Canadian Paediatric Society

Paediatrics & Child Health, 2018, 394–397
doi: 10.1093/pch/pxy082
Position Statement

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Position Statement

Guidelines for vitamin K prophylaxis in newborns

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A joint statement with the College of Family Physicians of Canada

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Abstract

Newborns are at risk for vitamin K deficiency bleeding (VKDB) caused by inadequate prenatal storage and deficiency of vitamin K in breast milk. Systematic review of evidence to date suggests that a single intramuscular (IM) injection of vitamin K at birth effectively prevents VKDB. Current scientific data suggest that single or repeated doses of oral (PO) vitamin K are less effective than IM vitamin K in preventing VKDB. The Canadian Paediatric Society and the College of Family Physicians of Canada recommend routine IM administration of a single dose vitamin K at 0.5 mg to 1.0 mg to all newborns. Administering PO vitamin K (2.0 mg at birth, repeated at 2 to 4 *and* 6 to 8 weeks of age), should be confined to newborns whose parents decline IM vitamin K. Health care providers should clarify with parents that newborns are at increased risk of VKDB if such a regimen is chosen. Current evidence is insufficient to recommend routine intravenous vitamin K administration to preterm infants undergoing intensive care.

Keywords: *HDNB; Newborn; Prophylaxis; Vitamin K; VKDB*

BACKGROUND

Hemorrhagic disease of the newborn (HDNB) was first identified over a century ago (1), and presents as unexpected bleeding, often with gastrointestinal hemorrhage, ecchymosis and, in many cases, intracranial hemorrhage. In newborns, HDNB is typically caused by vitamin K deficiency due to insufficient prenatal storage of vitamin K, combined with insufficient vitamin K in breast milk. Three types of vitamin K deficiency bleeding (VKDB) have been classified: early onset (occurring in the first 24 hours post-birth), classic (occurring at days 2 to 7) and late onset (at 2 to 12 weeks and up to 6 months of age). Early VKDB is commonly associated with maternal medications that inhibit vitamin K activity, such as antiepileptics. Classic VKDB is associated with low intake of vitamin K, and late VKDB with chronic malabsorption and low vitamin K intake (2).

Since 1961, the American Academy of Pediatrics (AAP) has recommended that a single 0.5 mg to 1.0 mg dose of vitamin K be administered intramuscularly (IM) to all newborns shortly after birth to prevent VKDB (3). The Canadian Paediatric Society (CPS) has recommended similar prophylactic treatment since 1988, but also proposed that 2.0 mg dose of oral (PO) vitamin K administered within 6 hours of birth, then repeated at 2 to 4 weeks and 6 to 8 weeks of age, was an acceptable alternative (4,5).

The AAP continues to advocate for sole use of IM vitamin K for all newborns. Their recommendation is based on a review of surveillance systems in four countries (Australia, Germany, the Netherlands, and Switzerland), which suggested that

administering vitamin K PO was less effective than by the IM route and may be associated with higher incidence of failure (6). Further, a 1993 review from the AAP vitamin K Ad Hoc Task Force effectively dispelled concerns that IM administration of vitamin K was associated with childhood cancers such as leukemia (7).

One recent practice review has confirmed that routine administration of IM vitamin K at birth effectively prevents VKDB (8). However, while clinical decisions should always be based on the best evidence available, potential for harm to the infant must also be considered. Although no significant complications following 420,000 vitamin K injections in newborns have been reported (9), the psychological effects of procedural pain on infants (and parents) are unknown. Pain experienced during the neonatal period may have long-term effects (10,11). The benefits of routine vitamin K administration have been demonstrated historically, but the most effective mode of delivery is yet to be fully determined (12). By supporting the PO route for administering vitamin K and a formulation designed for parenteral use, the CPS recommendations of 1988 aimed to secure all the apparent benefits of vitamin K for newborns without incurring unnecessary pain (4,13). Today, clinicians are more aware than ever of potential deleterious effects from early pain exposure and the need for strategies that minimize procedural pain in the neonate (14).

PREVENTION OF EARLY AND CLASSIC VITAMIN K DEFICIENCY BLEEDING (VKDB)

To prevent early VKDB, the CPS previously recommended administering PO vitamin K to expectant mothers who are taking medications, notably antiepileptics, which impair vitamin K metabolism (4). However, a systematic review of the literature on antiepileptic drug use in pregnancy by the American Academy of Neurology, published in 2009, concluded that evidence was insufficient to support vitamin K supplementation in the last weeks of pregnancy to reduce risk for VKDB (15).

Classic VKDB rarely occurs in newborns who have received parenteral vitamin K at birth (12). Two clinical trials conducted in the 1960s (8,16) compared various doses of IM vitamin K with no prophylaxis on classic VKDB rates. Their results demonstrated clearly that vitamin K prophylaxis effectively reduces VKDB of any severity in the first week of life (17,18).

PREVENTION OF LATE VKDB

Late (2 to 12 weeks and up to 6 months of age) VKDB, which occurs almost exclusively in breastfed infants, is a serious condition that manifests predominantly as intracranial hemorrhage (2). No clinical trial to date has evaluated the effect of vitamin K on late VKDB. Epidemiological studies from a number of countries suggest that the incidence of late VKDB has been reduced significantly through implementation of vitamin K prophylaxis programs. PO vitamin K appears to be less effective, however, with higher failure rates compared with IM vitamin K (6,19–21).

In countries where PO administration was the primary form of prophylaxis, the incidence of late VKDB varied: from 1.6 per 100,000 infants (in the UK), 1.9 (Japan), 5.1 (Sweden) to 6.4 (Switzerland) (19–22). Some of these infants may also have had underlying disorders that affected vitamin K metabolism (23). However, while the true failure rate of vitamin K may not be calculable when based primarily on surveys and surveillance studies, one study from Germany (19) estimated an occurrence of late VKDB cases—despite PO prophylaxis—of 1.4 per 100,000 infants. This failure rate followed a single PO dose, compared with a rate of 0.25 per 100,000 infants following IM administration. A similar study from the UK (20) showed a failure rate of 0.42 per 100,000 infants after administering a single PO dose of vitamin K. The relative risk for VKDB, when comparing PO versus IM vitamin K administration in these two studies, was 28.75 (95% CI 1.64 to 503.45) and 5.97 (95% CI 0.54 to 65.82), respectively (19,20).

In Canada, the specific incidence of late VKDB after PO or IM administration of vitamin K remains unknown. Reports from the Canadian Paediatric Surveillance Program (CPSP) between 1997 and 2000 confirmed five cases of late VKDB, including one infant who received no vitamin K and two who received PO vitamin K, yielding an estimated incidence of 1 per 140,000 to 170,000 births (24).

Without adequate vitamin K intake, an induced protein (PIVKA-II) becomes measurable in blood. This protein disappears by day five of life following PO administration of 1.0 mg of vitamin K at birth (25) and there appears to be no difference in these levels by day 5, whether vitamin K was administered PO or IM (26). At 4 to 6 weeks of age, however, biochemical signs of vitamin K deficiency (vitamin K_1 assay, noncarboxylated prothrombin) were observed in up to 19% of infants who received 2.0 mg of vitamin K PO at birth; by comparison, only 5.5% of infants who received 1.0 mg IM showed biochemical signs of vitamin K deficiency (27). A mixed micelle formulation for oral delivery of vitamin K may be better absorbed, but one study showed that a higher incidence of vitamin K deficiency occurred when the vitamin was delivered PO, even in this formulation, compared with IM delivery (28). The common limitation of these studies is a weak clinical correlation between the biochemical indicators and abnormal bleeding in infants.

In summary, the reported successes of using PO vitamin K prophylaxis in neonates (29) are consistently outweighed by data supporting the preferential use of IM over PO vitamin K in newborns. The reasons for additional benefits with IM delivery are not clear, but may pertain to better storage and slow release. Because risk for late VKDB is highest in exclusively breastfed infants, it has been suggested that administering PO vitamin K to lactating mothers could be beneficial (30,31). One study from Denmark reported that a program of weekly PO vitamin

K supplements for infants until they reached 3 months of age reduced the incidence of late VKDB, compared with a single PO dose (32). However, a repeated PO dose regimen may not be practical because of lower patient compliance (33). One epidemiological study, which included Australia, Germany, the Netherlands and Switzerland, confirmed that three doses PO of 1 mg vitamin K were less effective than IM vitamin K prophylaxis in neonates, although a daily PO dose of 25 micrograms (from week 1 to 13) after an initial PO dose of 1 mg may be as effective (6).

It is important to note that injected vitamin K does not completely protect infants from VKDB, especially if they are breastfed and their oral intake of vitamin K is low (34). Health providers should consider the possibility of vitamin K deficiency at an early stage when evaluating any case of bleeding that occurs in the first six months of life. Appropriate therapy with vitamin K should be instituted when required.

The large number of newborn infants required to conduct a strong prospective study comparing the efficacy of IM versus PO vitamin K (with and without repeated doses) makes it unlikely that such a study will be carried out. Also, given the higher risk for late VKDB after a single PO dose of vitamin K administered post-birth, compared with vitamin K administered IM, and the 50% chance that infants with late VKDB will experience serious intracranial hemorrhage (27), delivering vitamin K by the IM route seems prudent. Repeated PO doses should be reserved for infants whose parents decline injected vitamin K at birth.

VITAMIN K PROPHYLAXIS FOR PRETERM INFANTS

Preterm infants are at higher risk for VKDB, due to hepatic immaturity, delayed gut colonization with microflora and other factors. However, recommendations for vitamin K prophylaxis at birth for preterm infants vary widely in terms of dosage and routes of administration (35), and there is inadequate evidence to support any one clinical practice.

Some centres administer intravenous (IV) vitamin K to preterm infants undergoing intensive care, to avoid the pain inflicted by injection. In one small study of 14 preterm infants (36), a single 0.3 mg/kg ± 0.1 mg/kg dose of IV vitamin K achieved plasma levels at 24 and 120 hours similar to that achieved by PO or IM doses of 1.5 mg (37).

In one clinical trial (38), preterm infants born less than 32 weeks gestational age were randomized to receive a single dose of vitamin K at birth of 0.5 mg IM, or 0.2 mg IM, or 0.2 mg by IV injection. Biochemical indices of vitamin K status were measured at birth, at 5 days and after 2 weeks of achieving full enteral feeds (>150 mL/kg/day). Serum vitamin K_1 levels were above physiological norm for all infants on day 5. By day 25, serum vitamin K_1 levels had decreased in all infants, but significantly more in those who received IV vitamin K at birth. The pharmacokinetic differences may relate to the lack of sustained vitamin K release from the muscle depot following IV administration, leading to more expedient clearance.

RECOMMENDATIONS

The Canadian Paediatric Society continues to recommend the routine administration of vitamin K to newborns, preferably by IM injection, to prevent vitamin K deficiency bleeding (VKDB).

Administering one intramuscular (IM) dose of vitamin K (0.5 mg for infants weighing ≤1,500 g or 1.0 mg for infants weighing >1,500 g) routinely to all newborns within the first 6 hours post-birth and following initial stabilization and appropriate maternal/newborn interaction, is now the recommended best practice.

Implementing strategies that minimize the procedural pain associated with IM injections for all newborns is also recommended.

For parents who decline injection, counselling on the serious health risks of VKDB is advised. If they still decline, health care providers should recommend an oral (PO) dose of 2.0 mg vitamin K at the time of the first feeding, to be repeated at 2 to 4 *and* 6 to 8 weeks of age.

Health care providers should advise parents that:

- PO vitamin K is less effective than IM vitamin K for preventing VKDB
- Making sure their infant receives all follow-up doses is important, and
- Their infant remains at risk for developing late VKDB (potentially with intracranial hemorrhage) despite use of the parenteral form of vitamin K for PO administration, which is the only alternate formulation available at this time.

For preterm infants undergoing intensive care, limited data suggest that a single IV dose of 0.2 mg at birth may not be as protective against late VKDB as a 0.2 mg or 0.5 mg dose of vitamin K delivered IM. Therefore, current evidence is insufficient to recommend routine use of IV vitamin K in this population.

An excellent resource for parents on vitamin K prophylaxis, from the U.S. Centers for Disease Control and Prevention, can be found at: www.cdc.gov/ncbddd/vitamink/index.html.

Acknowledgements

This statement was reviewed by the Community Paediatrics and Drug Therapy and Hazardous Substances Committees of the Canadian Paediatric Society. Special thanks are due to members of the Maternity and Newborn Care Program Committee of the College of Family Physicians of Canada, who also reviewed this statement: William Ehman, Kate Miller, Sudha Koppula, Balbina Russillo, Amanda Pendergast, Michelle Abou-Khalil (resident rep), Kevin Desmarais and Heather Baxter.

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