td>12 M</td>
<td>35</td>
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<td>ND</td>
<td>&gt; 300</td>
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</table>

M – male; F – female; (1) – results before vitamin K therapy; (2) – results after vitamin K therapy; NC – not calculated; ND – not done; VKDB – vitamin K deficiency bleeding; PT – prothrombin time; aPTT – activated partial thrombin time; INR – international normalized ratio

Table 1. Relevant laboratory and clinical data on infants with late vitamin K deficiency bleeding despite intramuscular prophylaxis
Late vitamin K deficiency bleeding despite intramuscular prophylaxis at birth – Is there a need for additional supplementation?

male predominance [13, 14, 15, 25]. Although this striking gender discrepancy is not yet clarified, results of previously reported investigation suggest that male infants may require more dietary phytomenadione 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 one case per 50,000 live births (two per 100,000 live births). Possible explanations for the two- to threefold higher incidence than in developed countries could be inadequate maternal diet with low intake of vitamins, and less critical use of antibiotics in infants [10, 27, 28, 29].

Frequent occurrence of intracranial bleeding and 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 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 breastfed infants, previously given an IM injection of vitamin K at birth [2, 11]. To date, no adverse effects even of higher intake of vitamin K by standard milk formula containing 50–60 μg/l have been reported [1, 2, 21, 22]. Unlike weekly “pharmacological” regime, the daily oral supplementation with low doses of phytomenadione 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 breastfed infants with daily intake of 25 μg of phytomenadione from the second to the 12th week of life. Prolonged oral prophylaxis, even with higher doses of phytomenadione, is strongly advised if parents choose the oral route as the way of prophylactic use of vitamin K at birth instead of the IM mode.

Except in cases of cholestasis, an oral intake of 25 μg of vitamin K efficiently prevented 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 phytomenadione 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 IM 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 is no 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, professional assistance makes the weekly oral doses a costly alternative [10]. Therefore, we consider that in cases of transient disturbance of vitamin K intestinal turnover, an additional parenteral dose of 1 mg should be given to infants on the 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 a 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 phytomenadione in human milk. Therefore, an additional three-month daily oral supplementation with low doses of phytomenadione could be justified in solely breastfed infants in our country. In 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.

REFERENCES

Касни облик крварења услед недостатка витамина К у прописаним интрамускуларним профилаксама на рођењу — да ли је потребна додатна надокнада?

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САЖЕТАК
Увод/Циљ Увод: Без одговарајуће профилаксе, недостатак витамина К може довести до хеморагијског синдрома познатог под називом крварење новорођенца, као и других услед недостатка витамина К (КНВК). Недостатак витамина К у прописаном интрамускуларном витамино-К-препарату може довести до крварења новорођенца. Методе Ретроспективно је анализано 12 новорођенчади у којима је крварење на рођењу израз ухотворене крварења новорођенца. Резултати Сви болесници су биле искушени на природној исхрани. Повећан садржај фитоменадиона у хуманом млеку може посебно доприносити примени антибиотикотерапије. Кључне речи: крварење новорођенца, недостатак витамина К, профилакса

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