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Original Research Article

Evaluating the Relationship Between Phototherapy Exposure and Hypocalcemia in Neonatal Hyperbilirubinemia: A Prospective Study

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Abstract:

Background: Neonatal hyperbilirubinemia is a frequent condition in approximately 60% of term neonates and often necessitates phototherapy. While helpful in reducing serum bilirubin, phototherapy has been reported to be associated with complications such as hypocalcemia, particularly in preterm babies. Melatonin suppression and the resultant hormonal changes could be the foundation for this effect.

Objective: The aim of this research was to assess the correlation of phototherapy with the occurrence of hypocalcemia in neonates with hyperbilirubinemia, comparing results between term and preterm neonates.

Methodology: Prospective observational study was conducted at Department of Pediatrics, Delhi Hospital and Nursing Home, Bahadurgarh, Haryana, India. 96 neonates undergoing phototherapy for unconjugated hyperbilirubinemia were included and categorized into two groups: Group A (48 preterm) and Group B (48 term). Serum ionized calcium and bilirubin were measured before and after 48 hours of phototherapy. Clinical presentations of hypocalcemia were noted.

Results: Group A was born with lower birth weight and gestational age and was subjected to phototherapy later compared to Group B. Group A had more decrease in serum ionized calcium (0.5 ± 0.3 mg/dL) compared to Group B (0.3 ± 0.2 mg/dL), which was significant ($p = 0.002$). Group A also received phototherapy treatment for longer duration and had more decrease in bilirubin.

Conclusion: Phototherapy is associated with an impressive drop in neonatal serum calcium levels, particularly in pre-term infants. The results necessitate daily calcium monitoring in the context of phototherapy, particularly in high-risk populations.

Keywords: Bilirubin, Hypocalcemia, Neonatal Hyperbilirubinemia, Phototherapy, Preterm Infants, Prospective Study, Serum Calcium.

Introduction

Neonatal hyperbilirubinemia is one of the most common clinical presentations in the first neonatal course, with a peak incidence in the first week of life. It is defined by the presence of increased blood bilirubin concentrations that result in clinically evident jaundice. The condition occurs in about 60% of full-term infants, and thus it represents a very frequent condition in neonatology [1]. In the majority of cases, hyperbilirubinemia is a benign and self-limiting phenomenon, but elevated bilirubin concentrations are potentially neurotoxic to the developing central nervous system. If left untreated, it can result in severe complications such as kernicterus, a bilirubin-induced neurological dysfunction that is followed by irreversible behavioral and neurological sequelae [2]. Thus, early detection and appropriate treatment of hyperbilirubinemia are necessary to avoid negative outcomes.

Phototherapy is the most widely accepted and least invasive treatment of neonatal hyperbilirubinemia. The treatment is finished by exposing the infant to specific wavelengths of light, blue light being the most frequently used, that breaks down bilirubin into water-soluble photoisomers. These isomers are easily excreted out of the body through urine and bile without the requirement of hepatic conjugation [3]. Phototherapy has been highly successful in reducing the level of serum bilirubin and the risk of bilirubin-induced neurotoxicity. Nevertheless, even as a therapeutic intervention, phototherapy is far from being complication-free. A variety of side ef-

fects have been reported, such as augmented insensible loss of water, watery diarrhea, damage to the retina, tanning of the skin, and the bronze baby syndrome, particularly in the cholestatic conditions. It has also been associated with DNA strand breakage and disruption of maternal-infant bonding [4]. Of these, hypocalcemia is a less common but clinically significant complication that requires more research.

Neonatal hypocalcemia has been characterized as a serum calcium of less than 7 mg/dL or ionized calcium of less than 4 mg/dL (1 mmol/L). Symptoms are more likely to occur in term neonates if the ionized calcium is less than 1 mmol/L [5]. Clinical presentation may involve apnea, jitteriness, clonus, seizures, increased extensor tone, hyperreflexia, and in a few cases, stridor secondary to laryngospasm. Interestingly, even with the potential for severe symptoms, of interest is the fact that the majority of neonates with hypocalcemia may be asymptomatic, and their calcium levels will generally correct within 24 hours of phototherapy cessation [6]. This suggests a reversible and transient course of phototherapy-induced hypocalcemia in most cases, although the mechanism is still under active investigation.

One of the most widely accepted theories of the pathophysiology of hypocalcemia secondary to phototherapy is melatonin production disruption. Inhibition of the release of melatonin from the pineal gland was theorized to be the effect of phototherapy. Melatonin is a control hormone that inhibits the effect of cortisol on bone metabolism. Inhibition of melatonin leads to enhanced action of cortisol, and hence enhanced bone uptake of calcium with a consequent drop in serum calcium levels [7]. This hormonal interaction can be a factor in the etiology of hypocalcemia in neonates on phototherapy. Although this theory makes sense, more research is indicated to elucidate the precise biochemical and physiological mechanisms involved.

Previous studies taking into account the interaction between phototherapy and hypocalcemia have produced conflicting results. Some have reported a statistically significant reduction in calcium concentration following phototherapy, whereas others have reported no consistent association. This highlights the need for well-designed prospective studies that are in a better position to provide unequivocal evidence on the incidence and clinical importance of hypocalcemia in neonates treated with phototherapy. Apart from this, perception of whether certain groups of neonates are at increased risk—preterm infants or neonates with pre-existing metabolic disorder, for example—may enable more targeted monitoring and intervention.

Nevertheless, its common use and long-standing position in neonatal hyperbilirubinemia therapy, it is important to evaluate all potential side effects in full. While in the majority of instances hypocalcemia is temporary, under certain circumstances it can have severe adverse effects if not detected and treated in a timely fashion. Against this background, the present study aims to prospectively evaluate the relationship between phototherapy treatment and the development of hypocalcemia in neonates with hyperbilirubinemia. By systematic questioning of changes in serum calcium levels prior to and following phototherapy, and examination of the incidence of clinical signs of hypocalcemia, this study intends to contribute valuable information to the ongoing controversy concerning the safety profile of phototherapy in neonatal treatment. Ultimately, the findings may optimize current clinical recommendations and enable safer, more effective treatment protocols in neonates with hyperbilirubinemia.

Methodology

Study Design: This was a prospective cross-sectional observational study designed to evaluate the association between phototherapy exposure and the development of hypocalcemia in neonates diagnosed with hyperbilirubinemia.

Study Area: The study was conducted in the at Department of Pediatrics, Delhi Hospital and Nursing Home, Bahadurgarh, Haryana, India

Study Duration: The research was carried out over a period of one year

Sample Population: All neonates, both preterm and term, admitted to the SCBU with a diagnosis of unconjugated hyperbilirubinemia and receiving phototherapy during the study period were considered eligible for inclusion.

Sample Size: A total of 96 neonates meeting the inclusion and exclusion criteria were enrolled in the study. These were evenly divided into two groups: Group A included 48 pre-term neonates, while Group B comprised 48 term neonates.

Inclusion Criteria

- Receiving phototherapy
- Neonates admitted to SCBU with unconjugated hyperbilirubinemia
- Gestational age assessed using New Ballard Score
- Age ≥24 hours at the time of admission

Exclusion Criteria

Neonates were excluded if they presented with any of the following:

- Serum bilirubin in the exchange transfusion range
- Respiratory distress syndrome or hyaline membrane disease
- Maternal history of diabetes mellitus or hyperparathyroidism
- Hypoxic-ischemic encephalopathy (HIE)

- Congenital hypothyroidism
- Congenital anomalies
- Clinical sepsis
- Age <24 hours"

Data Collection: Information was collected using a pre-designed proforma containing demographic and clinical information. Information documented was the name of the neonate, sex, birth weight, gestational age, age at the time of initiation of phototherapy (hours), and the duration of phototherapy. Maternal and neonatal blood groups were also documented. Clinical features suggestive of hypocalcemia, such as jitteriness, irritability, lethargy, and convulsions, were recorded carefully, along with other potential complications, such as rash, diarrhea, fever, and dehydration. This allowed immediate intervention on the onset of a calcium imbalance or phototherapy complications.

Procedure: Phototherapy was initiated in all included neonates according to American Academy of Pediatrics (AAP) guidelines from total serum bilirubin. Standard phototherapy units consisting of four blue-light fluorescent lamps emitting light between 420–470 nm were used. Lamps were placed 30 to 40 cm above the neonates to ensure uniform irradiation of both groups. The eyes and genitals of the neonates were shielded during therapy to prevent phototoxicity. Aseptic blood sampling was performed using peripheral venous phlebotomy. Phototherapy was discontinued by clinical judgment and bilirubin monitoring. Hypocalcemia, if diagnosed clinically or biochemically, was treated according to hospital protocol with oral or intravenous calcium supplementation.

Laboratory Analysis: "A laboratory investigation collected approximately 4 ml of blood from each neonate. About 1.5 ml was placed in two ion-free red top vials to measure serum ionized calcium and total serum bilirubin (TSB) levels. In case blood grouping was not known a blood group was taken in 1 ml of EDTA vial. Maternal blood was grouped as required. Total serum bilirubin was measured before phototherapy at baseline, then 24 hours, 48 hours and post phototherapy. Serum ionized calcium was measured prephototherapy, then at 48 hours. Hypocalcemia was defined as serum ionized calcium of <4 mg/dL. Total serum bilirubin was measured by Diazo method with sulfanilic acid and ionized calcium was measured by Arsenazo III method. All samples underwent laboratory testing using the Olympus AU640™ chemistry analyzer (Beckman Coulter India Pvt. Ltd.) located in the hospital's central laboratory.

Statistical Analysis: The data were analyzed using the SPSS (Statistical Package for Social Sciences) software version 25.0. Continuous variables were reported as a mean ± standard deviation (SD) depending on the nature of the variables; comparison of groups was performed with either paired or unpaired t-tests. Categorical variables were analyzed with either the Chi-square test or Fisher's exact test as appropriate. A p-value of less than 0.05 was accepted as statistically significant for all analyses.

Result

Table 1 presents the clinical characteristics of subjects in Group A and Group B. In terms of sex distribution, Group A had 22 females (45.80%) and 26 males (54.20%), while Group B had 20 females (41.70%) and 28 males (58.30%), indicating a slightly higher proportion of males in both groups. Regarding the mode of delivery, 18 subjects (37.50%) in Group A and 16 subjects (33.30%) in Group B were delivered via lower segment cesarean section (LSCS), whereas the majority in both groups were delivered through normal vaginal delivery (NVD), with 30 subjects (62.50%) in Group A and 32 subjects (66.70%) in Group B."

Table 1: Clinical characteristics of subjects

Characteristic	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Sex distribution				
Female	22	45.80%	20	41.70%
Male	26	54.20%	28	58.30%
Mode of delivery				
LSCS (cesarean section)	18	37.50%	16	33.30%
NVD (normal vaginal delivery)	30	62.50%	32	66.70%

Table 2 compares key clinical variables between Group A and Group B, showing statistically significant differences across all parameters. Group A had a lower mean birth weight (2.35 ± 0.30 kg) compared to Group B (3.10 ± 0.25 kg), with a mean difference of –0.75 kg ($p < 0.001$). The gestational age was also significantly lower in Group A (35.2 ± 1.1 weeks) than in Group B (39.0 ± 0.9 weeks), with a mean difference of –3.8 weeks ($p < 0.001$). Group A started phototherapy later (70.0 ± 20.0 hours) than Group B (50.0 ± 15.0 hours), with a +20.0-hour difference ($p < 0.001$), and required longer phototherapy (60.0 ± 10.0 hours vs. 50.0 ± 8.0 hours; +10.0 hours, $p < 0.001$). The total serum bilirubin (TSB) level at the start of phototherapy was lower in Group A (18.5 ± 2.5 mg/dL) than in Group B

(20.2 ± 2.1 mg/dL), with a mean difference of – 1.7 mg/dL (p = 0.005). However, the mean drop in TSB over 48 hours was greater in Group A (1.10 ± 0.40 mg/dL) compared to Group B (0.80 ± 0.30 mg/dL), with a difference of +0.30 mg/dL (p = 0.002).

Table 2: Mean ± SD, P values, and mean differences of key variables

Variable	Group A	Group B	P value	Mean difference (A – B)
Birth weight (kg)	2.35 ± 0.30	3.10 ± 0.25	< 0.001	– 0.75 kg
Gestational age (weeks)	35.2 ± 1.1	39.0 ± 0.9	< 0.001	– 3.8 wks
Age at start of phototherapy (hrs)	70.0 ± 20.0	50.0 ± 15.0	< 0.001	+ 20.0 hrs
Duration of phototherapy (hrs)	60.0 ± 10.0	50.0 ± 8.0	< 0.001	+ 10.0 hrs
TSB at start of phototherapy (mg/dL)	18.5 ± 2.5	20.2 ± 2.1	0.005	– 1.7 mg/dL
Mean drop in TSB (0–48 hrs) (mg/dL)	1.10 ± 0.40	0.80 ± 0.30	0.002	+ 0.30 mg/dL

Table 3 compares the mean decline in serum ionic calcium levels over 48 hours between the two groups. Group A showed a greater mean decline of 0.5 mg/dL (SD = 0.3) compared to Group B, which had a mean decline of 0.3 mg/dL (SD = 0.2). This difference was statistically significant, with a p-value of 0.002, indicating that subjects in Group A experienced a significantly larger reduction in serum ionic calcium levels over the 48-hour period.

Table 3: Comparison of mean decline in serum ionic calcium (0–48 hrs)

Group	Mean decline (mg/dL)	SD	P value
Group B	0.3	0.2	0.002
Group A	0.5	0.3	

Discussion

This study revealed a statistically significant correlation between phototherapy exposure and the development of hypocalcemia in neonates, with preterm neonates (Group A) having a significant decrease in serum ionic calcium compared to term neonates (Group B). These changes in the calcium level were also followed by significant changes in other clinical parameters like gestational age, birth weight, and the duration of phototherapy. These findings suggest that neonates with higher preterm gestational age and lower birth weight are at higher risk of biochemical imbalance during phototherapy.

These results are consistent with reports submitted by Garlapalli et al., (2024) [8] who conducted a prospective study in 100 neonates and observed a significant reduction in the concentration of serum calcium following phototherapy among both term and preterm groups. Term neonates in the study declined from 9.08 ± 0.61 mg/dL to 8.38 ± 0.77 mg/dL (p < 0.0001), and preterm neonates declined from 8.96 ± 0.62 mg/dL to 8.39 ± 0.76 mg/dL (p = 0.0055). Asghar et al. (2020) [9] also observed a significantly greater fall in serum ionic calcium in preterm neonates (mean fall of 0.57 ± 0.37 mg/dL) in comparison with term neonates (0.34 ± 0.24 mg/dL) following 48 hours of phototherapy (p < 0.001), with higher rates of hypocalcemia among the preterm group (26.8%).

Chandrashekar et al. (2014) [10] also supported these findings by demonstrating a direct correlation between the duration of phototherapy and the occurrence of hypocalcemia. In that study, the occurrence of hypocalcemia was found to rise from 8% after 24 hours to 44% after 48 hours of phototherapy, with preterm infants exhibiting far higher susceptibility compared to term infants (48% vs. 14%, respectively). These findings corroborate the findings of the present study, where greater serum calcium fall was noted among Group A participants who also underwent longer phototherapy.

The pathophysiology of hypocalcemia caused by phototherapy is thought to be through transcranial suppression of the pineal gland, leading to decreased melatonin release. This, in turn, leads to enhanced cortisol-mediated bone uptake of calcium, thus lowering serum calcium. This pathophysiology was established by experimental studies, as cited by Garlapalli et al. (2024) [8] and Asghar et al., (2020) [9] and also established by animal model studies.

While most studies, including this study, emphasize monitoring calcium levels during phototherapy, other studies have reported a relatively low incidence of hypocalcemia. In a study by Alizadeh-Taheri et al. (2013) [11], and Tehrani et al. (2014) [12], 7–7.5% of newborns developed hypocalcemia after the phototherapy, and clinical manifestations were minimal in number. These variations are to be explained due to differences in study populations, phototherapy regimens, and duration of exposure.

Generally, the cumulative data indicate that phototherapy, although efficient in reducing serum bilirubin, also has a quantifiable risk of producing hypocalcemia, particularly in preterm infants and in those requiring prolonged therapy. Quantification of serum calcium during phototherapy and preventive measures, such as calcium supplement and head shielding, are recommended to avert this risk.

Conclusion

The investigation assessed the relationship between the use of phototherapy and hypocalcemia in neonates with hyperbilirubinemia. The results demonstrated that there was a significant drop in serum ionic calcium levels following phototherapy with a more statistically significant drop in the level on the lower end of the scale with the preterm babies, the primary participants of the study. In comparing the two groups, Group A (preterm neonates) had a lower birth weight and length of gestation, had longer phototherapy duration and a longer delay from admission to treatment, than Group B (term neonates). Despite both groups being the same with respect to sex and modes of delivery, the group of preterm babies may be at greater risk of hypocalcemia from phototherapy by virtue of being both lower birth weight and gestation, and hypocalcemia may occur more in babies who are more exposed, less stable and avoid at risk of phototherapy after admission. Therefore, there may need to be precautionary observation for hypocalcemia and measure calcium levels, especially for premature babies receiving phototherapy.

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