



SEVERE INTRACRANIAL HEMORRHAGE IN HEALTHY INFANTS: IMPORTANCE OF VITAMIN K PROPHYLAXIS

SAĞIKLI SÜT ÇOCUKLARINDA CİDDİ İNTRAKRANİYAL KANAMA: K VİTAMİNİ PROFİLAKSİSİNİN ÖNEMİ

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SUMMARY

We report intracranial hemorrhage secondary to late vitamin K deficiency bleeding in seven full term exclusively breast-fed infants who were born in state hospitals in western part of Turkey. None of the babies received vitamin K prophylaxis although it is strongly recommended by Turkish Ministry of Health. Intracranial hemorrhage is the first presenting clinical picture in all infants and no bleeding sign was noticed by the parents before. All had (seizures) and severe anemia, four of them required mechanical ventilation and one died. Late vitamin K deficiency bleeding remains a life threatening problem for the babies even in the most developed parts of our country.

ÖZET

Türkiye'nin batısında devlet hastanelerinde doğan ve sadece anne sütü ile beslenen 7 süt çocuğunda geç K vitamini eksikliğine bağlı olarak gelişen intrakraniyal kanmaları sunuyoruz. Türkiye Sağlık Bakanlığı tarafından önemle belirtilmiş olmasına rağmen bu bebeklerden hiçbirine doğumda K vitamini uygulanmamıştır. Bu bebeklerin tümünde intrakraniyal kanama ilk başvuru bulgusu olmakla beraber daha önce aileleri tarafından belirtilen herhangi bir kanama bulguları yoktur. Olguların tümünde konvülsiyon ve ciddi anemi olmakla beraber 4 olguda mekanik ventilatöre gereksinimi olmuş bir olgu ise eksitus olmuştur. Yenidoğanın Geç Hemorajik Hastalığı ülkemizin en gelişmiş bölgelerinde dahi halen hayatı tehdit eden bir sorun olarak gözlemlenmektedir

INTRODUCTION

The term of Hemorrhagic Disease of Newborn (HDN) was replaced by Vitamin K Deficiency Bleeding (VKDB) as neonatal bleeding is often not due to Vitamin K deficiency and VKDB may occur after the 4-week neonatal period (1). It is categorized as early, classical and late depending on the time of onset.

Late VKDB, a syndrome defined as unexpected bleeding attributable to severe vitamin K deficiency in infants usually 2 to 12 weeks of age, occurs, primarily in exclusively breast-fed infants who have received no or inadequate neonatal vitamin K prophylaxis (2).

However, late VKDB might be secondary to an underlying disease and appear anytime in the first year of life after 2nd week (3, 4). It is very important to supply parenteral

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vitamin K prophylaxis to all newborns since this cheap and simple method can prevent the development of both early and late VKDB efficiently in infants with rare exception of those with severe malabsorption syndromes (1).

In this study we present seven previously healthy infants with intracranial hemorrhage secondary to late VKDB from a well- developed part of Turkey

PATIENTS AND METHODS

All infants admitted to Pediatric intensive Care Unit of Ege University Hospital, with a diagnosis of intracranial hemorrhage due to vitamin K deficiency from January 1999 to September 2003 were evaluated. All patients were examined and laboratory investigations were done at the time of admission. Laboratory investigations included whole blood count, peripheral smear examination, PT, PTT, fibrinogen and α 1 antitripsin levels, liver and kidney function tests, and cranial tomography. A previously healthy baby who had intracranial hemorrhage after first week of life was defined as intracranial hemorrhage secondary to late VKDB if she/he had normal platelet count and normal peripheral blood smear with prolonged prothrombin time (PT) at the time of admission without any specific coagulation factor deficiency or underlying disease. After taking blood samples all children were given 5 mg vitamin K intravenously and 10 cc/ kg fresh frozen plasma (FFP). PT and activated partial thromboplastin time (PTT) levels were checked every six hour for 24 hours and ever day in the first week, then once a week until discharge and once a month for six months after discharge. If the patient had prolonged PT levels with or without prolonged PTT in any measurement time after first day they were evaluated for rare factor deficiencies or underlying diseases and not included the study. Infants were evaluated according to place of birth, vitamin K administration at birth, feeding history, history of prolonged diarrhea, use of antibiotics, clinical signs and symptoms, cranial tomography findings, duration of care in PICU and hospital, treatment modalities and outcomes.

RESULTS

Seven infants fulfilled the criteria of intracranial hemorrhage secondary to late VKDB; 5 were males and 2 females. The median age at the diagnosis was 49 days (range 33 to 102 days).

All babies were born at term. Five were born by normal vaginal delivery and 2 by cesarean section. All of the babies were born in a state hospital from a healthy mother with an uneventful delivery history. Vitamin K was not administered to any of 7 babies at birth and all were exclusively breast-fed infants. None of the babies received

antibiotics, had diarrhea or a history suggesting any kind of systemic disease or poor weight gain. Family histories were negative for any bleeding diathesis in all patients. None of the mother noticed any bleeding problem in their children before. Clinical manifestations are shown in Table-1.

Table-1. Clinical manifestations of patients with intracranial hemorrhage secondary to late Vitamin K Deficiency Bleeding

Symptoms and signs	N	%
Convulsion	7	100
Pallor	7	100
Tense anterior fontanel	6	85.7
Feed intolerance	6	85.7
Lethargy	6	85.7
Irritability	3	42.9
Bleeding from prick site	7	100

All patients had seizures and pallor. Bulging anterior fontanel, feeding intolerance, lethargy and irritation were the other common manifestations.

All the patients had normal fibrinogen, alanine and aspartate aminotransferase, bilirubin, α 1 antitripsin, urea and creatinine levels at the time of diagnosis. Hemoglobin (hb) level was (mean \pm SD) 4.9 \pm 0.9 g/dl (ranging from 4.4 to 5.8 g/dl) and platelet count (mean \pm SD) was 294 000 \pm 148 000 (ranging from 187 000 to 461 000). Before the administration of vitamin K, PT and PTT levels were found to be significantly prolonged in all patients and mean PT was 69.8 \pm 41.3 seconds, mean PTT was 93.7 \pm 36 seconds. In 3 patients no clot was detected over 120 sec. All children were given 5 mg vitamin K intravenously and since its maximum effectiveness took 6-12 hours they all were also given FFP.

All patients transfused with erythrocyte suspension, because they had a severe degree of anemia at the beginning. PT and PTT were repeated 6 hour later and were in normal ranges in all patients. None of the patients had to receive any other dose of vitamin K and FFP after initial treatment. Diphenylhidantoin (DPH) was started to control convulsion for all patients with a loading dose but in 6 patients, phenobarbital was added to treatment.

Three patients also received midazolam infusion for several days to control the convulsion. CT scan was done in all patients. All CT scans showed large intracranial hemorrhage. Most of the patients revealed hemorrhage at more than one site (n=4, 57.1%), intraparenchymal hemorrhage was the most common type alone or in combination (n=5, 71.4%) followed by subdural hemorrhage in 3 cases (42.9%) and subarachnoid hemorrhage in 2 (28.6%), (Table-2).

Table 2. Localisation of intracranial hemorrhage according to findings in computerised tomography

Localisation of hemorrhage	N	%
IPH	2	28.6
IPH + SAH	2	28.6
IPH + SAH + SDH	1	14.3
SDH + EDH	1	14.3
SDH	1	14.3

Patients were cared in PICU. Mean duration of stay in PICU was 9.1 ± 7.8 days (range from 1 to 18 days). Four of the patients required mechanical ventilation for 3 to 16 days (mean \pm SD was 9.6 ± 8.4). After stabilization of hemorrhagic diathesis 4 children underwent surgery. One patient died at the 18th day of admission despite intensive support, which had massive parenchymal and subarachnoid hemorrhage at the time of admission. We studied the factor II, V, X levels in this patient since he had elevated PT and PTT and no follow-up after 18th day. While factor II and X were found to be decreased before vitamin K administration, their levels were within the normal ranges at the end of 17th day and Factor V levels were normal in both evaluations. The other six patients survived without any other bleeding problem during the follow-up period (median 22 months, ranges 4 to 48 months) with normal PT, PTT and liver function tests.

DISCUSSION

Vitamin K is necessary for synthesis of coagulation factors II (prothrombin), VII, IX and X via carboxylation of glutamic acid, which allows them to bind calcium effectively. In the absence of this carboxylation, the proteins have normal antigenic structure but are functionally defective (5). Healthy neonates are at increased risk of vitamin K deficiency since transplacental passage of vitamin K is minimal (6) and hepatic content of vitamin K is 20% of an adult (5). VKDB in infancy is an acquired coagulopathy secondary to reduction of vitamin K dependent factors below hemostatic levels and 30-66% of patients are presented with intracranial hemorrhage (1). A healthy newborn can absorb 30% of ingested vitamin K, while it is 50-70 % in an adult. Breast milk is very low in vitamin K ($<5 \mu\text{g/l}$) when compared to the amount contained in cow's milk or formula ($50-60 \mu\text{g/l}$) (7). In the breast-fed infants bowel usually contains bacteria such as *Lactobacillus* which can not produce vitamin K, whereas in cow milk fed babies the bowel contains bacteria mostly *Bacteriodes fragilis* which can produce vitamin K (8). So, exclusively breast-fed infants are at higher risk for VKDB. This type of feeding is supported for infants at least four months as a public health policy in Turkey and in this study all the patients were exclusively breast-fed infants. In a bleeding infant a prolonged PT together with a normal fibrinogen level and platelet count is almost diagnostic of VKDB;

rapid correction of the PT and/or cessation of bleeding after vitamin K administration are confirmative (1). PIVKA is an excellent marker of vitamin K deficiency (5) but it is not widely available. In some studies, authors treated infants with severe intracranial hemorrhage due to VKDB only with vitamin K administration even they did not evaluate PIVKA or factor levels before (9- 11).

Although the effect of parenteral vitamin K is rapid, in very severe bleeding additional therapy should be given (12, 14). Especially if the rare coagulation factor deficiencies, which cause both prolonged PT and PTT (Factor II, V and X) were not excluded, pending for action of vitamin K might cause time lost which might have vital importance. We think our treatment modality with close monitorization of PT and PTT is more appropriate for those critically ill children with severe intracranial hemorrhage if detection of PIVKA is not possible. The mortality rate of our study population is lower than that of the reported series. This might be explained by that the patients were cared in an intensive care unit of a tertiary care hospital, where modern techniques for advanced life support are available. It was recommended in 1961 by American Academy of Pediatrics to administer 0.5-1 mg vitamin K intramuscularly to all healthy term babies at birth (15). Although the incidence of VKDB has been decreased significantly since the initiation of routine vitamin K prophylaxis at birth, there has been concern that this type of prophylaxis may be toxic and unnecessary for all newborns (13, 16).

Nowadays discussions are concentrated on the route and regimens of administration. The alternative method for prophylaxis is recommended as 2 mg dose at birth, between the 1st and 2nd week, and in 4th week by mouth. It was shown that oral administration of vitamin K can not completely prevent late VKDB, although intramuscular route effectively prevents both early and late VKDB and seems to be more appropriate for parents' compliance (13). While some studies revealed an association between intramuscular vitamin K prophylaxis and leukemia or childhood cancers (17, 18), the others did not confirm these findings (19-21).

Turkish Health Ministry and Turkish Neonatology Association accept the AAP recommendation of vitamin K prophylaxis at birth and suggest its' intramuscular administration to all healthy newborns. It may be difficult to represent this option all the babies in some developing parts of Turkey where the babies mostly born at home without any medical help. But it was expected that the babies were born in hospitals should have received this prophylaxis. However all the babies in this study were born in state hospitals in western part of Turkey and none of them received vitamin K prophylaxis at birth. This study

clearly shows VKDB still remains a very important health problem in Turkey and, recommendation of vitamin K prophylaxis is not applied effectively even in well-developed parts of our country. Public Health workers

should concentrate on this issue and remind the importance of vitamin K prophylaxis to the physicians in Turkey in order to eradicate VKDB, which has disastrous consequences in healthy babies.

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