Early Vitamin K Deficiency Bleeding in a Neonate Manifested as Pulmonary Hemorrhage

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Abstract

Background: A female neonate was born at 40 weeks and 5 days gestation via spontaneous vaginal delivery without complications. At 6 hours of life she was noted to have respiratory distress and bloody emesis. Following a non-traumatic intubation on the first attempt, bright red blood was suctioned from the endotracheal tube and a pulmonary hemorrhage was diagnosed. Initial labs revealed a prolonged PTT and INR. The infant did not receive vitamin K prior to development of respiratory distress and admission to the neonatal intensive care unit due to parental refusal.

Purpose: Vitamin K Deficiency bleeding in the neonatal period is a growing concern in the medical community as increasing numbers of parents are refusing vitamin K prophylaxis at birth. We herein report a complication of vitamin K deficiency that may be underreported in the literature.

Case findings/Results: After initial decompensation including suspected gastrointestinal bleeding, respiratory distress requiring intubation, and pulmonary hemorrhage, the infant improved clinically, the PT corrected, and the hemorrhage subsided following vitamin K administration.

Implications for practice: Pulmonary hemorrhage is not a commonly reported complication of early vitamin K deficiency bleeding, but health professionals should be aware of this as a potential complication of vitamin K prophylaxis refusal.

Implications for research: More research is necessary to describe the incidence of pulmonary hemorrhage attributable to vitamin K Deficiency.

Keywords: Vitamin K; Vitamin K deficiency bleeding; Hemorrhagic disease of the newborn; Pulmonary hemorrhage

Introduction

Bleeding in the neonate is a serious clinical situation that can progress rapidly if the coagulation cascade is compromised by either acquired or inborn factors. Bleeding caused by a deficiency of vitamin K dependent clotting factors is known as Vitamin K Deficiency Bleeding (VKDB) and can be classified as early, classic, or late. Early bleeding occurs in the first 24 hours of life and is typically associated with maternal medication intake during pregnancy. Substances associated with early bleeding can include but are not limited to anticonvulsants such as phenytoin, barbiturates, carbamazepine, the antitubercular drugs, rifampin and isoniazid, and vitamin K antagonists, warfarin and coumarin. Vitamin K associated bleeding occurs in this instance because these substances cross the placenta and either inhibit vitamin K or are vitamin antagonists [1].

Classic bleeding occurs during the first 0-2 weeks of life [2]. Classic bleeding has been associated with delayed or insufficient feeding. Late bleeding occurs from 2 weeks to 6 months of life and is mainly associated with strictly breastfed infants who did not receive adequate vitamin K prophylaxis [2,3]. Late bleeding was less frequently reported when formula feedings were more common. Breast milk has very low levels of vitamin K (between 1 and 4 μg/L of vitamin K) leading to increased reports of classic vitamin K deficiency bleeding as exclusive breastfeeding rates have risen and vitamin K refusal has become increasingly common. The main complications that are seen with early vitamin K deficiency bleeding are internal hemorrhage within 24 hours after birth or classically, gastrointestinal hemorrhages from days 2 to 7 [4]. The late form of VKDB is mainly reported as intracranial hemorrhages from 2 weeks of age to 6 months of age.

The incidence of bleeding during the first 2 weeks of life in babies who do not receive vitamin K prophylaxis is estimated to be between 0.25-1.7% [3]. VKDB resulting in ecchymoses, umbilical cord bleeding, circumcision site bleeding, and epistaxis have additionally been described [3]. Pulmonary hemorrhage, however, is not a commonly reported complication of early vitamin K deficiency bleeding. We report a case of pulmonary hemorrhage that may be attributed to vitamin K deficiency.
Case

Prenatal and delivery

A female neonate was born at 40 weeks and 5/7 days gestation via spontaneous vaginal delivery to a gravida 3 para 1 live birth 0 preterm birth 1 miscarriage 1 living child (G3P1011). There were no complications during pregnancy and no maternal history of tobacco, alcohol, or illegal drug use. The mother’s medications during pregnancy included: folic acid (800 mcg), cayenne (450 mg), vitamin D₃ (an unknown amount), GABA (100 mg), vitamin B₁₂ (1000 mcg), Vitamin B₉ (20 mg), zinc (30 mg), and vitamin K (15 mg) all dosed daily. The mother was blood type O positive and maternal serologies were unremarkable. During the second stage of labor there was a 1 minute shoulder dystocia. The baby’s Apgar’s were 7 and 9 at 1 and 5 minutes, respectively.

Initial presentation

Initial care of the infant was delivered in mother's room by the newborn nursery staff. The parents elected not to administer vitamin K, Hepatitis B vaccine, or erythromycin eye ointment upon delivery. At 6 hours of life while receiving a bath, the baby was noted to be tachypneic (respiratory rate 80-90 breaths/minute) with increased work of breathing. She had oxygen saturations in the mid 80s. At 10 hours of life the infant was transferred from the newborn nursery to the NICU and placed on nasal prong CPAP with a PEEP of 5, a rate of 30 and an inspiratory time of 0.4 seconds. V itamin K (phytonadione 1 mg intramuscular injection) was administered upon admission to the referring NICU at 10.5 hours of life.

Respiratory

At 10 hours of life the infant was transferred from the newborn nursery to the NICU and placed on nasal prong CPAP with a PEEP of 5. Physical exam revealed tachypnea with diminished breath sounds bilaterally, and an absence of nasal flaring and grunting. A chest radiograph showed evidence of reticulonodular air space opacity in the right upper lobe and in the perihilar distribution about the lower lobes. At 14 hours of life on initiation of the first bath the temperature was 98.6 thirty minutes later after the bath was completed was 99.5 degrees F , all taken axillary while skin to skin with mother. Temperature at 67 minutes of life on was 98.6 degrees F. At six hours of life on initiation of the first bath the temperature was 98.6 thirty minutes later after the bath was completed was 99.5 degrees F , all taken axillary. Temperature at 10 hours when the infant developed increased respiratory distress and bloody emesis was noted 98.6 degrees F; axillary, and the temperature at 14 hours of life, at the time of intubation was 99.1 degrees F.

Infection

Clinical presentation could not eliminate a possible pneumonia, so blood cultures, a CBC and CRP were obtained and ampicillin and gentamicin were started at 7 hours of life. An initial CBC demonstrated polycythemia and mild bandemia. A follow up CBC was within normal limits and antibiotics were discontinued after 48 hours of treatment. Blood cultures were negative (Table 1).

| Parameter          | 7 hrs of life | 18 hrs of life | 2 days | Institutional normal value |
|--------------------|--------------|---------------|--------|---------------------------|
| WBC                | 21.0         | 17.9          | 16.6   | 5.0-21 × 10⁶ E3/µL         |
| RBC                | 6.20         | 5.19          | 5.88   | 4.00-6.50 × 10⁶ E6/µL      |
| Hemoglobin         | 21.6         | 18.2          | 20.4   | 14.5-22.5 g/dL             |
| Hematocrit         | 65.7         | 52.0          | 58     | 44.0-64.0%                |
| MCV                | 106.0        | 100.2         | 98.6   | 95.0-125.0 fL              |
| MCHC               | 32.8         | 35            | 35.2   | 32.0-36.0%                |
| RDW                | 18.9         | 19.7          | 19.9   | 11.3-15.5%                |
| Platelet count     | 282          | 244           | 284    | 150-400 × 10³ E3/µL        |
| Automated Abs neutrophil count | 15.6         | 13.9          | -      | 1.0-8.5 × 10³ E3/µL       |
| Manual absolute neutrophil count | 15.3         | 15.4          | -      | 1.0-8.5 × 10³ E3/µL       |
| Segs relative %    | 43           | 64            | -      | -                         |
| Bands relative %   | 30           | 22            | -      | -                         |
| Lymphocytes relative | 22           | 9             | -      | -                         |
| Monocytes relative | 5            | 3             | -      | -                         |
| CRP                | <0.5         | 0.9           | -      | <1.0 mg/dL                |

Table 1: Laboratory Results.

Coagulation

As the infant developed increasing respiratory distress at 6 hours of age she was also noted to have multiple episodes of emesis that were dark in color and had the appearance of blood (these were not heme tested). Vitamin K (phytonadione 1 mg intramuscular injection) was administered upon admission to the referring NICU at 10.5 hours of life. This was done after a lengthy discussion with the family by the care team regarding the concern for bloody emesis consistent with a gastrointestinal bleed and the patient’s continuing clinical deterioration. Upon admission to the level IV NICU, (after administration of IM vitamin K) the patient had mildly prolonged partial thromboplastin time (PTT) and international normalized ratio (INR) as well as an elevated D-Dimer, but no further frank red blood was noted and no blood or factor transfusions were necessary. The subsequent day, repeat coagulation studies showed a prolonged PTT with a normal INR. A consultant from the hematology department...
suggested clotting factor studies but these were deferred as an inpatient at the parents' request with their stated intent to seek evaluation as an outpatient. On day of life 5, the patient had a normal PT/INR and a prolonged but improved PTT (Table 2). A head ultrasound was normal with no evidence of intracranial hemorrhage. The patient was discharged on day of life 6 with an outpatient follow-up with hematology scheduled for two weeks following discharge. The family was non-compliant with this appointment and has not rescheduled.

Table 2: Coagulation Studies/DIC Screen.

| Cytes                  | On admission to higher level NICU (18 hours of life) | DOL 2 | DOL 5 | Reference range               |
|------------------------|-----------------------------------------------------|-------|-------|-------------------------------|
| Protime                | 16.7                                                | 12.9  | 12.1  | 9.5-13.5 sec                  |
| INR                    | 1.5                                                 | 1.1   | 1.1   | 0.9-1.1                       |
| PTT                    | 52                                                  | 51.6  | 46.8  | 24.0-36.0 sec                 |
| Fibrinogen             | 163                                                 | 196   | -     | 160-450 mg/dL                 |
| D-Dimer                | 1879                                                | 1943  | -     | <500 ng/mL FEU                |
| Platelet count         | 244                                                 | 302   | -     | 150-400 × 10 E3/µL            |
| Schistocytes           | Occasional schistocytes                             | Occasional schistocytes | Occasional schistocytes | Occasional schistocytes |
| Antithrombin III activity | 51                                                | 46    | -     | 70-130%                       |

Case Discussion

Coagulation and vitamin K deficiency bleeding

Vitamin K is a cofactor in the γ-carboxylation glutamic residues on clotting factors II (prothrombin), VII, IX, and X. This γ-carboxylation enables these coagulation factors to bind calcium and attach to phospholipid membranes in order to establish clotting. The enzyme vitamin K reductase which reverts vitamin K [2,3] epoxide back to vitamin K hydroquinone for participation in additional γ-carboxylation reactions is also necessary for a fully functioning coagulation cascade and proper coagulation. A less well understood but important function of vitamin K in coagulation is the impact it has on protein C, protein S, and protein Z [5]. A deficiency of vitamin K or the presence of antagonists to vitamin K can inhibit coagulation and lead to significant bleeding in the newborn [6]. Factor levels that are affected by vitamin K deficiency are in the intrinsic, extrinsic and common coagulation pathways as illustrated in Figure 1, leaving a vitamin K deficient infant at risk from every standpoint, and underscoring the mechanism behind the severe bleeding that can be seen with vitamin K deficiency [7].

The newborn infant has significantly decreased stores of vitamin K in the liver as compared to adults. Additionally, the transfer of vitamin K across the placenta is very low [1]. So, despite the maternal oral supplementation with vitamin K as was present in this case, prenatal therapy does not increase neonatal stores at delivery. A combination of low liver vitamin K in the neonate and minimal maternal transfer from the placenta untreated infants to bleeding from a primary deficiency of vitamin K which is manifested by low levels of factors II, VII, IX, and X and abnormal clotting [8].

Vitamin K activity in the evaluation of bleeding is measured indirectly by measuring the coagulation factors that are dependent on vitamin K, factors II, VII, IX, X. These will all normalize rapidly when vitamin K is administered parentally.

Vitamin K prophylaxis has been the standard of care since 1961 when it was recommended by the American Academy of Pediatrics and it is efficacious for the prevention of early and late VKDB [2]. Oral and parental formulations have shown similar efficacy for the prevention of early VKDB. However, parental administration is preferred for all infants because of better prevention of late onset bleeding. Administration of vitamin K by intravenous route has been associated with increased risk of anaphylaxis, in some cases severe and fatal [9]. For this reason, the preferred method of parenteral administration of vitamin K in the neonate is intramuscular (IM).

Estimates of the overall risk of late VKDB range from 4.4 to 7.2 per 100,000 births. Studies involving a single oral dose of vitamin K show a decrease in that rate to 1.4 to 6.4 per 100,000 babies. Babies administered parenteral vitamin K does not develop late VKDB except for a few rare cases with underlying severe malabsorptive disease [2]. Even when multiple oral doses are administered, the incidence of late VKDB is higher than with parental administration [10].

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factors for bleeding in addition to vitamin K deficiency. There was no family history of hemophilia or other hematologic disorder. As the patient and family did not follow up with hematology for a full laboratory evaluation of coagulation, it is unknown whether or not she had an underlying clotting factor deficiency.

It is known that maternal anticonvulsants that interfere with vitamin K metabolism are risk factors for early VKDB in the neonate. This patient's mother took a significant number of natural supplements throughout the course of her pregnancy. These medications were mostly vitamins and although they are not known to be associated with inhibition of vitamin K are also unregulated and may contain contaminating compounds that have some impact on the coagulation cascade and vitamin K levels at delivery and birth. Of interest is the GABA supplement that the mother took. This substance is a neurotransmitter that inhibits neurotransmission in the brain and is commonly used as a supplement to relieve anxiety. Although no case reports have associated GABA with vitamin K antagonism, anti-convulsants that inhibit neurotransmission have been associated with vitamin K deficiency bleeding. This is a good reminder to only ingest necessary substances during pregnancy to avoid untoward and unanticipated side effects.

There are other lessons for health providers concerning this case. One is an awareness of the characteristics of parents who may refuse vitamin K prophylaxis. These characteristics have been studied and documented. Parents who had midwife assisted deliveries, planned home deliveries, and delivery in a birth center were more likely to refuse vitamin K as compared to those who had hospital deliveries. Also refusal of vitamin K was associated in this study with a higher relative risk of having no childhood vaccinations at 15 months of age [11].

A report from a children's hospital in Tennessee described six cases of vitamin K deficiency bleeding following refusal of vitamin K prophylaxis in 2013 [12]. The parents were surveyed about their refusal. All of the parents reported a lack of knowledge about the risk for their child developing late VKDB at the time of refusal. Some parents thought the shot was a "toxin" or was unnecessary [8]. Clearly there is room for improved parental education about the necessity, benefits, and lack of harm from administration of vitamin K to their newborns. All infants survived, however two required surgical intervention for intracranial hemorrhage and three have neurological impairment (one severe, two mild to moderate).

In order to prevent VKDB, the American Academy of Pediatrics recommends Vitamin K1 be administered to all newborns as one intramuscular dose of 0.5 to 1 mg. A policy statement from the AAP in 2003 recommends more research be conducted on oral formulations in order to ensure proper dosing to prevent late VKDB complications as there have been reported cases of late VKDB following incomplete oral prophylaxis [2].

There are concerning trends in refusal of evidence based medical care for mothers and newborns around the time of delivery. With increasing reports of late onset VKDB leading to neurologic impairment, it is important for neonatal and newborn providers to understand the safety and proven benefits of IM vitamin K prophylaxis. All newborn providers should have the ability to answer parents questions and concerns with evidence based information to decrease further episodes of VKDB.

**Summary of Recommendations**

**What we know:**

The American Academy of Pediatrics recommends Vitamin K1 is administered to all newborns as one intramuscular dose of 0.5 to 1 mg [2].

Vitamin K prophylaxis is efficacious for the prevention of early and late VKDB [2].

Oral and parenteral formulations have shown similar efficacy for the prevention of early VKDB [2].

Parenteral administration of vitamin K is preferred for all infants because of better prevention of late onset bleeding.

**What needs to be studied?**

More research should be conducted on oral vitamin K formulations in order to ensure proper dosing to prevent late VKDB complications as there have been reported cases of late VKDB following incomplete oral prophylaxis.

More research needs to be done about the incidence of pulmonary hemorrhage attributable to Vitamin K Deficiency.

More research should be conducted on parental rational for refusal of Vitamin K and strategies for caregivers to improve education and decrease refusal rates.

**What can we do today that would guide caregivers in the practice setting considering use of this evidence for guiding practice:**

Be aware of the characteristics of parents who may refuse Vitamin K prophylaxis. Studies have associated Vitamin K refusal with parents who had midwife assisted deliveries, planned home deliveries, and delivery in a birth center as well as refusal of childhood vaccinations [11].
Improve parental education about the necessity, benefits, and lack of harm from administration of vitamin K to their newborns.

One website targeted to educate parents is: (http://evidencebasedbirth.com/evidence-for-the-vitamin-k-shot-in-newborns/)

The CDC has developed parent educational sheets in order to improve the acceptance of vitamin K prophylaxis.

Health professionals should be aware of pulmonary hemorrhage as a potential complication of vitamin K prophylaxis refusal.

Hospitals and birthing centers should have protocols in place for education of parents who refuse vitamin K prophylaxis for their newborns.

Infant’s status for vitamin K prophylaxis should be clearly communicated to all members of the health care team including the PCP. Some institutions will choose to refuse circumcision and other elective surgical procedures to infants who have not received vitamin K prophylaxis.

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