Prophylactic Dosing of Vitamin K to Prevent Bleeding

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abstract

BACKGROUND AND OBJECTIVES: Based on a high incidence of Vitamin K deficiency bleeding (VKDB) in breastfed infants with thus far unrecognized cholestasis, such as biliary atresia (BA), the Dutch regimen to prevent VKDB in breastfed infants was changed from a daily oral dosage of 25 μg to 150 μg vitamin K. Infants continued to receive 1 mg of vitamin K orally at birth. We compared the efficacy of the 150-μg regimen with the 25-μg regimen and with the Danish regimen of a single intramuscular (IM) dose of 2 mg vitamin K at birth.

METHODS: Data were retrieved from the national BA registries: 25 μg group (Netherlands, January 1991 to February 2011); 150 μg group (Netherlands, March 2011 to January 2015); and IM 2 mg group (Denmark, July 2000 to November 2014). We compared the incidence of VKDB in the groups.

RESULTS: VKDB occurred in 45 of 55 (82%) infants of the 25 μg group, in 9 of 11 (82%) of the 150 μg group, but in only 1 of 25 (4%) of the IM 2 mg group ($P < .001$). Forty percent of all infants of the 25 μg group had an intracranial hemorrhage as presenting symptom, compared with 27% of the infants of the 150 μg group ($P = .43$). Intracranial hemorrhage was not observed in the IM 2 mg group (0%; $P < .001$).

CONCLUSIONS: A vitamin K prophylactic regimen of 1 mg of vitamin K orally at birth followed by a daily oral dosage of either 25 or 150 μg fails to prevent VKDB in breastfed infants with still unrecognized BA. The data support 2 mg vitamin K IM at birth as prophylaxis against VKDB.

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WHAT'S KNOWN ON THIS SUBJECT: The Dutch guideline to prevent vitamin K deficiency bleeding in breastfed infants has recently been increased from a daily dose of 25 μg to 150 μg vitamin K, based on a high incidence of vitamin K deficiency bleeding in infants with unrecognized cholestasis.

WHAT THIS STUDY ADDS: Increasing the daily dose of vitamin K to 150 μg failed to prevent vitamin K deficiency bleeding in breastfed infants with yet unrecognized biliary atresia and was far less effective than the Danish regimen, consisting of a single dose of 2 mg intramuscularly at birth.

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Vitamin K deficiency can cause severe bleeding in breastfed infants owing to insufficient amounts of vitamin K in breastmilk.[1] This bleeding, known as vitamin K deficiency bleeding (VKDB), can be classified according to the time of presentation: early (<24 hours of age), classic (first week after birth), and late (between 1 week and 6 months of age).[2] In ∼50% of patients with late VKDB, the bleeding location involves an intracranial hemorrhage, which is associated with high mortality and morbidity.[3–5] The absorption of vitamin K is strongly dependent on the intestinal availability of bile acids. Diminished or absent intestinal delivery of bile, which occurs during cholestasis, puts infants especially at risk for malabsorption of vitamin K and other fat-soluble vitamins.[6,7] Infants who have been breastfed exclusively are at the highest risk for late VKDB, particularly if the cholestasis has not yet been diagnosed.

Many countries have introduced prophylactic regimens of vitamin K supplementation to prevent VKDB (Table 1).[8] The optimal dose, route, and frequency of administration of vitamin K, however, are still unclear. Oral and intramuscular (IM) regimens of vitamin K administration at birth have been proven effective in the prevention of classic VKBD.[9] A single dose of IM vitamin K at birth can also prevent late VKDB.[10] Between 1990 and February 2011, all infants in the Netherlands received a single oral dose of 1 mg vitamin K at birth, followed by a recommended daily oral supplementation of 25 μg vitamin K between week 2 and 13 in breastfed infants.[11] This regimen significantly decreased the incidence of late VKDB.[12] Previously, however, we and others reported several cases of VKDB based on surveillance studies and studies in high-risk populations, despite strong indications of adherence to the recommendations. In fact, in >80% of infants with biliary atresia (BA), severe late VKDB was the presenting symptom.[13] This observation was in sharp contrast to a very low incidence of VKDB as presenting symptom in BA patients in Denmark, where other prophylactic vitamin K regimens are used.[14–17] The risk of VKDB in Dutch breastfed BA patients was 8 to 10 times higher than that of Danish BA patients, on either a weekly oral dose of 1 mg vitamin K or a single IM dose of 2 mg vitamin K at birth. Since March 2011, the prophylactic regimen was changed in the Netherlands; the recommended daily oral dose of 25 μg vitamin K was increased to 150 μg daily for all breastfed infants from week 2 to 13 of life. The single oral dose of 1 mg vitamin K at birth was maintained.

TABLE 1 Vitamin K Prophylaxis in Different Countries[8]

Country	Vitamin K Prophylaxis	Incidence of VKDB per 100 000 Infants, RR (95% CI)
Netherlands (1990–2011)	1 mg po at birth, 25 μg po daily weeks 2 to 13	3.2 (1.2–6.9)
Germany	3×2 mg po (days 1, 4–10, 28–42)	0.44 (0.2–0.9)
France	2 mg po weekly for 6 mo	No data available
Switzerland	3×2 mg po (day 1, day 4, week 4)	0.87 (0.24–2.24)
Denmark		
1994 to June 2000	2 mg po at birth, 1 mg po weekly for 3 mo	0.0 (0–0.9)
After June 2000	2 mg IM at birth	No data available
United Kingdom	1 mg IM at birth (day 1, week 1, week 4)	0.1
	3×2 mg po (day 1, week 1, week 4)	0.43
Australia	0.5–1 mg IM (day 1, days 3–7, week 6)	0.2
	3×2 mg po (day 1, days 3–7, week 6)	4.1
Canada	1 mg IM at birth	0.37
United States	1 mg IM at birth	No data available

CI, confidence interval; p.o., by mouth.

In the current study, we evaluated the preventive effect of the adapted Dutch guideline with respect to the incidence and severity of VKDB as the presenting symptom in breastfed children with BA. We compared the incidence and severity of VKDB with the repeated oral 25 μg, repeated oral 150 μg, and single 2 mg IM regimens.

METHODS

Study Population

The Netherlands Study group on Biliary Atresia Registry (NeSBAR) has been a joint effort of the Dutch Society for Pediatrics Section of Gastroenterology, Hepatology, and Nutrition and the Dutch Society for Pediatric Surgeons. Data of all patients with BA born from January 1991 to January 2015 and treated in 1 of the 6 specialized academic centers in the Netherlands were obtained from the NeSBAR database. Data of all Danish patients with BA born from July 2000 to November 2014 were retrieved from the Department of Pediatric Surgery at the University Hospital of Copenhagen (Rigshospitalet). Patients with a gestational age <37 weeks or birth weight <2000 g were excluded. Infants who were born abroad or were hospitalized from birth were also excluded. Relevant clinical data were obtained from the medical records. The study was performed according to the guidelines of the medical ethics committee of the University Medical Center Groningen. For anonymized, retrospective analysis of filed patient data, ethics approval is not required in our countries.

Vitamin K Deficiency Bleeding

VKDB was defined as bruising, bleeding, or intracranial hemorrhage in infants younger than 6 months, not due to other coagulopathies, in combination with

normalization of the coagulopathy (partial thromboplastin time or activated partial thromboplastin time) after administration of vitamin K.[2,7,13]

Vitamin K Prophylaxis

In this study, we evaluated the incidence of VKDB in breastfed children with BA who had received 1 of 3 prophylactic regimens: (1) 25 μg group: 1 mg orally at birth, followed by a daily oral dose of 25 μg vitamin K (Netherlands, January 1991 to February 2011); (2) 150 μg group: 1 mg orally at birth, followed by a daily oral dose of 150 μg vitamin K (Netherlands, March 2011 to January 2015); and (3) IM 2 mg group: a single IM dose of 2 mg vitamin K at birth (Denmark, July 2000 to November 2014).

Results of the 25 μg and IM 2 mg groups from before 2003 and 2005, respectively, upon which the vitamin K prophylaxis in the Netherlands was adapted, were partially published previously.[13,18] In the current study, we used these data, enriched with updated results on the new regimens, to compare the efficacy of the adaptation with regard to protection against VKDB.

Statistical Analysis

To analyze the clinical and biochemical data, we used a χ^2 test in case of dichotomous parameters, 1-way analysis of variance for parameters with a normal distribution, and Kruskal–Wallis test for parameters with a nonnormal distribution. The relative risks and 95% confidence intervals for VKDB were calculated, and the Fisher exact test was used for the comparison of incidences of VKDB and intracranial hemorrhage between groups. A *P* value <.05 was considered statistically significant. All analyses were performed with SPSS (version 22.0; IBM Corp, Armonk, NY).

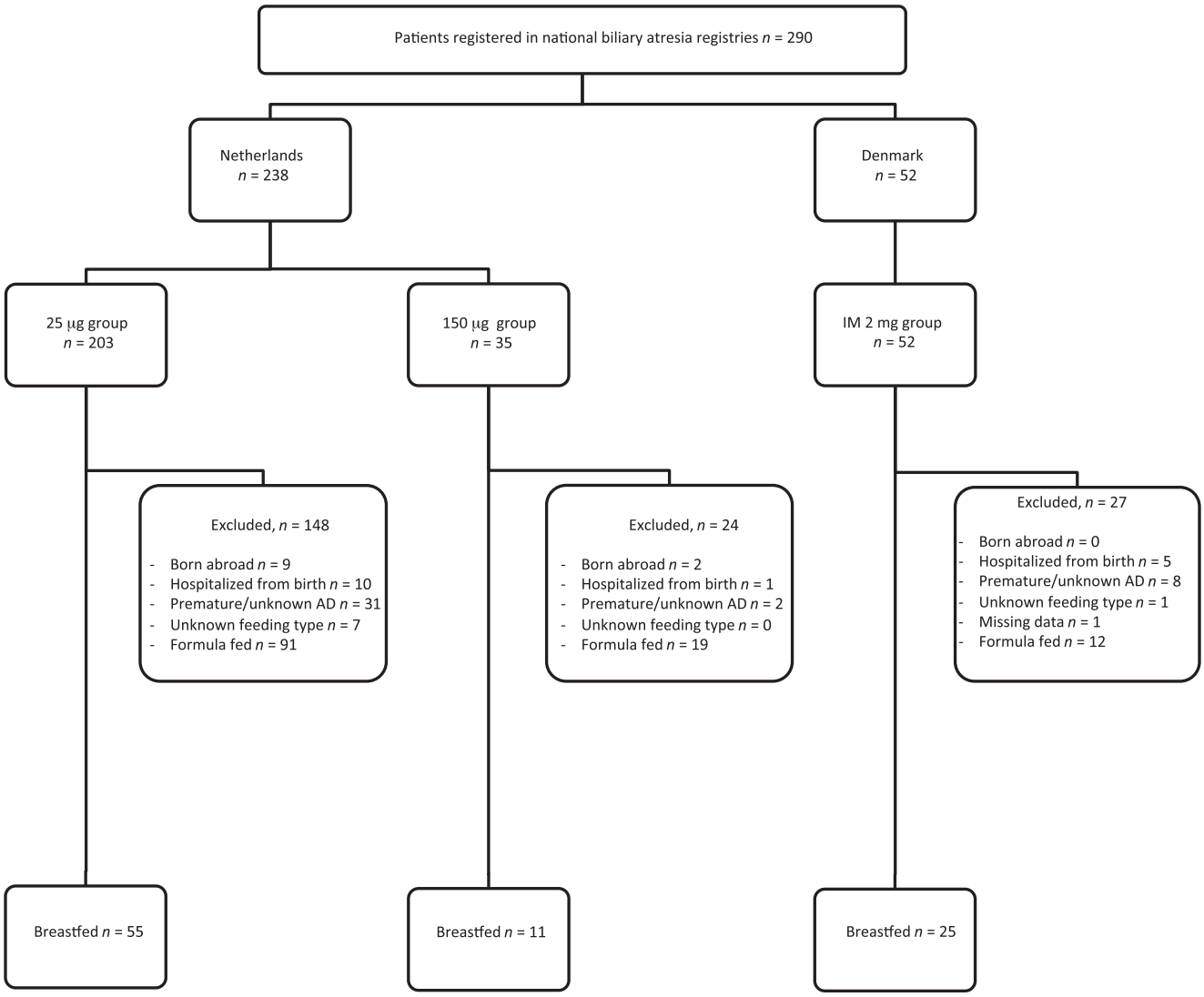

FIGURE 1
Flow chart of patient inclusion.

RESULTS

From January 1991 to January 2015, 238 patients with BA were registered in NeSBAR. Sixty-two patients were excluded for various reasons (Fig 1). Of the remaining infants, 110 (62%) received formula feeding or a combination of formula feeding and breastfeeding. Fifty-five exclusively breastfed patients were included in the 25 μg group and 11 in the 150 μg group (Fig 1). Between July 2000 and November 2014, 52 patients were registered in the Danish Biliary Atresia Registry. Fifteen infants were excluded for various reasons (Fig 1). Twenty-five (68%) of the remaining 37 were exclusively breastfed and included in the IM 2 mg group (Fig 1**).**

The incidences of BA in the Netherlands and Denmark were 1:19 000 and 1:17 000, respectively (Table 2). Table 3 summarizes the clinical characteristics of the 3 groups. Patients in each group had conjugated hyperbilirubinemia, as expected. Median age at diagnosis was 34, 31, and 42 days for 25 μg, 150 μg, and IM 2 mg, respectively (P = .47). There were no statistically significant differences between the 3 groups in the parameters listed.

Vitamin K Deficiency Bleeding

In the 25 μg group, VKDB occurred in 45 of 55 (82%) patients. Twenty-one (38% of total) were diagnosed with multiple bleedings. Twenty-two (40%) presented with intracranial hemorrhage, diagnosed with computed tomography or MRI scan. VKDB occurred in 9 of 11 (82%) of the 150 μg group. Six (55%) of these patients had multiple bleedings, and three (27%) presented with intracranial hemorrhage. In the Danish IM 2 mg group, VKDB occurred in only 1 of the 24 (4%) breastfed patients. None of the infants presented with intracranial hemorrhage (Tables 4 and 5).

TABLE 2 Patients and Populations

Characteristic	Group		
	25 μg	150 μg	2 mg IM
Prophylactic regimen	1 mg po at birth, 25 μg po daily	1 mg po at birth, 150 μg po daily	2 mg IM at birth
Live births, n[a]	3 902 956	672 531	897 156
Enlisted in BA registry	203	35	52
Incidence of BA	1:19 226	1:19 215	1:17 253

[a] Numbers of live births were obtained from Central Bureau of Statistics (http://statline.cbs.nl) and UN data (http://data.un.org).

DISCUSSION

We evaluated whether a vitamin K prophylactic regimen of 1 mg vitamin K orally at birth followed by 150 μg daily during weeks 2 to 13 sufficiently prevented VKDB in breastfed infants. Our data in a high-risk group, ie, undiagnosed children with BA, show that this regimen does not successfully prevent VKDB in these children, in contrast to a regimen consisting of a single IM injection of 2 mg vitamin K at birth.

This study shows that increasing the daily dose of the oral vitamin K prophylactic regimen from 25 to 150 μg fails to prevent VKDB in breastfed infants with yet undiagnosed BA. VKDB occurred in 82% of the infants and included several cases of intracranial hemorrhage, which has been associated with serious morbidity and high mortality.[5] The risk of VKDB in breastfed infants with BA on a daily oral dose of 150 μg of vitamin K was 20-fold higher than on a single IM dose at birth. Compared with the former regimen of 25 μg, there was no significant difference in the incidence of VKDB.

We studied the incidence of VKDB as the presenting symptom in breastfed infants with BA under 3 different prophylactic regimens. Because we used the nationwide databases in the Netherlands and Denmark, in which all patients with biliary atresia are registered, we minimized the risk of selection bias. Only biliary atresia patients who were not presented to an academic hospital could have been missed. Another argument pleading against selection bias is the calculated incidence of BA in our 3 cohorts. The incidences of BA in the Netherlands and in Denmark were 1:19 000 and 1:17 000, respectively (Table 2), which are similar to the reported incidences in other studies.[19–21] There were no statistically significant differences in clinical characteristics between the groups that might affect the risk of VKDB.

TABLE 3 Clinical Characteristics for Each Type of Prophylaxis

Characteristic	Group			P
	25 μg	150 μg	2 mg IM	
n	55	11	25	
Male gender	21 (38)	4 (36)	14 (56)	.30[a]
Birth weight, g	3431 ± 418	3404 ± 630	3383 ± 618	.92[b]
Age at diagnosis, d	34 (3–72)	31 (17–96)	42 (6–127)	.31[b]
Weight at diagnosis, g	4045 ± 562	4131 ± 761	4353 ± 1058	.47[b]
Total bilirubin, μmol/L	171 (74–418)	148 (92–286)	174 (72–414)	.54[b]
Direct bilirubin, μmol/L	135 (57–284)	122 (81–247)	131 (61–312)	.44[b]
Aspartate transaminase, U/L	190 (28–635)	169 (100–536)	238 (49–1205)	.43[b]
Alanine transaminase, U/L	117 (15–458)	132 (78–272)	127 (24–392)	.64[b]

Values are expressed as n (%), mean ± SD, or median (range).
[a] P value determined using χ^2 test.
[b] P value determined using Kruskal–Wallis test.

TABLE 4 Incidence of VKDB Under Different Prophylactic Regimens

Type	Group			*P*	25 μg vs 150 μg		150 μg vs 2 mg IM	
	25 μg	150 μg	2 mg IM		RR	95% CI	RR	95% CI
n	55	11	25					
VKDB	45 (82)	9 (82)	1 (4)	<.001	1.0	.7–1.4	20.5	2.9–142.4
Intracranial bleeding	22 (40)	3 (27)	0 (0)	<.001	1.5	.5–4.1	—[a]	—[a]
Multiple bleedings	21 (38)	6 (55)	0 (0)	<.001	.7	.4–1.3	—[a]	—[a]

Values are expressed as *n* (%). *P* values were determined by using Fisher exact (Fisher–Freeman–Halton) test. CI, confidence interval; RR, relative risk.
[a] Data could not be computed because no cases were present in the 2 mg IM group.

TABLE 5 Site of Bleeding

Site	Group			*P*
	25 μg	150 μg	2 mg IM	
n	55	11	25	
Gastrointestinal bleeding	13 (24)	4 (36)	1 (4)	.03
Umbilical bleeding	6 (11)	1 (9)	0 (0)	.19
Skin bleeding	25 (45)	6 (55)	0 (0)	<.001
Prolonged bleeding vein puncture	12 (22)	1 (9)	0 (0)	.02
Intracranial bleeding	22 (40)	3 (27)	0 (0)	<.001

Values are expressed as *n* (%). *P* values were determined by using Fisher exact test.

The Health Council of the Netherlands recommended an oral regimen with increased daily dosages instead of a single IM dose because, in the latter situation, a relatively large group would receive prophylaxis when it did not really need it, namely the infants who at birth (or shortly thereafter) started with formula feeding rather than breastfeeding. Another motivation was that oral prophylaxis was regarded to be as effective as intramuscular prophylaxis, as long as the dosage was adequate. Previous studies showed that a weekly oral prophylaxis of 1 mg vitamin K in the first 3 months of life was highly effective in preventing VKDB.[13,22] The hypothesis at that time was that a weekly prophylaxis of 1 mg was more effective than 25 μg daily prophylaxis, as the cumulative dose per week was 6-fold higher in the weekly prophylaxis (1.05 vs 0.175 mg). Our present data clearly show that this hypothesis needs to be rejected. The cumulative administration of 1.05 mg vitamin K (150 μg daily) did not decrease the incidence of VKDB in our study population. It is unclear why a single, weekly dose of 1 mg is apparently effective,[13] in contrast to a similar dose subdivided over daily fractions. One could speculate that the fractional absorption of 1 larger dosage is higher than that of multiple small dosages, but data on fractional vitamin K absorption in infants are lacking. Also, compliance with the daily administration could play a role. However, in the patients studied, we found that, for most patients, it was noted that the parents had complied with daily administrations, whereas nothing was noted in a minority of the patients. We therefore feel that poor adherence is not the major explanation for our present findings.

Similarly, it has remained unexplained why formula-fed infants are protected against VKDB, despite a relatively low intake of vitamin K compared with breastfed infants with vitamin K prophylaxis (25 to 50 μg daily, based on 150 mL formula per kg body weight, and 150 μg daily, respectively).[13] Together, these observations underline the need to understand in more detail, the absorption of vitamin K from the infant intestine, to prevent VKDB based on rational arguments.

Intramuscular administration of vitamin K at birth has been demonstrated as an effective prevention of VKDB.[10,12,23] Our present data confirm this observation, even upon analysis of a group of infants with an inherently higher risk of VKDB. A great benefit of this type of prophylaxis is that the prophylaxis does not depend on daily or weekly adherence to the advised administration or the still rather uncharacterized intestinal absorption of vitamin K in infants. Disadvantages of IM prophylaxis are pain and possibly hematoma at the site of the injection and, although extremely rare, complications such as osteomyelitis and intramuscular bleeding.[9,18] In this study, data about side effects of IM administration have not been collected systematically. Golding et al had suggested an increased risk of developing leukemia and other malignancies after IM vitamin K prophylaxis.[24] After these disturbing results, however, several studies on this topic could not reproduce the original epidemiologic association. Ross and Davies reviewed the epidemiologic studies and found no evidence for the originally suggested relationship between IM vitamin K prophylaxis and the development of childhood cancer.[25]

CONCLUSIONS

We conclude that a prophylactic regimen for breastfed infants consisting of 1 mg vitamin K orally at birth, followed by either 25 or 150 μg daily during weeks 2 to 13, does not sufficiently prevent VKDB in breastfed infants with still undiagnosed BA. We assume that this insufficient prevention is also present in infants with yet undiagnosed other forms of neonatal cholestasis. Efficient

prevention was obtained by a regimen consisting of a single IM injection of 2 mg vitamin K at birth, as performed successfully in Denmark.

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ABBREVIATIONS

BA: biliary atresia
IM: intramuscular
NeSBAR: Netherlands Study Group for Biliary Atresia Registry
VKDB: vitamin K deficiency bleeding

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ERRATA

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An error occurred in the article by Witt et al, titled "Prophylactic Dosing of Vitamin K to Prevent Bleeding" published in the May 2016 issue of *Pediatrics* (2016 May;137 (5): e20154222, doi:10.1542/peds.2015-4222). Throughout the article, the dosage of the Danish prophylactic vitamin K regimen is erroneously given as a single dose at birth of ***2*** mg vitamin K IM, but this should be a single dose at birth of ***1*** mg vitamin K IM.

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