Incidence of Phototherapy-Induced Hypocalcemia in Neonates with Hyperbilirubinemia

Running Title: Phototherapy-Induced Hypocalcemia in Neonates with Hyperbilirubinemia

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Abstract

Background: Hyperbilirubinemia is the most common clinical abnormality in newborns during the first week of life. Phototherapy is the standard treatment but may cause complications, including hypocalcemia, a lesser-known yet significant adverse effect. This study investigates the impact of phototherapy on serum calcium levels in neonates with hyperbilirubinemia.

Methods: This observational study was conducted in the NICU of BYL & T.N. Medical College, Mumbai, over 12 months after ethical approval. It included 100 neonates (>34 weeks gestational age) with hyperbilirubinemia receiving phototherapy. Serum calcium levels were measured before and after phototherapy, and neonates were monitored for clinical hypocalcemia. Data were recorded in a pre-formatted proforma and analyzed using SPSS version 27 ($p < 0.05$ considered significant).

Results: The mean age of neonates was 3±1.2 days, mean gestational age was 37±1.2 weeks, and mean jaundice duration was 2.8±1.10 days. Median serum calcium levels decreased significantly from 8.6 mg/dL (8.49-8.61) pre-phototherapy to 7.35 mg/dL (7.33-7.50) post-phototherapy ($p < 0.001$). Hypocalcemia (serum calcium ≤7 mg/dL) occurred in 16% of neonates, with 60% exhibiting mild symptoms like jitteriness or irritability.

Conclusion: Phototherapy significantly reduces serum calcium levels in jaundiced neonates, with a notable incidence of hypocalcemia. Clinicians should monitor calcium levels and watch for symptoms during phototherapy to prevent complications. Further studies are needed to establish preventive strategies.

Introduction

Hyperbilirubinemia in newborns is characterized by total blood bilirubin levels higher than 5 mg/dl, the 95th percentile of the population. It is observed in approximately 65% of full-term infants and 85% of preterm infants during the first week of life. (1). At normal levels or in cases of slight elevation, bilirubin is not harmful. On the other hand, unconjugated bilirubin levels exceeding 25 mg/dL are associated with an increased risk of kernicterus, or injury to the developing brain (2). Unconjugated bilirubin can pass across the blood-brain barrier, in contrast to conjugated bilirubin, which is lipid-insoluble and water-soluble (3). Exchange transfusions or phototherapy are used to treat severe hyperbilirubinemia in order to prevent kernicterus and acute bilirubin encephalopathy. The most frequent treatment for hyperbilirubinemia is phototherapy. The blue-green (460-490 nm) wavelength range is where bilirubin best absorbs light. It is either photo-isomerized and released in the bile or transformed into lumirubin, which is eliminated in the urine. Although phototherapy is a safe choice for treating hyperbilirubinemia, side effects include photo-retinitis, hypocalcemia, bronze baby syndrome, dehydration, burning of the skin, loose stools, and Hyperthermia might occur (4).

Hypocalcemia is a rare complication of phototherapy and is defined as a level of total serum calcium below 1.75 mmol/L (7 mg/dL) or ionized calcium <1 mmol/L (4 mg/dL) in preterm and in term neonates' serum calcium<2 mmol/L (8 mg/dL) or ionized calcium < 1.2 mmol/L(5). Hypocalcemia can cause lethargy poor feeding, jitteriness, irritability, and seizures. Neonates usually undergo a physiological nadir in serum calcium levels by 1st 2 days of life. This fall in serum calcium levels is caused by end-organ unresponsiveness to parathyroid hormone, hypoparathyroidism, hypercalcinaemia, abnormal vitamin D metabolism, hypomagnesemia, and hyperphosphatemia which occurs between 12 and 24 hours of age (6). On the third day, parathormone levels progressively increase and then return to normal serum calcium levels (7).

Phototherapy, according to Hawkinson and Hunter's theory, suppresses the pineal release of melatonin, inhibiting cortisol's role in calcium absorption in the bone. As a result, cortisol produces Hypocalcemia by increasing the absorption of calcium in the bone (8,9). However, study done by N. K. V. Vigneshwar et al reported no significant correlation between Phototherapy with serum melatonin levels (10).

There is not enough research on the frequency of phototherapy-induced hypocalcemia in neonates from India. Furthermore, no research has been done in Indian tertiary care institutions in india to far regarding the relationship between the birth weight of the infant and phototherapy-induced hypocalcemia. We intended to carry out this investigation since there is a lack of research on the prevalence of phototherapy-induced hypocalcemia and the relationship between the occurrence of this condition and the neonate's birth weight.

Methods

It was an observational study, conducted in the Neonatal intensive care unit (NICU) of BYL Nair Charitable Hospital and T.N. Medical College, Mumbai over a period of 12 months after obtaining permission from institutional ethics committee [ECARP/20/2020]. This study was performed on 100 neonates (>34 weeks of gestation age) with hyperbilirubinemia managed with phototherapy. Neonates suffering from birth asphyxia, congenital malformations, septicaemia, Infants of diabetic mothers and history of anticonvulsant intake, and hypocalcemia prior to phototherapy (<8 mg/dL) were excluded from the study. Informed consent was taken from the mother or legal guardian prior to enrolment. Once enrolled in the study, as is a standard operating procedure of the institution, blood sample was collected and the serum bilirubin, serum calcium and other routine parameters were noted. Phototherapy was administered as required till the serum bilirubin levels were reduced and the patient was fit for discharge from the NICU. All the neonates were clinically assessed for clinical features of

hypocalcemia i.e. jitteriness, irritability, lethargy, and convulsion as well as other complications such as loose stools, rash, fever, and dehydration during phototherapy . Post-phototherapy serum calcium levels noted to correspond with the last reading for serum calcium taken prior to discharge.
Statistical analysis: Data was analysed using SPSS software version 27. The effect of phototherapy on serum calcium levels was determined using Wilcoxon's test. The association between birth weight and phototherapy induced hypocalcemia was calculated using the odds ratio using a 2*2 contingency table.

Results

This study was done on 100 neonates. The gender distribution was equal. The majority of babies were born weighing between 2.6 and 3 kg, and the majority of them developed jaundice between the ages of 25 and 48 hours. The median serum calcium (mg/dL) level before phototherapy was 8.6 (8.49-8.61). After phototherapy, the median serum calcium (mg/dL) levels were reduced to 7.35 (7.33-7.50), which was significant ($p<0.001$).
Hypocalcemia was defined as a serum calcium level of 8 mg/dL, and the incidence of hypocalcemia in the study population was 16%.The proportion of male and female neonates who developed hypocalcemia was equal. Using the chi-square test, the values were found to be statistically insignificant for gender distribution. 60% of new-borns with hypocalcemia experienced mild symptoms like jitteriness or irritability; none experienced severe symptoms like apnoea, seizures and 40% remained asymptomatic despite having lower-than-normal serum calcium levels.
The Chi-squared test was used to determine whether there was any association between the duration of phototherapy and phototherapy-induced hypocalcemia. The prevalence of phototherapy-induced hypocalcemia in neonates was 14.47 % (1 day), 18.18% (2 days), and 50 % (3 days). No association was statistically significant ($p > 0.05$) between duration of phototherapy and phototherapy induced hypocalcemia.

Table 1. Prevalence of hypocalcemia with number of days of phototherapy

Days of phototherapy	Number of participants	Number with phototherapy induced hypocalcemia	Prevalence of phototherapy induced hypocalcemia (%)
1	76	11	14.47
2	22	4	18.18
3	2	1	50

The proportion of neonates with a birth weight < 2.5 kg who developed phototherapy-induced hypocalcemia was significantly higher than that of neonates with a higher birth weight. As a result, it appears that low birth weight is a significant risk factor for phototherapy-induced hypocalcemia.

Table 2. Effect of Birth Weight on Phototherapy Induced hypocalcemia

Birth weight	Number of participants	Number of participants with phototherapy induced hypocalcemia	Phototherapy induced hypocalcemia (%)
< 2.5kg	28	14	50
2.5-3.5 kg	70	2	2.85
> 3.5kg	2	0	0

Discussion

One of the most prevalent conditions in the first few days of life that affects both term and pre-term babies is jaundice. Unconjugated bilirubin's neurotoxicity causes several neurologic consequences. Thus, it becomes imperative to lower the bilirubin levels actively. The most popular method of treating hyperbilirubinemia is phototherapy. It has been suggested that the mechanism underlying phototherapy's hypocalcemia effect involves transcranial phototherapy-induced suppression of the pineal gland, which lowers melatonin release and hence reduces the impact of cortisol on calcium levels in the bone (8). Ernesto C et al. propose that cortisol increases the bone's absorption of calcium, which results in hypocalcemia (9).

In our study, no association was found between the gender of the baby and the risk of developing phototherapy-induced hypocalcemia. Similar findings were also noted in the study conducted by Manoj et al (11) in which they found the incidence of phototherapy-induced hypocalcemia was not affected by the newborn's sex.

Our study shows 16% (16/100) of neonates exhibited phototherapy-induced hypocalcemia. In the study by Jain et al. (12), it was found that 55% of preterm infants and 30% of neonatal infants developed hypocalcemia after phototherapy. Ehsan poor et al. (13) and Karamianet al. (14) reported the incidence of hypocalcemia to be 15% and 8.7% respectively. K.Pannerselvam (15) et al reported the incidence of hypocalcemia in term neonates to be 12.5%.

Jain et al (11) in their research, in preterm infants who were hypocalcemia, 63.6% had jitteriness, and 97.6% of them had irritability. Among the term neonates with Hypocalcemia, 50% of them had jitteriness and 16.7% of them had irritability, and since most infants were symptomatic newborns. Madhu Goyal (16) reported Jitteriness and irritability in 25% of the neonates. In our study, 60% of newborns with hypocalcemia experienced mild symptoms like jitteriness or irritation; none experienced severe symptoms like apnoea or seizures.

Sethi et al (17) found a higher prevalence of hypocalcemia after phototherapy in pre-term neonates as compared to term neonates. Jain et al. (11) noted phototherapy induced hypocalcemia in 55% of pre-term and 30% of full-term neonates, which was in comparison to our results. Various studies concluded that phototherapy-induced hypocalcemia can be a cause of serious concern in pre-terms, in whom the risk of physiological hypocalcemia is higher as compared to term neonates.

The incidence of hypocalcemia after phototherapy was more in LBW and preterm than in normal-weight and term neonates. The effect of gestational age could not be evaluated in our study as only 5% of the sample size consisted of preterm neonates. Thus, no statistically significant association was found between preterm neonates and their risk of developing phototherapy-induced hypocalcemia. However, the prevalence of phototherapy-induced hypocalcemia was 50% in the neonates with low birth weight and those with normal birth weight was only 2.85 %. Limitations of current study was low number of pre-term neonates, we were unable to study the relationship between gestational age and phototherapy-induced hypocalcemia.

Conclusion

According to this study, newborns with lower birth weights were more likely to develop phototherapy-induced hypocalcemia. Although statistically insignificant, the probability of hypocalcemia resulting from phototherapy increased as the number of phototherapy days increased. The hypocalcemia brought on by phototherapy did not appear to be related to other variables, such as gender. We conclude that the incidence of phototherapy-induced hypocalcemia is 16% among neonates with hyperbilirubinemia. Consequently, serum calcium levels should be routinely checked, and calcium supplementation should be taken into consideration as soon as low levels are detected.

Ethical Approval

Institutional Ethics Committee of TN Medical College; No: EC/NEW/INST/2023/136; dated: 26/02/2021

Consent to Participate

Not applicable

Consent to Publish

Not applicable

Authors Contributions

Dr. Mazhar Khan: Conceptualization, Methodology, Investigation, Writing - Original Draft.
Dr. Akash Sarkate: Writing – Review & Editing, Supervision.
Dr. Poonam Wade: Data Analysis, Visualization, Project Administration.
Dr. Sushma Malik: Writing – Review & Editing.

Funding source

None

Competing Interests

None

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Human Ethics

Approved by the Institutional Ethics Committee. [ECARP/20/2020].

Clinical Trial Number

Not applicable

Conflict Of Interest

None

Acknowledgement

None

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