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ORIGINAL ARTICLE

Prevention of vitamin K deficiency bleeding with three oral mixed micellar phylloquinone doses: results of a 6-year (2005–2011) surveillance in Switzerland

Bernard Laubscher · Oskar Bänziger · Gregor Schubiger · the Swiss Paediatric Surveillance Unit (SPSU)

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Abstract In 2003, the Swiss guidelines to prevent vitamin K deficiency bleeding (VKDB) were adapted. As two oral doses (2 mg, hour/day 4) of mixed micellar VK preparation had failed to abolish late VKDB, a third dose (week 4) was introduced. This report summarizes the new guidelines acceptance by Swiss pediatricians and the results of a prospective 6-year surveillance to study their influence on the incidence of VKDB. The new guidelines acceptance by Swiss pediatricians was evaluated by a questionnaire sent to all pediatricians of the Swiss Society of Paediatrics. With the help of the Swiss Paediatric Surveillance Unit, the incidence of VKDB was monitored prospectively from July 1, 2005 until June 30, 2011. Over a 6-year period (458,184 live births), there was one case of early and four cases of late VKDB. Overall incidence was $1.09/10^5$ (95 % confidence intervals (CI) 0.4–2.6). Late VKDB incidence was $0.87/10^5$ (95 % CI 0.24–2.24). All four infants with late VKDB had an undiagnosed cholestasis at the time of bleeding; parents of 3/4 had refused VK prophylaxis, and in 1/4, the third VK dose had been forgotten. Compared with historical control who had received only two oral doses of mixed micellar VK (18 cases for 475,372 live births), the incidence of late VKDB was significantly lower with three oral doses (Chi^2,Yates correction, $P=0.007$). *Conclusion* VKDB prophylaxis with 3×2 mg oral doses of mixed micellar VK seems to prevent adequately infants from VKDB. The main risk factors for VKDB in breast-fed infants are parental VK prophylaxis refusal or an unknown cholestasis.

Keywords Vitamin K deficiency bleeding · Vitamin K · Prophylaxis · Bleeding · Newborn · Infant

B. Laubscher (✉)
Department of Pediatrics, Hôpital Neuchâtelois, Maladière 45, 2000, Neuchâtel, Switzerland
e-mail: bernard.laubscher@ne.ch

O. Bänziger
Swiss Disability Insurance, Zürich, Switzerland

G. Schubiger
Department of Pediatrics, Kinderspital, Luzern, Switzerland

B. Laubscher
Department of Pediatrics, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Introduction

In 2003, the Swiss national guidelines to prevent vitamin K deficiency bleeding (VKDB) were adapted on the basis of a surveillance report [7, 8]. As it had been shown that two 2-mg oral doses (4 h, 4 days) of mixed micellar vitamin K preparation had failed to abolish VKDB, mainly late VKDB, a third 2 mg oral dose (4 weeks) was introduced in the hope it would permit complete eradication of VKDB.

This report summarizes the new guidelines acceptance by Swiss pediatricians and the results of a prospective 6-year surveillance to study their influence on the incidence of VKDB.

Subjects and methods

The new guidelines acceptance by Swiss pediatricians was evaluated by a questionnaire sent 3 years after their publications to all 728 pediatricians of the Swiss Society of Paediatrics.

The Swiss Paediatric Surveillance Unit (SPSU) has been described previously [15] and is comparable to other national surveillance units [2]. Briefly, using an internationally accepted definition of VKDB [11], data were collected from July 1, 2005 until June 30, 2011. Early and classical VKDB are defined as bleeding occurring on the first day of life,

respectively, between the second and seventh day. Late VKDB is defined by the following criteria: (1) occurrence between the eighth day and the completed 12th week of life; (2) Quick values ≤15 %, INR ≥4, prothrombin time ≥4 times the control value; and (3) at least one of the following: normal or increased platelet count, normal fibrinogen and absence of fibrin degradation products, or return of prothrombin time to normal values after VK administration. Cases occurring between the 13th and 26th week of life were also collected and described as late-onset VKDB.

In the present report, our 6-year experience is summarized and the incidence of VKDB is compared with Swiss historical controls from the 1995 to 2001 period [7] as well as reported incidence figures from other countries. The 95 % confidence intervals (CI) were computed according to Clopper-Pearson [3]. Chi square test with Yates correction for continuity [4] was used for comparison of different study populations. There were 458,184 live births in Switzerland during the study period (personal communication, C. Di Loreto, Swiss Federal Statistical Office).

Results

Out of 728 pediatricians, 629 replied (86 %) to the questionnaire. Six hundred eleven were directly involved with vitamin K prophylaxis: 586 (96 %) prescribed it according to the 2003 guidelines, 19 (3 %) depending whether the infants were breast or bottle fed and 6 (1 %) never, 2 of whom because they either forgot or had not been informed of the new guidelines.

The response rate of the surveyed units was 100 %. Figure 1 shows the breakdown of the 11 reported cases. Details of five confirmed VKDB are shown in Table 1: there

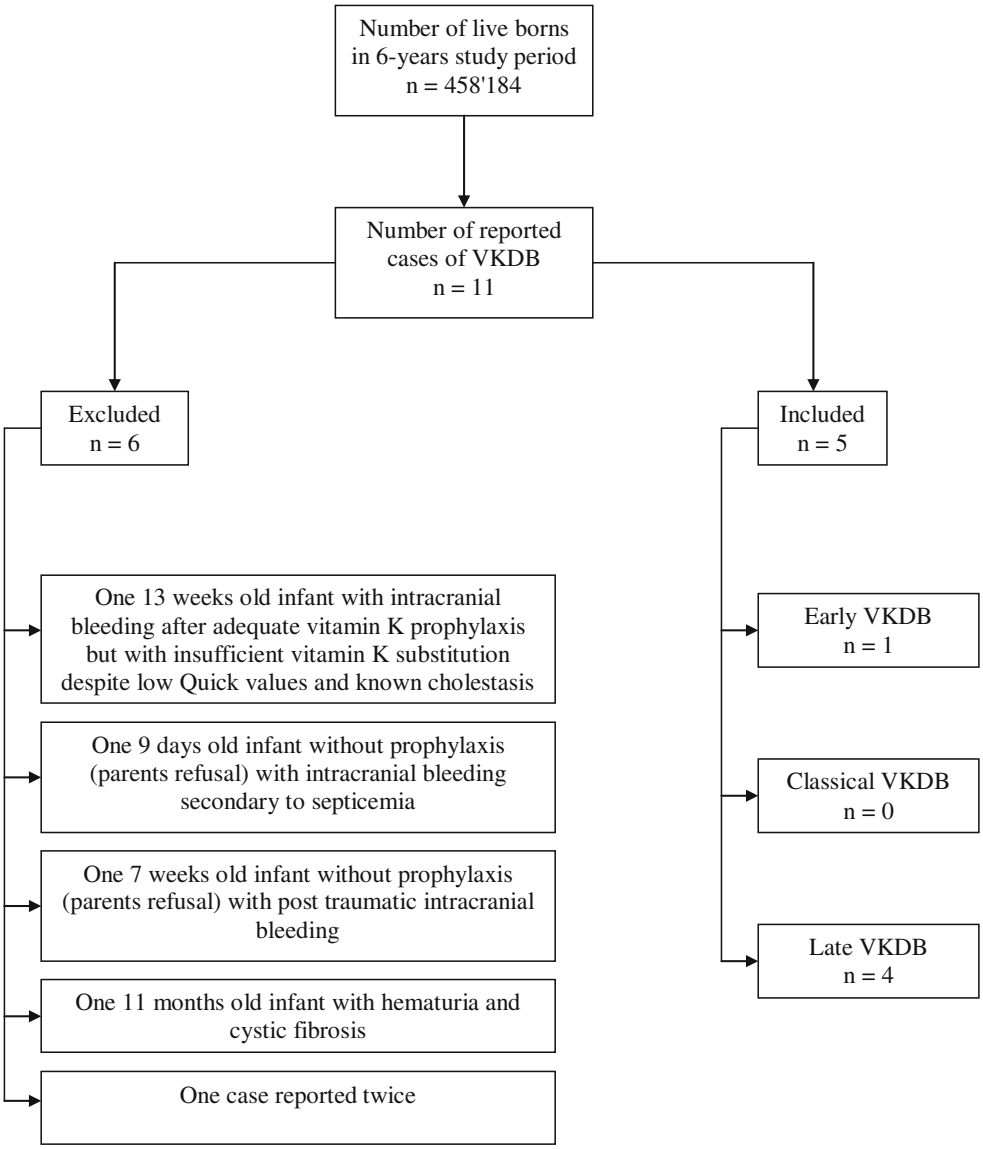

Fig. 1 Breakdown of patients with VKDB

Table 1 Confirmed cases of VKDB

Case no.	Vitamin K prophylaxis	Breast feeding	Age at bleeding	Localisation of bleeding	Hepatobiliary disease	Outcome
1	None (parents refusal)	Full	18 h	Intestinal; Intracranial	None	Good
2	None (parents refusal)	Full	13 days	Umbilical	Biliary atresia	Good
3	None (parents refusal)	Full	4 weeks	Intestinal; Intracranial	Cholestasis (tot/dir serum bili. 79/33 μmol/l), spont. regressive, unclear etiology	Severe cerebral palsy
4	None (parents refusal)	Full	4 weeks	Joint	Cholestasis; Giant cell hepatitis	Good
5	Day 1 and 4 doses only (week 4 dose omitted)	Full	10 weeks	Skin; (after blood sampling)	Cholestasis; α1-antitrypsin deficiency	Good

were one case of early and four cases of late VKDB. All of the four late VKDB infants were fully breast fed and had previously unrecognized cholestasis at the time of bleeding, three had received no prophylactic VK because of parents' refusal, and one had received only the day 1 and 4 VK doses as the third had been omitted. By definition [11], only case no. 1 represents an "idiopathic" case. The other four infants are secondary cases. These five cases represent prophylactic failures as, although refused or omitted, the advised prophylaxis did not prevent them from bleeding. However, no case represents a true prophylactic failure (VKDB after adequate prophylaxis and without predisposing factor). The main risk factors for VKDB were VK prophylaxis refusal by parents and/or an unknown cholestatic liver disease. One additional case of late-onset VKDB presented at week 24 with intestinal bleeding after adequate neonatal prophylaxis, being fully breastfed but with unknown cholestasis.

Overall, the incidence of late VKDB was $0.87/10^5$ (95 % CI 0.24–2.24). Compared with the 1995–2001 data [7], there were significantly less late VKDB (Chi square test with Yates correction for continuity, $P=0.007$). If patients who had received no or incomplete VK prophylaxis were excluded, the incidence of late VKDB was $0.00/10^5$ (95 % CI 0.00–0.81). If patients with cholestatic liver disease and inappropriate VK prophylaxis were excluded, the incidence of late VKDB was $0.00/10^5$ (95 % CI 0.00–0.81).

Discussion

In a nationwide prospective surveillance study including almost half a million live births, we have shown that VKDB could be eradicated in healthy infants who benefit from 3× 2 mg oral mixed micellar VK (hour 4, day 4, week 4). The main risk factors for VKDB were VK prophylaxis refusal by parents and/or an unknown cholestatic liver disease. Compared with historical controls that benefitted from 2×2 mg oral mixed micellar VK [7], 3×2 mg oral doses decreased significantly the risk of late VKDB.

In a previous nationwide questionnaire, we had shown that 99 % of all obstetric units in Switzerland followed the official guidelines (2 mg oral mixed micellar VK at hour and day 4) for VKDB prevention [9]. In the present study, we have found that 96 % of pediatricians who prescribed prophylactic VK followed the most recent guidelines (third dose of 2 mg oral mixed micellar vitamin K at week 4). We are thus fairly confident that our study population was very homogeneous with regard of the prophylactic regimen whose efficacy could therefore be appropriately tested on a large scale basis as in the present study.

There is still an ongoing debate about the most appropriate regimen for late VKDB prophylaxis [1, 6, 7, 9, 10, 12–14]. Different prophylactic schemes are used even within the same country. The lowest incidences of VKDB, especially late VKDB, are reported after a single intra muscular (im) 1 mg phylloquinone prophylaxis at birth or after im or oral 2 mg at birth followed by weekly 1 mg oral VK administration. The incidence of late VKDB after three oral doses of mixed micellar VK has been estimated to be $0.44/10^5$ (95 % CI 0.19–0.87) in Germany [14]. The present study has confirmed that the already known risk factors for oral prophylactic failure was mainly VK refusal and/or unknown cholestasis [1, 7]. Refusal of im prophylaxis has also been reported as a main risk factor for prophylactic failure [6]. If parental refusal is the commonest reason for prophylactic failure, it is surprising to us that a policy of giving a single im injection appears to offer better protection than the three oral doses. It also surprises us that in none of the infants reported by van Hasselt et al. [12], prophylaxis had been refused, suggesting greater parental acceptance of prophylaxis in Holland and Denmark than in Switzerland (also oral), New Zealand [1], or the UK [6].

Our findings of an incidence of $0.00/10^5$ (95 % CI 0.00–0.81) late VKDB in infants with adequate prophylaxis with 3×2 mg oral mixed micellar VK strongly suggests that such a prophylactic regimen is adequate for healthy infants. Infants with cholestasis could eventually benefit from another prophylaxis scheme such as the Danish regimen (mixed micellar VK: 2 mg im at birth or 2 mg oral at birth

followed by weekly 1 mg oral). More aggressive (im) or complicated (oral weekly) prophylactic regimens bear the risk to put more parents off any prophylaxis, thus increasing the final incidence of VKDB.

There are obvious limitations to our study. As case detection was limited to the SPSU clinical surveillance, underreporting of VKDB cases is possible. Dramatic conditions such as infant (intracranial) hemorrhages are however likely to be reported. Small umbilical or gastrointestinal bleeds, easily managed by general pediatricians without coagulation studies and with additional oral VK administrations could theoretically represent prophylactic failure that would not be reported. Such benign conditions would however be underreported irrespective of the VK prophylactic regimen (oral versus im) allowing valid interprophylactic regimen comparisons. Further, as the surveyed units response rate of the present and 1995–2001 study were 100 %, we are fairly confident that our study gives robust data to evaluate the efficacy of the current Swiss VKDB prophylaxis.

In conclusions, our study supports the oral administration of 3×2 mg mixed micellar VK (hour 4, day 4, week 4) to prevent VKDB. Pediatricians, midwives, and parents have to be aware of bleeding risks when any type of VK prophylaxis is refused. Further, pediatricians, midwives, and parents have to be aware of early clinical signs of cholestasis. To that extend, an early recognition program is being developed in Switzerland [5]. Using van the methodology of Hasselt et al. [12], an analysis of all biliary atresia cases that were diagnosed in Switzerland during the present study period is under way.

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Conflict of interest The authors declare that they have no conflict of interest.

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