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Original Research Article

Incidence and Clinical Correlation of Phototherapy-Induced Hypocalcemia in Neonates with Hyperbilirubinemia: A Retrospective Study

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Abstract:

Background: Neonatal hyperbilirubinemia is one of the most common conditions requiring hospital admission and phototherapy. While phototherapy effectively reduces bilirubin levels, it may lead to adverse metabolic complications such as hypocalcemia. The frequency and correlation of this complication with the duration of phototherapy need systematic evaluation.

Objectives: To determine the incidence of hypocalcemia among neonates receiving phototherapy for hyperbilirubinemia and to assess its correlation with the duration of phototherapy.

Methods: A Retrospective study was conducted at the Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India, over a period of one year (January 2023 to December 2023). A total of 120 neonates requiring phototherapy for neonatal hyperbilirubinemia were enrolled. Serum calcium levels were measured before initiation of phototherapy and then at 24-hour intervals until discontinuation of therapy. Clinical manifestations of hypocalcemia such as jitteriness, irritability, apnea, and seizures were carefully recorded. Statistical correlation between duration of phototherapy and development of hypocalcemia was analyzed.

Results: Out of 120 neonates, 38 (31.7%) developed hypocalcemia during the course of phototherapy. The incidence was significantly higher after 48 hours of continuous phototherapy ($p < 0.05$). Clinical features were noted in 15 neonates, ranging from mild irritability to seizures. A statistically significant negative correlation was observed between duration of phototherapy and serum calcium levels.

Conclusion: Hypocalcemia is a noteworthy complication of phototherapy in neonates with hyperbilirubinemia, particularly with therapy beyond 48 hours. Routine monitoring of serum calcium and early correction may be beneficial in preventing adverse clinical outcomes.

Keywords: Neonatal hyperbilirubinemia, phototherapy, hypocalcemia, neonatal calcium metabolism, phototherapy duration

Introduction

Neonatal hyperbilirubinemia is a frequently encountered clinical condition, affecting nearly 60% of term and 80% of preterm neonates during the first week of life. It is one of the most common causes of neonatal hospital admissions, particularly in developing countries [1]. Phototherapy remains the mainstay of treatment for significant hyperbilirubinemia, as it is effective, non-invasive, and relatively safe compared to exchange transfusion. The use of phototherapy has considerably reduced bilirubin-induced neurologic dysfunction, including acute bilirubin encephalopathy and kernicterus [2].

However, despite its widespread use, phototherapy is not without adverse effects. Documented complications include dehydration, diarrhea, hyperthermia, hypothermia, retinal injury, bronze baby syndrome, and electrolyte disturbances. Among these, hypocalcemia has been increasingly recognized as a potential and clinically relevant side effect. The exact mechanism of phototherapy-induced hypocalcemia is not fully understood, but proposed hypotheses include suppression of melatonin secretion from the pineal gland and increased release of calcitonin, leading to decreased serum calcium levels [3].

The reported incidence of hypocalcemia following phototherapy varies widely in the literature, ranging

from 7% to over 30%, depending on study population, duration of phototherapy, and diagnostic criteria for hypocalcemia. Clinically, hypocalcemia in neonates can present with subtle manifestations such as jitteriness, irritability, and poor feeding, or with severe complications including apnea and seizures. These outcomes underscore the importance of early detection and management [4].

Despite its clinical relevance, there remains a paucity of data on the incidence and correlation of hypocalcemia with phototherapy duration in Indian neonatal populations. Identifying the relationship between duration of phototherapy and development of hypocalcemia is essential to guide preventive strategies, including the consideration of routine calcium monitoring or prophylactic supplementation in high-risk neonates [5].

The present study was conducted with the objective of assessing the incidence of phototherapy-induced hypocalcemia in neonates with hyperbilirubinemia and analyzing its correlation with the duration of phototherapy, in a tertiary care teaching hospital in Bihar, India.

Materials and Methods

A retrospective study conducted in the Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India. The study duration was one year, from January 2023 to December 2023.

Study Population: All neonates admitted to the neonatal intensive care unit (NICU) or postnatal wards with a diagnosis of neonatal hyperbilirubinemia requiring phototherapy were considered for inclusion.

Inclusion Criteria:

- Neonates with hyperbilirubinemia requiring phototherapy as per the American Academy of Pediatrics (AAP) guidelines.
- Both term and preterm neonates up to 28 days of life.
- Written informed consent obtained from parents/guardians.

Exclusion Criteria:

- Neonates with congenital anomalies or metabolic bone diseases.
- Neonates already receiving calcium supplementation for other indications.
- Neonates with perinatal asphyxia, sepsis, or hypoxic-ischemic encephalopathy (as these conditions can independently affect calcium levels).

Sample Size: A total of 120 neonates fulfilling the eligibility criteria were enrolled consecutively during the study period.

Data Collection: Baseline demographic and clinical data were recorded, including gestational age, birth weight, sex, mode of delivery, and feeding history. Serum bilirubin and serum calcium levels were measured at admission before starting phototherapy.

Intervention (Phototherapy Protocol):

- All neonates received standard phototherapy using blue fluorescent lamps or LED phototherapy units, with the intensity maintained at 8–12 μW/cm²/nm at a distance of 30–40 cm.
- The duration of phototherapy was determined by serial bilirubin monitoring, and the therapy was discontinued once serum bilirubin reached safe levels according to AAP guidelines.

Monitoring of Serum Calcium:

- Serum total calcium levels were measured at baseline (before phototherapy) and at 24-hour intervals during phototherapy until discontinuation.
- Hypocalcemia was defined as:
    - Total serum calcium < 7 mg/dL in term neonates.
    - Total serum calcium < 7.5 mg/dL in preterm neonates.

Clinical Monitoring:

All neonates were closely monitored for signs of hypocalcemia, including jitteriness, irritability, apnea, laryngospasm, and seizures. Any clinical manifestations were promptly documented and managed according to standard NICU protocols.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 25. Descriptive statistics were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. The incidence of hypocalcemia was calculated, and the correlation between duration of phototherapy and serum calcium levels was assessed using Pearson's correlation coefficient. A p-value of <0.05 was considered statistically significant.

Results

A total of 120 neonates with hyperbilirubinemia requiring phototherapy were included. Among them, 68 (56.7%) were males and 52 (43.3%) were females. The mean gestational age was 37.2 ± 2.1 weeks, and the mean birth weight was 2.65 ± 0.48 kg. Term neonates constituted 72.5% of the cohort, and preterm neonates 27.5%. Phototherapy duration ranged from 24 hours to 96 hours.

Overall, 38 neonates (31.7%) developed hypocalcemia during phototherapy. Of these, 15 neonates (12.5%) exhibited clinical features such as jitteriness, irritability, apnea, or seizures. Hypocalcemia incidence was positively correlated with the duration of phototherapy, with significantly higher occurrence after 48 hours.

Table 1: Baseline Demographic Profile of the Study Population

Parameter	Value (n = 120)
Male : Female ratio	68 : 52 (1.3 : 1)
Mean gestational age (weeks)	37.2 ± 2.1
Term neonates (%)	87 (72.5%)
Preterm neonates (%)	33 (27.5%)
Mean birth weight (kg)	2.65 ± 0.48

Table 2: Mode of Delivery and Feeding Pattern

Parameter	n (%)
Vaginal delivery	78 (65.0%)
Cesarean section	42 (35.0%)
Exclusively breastfed	97 (80.8%)
Mixed feeding	23 (19.2%)

Table 3: Distribution of Neonates by Serum Bilirubin Levels at Admission

Serum Bilirubin Level (mg/dL)	Number of Neonates (n)	Percentage (%)
10 – 14	41	34.2%
15 – 18	46	38.3%
19 – 22	23	19.2%
> 22	10	8.3%

Table 4: Duration of Phototherapy Received by Neonates

Duration of Phototherapy	Number of Neonates (n)	Percentage (%)
≤ 24 hours	34	28.3%
25 – 48 hours	41	34.2%
49 – 72 hours	28	23.3%
> 72 hours	17	14.2%

Table 5: Incidence of Hypocalcemia During Phototherapy

Variable	n (%) of neonates
Developed hypocalcemia	38 (31.7%)
No hypocalcemia	82 (68.3%)

Table 6: Clinical Manifestations of Hypocalcemia

Symptom	n (%) of affected neonates (n=38)
Jitteriness	9 (23.7%)
Irritability	6 (15.8%)
Apnea	2 (5.3%)
Seizures	3 (7.9%)
Asymptomatic	18 (47.3%)

Table 7: Correlation of Duration of Phototherapy with Incidence of Hypocalcemia

Duration of Phototherapy	Total Neonates (n)	Hypocalcemia cases (n)	Percentage (%)
≤ 24 hours	34	4	11.8%
25 – 48 hours	41	9	22.0%
49 – 72 hours	28	13	46.4%
> 72 hours	17	12	70.6%

Table 8: Mean Serum Calcium Levels Before and After Phototherapy

Phototherapy Duration	Mean Serum Calcium Before (mg/dL)	Mean Serum Calcium After (mg/dL)	p-value
≤ 24 hours	8.9 ± 0.6	8.4 ± 0.5	0.08 (NS)
25 – 48 hours	8.8 ± 0.7	8.1 ± 0.5	<0.05
49 – 72 hours	8.7 ± 0.6	7.6 ± 0.6	<0.01
> 72 hours	8.6 ± 0.5	7.1 ± 0.4	<0.001

Table 9: Comparison of Hypocalcemia Incidence in Term vs Preterm Neonates

Group	Total (n)	Hypocalcemia cases (n)	Percentage (%)
Term neonates	87	22	25.3%

Preterm neonates	33	16	48.5%

Table 10: Logistic Regression Analysis of Risk Factors for Hypocalcemia

Risk Factor	Odds Ratio (OR)	95% CI	p-value
Preterm status	2.14	1.09 – 4.22	0.03
Duration > 48 hrs	3.65	1.72 – 7.76	<0.01
Birth weight < 2.5 kg	1.48	0.71 – 3.08	0.28
Serum bilirubin > 18 mg/dL	1.32	0.62 – 2.81	0.41

In this one-year prospective observational study of 120 neonates, the baseline demographic distribution showed a slight male predominance with a male-to-female ratio of 1.3:1, a mean gestational age of 37.2 ± 2.1 weeks, and mean birth weight of 2.65 ± 0.48 kg (Table 1). Most neonates were delivered vaginally (65%) and were predominantly breastfed (80.8%), while 19.2% were on mixed feeding (Table 2). At admission, the majority presented with serum bilirubin levels between 15–18 mg/dL (38.3%), followed by 10–14 mg/dL (34.2%) (Table 3). Phototherapy duration varied: 28.3% required ≤24 hours, 34.2% required 25–48 hours, 23.3% needed 49–72 hours, and 14.2% required >72 hours of therapy (Table 4). Overall, 38 neonates (31.7%) developed hypocalcemia during phototherapy (Table 5). Clinical evaluation revealed that nearly half of these neonates remained asymptomatic, while others exhibited jitteriness (23.7%), irritability (15.8%), apnea (5.3%), and seizures (7.9%) (Table 6). The incidence of hypocalcemia rose progressively with phototherapy duration, from 11.8% at ≤24 hours to 70.6% after >72 hours (Table 7). Mean serum calcium levels also demonstrated a statistically significant decline beyond 48 hours of phototherapy, dropping from baseline 8.7–8.9 mg/dL to as low as 7.1 ± 0.4 mg/dL after >72 hours (Table 8). A subgroup analysis showed that preterm neonates had a higher incidence (48.5%) of hypocalcemia compared to term neonates (25.3%) (Table 9). Finally, logistic regression analysis identified prolonged phototherapy (>48 hours) and preterm status as independent predictors of hypocalcemia, while birth weight and bilirubin levels did not show statistically significant associations (Table 10).

Discussion

The present study demonstrated that 31.7% of neonates undergoing phototherapy for hyperbilirubinemia developed hypocalcemia, with 12.5% exhibiting clinical manifestations such as jitteriness, irritability, apnea, or seizures [6]. The findings highlight that hypocalcemia is not merely a biochemical abnormality but may carry significant clinical consequences, especially when phototherapy is prolonged or when neonates are preterm [7].

Our results are consistent with previous reports indicating that the incidence of phototherapy-induced hypocalcemia ranges from 20% to 35%. Studies by Jain et al. (India, 2016) and Sethi et al. (Nepal, 2019) reported incidences of 28% and 32%, respectively, similar to our findings. However, lower incidences (7–12%) have been noted in studies from developed countries, likely due to differences in baseline neonatal health status, feeding practices, and use of modern LED-based phototherapy units with narrower wavelength emissions [8].

The pathophysiology of phototherapy-induced hypocalcemia is complex and not fully understood. One widely accepted mechanism is that phototherapy suppresses melatonin secretion by the pineal gland, thereby disrupting calcium homeostasis. Another proposed mechanism is increased secretion of calcitonin, which promotes calcium deposition into bone, reducing circulating calcium levels. In addition, prolonged light exposure may alter parathyroid function and reduce maternal-neonatal calcium transfer, particularly in preterm neonates [9].

Duration of phototherapy emerged as a significant risk factor in this study, with hypocalcemia incidence rising from 11.8% at ≤24 hours to 70.6% after >72 hours. This strongly supports the hypothesis that prolonged exposure increases risk through cumulative hormonal suppression and metabolic disturbances. Similar trends have been documented by Karamifar et al. (Iran, 2011), who found that hypocalcemia incidence was significantly higher after 48 hours of therapy. Our findings reinforce the recommendation that calcium monitoring should be prioritized when therapy extends beyond 48 hours [10].

Gestational maturity was another key determinant. Hypocalcemia incidence was 48.5% among preterm neonates, significantly higher than the 25.3% seen in term neonates. Preterm neonates are inherently vulnerable due to immature calcium regulatory mechanisms, reduced calcium stores, and inadequate intestinal absorption. These factors, when combined with phototherapy-induced changes, amplify the risk. Logistic regression in our study confirmed preterm status as an independent predictor of hypocalcemia, consistent with observations from Sharma et al. (India, 2018), who also identified prematurity as a major risk factor [11].

Interestingly, birth weight and initial serum bilirubin levels were not significant predictors in our study. While some researchers have suggested that low birth weight may predispose neonates to electrolyte imbalances, our findings indicate that phototherapy

duration and gestational age are more decisive factors. This aligns with conclusions from studies in other South Asian neonatal populations [12].

From a clinical perspective, nearly half of hypocalcemic neonates remained asymptomatic, underscoring the importance of biochemical monitoring rather than relying solely on clinical manifestations. However, in symptomatic cases, seizures and apnea were noted, which could potentially result in life-threatening complications if left untreated. This calls for a preventive strategy in at-risk neonates, either through routine calcium monitoring or selective prophylactic supplementation.

The implications of these findings are significant in low-resource settings where prolonged phototherapy is common, and routine calcium monitoring may not always be feasible. Incorporating simple preventive measures, such as timely calcium supplementation in preterm neonates undergoing prolonged phototherapy, may help avert serious complications.

Limitations: The study was single-centered and limited to 120 neonates, which restricts generalizability. Ionized calcium, a more accurate measure of calcium status, was not evaluated due to logistic constraints. Long-term follow-up was not conducted to assess developmental outcomes of neonates who experienced hypocalcemia.

Strengths: This study adds to the limited Indian data on phototherapy-induced hypocalcemia, providing robust evidence of the correlation with therapy duration and gestational age. The use of serial biochemical monitoring alongside clinical evaluation strengthens the validity of our findings.

Conclusion

This study demonstrates that phototherapy-induced hypocalcemia is a significant complication in neonates treated for hyperbilirubinemia, with an overall incidence of 31.7% and a higher risk in preterm infants and those undergoing therapy beyond 48 hours. While nearly half of the affected neonates were asymptomatic, others presented with clinically important manifestations such as jitteriness, irritability, and seizures. Prolonged phototherapy and prematurity were identified as independent predictors, underscoring the importance of routine serum calcium monitoring during extended phototherapy and consideration of prophylactic supplementation in high-risk neonates to prevent adverse outcomes.

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