CLINICAL PROFILE AND RISK FACTORS IN LATE HAEMORRHAGIC DISEASE OF NEWBORN: OUR EXPERIENCE

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ABSTRACT

Background: Haemorrhagic disease of the newborn (HDN) is not an uncommon entity in developing countries particularly in under previleged rural areas like southren punjab, where the prophylactic administration of vitamin-K at birth is not routinely practiced. The commonest mode of presentation of late HDN is intracranial hemorrhage. **Objective:** The present study was conducted to assess the clinical profile and risk factors of patients with Late (HDN). **Patients and Methods:** All infants above the age of 7 days were admitted in pediatric unit with vitamin K deficiency bleeding. An infant fulfilling the criteria of late HDN was included in the study.Infants with clinical and laboratory evidence of liver disease were excluded from the study. In these selected infants a detailed history, physical examination and investigations were carried out with special emphasis on risk factors for vitamin K deficiency and clinical features secondary to bleeding. Vitamin K 5 mg intravenous was given to all the patients and investigations were repeated after 24 hours. **Results:** Thirty two infants fulfilled the criteria of late HDN; 24 (75%) were males and 8 (25%) females. Majority of the babies (75%) were in the age group 4 to 12 weeks. Prophylactic Vitamin K was not given to any of the infants at birth or later. All were on exclusive breastfeeding, two had history of prolonged diarrhea and two had received antibiotics for one week. Majority of the infants 24 (75%) presented with neurological features i.e. convulsions 62%, altered sensorium 56%. Purpura and bleeding from other orifices were less frequent i.e. <10%. Six (18.75%) infants died. **Conclusion:** Intracranial hemorrhage is the commonest mode of presentation of late HDN and carries significant morbidity and mortality. Hence, vitamin K prophylaxis at birth is a deadly desirable intervention to avoid this potentially preventable life threatening condition.

Key words: Late Haemorrhagic disease of the newborn, intracranial hemorrhage, Vitamin K.

INTRODUCTION

Haemostasis is a complex process which depends upon interactions between vessel wall, platelets and coagulation factors. When blood vessels are injured, haemostasis maintains vascular integrity or causes blood flow to cease through the injured vessel. Bleeding is the result of loss of hemostasis. Haemostatic disorders in infancy may be congenital or acquired in origin. Newborns are prone to have acquired coagulopathies as they have only 20-50% of adult coagulation activity.[1] Haemorrhagic disease of the newborn (HDN) is one of the most common causes of acquired haemostatic disorders in early infancy.[2]

The subnormal plasma coagulation activity in newborn makes them prone to have various coagulopathies.[3] The low concentration of vitamin K in human breast milk further complicates the picture in exclusively breast fed infants. Lack of vitamin K administration at birth, exclusive breastfeeding, prolonged diarrhea and prolonged use of antibiotics make them more prone to have vitamin K deficiency bleeding. There is no standard recommendation to routinely administer vitamin k to all neonates in developing countries, where exclusive breastfeeding is strongly advocated for optimal health of the infants.[4]

Haemorrhagic disease of the newborn has three distinct patterns of clinical presentation. Early HDN is seen within 24 hours of birth usually manifesting as cephalhaematoma in neonates whose mothers have been on anticonvulsant or anti-tuberculous durgs during pregnancy and can possibly be prevented by intravenous administration of vitamin K either to the newborn at birth or to the mother (20 mg) before birth.[5] Classic HDN occurs between 2-7 days of life, commonly presenting as gastrointestinal bleeding with most of the cases being either idiopathic or exclusively breast fed infants and can effectively be prevented by administering intramuscular vitamin K at birth.[6] Late HDN is characterized by bleeding in infants aged 1-24 weeks due to severe vitamin K deficiency, occurring primarily in exclusively breast fed infants particularly in those who either have prolonged diarrhea or have been on prolonged antibiotic

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therapy.[3,4] It commonly manifests as intracranial bleeding and is usually associated with significant morbidity and subsequent mortality. An idiopathic variety of late HDN has also been recognized in Asians.[7] Incidence of Late HDN in the Eastern world is 25-80/100,000 birth which is higher than that in the western world (4-25/100,000 births).[3,5] Since visible hemorrhage is an alarming manifestation and clinical features of Intracranial hemorrhages (ICH) are unlikely to be ignored by the parents without hospitalization, it may be assumed that the incidence of hospitalization reflects the actual incidence in the community.[8] However, the exact incidence of HDN is possible only in an elaborated population based study.There are few case reports available on this aspect from the region. The present hospital based study was carried out to assess the clinical profile and risk factors of patients with late HDN.

PATIENTS AND METHODS

The study was conducted in the Department of Paediatrics, Bhawalpur Victoria Hospital Bahawalpur from 1st June 2004 to 31st May 2006 and Sheikh Zayed Hospital Rahim yar Khan from 1st June 2006 to 31st May 2007. The study period was three years, from 1st June 2004 to 31st May 2007.

Inclusion criteria

All the infants above the age of 7 days admitted in the pediatric unit with vitamin K deficiency bleeding were evaluated. An infant fulfilling the following criteria was defined as having late HDN: (*i*) bleeding in an exclusively breast fed infant after 7 days of life to six months of age, (*ii*) no thrombocytopenia and normal bleeding time (BT), (*iii*) normal peripheral blood smear examination,(*iv*). No evidence of infection (v) pro-longed prothrombin time (PT) and activated partial thromboplastin time (APTT), which normalized within 24 hours after administering vitamin K.

Protein induced in vitamin K absence (PIVKA) and serum fibrinogen levels were not available and were not considered essential in the case definition.

Exclusion criteria

Infants with significant hepatomegaly and / or derangement of liver enzymes and failure of PT to return to normal after 24 hours of introduction of a single intravenous dose of 5 mg vitamin K were considered to have liver disease and were excluded from the study.

Infants fulfilling the criteria were evaluated with regard to following aspects: place of birth, prior prophylactic vitamin K administration, feeding history, history of prolonged diarrhea, use of antibiotics, clinical signs of any other underlying illness, investigations including complete blood picture, BT, PT, APTT, liver function tests and CT scan brain. Vitamin K 5mg intravenous was given to all the patients and investigations were repeated after 24 hours.

RESULTS

Thirty two infants fulfilled the criteria of late HDN; 24 (75%) were males and 8 (25%) females. Majority of the babies; i.e 24 (75%) were in the age group 4 to 12 weeks. There were 5 babies of less than 4 weeks of age while 3 were between 12 to 24 weeks (Table I). All were born at term. The place of delivery was home in 18 (56%) while the remaining 14 (44%) were born in hospitals / private clinics. Prophylactic vitamin K was not given to any of these infants at birth or later. All the babies were on exclusive breast feeding. Two babies had prolonged diarrhea (duration >14 days), while another two babies had received antibiotics for about a week just prior to bleeding. Fever was reported in 25 % cases.

Majority of the infants 24 (75%) presented with neurological features in the form of excessive cry, lethargy, bulging / tense anterior fontanel, convulsions and / or loss of consciousness. Only 8 (25 %) patients had visible bleeding as the presenting feature in the form of hematuria, hematemesis, per rectal bleeding and bruises / ecchymotic spots. Fifty percent of the patients had pallor on examination.(Table II)

Table I:
Age Groups of Patients with Late-HDN (n = 32)

Age Group	No. of Patients	%age
1-4 weeks	05	15.75%
4-12 weeks	24	75 %
12-24 weeks	03	9.25 %

Table II: Clinical Profile of Patients with Late-HDN (n=32)

Presenting Symptoms	No.	%age
Neurological Features	***24***	***75***
Convulsions	20	62
Altered sensorium	18	56
Excessive crying	16	50
Tense anterior fontanel	22	70
Lethargy	16	50
Projectile vomiting	10	31
Non-Neurological Features	***8***	***25***
Pallor	16	50
Bruises/Ecchymotic spots	3	9
Haemetemesis	2	6
Haematuria	2	6
Bleeding Per rectum	2	6

Hemoglobin levels of =5 g/dl, 6-10 g/dl and >10 g/dl were seen in 15%, 35% and 50% babies, respectively. Mean platelet count was 3 Lac/cumm. PT and APTT were prolonged in all the cases. Both the PT and APTT returned to normal after 24 hours of intravenous vitamin K (5mg) therapy in all the cases.

CT scan revealed variable degree of intracranial hemorrhage. The majority of the patients 16 (66%) showed hemorrhage at more than one site. All patients with intracranial bleeding were managed in the pediatric intensive care unit. Six cases (18.75%) expired and all these had significant intracranial hemorrhage.

DISCUSSION

Mother's milk is an ideal food and feed for the infant and optimum breast feeding is absolutely essential for the optimal health of the growing young infant and the mother, as well. The low concentration of vitamin K in human breast milk and the consequent predisposition to vitamin K deficiency bleeding following exclusive breast feeding is emerging as a matter of concern especially in developing countries where exclusive breast feeding is vigorously advocated to promote optimal health of the infants.[9,10] In developed countries due to the routine use of vitamin K prophylaxis at birth HDN has now become a rarity.[4,6]

Late HDN may be truely idiopathic or may have secondary/additional contibutory / precipitating factors like prolonged diarrhea, prolonged use of antibiotics, cystic fibrosis, biliary atresia, alpha-1-antitrypsin deficiency, neonatal (NN) hepatitis, abetalipoproteinemia, malabsorptive disorders or chronic warfarin exposure.[1,2,10] In the present study prolonged diarrhea and prolonged use of antibiotics were seen in two (6 %) cases each, as secondary factors in addition to exclusive breast feeding.

Vitamin K (menaquinones) is neither present in newborn's liver nor it can be synthesized in situ due to the absence of gut flora. However, it gradually accumulates after birth. This, together with low concentration of vitamin K in human breast milk (1.5 µg/dl)as compared to cow's milk (6 µg /dl) are the likely reasons for HDN in infants on exclusive breast feeding, as favoured by the results of current study.[1,9,11] The common clinical manifestations of late HDN reported in literature are evidence of intracranial hemorrhage, ecchymosis, bruises, bleeding from GI tract and other mucus membranes, skin punctures, circumcision site or surgical incisions.[11,12] Intracranial hemorrhage (ICH) has been seen in 50-80% of affected babies in various studies.[12,13] In the present study ICH was seen in 75 % cases while 25 % cases presented with non-neurological featutures including hematuria, hematemesis, per rectal and cutaneous bleeding which is quite comparable to other studies.[6,7]

Most reports of late HDN have been in babies born at home and in the present study 56% cases were delivered at home.[13,14] However in our study, 44% deliveries were conducted at hospitals/private clinics, where the practice of routine vitamin K administration at birth does not exist regularly. Though the age range for late HDN described in litreture is 1 to 24 weeks, however, the majority of cases occur between 4 to 12 weeks of age.[3,5,15] In current study, majority of the babies; *i.e*. 24 (75%) were in the age group 4 to 12 weeks. There were 5 babies of less than 4 weeks of age while the remaining 3 were between 12 to 24 weeks (Table. I).
An overall mortality of 14% to 50% has been reported in literature.[2,11,16] It was 25 % in cases of intracranial hemorrhage in the present study.

Most of the survivors had some sort of neurological sequelae. However, to determine the true picture of the sequele, long term follow-up is desired.

Almost all of the infants of late HDN in various studies received exclusive breast feeding and did not receive vitamin K prophylaxis at birth .[10,12,17] In the present study as well, all the babies were on breast milk exclusively and had not received prophylactic vitamin K at birth or later. Late HDN may mimic findings of non-accidental head injury and may lead to mistaken diagnosis of child abuse.[16,18,19] However, in our study we were unable to find any case of non-accidental head injury.
Vitamin K prophylaxis reduces the incidence of late HDN from 5.1 cases per 100,000 births by 90%. A single parenteral dose reduces the risk by a factor of 14.3.[5,20,21] Routine vitamin K prophylaxis at birth brought down the incidence of late HDN from 7/100,000 to 1.1/100,000 live births in Netherlands.[3] In the present study vitamin K was not administered at birth or later in any case. The results of the meta-analysis on vitamin K administration have shown that intramuscular vitamin K is more effective than oral vitamin K in the prevention of late HDN.[9,22] Though oral route is economical, effective, practical and more acceptable to the parents but many studies have shown that oral vitamin K is less effective in preventing late HDN.[7,9, 26 4, 6,15] Single oral dose of 1 mg vitamin K is not effective, and the efficacy is increased with 3 oral doses of 2 mg (at birth, 1-2 weeks and 4 weeks), rather than 1 mg dose.[7,23]

A few case reports of late HDN are available in babies even after receiving pophylactic injection vitamin K.[20, 24] An epidemiological study from Germany by von Kries showed a failure rate (occurrence of late HDN) of 0.25 per 100,000 infants after IM administration compared with 1.4 per 10,000 in countries where oral vitamin K is given.[21] There are reports of preterm babies who had received intravenous injections of vitamin K at birth presenting with late HDN; this is because IM route has longer duration of effect than IV as a result of depot preparations.[25] Intravenous route is less effective for long-term prophylaxis of HDN.
Prolonged diarrhea with subsequent malabsorption of fat soluble vitamins (including vitamin K) and prolonged use of antibiotics leading to transient elimination of vitamin K producing gut flora and thus rendering the affected exclusively breast fed neonates prone to have HDN. Hence the American Academy of Pediatrics recommends to repeat a dose of vitamin K in every exclusively breast fed baby, whose diarrhea gets prolonged for more than five days.[10,27] In the present study prolonged diarrhea and prolonged use of antibiotics were seen in two (6 %) cases each as additional contributory factors, in addition to exclusive breast feeding. Warning bleeds (which may precede and predict intracranial bleeds) like umbilical bleed, epistaxis or skin bleeds should be taken seriously and given due attention in any breast-fed infant.[2,20,28] In the present study only two cases had preceeding warning bleeds in the form of cutaneous bleeds which were not given the desired serious attention by the parents.

The occurrence of a significant hemorrhage like ICH leading to death or life-long neurological deficit in a potentially preventable HDN is enough justification for absolute recommendation of prophylactic vitamin K administration at birth. Although there was initial reservation, it has been shown now that vitamin K administration does not increase the risk of leukemia.[12,20,29] Though it may be difficult to organize the administration of vitamin K injection to all newborns especially those born at home which form the bulk of total deliveries in a country like Pakistan; however, there is dire need of a massive campaign for ensuring prophylactic vitamin K administration at birth.

Our study had certain limitations. 1: Protein induced in vitamin K absence (PIVKA) serum level, the most sensitive diagnostic marker of HDN was not available and not carried out. 2: CT scan brain was only carried out in those cases having clinical suspicion of ICH and we might have missed cases of minor subclinical ICH.

CONCLUSION

Intracranial hemorrhage, carrying significant morbidity and subsequent mortality, is the commonest mode of presentation of late HDN. As there is ample evidence that late Haemorrhagic disease of the newborn is prevalent because of lack of vitamin K prophylaxis at birth, hence prophylactic vitamin K administration at birth is a deadly desirable intervention, to avoid this potentially preventable life-threatening condition. Our opinion is to adopt a more enthusiastic, aggressive and

effective approach at obstetricians, general practitioners and Traditional Birth Attendants (TBA) level to enhance vitamin K prophylaxis at birth. However, more studies are suggested on the subject in the region.

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