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Research Article

TOTAL AND IONIC SERUM CALCIUM LEVELS BEFORE AND AFTER PHOTOTHERAPY IN FULL TERM NEONATES

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ABSTRACT

Introduction: Phototherapy is the standard treatment for neonatal jaundice bringing about tremendous physiological changes. Some recent reports have shown that phototherapy has an adverse impact on the serum electrolyte levels, including serum calcium levels.
Objective: To assess change in serum calcium levels following phototherapy in full-term neonates.
Methods: A total of 70 full term neonates having unconjugated hyperbilirubinemia were enrolled in the study. At admission serum bilirubin (total, conjugated and unconjugated) were noted. A blood sample was obtained and complete hematological assessment and serum calcium (total and ionic) level assessment was done. Hypocalcium and hypercalcemia were defined as serum total calcium levels <7 mg/dl and >11 mg/dl respectively. Duration of phototherapy was noted. Following phototherapy, a reassessment of serum bilirubin and calcium levels was done. Change in calcium levels was assessed. Data was analyzed using SPSS 21.0 software.
Results: At admission mean total, unconjugated and conjugated bilirubin levels were 14.47±4.22, 0.61±0.27 and 13.87±4.16 mg/dl respectively. A total of 23 (32.9%) required >72 hours phototherapy. Mean total and ionic calcium levels were 8.58±1.08 and 1.06±0.20 mg/dl respectively before phototherapy and 8.27±1.01 and 0.98±0.15 mg/dl respectively. There was a significant decline in total and ionic calcium levels following phototherapy.
Conclusion: Phototherapy had a significant impact on serum calcium levels in full-term neonates. Prophylactic calcium supplementation could be considered as a viable balancing strategy.

INTRODUCTION

Neonatal jaundice is a commonly occurring birth complication that affects nearly 60% of full-term and 80% of preterm births[1-4]. Conversion of these proportions into numbers shows that around 84-112 million babies out of a total of 140 million births in a year are affected with this condition during the first two weeks of life[5].

Neonatal jaundice is the result of an imbalance between bilirubin production and conjugation, manifested in terms of a sharp increase in bilirubin levels[6]. The underlying reason for this imbalance is multifactorial in nature but is primarily attributable to immaturity of neonatal liver which fails to match the rapid breakdown of red blood cells[6]. Marked hyperbilirubinemia can lead to acute bilirubin encephalopathy (ABE) and evolve into chronic bilirubin encephalopathy (CBE), a devastating, permanently disabling neurologic disorder[7-11] synonymous with kernicterus[12]. There could be four types of neonatal jaundice – physiological jaundice, pathological jaundice, jaundice due to breast milk and haemolytic jaundice. Of these four types, physiological jaundice is the most common. It comprises nearly 75% of neonatal unconjugated hyperbilirubinemia[13].

Phototherapy is the standard management modality in neonatal jaundice. Phototherapy helps to reduce the bilirubin levels, however, the physiological effect of phototherapy is not limited to lowering of unconjugated bilirubin. During the process of this conversion, a number of physiological changes occur simultaneously with the reduction of unconjugated bilirubin levels. Electrolytes and trace elements are known to have their own role in maintaining the neonatal growth, development and well-being[14,15]. Calcium is an important electrolyte playing an important role in neonatal metabolism, early childhood growth and development. Hence, the present study was carried out to study the impact of phototherapy on serum calcium levels in order to estimate the potential impact of phototherapy on physiological dimensions other than reduction in unconjugated hyperblirubin levels.

MATERIAL AND METHODS

The present study was carried out at Department of Physiology in collaboration with Department of Pediatrics, King George's Medical University, Lucknow, India after obtaining approval from the Institutional Ethics Committee and obtaining informed consent from the parents of the participating neonates. The sample size estimations were based on a

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previous study by Rozario *et al.*[16] who reported the mean change in serum calcium levels following phototherapy to be -0.39±0.71 mg/dl. The sample size projections were done at 95% confidence and 80% power and 25% contingency provision. The calculated sample size was 68. Finally a total of 70 full term neonates having unconjugated hyperbilirubinemia were enrolled in the study.

The inclusion criteria of the study was: Full term neonates with unconjugated hyperbilirubinemia requiring phototherapy. Preterm neonates (born before 37 weeks of gestation), those having Apgar score <7 at 1 and 5 min, having onset of jaundice within 24 hours of birth, hemolytic jaundice, mothers having diabetes or on anticonvulsant drugs, those undergoing exchange transfusion, having sepsis, cow milk-fed neonates and those having any major congenital anomaly were excluded from the study.

At admission serum bilirubin (total, conjugated and unconjugated) were noted.

A blood sample was obtained and complete hematological assessment and serum calcium (total and ionic) level assessment was done. Serum calcium levels were assessed using ARSENAZO-III (2,2′-[1,8-dihydroxy-3,6-disulphonaphthylene-2,7-bisazo]-bisbenzenear-sonic acid) colorimetric method. In this method, the Ca^{2+} ions react with Arsenazo-III resulting in a purple color complex formation. The absorbance of the Ca-Arsenazo III complex was thereafter measured bichromatically at 660/700 nm. The resultant rise in absorbance of the reaction mixture was directly proportional to the calcium concentration in the sample.

Hypocalcium and hypercalcemia were defined as serum total calcium levels <7 mg/dl and >11 mg/dl respectively.

Following phototherapy, serum calcium levels were reassessed. Change in calcium levels was calculated.

Data Analysis: Data was analyzed using IBM SPSS 21.0 software. Data has been presented as numbers and percentages or mean±standard deviation. Paired 't'-test was used to compare the significance of change in mean calcium levels following phototherapy. Association of change in serum calcium (total and ionic) in relation to duration of phototherapy was assessed using Independent samples 't'-test. A 'p' value less than 0.05 was considered to be statistically significant.

RESULT

Birth weight of enrolled neonates ranged from 2.1 to 3.9 kg. Mean birth weight of neonates was 2.95±0.36 kg. Majority of neonates were males (57.1%). A total of 13 (18.6%) of these were small for gestational age (SGA). Total bilirubin levels ranged from 4.17 to 27.90 mg/dl. Mean total bilirubin level was 14.47±4.22 mg/dl. Serum conjugated bilirubin levels ranged from 0.06 to 1.55 mg/dl with a mean of 0.61±0.27 mg/dl whereas serum unconjugated bilirubin levels ranged from 3.42 to 27.30 mg/dl with a mean of 13.87±4.15 mg/dl. Mean serum total and ionized calcium levels were 8.58±1.08 (range 6.4-11.2) mg/dl and 1.06±0.20 (range 0.70-1.60) mg/dl respectively. Duration of phototherapy ranged from 20 to 122 hours with a mean of 62.38±21.87 hours. A total of 23 (32.9%) neonates had phototherapy for >72 hours (Table 1).

Table 1 Neonatal characteristics and baseline serum bilirubin and calcium levels (n=70)

SN	Characteristics	No. of neonates	Percentage
1.	Mean Birth weight±SD (Range) in kg	2.95±0.36 (2.1-3.9)	
	Sex		
2.	Male	40	57.1
	Female	30	42.9
3.	Small for gestational age (SGA)	13	18.6
4.	Mean S. Total bilirubin (range) mg/dl	14.47±4.22 (4.17-27.90)	
5.	Mean S. Conjugated bilirubin (range) mg/dl	0.61±0.27 (0.06-1.55)	
6.	Mean S. Unconjugated bilirubin (range) mg/dl	13.87±4.16 (3.42-27.30)	
7.	Mean S. Total Calcium±SD (range) mg/dl	8.58±1.08 (6.4-11.2)	
8.	Mean S. Ionized Calcium±SD (Range) mg/dl	1.06±0.20 (0.70-1.60)	

After the phototherapy, mean total calcium and ionized calcium levels were 8.27±1.01 and 0.98±0.15 mg/dl respectively, thereby showing a decline of 0.31±0.76 (3.61%) in total calcium and 0.08±0.18 (7.55%) in ionized calcium levels. Statistically, there was a significant change in both total as well as ionic calcium levels (p<0.001) following phototherapy. Proportion of patients with hypocalcemia was 2.9% before phototherapy, however, after phototherapy it increased to 12.9% (Table 2).

Table 2 Total & Ionized Calcium levels before and after phototherapy (n=70)

SN	Time interval	Total Calcium (mg/dl)	Ionized Calcium (mg/dl)
1.	Before phototherapy [Range]	8.58±1.08 [6.4-11.2]	1.06±0.20 [0.70-1.60]
2.	After phototherapy [Range]	8.27±1.01 [6.1-10.8]	0.98±0.15 [0.60-1.40]
3.	Change	-0.31±0.76 (-3.61%)	-0.08±0.18 (-7.55%)
	't'-test (Paired t-test)	3.410	3.544
	'p' value	<0.001	<0.001
	No. of patients with hypocalcemia	2 (2.9%)	9 (12.9%)

DISCUSSION

In the present study, we found a significant decline in both total as well as ionized calcium levels following phototherapy. In proportional terms, the decline was higher in ionized calcium (7.55%) as compared to total calcium (3.61%0 whereas in absolute terms, the change was higher in total calcium (-0.31±0.75 mg/dl) as compared to that in ionized calcium levels (-0.08±0.18 mg/dl).

Most of the previous studies have primarily focused on the change in total calcium levels and did not assess change in ionized calcium levels. Eghbalian and Monsef[17] in their study showed a decline of 0.76 mg/dl which in percentage terms transformed into 7.73%. Alizadeh-Taheri[18] reported this mean decline to be 0.3 mg/dl (3.1%). In other studies it ranged from 0.12 to to 1.26 mg/dl[Error! Bookmark not defined.,19-27]. In % terms, it ranged from 1.3% to 14.4%. Among different studies reviewed by us only one study despite finding a declining trend did not find it to be significant in statistical terms[20] while all the other studies despite difference in magnitude of change found it to be significant statistically as also in the present study. As far a relatively higher proportional change in ionized calcium levels is concerned, it could be owing to a more active role of ionic form in the transformation process of unconjugated bilirubin into bioproducts that can be excreted out.

A number of earlier studies have evaluated the change in calcium levels in categorical terms, *i.e.* increment in number of hypocalcemic neonates following phototherapy. In our study, we evaluated the effect of phototherapy in terms of increment in number of hypocalcemic neonates too. In the present study before phototherapy, 2 (2.9%) neonates were hypocalcemic and following phototherapy this number increased to 9 (12.9%), thus showing an increment in number of hypocalcemic neonates to be 10%. The probable reason for this as given by earlier studies could be the inhibition of pineal gland through transcranial illumination which might result in decline of melatonin secretion that could in turn inhibit the effect of cortisol on bone calcium. The hypocalcemic effect of cortisol then increases the bone uptake of calcium resulting in decline in serum calcium levels[28]. This possible mechanism has also been endorsed by other workers too[29,30].

However, Eghbalian & Monsef[17] in their study did not find hypocalcemia as a significant issue and reported occurrence of it in only 1 (1.6%) case. Karamifar *et al.*[31] who included both pre-term and term neonates noticed this in 14.4% of their neonates. Another study reported it to be 6.8% only[18]. A much higher incidence of hypocalcemia following phototherapy for neonatal hyperbilirubinemia was reported by Yadav *et al.*[32] who reported development of hypocalcemia in 80% of preterm and 66.6% of full-term neonates who received phototherapy. Chandrashekhar *et al.*[33] in their study observed post-phototherapy hypocalcemia in 8.3 to 43.7% patients in their three study groups differentiated by duration of phototherapy. Overall incidence of hypocalcemia in their study was 31%. In some other studies too, the incidence of hypocalcemia was between 20 to 35%[19,20,23,34]. The findings in the present study were in consonance with the observations of Bhat *et al.*[35] **Error! Bookmark not defined.** who reported the incidence of post-phototherapy hypocalcemia to be 12.63%. Jagannath *et al.*[36] too observed it in 15% of their neonates. One of the reason for lower incidence of hypocalcemia in the present study could be selection of a relatively lower cut-off to decide hypocalcemia. In the present study, we considered hypocalcemia at total calcium levels <7 mg/dl. Contrary to this, Subhashini *et al.*[37] in their study took the cut-off value as <8 mg/dl. As such incidence of hypocalcemia in different studies might vary owing to this factor. However, with respect to mean and % change in total calcium levels, the findings of the present study are in agreement with the existence literature.

The findings in the present study show that there is a change in serum calcium levels following phototherapy in neonates with hyperbilirubinemia. Although this relationship has been explored previously too yet most of the previous studies focused on change in total calcium levels too, the present study is one of the only few studies evaluating it in terms of change in ionized calcium levels too and is able to provide a better physiological explanation for this change. It must be kept in mind that degradation of unconjugated bilirubin is a complex process involving various biochemical changes. Further studies to evaluate the impact of phototherapy on a wider spectrum of electrolytes with a larger sample size are recommended. We also recommend further studies to evaluate the role of ionic calcium in maintenance of unconjugated bilirubin levels during phototherapy to endorse the findings of the present study.

CONCLUSION

The findings of the present study showed that phototherapy induced hypocalcemia is a significant problem in neonates. Therefore close monitoring of serum calcium level (total and ionic) should be done before and after phototherapy. Thus we may suggest that calcium supplementation may be helpful for preventing phototherapy induced hypocalcemia in neonates. There is a need of large sample size study for prophylactic use of calcium during phototherapy.

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