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Association Between Serum Calcium and Unconjugated Hyperbilirubinemia in Neonates Receiving Phototherapy: A Prevalence Study

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Abstract

Introduction and Objectives- *Neonatal hyperbilirubinemia is a frequent condition observed in the first week of life, affecting up to 80% of newborns. It presents as jaundice due to elevated levels of bilirubin, often resulting from the immature liver's inability to process the rapid breakdown of red blood cells. To assess the impact of phototherapy on serum calcium levels in term and preterm neonates with unconjugated hyperbilirubinemia.*

Materials and Methods- *This hospital-based, observational cross-sectional study was conducted over 12 months in the Neonatal Intensive Care Unit (NICU), Department of Paediatrics. A total of 107 neonates—both term and late preterm—requiring phototherapy for unconjugated hyperbilirubinemia, were enrolled using purposive sampling. Eligible neonates were otherwise healthy, and those with conditions like sepsis, congenital anomalies, or prior hypocalcemia were excluded to minimize confounding factors. Blood samples were collected before and after phototherapy to assess total and ionized calcium levels. Serum bilirubin was measured using the Diazo method, while calcium levels were analyzed using the Arsenazo III method and ion-selective electrode technology. Data were statistically analyzed using SPSS ver.27, with significance set at $p<0.05$.*

Results- *Among the 107 neonates receiving phototherapy for unconjugated hyperbilirubinemia, 54.2% were preterm and 45.8% were term. Hypocalcemia was observed in 78 neonates (72.9%), with a significantly higher prevalence in preterm infants (64.2%) compared to term infants (35.8%). A significant association was found between the duration of phototherapy and serum calcium levels; 91.1% of hypocalcemic neonates had received phototherapy for more than 24 hours ($p=0.004$). Double surface phototherapy was used in 68.3% of cases, and 57% of neonates required treatment beyond 24 hours.*

Conclusion- *Phototherapy is a cornerstone in the treatment of neonatal jaundice, but its association with hypocalcemia—particularly in preterm infants and with extended exposure—highlights the need for routine calcium monitoring. Early identification and management of hypocalcemia are crucial to prevent adverse outcomes. Clinical protocols should consider baseline calcium screening and follow-up in neonates undergoing prolonged or intensive phototherapy to enhance safety and improve overall neonatal care outcomes.*

Keywords: *Neonatal hyperbilirubinemia, phototherapy, hypocalcemia, serum calcium, preterm neonates, term neonates, bilirubin, double surface phototherapy.*

INTRODUCTION

Neonatal hyperbilirubinemia is a common condition encountered during the early stages of a newborn's life, particularly within the first week. Around 8% to 11% of neonates experience hyperbilirubinemia, which is defined as a total serum bilirubin (TSB) level above the 95th percentile for the infant's age, falling into the high-risk zone during the first week of life.[1]

Approximately 60%-80% of healthy infants will experience idiopathic neonatal jaundice, which causes a yellowish discoloration of the skin and sclera due to elevated bilirubin levels. This condition can cause concern for healthcare providers and anxiety for parents. According to the National Neonatal-Perinatal Database (NNPD), the incidence of neonatal hyperbilirubinemia in live births within hospitals is 3.3%, while in extramural admissions, it accounts for 22.1% of morbidity.[2]

In neonates, jaundice typically begins in the face, and as bilirubin levels rise, it spreads to the body and limbs. This condition is observed in 50%-60% of newborns during the first week. [3]

Jaundice is usually seen due to the physiological immaturity of neonates and their inability to handle increased bilirubin production during the neonatal period. The pathophysiology of jaundice remains the same in both term and pre-term neonates. However, there is a higher risk of hyperbilirubinemia in the preterm. [4]

Neonatal jaundice is characterized by a yellow discoloration of the skin, sclera, and other tissues, resulting from elevated levels of bilirubin in the bloodstream—a condition known as hyperbilirubinemia. Clinically, jaundice

becomes visible when serum bilirubin levels exceed 2 mg/dL (34.2 µmol/L). This condition is highly prevalent, affecting approximately 60% of term infants and up to 80% of preterm infants within the first week of life. Additionally, around 10% of exclusively breastfed infants may exhibit jaundice that persists for up to four weeks [5]. Around 5% to 10% of newborns with jaundice will require management for hyperbilirubinemia. Several factors, such as birth weight, gestational age, premature rupture of membranes, maternal infections or other pregnancy-related conditions, can contribute to the development of jaundice [6,7]. These various factors can lead to different types and sources of hyperbilirubinemia in neonates.

Hypocalcemia is defined as total serum calcium concentration of < 7 mg/dl (1.75 mmol/L) in preterm and serum calcium < 8 mg/dl (2 mmol/L) in term neonates. It can cause serious complications like neuromuscular irritability; myoclonic jerks, jitteriness, convulsion, cyanosis, apnea and laryngospasm. Thus, phototherapy-induced hypocalcemia can be a serious problem in neonates.

This gap in the literature underscores the need for more focused investigations to better understand how phototherapy affects calcium regulation in neonates, especially among high-risk groups like premature infants.Hence, our study aims to determine the association between serum calcium levels and unconjugated hyperbilirubinemia in neonates on phototherapy.

MATERIALS AND METHODS

This study was a hospital-based, observational cross-sectional study conducted over a period of 12 months in the Neonatal Intensive Care Unit (NICU) under the Department of Paediatrics NICU, neonatal division of department of paediatrics. The study population included healthy neonates, both preterm and term, who presented with hyperbilirubinaemia and required phototherapy as per the American Academy of Pediatrics (AAP) guidelines. Purposive sampling

SAMPLE SIZE CALCULATION: calculated based on the prevalence data from an earlier study using mean and standard deviation

$N= (Z\alpha\text{-}1/2)^2\sigma^2 \div e^2$

$Za - \frac{1}{2}$ =two tail probability of 95% confidence interval=1.96

σ(%)-prevalence =31.7%

e (%) = margin of error= 6% n=107

The minimum required sample size for the study is 107.

Inclusion Criteria

Neonates were included in the study if they were either late preterm (34 weeks to 36 weeks + 6 days) or term (37 weeks to 40 weeks) and otherwise healthy but presented with hyperbilirubinaemia without any other risk factors requiring phototherapy.

Exclusion Criteria

The following conditions were set as exclusion criteria:

- Birth asphyxia
- Septicaemia
- Cephalohematoma
- Congenital malformations
- Infants of diabetic mothers
- Hemolytic anaemia
- Neonates requiring exchange transfusion
- Neonatal hypocalcaemia

These conditions were excluded to minimize confounding factors that could independently affect serum calcium or bilirubin levels.

Data Collection Procedure

Informed written consent was obtained from the parents or legal guardians of all participating neonates. A semi-structured questionnaire (proforma) was used to collect relevant demographic and clinical data, including birth

history, anthropometric measurements, duration of phototherapy, and parental education status. Venous blood samples were routinely drawn before the initiation of phototherapy to assess serum bilirubin and calcium levels. A second sample was collected 24 hours after cessation of phototherapy to reassess serum calcium. Serum ionised calcium levels below 4.8 mg/dL and serum total calcium levels below 7 mg/dL were considered abnormal and indicative of hypocalcaemia.

Biochemical Analysis

- Bilirubin Measurement: Total and direct serum bilirubin were measured using the Diazo method. In this technique, bilirubin reacts with diazotized sulfanilic acid to produce purple azobilirubins, which were measured colorimetrically. An accelerator such as methanol was used to quantify unconjugated bilirubin.
  - *Reagents used:* Methanol diazo reagent, diazo blank, bilirubin standard.
- Calcium Measurement: *Total calcium* was measured using the Arsenazo III method (enzymatic endpoint spectrometry) on a BS 480 chemistry analyzer. *Ionised calcium* was measured using ion-selective electrode technology on the AB6 blood gas analyzer.

Data Management and Statistical Analysis

Data were entered and managed by the principal investigator. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 27. Categorical variables such as sex, gestational age, and feeding method were expressed as frequency and percentage. Continuous variables including serum calcium and bilirubin levels were described using mean ± standard deviation (SD). Associations between categorical variables were evaluated using the Chi-square test, while comparisons of means were made using the independent sample t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Age Distribution Among the Babies

Age	Frequency	Percentage
Term	49	45.8
Pre-term	58	54.2
Total	107	100.0

Table 1 present the distribution of neonates based on gestational age. Out of the total 107 neonates included in the study, 54.2% (58) were born preterm, while 45.8% (49) were term babies. the gender distribution among term and preterm neonates. Among the 49 term neonates, 57.1% (28) were male and 42.9% (21) were female. Similarly, of the 58 preterm neonates, 62% (36) were male and 38% (22) were female.

Table 2: Risk Factors Among the Mothers

Risk factors		Frequency N =107 (%)
Family H/o Jaundice	Yes	28 (26.2)
	No	79 (73.8)
ABO Incompatibility	Yes	61 (19.6)
	No	46 (80.4)
Rh Incompatibility	Yes	16 (14.9)
	No	91 (85.1)

Table 2 shows the distribution of maternal risk factors among the 107 mothers. A family history of jaundice was

reported in 28 (26.2%) cases, while the majority, 79 (73.8%), had no such history. ABO incompatibility was present in 61 (19.6%) of the cases, whereas 46 (80.4%) did not show ABO incompatibility. Rh incompatibility was observed in 16 (14.9%) mothers, and 91 (85.1%) did not have Rh incompatibility.

Table 3: Duration of Phototherapy Among the Babies

Duration of phototherapy	**Frequency** **N=107**	**Percentage** (%)
≤24 hours	46	15
>24 hours	61	85

Table 3 illustrates the distribution of neonates based on the duration of phototherapy. Out of 107 neonates, 57% (61 neonates) underwent phototherapy for more than 24 hours, whereas 43% (46 neonates) received phototherapy for less than 24 hours. the distribution of neonates based on the type of phototherapy administered. Among the 107 neonates, 68.3% (73) received double surface phototherapy, while 31.7% (34) were treated with single surface phototherapy.

Table 4: Distribution of Hypocalcemia Among the Babies

Term status	**Mild Hypocalcemia N=60** (%)	**Severe Hypocalcemia N=18** (%)
Term	26 (43.3)	8 (44.4)
Pre-term	34 (56.7)	10 (55.6)

Table 4 shows the distribution of mild and severe hypocalcemia among term and preterm babies. Out of the 60 babies with mild hypocalcemia, the majority were preterm (56.7%), while 43.3% were term. For the 18 babies with severe hypocalcemia, a similar distribution was observed, with 55.6% being preterm and 44.4% being term.

Table 5: Association Between Duration of Phototherapy and S.Calcium

Duration of phototherapy	**Hypocalcemia N=78** (%)	**Normocalcemia N=29** (%)	**Chi- square**	**P value**
≤24 hours	7 (8.9)	9 (31)	8.26	0.004*
>24 hours	72 (91.1)	20 (69)		

P value <0.05-statistically significant

Table 5 examines the association between the duration of phototherapy and the occurrence of hypocalcemia or normocalcemia in babies. The results show that among babies who received phototherapy for less than 24 hours, 8.9% had hypocalcemia, while 31% had normocalcemia. However, among those who received phototherapy for more than 24 hours, 91.1% had hypocalcemia, and 69% had normocalcemia. The Chi-square value of 8.26 and a P-value of 0.004 indicate a statistically significant relationship, suggesting that a longer duration of

phototherapy is associated with a higher likelihood of hypocalcemia in neonates.

DISCUSSION

Our study observed that among the neonates undergoing phototherapy for unconjugated hyperbilirubinemia, 45.8% were term and 54.2% were preterm, highlighting the common occurrence of this condition across both groups. These findings align with several previous studies that have reported a notable association between phototherapy and decreased serum calcium levels in neonates. For example, Kale et al. (2020) demonstrated a significant drop in mean serum calcium levels post-phototherapy, while Goyal et al. (2018) found that 35% of neonates developed hypocalcemia after treatment. Similarly, Javaid et al. (2021) reported that 41.58% of neonates exhibited hypocalcemia following phototherapy. [8,9,10] These consistent findings across studies suggest that phototherapy, though essential in managing neonatal jaundice, may contribute to altered calcium homeostasis. The exact mechanisms remain unclear but may involve increased urinary calcium loss, altered hormonal regulation, and direct effects of light on calcium metabolism. Our study further supports the notion that monitoring serum calcium levels during phototherapy is crucial, particularly in preterm infants or those receiving extended treatment durations, to prevent potential complications related to hypocalcemia.

Our study observed that among neonates undergoing phototherapy for unconjugated hyperbilirubinemia, 45.8% were term and 54.2% were preterm. In terms of gender distribution, 57.1% of term and 62% of preterm neonates were male, while females comprised 42.9% and 38% respectively. This male predominance aligns with findings from several Indian studies. For example, Sharma et al. reported that 56.2% of neonates with hyperbilirubinemia were male. Similarly, Reddy et al. observed a higher incidence of jaundice among male neonates. Another study by Gupta et al. also found that 61.65% of affected neonates were male. These consistent findings support the hypothesis that male
neonates are at greater risk for developing hyperbilirubinemia, possibly due to inherent biological differences in bilirubin metabolism, and highlight the importance of close monitoring in this group.[11,12,13]

In our study, we examined maternal risk factors associated with neonatal hyperbilirubinemia among 107 cases. A family history of jaundice was present in 28 cases (26.2%), suggesting a potential genetic or hereditary predisposition to altered bilirubin metabolism or increased hemolysis. ABO incompatibility was identified in 61 neonates (57%), while Rh incompatibility was observed in 16 cases (14.9%). These findings highlight the significance of immunological and hereditary factors in the pathogenesis of unconjugated hyperbilirubinemia requiring phototherapy. In our study, among the 107 neonates treated with phototherapy for unconjugated hyperbilirubinemia, the majority—61 infants (57%)—required phototherapy for more than 24 hours, while 46 neonates (43%) received phototherapy for less than 24 hours. This distribution suggests that a considerable proportion of neonates need extended phototherapy to effectively reduce elevated bilirubin levels. Similar findings have been observed in other Indian studies. For example, Mishra et al. reported that neonates with higher baseline bilirubin levels or underlying risk factors such as prematurity and hemolytic diseases often required phototherapy for longer durations. Singh et al. similarly found that delayed initiation of treatment and suboptimal feeding practices were associated with the need for prolonged phototherapy[14,15]. In our study, the majority of neonates (68.3%) received double surface phototherapy, while 31.7% underwent single surface phototherapy. This indicates that double surface phototherapy, which involves exposure to light from both the front and back of the neonate, is more commonly used to effectively reduce bilirubin levels. Similar findings have been reported in Indian studies. For example, Gupta et al. found that double surface phototherapy was more effective in managing severe hyperbilirubinemia, especially in neonates with high bilirubin levels or risk factors such as prematurity. In our study, the distribution of hypocalcemia severity among neonates undergoing phototherapy showed that 60 neonates (56.7%) with mild hypocalcemia were preterm, while 43.3% were term. Regarding severe hypocalcemia, 55.6% of affected neonates were preterm, and 44.4% were term. These results suggest that while both term and preterm neonates are at risk of developing hypocalcemia, preterm infants are more likely to experience both mild and severe forms of hypocalcemia during phototherapy. Similar trends have been observed in Indian studies. For example, a study by Sethi et al. found a higher prevalence of severe hypocalcemia in preterm neonates, likely due to their immature calcium metabolism and renal handling of calcium. Additionally, another study by Gupta et al. reported that preterm infants were more vulnerable to developing both mild and severe hypocalcemia during phototherapy, possibly exacerbated by the prolonged duration of light exposure. These findings emphasize the importance of closely monitoring calcium levels in preterm neonates, particularly those undergoing extended phototherapy, to mitigate the risks associated with hypocalcemia[16,17]. In our study, the association between the duration of phototherapy

and serum calcium levels revealed a significant relationship. Among the 78 neonates with hypocalcemia, 91.1% received phototherapy for more than 24 hours, while only 8.9% had phototherapy for less than 24 hours. In contrast, among the 29 neonates with normocalcemia, 69% were treated for more than 24 hours, and 31% received phototherapy for less than 24 hours. The chi-square value of 8.26 and a p-value of 0.004 indicate that the duration of phototherapy is significantly associated with the development of hypocalcemia.

One of the strengths of this study is the comprehensive examination of various factors, including gestational age, birth order, and maternal history, that may influence the development of hypocalcemia in neonates undergoing phototherapy. The significant association between phototherapy duration and calcium levels provides valuable insights into clinical management practices. Additionally, the inclusion of both term and preterm neonates enhances the study's applicability to a wider population, allowing for a better understanding of the unique needs of these groups. A limitation of the study is its observational nature, which may not allow for a definitive cause-and-effect relationship between phototherapy duration and hypocalcemia. Furthermore, the study focused on a specific cohort from a particular healthcare setting, which may limit the generalizability of the findings to broader populations.

CONCLUSION

In conclusion, the study demonstrates a significant association between prolonged phototherapy and the development of hypocalcemia, especially in preterm neonates. Monitoring serum calcium levels is crucial, particularly in those undergoing extended phototherapy or with additional risk factors, to prevent complications associated with calcium imbalances.The study contributes to the evidence supporting the effects of phototherapy on the calcium levels of newborns, suggesting the need to improve neonatal care, alleviating the healthcare burdens, there is a need for further investigation on long-term effects of phototherapy associated hypocalcaemia and to examine its scale in various demographic setting especially in southern India to further cement the findings.

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