

ORIGINAL RESEARCH

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Late-onset vitamin K deficiency bleeding: a preventable yet prevailing cause of intracranial hemorrhage in young infants— an ambispective descriptive study

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Abstract

Background Vitamin K deficiency bleeding (VKDB) may present as intracranial hemorrhage (ICH) in young infants, which results in severe morbidity and mortality. This study aims to determine the clinical presentation, risk factors, and outcome of children with VKDB.

Methods This was an ambispective descriptive study conducted from January 2015 to August 2023 in southern India. Infants from 8 days to 6 months of age, diagnosed as VKDB based on bleeding with elevated PIVKA (protein induced by vitamin K absence) and prolonged prothrombin time, which is rapidly corrected 24 h after administration of vitamin K, were included. Infants with bleeding due to other causes, such as inherited clotting factor deficiency, cholestasis, and sepsis, were excluded. A structured data collection proforma was used to collect data.

Results Out of 62 cases, 28 were excluded due to various causes, and 34 were analyzed. The median age at symptom onset was 54 days, and males were 22 (64.7%). Term gestation was 25 (73.5%), and low birth weight was 13 (38.2%), and 8 (23.5%) required NICU admission. All received vitamin K prophylaxis at birth. Thirty-three (97%) were exclusively breastfed. The most common presenting complaints were poor activity and convulsion. A total of 97% of children had ICH, and 5 (14.7%) had skin bleed. Twenty-three (67.6%) infants had complete recovery, 6 (17.6%) had sequelae (2 had hemiparesis, 2 monoparesis, and 2 quadriplegia), and 5 (14.7%) children expired.

Conclusion Vitamin K deficiency commonly presents as intracranial hemorrhage in infants. Exclusive breastfeeding is a significant risk factor for vitamin K deficiency, followed by low birth weight and prematurity.

Keywords Vitamin K deficiency, Intracranial hemorrhage, Infants, PIVKA

Background

The vitamin K deficiency leads to bleeding manifestations due to insufficient activity of coagulation factors (II, VII, IX, X). Vitamin K deficiency bleeding (VKDB) most commonly presents in infants due to multiple factors

such as limited placental transport, sterile gut, and poor level of breast milk and low activity level of vitamin K epoxide reductase [1]. VKDB can be classified by age of onset into early (<24 h), classical (days 1–7), and late (>1 week & <6 months). Early VKDB is associated with maternal intake of drugs like antiepileptics, antitubercular drugs, antibiotics, and maternal malabsorption; classical is associated with vitamin K deficiency or exclusive breastfeeding, and late is due to exclusive breastfeeding, malabsorption, and prolonged antibiotics usage [2]. The American Academy of Pediatrics recommends an

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intramuscular injection (IM) of 1 mg of vitamin K single dose to all newborns weighing >1500 g whereas 0.3 to 0.5 mg/kg to infants less than <1500 g to prevent VKDB [3]. Bleeding manifestations in these patients range from minor skin or mucus membrane bleeds to life-threatening central nervous system bleeds [2]. The incidence of classical VKDB without prophylaxis is 1.7%, and the burden of late VKDB without prophylaxis is 80 per 100,000 live births [4]. The incidence of late VKDB after prophylaxis has been reported as 0.24 to 3.2 cases per 100,000 live births [5]. Late VKDB presents predominantly as intracranial hemorrhage (ICH), which results in severe morbidity and mortality. In spite of prophylaxis for more than 50 years, VKDB is still a concern today, especially in breastfed infants less than 6 months [3].

This study aims to determine the clinical presentation, risk factors, and outcome of children with VKDB.

Methods

This was an ambispective descriptive study in the Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) — a tertiary healthcare center in southern India. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institute Ethics Committee for Observational Studies (DHR Reg. No. EC/NEW/INST/2020/331) vide letter no. JIP/IEC/2022/098 dated 5th April 2022. While the retrospective study extended from January 2015 to March 2022, the prospective study began in April 2022 and was completed by August 2023. Late VKDB in infants from 8 days of life to 6 months of age is defined as follows: (a) when the child presents with bleeding manifestations and elevated PIVKA (protein induced by vitamin K absence) or (b) if PIVKA is not available when the child presents with bleeding and prolonged prothrombin time which is rapidly corrected 24 h after administration of vitamin K [6].

Prospective cases were recruited after obtaining written consent for participation from the parent/guardian. The management protocol was based on the treating physician's discretion. For retrospective claims, pediatric medical records diagnosed with late-onset VKDB from the Institute's Medical Records Department (MRD) were retrieved after obtaining permission from the concerned authority. A structured data collection proforma was prepared with particulars comprising necessary demographic details, clinico-laboratory profile, treatment administered, and the disease outcome. The child's outcome, i.e., recovery, sequelae, and death, was assessed at the time of discharge, as mentioned in the case records. Through telephonic conversation, the child's condition was enquired to evaluate for any complication due to VKDB. Data from these were analyzed to describe the

frequency of occurrence of each clinical feature, as well as the outcomes and the factors which may play a role in the eventual development.

Statistical analysis

The data collected were analyzed using SPSS software version 20.0. The normality of data was tested with the Kolmogorov–Smirnov test for normality. Continuous variables were expressed as median with interquartile range (IQR) or mean with standard deviation based on the normality of data. The categorical variables were expressed as frequencies with proportion.

Results

Out of the 62 cases recruited with bleeding manifestations, 28 were excluded due to cholestasis ($n=21$), sepsis ($n=5$), and congenital bleeding disorders (hypofibrinogenemia) ($n=2$). The remaining 34 cases were analyzed, out of which 6 were prospectively recruited and 28 were retrospectively recruited. The median age at presentation of onset of symptoms was 54 days (10–180). There was a male preponderance with $n=22$ (64.7%), and the male-to-female ratio was 1.8:1. The median duration of hospital stay among the participants was 11 days (2–30). There was no history of maternal drug intake in the study population. Out of the 34 children studied, 25 (73.5%) were born at term gestational age, 9 (26.5%) were preterm, 13 (38.2%) were low birth weight, and 8 (23.5%) children required NICU admission [low birth weight ($n=2$), post-resuscitation care ($n=2$), early onset neonatal sepsis ($n=3$), and neonatal jaundice ($n=1$)]. All the children were born in the hospital and received 1 mg of IM vitamin K prophylaxis at birth. Among the study population, 33 (97.1%) were exclusively breastfed (EBF), and the remaining 1 (2.9%) was on formula feeds. History of antibiotic usage was present in 2 (5.88%) children, and 1 (2.9%) child had a history of diarrhea. The clinical parameters are discussed in Table 1. Among the recruited children, 6 (17.6%) were underweight, 4 (11.8%) had stunting, and 3 (8.8%) had microcephaly.

Among the study population, 20 (58%) were found to have severe anemia (hemoglobin <7 g/dl), and all had normal platelet counts and liver function tests. PIVKA levels were done for 15 children (44.11%), and the results of all the children were found to be elevated; PT/INR was prolonged in 7 children, and the normal value of PT/INR in other children was attributed to vitamin K administration prior to sampling. Other laboratory parameters are discussed in Table 2.

Among the population studied, one (2.9%) child had an ultrasonogram (USG) cranium done, which revealed communicating hydrocephalus. Computed tomography (CT) of the brain was done in 32 children. The neuroimaging

Table 1 Clinical profile of the study population

Clinical parameter	n (%) Total N = 34
Presenting complaints	
Poor activity	26 (76)
Convulsions	26 (76)
Vomiting	17 (50)
Altered sensorium	16 (47)
Fever	12 (35)
Pallor	9 (26)
Bulging fontanelle	7 (20)
Irritability	2 (5.9)
Loose stools	1 (2.9)
Left thigh hematoma	1 (2.9)
Bleeding from left ear	1 (2.9)
Umbilical bleeding	1 (2.9)
Poor feeding	1 (2.9)
Site of bleeding	
Intracranial	33 (97.1)
Skin bleeding	5 (14.7)
Umbilical bleeding	1 (2.9)
Prick site bleeding	1 (2.9)
Bleeding from ear	1 (2.9)
Left thigh	1 (2.9)

Table 2 Laboratory parameters

Laboratory parameter (units)	Median (range)
Hemoglobin (g/L)	63.5 (34–115)
Platelet counts ($\times 10^9/L$)	3.63 (1.07–8.09)
Aspartate aminotransferase (U/L)	35 (11–79)
Alanine aminotransferase (U/L)	32 (11–116)
Total bilirubin ($\mu\text{mol/L}$)	23.76 (4.27–123.12)
Direct bilirubin ($\mu\text{mol/L}$)	7.6 (0.86–26.67)
PIVKA (ng/ml) ^a	37,926.7 (5120–211,535)

^a PIVKA (protein induced by vitamin k absence)

Table 3 Neuroimaging findings

Neuroimaging finding	n (%)
Intraparenchymal hemorrhage	13 (38.23)
Subdural hemorrhage	13 (38.23)
Midline shift	8 (23.5)
Subarachnoid hemorrhage	6 (17.6)
Intraventricular hemorrhage	4 (11.7)
Extradural hemorrhage	4 (11.7)

findings are mentioned in Table 3. Twenty-eight (82%) children required pediatric intensive care unit (PICU) transfer, all 34 (100%) received inj. vitamin K, 30 (88.2%)

Table 4 Neurosurgical intervention

Neurosurgical intervention	n (%)
Decompressive craniectomy	12 (35.2)
External ventricular drainage	2 (5.8)
Ventriculoperitoneal shunt	1 (2.9)
Burr-hole evacuation	1 (2.9)

children required both packed red blood cells (PRBC) and fresh-frozen plasma (FFP) transfusion, and 1 (2.9%) child required PRBC transfusion alone. Sixteen (47.05%) children required neurosurgical intervention which was mentioned in Table 4. Twenty-five (73.5%) children required antiepileptics among which 8 (23.5%) received phenobarbitone, 4 (11.7%) received phenytoin, 5 (21%) required dual antiepileptics (phenytoin + phenobarbitone), and 3 (13%) required triple antiepileptics (phenytoin + phenobarbitone + midazolam infusion).

Among the 34 study participants, 23 (67.6%) recovered, 6 (17.6%) had sequelae, and 5 (14.7%) expired. The various sequelae observed in our study are hemiparesis ($n=2$), monoparesis ($n=2$), and quadriplegia ($n=2$).

Discussion

Vitamin K deficiency bleeding is a well-recognized but potentially preventable condition that affects neonates and young infants. It results from an inadequate supply of vitamin K, which is essential for the synthesis of clotting factors, primarily factors II, VII, IX, and X, as well as protein C and protein S [7]. The present study sheds light on the clinical presentation, risk factors, and outcomes associated with VKDB in a cohort of pediatric patients. The study population consisted of 34 cases, excluding those with cholestasis, sepsis, and congenital bleeding disorders. Term children have 50% of vitamin K-dependent clotting factor levels when compared to adults, and pre-term has even lesser levels [2]. In our study, VKDB is more at term gestational age (73.5%) as most recruited children were born at term. This finding is consistent with a previous study by Pooni et al. (100% term) [8]. A noteworthy observation is the relatively high percentage of children born with low birth weight (38.2%), and those requiring NICU admission (23.5%) had VKDB, which could be explained by low clotting factors level in these babies and antibiotic usage in admitted newborns.

Male preponderance is noticed in our study (64.7%), which is similar to the previous study (62%), but the exact reason is not known [9]. The mean age at presentation in our study is 7 weeks, and previous studies have reported from 5 to 7 weeks [9, 10]. All children were delivered at the hospital and received vitamin K prophylaxis at birth. In contrast, in previous studies, the majority were

delivered at home and did not receive vitamin K prophylaxis (Pooni et al. — 100% did not receive vitamin K and 47% home delivery and Chandra et al. — 100% did not receive vitamin K and 75% home delivery) [6, 8]. This is because Tamil Nadu and Puducherry state in India have a 100% institutional delivery rate as per NFHS 5 phase 2 data [11]. However, despite vitamin K prophylaxis, a significant number of children are affected with VKDB, highlighting the importance of understanding factors like EBF, antibiotic usage, diarrhoea, and prematurity that contribute to its development.

The majority of cases (97.1%) were exclusively breastfed, attributed to low vitamin K content in breast milk (2.1 mcg/L) when compared to cow milk (4.9 mcg/L) and formula milk (4.2 mcg/L) [6], which correlate with the result of other studies [6, 8, 12]. Exclusively, breastfed infants are at higher risk for VKDB due to poor placental transfer and low vitamin K content in breast milk. Clarke P. et al. observed low vitamin K1 levels, higher PIVKA-II, and a higher percentage of osteocalcin in breastmilk-fed preterm babies than those receiving a formula/mixed-feed diet [13]. Greer et al. also showed persistently low vitamin K levels in EBF infants at 4 weeks of life and suggested supplementation of 5 mg of vitamin K to lactating mothers to increase vitamin K concentration in human milk as well as infant plasma [14].

The clinical profile of the study population revealed a range of presenting complaints. The most common symptoms included poor activity and convulsions followed by vomiting and altered sensorium, which might be attributed to the intracranial bleeding associated with VKDB, which is a common site of bleeding in other studies also. IC bleed was reported in 82% of Chuansumrit et al., 58% in Sutor et al., and 61.5% in Karaci et al., whereas we observed it in 97% of cases [9, 15, 16]. The exact reason for the increased incidence of IC bleed in VKDB is not understood. The immaturity of the cerebral vascular system in young infants may be contributing to intracranial bleeding. Additionally, skin bleeding, umbilical bleeding, prick site bleeding, and bleeding from the ear and left thigh were observed, which amounts to 26%, further emphasizing the diverse clinical manifestations of this condition. This is consistent with a previous study by Karachi et al., which showed 36% of other site bleeding [9]. The study's focus on clinical presentation helps to elucidate the spectrum of symptoms that should raise suspicion for VKDB in neonates and young infants.

Laboratory parameters provided valuable insights into the severity of VKDB in the study population. The finding that 58% of the study population had severe anemia is consistent with the hematological consequences of VKDB due to bleeding manifestations. The normal platelet counts and liver function tests among these children

suggest that the primary cause of bleeding was likely related to clotting factor deficiencies rather than other systemic abnormalities.

PIVKA-II levels indirectly measure the vitamin K levels of the last 3 to 4 days. A rise in these proteins is a sensitive and specific marker for subclinical VKDB. PIVKA level was measured in 44% of cases, and everyone had elevated levels in our study. PIVKA-II level of more than 2 ng/mL will be considered as abnormal [17]. In a study conducted by Motohara et al., PIVKA-II, more than 0.1 AU (arbitrary unit)/mL (1 AU = 1- μ g purified prothrombin = 1000 ng/mL) [18], was considered as significant VKDB. The mean PIVKA level in this study was 37,926.7 (5120–211,535) ng/ml.

The high proportion of children with normal PT/INR (83%) assessments in our study is attributable to receiving vitamin K before our hospital admission. The normalization of PT/INR after vitamin K administration reinforces the role of this intervention in diagnosing the VKDB.

The universal vitamin K administration to all 34 participants emphasizes revising the prophylaxis protocol to prevent VKDB. There are different vitamin K prophylaxis regimens in various countries. Some centers administer oral vitamin K due to parental concern about giving injections to newborn babies, whereas many prefer intramuscular injections due to unpredictable oral drug absorption. Witt M. et al. observed that a vitamin K prophylactic regimen of 1 mg oral at birth followed by a daily oral dosage of either 25 or 150 μ g (Dutch regimen) still fails to prevent VKDB in breastfed infants and supported 1-mg vitamin K IM at birth (Danish regimen) as prophylaxis against VKDB [19]. A systematic review by Sankar et al. concluded that a single IM prophylaxis (1 mg) is better than a single oral dose (1–2 mg) [4]. However, the effect of multiple oral dosing needs to be studied. Further, the review by Jullien mentioned various existing prophylaxis programs in different parts of the world and concluded that there is no significant difference between the intramuscular and the oral regimens for preventing classical and late HDN, provided that the oral regimen is duly completed [20].

The necessity of PICU transfer for 82% of the children brings out the severity of VKDB and the need for intensive care management. Neuroimaging plays a crucial role in understanding the extent of bleeding and its impact on brain structures. Intraparenchymal and subdural hemorrhages were the most common findings in our study. This is inconsistent with previous studies in which subdural is most common (28%) in Ozdemir et al., and intraparenchymal is most common (43.7%) in Karachi et al. [9, 21]. Neurosurgical interventions, including decompressive craniectomy and ventricular shunt placement, were often necessary to manage the complications of VKDB.

The outcomes observed in the study population reflect the spectrum of VKDB severity. While a significant portion of children recovered, a notable percentage (17.6%) experienced sequela, such as hemiparesis, monoparesis, and quadriplegia, which is less (28%) compared to previous studies [10, 16], and Karachi et al. reported as high as 50% (3 epilepsy, 4 motor, and mental retardation, 4 hydrocephalus) [9]. Tragically, 14% of children succumbed to the complications of VKDB; this is consistent with another study with 20% mortality in Winckel et al. and 31% mortality in Ozdemir et al. [21, 22], reinforcing the importance of early diagnosis, prevention, and intervention.

There is a paucity of literature regarding VKDB in children. This study contributes valuable insights into the clinical presentation, risk factors, and outcomes associated with vitamin K deficiency bleeding in the pediatric population. Also, we included infants with only VKDB and excluded other secondary causes of vitamin K deficiency. However, the majority of cases are retrospectively included, and long-term follow-up details were not available in our study. A prospective multicentric study with long-term follow-up will throw better light on this severe yet preventable cause of intracranial bleeding.

Conclusion

In conclusion, vitamin K deficiency commonly presents as intracranial hemorrhage in infants. Exclusive breastfeeding is a significant risk factor for vitamin K deficiency, followed by low birth weight and prematurity. One-third of children had serious adverse outcomes in terms of death or severe neurological sequelae. Despite receiving prophylaxis at birth, infants develop vitamin K deficiency. This highlights the importance of revising the existing vitamin prophylaxis program.

Acknowledgements

We thank Dr. Likhitha Siddarajaiah, an MBBS student, for helping with data collection.

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Clinical trial registration number

Not applicable. This is only observational study, and no intervention is performed.

Code availability

Not applicable.

Authors' contributions

CGD and AA, conceptualized the study. AA, collected the data and drafted the initial manuscript. CGD and NP, analysis of data and literature search; CGD, AA, and SMP, intellectual input in final drafting and overall supervision. All authors contributed to the critical revision of the article.

Funding

No funding was received for conducting this study.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The study was approved by the Institute Ethics Committee for Observational Studies (DHR Reg. No. EC/NEW/INST/2020/331) vide letter no. JIP/IEC/2022/098 dated 5th April 2022, and this study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all the individual participants included in the study.

Consent for publication

Patients signed informed consent regarding publishing their data.

Competing interests

The authors declare that they have no competing interests.

Received: 11 October 2023 Accepted: 4 January 2024

Published online: 24 January 2024

References

- Majid A, Blackwell M, Broadbent RS, Barker DP, Al-Sallami HS, Edmonds L et al (2019) Newborn vitamin K prophylaxis: a historical perspective to understand modern barriers to uptake. *Hosp Pediatr* 9:55–60
- Pichler E, Pichler L (1946) The neonatal coagulation system and the vitamin K deficiency bleeding - a mini review. *Wien Med Wochenschr* 2008(158):385–395
- Hand I, Noble L, Abrams SA (2022) AAP Committee on Fetus and Newborn, Section on Breastfeeding, Committee on Nutrition. Vitamin K and the newborn infant. *Pediatrics*. 149(3):e2021056036
- Sankar MJ, Chandrasekaran A, Kumar P, Thukral A, Agarwal R, Paul VK (2016) Vitamin K prophylaxis for prevention of vitamin K deficiency bleeding: a systematic review. *J Perinatol Off J Calif Perinat Assoc* 36(Suppl 1):S29–35
- Sachin KR, Ramesh H, Chaya KA (2020) Late haemorrhagic disease of newborn: can it be prevented by changing prophylaxis policy? *Asian J Pediatr Res* 3:14–19
- Chandra Jagdish, Mandal piali (2018) Fetal & Neonatal Haematology, Oncology, and Immunology, 1st ed
- Newman P, Shearer MJ (1998) Vitamin K metabolism. *Subcell Biochem* 30:455–488
- Pooni PA, Singh D, Singh H, Jain BK (2003) Intracranial hemorrhage in late hemorrhagic disease of the newborn. *Indian Pediatr* 40:243–248
- Karaci M, Toroslu E, Karsli T, Kanber Y, Uysal S, Albayrak D (2015) Intracranial hemorrhage due to late onset vitamin k deficiency. *HK J Paediatr (new series)* 20:80–85
- IJland MM, Pereira RR, Cornelissen EAM (2008) Incidence of late vitamin K deficiency bleeding in newborns in the Netherlands in 2005: evaluation of the current guideline. *Eur J Pediatr*. 167:165–9
- Union Health Ministry releases NFHS-5 Phase II Findings n.d. <https://www.pib.gov.in/www.pib.gov.in/Pressreleaseshare.aspx?PRID=1774533>. Accessed August 29, 2023
- D'Souza and Subba Rao (2003) Late hemorrhagic disease of newborn. *Indian Pediatr* 40(3):226–9
- Clarke P, Shearer MJ, Card DJ et al (2022) Exclusively breastmilk-fed preterm infants are at high risk of developing subclinical vitamin K deficiency despite intramuscular prophylaxis at birth. *J Thromb Haemost* 20(12):2773–2785
- Greer FR (2001) Are breastfed infants vitamin K deficient? *Adv Exp Med Biol* 501:391–395
- Chuansumrit A, Isarangkura P, Hathirat P (1998) Vitamin K deficiency bleeding in Thailand: a 32-year history. *Southeast Asian J Trop Med Public Health* 29(3):649–654
- Sutor AH, Dagres N, Niederhoff H (1995) Late form of vitamin K deficiency bleeding in Germany. *Klin Padiatr* 207:89–97

17. Chawla D, Deorari AK, Saxena R, Paul VK, Agarwal R, Biswas A, Meena A (2007) Vitamin K1 versus vitamin K3 for prevention of subclinical vitamin deficiency: a randomized controlled trial. *Indian Pediatr* 44(11):817–822
18. Motohara K, Endo F, Matsuda I (1985) Effect of vitamin K administration on acarboxy prothrombin (PIVKA-II) levels in newborns. *Lancet Lond Engl* 2:242–244
19. Witt M, Kvist N, Jørgensen MH et al (2016) Prophylactic dosing of vitamin K to prevent bleeding. *Pediatrics* 137(5):e20154222
20. Jullien S (2021) Vitamin K prophylaxis in newborns. *BMC Pediatr* 21(Suppl 1):350
21. Ozdemir MA, Karakukcu M, Per H, Unal E, Gumus H, Patiroglu T (2012) Late-type vitamin K deficiency bleeding: experience from 120 patients. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg* 28:247–251
22. Van Winckel M, De Bruyne R, Van De Velde S, Van Biervliet S (2009) Vitamin K, an update for the paediatrician. *Eur J Pediatr* 168:127–134

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