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Frequency of Phototherapy-Induced Hypocalcemia in Neonates with Unconjugated Hyperbilirubinemia

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ABSTRACT

Background: Phototherapy remains the cornerstone in the management of neonatal unconjugated hyperbilirubinemia. While effective and widely used, it is not devoid of adverse effects. **Objective:** To determine the frequency of hypocalcemia in full-term neonates receiving phototherapy for unconjugated hyperbilirubinemia and to evaluate its clinical manifestations and associated factors. **Methods:** This prospective observational study was conducted at the Department of Pediatrics, Chaudhary Muhammad Akram Teaching and Research Hospital, Lahore from 12-6-24 to 12-12-24. A total of 125 full-term neonates requiring phototherapy were enrolled using non-probability consecutive sampling. Neonates with perinatal asphyxia, prior hypocalcemia, suspected hemolysis, or maternal diabetes were excluded. Phototherapy was administered according to AAP 2022 guidelines using narrow-spectrum LED blue light. Serum total calcium and bilirubin levels were measured pre-treatment and two hours post-therapy. **Results:** Out of 125 neonates, 32 (25.6%) developed hypocalcemia after phototherapy. Among these, 12 neonates (37.5%) were symptomatic, presenting with jitteriness (n=6), apnea (n=3), and irritability (n=3). The mean pre- and post-phototherapy calcium levels were 9.42 ± 0.58 mg/dL and 8.12 ± 0.76 mg/dL, respectively. A significant association was found between hypocalcemia and phototherapy duration >24 hours ($p = 0.018$). **Conclusion:** Phototherapy-induced hypocalcemia is a common and clinically relevant complication in term neonates treated for unconjugated hyperbilirubinemia. Routine post-therapy calcium monitoring, especially in those undergoing extended phototherapy, is strongly recommended to detect and manage this preventable adverse outcome.

INTRODUCTION

Hyperbilirubinemia stands out as a prevalent concern in neonatal units, often manifesting as neonatal jaundice during the initial stages of a newborn's life. This issue affects both preterm and term infants, with approximately 80% and 60% experiencing jaundice within their first week of life, respectively [1]. The primary therapeutic approach for neonatal hyperbilirubinemia is phototherapy, a standard treatment that has been pivotal in saving lives and preventing disabilities since its introduction in 1957 [2]. It lowers serum bilirubin level by converting bilirubin through structural photoisomerization and photo-oxidation into nontoxic form that is excreted out of the body [3]. In severe cases, it may be complemented with immunoglobulin treatment and exchange transfusion. Neonatal jaundice, characterized by elevated levels of unconjugated bilirubin, is one of the most common clinical conditions encountered in the first week of life. It affects approximately 60% of term and 80% of preterm neonates, and although often physiological, it may require intervention to prevent bilirubin-induced neurological damage such as kernicterus. Among the various treatment options, phototherapy remains the gold standard for managing unconjugated hyperbilirubinemia due to its safety, efficacy, and non-invasive nature [4].

While phototherapy has proven effective, its application is not without consequences. Adverse effects, including insensible water loss, watery diarrhea leading to increased fecal water loss, dehydration, retinal damage, bronze baby syndrome, and the potential opening of the patent ductus arteriosus (PDA) in low-birth-weight (LBW) infants, have been observed. A thorough understanding of these adverse effects enables proactive measures to mitigate them and optimize the efficacy of this treatment modality. Hypocalcemia as a consequence of phototherapy was first noted by Romagnoli in 1979 [5]. The reported prevalence of hypocalcemia in term babies receiving phototherapy has a wide range (3-75%) [6]. Studies have reported symptomatic hypocalcemia with signs including hypotonia, tachycardia, tachypnea, apnea, poor feeding, jitteriness, tetany, and seizures [7]. In a recent study by

Panneerselvam [8] in 2022, the reduction in serum total calcium level after phototherapy was statistically significant (p<0.001) in 12.5% neonates. But none of them showed clinical symptoms of hypocalcemia. In another study by Saeed [9] in 2022, the frequency of hypocalcaemia was 34.5%. In another study carried out in Egypt by Elshenawi [10], the incidence of hypocalcemia was found to be 15% and the decrease was statistically significant (p < 0.001). The strained Pakistani healthcare system, operating with limited resources, risks further overload from unnecessary lab tests and treatments. However, neglecting potential risks can jeopardize patient health. Achieving the optimal balance necessitates ongoing, thorough research to refine existing medical practices [11]. The purpose of this study is to comprehend the occurrence of hypocalcemia and determine its significance. Additionally, the research aims to investigate whether routine monitoring of serum calcium is necessary for healthy term neonates undergoing phototherapy and if there is a basis for considering prophylactic calcium supplementation for these neonates.

Objective

This study seeks:

- To determine frequency of phototherapy induced hypocalcemia as an adverse effect in term neonates with indirect hyperbilirubinemia in Chaudhary Muhammad Akram teaching hospital, Lahore.
- To assess the severity of hypocalcemia, and determine the frequency at which it occurs within the therapeutic range.

METHODOLOGY

This Prospective observational study was conducted at Department of Pediatrics, Chaudhary Muhammad Akram Teaching and Research Hospital, Lahore from 12-6-24 to 12-12-24. Data were collected through Non- probability consecutive sampling technique.

Sample Size

Size: 125 full term neonates
Calculator: Epi info CDC
n=[Z^2*P(1-P)]/d^2 Where n=Sample size
P= Expected Prevalence
Z=Statistic corresponding to level of confidence
d=Precision (corresponding to effect size)

Inclusion Criteria

- Term neonates (>37 weeks gestation)
- Diagnosed with indirect (unconjugated) hyperbilirubinemia
- Eligible for phototherapy as per AAP Clinical Practice Guidelines (2022)

Exclusion Criteria

- Perinatal asphyxia (Apgar score <4)
- Clinically apparent jaundice within 24 hours of birth
- Prior hypocalcemia (serum calcium <8 mg/dL or <2 mmol/L)
- History of prior exchange transfusion
- Known or suspected hemolysis
- Infants of diabetic mothers
- Formula-fed neonates

Data Collection

After ethical approval and informed consent, eligible neonates were enrolled. Demographic information including name, age, and gender was recorded. Phototherapy was administered using narrow-spectrum LED blue light (410–470 nm), in accordance with the AAP guidelines. Total serum bilirubin was measured before phototherapy and again after 24 hours. Phototherapy was discontinued once serum bilirubin had decreased by ≥2 mg/dL below the initiation threshold. Total serum calcium was measured prior to initiating phototherapy and two hours post-cessation. Neonates were monitored for clinical signs of hypocalcemia including apnea, jitteriness, irritability, hypoxia, cyanosis, vomiting, heart failure, tachycardia, convulsions, or prolonged QT interval. Any such findings were managed as per standard clinical protocols.

Data Analysis

Data were recorded using a structured proforma and analyzed using SPSS version 23.0. Quantitative variables like bilirubin and calcium levels were presented as means and standard deviations. Data were stratified by gender, age, and phototherapy duration. Post-stratification, the Chi-square test was applied to assess statistical significance, with a p-value ≤ 0.05 considered significant.

RESULTS

Among 125 neonates, 54.4% were male (n = 68) and 45.6% female (n = 57). The mean gestational age was 38.6 ± 0.9 weeks, and the average birth weight was 3.01 ± 0.35 kg. Phototherapy was administered for an average duration of 24.1 ± 6.8 hours. Clinical symptoms observed during or after treatment included jitteriness in 6 cases (18.8%), apnea and irritability in 3 cases each (9.4%), while cyanosis and convulsions were not reported in any neonates.

Table 1

Demographic Characteristics of Neonates (n = 125)

Variable		Value
Total Patients		125
Male		68 (54.4%)
Female		57 (45.6%)
Mean Gestational Age (weeks)		38.6 ± 0.9
Mean Birth Weight (kg)		3.01 ± 0.35
Mean Duration of Phototherapy (hours)		24.1 ± 6.8
Clinical Symptom	Jitteriness	6 (18.8%)
	Apnea	3 (9.4%)
	Irritability	3 (9.4%)
	Cyanosis	0 (0%)
	Convulsions	0 (0%)

Phototherapy resulted in a significant reduction in serum calcium and bilirubin levels. The mean calcium level dropped from 9.42 ± 0.58 mg/dL pre-phototherapy to 8.12 ± 0.76 mg/dL post-phototherapy. Similarly, total bilirubin levels decreased from 16.2 ± 2.4 mg/dL to 11.5 ± 2.1 mg/dL, with a mean bilirubin reduction of 4.7 ± 1.3 mg/dL. These changes suggest effective bilirubin clearance but a notable decline in calcium levels.

Table 2

Serum Calcium and TBR Levels Before and After Phototherapy

Parameter	Mean ± SD
Pre-Phototherapy Calcium (mg/dL)	9.42 ± 0.58
Post-Phototherapy Calcium (mg/dL)	8.12 ± 0.76
Pre-Phototherapy Total Bilirubin (mg/dL)	16.2 ± 2.4
Post-Phototherapy Total Bilirubin (mg/dL)	11.5 ± 2.1
Mean Decrease in Bilirubin (mg/dL)	4.7 ± 1.3

Figure 1

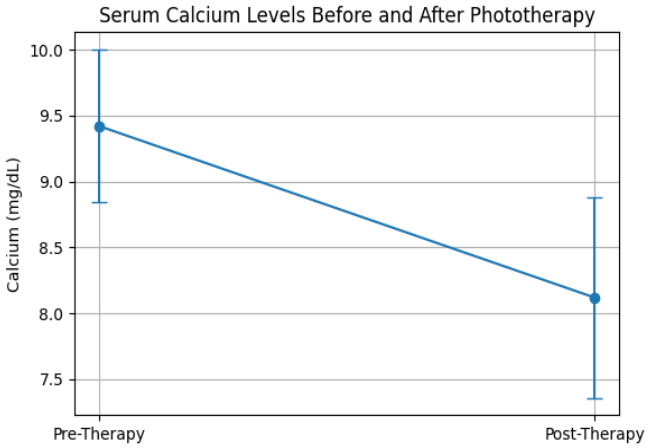
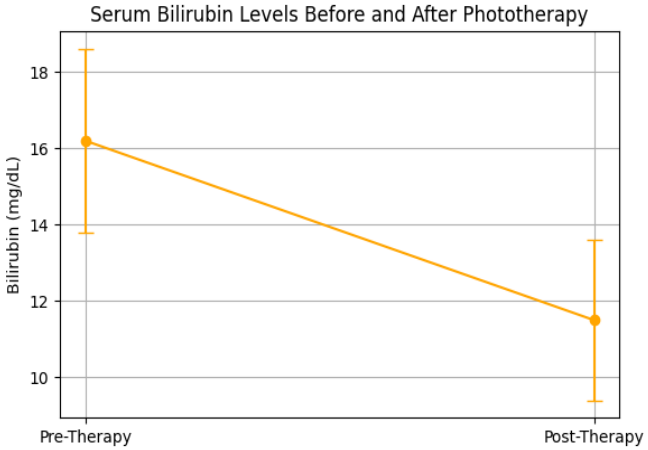


Figure 2



Hypocalcemia was observed in 32 out of 125 neonates (25.6%), and 12 of these (37.5%) exhibited clinical symptoms. Jitteriness was the most common symptom (n=6), followed by apnea (n = 3) and irritability (n = 3). These findings suggest that while many hypocalcemic neonates were asymptomatic, over one-third experienced neurologically relevant signs.

Table 3

Frequency of Hypocalcemia and Related Symptoms

Variable	Number (%)
Neonates with Hypocalcemia	32 (25.6%)
Symptomatic Hypocalcemia	12 (37.5% of hypocalcemic cases)
Jitteriness	6
Apnea	3
Irritability	3

The occurrence of hypocalcemia was significantly associated with longer phototherapy durations. Among neonates who received phototherapy for more than 24 hours, 22 (34.9%) developed hypocalcemia, compared to only 10 (15.9%) in those treated for ≤24 hours (p = 0.018). This indicates that extended phototherapy is a risk factor for post-treatment hypocalcemia.

Table 4

Hypocalcemia Stratified by Phototherapy Duration

Duration of Phototherapy	Hypocalcemia Cases (%)	p-value
≤ 24 hours	10 (15.9%)	0.018
> 24 hours	22 (34.9%)	

DISCUSSION

This prospective observational study assessed the frequency of hypocalcemia in full-term neonates undergoing phototherapy for unconjugated hyperbilirubinemia. Our results showed that 25.6% of neonates developed hypocalcemia following phototherapy, with a subset (37.5%) exhibiting clinical symptoms such as jitteriness, apnea, and irritability. These findings emphasize that phototherapy, though widely accepted and safe, is not without potential complications [12]. The observed frequency of hypocalcemia in our study aligns closely with previous literature. The underlying mechanism is believed to involve phototherapy-induced inhibition of melatonin secretion, which disrupts the calcium-regulating effects of parathyroid hormone, particularly in the immature neonatal parathyroid axis [13]. Moreover, continuous light exposure suppresses pineal gland activity, contributing to altered calcium homeostasis [14].

Interestingly, our data showed a statistically significant association between the duration of phototherapy exceeding 24 hours and an increased risk of hypocalcemia (p = 0.018). This supports the hypothesis that prolonged light exposure exacerbates calcium depletion and suggests that duration of phototherapy may be a modifiable risk factor [15]. While most cases of hypocalcemia in our study were asymptomatic, the clinical significance lies in the potential for life-threatening events such as seizures or cardiac arrhythmias if hypocalcemia remains undetected [16,17]. This justifies the need for routine post-phototherapy calcium monitoring, particularly in neonates exposed for extended durations. It is important to note that none of the neonates in our cohort required IV calcium therapy, and all improved with supportive care. This implies that while hypocalcemia is relatively common, it is often mild and transient.

CONCLUSION

It is concluded that phototherapy, though effective in managing unconjugated hyperbilirubinemia, is associated with a considerable risk of inducing hypocalcemia in full-term neonates. In this study, 25.6% of neonates developed post-phototherapy hypocalcemia, with a notable proportion exhibiting clinical symptoms. Prolonged duration of phototherapy was significantly associated with a higher incidence of calcium depletion. These findings highlight the need for vigilant biochemical monitoring of serum calcium levels following phototherapy, especially in neonates requiring extended treatment.

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