Original Article

Frequency of Intracranial Bleed in Infants with Vitamin-K Deficiency in 7-180 Days of Age

Ihsanul Haq, Ashfaq Ahmad, Sardar Khan and Zahir Said

ABSTRACT

Objective: To determine the frequency of intracranial bleed in infants with vitamin-K deficiency in 7-180 days of age.

Study Design: Descriptive / cross sectional study

Place and Duration of Study: This study was conducted at the Department of Pediatrics STH, Swat from 1st July 2016 to 30th June 2017.

Materials and Methods: Biodata, clinical profile and results of the investigations (coagulation profile and neuroimaging) of all theselected patients were collected on a pre designed proforma. Total of 100 patients were included who fulfilled the inclusion criteria of the study. Exclusion criteria were strictly observed to prevent confounder and bias.

Results: Out of 100 patients 65(65%) were male and 35(35%) were female. Intracranial bleed due to Vitamin-K deficiency was confirmed in 31(31%) patients. The mean age of onset of symptoms was 45.65 ± 15.35 days and male to female ratio 1.85:1 (p=0.047). 16 (51.61%) out of 31 patients with intracranial bleed were from 7-60 days of life, 10(32.25%) were from 61-120 days of life and only 5(16.12%) beyond 120 days of life.

Conclusion: Intracranial hemorrhage remains a disabling disease mostly due to unidentifiable causes, however in many cases a high index of suspicion of Vitamin K deficiency should be kept in mind which often leads to bleeding as identified in our study.

Key Words: Intracranial bleed, Vitamin-K deficiency

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INTRODUCTION

Intracranial bleed is the pathological accumulation of blood within the cranial vault. Intracranial bleed is a rare but often disabling disease leading to high rate of morbidity and mortality in this population[1], it may occur within brain parenchyma or the surrounding meningeal spaces.[2] Bleeding into the brain and related structures is a very common neonatal event and is most frequently recognized in premature infants.[3]

Intracranial hemorrhage usually presents with neurological symptoms and signs like altered level of consciousness, reluctance to feed, seizures, vomiting or fever.[4-5] It may be epidural, subdural, parenchymal or intraventricular.[6] Vascular malformation is the most frequent cause of intracranial bleed in children.[6-7] Other causes are, hematological diseases such as coagulopathies,[8] Vitamin-K deficiency or thrombocytopenia, cerebral tumors and septicemia.

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Arteriovenous malformations (AVMs) account for 14% to 46% of hemorrhagic strokes in children and nearly 50% of intraparenchymal hemorrhage. Hematologic abnormalities are reported to be the major risk factors in 10% to 30% of hemorrhagic strokes.[9]

Various pediatrics studies report different results on intracranial bleed, depending on population studied, differences in sensitivity and timing of the modality used.[1]

Imaging is the most important method for confirming or excluding the diagnosis of ICH. Ultrasound is widely used in neonatal intensive care units for brain imaging and is valuable in term neonates as a screening technique when ICH is suspected. Other modalities are CT-brain or MRI brain.[10,11,12,13]

Vitamin K is a fat soluble vitamin essential for the synthesis of functional prothrombin, factor VII, factor IX and factor X in the liver.[14,15] Because of the short half-life of these factors, and the small amounts of vitamin K that can be stored in the body, inadequate intake of vitamin K can result in deficiency in a short period of time. Infants are at higher risk for hemorrhagic disease ofthe newborn, because of a lack of vitamin K reaching the fetus across the placenta[16], the low level of vitamin K levels in breast milk[17], immature liver and low colonic bacterial synthesis.[18]

The bleeding manifestations associated with vitamin K deficiency can occur in three general time frames. Early onset vitamin K deficiency bleeding that occurs less than 24 h after birth is rare and is almost always associated with maternal medications that interfere with vitamin K metabolism. The various drugs include anticonvulsants (Phenobarbital and Phenytoin), oral anticoagulants, and anti-tuberculous drugs. Postnatal administration of vitamin K has no effect in preventing early-onset disease. Vitamin K supplementation to at risk mothers, administered prenatally may prevent this form of vitamin K deficiency bleeding.[17-19]

The classic onset of vitamin K deficiency bleeding occurs between second and seventh day after birth in breastfed infants. Causes include low vitamin K content in breast milk, which is less than 5 microgram/liter compared to 50-60micrograms/liter in formula milk, poor oral intake and sterile gut. Clinical manifestations include bleeding in to the skin or from mucosal surfaces, circumcision, or venipuncture sites. It can be prevented by vitamin K supplementation at birth.[20-21]

Late-onset vitamin K deficiency bleeding occurs one to two weeks after birth. It can, however, occur as late as 3 months postpartum. In addition to breastfeeding, risk factors includevarious disorders that reduce Vitamin K absorption like diarrhea, hepatitis, biliary atresia, cystic fibrosis (CF), celiac disease, and alpha - 1-antitrypin deficiency or absence of prophylaxis in otherwise healthy infants. Late-onset vitamin K deficiency bleeding tends to be more severe than early-onset or classic disease and has a high frequency of intracranial hemorrhage. Intracranial hemorrhage is observed in more than 50% of infants with late-onset disease.[20, 22, 23]

A recent Cochrane database systemic review concludes that intramuscular Vitamin K has been proven to prevent classical disease and oral Vitamin K has been proven to improve biochemical parameters of Vitamin K deficiency in the first week of life.[24]

In a bleeding infant, a prolonged PT without any finding considering other bleeding disorders is almost diagnostic of VKDB. Rapid correction of PT and/or cessation of bleeding after vitamin K administration confirms the diagnosis.[25]

In infants who receive no vitamin K prophylaxis, late onset VKDB has been reported to be more common in Asian countries and in warmer climates.[26]

MATERIALS AND METHODS

This descriptive cross sectional study was conducted at the Pediatrics Department (General Pediatrics, Pediatrics Intensive care unit and Neonatal Intensive Care Unit) Saidu Teaching Hospital, Saidu Sharif Swat. Total duration was 12 months that was from 1st July 2016 to 30th June 2017.

Sample size: Total of 100 patients were include in this study with confidence level of 95% and margin error 0.07%.

Methodology: The study was first approved from Ethics and Research Committee of the Hospital. All the patient who met the inclusion criteria were asked to be a part of the study, after proper counselling and consent.

Inclusion criteria:

1. Age: 7-180 days
2. Clinical suspicion of intracranial bleed, which may be any one or combination of the following
   a) Altered level of consciousness
   b) Focal neurological signs
   c) Bulging Anterior fontanelle
   d) With or without evidence of mucosal and skin bleeding
3. Prolonged PT and APTT and normalization of PT and APTT after Vitamin-K or FFPs administration.

Exclusion criteria: Patient with obvious predisposing cause of bleeding like hemophilia, thrombocytopenia, functional platelets disorders and history of trauma were excluded from study.

Total of 100 patients fulfilling the inclusion criteria were included in the study. All these patients were subjected to detailed history and clinical examination, laboratory investigations, including complete blood count, coagulation profile(PT, APTT, BT, CT and platelets count) were performed in all these patients.

Neuroimaging in the form of CT, MRI brain or U/S skull were also performed for confirmation of intracranial bleed.

Details regarding pregnancy, delivery, clinical feature and the results of theabove mentioned investigations were recorded on pre designed proforma .

The diagnosis of vitamin K deficiency was established by history and clinical examination supported by prolonged PT, APTT and prothrombin ratio with normal level of platelets count, bleeding time and fibrinogen level along with normalization of PT and APTT 24 hours after the vitamin-K or FFPs administration which were both elevated before Vitamin-K or FFPs administration.

In this study INR was used as a PR ratio which was calculated by using the following formula

PR ratio = PT (patient) / PT (control)

RESULTS

Total of 100 patients who fulfilled the inclusion criteria were enrolled in the study. Out of one hundred enrolled patients 65 were male and thirty five were female with male to female ratio of 1.85:1.

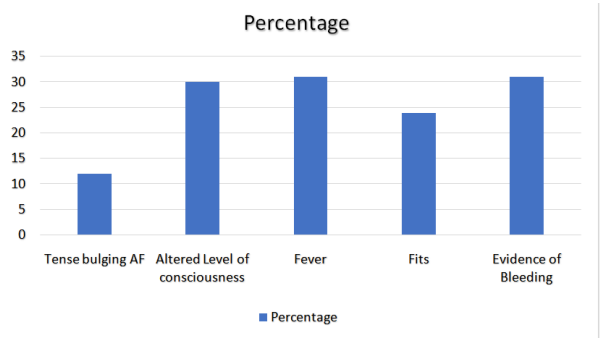
Out of 100 patients with vitamin-K deficiency 31 have been found to have intracranial bleed confirmed on neuroimaging (U/S skull, CT/MRI brain). Out of these 31 patients 20 (20%) patients were male and 11 (11%) were female.

Vitamin-K deficiency usually presents with diverse clinical signs and symptoms, the data has been stratified with clinical history and examination findings which

shows the following results presented in Table 1 and Graph 1.

Table No.1: Stratification of vitamin-k deficiency with history (n=100)

History	Vitamin-K deficiency	Frequency	%age
Term of Gestation	Full term	20	20 %
	Preterm	11	11 %
Mode of delivery	NVD	19	19 %
	C-Section	12	12 %
Vitamin-K prophylaxis at Birth	Yes	0	0 %
	No	31	31 %



Graph No.1: Frequency and percentages of clinical examination/findings in infants with intracranial bleed (n=31).

All patients with intracranial bleed belonged to age group 7- 180 days of life, the mean age of presentation was 45±2.5 days. Data is presented in Table 2.

Table No.2: Stratification of intracranial bleed with age (N=31)

Age	Frequency	Percentage
07- 60 Days	16	51%
61-120 Days	10	32.2%
121-180 Days	5	5%
Total	31	100%

As per diagnostic criteria the diagnosis of Vitamin-K deficiency was confirmed if the patient initially having deranged PT/APTT and rest of coagulation profile was normal and rapid normalization after vitamin K or FFP administration. Data stratification in the form of PT, APTT and PR ratio with pre and post treatment quantification data is presented in Table 3.

Table No.3: Pre and post treatment mean SD of pt/aptt/pr ratio

Pre treatment	Mean SD	Post reatment	Mean SD
PT (seconds)	25.2 ± 2.5	PT (seconds)	12 ± 2.5
APTT (seconds)	87.74 ± 5.44	APTT (seconds)	35.96 ± 4.08
PR ration	2.15 ± 0.16	PR ration	1.08 ± 0.09

DISCUSSION

Vitamin-K deficiency is common in early infancy due to certain risk factors suchas exclusive breast feeding, inadequate synthesis and absorption etc.Intracranial bleed is the frequent complication of vitamin-K deficiency as identified in our study which is 31%. Previous research works which shows different results depending on geographical variation of population studied, difference in the sensitivity, timing of the modality used and the selection of inclusion and exclusion criteria andthe use of prophylactic dose of Vitamin K etc.

In our study all patients diagnosed with Vitamin-K deficiency as per inclusion criteria were screened for complication of intracranial bleed.Amongst them 31% of patients with Vitamin K deficiency suffered from intracranial bleed. Two other studies conducted by Visser DY et al[22](march 2011), and M etal[18] respectively shows 25% and 40% frequency of intracranial bleed associated with vitamin K deficiency which are comparable to our study results.

Rana MT et al[17] and KavchiM et al[16] have shown results of 48% and 61.5% respectively in their studies, while in another research paper by Majeed et al[4]thereported frequency is only 11.4%.

In our study the male to female ratio of total patient was 1.85 to 1and inpatients with intracranial bleed male to female ratio was 1.81:1.KaraciM etal[16]and AdhikaliS et al[23] in their studies have shown comparable results of 1.6:1 and 1.66:1 respectively while Majeed R et al [4] and Rana MT et al[17] have reported higher male to female ratio of 2.18:1 and 2.12:1 respectively.

Common clinical presentation of infants with intracranial bleed identified by our study was the evidence of bleeding, deterioration of conscious status, fever and fits. The relative frequencies of the different clinical features were very much similar to those observed by Visser DY et al[22], Majeed R eta l [4],Misirliogku ED et al[27] and Klironomi I et al [8].

Mean age of presentation was 45 days which is comparable to some national and international studies results.[6, 7, 8] Prematurity and small for gestational age is not a risk factor, it is common in full term as identified in our study. The same has also been observed by Pooni PA et al[24] in their research paper.

CONCLUSION

It is concluded that Intracranial hemorrhage remains a disabling disease mostly due to unidentifiable causes, however in many cases a high index of suspicion of Vitamin K deficiency should be kept in mind which often leads to bleeding as identified in our study.

Recommendation: This study provide a proof that Vitamin K prophylaxis is mandatory in order to reduce the burden of morbidity and mortality in the form of hospitals stay, expense and outcome.

Author's Contribution:

Concept & Design of Study:	Ihsanul Haq
Drafting:	Ashfaq Ahmad, Sardar Khan
Data Analysis:	Ihsanul Haq, Ashfaq Ahmad
Revisiting Critically:	Sardar Khan, Zahir Said
Final Approval of version:	Ihsanul Haq

Conflict of Interest: The study has no conflict of interest to declare by any author.

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