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Effect of Phototherapy on Serum Levels of Calcium, Magnesium, Phosphorus, and Vitamin D in Infants with Hyperbilirubinemia

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Abstract

Background and Aims: Neonatal hyperbilirubinemia (NH) is a common neonatal condition, affecting 60% of full-term and 80% of preterm infants, especially in regions with limited healthcare resources. Phototherapy is the standard treatment for NH, utilizing blue-green light to convert bilirubin into excretable isomers. However, phototherapy has been associated with side effects, including alterations in serum levels of calcium, magnesium, phosphorus, and vitamin D, which are critical for bone metabolism and neonatal health. This study aimed to assess the impact of phototherapy on these biochemical parameters in neonates with NH.

Methods: A prospective observational study was conducted in the Nursery Ward, tertiary medical hospital of north India, from September 2022 to March 2024. Sixty neonates with NH requiring phototherapy were included, following ethical approval and informed consent. Serum levels of calcium, magnesium, phosphorus, and vitamin D were measured at baseline and after 48 hours of phototherapy using chemiluminescence and enzymatic methods. Statistical analysis included paired t-tests to determine significant changes.

Results: Phototherapy significantly reduced calcium, magnesium, and vitamin D levels in the 3rd samples compared to baseline ($P<0.05$), with stabilization by the 4th sample ($P>0.05$). Phosphorus levels showed similar trends. Weak correlations were observed between these parameters, neonatal weight, and gestational age.

Conclusion: Phototherapy transiently affects serum calcium, magnesium, phosphorus, and vitamin D levels. Routine monitoring and early supplementation may mitigate potential risks and optimize neonatal care.

Keywords: Hyperbilirubinemia, Phototherapy, Neonates, Calcium and Vitamin D

Introduction

Neonatal hyperbilirubinemia (NH) is one of the most common medical conditions affecting newborns, particularly during their first week of life. It is characterized by yellowish discoloration of the skin and sclera due to elevated bilirubin levels in the blood. Approximately 60% of full-term infants and 80% of preterm infants are affected by NH globally, with the prevalence being significantly higher in regions like Southeast Asia where neonatal healthcare challenges persist [1-3]. The condition arises from the accumulation of unconjugated bilirubin (UCB) in the bloodstream, resulting from factors such as immature hepatic enzymes, increased bilirubin production, ineffective conjugation, and delayed bilirubin excretion [4-7].

While NH is often a transient condition, its complications can be severe if not promptly managed. Unconjugated bilirubin can cross the blood-brain barrier, leading to bilirubin-induced neurological damage, including kernicterus, which is associated with long-term neurodevelopmental impairments [5-9]. Additionally, hereditary conditions such as Gilbert syndrome, Crigler-Najjar syndrome, and hemolytic disorders may exacerbate the severity of NH in neonates [10-12]. Early diagnosis and effective management of NH are, therefore, critical to preventing these adverse outcomes.

Phototherapy remains the cornerstone of NH management. This non-invasive technique involves exposing the neonate to blue-green light (wavelengths 460–490 nm), which converts bilirubin into water-soluble isomers such as lumirubin that can be excreted through urine and stool [6,13,14]. The primary mechanisms include configurational isomerization, structural isomerization, and photo-oxidation, all of which facilitate bilirubin clearance [8,9]. Despite its efficacy in reducing bilirubin levels and minimizing the need for invasive procedures like exchange transfusion, phototherapy is not without side effects. These include dehydration, skin rash, hyperthermia, and electrolyte imbalances such as hypocalcemia and hypomagnesemia [15,16].

Electrolyte disturbances following phototherapy are particularly concerning. Phototherapy is thought to increase urinary calcium excretion and suppress melatonin levels by inhibiting the pineal gland, which may alter corticosterone activity and reduce calcium absorption in bones [6,7,17]. Furthermore, recent studies suggest that phototherapy may also affect vitamin D metabolism due to increased UV exposure. Vitamin D is essential for calcium and phosphorus homeostasis, and its deficiency could lead to impaired bone mineralization and growth in neonates [5,9].

Although there is substantial evidence from developed countries regarding the metabolic effects of phototherapy, data from resource-limited settings such as India remain scarce. These regions face unique challenges, including limited access to advanced neonatal care, lack of trained healthcare personnel, and insufficient parental awareness about neonatal conditions [1]. Addressing these gaps is crucial to improving neonatal health outcomes and minimizing the risks associated with phototherapy.

This study aims to explore the effects of phototherapy on serum levels of calcium, magnesium, phosphorus, and vitamin D in neonates with NH. By providing insights into the biochemical alterations induced by phototherapy, this research seeks to enhance our understanding of its metabolic implications and inform strategies to optimize neonatal care while minimizing potential complications.

Material and Methods

StudySetting

This study was conducted in the Nursery Ward, Department of Pediatrics of tertiary medical hospital of north India.

Study Period

The study was carried out from September 2022 to March 2024.

Study Subjects

Neonates with hyperbilirubinemia requiring phototherapy and admitted to the nursery were included in the study.

Ethics Approval and Consent to Participate

Ethical clearance was obtained from the institutional ethics committee. Written informed consent was taken from parents or guardians before enrolling neonates in the study.

Sample Size

The study included 60 neonates.

Inclusion Criteria

- Neonates with hyperbilirubinemia >35 weeks of gestation requiring phototherapy.

Exclusion Criteria

- Neonates receiving intravenous fluids.
- Neonates born to mothers with diabetes mellitus.
- Neonates with birth asphyxia.
- Preterm neonates (<35 weeks of gestation).

Sample Collection and Processing

Venous blood samples (4 mL) were collected aseptically in plain red vials before starting phototherapy and after 48 hours of phototherapy. Samples were centrifuged at 4500 rpm for 10 minutes and processed using the ABBOT Ci400 Architect Plus system in the WHO Research Lab, Department of Pediatrics of tertiary medical hospital of north India.

Biochemical Analysis

- **Vitamin D:** Measured using chemiluminescence.
- **Calcium:** Measured using the Arsenazo III method.
- **Phosphorus:** Measured using the phosphomolybdate method.
- **Magnesium:** Measured enzymatically.

Phototherapy Protocol

Phototherapy was initiated based on total serum bilirubin (TSB) levels and neonatal age, following the 2004 AAP Clinical

Practice Guidelines. Equipment included:

• Four blue fluorescent lamps (wavelength: 412–472 nm), positioned 25–45 cm from the neonate's skin surface.
• An LED phototherapy system (Bird Meditech, Thane, Maharashtra) with intensity >25 μW/cm²/nm (spectrum: 450–470 nm).

During phototherapy, neonates' genitalia and eyes were shielded for safety. The duration ranged from 48 to 72 hours. No additional clinical interventions were required for any neonates.

Comparative Analysis

The first blood sample (before phototherapy) served as the control. Biochemical parameters, including levels of calcium, magnesium, phosphorus, and vitamin D, were measured before and after phototherapy, and changes were analyzed for statistical significance.

Results

A higher proportion of neonates were male (73.33%) and weighed ≤2.5 kg (71.67%). Additionally, the mode of delivery was predominantly LSCS (53.33%). These observations provide a baseline understanding of the study population.

Characteristic	Category	Frequency (%)
Gender	Male	44 (73.33%)
	Female	16 (26.67%)
Weight	≤ 2.5 kg	43 (71.67%)
	2.5–3 kg	14 (23.33%)
	> 3 kg	3 (5.00%)
Mode of Delivery	LSCS	32 (53.33%)
	NVD	28 (46.67%)

Table 1: The Demographic and Clinical Characteristics of Neonates with Hyperbilirubinemia Included in the Study

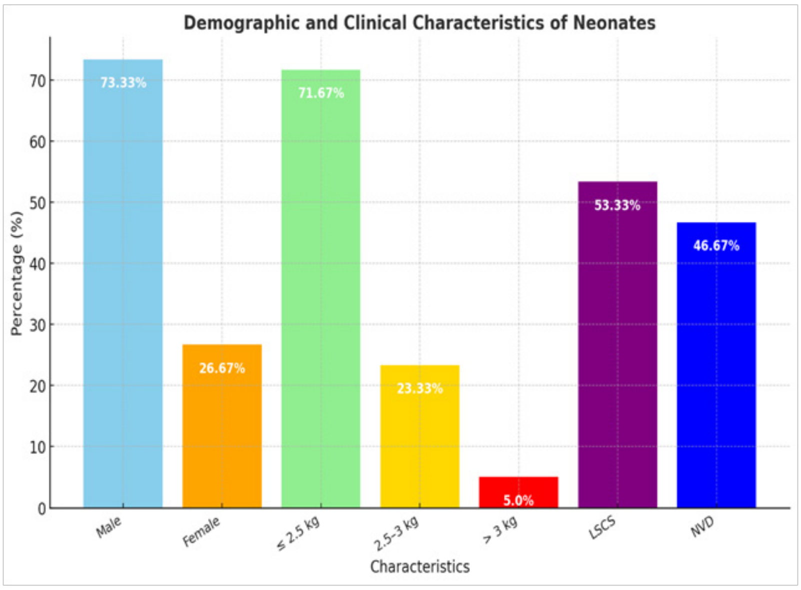

Figure 1: Demographic and Clinical Charcteristics of Neonates

Significant variations are observed between the initial and subsequent samples, reflecting the impact of phototherapy on these biochemical parameters

Parameter	1st Sample (Min-Max)	1st Sample (Mean ± SD)	2nd Sample (Min-Max)	2nd Sample (Mean ± SD)	3rd Sample (Min-Max)	3rd Sample (Mean ± SD)	4th Sample (Min-Max)	4th Sample (Mean ± SD)
Vitamin D	2.1–11.1	5.76 ± 2.16	5.8–11.0	7.89 ± 1.06	1.7–8.9	2.67 ± 1.06	3.4–12.0	6.22 ± 1.92
Calcium	2.3–11.1	5.87 ± 2.10	6.2–11.0	8.36 ± 0.85	1.7–9.5	2.82 ± 1.36	3.4–12.0	6.37 ± 2.40
Magnesium	2.00–11.6	5.62 ± 2.20	3.21–14.2	8.74 ± 1.44	1.80–4.90	2.57 ± 0.54	2.40–12.0	5.84 ± 2.26
Phosphorus	2.20–11.4	5.99 ± 2.15	5.30–12.9	8.43 ± 1.12	1.80–4.8	2.67 ± 0.62	2.70–>12.0	5.74 ± 2.16

Table 2: The Biochemical Changes in Vitamin D, Calcium, Magnesium, and Phosphorus Levels across Four Samples of Neonates Undergoing Phototherapy

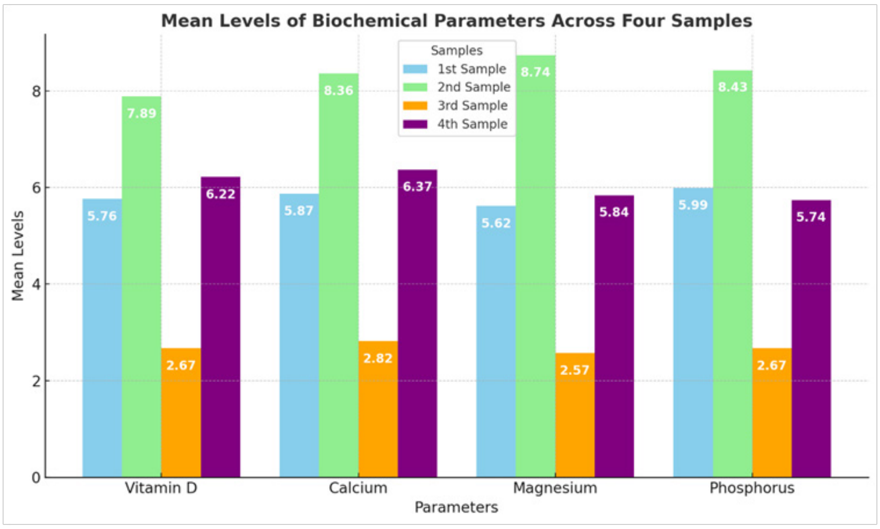

Figure 2: Mean Levels of Biochemical Parameters across Four Samples

While correlations of weight and gestational age with biochemical parameters such as calcium, magnesium, phosphorus, and vitamin-D were predominantly weak, some parameters, particularly calcium and vitamin-D, demonstrated a positive correlation with gestational age in the 4th sample.

Parameter	Weight Correlation (1st)	Weight Correlation (2nd)	Weight Correlation (3rd)	Weight Correlation (4th)	Gestational Age Correlation (1st)	Gestational Age Correlation (2nd)	Gestational Age Correlation (3rd)	Gestational Age Correlation (4th)
Calcium	-0.051	-0.21	-0.13	0.11	-0.130	0.0529	0.134	0.299
Magnesium	0.08	-0.018	0.034	0.35	-0.159	-0.073	0.056	0.1793
Phosphorus	-0.12	0.004	-0.031	0.22	-0.212	0.044	0.091	0.1103
Vitamin D	0.07	-0.1396	-0.15	0.187	-0.0273	0.0496	0.1530	0.2403

Table 3: The Correlations of Weight and Gestational Age with Biochemical Parameters Such as Calcium, Magnesium, Phosphorus, and Vitamin-D

Discussion

Phototherapy is a widely used treatment for neonatal hyperbilirubinemia, but its impact on essential biochemical parameters such as calcium, magnesium, phosphorus, and vitamin-D necessitates further exploration. These elements are vital for neonatal health, playing key roles in bone metabolism, enzymatic activity, and immune function. Our study aimed to evaluate the effect of phototherapy on these parameters, analysing changes across four samples collected during and after treatment (Table 2 and Figure 2).

In this study, 60 neonates were included, with a majority being male (73.33%) and weighing less than 2.5 kg (71.67%). Most neonates were delivered via LSCS (53.33%) and were born at gestational ages under 35–35+6 weeks (41.67%) (Table 1 and Figure 1). Baseline hemoglobin levels ranged from 7.00 to 22.10 g/dL, with a mean of 17.05 g/dL. These demographic and clinical characteristics align with the common profile of neonates requiring phototherapy.

Vitamin D levels exhibited significant changes during phototherapy, with transient rise in the 2nd sample and marked reduction in the3rd sample, followed by stabilization in the 4th sample. The mean levels ranged from 2.67 to 7.89 ng/mL, with significant differences observed between the baseline and subsequent samples ($P<0.05$) (Table 2 and Figure 2). These findings align with the study by Gillies et al., who noted an upward trend in vitamin-D levels after phototherapy, although the increase was not statistically significant. The transient decrease in vitamin-D levels observed in our study may be attributed to altered absorption and metabolism during phototherapy [18].

Calcium levels showed a similar pattern, with significant reductions during phototherapy. The mean levels ranged from 2.82 to 8.36 mg/dL across the samples, with significant differences between the baseline and the 3rd sample ($P<0.05$) (Table 2 and Figure 2). This reduction was consistent with findings by Shahriarpanah et al. and Barak et al., who reported decreased calcium levels during phototherapy [19,20]. The hypocalcemia observed in our study may be linked to phototherapy-induced inhibition of melatonin, which disrupts calcium absorption and metabolism.

Magnesium levels ranged from 2.57 to 8.74 mg/dL, with transient rise in the 2nd sample and significant reduction in the 3rd sample, stabilizing by the 4th sample (Table 2 and Figure 2). Previous studies by Imani et al.and Khosravi et al.reported similar findings, highlighting the role of magnesium in mitigating stress caused by phototherapy-induced Bilirubin metabolism [21,22]. Phosphorus levels, which ranged from 2.67 to 8.43 mg/dL, showed significant changes during phototherapy, with a pattern similar to calcium and magnesium. These findings suggest that phototherapy influences calcium-phosphorus metabolism, consistent with limited studies indicating similar effects.

The correlation analysis provided further insights into the relationship between weight, gestational age, and biochemical parameters. Neonatal weight showed a weak negative correlation with calcium, magnesium, phosphorus, and vitamin-D levels in the 1st, 2nd and 3rd samples, transitioning to weak positive correlations in the 4th sample. Magnesium demonstrated the strongest positive correlation with weight in the 4th sample (Table 3). These findings align with the study by Sangsari et al., who reported a significant positive correlation between neonatal weight and vitamin-D levels [23].

Gestational age showed weak negative correlations with calcium, magnesium, phosphorus, and vitamin-D levels in the 1st sample, which transitioned to weak positive correlations in the 2nd, 3rd, and 4th samples (Table 3). The gradual stabilization observed in our study aligns with findings by Bhat et al., who highlighted that lower gestational ages contribute to biochemical imbalances [24]. Additionally, their study emphasized that neonates with hyperbilirubinemia and their mothers often exhibit significantly lower vitamin-D levels, suggesting a need for targeted supplementation in this population.

Previous studies have extensively documented the effects of phototherapy on these parameters. Shahriarpanah et al and Sethi et al highlighted significant reductions in calcium levels, with hypocalcemia observed in a majority of neonates undergoing phototherapy [19,25]. Imani et al and Khosravi et al reported decreases in magnesium levels post-phototherapy, while Gillies et al. suggested a potential, albeit statistically insignificant, increase in vitamin-D levels [18,21,22]. Sangsari et al. emphasized the importance of addressing vitamin-D deficiency in neonates, linking it to prolonged hospital stays and increased morbidity [23].

Clinical Implications
Phototherapy-induced changes in calcium, magnesium, phosphorus, and vitamin-D levels are transient, with stabilization observed by the 4th sample. However, the temporary reductions in these parameters can pose risks, including hypocalcemia, hypomagnesemia, and reduced bone mineralization. Addressing these changes through supplementation and monitoring could mitigate complications in vulnerable neonates.

Strengths and Limitations
This study provides valuable insights into the biochemical effects of phototherapy in neonates with hyperbilirubinemia. However, limitations include the relatively small sample size and the single-centre design, which may limit the generalizability of findings. Future studies with larger, multicentre cohorts could validate and expand upon these results.

Conclusion
Phototherapy significantly impacts calcium, magnesium, phosphorus, and vitamin D levels, particularly during the early stages of treatment. Our study underscores the importance of monitoring and addressing these changes to optimize neonatal care. The study also highlights the need for routine assessment of vitamin D levels in neonates undergoing phototherapy, given its critical role in calcium absorption and overall health.

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Ethics Approval and Consent to Participate: Ethical approval was obtained and documented as per institutional guidelines (University Ethics Committee Swami Vivekanand Subharti University- SMC/UECM/2023/520/254)

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