HK J Paediatr (new series) 2002;**7**:157-161

Vitamin K Deficiency Bleeding Revisited

ACW ***Lee***, CH ***Li***, KT ***So***

Abstract We report a case of late vitamin K deficiency bleeding (VKDB) in a two-month-old girl who had not received prophylaxis at birth. She was exclusively breastfed without oral vitamin K supplement. She presented with catastrophic central nervous system bleeding when laboratory findings revealed mild cholestasis and coagulopathy compatible with vitamin K deficiency. She died despite intensive care and correction of coagulopathy. VKDB remains an uncommon but significant risk to infants without vitamin K prophylaxis. The current medical literature supports that intramuscular vitamin K injection given at the time of birth is the most effective and reliable means of prophylaxis. The risk of childhood cancer associated with parenteral vitamin K injection at birth has not been proven and is unlikely to be clarified in the near future. If a regimen of oral prophylaxis is adopted, the physicians and the parents must closely follow the drug administration and accept the slightly increased risk of VKDB.

Key words Haemorrhagic disease of newborn, Intracranial haemorrhage, Vitamin K, Vitamin K deficiency

Introduction

Normal newborn infants are at risk of vitamin K deficiency.[1-3] Vitamin K deficiency bleeding (VKDB, also known as haemorrhagic disease of newborn) may present from birth to 6 months of life with cutaneous, gastro-intestinal or central nervous system haemorrhage. All forms of VKDB can be prevented by vitamin K prophylaxis given either via the intramuscular or oral routes.[1]

Concerns about the necessity or toxicities of parenterally administered vitamin K have repeatedly emerged during the second half of the last century.[4-5] However, it was the 1992 report by Golding et al.[6] about an increased risk of cancer and leukaemia after intramuscular vitamin K injection at birth that raised most of the concerns and controversies. A debate among local paediatricians also took place, which culminated in a Joint Statement from the Hong Kong Paediatric Society and Hong Kong College of Paediatricians in 1993.[7] At a regional hospital, we have been watching out for VKDB and only a single case had been diagnosed since 1993 through 2000. As the pros and cons of different forms of vitamin K prophylaxis have been carefully studied in the last few years, our case report and re-examination of the current understanding on the vitamin K controversy would be of interest to the professionals practising in paediatrics, obstetrics and family medicine.

Department of Paediatrics, Tuen Mun Hospital, Tuen Mun, N.T., Hong Kong, China

ACW **Lee** （李志偉） *FHKAM(Paed)*
CH **Li** （李澤荷） *MRCP*
KT **So** （蘇鈞棠） *FRCP*

Correspondence to: Dr ACW **Lee**

Received July 21, 2001

Case Report

In 1995, a Chinese girl was born vaginally at birth with a weight of 3.2 kg. The delivery was uneventful and intramuscular vitamin K was not given. The neonatal period was unremarkable except for mild jaundice. She was exclusively breastfed after discharge and remained well. At two months of age, her mother noted some cutaneous bruises from minor trauma. There was also prolonged swelling after vaccination for two weeks. The family history was negative for bleeding tendency.

She was lethargic and drowsy on admission. A haematoma of 3 cm diameter was noted over the right arm from previous vaccination. No other external injury was found. The anterior fontanelle was tense and bulging. There was hypertension (135/75 mmHg) and bradycardia. Both pupils were dilated and responded sluggishly to light. Fundoscopic examination revealed bilateral retinal haemorrhages. The liver was enlarged at 7 cm below the costal margin and the splenic tip was palpable.

The initial investigations showed haemoglobin 7.1 g/dL, white cell count 23.7 x 10^9/L, platelet count 799 x 10^9/L, prothrombin time: 35.8 s with INR: 3.3, and activated partial thromboplastin time 56.1 s (normal 26-40 s). The liver function tests showed total bilirubin 93 μmol/L (normal <22), direct bilirubin 70 μmol/L, alkaline phosphatase 303 u/L (normal <320) and alanine aminotransferase 68 u/L (normal <40). Factor IX and Factor X levels were markedly diminished at 0.03 iu/mL and 0.16 iu/mL, respectively. CT of the brain showed a large frontoparietal haematoma on the left side with ventricular and subarachnoid bleeding (Figure 1). No skull fracture was seen. Skeletal survey was negative.

The baby was aggressively resuscitated with mechanical ventilation and empirical broadspectrum antibiotics treatment. The coagulopathy was corrected and remained normal after a single dose of intravenous vitamin K and fresh frozen plasma infusion. However, she died eleven days after admission.

Discussion

Vitamin K Deficiency Bleeding (VKDB)

Newborn infants are at risk of vitamin K deficiency.[1-4] Without vitamin K supplement from prophylactic therapy or formula feeding, a bleeding diathesis characterized by a prolonged prothrombin time may occur.[1-2] Three forms of VKDB have been described. An early VKDB that occurs in the first 48 hours of life is usually associated with maternal anticonvulsant therapy. It can be prevented by antenatal maternal vitamin K supplementation. The classic VKDB, which takes place on the third to seventh day of life, usually manifests as gastrointestinal bleeding or prolonged oozing after needle puncture. Late VKDB may occur from the second week of life to 6 months and is frequently associated with hepatic or gastrointestinal disorders. It is characterized by central nervous system bleeding with significant mortality and morbidity.

A single dose of vitamin K 0.5-1.0 mg given intramuscularly at the time of birth is effective in preventing all forms of VKDB.[1-3] Similarly, an oral dose of vitamin K 1.0-2.0 mg is effective in preventing classic VKDB, but it is less effective against late VKDB especially in exclusively breastfed infants and those with hepatic or gastrointestinal problems.[1-3] Hence, repeated dosing is necessary.[8]

Early Concerns About Parenteral Vitamin K

Although the importance and efficacy of intramuscular vitamin K had been established,[4] the practice of prophylaxis against VKDB has not been uniform because of concerns about the potential toxicities of parenterally administered vitamin K. Half a century ago, the occurrence of severe haemolytic anaemia in infants who received vitamin K had been observed.[9,10] It was related to the use of water-soluble vitamin K and the massive doses of up to 80 mg/kg administered.[1,4] The risk of jaundice was virtually eliminated when natural lipid soluble preparations at the presently recommended dosage were utilized.[1]

Others queried the necessity of prophylaxis and argued that newborn infants did not have vitamin K deficiency at birth.[5] It is now clear that newborn infants develop vitamin K deficiency soon after birth when the small quantity of hepatic store is used up in the presence of limited supply

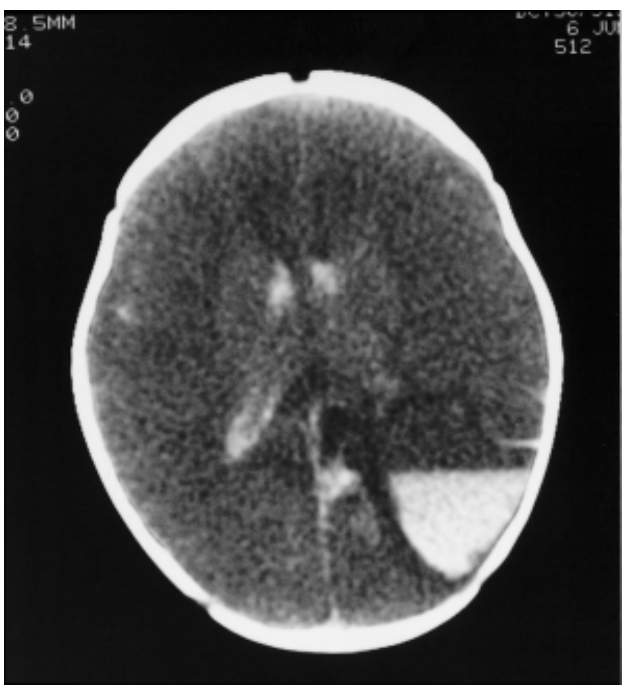

Figure 1 Non-contrast CT showing a left fronto-parietal haematoma, subarachnoid and intraventricular haemorrhages with diffuse cerebral oedema.

from the breast milk.[1,2] Nonetheless, a 1978 editorial in the Lancet[11] proclaimed that "a programme of selective vitamin K prophylaxis should appeal to those clinicians who rightly question the wisdom of injecting the majority of normal babies unnecessarily". Following this, a "selective" approach was adopted in some hospitals in the United Kingdom where vitamin K prophylaxis was given only to "high risk" cases.[12] Not surprisingly, VKDB reappeared and McNinch et al.[12] reported six cases out of 1,200 births five years later. Five of the six affected infants were normal at delivery. None had received vitamin K and three of them died. This prompted the authors to conclude that the "selective" approach of vitamin K prophylaxis was inadequate in preventing VKDB.

Intramuscular Vitamin K and Childhood Cancer

In 1992, Golding et al.[6] published a case control study and concluded that vitamin K given intramuscularly at birth, when compared with oral or no administration, increased the risk of developing cancer (OR, 95% CI: 1.72, 1.04-2.84) and leukaemia (OR, 95% CI: 2.65, 1.34-5.24) in subsequent childhood. There were potential biases in their study[13] and the observation on trends of childhood cancer and the sales of vitamin K in the United Kingdom did not support a causal association between vitamin K and childhood leukaemia.[14] Despite these challenges, the findings by Golding et al. had raised sufficient concern and additional studies from the United Kingdom and elsewhere were reported (See Table 1).[15-23]

Three types of epidemiologic study were designed: ecologic, case-control and cohort studies. In the ecologic studies by Olsen et al.[17] and Passmore et al.,[20] the summary measures of the frequency of exposure to parenteral vitamin K and the frequency of childhood cancers are reckoned. Both studies did not find any evidence that introduction of intramuscular vitamin K at birth resulted in an increased incidence of childhood leukaemia.

In case-control studies, individuals with childhood cancers are identified and compared to a similar population of individuals who do not have malignant disorders. Three of the five studies did not find an increased risk of leukaemia in relation to intramuscular vitamin K administration.[18,19,21] Parker et al.[22] did not find an increased risk of cancer (OR, 95% CI: 0.89, 0.69-1.15) for those children who had received intramuscular vitamin K. However, an increased risk for acute lymphoblastic leukaemia in the 1-5 years of age (OR, 95% CI: 1.02-3.15) was observed. Passmore et al.[23] found that children who developed cancer had received

Table 1 Estimated relative risks of intramuscular vitamin K versus no or oral vitamin K at birth for childhood malignancies

Ref.	Region	Type of study	Age group (years)	Odd ratios (95% confidence intervals)			
				All cancers	Leukaemia	ALL 1-5 years	Other cancers
6	Bristol, UK	Case-control	0-14	2.16 (1.27-3.67)	2.65 (1.34-5.24)	-	1.72 (1.04-2.84)
15	USA	Cohort	0-7.5	0.84 (0.41-1.71)	0.47 (0.14-1.55)	-	1.08 (0.45-2.61)
16	Sweden	Cohort	0-17	0.96 (0.80-1.14)	0.83 (0.61-1.14)	-	-
			0-9	1.11 (0.88-1.40)	1.20 (0.69-2.08)	-	-
17	Denmark	Ecologic	0-12	1.29 (1.23-1.35)	1.00 (0.93-1.09)	-	1.15 (0.97-1.36)^
18	Saxony, Germany	Case-control	0-14	1.04 (0.74-1.48)	1.24 (0.68-2.25)	2.28 (0.94-5.54)	1.19 (0.77-1.83)
19	Oxford, Cambridge, Reading, UK	Case-control	0-14	-	1.2 (0.7-2.3)	1.0 (0.5-1.9)#	-
20	UK	Ecologic	1-14	1.03*	1.12*	1.11*	0.95*
21	Scotland, UK	Case-control	0-14	-	1.23 (0.77-1.97)	1.08 (0.60-1.94)	1.70 (0.59-4.95)^
22	England, UK	Case-control	0-14	0.89 (0.69-1.15)	-	1.79 (1.02-3.15)	0.79 (0.59-1.08)
23	England, UK	Case-control	1-14	1.44 (1.00-2.08)	1.53 (0.82-2.85)	1.03 (0.48-2.20)	1.39 (0.88-2.20)

^ For lymphomas alone.

For acute lymphoblastic leukaemia under age 15.

* Risk ratios expressed as the ratio of observed: expected cases between hospitals with non-selective and selective policy of vitamin K administration. The x^2 values are not significant.

Abbreviations: ALL=acute lymphoblastic leukaemia; USA=United States of America; UK=United Kingdom

vitamin K intramuscularly more often than the controls but the difference was of borderline significance (OR, 95% CI: 1.44, 1.00-2.08; p=0.05). This difference was lost when the effect of vitamin K was adjusted for the type of delivery (OR: 1.07; p=0.82).

In addition, there were two nested case-control studies within cohort studies in which the risk of intramuscular vitamin K at birth and subsequent cancer development was evaluated.[15,16] No significant association was found. Hence, there is no definite evidence that intramuscular vitamin K administered to newborns causes cancer or leukaemia in their subsequent childhood. Similarly, an association has not been ruled out but any additional risk of childhood cancer, if this risk is genuine, must be substantially less than the twofold increase suggested by Golding et al.[9]

The Efficacy of Oral Vitamin K Prophylaxis

Orally administered vitamin K, either with the parenteral preparation or the mixed micellar preparation, has been advocated as an equally efficacious prophylaxis against VKDB alternative to intramuscular injection in apparently well babies.[8,24] The different regimens adopted in Europe and Australia are listed in Table 2. This approach, however, has met with problems with compliance[25] and unreliable absorption in infants with unsuspected cholestasis.[26] With the exception of the Netherlands, VKDB continued to appear in countries where oral prophylaxis was adopted.[8] The prophylaxis failure rate for the Netherlands, Germany, Australia and Switzerland were 0, 1.8, 1.5 and 1.2 per 100,000 live births, respectively. These failure rates were likely to be underestimates because the proportion of eligible children must be smaller than 100%. VKDB was not only observed in cases in whom the repeated doses were forgotten, but also in children who were given the recommended vitamin K solution. Indeed, the national policy in Australia has reversed back into the parenteral route of vitamin K prophylaxis since 1994 and VKDB has practically disappeared afterwards.[8]

Hence, oral vitamin K prophylaxis even if repeated after birth appears to be less effective when compared with intramuscular vitamin K injection at birth. The only exception was the regimen adopted in the Netherlands in which exclusively breastfed babies were given a daily supplement of 25 μg of vitamin K to mimic the amount of vitamin uptake in formula fed babies.

The Situation in Hong Kong

The practice of vitamin K prophylaxis in relation to VKDB has not been overtly announced until 1993, when the Hong Kong Paediatric Society and the Hong Kong College of Paediatricians jointly published their statement on the issue.[7] Both the intramuscular and the oral routes of administration were recommended. A monitoring committee was set up to detect any resurgence of VKDB, but no further report has been published since then. Our case report therefore would be reminiscent of the dreadful consequence of VKDB and the importance of an efficacious programme on vitamin K prophylaxis. Following the occurrence of this case, we had changed to the use of intramuscular vitamin K prophylaxis for all infants born in our hospital. We have not seen another case of VKDB since we adopted this policy six years ago.

In Hong Kong, the only preparation of vitamin K suitable for neonatal use is a mixed micellar preparation (Konakion MM®) supplied in an ampoule of 2 mg/0.2 mL, which can be used parenterally or orally. If the Dutch regimen is to be used, a new preparation needs to be marketed locally. It is worth noting that the vitamin K blood levels achieved after oral administration are comparable to those after intramuscular injection.[24] If the risk of childhood cancer were related to the high serum levels of vitamin K,[1,2] the safety of using the Konakion MM® preparation orally would be questionable.

Conclusion

While the association of parenteral vitamin K administration and childhood cancer cannot be established and the risk of vitamin K leading to subsequent childhood

Table 2 Different regimens of oral vitamin K prophylaxis for apparently well babies[8,24]

Country	Dose at birth	Subsequent doses
Netherlands	1 mg	25 μg daily from second week to 3 months old
Germany/Australia	1 mg	1 mg once on day 4-10 (Germany) or day 3-5 (Australia)
		1 mg once during week 5-6 (Germany) or week 4 (Australia)
Switzerland	2 mg	2 mg day 4
Denmark	2 mg	1 mg weekly until 3 months old

cancer cannot be quantified,[3,9] the risks of VKDB in early infancy has been well proven.[27] Because of the reliability of the intramuscular route of administration in preventing VKDB over the oral route, we would recommend the routine use of intramuscular vitamin K at birth for all newborn infants: 0.5 mg for birth weight 1,500 g or less and 1.0 mg for birth weight greater than 1,500 g.[3,28] The employment of the oral route of prophylaxis, either because of physician or parental preference, should be carefully monitored with respect to subsequent dosages and early signs of bleeding. Parents should be reminded of the small but definite risk of VKDB, including the occurrence of fatal intracranial bleeding, if they have chosen the oral route of prophylaxis.[28]

References

1. Zipursky A. Prevention of vitamin K deficiency bleeding in newborns. Br J Haematol 1999;104:430-7.
2. Sutor AH, von Kries R, Cornelissen EA, McNinch AW, Andrew M. Vitamin K deficiency bleeding (VKDB) in infancy. ISTH Pediatric/Perinatal Subcommittee. International Society on Thrombosis and Haemostasis. Thromb Haemost 1999;81: 456-61.
3. American Academy of Pediatrics. Vitamin K Ad Hoc Task Force: Controversies concerning vitamin K and the newborn. Pediatrics 1993;91:1001-3.
4. American Academy of Pediatrics. Vitamin K compounds and their water soluble analogues: use in therapy and prophylaxis in pediatrics. Pediatrics 1961;28:501-7.
5. van Doorm JM, Muller AD, Hemker HC. Heparin-like inhibitor not vitamin-K deficiency, in the newborn. Lancet 1977;1: 852-3.
6. Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. BMJ 1992; 305:341-6.
7. Chow CB, Yeung CY. Joint statement on the vitamin K controversy by Hong Kong Paediatric Society and Hong Kong College of Paediatricians. HK J Paediatr 1993;10:93-5.
8. Cornelissen M, von Kries R, Loughnan P, Schubiger G. Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. Eur J Pediatr 1997; 156:126-30.
9. Tripp JH, McNinch AW. The vitamin K debacle: cut the Gordian knot but first do no harm. Arch Dis Child 1998;79:295-7.
10. Laurance B. Danger of vitamin-K analogues to newborn. Lancet 1955;1:819.
11. Anon. Vitamin K and the newborn. Lancet 1978;1:755-7.
12. McNinch AW, Orme RL, Tripp JH. Haemorrhagic disease of the newborn returns. Lancet 1983;1:1089-90.
13. Kaiser D, Hooper PA. Intramuscular vitamin K and childhood cancer. BMJ 1992;305:710.
14. Draper GJ, Stiller CA. Intramuscular vitamin K and childhood cancer. BMJ 1992;305:709.
15. Klebanoff MA, Read JS, Mills JL, Shiono PH. The risk of childhood cancer after neonatal exposure to vitamin K. N Engl J Med 1993;329:905-8.
16. Ekelund H, Finnstrom O, Gunnarskog J, Kallen B, Larsson Y. Administration of vitamin K to newborn infants and childhood cancer. BMJ 1993;307:89-91.
17. Olsen JH, Hertz H, Blinkenberg K, Verder H. Vitamin K regimens and incidence of childhood cancer in Denmark. BMJ 1994;308:895-6.
18. von Kries R, Gobel U, Hachmeister A, Kaletsch U, Michaelis J. Vitamin K and childhood cancer: a population based case-control study in Lower Saxony, Germany. BMJ 1996;313: 199-203.
19. Ansell P, Bull D, Roman E. Childhood leukaemia and intramuscular vitamin K: findings from a case-control study. BMJ 1996;313:204-5.
20. Passmore SJ, Draper G, Brownbill P, Kroll M. Ecological studies of relation between hospital policies on neonatal vitamin K administration and subsequent occurrence of childhood cancer. BMJ 1998;316:184-9.
21. McKinney PA, Juszczak E, Findlay E, Smith K. Case-control study of childhood leukaemia and cancer in Scotland: findings for neonatal intramuscular vitamin K. BMJ 1998;316:173-7.
22. Parker L, Cole M, Craft AW, Hey EN. Neonatal vitamin K administration and childhood cancer in the north of England: retrospective case-control study. BMH 1998;316:189-93.
23. Passmore SJ, Draper G, Brownbill P, Kroll M. Case-control studies of relation between childhood cancer and neonatal vitamin K administration. BMJ 1998;316:178-84.
24. Anon. Which vitamin K preparation for the newborn? Drug Ther Bull 1998;36:17-9.
25. Croucher C, Azzopardi D. Compliance with recommendations for giving vitamin K to newborn infants. BMJ 1994;308:894-5.
26. Humpl T, Bruhl K, Brzezinska R, Hafner G, Coerdt W, Shearer MJ. Fatal late vitamin K-deficiency bleeding after oral vitamin K prophylaxis secondary to unrecognized bile duct paucity. J Pediatr Gastroenterol Nutr 1999;29:594-7.
27. Hull D. Vitamin K and childhood cancer. BMJ 1992;305: 326-7.
28. Fetus and Newborn Committee. Routine administration of vitamin K to newborns. Joint position paper of the Canadian Paediatric Society and the Committee on Child and Adolescent Health of the College of Family Physicians of Canada. Can Fam Physician 1998;44:1083-90.