Phototherapy induced hypocalcemia in neonates: A case–control prospective study

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ABSTRACT

Objective: The objective of the study was to evaluate the adverse effects of phototherapy both total and ionic calcium levels in neonates. **Methods**: A case–control prospective study was conducted in the Department of Pediatrics, over a period of 15 months. All neonates preterm or term with icterus in phototherapy range formed the study group(s). Serum calcium total and ionized were measured on a serial basis. **Results**: Neonates in the study group had significant fall in total serum calcium after phototherapy (0.94±0.49 mg/dl). Similarly, ionized serum calcium also decreased after phototherapy in study group (0.56±0.36 mg/dl), p<0.001 statistically significant. The overall incidence of hypocalcemia was 9.6%, higher in preterm (11.7%) than term (8.5%) neonates. Jitteriness and irritability both were seen in 25% of the neonates. None of the neonate had convulsion, but it may occur if the level falls further. **Conclusions**: While giving phototherapy to a premature baby or a sick baby we should monitor serum calcium levels. Prophylactically oral supplementation of calcium may be considered in newborns receiving phototherapy as it induces hypocalcemia.

Key words: *Hypocalcemia, Neonates, Phototherapy*

Hyperbilirubinemia is the most common abnormal physical finding in the 1st week of life and is observed in approximately 60% of term neonates and 80% of preterm neonates [1]. Bilirubin is potentially toxic to the central nervous system; phototherapy plays a significant role in the treatment and prevention of hyperbilirubinemia in neonates. Several adverse effects of phototherapy have also been reported [2]. A lesser-known but potential adverse effect of phototherapy is hypocalcemia. Most of the studies done till now had either observed serum total calcium levels or changes in ionic calcium with phototherapy [3,4] but did not observe them simultaneously. Hence, the present study was conducted to evaluate the effects of phototherapy on both total and ionic calcium levels.

METHODS

This case–control prospective study was conducted in the neonatal intensive care unit of the Department of Pediatrics, Umaid Hospital, Jodhpur (Rajasthan), over a period of 15 months after getting proper clearance from the Ethical Committee of our Institution. A proper consent was obtained from the parent(s) of newborns. All neonates preterm or term admitted from outside (extramural) or delivered at (intramural) Umaid Hospital with icterus in phototherapy range formed the study group(s).

Exclusion criteria were (a) newborns having, (i) icterus within 24 h or more than 14 days, (ii) received sodium bicarbonate, (iii) history suggestive of birth asphyxia, (iv) neonatal septicemia, (v) respiratory distress syndrome, (vi) major or life-threatening congenital malformations, (vii) icterus in the range requiring exchange transfusion, and (viii) documented hypocalcemia at start of phototherapy. (b) Maternal and perinatal factors, (i) mother taken phenobarbitone during antenatal period, (ii) history of hyperthyroidism in mother, (iii) diabetic mother, and (iv) prolonged difficult labor. Phototherapy for management of hyperbilirubinemia in the healthy newborn was decided according to following guidelines [5] (Table 1).

Age, sex, and gestational age-matched hyperbilirubinemia neonates including term and preterm who did not fulfill the criteria for phototherapy were taken as the control group (c). After registration of these babies, detailed maternal and newborn-related antenatal, natal and postnatal history was taken. General physical examination and systemic examination were performed. Gestational age was assessed by modified Parkin's criteria.

All study group newborns received continuous double surface phototherapy with MEDITRIN. Double surface phototherapy unit has a combination of eight white and four blue tube lights at a distance of 45 cm. For effective phototherapy, it was checked that minimal spectral irradiance or flux of 4–6 $\mu W/nm^2$ (at 425–475nm) was available and maintained at the level of infant's skin. Babies were kept naked except for diapers and eye bandage. The position of the infant was changed every 2 h. Parameters evaluated on serial basis were (daily): Total serum bilirubin (direct and indirect) and serum calcium (Total and ionized). Serum bilirubin was done by Jendrassik and Grof method utilizing the reagent kit of Bayer diagnosis India Ltd. by bilirubin analyzer Erba chem - 5 plus Transasia. Indirect bilirubin was estimated by Vandenberg reaction. For quantitative estimation of calcium (total) in serum reagent, Arsenazo III was used, utilizing the kit of Ranbaxy laboratories limited by analyzer RA-50. For quantitative estimation of Ca+2, AVL electrolyte analyzer was used which was based on the principle of ion sensitive electrode measurement.

Phototherapy was discontinued when serum bilirubin levels reached 13.0±0.7 mg/dL in term and 10.7±1.2 mg/dL in preterm infants [2]. If bilirubin level had risen to the extent that exchange transfusion had to be done, case was excluded from the study. As we have compared two groups with continuous data (serum bilirubin and serum calcium) so matched pair t-test applied for statistical analysis. Qualitative data were analyzed by the χ^2-test and Fisher's exact test. The test is considered significant when $p<0.05$.

RESULTS

The present study included 78 neonates admitted in the neonatal intensive care unit. Among them, (66.7%) 52 neonates were with icterus in the phototherapy range formed the study group and (33.3%) 26 neonates age, sex and gestational age-matched, formed the control group. Among the study group, 53.8% were males and 46.2% were females. While in control group 57.7% were males and 42.3% were females. These two groups were statistically comparable (p>0.7).

Mean age at the time of enrollment in the study group was 3.61±0.79 days and in control group was 3.71±0.61 days (p>0.6). In the study group out of 52, 67.3% (35) was term and 32.7% (17) were preterm while in control group out of 26, 69.3% (18) was term and 30.7% (8) were preterm. Difference was statistically insignificant (p>0.1). Most of the patients in study and control group (>92%) were appropriate for gestational age.

Neonates in the study group had a significant fall in total serum calcium after phototherapy (0.94±0.49 mg/dl). The difference was highly significant (p<0.001). The control group also had fall in total serum calcium, but it was statistically insignificant (p>0.9). Variation of pre and post total serum calcium value in the study and control group was highly significant (p<0.001). Similarly, ionized serum calcium also decreased after phototherapy in the study group (0.56±0.36 mg/dl, p<0.001) and was statistically significant while in control group levels did not change. Variation of pre- and post-ionized serum calcium value in the study and control group was highly significant (p<0.001) (Table 2).

In the study group fall in total serum calcium value increases with duration of phototherapy. However, the difference in fall was more between 24 h and 48 h duration. It was statistically highly significant (p<0.001). The fall in total serum calcium from 48 h to 72 h duration was statistically insignificant (p>0.5). Similarly, the fall in ionized serum calcium value increases with duration of phototherapy. Variation in total serum calcium and ionized serum calcium was studied at 48 h of enrollment, the study and control group values were compared which was statistically highly significant (p<0.001) (Tables 3 and 4).

Pre- and post-study variation of serum calcium (total and ionized) in both term and preterm babies and among study and control group was highly significant (p<0.001) (Table 5).

The overall incidence of hypocalcemia was 9.6%, higher in preterm 11.7% than term 8.5%. In study group overall, jitteriness

Table 1: Guidelines for management of hyperbilirubinemia

Study population	Weight	Age	Total serum bilirubin level
Term neonates	≥2.5 kg	25–48 h	15–19.99 mg/dl
		49–72 h	18–24.99 mg/dl
		>72 h	20–24.99 mg/dl
Preterm neonates	1000–1500 g		7–11.99 mg/dl
	1500–2000 g		10–14.99 mg/dl
	2000–2500 g		13–17.99 mg/dl

Table 2: Pre- and post-study serum calcium

Parameters	Study group mean±SD	Control group mean±SD	Statistical analysis	t value	p value
Total serum calcium (mg/dl)					
Pre-study (a)	9.60±0.95	9.38±1.05	a versus b study group	4.66	<0.001
Post-study (b)	8.74±0.93	9.35±1.05	a versus b control group	0.10	>0.9
Variation (c)	0.94±0.49	0.03±0.08	Variation study versus control group	13.04	<0.001
Ionized serum calcium (mg/dl)					
Pre-study (d)	4.89±0.49	4.69±0.47	d versus e study group	6.89	<0.001
Post-study (e)	4.32±0.34	4.70±0.48	d versus e control group	0.07	>0.9
Variation (f)	0.56±0.36	0.003±0.05	Variation study versus control group	10.94	<0.001

SD: Standard deviation

Table 3: Pre- and post-study variation of serum calcium values in relation to duration of phototherapy

Variation of serum electrolytes	24 h mean±SD (a) (n=3)	48 h mean±SD (b) (n=41)	72 h mean±SD (c) (n=8)	Statistical analysis	t value	p value
Total serum calcium (mg/dl)	0.3±0.17	0.96±0.48	1.1±0.54	a versus b	5.82	<0.001
				b versus c	0.83	>0.5
				a versus c	3.82	<0.01
Ionized serum calcium (mg/dl)	0.26±0.15	0.52±0.3	0.84±0.53	a versus b	2.94	<0.01
				b versus c	1.65	>0.2
				a versus c	2.80	<0.02

SD: Standard deviation

Table 4: Pre- and post-study variation of serum calcium after 48 h of enrollment

Variation of serum electrolytes	Group		t and P value
	Study mean±SD	Control mean±SD	
Total serum calcium (mg/dl)	0.96±0.48	0.11±0.04	t 12.68, P<0.001
Ionized serum calcium (mg/dl)	0.52±0.3	0.02±0.04	t 11.81, P<0.001

SD: Standard deviation

Table 5: Gestational maturity versus pre- and post-study variation of serum calcium values

Variation of serum calcium	Group				Statistical analysis	t value	p value
	Study		Control				
	Preterm (a) mean±SD (n=17)	Term (b) mean±SD (n=35)	Preterm (c) mean±SD (n=8)	Term (d) mean±SD (n=18)			
Serum calcium total (mg/dl)	0.98±0.55	0.92±0.49	0.1±0	0.12±0.05	a versus b	0.38	>0.8
					c versus d	1.69	>0.2
					a versus c	6.59	<0.001
					b versus d	9.56	<0.001
Serum calcium ionized (mg/dl)	0.56±0.36	0.55±0.37	0±0.06	0.02±0.05	a versus b	0.09	>0.9
					c versus d	0.82	>0.5
					a versus c	6.23	<0.001
					b versus d	8.32	<0.001

SD: Standard deviation

and irritability both were seen in 25% of the neonates followed by irritability only (21.1%). Jitteriness only was seen in 23.5% preterm subgroup neonates while in term subgroup it was seen in only 11.4%. Both irritability and rashes were seen in 31.4% and 11.7% of neonates in term and preterm subgroup, respectively. None of the neonate had a convulsion.

DISCUSSION

Most of the physiological function of the body requires an active form of calcium, i.e., ionized calcium. In the present study, ionized serum calcium levels had shown a significant fall in levels after phototherapy (p<0.001), in the same manner as total serum Calcium. Romagnoli *et al*. [6] noted the associated of hypocalcemia with the use of phototherapy. The results of our study agree with all the previously done work by different authors in relation to calcium and phototherapy and confirm the results of previous authors [7-14] (Table 6).

These observations indicate that duration of phototherapy has a definite correlation with disturbance (fall) in calcium level. Serum fall in calcium starts right from the beginning of phototherapy and relatively faster during first 48 h; thereafter, the fall is more gradual to attain any statistical significance.

Phototherapy induced hypocalcemia is not related to bilirubin metabolism. Phototherapy leads to inhibition of pineal gland through transcranial illumination, resulting in a decline in melatonin levels and, in turn, diminishing corticosterone to finally decrease calcium resorption from bones, producing hypocalcemia. Cortisol, unchecked, exerts a direct hypocalcemia effect and increase bone uptake of calcium as well [15]. Melatonin secretion normally starts around about 2–3 days after birth is less in premature babies increases over in childhood and again falls in adolescence and continues to decrease with aging. Phototherapy associated hypocalcemia can be prevented by occipital shielding [16], exogenous melatonin or inhibition of corticosteroid synthesis. Other causes suggested for this hypocalcemia include a decreased secretion of parathormone and higher urinary excretion of calcium in the phototherapy group [17]. Administration of 25-hydroxyvitamin-D3 was not able to lower the incidence of the phototherapy-induced hypocalcemia in preterm infants and

Table 6: Comparison with previous studies

Name of authors	**Calcium level mg/dl**		
	Before phototherapy		**After phototherapy**
Sethi *et al*.[7] preterm	7.59 ± 0.35		6.34 ± 0.44
Term	7.94 ± 0.64		6.49 ± 0.61
Jain *et al*.[8] preterm	9.67 ± 1.10		7.90 ± 1.41
Term	9.15 ± 1.19		6.32 ± 1.30
Eghbalian and Monsef[9] overall	9.85 ± 1.23		9.09 ± 0.93
Bahbah *et al* [11] Term	9.36 ± 0.29		8.58 ± 0.76
Present study Overall	9.60 ± 0.95		8.74 ± 0.93
Preterm	9.38 ± 0.89		8.47 ± 1.04
Term	9.82 ± 0.96		8.86 ± 0.86
Ionized S. Calcium			
Sethi *et al* (1993) Preterm	4.25 ± 0.17		2.58 ± 0.59
Term	4.22 ± 0.16		2.79 ± 0.70
Present study Overall	4.89 ± 0.49		4.32 ± 0.34
Preterm	4.83 ± 0.43		4.31 ± 0.31
Term	4.91± 0.53		4.32 ± 0.36
Name of authors	**Incidence of hypocalcemia (%)**		
	Preterm	**Term**	**Overall**
Romagnoli *et al.* [6]	52.3		
Sethi *et al*.	90	75	
Jain *et al.* 1998	55	30	
Sourabh Dutta (2001)	90	75	
Karamifar *et al.* 2002 [10]	22.6	8.7	
Yadav *et al.* 2012 [3]	80	66.6	
Bahbah *et al*. 2015 [11]		26	
Arora *et al.* 2014 [12]	43	56	
Reddy *et al.* 2015 [13]	41.2	6.2	13.1
Indira *et al.* 2015 [14]	14.6	5.08	6
Present study (2006)	11.7	8.5	9.6

concluded that Vitamin D was unlikely to play an important role in the pathogenesis of phototherapy induced hypocalcemia.

Yadav *et al.* 2012 [3] observed symptoms of hypocalcemia were jitteriness, irritability, and lethargy but none had a convulsion. Bahbah *et al*. [11] and Rastogi [18] showed jitteriness as the most common symptom of hypocalcemia. Arora *et al*. [12] observed symptomatic hypocalcemia more in preterm than term. Since our study was a case–control study. Hence, it was difficult to generalize the findings of the study. Hence, further controlled trials on the same topic are proposed with a larger number of study subjects.

CONCLUSION

The fall in ionized serum calcium is responsible for the different clinical manifestation of hypocalcemia starting from irritability and jitteriness to frank convulsions. Although we did not find any case with convulsions, there is a possibility of developing convulsions in newborns if they are either premature or sick. Hence, monitoring of serum calcium level is very important before starting of phototherapy, especially in premature baby or a sick baby. An oral supplementation of calcium may be considered in newborns receiving phototherapy, however this need to be made clear further by few more studies.

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