Serum Level of Calcium, Phosphorus and 25 OH Vitamin D in Neonates with Indirect Hyperbilirubinemia Treated with Phototherapy

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Abstract: *Background*: Phototherapy is the standard treatment for neonatal indirect hyperbilirubinemia. However, it may affect calcium-phosphorus metabolism and vitamin D status in neonates.

Objective: To evaluate changes in serum calcium, phosphorus, and 25-hydroxyvitamin D levels after phototherapy in neonates with indirect hyperbilirubinemia.

Methods: An observational prospective study was conducted over six months at Ain Shams University hospitals. Sixty neonates with indirect hyperbilirubinemia requiring phototherapy were included. Total and direct bilirubin, serum calcium, phosphorus, and serum 25 OH vitamin D were measured before initiation and after 48 hours of phototherapy.

Results: Phototherapy significantly reduced total serum bilirubin. However, it was also associated with a decline in serum calcium and phosphorus levels. Additionally, vitamin D levels increased.

Conclusion: Phototherapy effectively reduced bilirubin levels but was associated with decreased serum calcium and phosphorus levels and increased serum 25-hydroxyvitamin D levels. Monitoring of mineral status during phototherapy may therefore be beneficial.

Keywords: Hyperbilirubinemia, phototherapy, neonates.

INTRODUCTION

Neonatal indirect hyperbilirubinemia (IHB) results from a disruption between the production and clearance of bilirubin [1]. It is the product of Red Blood Cells (RBCs) hemolysis that is conjugated in the liver prior to its excretion [2]. It is classified as a physiological condition that typically appears after 24 hours and resolves within 2 to 3 weeks [3]. and pathological, which may appear on the first day and require treatment according to the American Academy of Pediatrics (AAP) [4].

The most common treatment for indirect hyperbilirubinemia is phototherapy [5]. which uses Ultraviolet (UV) light on exposed skin and acts by transforming bilirubin near its main wavelength peak at 460 nm into water-soluble photoproducts that cannot cross the blood-brain barrier and can be excreted directly in bile or urine without hepatic metabolism [6-8].

Phototherapy may influence calcium-phosphorus metabolism and vitamin D status through its ultraviolet effects on skin metabolism and hormonal regulation. Previous studies have reported associations between phototherapy and hypocalcemia, hypophosphatemia, and alterations in vitamin D levels in neonates [8-10].

Despite previous studies, the effect of phototherapy on vitamin D and mineral metabolism remains incompletely understood, particularly in Egyptian neonates [9-12]. Therefore, this study aimed to evaluate changes in serum calcium, phosphorus, and 25-hydroxyvitamin D levels in neonates with indirect hyperbilirubinemia after 48 hours of phototherapy.

PATIENTS AND METHODS

This observational prospective study was conducted for 6 months, from March 2024 to September 2024, in the the Neonatal Intensive Care Unit (NICU) at Ain Shams University, Cairo, Egypt.

Study Population

The study included both late preterm and term neonates with indirect hyperbilirubinemia requiring phototherapy according to the American Academy of Pediatrics (AAP) guidelines.

The Inclusion criteria were all neonates with indirect hyperbilirubinemia requiring phototherapy according to the American Academy of Pediatrics (AAP) [5].

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The exclusion criteria were neonates with sepsis, neonates with indirect hyperbilirubinemia requiring exchange transfusion, and neonates receiving calcium or vitamin D before admission or during the study period.

These exclusion criteria were applied to minimize potential confounding factors that could independently influence serum calcium, phosphorus, and vitamin D levels. Neonatal sepsis and exchange transfusion may alter mineral metabolism and biochemical parameters, whereas prior calcium or vitamin D supplementation may affect baseline measurements and interfere with the assessment of the direct effects of phototherapy.

Laboratory Investigations

Venous blood samples were collected under aseptic conditions before initiation of phototherapy and after 48 hours of treatment. Laboratory investigations included complete blood count, reticulocyte count, C-reactive protein, total and direct bilirubin, serum calcium, phosphorus, alkaline phosphatase, and serum 25-hydroxyvitamin D levels.

Total and direct bilirubin were measured using the diazo method. Serum calcium was assessed by the arsenazo III method, phosphorus by the phosphomolybdate method, and alkaline phosphatase using the IFCC method on the AU 680 chemistry analyzer (Beckman Colter, USA). Serum 25-hydroxyvitamin D was measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Sunred Biological Technology Co., China). Complete blood count was analyzed using the Sysmex XN-1000 analyzer.

All studied newborn were managed according to the usual protocol of our NICU, and were subjected to and followed up by the following: full antenatal, natal, postnatal history and family history, Gestational age was calculated by date of last menstrual period, anthropometric measurement: body weight, length, occipitofrontal circumference were plotted on corresponding centile for gestational age and gender, full clinical examination (head and neck, chest, heart, abdomen, upper and lower limb and neurological examination) and assessment of Bilirubin Induced Neurologic Dysfunction (BIND) score.

BIND score with a ranking of 1 to 3 indicating the presence of subtle, non-specific signs. Acute Bilirubin Encephalopathy (ABE), 4 to 6 indicating moderate ABE and likely to be reversible, and 7 to 9 indicating advanced ABE [13, 14].

Assessment of feeding during admission: type (parenteral, enteral, or mixed) and identification of milk type and any signs of feeding intolerance.

Table 1: Bilirubin-Induced Neurologic Dysfunction (BIND) Score and Clinical Signs

BIND score	Clinical signs
Mental state	
0	Normal
1	Sleep but arousal, decreased feeding
2	Lethargy, poor suck and /or irritable/jittery with strong suck
3	Semi-coma, unable to feed, seizures, coma
Muscle tone	Muscle tone
0	Normal
1	Persistent mild to moderate hypotonia
2	Hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation
3	Persistent retrocollis and opisthotonos, bicycling or twitching of hands and feet
Cry pattern	Cry pattern
0	Normal
1	High pitched when aroused
2	Shrill, difficult to console
3	Inconsolable crying or cry weak or absent

Identify: Strength of phototherapy (single, double, triple or tunnel), type of phototherapy (blue light, white light, fiberoptic blankets, light emitting diodes "LED" or double surface phototherapy "DSP"), side effect of phototherapy (skin rash, dehydration, hyperthermia) and all neonates should be 15-20 cm away from phototherapy with a good coverage of their eyes and genitalia.

Sample Size Calculation

Sample size was calculated using the Power Analysis and Sample Size (PASS) software program. The calculation was based on detecting a significant difference in serum calcium levels before and after phototherapy using a paired-samples design. According to Gaafar *et al*. [13], the mean serum calcium level before phototherapy was 9.63 ± 0.79 mg/dL and decreased to 9.04 ± 0.78 mg/dL after phototherapy, corresponding to an expected mean difference of 0.59 mg/dL. Assuming a power of 80%, a two-sided alpha error of 0.05, and an effect size derived from the reported difference in calcium levels, the minimum required sample size was estimated to be 60 neonates.

Statistical Analysis

Data were coded, tabulated, and analyzed using Statistical Package for Social Sciences (SPSS version 27). Quantitative variables were tested for normality using the Shapiro–Wilk test. Normally distributed data were presented as mean ± standard deviation (SD), while non-normally distributed data were expressed as median and interquartile range (IQR). Qualitative variables were presented as frequencies and percentages. Comparisons between paired quantitative variables with normal distribution were performed using the paired Student's t-test, while non-parametric paired data were analyzed using the Wilcoxon signed-rank test. The Kruskal–Wallis test was used to compare more than two independent groups with nonparametric data. A p-value <0.05 was considered statistically significant.

RESULTS

This study was conducted on 60 neonates with indirect hyperbilirubinemia receiving phototherapy to assess the effects of phototherapy on serum 25-hydroxyvitamin D levels, serum calcium, and serum phosphorus.

Table 2: Demographic Characteristics of the Study Population

		Number and (%)
Gestational age (weeks)	Mean ± SD	37.23 ± 0.83
Gender	Male	35 (58.33%)
	Female	25 (41.67%)
Postnatal age at admission (days)	Mean ± SD	3.83 ± 1.76
Weight (kg)	Mean ± SD	2.89 ± 0.34

This table shows that the study population consisted predominantly of term neonates with a slight male predominance.

Table 3: Laboratory Parameters Before and 48 Hours after Phototherapy

		Normal ranges	Pre-phototherapy	48 hours Post-phototherapy	Statistical analysis		
					Test statistic	p-value	Significance
Total bilirubin (mg/dl)	Mean ± SD	0.3-1	16.02 ± 3.29	12.81 ± 2.65	17.751	<0.001*	S
Direct bilirubin(mg/dl)	Mean ± SD	Up to 0.2	0.95 ± 0.36	0.83 ± 0.28	2.397	0.02*	
Calcium (mg/dl)	Mean ± SD	9-11	9.02 ± 0.89	7.48 ± 0.7	13.197	<0.001*	
25-OH Vitamin D (ng/ml)	Median (IQR)	30-100	14.01 (9.35 - 18.69)	19.25 (13.54 - 25.01)	-4.115	<0.001**	
Phosphorus (PO_4) (mg/dl)	Mean ± SD	4-7	6.29 ± 0.88	5.39 ± 0.88	6.041	<0.001*	

*Paired t-test of significance; ** Wilcoxon signed rank test of significance.

Table 4: Distribution of Maternal-Neonatal Blood Group Incompatibility

		N (%)
maternal and neonatal blood group and RH	ABO incompatibility	32 (53.3%)
	Rh incompatibility	9 (15.0%)
	Other causes of hyperbilirubinemia	23 (38.3%)

This table shows that ABO incompatibility was the most common identified cause of indirect hyperbilirubinemia in the study population.

Table 5: Reticulocyte Count According to the Type of Blood Group incompatibility

reticulocyte count %		
Rh incompatibility	Mean ± SD	6.7 ± 1.13
ABO incompatibility		6.1 ± 1.84
Other causes of hyperbilirubinemia		4.95 ± 1.68

This table shows that Reticulocyte counts were higher among neonates with Rh and ABO incompatibility than among those with other causes of hyperbilirubinemia.

Table 6: Association between Phototherapy Intensity and Percentage Change in Calcium, Phosphorus, and 25-OH Vitamin D Levels

% of change	% of change	Phototherapy intensity			Kruskal Wallis test		
		Double (N= 17)	Triple (N= 34)	Tunnel phototherapy (N= 9)	H	p-value	Sig.
Ca(mg/dl)	Median (IQR)	-16.28 (-22.5 - -10)	-16.75 (-20 - -11.36)	-22.45 (-28.18 - -17.53)	3.461	0.177	NS
25-OH Vitamin D (ng/ml)		30.37 (1.28 - 95.67)	19.29 (-1.02 - 79.11)	49.59 (14.85 - 53.25)	0.182	0.913	
Phosphorus (PO_4) (mg/dl)		-20 (-25 - -10.71)	-18.5 (-28.57 - -1.43)	-21.43 (-22.86 - -16)	0.231	0.891	

This table showed that no statistically significant association was found between phototherapy intensity and changes in calcium, phosphorus, or vitamin D levels.

Phototherapy significantly reduced bilirubin levels and was associated with decreased serum calcium and phosphorus levels, while serum 25-hydroxyvitamin D levels increased after treatment.

DISCUSSION

Neonatal hyperbilirubinemia is one of the leading causes of admission in the Neonatal Intensive Care Unit (NICU). Unconjugated hyperbilirubinemia can cross the blood-brain barrier and exerts its neurotoxic effects if not treated early [15].

Phototherapy is the first step in the management of unconjugated hyperbilirubinemia. It is a safe and convenient method of lowering serum bilirubin levels and reducing the need for more invasive treatment. The efficacy of phototherapy depends on light wavelength, irradiance, the exposed surface area, and the distance of the light from the infant [16].

The current study aimed to evaluate the effects of phototherapy on serum vitamin D levels, serum calcium, and serum phosphorus in neonates with indirect hyperbilirubinemia.

This prospective observational study, conducted at Ain Shams University, Cairo, Egypt, in the Neonatal Intensive Care Unit (NICU), included 60 Neonates with indirect hyperbilirubinemia requiring phototherapy.

All patients were preterm to full term with an average gestational age of 37.23 weeks. The gender distribution was skewed towards males, with a male-to-female ratio of 1.4:1, and the average age on admission was 3.83 days, ranging from 1 to 7 days, and the mean birth weight was 2.89 kg, with most neonates (36.67%)

Many studies have shown that the predominant gender among most neonates with indirect hyperbilirubinemia was males, as the studies done by Shahriarpanah *et al*. [8] and Abohussein *et al*. [17].

Additionally, Shahriarpanah *et al*. [8] found that the mean ± standard deviation (SD) of calendar age in the

study population was 5.52 ± 2.45 days, and the mean gestational age was 38.14 ± 0.83 weeks.

The observed biochemical changes following phototherapy suggest that light exposure may influence neonatal mineral metabolism in addition to reducing bilirubin levels. The reduction in serum calcium and phosphorus levels may reflect phototherapy-associated alterations in hormonal regulation of mineral homeostasis, while the increase in vitamin D levels could be related to enhanced cutaneous vitamin D synthesis induced by light exposure.

Although the observed biochemical changes were statistically significant, their clinical impact may vary depending on gestational age, nutritional status, and duration of phototherapy. This highlights the importance of individualized monitoring during treatment.

These findings reinforce the need to be aware of the potential for electrolyte disturbances during phototherapy, particularly in neonates receiving prolonged or intensive treatment, even in the absence of overt clinical symptoms.

The reduction in serum calcium and phosphorus levels observed after phototherapy may be related to alterations in hormonal regulation of mineral metabolism induced by light exposure. The increase in vitamin D levels could be explained by enhanced cutaneous vitamin D synthesis following phototherapy. Similar findings have been reported in recent studies evaluating the metabolic effects of phototherapy in neonates [8, 17-20].

In support of Khan *et al*. [21], found that among 143 neonates in the study group who received phototherapy, the mean serum calcium levels before and after phototherapy were 9.28 mg/dl ± 0.23 and 8.54 mg/dl ± 0.68, respectively. There is a statistically significant decrease in serum calcium after phototherapy in the study group. This cross-sectional study was carried out at the neonatal intensive care unit of King Abdullah Teaching Hospital.

In accordance with Shahriarpanah *et al*. [8], the mean serum vitamin D significantly increased after phototherapy (before 17.44 mg/dL and after 21.77 mg/dL). The serum calcium was 9.85 mg/dL before phototherapy and significantly decreased after it (9.51 mg/dL) (P<0.001). The current study showed that phototherapy could decrease calcium levels and increase vitamin D levels.

In our study, ABO incompatibility was the leading cause of indirect hyperbilirubinemia, accounting for 53.3% of cases. This was followed by other causes, which made up 38.3%. In contrast, Rh incompatibility was less common, with an incidence of 15.0%.

These findings are consistent with those of Routray *et al*. [22], who conducted a cross-sectional study of 240 neonates with indirect hyperbilirubinemia at a tertiary care hospital. The study identified hemolytic disease of the newborn (HDN) as the most common pathological cause, accounting for 42.6% of cases. Among HDN cases, ABO incompatibility was the most prevalent cause (39.2%), followed by Rh incompatibility and G6PD deficiency, each contributing 1.7%.

In this study, reticulocyte counts in the RH and ABO incompatibility group were higher than in the other group. RH incompatibility had the highest mean reticulocyte count (6.7) and the lowest standard deviation (1.13), followed by ABO incompatibility.

This finding aligns with the study by Cherepnalkovski *et al*. [23], which examined 167 neonates with indirect hyperbilirubinemia and found that 24.6% had ABO/Rhesus incompatibility. This group exhibited significantly higher reticulocyte counts than those with jaundice of unspecified etiology.

Furthermore, Rugmini *et al*. [24] reported that among the 100 neonates studied with indirect hyperbilirubinemia, Rh incompatibility was observed in 8%, while ABO incompatibility was present in 23%. Reticulocytosis was detected in 100% of neonates with Rh incompatibility, compared to 56.5% of those with ABO incompatibility.

In general, ABO incompatibility is the most common cause of unconjugated hyperbilirubinemia. In mothers with blood groups A and B, anti-A and anti-B antibodies are predominantly IgM, which do not cross the placenta. However, in mothers with blood type O, the alloantibodies are IgG, which can cross the placenta. As a result, ABO incompatibility is most observed in type O mothers carrying a fetus with blood group A or B. ABO incompatibility can occur during the first pregnancy without prior sensitization [25].

The predominance of ABO incompatibility among study participants is consistent with the recognized epidemiology of neonatal indirect hyperbilirubinemia and may explain the elevated reticulocyte counts observed in hemolytic cases.

Rh incompatibility occurs when a mother with a Rh-negative blood group carries a fetus with a Rh-positive blood group, triggering the production of anti-D antibodies (IgG) through a process known as isoimmunization. This sensitization typically occurs during the first pregnancy. In subsequent pregnancies, these maternal alloantibodies can cross the placenta and enter the fetal circulation, where they bind to the fetal erythrocytes' surface D antigen, leading to their destruction. As a result, the first baby is usually not affected [26].

Our study presented data on the relationship between phototherapy intensity (Double, Triple, and Tunnel) and the percentage change in calcium (Ca), vitamin D (Vit. D), and phosphate (PO4) levels. The median percentage change in calcium levels is slightly more negative in the Tunnel group (-22.45%) compared to the Double (-16.28%) and Triple (-16.75%) groups. This difference among the groups is not statistically significant (NS). The median percentage change in vitamin D levels varies widely, with the Tunnel group showing the highest median change (49.59%) and the Triple group showing the lowest (19.29%). The wide range of values suggests significant variability in responses with no significant difference among the groups. The median percentage change in phosphorus levels was relatively similar across the groups, with slight differences: Double (-20%), Triple (-18.5%), and Tunnel (-21.43%), indicating no statistically significant difference among the groups.

While phototherapy remains a safe and effective intervention for neonatal jaundice, the associated biochemical changes observed in this study suggest that monitoring mineral metabolism may be beneficial, particularly in vulnerable neonates.

Although vitamin D levels increased after phototherapy, these findings should be interpreted cautiously because variability in neonatal vitamin D metabolism, baseline nutritional status, and environmental factors may influence the observed responses.

CLINICAL IMPLICATIONS

Routine monitoring of serum calcium and phosphorus levels may be considered in neonates receiving prolonged or intensive phototherapy, particularly in preterm or clinically vulnerable infants. Early detection of electrolyte disturbances may allow timely intervention and improve neonatal safety. Calcium supplementation should be reserved for neonates with confirmed or symptomatic hypocalcemia based on clinical and laboratory evaluation.

STRENGTH POINTS

This study has several strengths. It employed a prospective observational design, allowing for direct comparison of biochemical parameters before and after phototherapy within the same neonates, thereby reducing inter-individual variability. The inclusion of multiple laboratory parameters-serum calcium, phosphorus, and 25-hydroxyvitamin D-provides a comprehensive evaluation of mineral and vitamin metabolism affected by phototherapy. Additionally, the standardized timing of post-phototherapy assessment (48 hours) and the use of validated laboratory methods strengthen the reliability of the results. Excluding neonates with sepsis, performing exchange transfusion, or prior calcium/vitamin D supplementation minimized confounding factors, thereby enhancing the internal validity of the study.

LIMITATIONS

Despite its strengths, the study has some limitations that should be acknowledged. The relatively small sample size and single-center design may limit the generalizability of the findings to broader neonatal populations. Furthermore, long-term follow-up was not performed, so the persistence or clinical consequences of the observed biochemical changes beyond the phototherapy period could not be assessed. Maternal vitamin D status and neonatal feeding type were not assessed in this study, although both factors may influence neonatal vitamin D and mineral metabolism. Their potential confounding effects should therefore be considered when interpreting the results. Another important limitation is the absence of a control group of jaundiced neonates not receiving phototherapy. Consequently, it was not possible to fully differentiate biochemical changes directly attributable to phototherapy from physiological neonatal metabolic changes occurring during the early postnatal period.

CONCLUSION

Phototherapy effectively reduced bilirubin levels in neonates with indirect hyperbilirubinemia but was associated with decreased serum calcium and phosphorus levels and increased 25-hydroxyvitamin D levels after 48 hours of treatment. Monitoring mineral status during phototherapy may help detect early

electrolyte disturbances, particularly in neonates requiring prolonged or intensive therapy.

While phototherapy was associated with increased serum 25-hydroxyvitamin D levels, further studies with larger controlled populations are needed to better clarify this relationship.

LIST OF ABBREVIATIONS

IHB = Indirect Hyperbilirubinemia

NICU = Neonatal Intensive Care Unit

AAP = American Academy of Pediatrics

UV / UVR = Ultraviolet / Ultraviolet Rays

Ca = Calcium

PO_4 = Phosphorus

25-OH Vit D = 25-Hydroxyvitamin D

ALP = Alkaline Phosphatase

CBC = Complete Blood Count

CRP = C-Reactive Protein

PTH = Parathyroid Hormone

BIND = Bilirubin-Induced Neurologic Dysfunction

ELISA = Enzyme-Linked Immunosorbent Assay

SD = Standard Deviation

IQR = Interquartile Range

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Approval of the study protocol was obtained from the Research Ethics Committee of the Faculty of Medicine, Ain Shams University (Ethical Committee Reference Number: FMASU MS446/2024). Written informed consent was obtained from the parents or legal guardians of all enrolled neonates prior to participation. All procedures performed were part of routine clinical care, and no additional risk was imposed on the participants.

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None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this study.

CONFIDENTIALITY OF DATA

All patient data were handled with strict confidentiality. Each participant was assigned a unique identification code, and no personal identifiers were included in the data analysis or manuscript. Access to collected data was restricted to the research team only and used exclusively for scientific purposes.

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