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Vitamin K Prophylaxis for Preterm Infants: A Randomized, Controlled Trial of 3 Regimens

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ABSTRACT

OBJECTIVE. Preterm infants may be at particular risk from either inadequate or excessive vitamin K prophylaxis. Our goal was to assess vitamin K status and metabolism in preterm infants after 3 regimens of prophylaxis.

METHODS. Infants <32 weeks' gestation were randomized to receive 0.5 mg (control) or 0.2 mg of vitamin K₁ intramuscularly or 0.2 mg intravenously after delivery. Primary outcome measures were serum vitamin K₁, its epoxide metabolite (vitamin K₁ 2,3-epoxide), and undercarboxylated prothrombin assessed at birth, 5 days, and after 2 weeks of full enteral feeds. Secondary outcome measures included prothrombin time and factor II concentrations.

RESULTS. On day 5, serum vitamin K₁ concentrations in the 3 groups ranged widely (2.9–388.0 ng/mL) but were consistently higher than the adult range (0.15–1.55 ng/mL). Presence of vitamin K₁ 2,3-epoxide on day 5 was strongly associated with higher vitamin K₁ bolus doses. Vitamin K₁ 2,3-epoxide was detected in 7 of 29 and 4 of 29 infants from the groups that received 0.5 mg intramuscularly and 0.2 mg intravenously, respectively, but in none of 32 infants from group that received 0.2 mg intramuscularly. After 2 weeks of full enteral feeding, serum vitamin K₁ was lower in the infants who received 0.2 mg intravenously compared with the infants in the control group. Three infants from the 0.2-mg groups had undetectable serum vitamin K₁ as early as the third postnatal week but without any evidence of even mild functional deficiency, as shown by their normal undercarboxylated prothrombin concentrations.

CONCLUSIONS. Vitamin K₁ prophylaxis with 0.2 mg administered intramuscularly maintained adequate vitamin K status of preterm infants until a median age of 25 postnatal days and did not cause early vitamin K₁ 2,3-epoxide accumulation. In contrast, 0.2 mg administered intravenously and 0.5 mg administered intramuscularly led to vitamin K₁ 2,3-epoxide accumulation, possibly indicating overload of the immature liver. To protect against late vitamin K₁ deficiency bleeding, breast-fed preterm infants given a 0.2-mg dose of prophylaxis should receive additional supplementation when feeding has been established.

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Key Words

vitamin deficiency, preterm, prophylaxis, vitamin K, phytomenadione

Abbreviations

VKDB—vitamin K deficiency bleeding
IM—intramuscular
IV—intravenous
PIVKA-II—undercarboxylated prothrombin
PT—prothrombin time
K₁O—vitamin K₁ 2,3-epoxide
AU—arbitrary units
FII—factor II (prothrombin)
TPN—total parenteral nutrition
IQR—interquartile range
VKOR—vitamin K epoxide reductase

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ALL NEWBORNS HAVE precariously low vitamin K₁ stores and essentially undetectable plasma concentrations.^{1,2} The American Academy of Pediatrics and the Department of Health of the United Kingdom recommend that all newborn infants receive vitamin K to prevent vitamin K deficiency bleeding (VKDB), a potentially serious and sometimes fatal condition.^{3,4} For the intramuscular (IM) route, the current dosage recommendation of 1 mg of vitamin K₁ is based on evidence obtained for term infants, and no guidelines are offered for preterm infants in the United Kingdom.⁴ Recent surveys highlighted the wide variation in dose, route, and formulation of vitamin K₁ used for preterm infants and the lack of national and international consensus.^{5,6}

Without adequate prophylaxis, preterm infants may be at particular risk of VKDB. They have hemostatic and hepatic immaturity,⁷ and hepatic morbidity often coexists. They are preferentially fed maternal milk, which contains low concentrations of vitamin K₁,^{8,9} and enteral feeding is often delayed. Microfloral gut colonization may be retarded¹⁰ and delay endogenous synthesis of menaquinones (vitamin K₂), which may also play a role in protection against VKDB.⁹ In addition, they frequently receive drugs such as antibiotics and anticonvulsants that antagonize vitamin K directly or reduce its availability. The intravenous (IV) route of prophylaxis is commonly used⁶ but has unproven efficacy and may not give sustained protection against late-onset VKDB.¹¹

Conversely, preterm infants may be at risk from excessively high doses of prophylactic vitamin K₁. Many receive doses used for term infants, even doses as high as 5 mg.⁵ Although earlier fears of an epidemiologic association between parenteral vitamin K and later childhood cancer have receded,^{12,13} such studies cannot prove absence of risk.¹⁴ Furthermore, a World Health Organization International Agency for Research on Cancer Working Group concluded that vitamin K₁ has not been adequately studied for mutagenicity.¹⁵ With their immature hepatic function, very preterm infants may be especially susceptible to any adverse consequences of large vitamin K₁ doses. The desired goal must be provision of adequate protection against VKDB while avoiding unnecessary overload.

This prospective, randomized trial assessed 3 prophylactic regimens using undercarboxylated prothrombin (PIVKA-II) (a protein induced in vitamin K absence/antagonism) as a sensitive functional marker of vitamin K deficiency and serum vitamin K₁ to assess uptake, tissue stores, and metabolic clearance. In addition, concentration of the epoxide metabolite of vitamin K₁ is used as a novel marker of the metabolic capacity of the premature liver to recycle vitamin K. We also assessed the total intake of vitamin K₁ from all sources during the study period. Measurements were made at birth, after 5 days, and 2 weeks after the establishment of full enteral feeding.

METHODS

Patients

Eligible infants were inborn at <32 weeks' gestational age and admitted for neonatal intensive care in 1 of 3 participating United Kingdom neonatal units (Hope, Royal Bolton, and Billinge Hospitals). Exclusion criteria were fetal intracranial hemorrhage suspected on routine antenatal ultrasound scan (18–20 weeks' gestation), maternal antiplatelet antibodies, history of alloimmune thrombocytopenia, maternal drug treatment with known vitamin K antagonists, major congenital abnormality, and marked bruising at birth. Recruitment was between November 2001 and October 2003. Local research ethics committees approved the study, and written informed parental consent was obtained.

Randomization and Study Protocol

We randomly assigned infants to receive 1 of 3 regimens of vitamin K₁ prophylaxis. Independent personnel prepared the computer-generated allocation sequence using variable block sizes of 6 and 12. The allocated regimen and study number were sealed in sequentially numbered, opaque envelopes. Infants were stratified by gestational age, using 1 set of envelopes for <28 weeks' and another for 28 to 31 weeks 6 days'. All were randomized at a single lead center (Hope) by duty medical personnel. Infants recruited at peripheral units were randomized by telephoning the lead unit; faxed confirmation of allocation group was provided.

The vitamin K preparation used was Konakion Neonatal (Roche Ltd, Basel, Switzerland), which contains phytomenadione (2 mg/mL) and has Cremophor EL as the solubilizer. The 3 regimens of vitamin K₁ prophylaxis were as follows: 0.5 mg IM (control), 0.2 mg IM, and 0.2 mg IV. The control dose of 0.5 mg IM was chosen as the lower of the doses recommended (0.5–1.0 mg) for preterm infants in North America since 1998^{16–18} and the median dose being used in our region.⁶ A reduced dose of 0.2 mg has previously been shown to maintain a normal prothrombin time (PT) in preterm infants during the first 6 weeks of life.¹⁹ The allocated vitamin K₁ regimen was prescribed by the attendant doctor and given by either medical or nursing staff as soon as possible after admission. A single additional dose of 0.2 mg IM of vitamin K₁ was to be given to any infant who, at any time, had an abnormal coagulation test or clinical signs of bleeding in case these findings represented vitamin K₁ deficiency.

We obtained cord blood at delivery and peripheral venous blood samples after 5 days and after each infant had completed a continuous 2-week period of full enteral feeds with breast milk and/or formula milk. We deemed infants to be established on full enteral feeds when tolerating ≥ 150 mL/kg per day of milk. Human milk fortifier was routinely added to breast milk on

attainment of this volume. Blood samples were protected from light and immediately transported for centrifugation and serum storage at -70°C until analysis.

Measures of Vitamin K Status and Metabolism

Primary outcome measures of vitamin K_1 status and metabolism were serum vitamin K_1 , vitamin K_1 2,3-epoxide (K_1O), and PIVKA-II. Serum K_1 and K_1O were measured by high-performance liquid chromatography as described^{20,21} but with slight in-house modifications.²² For day 5 samples, volumes of 0.02 mL of serum were analyzed by a protocol designed to measure vitamin K_1 concentrations in the pharmacological range (>5 ng/mL). If the vitamin K_1 concentration was <10 ng/mL (ie, some day-5 samples and nearly all of the postenteral feed samples), volumes of 0.2 mL were analyzed by a modified protocol. The lower limit of detection for serum vitamin K_1 was 5 ng/mL when 0.02 mL serum was processed and 0.13 ng/mL for 0.2 mL serum volumes. The laboratory adult reference range for serum vitamin K_1 is 0.17 to 0.68 ng/mL (median: 0.37 ng/mL) in fasting subjects and 0.15 to 1.55 ng/mL (median: 0.53 ng/mL) in nonfasting subjects. The lower limit of detection for K_1O was 10 ng/mL when 0.02 mL serum was processed and 0.30 ng/mL for 0.2 mL-serum volumes. There is no laboratory adult reference range for K_1O , because this metabolite is normally undetectable in healthy adults (<0.12 ng/mL). PIVKA-II was measured by enzyme-linked immunosorbent assay using a conformation-specific monoclonal antibody that selectively binds undercarboxylated species of prothrombin.²³ Because PIVKA-II may comprise multiple undercarboxylated forms, concentrations are expressed in arbitrary units (AU), with 1 AU equivalent to ~ 1 μg of purified PIVKA-II. The limit of detection was 0.2 AU/mL (~ 200 ng/mL), and levels <1.0 AU/mL are considered clinically insignificant. In overt vitamin K deficiency, PIVKA-II circulates at high levels: Values were 6.9 to 99.5 AU/mL (mean: 40.0) in 43 adults on warfarin therapy (international normalized ratio ≥ 1.5) and 67.9 AU/mL in an infant with fatal late VKDB.²⁴ Secondary outcome measures were PT and factor II (FII) concentrations measured on citrated plasma on day 5 and at full feeds. PT was measured using an ACL 200 semi-automated coagulation analyzer calibrated with recombinant thromboplastin (Instrumentation Laboratory, Ltd, Warrington, United Kingdom). We used the PT result as a crude but immediate indicator of possible vitamin K_1 deficiency. Thus, we empirically gave a single additional dose of vitamin K_1 (0.2 mg IM) to any infant with a PT prolonged beyond the 95th percentile preterm reference for age.⁷ Assays were performed by laboratory staff blinded to the allocated regimens.

Total Vitamin K Intake

For each infant completing the study, absolute vitamin K_1 intake by the time that 2 weeks of full enteral feeds had been tolerated was calculated from the sum amounts received from allocated prophylaxis dose, any extra bolus dose, enteral feeds, and total parenteral nutrition (TPN). Average daily vitamin K_1 intake was calculated for each infant from the total vitamin K_1 intake (milligrams per kilogram using weight at study completion) divided by the number of days from birth to study completion. We calculated vitamin K_1 intake from enteral feeds according to milk types and actual volumes fed to each infant between birth and study completion. For preterm human milk, a vitamin K_1 concentration of 3.0 $\mu\text{g}/\text{L}$ was assumed.²⁵ Addition of human milk fortifier to expressed breast milk provided a total vitamin K_1 concentration of 5 to 66 $\mu\text{g}/\text{L}$, depending on brand (manufacturers' data). Artificial preterm milk formula provided 40 to 66 $\mu\text{g}/\text{L}$ of vitamin K_1 , depending on brand (manufacturers' data). The vitamin K_1 content of Vitlipid N Infant (fat-soluble vitamin emulsion) is 20 mg/L. The vitamin K_1 content of 20% Intralipid IV fat emulsion varies between batches, ranging from 0.50 to 0.77 mg/L (Dr Richard Smith, Fresenius Kabi Ltd, United Kingdom, written communication, March 2004); for calculation purposes we used a figure of 0.6 mg/L. Infants on TPN received 4 mL/kg of Vitlipid (Fresenius Kabi Ltd, Runcorn, Cheshire, United Kingdom) and 5 to 15 mL/kg of 20% Intralipid (Fresenius Kabi Ltd) per day, providing daily vitamin K_1 supplementation of 80 and 3 to 9 $\mu\text{g}/\text{kg}$, respectively.

Comparison With Current American Academy of Pediatrics Recommendations

To compare the bolus prophylaxis doses used in this study with those currently recommended by the American Academy of Pediatrics (0.3 mg/kg for infants <1000 g and 0.5- to 1.0-mg bolus for infants >1000 g),¹⁸ we retrospectively subdivided the whole cohort according to birth weight (<1000 or 1000–2000 g) to assess vitamin K_1 status in respect to vitamin K_1 study dose received.

Sample Size and Statistical Analysis

There were no previous studies comparing regimens of prophylaxis in preterm infants. We, therefore, chose an arbitrary sample size based on the anticipated number of eligible infants that would be admitted in an 18-month period and determined a priori to terminate the study when a day-5 blood sample had been collected from 90 infants. Concentrations were compared using the Mann-Whitney test and proportions using χ^2 and Fisher's exact tests. The effects of TPN and exclusive breast-milk feeding on vitamin K_1 concentrations were examined using a logistic-regression model. The primary statistical analysis was by intention-to-treat and included all randomized infants with a valid sample. A secondary analysis

was performed on a per-protocol basis and excluded infants who received multiple or excessive vitamin K₁ doses outside the protocol and 1 infant who was incorrectly assigned. A 2-tailed *P* value of <.05 was considered significant.

RESULTS

Of 152 eligible infants, 98 were randomized and 80 completed the study (Fig 1). Baseline characteristics are shown in Table 1. Gestational ages ranged from 22.4 to 31.9 weeks, and birth weights ranged from 454 to 1950 g. The median age at vitamin K₁ administration was 2.0 hours (interquartile range [IQR]: 1.4–2.4 hours). Cord blood was obtained from 90 infants. The

TABLE 1 Baseline Characteristics

	Vitamin K ₁ Regimen		
	0.5 mg IM (n = 31)	0.2 mg IM (n = 34)	0.2 mg IV (n = 33)
Gestation, mean (SD), wk	28.3 (2.5)	28.6 (2.3)	28.1 (2.6)
Birth weight, mean (SD), g	1025 (379)	1138 (379)	1060 (371)
Male gender, n (%)	11 (36)	19 (56)	18 (55)
Received TPN, n (%)	19 (61)	22 (65)	26 (79)
Exclusive EBM feeds, n (%)	10 (32)	11 (33)	11 (33)
Antenatal steroids, n (%)	29 (94)	33 (97)	28 (85)
Singleton pregnancy, n (%)	26 (84)	27 (79)	27 (82)
Cesarean section, n (%)	18 (58)	16 (47)	16 (48)
Apgar score at 5 min, median (IQR)	9 (7–9)	9 (7–9)	8 (7–9)
CRIB score, median (IQR)	2 (1–5)	1 (1–5)	3 (1–8)

CRIB indicates Clinical Risk Index for Babies; EBM, expressed breast milk.

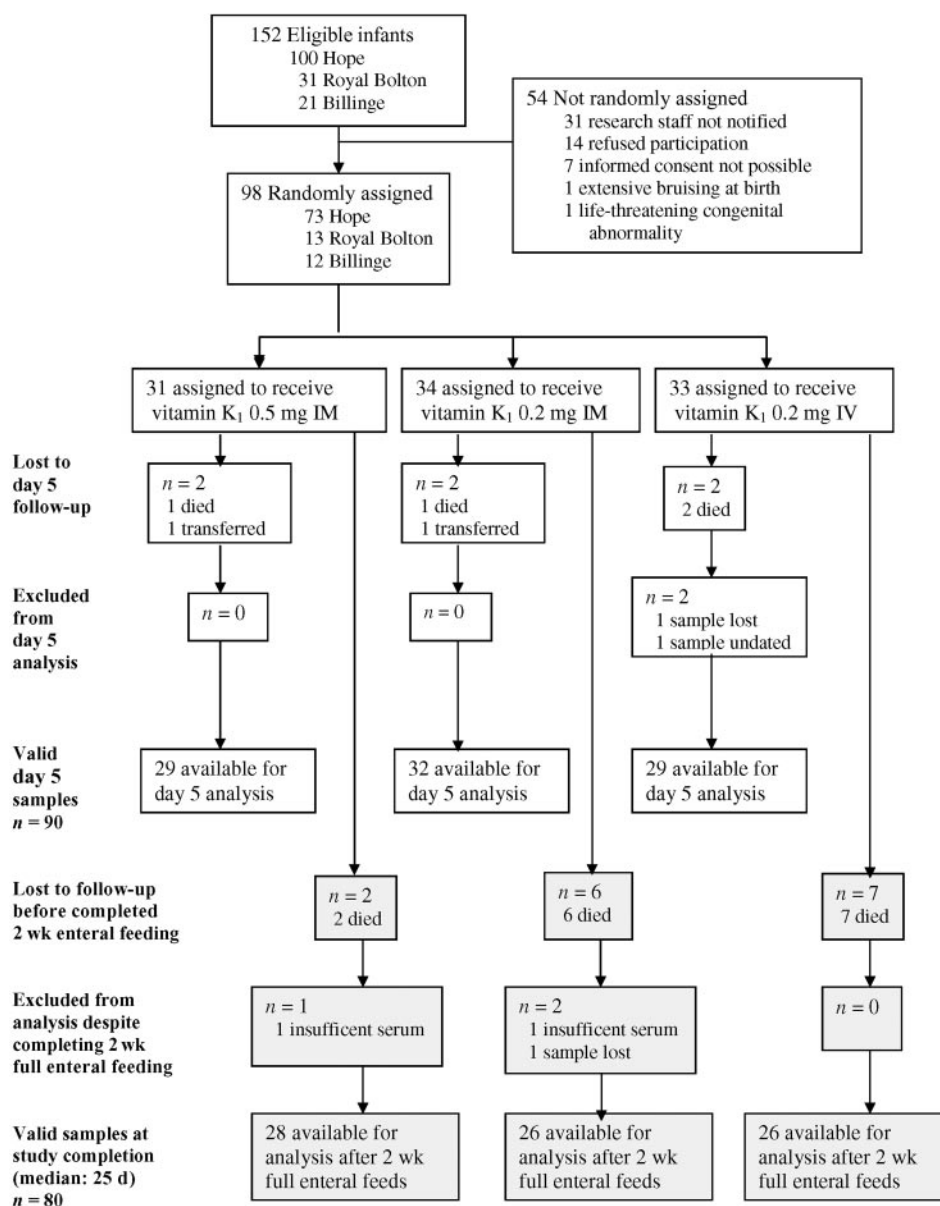


FIGURE 1 Study flow diagram.

day-5 blood sample was collected at a median of 4.9 days (IQR: 4.8–5.2 days). Full enteral feeding was established at a median of 10 days (IQR: 7–15 days), and the final blood sample was taken at a median of 25 days (IQR: 22–31 days). There were no significant differences between groups for any baseline data shown in Table 1, nor in timing of vitamin K₁ administration, establishment of enteral feeds, or blood sampling.

Serum Vitamin K₁ Concentrations

Table 2 shows serum vitamin K₁ concentrations at day 5 and median 25 days. There were 90 valid day-5 samples and 80 valid day-25 samples. At 5 days postnatal, all infants had supraphysiologic vitamin K₁ concentrations, but there was striking interindividual variation. Group median vitamin K₁ concentrations were 100 to 200 times higher than normal nonfasting adult values. Compared with the control group, day-5 serum vitamin K₁ levels were significantly lower after 0.2 mg IM ($P = .045$) but not significantly different after 0.2 mg IV ($P = .056$).

After completion of 2 weeks' enteral feeds (median age: 25 days), vitamin K₁ concentrations had declined markedly in all infants. Compared with the infants in the 0.5-mg IM control group, serum vitamin K₁ levels were lower after both 0.2 mg IM and 0.2 mg IV, but this only

reached significance in the IV group. Three infants who received lower-dose prophylaxis of 0.2 mg (2 in the IV group and 1 in the IM group) now had undetectable vitamin K₁ concentrations.

Serum PIVKA-II Concentrations

Table 2 shows PIVKA-II concentrations in infants who had detectable PIVKA-II (ie, ≥ 0.2 AU/mL) at birth, day 5, and day 25. There were no significant differences in PIVKA-II prevalence or concentrations between groups. All PIVKA-II concentrations at all time points were at or below clinically insignificant levels. The 3 infants with barely detectable PIVKA-II at day 25 had concurrent vitamin K₁ concentrations that were 2 to 6 times higher than adult norms; in each case, PT on day 5 was normal and none required any extra vitamin K. The 3 other infants with undetectable vitamin K₁ at day 25 also had undetectable PIVKA-II.

Serum Vitamin K₁O Concentrations

On day 5, K₁O was detectable in the serum of 11 (12%) of 91 infants (Table 2). Compared with infants that had undetectable K₁O, these 11 infants received a higher dosage of vitamin K₁ via bolus before day 5 ($P = .002$) and a higher birth weight–adjusted vitamin K₁ dose ($P = .001$), had higher vitamin K₁ concentrations on day 5 (P

TABLE 2 Primary Outcome Measures at 5 Postnatal Days and After Completing 2 Weeks of Full Enteral Feeds

	All Infants	Vitamin K ₁ Prophylaxis		
		0.5 mg IM (Control)	0.2 mg IM	0.2 mg IV
Vitamin K ₁ concentrations				
Day 5				
Median (range), ng/mL	74.5 (2.9–388.0)	111.8 (12.1–388.0)	59.3 (3.2–318.8) ^a	74.5 (2.9–259.5)
<i>n</i>	90	29	32	29
Day 25				
Median (range), ng/mL	1.7 (ND–33.2)	2.5 (0.5–33.2)	1.6 (ND–6.8)	1.3 (ND–6.2) ^b
<i>n</i>	80	28	26	26
PIVKA-II concentrations ^c				
Cord blood				
Median (range), AU/mL	0.44 (0.20–1.09)	0.44 (0.22–0.97)	0.71 (0.22–1.09)	0.43 (0.20–0.97)
<i>n</i> (%) in whom detected (ie, ≥ 0.2 AU/mL)	21/90 (23)	9/29 (31)	5/33 (15)	7/28 (25)
Day 5				
Median (range), AU/mL	0.41 (0.26–0.74)	0.62 (0.56–0.68)	0.51 (0.41–0.74)	0.36 (0.26–0.38)
<i>n</i> (%) in whom detected (ie, ≥ 0.2 AU/mL)	9/89 (10)	2/29 (7)	3/32 (9)	4/28 (14)
Day 25				
Median (range), AU/mL	0.25 (0.20–0.36)	0.20 (NA)	0.36 (NA)	0.25 (NA)
<i>n</i> (%) in whom detected (ie, ≥ 0.2 AU/mL)	3/78 (4)	1/26 (4)	1/27 (4)	1/25 (4)
Vitamin K ₁ O concentrations ^c				
Day 5				
Median (range), ng/mL	30.8 (12.2–130.9)	30.8 (12.2–130.9)	<10 ng/mL	33.6 (13.0–50.6)
<i>n</i> (%) in whom detected (ie, ≥ 10 ng/mL)	11/91 (12)	7/29 (24)	0/32 (0) ^d	4/29 (14)
Day 25				
Median (range), ng/mL	1.4 (1.0–2.4)	1.5 (1.3–2.4)	1.0 (NA)	< 0.3 ng/mL
<i>n</i> (%) in whom detected (ie, ≥ 0.3 ng/mL)	5/80 (6)	4/28 (14)	1/26 (4)	0/26 (0)

ND indicates not detected (<0.13 ng/mL); NA, range not applicable.

^a 0.2 mg IM versus control, $P < .05$.

^b 0.2 mg IV versus control, $P < .05$.

^c Reported only for infants with detectable concentrations.

^d versus control, $P < .01$.

= .001), and were of lighter birth weight ($P = .037$) but similar gestational age ($P = .1$). The difference in K_1O prevalence between groups was highly significant ($P = .006$; Table 2). Compared with infants in the 0.5 mg IM group, K_1O prevalence on day 5 was not significantly different after 0.2 mg IV ($P = .3$) but was undetectable after 0.2 mg IM ($P = .004$).

At 25 days, K_1O was detected in only 5 infants, all of whom had all tested negative for K_1O on day 5, and there was no difference in prevalence or concentrations between study groups. These 5 infants had similar vitamin K_1 levels at day 25 compared with 75 infants without detectable K_1O on day 25. They received a significantly higher parenteral bolus vitamin K_1 dosage by study completion ($P = .01$), but this was no longer significant after adjustment of dosage for weight at study completion ($P = .1$). The 5 infants also received similar absolute and weight-adjusted total vitamin K_1 intake at study completion compared with 75 infants without detectable K_1O and showed no birth weight or gestational age differences.

PT and FII Concentrations

Table 3 shows the secondary outcome measures of PT and FII concentrations. There were no differences between groups in PT measured at days 5 and 25. Infants who received 0.2 mg IV at birth showed lower FII concentrations on day 5 compared with control infants ($P = .04$), but by day 25 there were no significant differences in FII concentrations between groups.

Eighteen infants (median gestational age: 27.3 weeks [range: 22.4–31.3 weeks] and birth weight: 844 g [range: 466–1434 g]) had a prolonged PT on day 5 (median PT: 17.8 seconds [range: 15.4–28.8 seconds]). Seven (39%) of 18 had comorbidity, including necrotizing enterocolitis, sepsis, and bleeding. All 18 infants had concurrent serum vitamin K_1 levels (median: 89.0

ng/mL [range: 2.9–388.0 ng/mL]) in excess of the normal adult range, and PIVKA-II was undetectable in all but 1 infant (0.74 AU/mL). Only 3 of 18 had detectable K_1O on day 5 (median: 50.6 ng/mL [range: 30.8–57.1 ng/mL]), and the paired serum vitamin K_1 level in each of them exceeded 250 ng/mL. Fifteen of 18 infants subsequently received a additional dose of vitamin K_1 according to the protocol (8 infants in 0.2-mg IM group, 5 infants in each of the other groups; $P = .6$). The 3 infants who failed to receive an extra dose nevertheless had serum vitamin K_1 levels ranging from 45.9 to 114.6 ng/mL and died before postnatal day 10 as a result of complications of prematurity.

Vitamin K Intake

Table 4 shows vitamin K intake from all sources between birth and study completion. Adjusted for birth weight, the allocated study doses represented a median (range) of 0.487 (0.256–1.073) mg/kg for control infants and 0.186 (0.105–0.408) mg/kg for those given a 0.2-mg dose. In the 27 infants who weighed <1000 g and received 0.2 mg, the dose represented 0.279 (0.201–0.408) mg/kg. In the 40 infants who weighed >1000 g and received 0.2 mg, the dose represented 0.154 (0.105–0.200) mg/kg. Considering the 56 infants who received TPN and completed the study, vitamin K_1 intake from TPN was comparable in infants in the control ($n = 18$) and 0.2-mg IV ($n = 21$) groups, and slightly higher in the 0.2-mg IM group ($n = 17$). Median duration of TPN in these groups was, respectively, 8.5 days (IQR: 13–18 days), 10 days (IQR: 9–21), and 9 days (IQR: 5–18 days; $P = .5$). Infants who received TPN and completed the study, numbered 28 of 29 of birth weight <1000 g, and 27 of 51 infants of >1000 g. Vitamin K_1 intake from enteral feeds did not differ significantly between groups. Absolute intakes of vitamin K_1 were similar at study completion, although infants in the control

TABLE 3 Secondary Outcome Measures at 5 Postnatal Days and After Completing 2 Weeks of Full Enteral Feeds

	All Infants	Vitamin K_1 Prophylaxis		
		0.5 mg IM (Control)	0.2 mg IM	0.2 mg IV
PT				
Day 5				
Median (range), s	12.9 (9.0–28.8)	12.8 (9.0–18.0)	13.0 (10.3–28.8)	12.8 (10.0–22.2)
<i>n</i>	92	29	32	31
Day 25				
Median (range), s	11.4 (9.2–16.6)	11.3 (9.2–16.3)	11.5 (9.3–16.6)	11.6 (9.4–13.9)
<i>n</i>	83	29	28	26
FII concentrations				
Day 5				
Median (range), IU/mL	0.41 (0.26–0.74)	0.56 (0.37–1.19)	0.54 (0.14–1.03)	0.53 (0.13–0.68) ^a
<i>n</i>	86	27	30	29
Day 25				
Median (range), IU/mL	0.25 (0.20–0.36)	0.59 (0.40–1.00)	0.58 (0.39–0.96)	0.56 (0.31–0.89)
<i>n</i>	82	28	28	26

^a Versus control, $P < .05$.

TABLE 4 Sources of Vitamin K₁ and Total Intake by the Time of Study Completion

	All Infants (n = 80)	0.5 mg IM (Control) (n = 28)	0.2 mg IM (n = 26)	0.2 mg IV (n = 26)
Vitamin K ₁ intake, μg				
Via bolus doses	378 (256)	629 (264)	238 (80) ^a	246 (130) ^a
From TPN ^b	1120 (940)	950 (1077)	1153 (658) ^c	1240 (1027)
Via enteral feeds	124 (90)	118 (85)	125 (97)	131 (91)
Total vitamin K ₁ intake				
μg	1286 (1025)	1357 (1133)	1118 (775)	1378 (1136)
$\mu\text{g}/\text{kg}$	914 (597)	1070 (633)	808 (591)	853 (548)
$\mu\text{g}/\text{kg}$ per day	30 (15)	37 (15)	26 (15) ^c	27 (11) ^c

All data are shown as mean (SD).

^a Versus control group, $P < .001$.

^b For infants who received any period of TPN.

^c Versus control group, $P < .05$.

group received a higher average daily intake per kilogram of body weight, reflecting the larger prophylactic dose at birth.

Of the 3 infants given 0.2-mg prophylaxis who had undetectable vitamin K₁ concentrations at study completion (on days 20, 22, and 24), median (range) birth weights and gestations were 1400 g (1180–1434 g) and 30.0 weeks (28.9–30.1 weeks); only 1 received TPN (for 4 days); 2 were fed with fortified human milk, and 1 was fed with a preterm formula. They had median (range) total vitamin K₁ intake of 0.394 mg (0.214–0.782 mg), and average vitamin K₁ intake of 11 $\mu\text{g}/\text{kg}$ per day (7–23 $\mu\text{g}/\text{kg}$ per day). In comparison, infants with detectable vitamin K₁ concentrations at study completion ($n = 77$) showed higher total (1.016 mg [0.332–6.574 mg]; $P = .028$), and average intakes (29 $\mu\text{g}/\text{kg}$ per day [8–75 $\mu\text{g}/\text{kg}$ per day]; $P = .033$).

Effect of TPN and Exclusive Human Milk Feeding on Vitamin K₁ Concentrations

A regression model was used to explore the effect of TPN and human milk feeding on vitamin K₁ concentrations at the time when full enteral feeds were tolerated for 2 weeks. Randomization group, total vitamin K₁ administered, gender, birth weight, and age at sampling were included as potential confounding factors. Vitamin K₁ concentrations were not significantly affected by administration of parenteral nutrition ($P = .7$) or by enteral feeding exclusively with fortified human milk ($P = .3$).

Analysis After Excluding Protocol Violations

There were 3 protocol violations by day 5 (2 infants were given supplementary vitamin K₁ doses before day 5, and 1 infant assigned to the 0.2-mg IV group received the dose IM). By day 25, 7 had violated the protocol (6 received excessive supplementary vitamin K₁ doses in addition to the 1 incorrectly assigned). All statistical analyses were repeated after excluding these infants. Per-protocol analyses at day 5 ($n = 87$) and after 2 weeks

of full enteral feeding ($n = 73$) showed similar results as for the intention-to-treat analyses.

Adversity

There was no case of VKDB in the study group. Fifteen infants, all <29 weeks' gestation, died as a result of complications of prematurity before study completion. Mortality rates did not differ significantly between groups ($P = .2$; Fig 1).

DISCUSSION

To our knowledge, this is the only randomized, controlled trial of vitamin K prophylaxis in preterm infants. It shows that IM prophylaxis with a reduced dose of 0.2 mg of vitamin K₁ maintains satisfactory vitamin K status in preterm infants without producing evidence of hepatic overload. Evidence of equivalence of 0.2 mg IM of vitamin K₁ to the control regimen (0.5 mg IM) is based on both the assessment of PIVKA-II and serum concentrations of vitamin K₁. PIVKA-II is an abnormal molecule, and its measurement provides a particularly sensitive functional assessment of vitamin K status because it can indicate subclinical vitamin K deficiency. FII levels in preterm infants are ~40% of adult levels,²⁶ and the PIVKA-II assay enables the detection of undercarboxylated FII species corresponding to ~0.5% of their total circulating functional FII. In our study, only 3/78 infants (1 in each group) had detectable PIVKA-II at study completion, and these concentrations (0.20–0.36 AU/mL) were at once clinically insignificant and associated with a normal serum vitamin K₁.

In this study, we used PT as a proxy for possible vitamin K₁ deficiency and, as was common clinical practice, prescribed additional vitamin K₁ on a presumptive basis for infants with apparently prolonged PTs. However, use of PT is several hundredfold less sensitive for detection of vitamin K₁ deficiency than is PIVKA-II,²⁷ and there are many other causes of a prolonged PT in preterm infants including sepsis, disseminated intravascular coagulation, and liver disease.²⁸ Furthermore, we have now shown that none of the 18 infants with prolonged PT or clinical bleeding was vitamin K₁ deficient in the study period²⁸; with hindsight, our protocol stipulation for extra vitamin K₁ based on prolonged PT was superfluous. Also, because of a lack of an up-to-date reference range for everyday coagulation values in very premature infants, we relied on historical reference values for PT that were derived from more mature infants. Many PT results we regarded as prolonged were undoubtedly physiologic.²⁸

The wide variability in serum vitamin K₁ levels (up to 100-fold) within each regimen at each time point was notable but is typical of previous studies.^{29–31} For the IM route, the large variability may reflect both the rate of diffusion from the site of injection and the rate of clearance from the circulation. Using a logistic-regression

model, we showed that serum vitamin K₁ concentrations were not significantly affected by the additional vitamin K₁ intake provided by parenteral or enteral feeding.

Larger doses have been studied in preterm infants: After 1 mg IM, Kumar et al³⁰ showed mean (SD) plasma vitamin K₁ concentrations at 2 weeks of age that were 130.7 (125.6) ng/mL in infants of gestational age <28 weeks' and 60.8 (52.9) ng/mL in infants of 29 to 32 weeks'; Costakos et al³¹ compared 1-mg and 0.5-mg doses given IM or IV to 27 infants <32 weeks' gestation and showed day-10 mean (SD) plasma vitamin K₁ levels of 274.9 (255.3) ng/mL and 297.9 (213.7) ng/mL, respectively. Infants in both studies received additional vitamin K₁ supplementation from TPN comparable with that in our study. Neither study measured K₁O concentrations. Both studies concluded that current parenteral vitamin K₁ supplementation of preterm infants was excessive and should be reduced. Our finding of adequate vitamin K₁ status after reduced-dose prophylaxis, irrespective of TPN reception, not only supports calls for a reduction in the amount of vitamin K₁ added to standard TPN multivitamin solution³⁰⁻³² but also supports lower initial doses at birth.

Concerns have been raised about the possible risks of supraphysiologic vitamin K₁ doses used for preterm infants.³⁰⁻³³ Although adverse effects are unknown, we provide the first data, to our knowledge, to show that there is a highly significant association between vitamin K₁ dose given and subsequent K₁O presence in serum. We have also shown that 0.5-mg IM and 0.2-mg IV regimens can lead to K₁O accumulation. The metabolite K₁O is formed concomitantly with the posttranslational modification of vitamin K-dependent proteins and derives directly from the reduced quinol form of vitamin K that participates as a cofactor for the carboxylation of peptide-bound glutamyl residues to γ -carboxyglutamyl residues.³⁴ Normally, K₁O is efficiently recycled back to vitamin K quinone by vitamin K epoxide reductase (VKOR).³⁴ Newborn cord plasma, unlike adult plasma, often has detectable levels of K₁O suggesting inefficient recycling of this metabolite by the immature liver.³⁵ Direct enzymatic assays suggest that midtrimester fetuses and preterm infants <30 weeks' gestation have lower activities of VKOR than in early infancy.³³ Our detection of serum K₁O at substantial levels on day 5 after vitamin K₁ administration provides the first biochemical evidence that the VKOR system of preterm infants may be overloaded by current regimens. Only infants who received 0.2 mg IM did not show any evidence of hepatic saturation at 5 days of age.

Current dosage recommendations of 0.3 mg/kg for preterm infants with birth weights <1000 g and 0.5 to 1.0 mg for those >1000 g¹⁸ are empirical rather than evidence-based. In our study, all 27 infants of birth weight <1000 g given 0.2 mg had satisfactory vitamin

K₁ status throughout the study period. Their 0.2-mg prophylactic dose of vitamin K₁ equated to median 0.279 mg/kg (range: 0.201–0.408 mg/kg). Our findings, therefore, support the recommended initial dose of 0.300 mg/kg in infants <1000 g who receive TPN. Many heavier and less premature infants do not routinely receive TPN. We nevertheless show that all study infants of birth weight 1000 to 2000 g given 0.2-mg prophylaxis also maintained a satisfactory vitamin K₁ status irrespective of TPN administration. Their 0.2-mg prophylactic dose adjusted for birth weight equated to median 0.154 mg/kg (range: 0.105–0.200 mg/kg). Our data suggest that reduced initial doses are appropriate for all preterm infants of <32 weeks' gestation, and for all infants <2000 g.

Even 0.2 mg of vitamin K₁ represents an extremely large dose compared with physiologic intakes. Breast milk typically provides <1 μ g of vitamin K₁ per day^{8,9,15}; its low concentration is the major reason why exclusively breastfed infants are at risk of late-onset VKDB, often with catastrophic intracranial bleeding.¹ Three infants in the study group given 0.2-mg prophylaxis at birth had undetectable vitamin K₁ concentrations after only 3 weeks. Although the absence of PIVKA-II was reassuring, these infants were effectively already back to the precarious vitamin K state of the newly born infant. Exclusively breast milk-fed preterm infants given lower-dose prophylaxis at birth could, therefore, be at risk of late-onset VKDB without additional K₁ supplementation. We, therefore, recommend that such infants be routinely given additional K₁ supplements after enteral feeding is fully established. The simplest way to ensure adequate ongoing vitamin K₁ intake is routine fortification of breast milk using commercially available human milk fortifiers; these fortify human milk with vitamin K₁ to levels comparable with preterm formulae. Where use of human milk fortifiers is not routine, or where ceased on discharge home of exclusively breastfeeding infants, oral supplements may be given weekly³⁶ or via daily dose drops³⁷ and should continue until at least 3 months of age^{36,37} However, no commercially available vitamin K₁ preparation is presently approved for oral use in the United States.

The route of administration also significantly influences vitamin K status. The IM route is the norm. Its proven efficacy probably derives from the sustained release of vitamin K₁ from the muscle depot³⁸ as evidenced by the plateau pharmacokinetics in adults³⁹ and the long duration of raised serum concentrations in infants.^{40,41} The IV route is convenient, painless, and commonly used in small preterm infants^{5,6,31} yet may not fully protect against late-onset VKDB.¹¹ Isotopic studies in adults show that some 60% to 70% of a single IV dose of vitamin K₁ is rapidly metabolized by the liver and lost to the body within 3 days.⁴² Besides overloading the hepatic VKOR cycle, excessive vitamin K may overwhelm

the hepatic pathway⁴² responsible for its catabolism and excretion. In neonates the terminal half-life for plasma clearance of vitamin K is considerably longer than in adults, whatever the route.⁴³ This impaired elimination capacity may also be explained by the immaturity of organ and metabolic systems in preterm infants.

CONCLUSIONS

An initial prophylactic vitamin K₁ dose of 0.2 mg IM will maintain vitamin K sufficiency in preterm infants <32 weeks' gestation until at least the fourth postnatal week, and it will do so without causing overload of the hepatic vitamin K₁-recycling pathway in the first week of life. The results of this study should guide more appropriate vitamin K₁-dosing regimens for preterm infants and support the tailoring of initial prophylactic doses to their lower body mass and underdeveloped metabolic capacity.

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