Original Article

A study of serum-ionized calcium in neonates with unconjugated hyperbilirubinemia on phototherapy

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ABSTRACT

Objectives: The objective is to study the occurrence of phototherapy-induced hypocalcemia in neonates with unconjugated hyperbilirubinemia and to compare the occurrence between pre-term and full-term neonates. **Materials and Methods:** The study was conducted in the Neonatology Unit of Department of Pediatrics, at a tertiary care teaching hospital for 12 months. A total of 230 full-term and pre-term neonates with jaundice were recruited. Of 230 neonates, 150 were given phototherapy (cases), while 80 did not receive phototherapy and were used as control. Serum-ionized calcium levels were measured at initiation, after 24 h and after 48 h, or at the end of phototherapy in the case duration of phototherapy was <48 h. Serum-ionized calcium was repeated at 24 h after the completion of phototherapy. In the control group, ionized calcium levels were measured at the time of development of jaundice and 24 h after the initial measurement. **Results:** Of 150 cases who received phototherapy, 105 were term and 45 were preterm. 69 babies (46%) developed hypocalcemia after 24 h of phototherapy. Of these, 28 (40.5%) were preterm and 41 were term (59.5%). 4 patients developed symptoms, which included jitteriness and seizures. 62.2% of the total pre-term and 39% of term neonates developed hypocalcemia after phototherapy. **Conclusion:** This study suggests that neonates exposed to phototherapy are at the risk of developing hypocalcemia. There is a significant decline in the ionized calcium levels after exposure to phototherapy, and this level can even fall to hypocalcemic levels. As the duration of phototherapy increases, the serum levels of calcium may decline further. The risk of developing hypocalcemia is higher in pre-term neonates.

Key words: *Hyperbilirubinemia, Hypocalcemia, Ionized calcium, Phototherapy*

Jaundice in a neonate is one of the most common physical findings, seen in the 1st week of life. Around 60% of term and 80% of preterm neonates develop jaundice in the 1st week of life [1]. Jaundice is usually seen due to physiological immaturity of neonates, and their inability to handle increased bilirubin production during the neonatal period. The pathophysiology of jaundice remains the same in both term and pre-term neonates. However, there is a higher risk of hyperbilirubinemia in pre-terms. If not managed, hyperbilirubinemia can lead to bilirubin encephalopathy and can cause permanent neurodevelopmental handicap [2].

Phototherapy is one of the modalities used in the management of hyperbilirubinemia in neonates and is convenient, readily available, and easy to use. Long-term experience with phototherapy has demonstrated its safety as well as efficacy. It converts bilirubin into its water-soluble isomers that can be readily excreted without conjugation in the liver. Phototherapy, however, also invokes some adverse effects that include loose stools, development of rash, overheating, dehydration, damage to DNA, retinal injury, hypocalcemia, and a benign condition called Bronze Baby Syndrome in cholestasis [3].

Hypocalcemia is one of the known size effects of phototherapy. 90% of the preterm and 75% of full-term neonates develop hypocalcemia in the wake of being subjected to phototherapy [4]. Neonates undergo a physiological nadir in serum calcium levels, usually by 24–48 h of age, termed early onset hypocalcemia and require treatment with calcium supplementation for the first 72 h. In contrast, late onset hypocalcemia usually presents after 7 days and requires long-term therapy [5]. The risk of early onset hypocalcemia is higher in preterm neonates as well as in other high-risk babies.

Serum calcium is present in free physiological form and in the bound state. Calcium can be found bound to albumin (40%), anions such as phosphate, citrate, sulfate, lactate, and phosphate (10%), and free or ionized form (50%). The free form is considered to be the most physiologically active form [6]. Estimation of total calcium may not reflect actual free calcium levels as correlation between the two values may be poor when serum albumin concentration is low or in the case of acid-base imbalance. Both these conditions may be seen in preterm or sick neonates. Hence, measurement of ionized calcium is a far more reliable indicator of actual calcium levels of pre-term neonates.

Hypocalcemia can cause serious manifestations such as convulsions, apnea, irritability, and jitteriness [7]. Hence, phototherapy-induced hypocalcemia can be a significant problem in neonates. Most of the studies done previously have observed a decline in total serum calcium level in neonates undergoing phototherapy. This study was undertaken to determine hypocalcemia in neonates with unconjugated hyperbilirubinemia that have received phototherapy, by measuring ionized calcium, which is a more reliable indicator of clinically significant hypocalcemia as well as to compare the occurrence of phototherapy-induced hypocalcemia between term and pre-term neonates.

MATERIALS AND METHODS

The study was conducted in the Neonatology Unit of Department of Pediatrics, at a tertiary care teaching hospital in North India for 12 months. Prior approval of the Ethics Committee was obtained and a written informed consent was taken from the parents. All neonates with unconjugated hyperbilirubinemia, both term and preterm, were enrolled in the study. The sample size was determined based on Cochran's estimation of sample size. Infants with birth asphyxia (APGAR score <7 at 5 min), conjugated hyperbilirubinemia, infants requiring exchange transfusion, infants receiving intravenous calcium supplementation, and infants of diabetic mother were excluded from the study.

Neonates with jaundice that required phototherapy were included in the case group, and serum-ionized calcium levels were measured at initiation of phototherapy, then after 24 h and again after 48 h or at the end of phototherapy in case duration of phototherapy was <48 h. Serum-ionized calcium was repeated at 24 h after completion of phototherapy. In the control group, neonates with jaundice not requiring phototherapy were included and ionized calcium levels were measured at the time of development of jaundice and 24 h after the initial measurement. Requirement of phototherapy was decided based on AAP Guidelines and according to birth weight in preterm neonates [8]. Both light-emitting diode (LED) and compact fluorescent light (CFL) units were used for phototherapy. Ionized calcium was measured by ion selective electrode method using ST -200 Plus Electrolyte Analysis. Serum-ionized calcium level <1.1 mmol/l was taken as abnormal.

Data were analyzed using statistical software SPSS 22. 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 or Fisher's exact test as appropriate. $p<0.05$ was considered statistically significant.

RESULTS

A total of 230 full-term and pre-term neonates with unconjugated hyperbilirubinemia were recruited, of which 150 received phototherapy (cases), while 80 did not receive phototherapy and were used as control. The total number of males in the study was 139 and females was 91, with a male:female ratio of 1.5:1. There was no statistically significant difference between the two groups based on sex of the newborns. Of a total of 230 neonates, 178 were born full-term (77.4 %) and 52 were pre-term (22.6 %). Of 150 cases, 105 (70 %) were term deliveries and 45 (30%) were preterm. Of 80 controls, there were 73 term newborns (91.3 %) and 7 pre-terms (8.8%). The difference between the two was statistically significant. The mean birth weight of cases was 2596.93±561.37 g and controls was 2900.34±465.51 g ($p<0.001$).

The serum total bilirubin levels were measured in 230 newborns with jaundice at the time of detection of icterus. The mean bilirubin levels at the time of starting phototherapy among 150 cases were 14.53±3.17 mg/dl, while in the control group, it were 10.59±2.12 ($p<0.001$) as shown in Table 1. Ionized calcium levels were measured in all neonates included in the study. The mean ionized calcium at the time of detection of jaundice in the case group was 1.26±0.14 and in the control group was 1.26±0.15, which was comparable.

The mean ionized calcium after 24 h of phototherapy in case group was 1.13±0.20. In the control group, ionized calcium was repeated after 24 h of initial measurement and mean level was 1.28±0.11 ($p<0.001$). In the case group, serial decline in ionized calcium levels was noted as the duration of phototherapy increased, and this decline was statistically significant (Table 2). Mean ionized calcium levels at 24 h after stopping phototherapy (post PT) were 1.23±0.10. In the neonates where calcium levels did not return to normal despite stopping phototherapy, repeat levels were measured on day 7 and showed a mean value of 1.20±0.06.

Table 1: Comparison of baseline characteristics between cases and controls (total *n*=230)

Baseline characteristics	Cases, n (%)	Control, n (%)	P
Sex distribution			
Male	96 (64)	43 (53.8)	0.130
Female	54 (36)	37 (46.3)	
Mode of delivery			
NVD	68 (45.3)	27 (33.8)	0.089
LSCS	82 (54.7)	53 (66.3)	
Birth weight (g) (mean)	2596.93±561.37	2900.34±465.51	<0.001
Total bilirubin at admission (mg/dl) (mean)	14.53±3.17	10.59±2.12	<0.001
AGA	124	73	
SGA	26		
Birth weight category			
Normal	88 (58.7)	67(83.8)	
LBW	57 (38)	13 (16.3)	
VLBW	5 (3.3)	0 (0)	

NVD: Normal vaginal delivery, LSCS: Lower segment cesarean section, SGA: Small for gestational age, AGA: Average for gestational age, LBW: Low birth weight, VLBW: Very low birth weight

Of 230 patients included in the study, the number of patients developing hypocalcemia (ionized calcium value <1.1 mmol/L) after 24 h of initial testing was 73 (31.7%), which included both cases and controls. Of 150 cases, 69 developed hypocalcemia after 24 h of phototherapy (46%). Of 80 controls, only 4 patients developed hypocalcemia (5%). The difference between the two groups was statistically significant (p<0.001), (Table 3).

Of a total of 150 cases, there were 45 preterm and 105 term patients. Of 45 preterm neonates who received phototherapy, 62.2% developed hypocalcemia (28 cases) and 39% term neonates, of 105 (41 cases) who received phototherapy showed a decline in ionized calcium to hypocalcemic levels. This difference was statistically significant (p=0.009). 4 neonates (2.7%) of 150 cases developed symptoms that included jitteriness and seizures. 97.3% neonates were asymptomatic. None of the patients in the control group showed any symptoms. The most common symptom was jitteriness.

DISCUSSION

Neonatal hyperbilirubinemia is one of the most common morbidities in neonates and a common cause of readmission to hospitals. It occurs in both term and preterm neonates. The growing practice of early discharge of newborns has resulted in a re-emergence of bilirubin-related neurological sequelae, and hence, there is a growing use of interventions for the management of hyperbilirubinemia in newborns. With an increase in the use of phototherapy, there is also concern about an increase in the development of side effects in the babies exposed to these special blue lamps.

Table 2: Mean ionized calcium levels in study population (*n*=230)

Ionized calcium levels (mmol/L) mean±SD	Cases	Control	P
0 h	1.26±0.14	1.26±0.15	0.868
24 h	1.13±0.20	1.28±0.11	<0.001
48 h	1.079±0.21	–	–
Post PT	1.23±0.10	–	–
Day 7	1.2±0.06	–	–

SD: Standard deviation

Table 3: Neonates developing hypocalcemia in the study population (n=230)

I.Ca	Frequency (%)		P
	Cases	Control	
0 h			
Normal	139 (92.7)	76 (95.0)	0.585
Abnormal	11 (7.3)	4 (5.0)	
Total	150 (100)	80 (100)	
24 h			
Normal	81 (54.0)	76 (95.0)	<0.001
Abnormal	69 (46.0)	4 (5.0)	
Total	150 (100)	80 (100)	

Our aim was to estimate the occurrence of hypocalcemia induced by phototherapy and to compare the occurrence between terms and pre-terms. Currently, there are no established protocols for the routine supplementation of calcium to neonates receiving phototherapy. We aimed at studying the occurrence of phototherapy-induced hypocalcemia as well as the occurrence of possible symptoms due to hypocalcemia.

Ionized calcium is the active form of calcium in the body. Estimation of total calcium at times may not reliably give a measure of the active serum calcium levels. In our study, estimation of ionized calcium was done to allow for a reliable correlation of serum value and careful observation could be done for neonates developing hypocalcemia for early detection of any possible symptoms. In our study, 150 newborns were taken as cases and 80 neonates were included in the control group. In the case group, ionized calcium levels were measured at 24 h after the neonate underwent phototherapy. 69 of 150 cases developed hypocalcemia (46%), which was comparable to that found in a study by Durga and Kumar [9].

Serial measurement of ionized calcium levels was done in our study after starting phototherapy. There was a significant decline in the level of calcium as the duration of phototherapy increased, measured at 24 h and 48 h after starting phototherapy, which was also recorded by Srinivasa *et al*. [10]. Eghbalian and Monsef also found a decline in calcium levels as the duration of phototherapy increased [11].

Ionized calcium values measured at 48 h after starting phototherapy showed a significant decline as compared with values at 24 h. In studies by Alizadeh-Taheri *et al*., 56% of the neonates showed a decline in calcium levels. However, in their study, development of hypocalcemia was documented only in 7% of neonates, measured 48 h after phototherapy. Although the absolute number of patients developing hypocalcemia was low, there was a statistically significant decline in the calcium levels after 48 h of phototherapy, which was comparable in our study [12].

Follow-up ionized calcium levels were done in all neonates who received phototherapy 24 h after stopping phototherapy in our study. Out of the 69 patients that developed hypocalcemia, calcium values returned to normal after 24 h of stopping phototherapy in all but 4 patients (5.7 %). Karamifar *et al*. found in their study that in all cases of hypocalcemia, serum calcium levels came back to normal after 24 h of stopping phototherapy [13]. Xiong *et al*. also noted that in almost all cases, levels of calcium returned to normal 24 h after stopping phototherapy [14], whereas, in a study by Yadav *et al*., serum calcium levels returned to normal values by 10 days of life [15]. In our study, serum calcium was repeated on day 7 after phototherapy for the 5.7% of patients in whom calcium values did not return to normal at 24 h after stopping phototherapy. It was found that in all cases, calcium values attained normal level as confirmed in above study [15].

Comparison was made between the number of term babies developing hypocalcemia against the number of pre-terms after receiving phototherapy. Hence, in our study, 62.2% of pre-terms and

39% of term neonates developed hypocalcemia after phototherapy, and this difference was statistically significant. Sethi *et al*. also found a higher prevalence of hypocalcemia after phototherapy in pre-term neonates as compared to term neonates [4]. Jain *et al*. noted phototherapy-induced hypocalcemia in 55% of pre-terms and 30% of full-term neonates, which was in comparison to our results [16]. Various studies concluded that phototherapy-induced hypocalcemia can be a cause of serious concern in pre-terms, in whom the risk of physiological hypocalcemia is higher as compared to term neonates [17]. Further studies need to be undertaken before the development of policies that advise for prophylactic intervention in neonates on phototherapy.

Although many studies have documented a significant decline in levels of calcium after phototherapy, as was also seen in our study, some studies show a lower prevalence of hypocalcemia. Gheshmi *et al*. found that while 54% of patients had decreased calcium levels after phototherapy, only 9% of patients developed hypocalcemia. They concluded that the risk of hypocalcemia was low in healthy term neonates and did not recommend the use of prophylactic calcium in these neonates [18].

In contrast, a study by Prabhakar *et al*. where ionic calcium levels were measured instead of total calcium observed a significant decline in serum ionic calcium level in the study group as compared to control. They also noted the development of symptoms including jitteriness, lethargy, and irritability. However, in their study, none of the neonates developed seizures. They advised for the supplementation of calcium prophylactically in neonates who are at high risk of developing symptomatic hypocalcemia [19].

The underlying mechanism for phototherapy-induced hypocalcemia is although not yet well understood, but it seems that hypocalcemia is accompanied by a decrease in serum melatonin concentration. Melatonin secretion is regulated by the pineal gland, which is shown to be influenced by the diurnal variation. Melatonin increases the release of cortisol, which plays an important role in calcium homeostasis by decreasing calcium absorption by bones, hence maintaining serum calcium levels. Phototherapy prompts restraint of pineal gland by transcranial brightening and inhibits pineal secretion of melatonin bringing about a decrease in melatonin levels. Subsequently, hypocalcemia develops due to decrease in cortisol levels as the uptake of calcium by bones is increased [20].

Kargar *et al*. studied the effect of covering the neonate's heads with hats/caps while providing phototherapy. The neonates in the case group received phototherapy while wearing a hat, and the control group received phototherapy without hats. Calcium levels were tested in both groups at baseline and 24 as well as 48 h after phototherapy. 38.8% of newborns in the control group and 13.8% in the case group had hypocalcemia after phototherapy. A significant difference was found between the incidence of hypocalcemia in these two groups (p=0.03). Hence, they concluded that phototherapy-induced hypocalcemia can be prevented by the head cap during phototherapy with no need for prophylactic administration of calcium [21].

Limitations of this study include the use of both CFL and LED phototherapy and no correlation between the level of hypocalcemia and type of phototherapy used as well as unequal number of term and preterm neonates enrolled in both study and control groups. Age at the onset of jaundice and starting phototherapy was not correlated with the onset of hypocalcemia. Physiological hypocalcemia noted during the first 72 h of life may be a cause for further decline in serum calcium levels and may affect the results and be indistinguishable from phototherapy-induced hypocalcemia.

CONCLUSION

This study showed that neonates on phototherapy are at risk of developing hypocalcemia and hence should be monitored with serial serum calcium measurement for timely detection of hypocalcemia before the occurrence of symptoms.

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