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Original Research Article

A Study of Impact of Phototherapy on Serum Calcium Levels in Term Neonates with Hyperbilirubinemia

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Abstract

Introduction: Hyperbilirubinemia is one of the most prevalent problems in neonates and clinically manifesting as jaundice. Hypocalcaemia is defined as total serum calcium concentration of <7 mg/dl (1.75mmol/L) in preterm and serum calcium of <8 mg/dl (2mmol/L) in term neonates.

Aims: To determine the incidence and clinical feature of phototherapy induced hypocalcemia and short-term outcome of phototherapy.

Materials & Methods: A hospital-based cohort study was conducted among term neonates admitted with hyperbilirubinemia. Data was analysed using IBM SPSS V21.0 for windows. Categorical variables like gender are expressed as frequency and percentages. Continuous variables like age are expressed as mean (SD), depending on the type of distribution. Chi-square test was used to determine the association between the categorical variables. Independent t-test and paired t test were used to determine the association for continuous variables. A p-value of less than 0.05 was considered statistically significant.

Results: Incidence of hypocalcaemia after phototherapy was 28.8% (CI: 22.7-35.5). Among the hypocalcaemia neonates, five of them had symptoms of jitteriness. The presence of hypocalcaemia was significantly higher among those neonates who had undergone phototherapy for 48 hours compared to 24 hours ($p<0.001$).

Conclusion: The presence of hypocalcaemia was significantly higher among those neonates who had undergone phototherapy for 48 hours compared to 24 hours ($p<0.001$). The mean serum calcium level after phototherapy significantly reduces when compared to the mean serum calcium level before phototherapy. Neonates requiring phototherapy are at higher risk of developing hypocalcaemia.

Keywords: Phototherapy, Hyperbilirubinemia, Term Neonates, Hypocalcaemia.

Introduction

Hyperbilirubinemia is one of the most prevalent problems in neonates and clinically manifesting as jaundice. Jaundice is observed during first week of life in approximately 60% of term neonates and 80% of preterm neonates. It is a cause of concern for the physician and a source of anxiety for the parent. About 60% of term and 80% of preterm infants develop jaundice in the first week of life.[1,2] Neonatal jaundice is benign and no intervention is required in most of the cases. Approximately 5-10% of them have clinically significant hyperbilirubinemia in whom the use of phototherapy becomes mandatory.[3] Neonatal hyperbilirubinemia is a condition due to the liver's immature excretory pathway for bilirubin and is the most common cause for admission of neonates in the first week of life in current time after postnatal discharge from hospital.[4] Elevated levels of unconjugated bilirubin is known to cause bilirubin encephalopathy and then kernicterus, with devastating, permanent neurodevelopment handicaps.[5] Phototherapy is one of the routine methods for management of hyperbilirubinemia. However, it is not a harmless intervention. It can produce adverse effects such as dehydration, temperature instability, skin rashes, loose stools, retinal damage, hypocalcaemia, bronze baby syndrome, redistribution of blood flow and genotoxicity. It causes photo oxidation of bilirubin into water soluble or less lipophilic colourless form of bilirubin which is easily excreted in bile, faeces and urine. Hypocalcaemia is one of the lesser-known adverse effects of phototherapy.[4,6] Decrease in serum calcium during phototherapy

results from trans cranial photic inhibition of melatonin synthesis. It has been suggested that phototherapy reduces melatonin secretion which not only regulates sleep cycle but also decreases glucocorticoid secretion leading to an increase in bone calcium uptake resulting in hypocalcaemia. Other causes suggested for this hypocalcemia include a decreased secretion of parathyroid hormone and a higher urinary excretion of calcium in the phototherapy group. The differential effect on serum electrolytes with phototherapy might be due to absorption of water, sodium chloride, and potassium in patients' receiving phototherapy. Phototherapy even for 72 hours does not significantly affect the fluid and electrolytes status of hyperbilirubinemia infants fed with fairly high solute load meal formulas. Among the side effect one of the side effects is diarrhea.[5]

Objectives

Among term neonates with hyperbilirubinemia:

1. To determine the incidence of phototherapy induced hypocalcemia
2. To assess the clinical feature of phototherapy induced hypocalcemia
3. To determine the short-term outcome of phototherapy

Material and Methods

A hospital-based cohort study was conducted among term neonates with hyperbilirubinemia admitted in the Department of Pediatrics, in collaboration with Department of Biochemistry, in a tertiary care hospital, Imphal. The study was conducted from October 2019 to September 2021.

Inclusion Criteria: Term neonates (37 completed weeks to 42weeks) with unconjugated hyperbilirubinemia requiring phototherapy.

Exclusion Criteria

Newborns with:

- Onset of jaundice within 24 hrs of age
- Perinatal asphyxia (Apgar <4 at one minute of birth)
- Whose mother had history of taking anticonvulsants
- Fed with cow's milk
- Who had exchange transfusion
- Jaundice lasting more than 14 days of life
- Sepsis
- Jaundice having hypocalcemia prior to the start of phototherapy
- Apparent major congenital anomalies
- ABO incompatibility
- Those parents/guardians not willing to participate in the study

Sample size

Taking the incidence of hypocalcemia among term neonates with hyperbilirubinemia as 35% from a study conducted by Goyal S et al[7], the sample size was calculated using the formula,

$$N= \frac{4pq}{L^2}$$

where q= 100-p and taking L=7= 185.7

After addition of non-response rate of 10% i.e. 19, the final sample size calculated was 205.

Sampling: The study participants were consecutively selected from the Department of Paediatrics, using convenience sampling until the sample size was reached.

Study tools

- A predefined proforma was used for collecting the socio-demographic profile and clinical characteristics.
- Weighing machine for baby, electronic weighing machine. Maximum capacity 20 k (d=10 gram), KONIG KN-BS10, Made in India.
- **Stethoscope:** Littmann quality, K17H13477. Made in USA
- **Infantometer:** Indosurgical product.
- **Product code:** 200014. Made in India
- Sterile container for collecting blood samples
- Sterile gloves and syringes
- A conventional phototherapy equipment (NEOTECH PHOTOTHERAPY LED SEEFAR NICE 4000 SPOT), Made in USA

Study Procedure: After obtaining permission from the ethics committee and informed consent from the parents of the neonates after informing the nature of the study. The sociodemographic and clinical history of the neonates were then obtained using a predefined proforma. Anthropometric measurements (weight, length and head circumference) of neonates at the time of admission. Serum calcium and total serum bilirubin (TSB) were assessed in the department of Biochemistry by Enzymatic Ion Selective Electrode method and Colorimetric method respectively using Randox Rx Imola Autoanalyzer (manufactured 2007, United Kingdom). TSB and serum calcium levels before and at the end of phototherapy were recorded.

Operational Definitions: Hyperbilirubinemia [8]: Total serum bilirubin concentrations have been defined as non-physiologic if concentration exceeds 5 mg/dl on first day of life in term neonate, 10 mg/dL on second day, or 12-13 mg/dl thereafter in term neonates. Any TSB elevation exceeding 17 mg/dL should be presumed pathologic and warrants investigation for a cause and possible intervention, such as phototherapy.

Hypocalcemia [9]: Total serum calcium level less than 8mg/dl in term neonates.

Term neonates: Live birth after 37 completed weeks to 42 weeks of gestational age.

Intervention (Phototherapy procedure)[8]: A conventional phototherapy equipment (NEOTECH PHOTOTHERAPY LED SEEFAR NICE 4000 SPOT), containing four blue light fluorescent lamps with wavelengths of 410-470nm, was placed at a distance of 25-35cm from the skin surface of neonates under standard protocol with eyes and genitals completely covered. The irradiance during phototherapy was measured and maintained consistently at 15µW/cm2/nm at the level of infant's skin.

Study Variables

Independent variables:

1. Age of neonate (in days)
2. Gender
3. Weight (kg) at birth and at admission time
4. Mode of delivery (Normal/Caesarean section)
5. Age of onset of developing jaundice (in days)
6. Total serum bilirubin levels (mg/dl)
7. Duration of appearance of jaundice (in days)
8. Duration of phototherapy
9. Level of serum calcium during admission

Dependent variables: Incidence of hypocalcaemia and its clinical features in term neonates with hyperbilirubinemia requiring phototherapy and short-term outcome

Statistical analysis: Data was analysed using IBM SPSS V21.0 for windows. Categorical variables like gender are expressed as frequency and percentages.

Continuous variables like age are expressed as mean (SD), depending on the type of distribution. Chi- square test was used to determine the association between the categorical variables. Independent t-test and paired t test were used to determine the association for continuous variables. A p-value of less than 0.05 was considered statistically significant.

Approval of research review Board: The ethical approval was obtained from the Research Ethics Board, RIMS, Imphal (Ref. No. A/206/REB-Comm(SP)/RIMS/2015/576/54/2019).

Informed consent was obtained from the parents of the neonates before data collection. Confidentiality was maintained by limiting the identifying variables to the minimum. Data was analyzed in aggregate and access to the collected data was limited only to me, my guide and co-guide.

Results

Table 1: Association between duration of phototherapy and hypocalcaemia (N=205)

Duration of phototherapy	Hypocalcaemia, n (%)		p value
	Present	Absent	
24 hours	21 (18.8)	91 (81.3)	< 0.001
48 hours	38 (40.9)	55 (59.1)	
Hypocalcaemia	Mean	SD	p value
Present	17.6	1.3	0.007
Absent	17.1	1.2	

Table 2: Association between total serum bilirubin at the time of admission and hypocalcaemia after phototherapy (N=205)

Serum calcium level	Mean	SD	p value
Before	9.1	0.6	<0.001
After	8.4	0.5	

Table 3: Association between serum calcium level before and after phototherapy (N=205)

Serum calcium level	Mean	SD	p value
Before	9.1	0.6	<0.001
After	8.4	0.5	

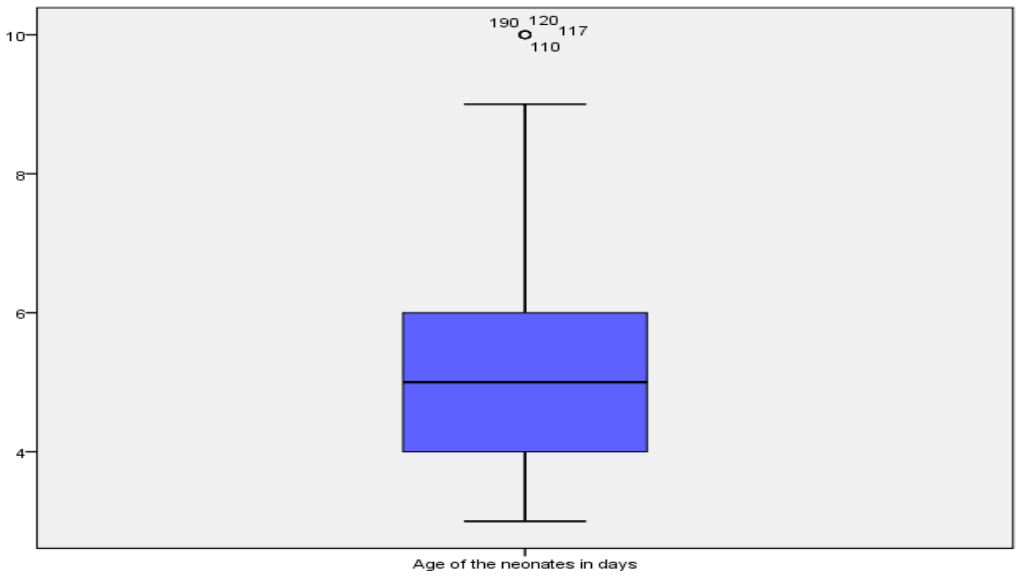

Figure 1: Distribution of the neonates according to age in days (N= 205)

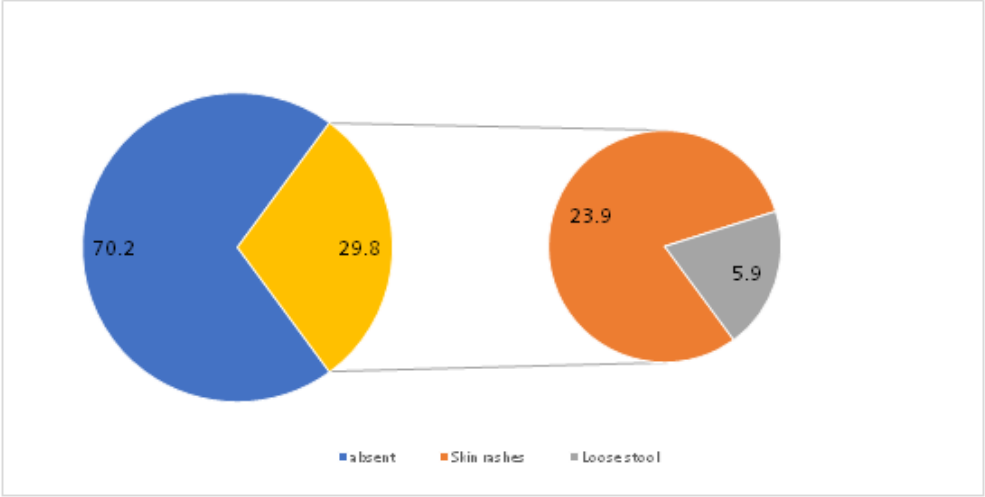

Figure 2: Distribution of the neonates according to the adverse effects following phototherapy (N= 205)

Total of 205 neonates who fulfilled the criteria were included in the study. The mean ± SD age of the neonates was 5.3 ±1.4 days. The median (Interquartile Range) age was 5.0 (4-6) days with minimum age of 3 days and maximum age of 10 days (Figure 1). The Incidence of hypocalcaemia after phototherapy was 28.8% (CI: 22.7-35.5). Among the hypocalcaemia neonates, five of them had symptoms of jitteriness. The presence of hypocalcaemia was significantly higher among those neonates who had undergone phototherapy for 48 hours compared to 24 hours ($p<0.001$) (Table 1). The mean serum bilirubin at the time of admission of the neonates was higher among those with hypocalcaemia after phototherapy then those without hypocalcaemia ($p=0.007$) (Table 2). The mean serum calcium level after phototherapy significantly reduces when compared to the mean serum calcium level before phototherapy ($p<0.001$) (Table 3). Among the 205 neonates undergoing phototherapy, 71 (29.8%) of them had adverse effects of which majority had skin rashes followed by loose stool (Figure 9).

Discussion

Neonatal jaundice is a common clinical problem observed during the first week of life affecting approximately 60% of term and 80% of preterm infants. Phototherapy for neonatal jaundice is a common treatment in neonatal medicine and is used to prevent the neurotoxic effects of bilirubin. It is a cost-effective and non-invasive treatment opted as a first line in most of the infants with neonatal jaundice. However, there is evidence that its use is associated with hypocalcaemia which is a serious concern.[10] Our study reported that the incidence of hypocalcaemia after phototherapy was 28.8%. Comparable finding was reported in a study conducted by Jain et al [11] where the prevalence of hypocalcaemia was 30% in full term neonates. Higher incidence was reported in different studies conducted by Singh PK et al [12] where the

incidence was 35%, Yadav et al [13] observed that 66% of the term neonates developed hypocalcaemia after phototherapy. Whereas lower incidence was reported in studies conducted by Alizadeh et al[14] and Karamifar et al [15] where the incidences were 7% and 8.7% respectively. The reason for this difference is not clear. However, the type of fluorescent tube, serum vitamin D, bilirubin levels and also the patient's skin colour may play a role or else the operational definitions used to define hypocalcaemia and the differences in the time frame taken to measure the serum calcium level after exposure to phototherapy.

The mean ± SD age of the neonates was 5.3 ±1.4 days with minimum age of 3 days and maximum age of 10 days. Majority of the neonates were male with M:F ratio is 1.8:1. The mean ± SD birth weight was 2.9 ±0.3 kg with minimum and maximum birth weight being 2.4 kg and 3.8 kg respectively. The mode of delivery of more than three-fifth of the neonates was normal delivery. Two-fifth of the neonates have jaundice onset on day four. It is noteworthy to mention that the mechanism underlying the development of hypocalcaemia driven by phototherapy remains unclear, but it may be associated with increased excretion of calcium in the urine during phototherapy. It may also be caused by light passing through the skull, which exerts an inhibitory effect on the pineal gland, thus leading to decreased melatonin secretion, which in turn leads to a decrease in cortisol secretion, thus enhancing the absorption of calcium by bone tissue and causing a decrease in blood calcium levels. Therefore, it has been hypothesized that hypocalcaemia may be alleviated by wearing protective headgear during phototherapy. [11, 16, 17, 18] In our study, among the hypocalcaemic neonates, five of them had symptoms of jitteriness. Similarly, in the study conducted by Yadav et al,[13] the most common sign among the hypocalcaemic was jitteriness. In our study among the 205 neonates undergoing phototherapy, 29.8% of them had adverse effects of which majority had skin rashes followed by loose stool. Similar findings were reported in the studies conducted by Xiong Tao et al [19] and Wang J et al.[20]

This study reported that there was no association between gender of neonates, birth weight of the neonates, gestational age at the time of delivery of the neonates, mode of delivery with hypocalcaemia after phototherapy. Comparable results were found in the study conducted by Muzaffar M.[21] In this study, the presence of hypocalcaemia was significantly higher among those neonates who had undergone phototherapy for 48 hours compared to 24 hours ($p<0.001$). The mean serum bilirubin at the time of admission of the neonates was higher among those with hypocalcaemia after phototherapy then those without hypocalcaemia. These findings can be compared with the study conducted by Gupta R et al. [22] Also, Habibzadeh F et al [23], Zarkesh et al [24] and Ghosh UK et al25 showed the significantly higher hypocalcemia with longer exposure to phototherapy. This study also showed that the mean serum calcium level after phototherapy significantly reduces when compared to the mean serum calcium level before phototherapy. Similar findings were reported in different studies conducted by Karamifar et al [15], Taheri et al [14] and Singh PK et al.[12]

One of the strengths of our study is that the results could be generalized to the population of the similar setting. The limitation of our study is that we considered the total serum calcium level which can be affected by the pH of the body. Normal neonates were not included in our study and hence the relative causal association of the hypocalcaemia could not be commented. Hence, study focusing on the ionised calcium level should be conducted. Also, further large multicentric analytical studies for estimating the incidence rate and the predictor variables to add more robustness to our study findings.

To conclude, neonates requiring phototherapy are at higher risk of developing hypocalcaemia. Hence, it can be recommended that calcium level be assessed in new-borns treated with phototherapy for 48 hours or more and managed accordingly to avoid severe complications caused by hypocalcaemia, such as convulsions, laryngeal spasm or apnoea.

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