

Assessment of phototherapy-induced hypocalcemia and its correlation with urinary calcium excretion in term and preterm newborns with neonatal hyperbilirubinemia: A cross-sectional study with controls

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ABSTRACT

Introduction: Although hypocalcemia is often proposed to be associated with phototherapy in both term and preterm newborns, its exact incidence, clinical significance, and underlying mechanism still remain to be elucidated. **Objective:** The objective of this study was to determine the prevalence of hypocalcemia and its etiopathogenesis in terms of urinary calcium excretion. **Methods:** This study was carried out in a tertiary care center in North India with 50 neonates (29 term and 21 preterm) in the test group receiving single surface phototherapy. The other 50 age, sex, and gestational age-matched neonates were taken as controls who did not receive phototherapy. Serum calcium levels at 0 and 48 h and urinary calcium/creatinine ratio (mg/mg) at 0 and 24 h of starting phototherapy were determined in both the groups and compared. **Results:** Total 12 preterm (57.1%) and 9 term newborns (31%) developed hypocalcemia after 48 h of phototherapy. The mean difference of serum ionized calcium between two groups was statistically significant at 48 h (4.58 mg/dl in the test group vs. 4.94 mg/dl in the control group, $p < 0.001$). Percentage change in mean of urinary calcium/creatinine ratio at 24 h from baseline was 1.39% in the control group while it was 60.7% in the test group with statistically significant difference ($p < 0.001$) between two groups. Only a weak negative correlation between serum ionized calcium and urinary calcium/creatinine ratio with correlation coefficient $r = -0.316$ could be established in the study among both term and preterm neonates. **Conclusion:** Both preterm and term neonates undergoing phototherapy are at increased risk for hypocalcemia and increased urinary calcium excretion. A universal recommendation regarding calcium supplementation in neonates undergoing phototherapy is yet to be established but seems like a reasonable intervention.

Key words: Hyperbilirubinemia, Hypocalcemia, Phototherapy, Preterm

Jaundice may be present at the time of birth or may appear at any time during the neonatal period, depending on etiology [1]. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase [2]. Hyperbilirubinemia in infants ≥ 35 weeks gestation is defined as total bilirubin $> 95^{\text{th}}$ percentile on the hour-specific Bhutani normogram [3]. Term “acute bilirubin encephalopathy” describes the acute clinical manifestations of bilirubin-induced neurological dysfunction [4]. Appropriate intervention is important to consider in every infant with severe hyperbilirubinemia [4]. Phototherapy and, if it is unsuccessful, exchange transfusion remain the primary treatment modality to keep the maximal total serum bilirubin below pathologic levels [5]. Infants under phototherapy have long been proposed to be at risk for developing hypocalcemia, especially preterm newborn [1].

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but in a large series, kernicterus occurred only in infants with a bilirubin > 20 mg/dl [6]. 90% percent of the infants, in whom kernicterus developed, were previously healthy predominantly breastfed term and near-term infants [7]. The duration of exposure to high bilirubin levels needed to produce toxic effects is unknown [3]. The more immature the infant is, the greater is the susceptibility to kernicterus [2]. A number of studies are available on this regard in literature, but with conflicting results, and moreover, the mechanism for this hypocalcemia is also not clearly elucidated till now. However, increased urinary calcium excretion is one of the most promising theoretical hypothesis till now. Only a few studies have demonstrated hypocalcemia in neonates receiving phototherapy; therefore, this study was planned to determine the effect of phototherapy on

ionized serum calcium level and ratio of spot urinary calcium and urinary creatinine in newborns.

MATERIALS AND METHODS

This observational analytic study was carried out at the neonatal intensive care unit of the Department of Paediatrics, of a tertiary care hospital, New Delhi, between November 2013 and June 2015. Prior approval from the institutional ethics committee was obtained and neonates were recruited after obtaining informed consent from the primary caregiver. The study population included all newborns, including male and female, and preterm and term, admitted in hospital for phototherapy and observation due to hyperbilirubinemia. All those babies who were at known risk of developing hypocalcemia such as small for gestation, infants of diabetic mothers, exposed to asphyxia, having respiratory distress, neonatal sepsis, sodium bicarbonate therapy, hemolytic conditions such as Rh incompatibility and glucose-6-phosphodehydrogenase (G6PD) deficiency, and hypothyroidism were excluded from the study.

The participants were divided into test and control group, having 50 newborns enrolled in each group. The test group included the newborn babies with neonatal hyperbilirubinemia, with serum bilirubin levels above the minimum value requiring phototherapy; irrespective of the fact whether they also

required exchange transfusion of blood during the course of illness. Phototherapy and exchange transfusion charts given by the American Academy of Pediatrics in 2004 for term babies and in preterm exchange transfusion level was taken by recommendations given by National Neonatology Forum in 2006 guidelines, were followed. Initially, the newborns were started on single surface phototherapy; if the serum bilirubin value was not touching the exchange transfusion level. The controls included newborns, both term and preterm, who had neonatal hyperbilirubinemia, but their level was not high enough to need phototherapy. These controls were enrolled in such a way to match the test group with respect to age, sex, period of gestation, and birth weight. These babies were managed without phototherapy.

All enrolled neonates were evaluated with detailed history and thorough physical examination. A relevant antenatal, natal, postnatal, and family history were inquired and a detailed general and systemic examination were performed in each case. Every case was investigated for serum ionized calcium, serum bilirubin, blood group, and Rh typing, hemoglobin, peripheral blood smear, urinary calcium, urinary creatinine, erythrocyte G6PD enzyme deficiency, serum thyroid-stimulating hormone, C-reactive protein, microerythrocyte sedimentation rate, total leukocyte count, absolute neutrophilic count, and immature-to-mature neutrophils ratio.

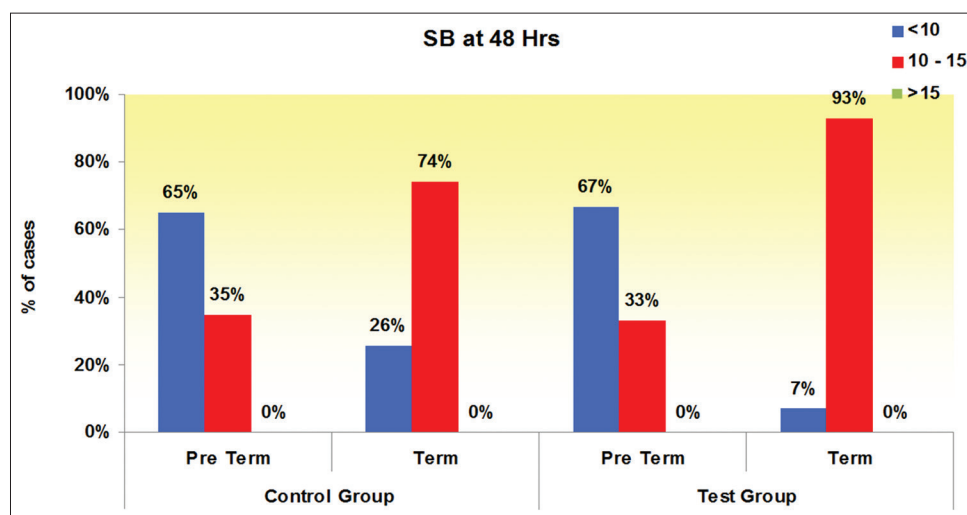


Figure 1: Distribution of cases according to total serum bilirubin (mg/dl) in preterm and term of the control and test group at 48 h of enrolment

Table 1: Mean distribution of serum ionized calcium and urinary calcium/urinary creatinine ratio in the control group between preterm and term

Parameters	Preterm (n=23)		Term (n=27)		p value
	Mean±SD	Min–Max	Mean±SD	Min–Max	
Serum ionized calcium					
0 h	4.84±0.20	4.40–5.21	5.04±0.09	4.86–5.20	<0.001*
48 h	4.84±0.23	4.38–5.20	5.03±0.10	4.8–5.24	<0.001*
Ratio					
0 h	0.27±0.03	0.23–0.34	0.25±0.02	0.21–0.28	0.009*
24 h	0.27±0.05	0.19–0.40	0.24±0.03	0.20–0.29	0.028*

SD: Standard deviation

Mothers were also examined for their blood group and Rh typing. Serum ionized calcium level was measured at 0 h of starting phototherapy and at 48 h for both the groups. Urinary calcium/creatinine ratio was determined at 0 h and 24 h for both the groups. Normal serum ionized calcium in term neonates was taken as 4.8 mg/dl and preterm neonates at 4.0 mg/dl on the basis of the available literature. The normal values for spot urinary calcium and urinary creatinine ratio were taken on the basis of previously done studies, and the spot urinary calcium and urinary creatinine ratio ≥ 0.8 were considered as hypercalciuria.

The required data were recorded in a predesigned case record form and later on shifted to Microsoft Excel spreadsheet for statistical analysis. Statistical testing was conducted with the Statistical Package for the Social Sciences system version SPSS

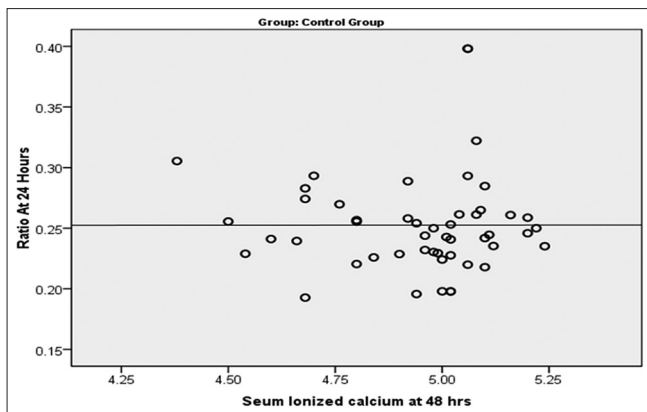


Figure 2: Correlation of urinary calcium/urinary creatinine ratio and serum ionized calcium in the control group after 24 h and 48 h of enrolment, respectively

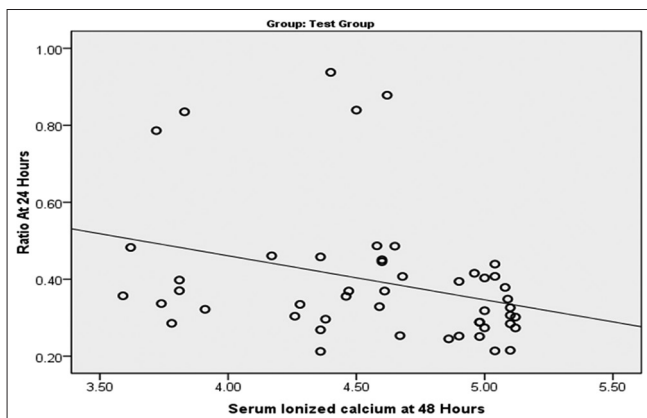


Figure 3: Correlation of urinary calcium/urinary creatinine ratio and serum ionized calcium in the test group after phototherapy

17.0. Continuous variables are presented as mean \pm standard deviation, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t-test. Nominal categorical data between the groups were compared using Chi-squared test. Spearman correlation was also used to see the relationship between serum ionized calcium and urinary calcium/creatinine ratio at 0 h and 48 h. For all statistical tests, $p > 0.05$ was considered as statistically significantly different.

RESULTS

The total number of newborns enrolled in the current study was 100, of which 50 cases (50%) were included in the test group and 50 cases (50%) were included in the control group. Distribution of cases according to total serum bilirubin in preterm and term newborns at 48 h of enrolment is presented in Fig. 1. Of the 50 cases, 29 (58%) were term and 21 (42%) were preterm and among the 50 controls, 27 (54%) were term and 23 (46%) neonates were preterm. In the test group, of 21 preterm newborns, 12 (57.1%) and of 29 term newborns, 9 (31%) developed hypocalcemia after 48 h of phototherapy Table 1. The mean difference of serum ionized calcium between the two groups was found that statistically significant at 48 h with mean for the test group was 4.58 mg/dl compared to 4.94 mg/dl for the control group ($p < 0.001$).

The percentage change in mean serum ionized calcium in the test group at 48 h from baseline (0 h) was statistically significant with a value of -7.76% ($p < 0.001$). The percentage change in mean of urinary calcium/creatinine ratio in the control group at 24 h from baseline (0 h) was -1.39% while for the test group, the value was 60.7% . It was found that there was significant difference in percentage change in mean of urinary calcium/creatinine ratio between the two groups ($p < 0.001$). However, only 2 preterm neonates (9.5%) and 2 term neonates (6.9%) had significant hypercalciuria after 24 h of phototherapy, according to accepted norms in literature; whereas, none of the neonate in the control group showed hypercalciuria Tables 2 and 3.

Only a weak negative correlation between serum ionized calcium and urinary calcium/creatinine ratio with correlation coefficient $r = -0.316$ could be established in this study among both term and preterm neonates; however, it might be confounded by small number of newborns with hypercalciuria Figs. 1 and 2. There were a total of 10 preterm neonates (47.3%)

Table 2: Relation between serum ionized calcium and urinary calcium/urinary creatinine ratio among preterm and term of both groups at the time of enrolment

Serum ionized calcium at 0 h (mg/dl)	Urinary calcium/urinary creatinine ratio mg/mg	Control group		Test group	
		Preterm (%)	Term (%)	Preterm (%)	Term (%)
≤ 4.0 for preterm	< 0.8	0 (0)	0 (0)	0 (0)	0 (0)
≤ 4.8 for term babies	≥ 0.8	0 (0)	0 (0)	0 (0)	0 (0)
≥ 4.0 for preterm	< 0.8	23 (100)	27 (100)	21 (100)	29 (100)
≥ 4.8 for term babies	≥ 0.8	0 (0)	0 (0)	0 (0)	0 (0)
Total		23	27	21	29

Table 3: Relation between serum ionized calcium and urinary calcium/urinary creatinine ratio among preterm and term neonates of both groups after 48 and 24 h

Serum ionized calcium at 0 h (mg/dl)	Urinary calcium/urinary creatinine ratio mg/mg	Control group		Test group		p value
		Preterm (%)	Term (%)	Preterm (%)	Term (%)	
<4.0 for preterm	<0.8	0 (0)	0 (0)	11 (52.3)	9 (31)	-
<4.8 for term babies	≥0.8	0 (0)	0 (0)	1 (4.7)	0 (0)	-
≥4.0 for preterm	<0.8	23 (100)	27 (100)	8 (38.1)	18 (62.6)	0.200
≥4.8 for term babies	≥0.8	0 (0)	0 (0)	1 (4.7)	2 (6.9)	-
Total		23	27	21	29	

in the test group who showed hypocalcemia, but non-significant hypercalciuria and only 2 preterm neonates (9.5%) showed hypercalciuria with low serum ionized calcium. Among the nine term newborns of the test group, who developed hypocalcemia, only 2 preterm neonates (9.5%) showed hypercalciuria with remaining 7 preterm neonates (38.1%) of the test group did not show hypercalciuria.

DISCUSSION

The current study showed that the incidence of hypocalcemia and increased urinary calcium excretion was significantly higher in both term and preterm newborns, although there is only weak negative correlation between serum calcium level and urinary calcium excretion among newborns who received phototherapy. Sethi [8] studied 60 neonates with hyperbilirubinemia including 20 preterm (Group A) and 20 full-term (Group B) neonates undergoing phototherapy. 10 neonates from each group formed the control group, and they noticed that 90% preterm neonates and 75% term neonates developed hypocalcemia after phototherapy. In this study, 57% preterm and 30% term babies developed hypocalcemia after phototherapy which is not consistent with the above study results.

They recommended that neonates under phototherapy should be supplemented with calcium to prevent hypocalcemia. Jain *et al.* [9] showed similar results in 40 newborn babies with hyperbilirubinemia. In their study, the prevalence of phototherapy-induced hypocalcemia was 55% in preterm infants and 30% in full-term neonates. They noticed that 63.6% had jitteriness and 27.3% had irritability in preterm babies with hypocalcemia. In the hypocalcemic full-term neonates, 50% had jitteriness and 16.7% had irritability.

They also recommended administration of supplemental calcium in phototherapy exposed neonates, to prevent hypocalcemia. They have also found the prevalence of hypocalcemia to be higher in patients with high level of serum bilirubin, although this difference was not statistically significant. They concluded that the phototherapy-induced hypocalcemia in premature neonates was due to higher penetration of light in premature neonates. They also suggested that although phototherapy induces hypocalcemia in newborn infants, no calcium supplement seems to be required except in symptomatic cases. Habibzadeh *et al.* [10] showed similar results and also proposed that hypocalcemia might be due to changes in serum

melatonin concentration which is regulated by the pineal gland. The pineal gland influences diurnal light-dark cycle in normal human.

Medhat [11], Karamifar *et al.* [12], and Yadav *et al.* [13] had also documented hypocalcemia in neonates undergoing phototherapy. Karamifar *et al.* also noticed that none of hypocalcemic neonate became clinically symptomatic and the serum calcium level was in normal range 24 h after discontinuation of phototherapy. Hooman *et al.* [14], in 2005, concluded that phototherapy may be the risk factor of hypercalciuria in neonates, more for preterm newborns, but like our study, they could not show any correlation between hypercalciuria and serum calcium levels and proposed further research is necessary to reveal the underlying pathomechanism. Zarkesh *et al.* [15] also showed a statistically significant difference in urinary calcium/creatinine ratio (mg/mg) at commencement and after 48 h of phototherapy in enteric term newborn. They also recommended further investigation for clarifying the importance of this phenomenon.

CONCLUSION

The current study showed the existence of the hypocalcemia in newborns undergoing phototherapy, both in preterm and term newborns. However, its clinical relevance in the form of symptomatology and underlying pathomechanism like increased urinary calcium excretion needs to be studied in studies with larger sample size.

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