Effect of Phototherapy on Serum Calcium in Neonatal Jaundice in Baghdad: Single Center Experience

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ABSTRACT:

BACKGROUND:

The most frequent abnormal physical finding in the first week of life is hyperbilirubinemia, which is found in 60% of term and 80% of preterm newborns. It can be managed by phototherapy, exchange transfusions, and pharmaceuticals.

OBJECTIVE:

This study aimed to assess the impact of phototherapy and its duration on serum calcium levels in newborns hospitalized for neonatal jaundice.

PATIENTS AND METHODS:

A prospective cross-sectional study was conducted on 100 neonates with exaggerated physiological jaundice who had been treated with phototherapy in Baghdad over a period of 10 months. The levels of total serum bilirubin and calcium were measured before and after phototherapy, and the number of hours spent receiving phototherapy was noted.

RESULTS:

The mean serum level of calcium and total bilirubin at admission was 9.43±0.67 mg/dl and 18.2±2.78 mg/dl, respectively which dropped to 8.06±1.18 mg/dl and 8.96±2.0 mg/dl, respectively at discharge with highly significant differences. Serum calcium demonstrated a positive significant correlation with birth weight ($r= 0.208$, $p= 0.038$, and a significant negative correlation with the duration of phototherapy ($r= -0.492$, $p<0.001$). Each age, gender, and mode of delivery had non-significant relationships with post-phototherapy hypocalcemia.

CONCLUSION:

Phototherapy is a significant risk factor for the occurrence of hypocalcemia, and serum calcium has a negative correlation with the duration of phototherapy and a positive correlation with birth weight.

KEYWORDS: Hyperbilirubinemia, Phototherapy, Serum Calcium.

INTRODUCTION:

The most frequent abnormal physical finding in the first week of life is hyperbilirubinemia, which is found in 60% of term and 80% of preterm newborns [(1,2)]. Jaundice is caused by the physiological immaturity of newborns to handle high bilirubin production, and it often manifests between 24 and 72 hours after birth [(3-5)]. Even though the majority of jaundiced newborns are generally healthy, bilirubin has the potential to be harmful to the central nervous system [(6)].

Neonatal jaundice can be managed by phototherapy, exchange transfusions, and pharmaceuticals. One of the common and safest options to treat hyperbilirubinemia is phototherapy. It transforms bilirubin into a colourless, less lipophilic, water-soluble form that is easily eliminated in bile, faeces, and urine [(2,7,8)]. It may result in negative side effects like dehydration, fluctuating body temperature, skin rashes, loose stools, retinal damage, bronze baby syndrome, and genotoxicity[(9)]. Additionally, multiple studies showed that phototherapy can cause a reduction in total and ionized calcium in newborns, which may occur concurrently with an increase in calcium excretion from the urine [(10-14)].

Neonatal hypocalcemia is defined as having an ionized calcium concentration of less than 4 mg/dl (less than 1 mmol/L) or a total blood calcium concentration of less than 7 mg/dl (1.75 mmol/L) and 8 mg/dl (2 mmol/l) in preterm and term neonates, respectively. Numerous biochemical activities depend on the presence of ionized calcium, such as coagulation of the blood,

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integrity and function of cell membranes, neuromuscular excitement, and cellular enzymatic and secretory activities [9, 15].

The association between hypocalcemia and phototherapy in premature newborns was initially suggested by Ramagnoli et al [16]. It was proposed that phototherapy suppresses the production of melatonin from the pineal gland, blocking cortisol's effect on bone calcium. Therefore, it has been suggested that decreased parathyroid hormone secretion is the cause of hypocalcemia in phototherapy patients and that cortisol enhances bone uptake of circulating calcium and promotes hypocalcemia [1, 3, 12, 17]. As a result, there is an increased risk of hypocalcemia in newborns receiving phototherapy for hyperbilirubinemia. Consequently, it is advised that the administration of calcium to such neonates be taken into consideration [4]. This study aimed to assess the impact of phototherapy and its duration on serum calcium levels in infants hospitalized for neonatal jaundice.

PATIENTS AND METHOD:

100 neonates (55 males and 45 females) with jaundice who were admitted to the neonatal care unit at Al-Kadhymiah Pediatric Hospital in Baghdad, Iraq for a period of 10 months, from the first of August 2022 to the end of May 2023, were the subjects of a prospective cross-sectional study. Age ranged between 3 to 10 days old, had exaggerated physiological jaundice, and received phototherapy for treatment. Exclusion criteria include:

1. Pregnancy of less than 34 weeks
2. Newborns' first-day jaundice and/or hemolytic illnesses
3. Jaundice for more than 14 days.
4. Exchange transfusions had been used to treat the patients
5. Neonates with severe congenital abnormalities, signs of sepsis, and symptoms of hypoxic-ischemic encephalopathy
6. Obstetric disorders like gestational diabetes mellitus, hypothyroidism, and hypoparathyroidism
7. Mothers used anticonvulsants while they were pregnant
8. Individuals who were hypocalcemic at admission

The phototherapy device utilized consisted of four 20 W blue light lamps that emit 5 $mW/cm^2/nm$ of spectrum irradiance between 450 and 470 nm/cm^2. While keeping their eyes and genitalia covered, newborns were positioned naked 45–50 cm away from the phototherapy device. The baby's position was frequently changed. According to a standardized questionnaire, a thorough history and physical examination were performed on each neonate. Age at admission, gender, birth weight, gestational age (term if completed 37 to 42 weeks, preterm if gestational age <37 weeks), and delivery method (vaginal vs. caesarian procedure) are all included under the heading of "neonatal information". The levels of total serum bilirubin and calcium were measured before and after phototherapy, and the number of hours spent receiving phototherapy was noted. In order to enroll the newborns in the study, informed consents were obtained from their parents. The local ethics committee at Mustansiriyah University approved the study (IRB 9 in August 2022).

Statistical Analysis

SPSS software, version 25.0 (SPSS, Chicago), was used to conduct all statistical analyses. Continuous data were submitted to a normality test (Shapiro-Wilk test). The Student t-test was used to evaluate the data, which had a normal distribution and was presented as mean and standard deviation. The Mann-Whitney U test was used to assess those with non-normal distribution and show them as median and range. The mean serum levels of calcium and total bilirubin at admission and discharge were compared using a paired t-test. Categorical variables were presented as percentages and numbers, and a Chi-square test was used to analyze them. To identify the independent risk factors for hypocalcemia, binary logistic regression was used. From this test, it was determined the odds ratio (OR) and its associated 95% confidence interval (CI). A statistically significant difference was considered to exist when the p-value was less than 0.05.

RESULTS:

Patients' demographic and medical characteristics

The mean age of neonates was 5.26±1.84 days. Males had a preponderance over females (55% versus 45%). More than one-third of neonates (39%) were preterm. The mean birth weight of the patients was 2.74±0.53 kg. The mode of delivery was almost equal between vaginal delivery and cesarean section (51% vs 49%). The median duration of phototherapy was 72 hours (range= 10-120 hours).

Serum level of Ca and total bilirubin at admission and discharge

The mean serum level of calcium and TSB at admission was 9.43±0.67 mg/dl and 18.2±2.78 mg/dl, respectively which dropped to 8.06±1.18 mg/dl and 8.96±2.0 mg/dl, respectively at discharge with highly significant differences (Table 1).

Table 1: Serum level of Ca and total bilirubin at admission and discharge.

Variables	At admission	At discharge	p-value
Serum calcium, mg/dl Mean±SD Range	 9.43±0.67 8.42-11.22	 8.06±1.18 4.81-11.22	 <0.001
TSB, mg/d Mean±SD Range	 18.2±2.78 10-25	 8.96±2.0 5.0-14	 <0.001

Incidence of hypocalcemia

Out of 100 neonates, 28 (28%) developed hypocalcemia after completion of the phototherapy treatment (Figure 1).

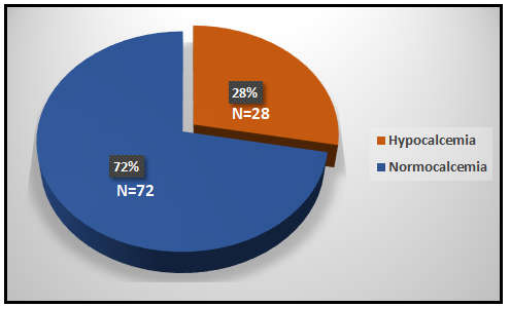

Figure 1: The incidence of hypocalcemia in neonates after phototherapy

Association of Demographic and Clinical Characteristics Hypocalcemia

Only one factor was significantly associated with the serum level of calcium. The median duration of phototherapy in neonates with hypocalcemia was 96 hours (range= 48-120 hours) which was much higher than that of neonates with normocalcemia (medina= 50 hours, range= 10-120 hours) with a highly significant difference (Table 2). Although neonates with hypocalcemia had lower birth weight and more frequent cases of preterm than those with normocalcemia, the differences exceeded the acceptable limit of significance.

Table 2: Relationship between demographic and clinical characteristics and serum calcium levels .

Variables	Calcium level		p-value
	Hypocalcemia (n=28)	Normocalcemia (n=72)	
Age, days Mean±SD	5.0±1.84	5.36±1.84	0.351
Gender Male Female	 14(50%) 14(50%)	 31(43.06%) 41(56.94%)	0.531
Birth weight, kg Mean±SD	2.58±0.51	2.81±5.52	0.082
Gestational age Term Preterm	 13(46.43%) 15(53.57%)	 48(66.67%) 24(33.33%)	0.062
Mode of delivery Vaginal Cesarean section	 18(64.29%) 10(35.71%)	 33(45.83%) 39(54.17%)	0.097
Duration of phototherapy, hours Median(range)	96(48-120)	50(10-120)	<0.001
Serum Ca at admission, mg/dl Mean±SD	9.34±0.64	9.58±0.61	0.154
TSB at admission, mg/dl Mean±SD	18.87±3.16	18.17±2.64	0.577
TSB at discharge, mg/dl Mean±SD	8.08±2.33	8.93±2.0	0.086

Logistic regression

To find independent risk factors for hypocalcemia, a logistic regression test was used. For this test, all factors with p-value ≤ 0.100 were entered into the model. Continuous variables were categorized into categorical variables using appropriate cut-off values. The results are shown in Table 3. Each of low birth weight (OR= 2.91, 95%CI=1.27-18.23, p= 0.037), preterm birth (OR= 2.6, 95%CI= 1.18-11.98, p= 0.042), and prolonged phototherapy 24-72 hours (OR= 5.0(1.04- 24.1, p= 0.045), >72 hours (OR= 7.0, 95%CI= 1.36-35.92, p=0.020) are independent factors associated for hypocalcemia in neonates (Table 4).

Table 3: Logistic regression

Variables	Hypocalcemia (n=28)	Normocalcemia (n=72)	p-value	OR(95%CI)
Birth weight, kg ≥2.5 <2.5	 16(57.14%) 12(42.86%)	 54(75%) 18(25%)	0.037	 1.0 2.91(1.27-18.23)
Gestational age Term Preterm	 13(46.43%) 15(53.57%)	 48(66.67%) 24(33.33%)	0.042	 1.0 2.6(1.18-11.98)
Mode of delivery Vaginal Cesarean section	 20(71.43%) 8(28.57%)	 31(43.06%) 41(56.94%)	0.158	 1.0 0.62(0.182-1.45)
Duration of phototherapy, hours ≤24 24-72 >72	 1(3.75%) 11(39.29%) 16(57.14)	 18(25%) 40(55.56%) 14(19.44%)	 0.066 0.045 0.020	 1.0 5.0(1.04-24.1) 7.0(1.36-35.92)
TSB at discharge, mg/dl <18 ≥18	 11(39.29%) 17(60.71%)	 33(45.83%) 39(54.17%)	0.614	 1.0 1.42(0.43-14.18)

Correlation of serum calcium at discharge with other variables

Serum calcium demonstrated a positive significant correlation with birth weight (r= 0.208, p= 0.038, and a significant negative correlation with the duration of phototherapy (r= -0.492, p<0.001) as shown in Table 4, figures 2 and 3.

Table 4: Pearson's correlation of calcium at discharge with other quantitative variables.

Variable	Correlation coefficient	p-value
Age	-0.032	0.750
Birth weight	0.208	0.038
Duration of phototherapy	-0.492	<0.001
TSB at admission	0.018	0.861
TSB at discharge	0.045	0.645

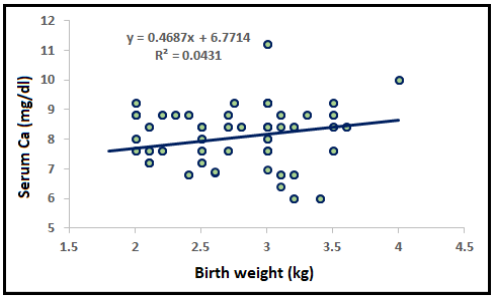

Figure 2: Scatter plot and regression line between birth weight and serum calcium

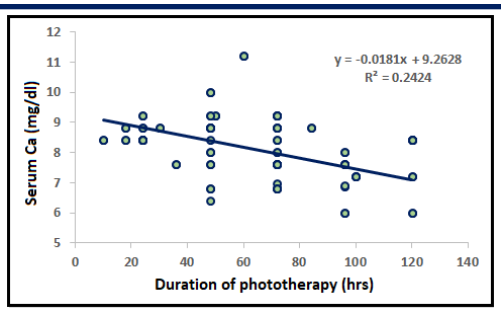

Figure 3: Scatter plot and regression line between duration of phototherapy and serum calcium

DISCUSSION:

This study assessed the impact of phototherapy on serum calcium levels in 100 newborns (61 terms, 39 preterms). Mean serum calcium on admission was 9.43±0.67 mg/dl, which had dropped to 8.06±1.18 mg/dl after completing the phototherapy course of treatment, with a significant difference (P<0.001). This result is in accordance with several previous studies by Yadav et al, Sharma et al, Yeasmin et al, Shrestha et al, Ishfaq et al, Tehrani et al, and Goyal et al. [9-15] Out of 100 neonates with jaundice, 28% developed hypocalcemia after phototherapy, which was equally distributed between males and females, and the majority were preterm (53.57%) and had lower birth weights than those with normal calcium levels. This result is approximately similar to a study conducted in India by Chandrashekar et al. [3], who discovered that 31% of patients who received phototherapy experienced hypocalcemia.

Another Indian study by Durga et al [18] was carried out on 100 neonates (55 terms, 45 preterms) and showed that 46% of cases had developed a significant reduction of serum calcium levels after 48 hours of phototherapy, while other Indian studies by Goyal et al [15] and Singh et al [19] discovered that hypocalcemia had developed in 35% and 33% respectively. Further studies by Ishfaq et al in Saudi Arabia [13] and Shrestha et al in Nepal [12] found that the incidence of hypocalcemia after phototherapy was 32% and 22.5%

respectively. These disparities in findings among studies could be explained through variations in sample size, gestational age, birth weight, and general demographic characteristics.

The current study also found that the duration of phototherapy was substantially related to the decrement of serum calcium levels (P <0.001), in agreement with an Iranian study by Barak et al [20] and Indian studies by Chandrashekar et al [3] and Singh et al [19].

A logistic regression test further demonstrated that prematurity and low birth weight are independent risk factors for hypocalcemia after neonatal exposure to phototherapy. According to categorization based on the length of phototherapy, extended phototherapy (24–72 hours and >72 hours) was an independent risk factor for hypocalcemia but short phototherapy (less than 24 hours) was not. Additionally, the current study observed that serum calcium had a positive significant correlation with birth weight and a negative significant correlation with the duration of phototherapy.

Chandrashekar et al [3] study was conducted on 200 neonates (100 terms, 100 preterms) and found that the incidence of hypocalcaemia varied with the length of phototherapy: 2 out of 24 (8%) at 24 hours of phototherapy, 15 out of 73 (21%) at 36 hours, 45 out of 103 (44%) at 48 hours. While Barak et al study [20] found that 17.5% of neonates experienced hypocalcemia after 24 hours of phototherapy, 29.5% after 48 hours, and 34.6% after 72 hours. Demonstrating that the duration of phototherapy as well as the treatment itself have an impact on the development of hypocalcemia.

In accordance with earlier studies by Bahbah et al in Egypt [1], Barak et al in Iran [20], and Muhssin et al in Iraq [21], the present study also revealed that each age, gender, and mode of delivery had non-significant relationships with post-phototherapy hypocalcemia.

CONCLUSION:

In neonatal jaundice, phototherapy is a significant risk factor for the occurrence of hypocalcemia. Serum calcium has a negative correlation with the duration of phototherapy and a positive correlation with birth weight. Age, gender, and

mode of delivery did not significantly affect the level of hypocalcemia following phototherapy.

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