Section: Pediatrics

Original Research Article

THE EFFECT OF PHOTOTHERAPY ON TOTAL SERUM CALCIUM AND IONIZED CALCIUM LEVELS IN TERM NEONATES WITH UNCONJUGATED HYPERBILIRUBINEMIA – A TERTIARY HOSPITAL BASED CROSS SECTIONAL STUDY

Poojitha Kiran[1], S Likhita[1], Joy Liston Pratap D Souza[2], Shivalingappa B.M[3]

[1]Post Graduate 3rd Year Resident, Department of Pediatrics, Vydehi Institute of Medical Sciences and Research Centre, Bangalore India
[2]Professor, Department of Pediatrics, Vydehi Institute of Medical Sciences and Research Centre, Bangalore India
[3]Professor & Head, Department of Pediatrics, Vydehi Institute of Medical Sciences and Research Centre, Bangalore India

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Corresponding Author:
Dr. Poojitha Kiran,
Email: poojithakiraan@gmail.com

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Abstract

Background: One of the most frequent issues among full term and preterm newborns in the first week of life is neonatal hyperbilirubinemia. Electrolyte disequilibrium from phototherapy, such as hypocalcemia, is possible. Neonatal hypocalcemia is described as total or ionized calcium levels in the serum that is less than 8 mg/dl (2.2mmol/L) or 4.8 mg/dl (1.2mmol/L), respectively. To examine the impact of phototherapy on serum and ionized calcium levels as well as the clinical symptoms brought on by hypocalcemia. **Materials and Methods:** This cross-sectional study was conducted at Vydehi Institute of Medical Sciences and Research Center, Karnataka, India for 18 months from February 2021 to August 2022. A total of 94 full-term neonates with unconjugated hyperbilirubinemia were enrolled. Phototherapy was given to neonates depending upon their serum bilirubin values, according to the American Academy of Pediatrics criteria. Serum calcium, ionized calcium and serum bilirubin concentrations were measured at the start of phototherapy, and at discontinuation of phototherapy or at 48 hours of phototherapy, whichever was earlier. **Result:** 45.7 % and 41.5% of neonates developed post phototherapy hypocalcemia based on ionic calcium & total serum calcium concentrations respectively. It was found that ionized calcium testing had higher sensitivity for detecting hypocalcemia. However excellent inter-test agreement was seen between both tests on applying kappa-statistics. Incidence of hypocalcemia increased with duration of phototherapy($p<0.001$). 17% of the neonates developed irritability and 21.3% developed jitteriness. **Conclusion:** This study concluded that full-term neonates with unconjugated hyperbilirubinemia exposed to phototherapy are at risk of developing hypocalcemia. There was a significant decline in ionic & total serum calcium concentration in neonates receiving phototherapy. Ionized calcium concentrations were more sensitive for hypocalcemia compared to total serum calcium concentrations.

INTRODUCTION

The primary cause of neonatal admission is neonatal hyperbilirubinemia, which is brought on by the liver's failure of ability to excrete bilirubin.[1] Jaundice in newborns may develop if there is a disturbance in the equilibrium between bilirubin production and conjugation and excretion. The neonatal liver's immaturity and failure to keep up with the red blood cell breakdown process is the primary cause of an unbalanced state, though other factors may also play a role.[2] If left untreated, this disease may result in systemic involvement, which may include a few neurological manifestations like encephalopathy and cause severe, lifelong developmental disabilities.[3-5]Sharp increase in bilirubin levels causes acute bilirubin encephalopathy (ABE) which may lead to chronic bilirubin encephalopathy (CBE), Bilirubin Induced Neurological Damage (BIND) a permanent neurological disability that is debilitating.[6-8]

One of the common treatment strategies for treating neonatal jaundice is phototherapy. In infants with unconjugated hyperbilirubinemia, phototherapy not only lowers serum bilirubin levels but also has a number of physiological effects. Recent research has demonstrated that phototherapy affects blood electrolyte levels—including serum calcium levels—unfavorably.[9] These electrolytes and trace elements are essential for supporting the development, growth, and general health of newborns.[10,11]Calcium is one of the most significant electrolytes and is essential for newborn metabolism, early childhood growth, and development.

According to American academics of Paediatrics, the neonates with mild to moderate hyperbilirubinemia phototherapy is advised whereas for cases with severe hyperbilirubinemia where they are at risk of neurological damage exchange transfusion is indicated. During phototherapy, infants are exposed to blue light with wavelengths between 460 and 490 nm. This light transforms unconjugated bilirubin in the skin into less dangerous water-soluble photo-isomers, which are then excreted in their unconjugated forms in the bile and urine. Additionally documented adverse effects of phototherapy include a rise in body temperature, loose stools, skin rashes, bronze baby syndrome, changes in the retina, dehydration, a drop in serum calcium levels, and genotoxicity.[12]

In light of the aforementioned factors and the significant proportion of term neonates who present with unconjugated hyperbilirubinemia, the current study was conducted to examine the impact of phototherapy on serum and ionized calcium levels as well as the clinical symptoms brought on by hypocalcemia. This research focused solely on term neonates because preterm infants and infants with other co-morbidities may have a confounding impact on calcium metabolism.

MATERIALS AND METHODS

This cross-sectional study was carried out at a tertiary care hospital in south India at Vydehi Institute Of Medical Sciences & Research Centre, Bangalore, Karnataka, India for 18 months between February 2021 and August 2022, enrolling 94 neonates who met the inclusion criteria. Prior approval of the Ethics Committee was obtained and a written informed consent was taken from the parents.

Infants with birth asphyxia, conjugated hyperbilirubinemia, neonates with sepsis, Hyperbilirubinemia requiring exchange transfusion & preterm neonates were excluded from the study. Babies who were found to be hypocalcaemic prior to phototherapy were excluded from the study.

Detailed history including mode of delivery, intranatal history, immediate postnatal history, maternal history, history of phototherapy in sibling, death of sibling due to hypercalcemia, family history of seizure disorders and congenital anomalies (as given by the neonate's mother) was taken.

Both inborn & referred neonates having unconjugated hyperbilirubinemia requiring phototherapy as per American academy of pediatrics guidelines were included in the study after considering the inclusion & exclusion criteria.

Blood samples were forwarded to estimate serum calcium levels, ionized calcium levels and serum bilirubin levels at the start of phototherapy and at discontinuation of phototherapy or at 48 hours of phototherapy, whichever was earlier.

Cases were given single or double surface phototherapy depending upon their serum bilirubin values. Phototherapy was given according to the criteria of American Academy of Pediatrics.

Hypocalcemia was defined as total serum calcium level less than 8mg/dl (2mmol/L) or ionized calcium level less than 4.8mg/dl (1.2mmol/L).

Total bilirubin was estimated by JendrassikGroffs method. Direct bilirubin was estimated by Diazo method. Total calcium was measured using ISE Electrolyte buffer reagent and ISE electrolyte reference reagent kit method. Ionized calcium was estimated by calcium ion-selective electrode (ISE) direct potentiometry technique (Acid base analyzer machine).

Phototherapy was given using blue LED lights having a wavelength of 450-465nm and irradiance of up to 45 µW/cm2/nm. Eyes and genitalia were completely covered during phototherapy.

The data was analyses using SPSS (Statistical package for social sciences) Version 20th software. Continuous variables were presented as Mean ± SD or Median (Q1, Q3). Qualitative variables were presented as frequency & percentage. Kappa value was evaluated between the Serum & ionic calcium test, so as to evaluate the agreement between both the tests. P value <0.05 was considered as statistically significant.

RESULTS

The present study is a cross-sectional comparative study in which serum and ionized calcium levels of term babies with unconjugated hyperbilirubinemia undergoing phototherapy were studied. The data obtained using different parameters, like pre and post serum bilirubin levels, pre and post ionized and total serum calcium levels were analyzed.

In the present study, 34.0% of babies were delivered around 38 weeks of gestation followed by 33% at 39 weeks of gestation, 20.2% at 37 weeks of gestation and 12.8% at 40 weeks of gestation. In the present study majority of the neonates were males (51.1%) whereas 48.9% were females, birth weight of majority of the neonates (66%) was more than 2500 grams and above. Whereas in 34% of the neonates the birth weight was <2500 grams , a majority

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neonates – 57.4% had normal vaginal delivery and 42.6 % were delivered by caesarean section.

The mean Serum Total Bilirubin level before phototherapy in neonates was 15.05 mg/dl with standard deviation of 1.51 mg/dl. Whereas after phototherapy mean Serum Total Bilirubin level in neonates was 12.18 mg/dl with standard deviation of 1.78 mg/dl. [Table 1]

Table 1: Comparison of mean Serum Total Bilirubin levels before and after phototherapy.

Total Bilirubin (mg/dl)	Minimum	Maximum	Mean	Median	SD	IQR	P-value
Pre-PT	12.20	18.00	15.05	15.05	1.51	2.10	<0.001
Post-PT	8.50	14.98	12.18	12.81	1.78	2.84	

In the present study, majority of the neonates (47.9%) were exposed to phototherapy for between 24 to 48hours. Whereas 41.5% were exposed for 12-24 hours and 10.6% were exposed to phototherapy for less than 12 hours. [Table 2]

Table 2: Distribution of neonates based on duration phototherapy administered

Duration of PTadministered (hours)	Frequency	Percent
<12	10	10.6
12--24	39	41.5
24--48	45	47.9
Total	94	100.0

The mean Serum Direct Bilirubin levels before phototherapy in neonates was 0.58 mg/dl with standard deviation of 0.14 mg/dl. Whereas after phototherapy mean Serum Direct Bilirubin level in neonates was 0.51 mg/dl with standard deviation of 0.14 mg/dl.

The mean Serum Calcium level before phototherapy was 9.09 mg/dl with standard deviation of 0.50 mg/dl. Whereas after phototherapy mean Serum Calcium level in neonates was 8.39 mg/dl with standard deviation of 0.54 mg/dl. [Table 3]

Table 3: Comparison of mean total serum calcium levels before and after phototherapy.

Serum Calcium (mg/dl)	Minimum	Maximum	Mean	Median	SD	IQR	P-value
Pre-PT	8.30	9.98	9.09	9.11	0.50	0.88	<0.001
Post-PT	7.58	9.55	8.39	8.49	0.54	0.88	

The mean Serum Ionized Calcium level before phototherapy in neonates was 1.30 mmol/L with standard deviation of 0.05 mmol/L. Where as after phototherapy mean Serum Ionized Calcium level in neonates was 1.18 mmol/L with standard deviation of 0.13 mmol/L [Table 4].

Table 4: Comparison of mean ionized calcium levels before and after phototherapy.

Ionized Calcium	Minimum	Maximum	Mean	Median	SD	IQR	P-value
Pre-PT	1.22	1.37	1.30	1.32	0.05	0.09	<0.001
Post-PT	0.85	1.36	1.18	1.24	0.13	0.19	

It was observed that as the duration of phototherapy increases the incidence of hypocalcemia increased. Overall, 41.5% of neonates developed hypocalcemia and the remaining 58.5% were normal at the end of phototherapy.

Hypocalcemia was seen most commonly in neonates requiring phototherapy for more than 24hours. Only 3 neonates developed hypocalcemia on exposure to phototherapy for 12 to 24 hours. None of the neonates who received phototherapy for <12 hours developed hypocalcemia.There was a statistically significant association between decline in serum calcium levels and the duration of exposure to phototherapy. [Table 5]

Table 5: Relationship between the duration of phototherapy with the incidence of hypocalcemia based on Serum Calcium testing.

Duration of PT administered (hours)	Serum Cal Post				Total hypocalcaemic neonates at the given time interval	
	New onset Hypocalcemia		Normal		Number	%
	Count	%	Count	%		
<12	0	0.0%	94	100.0%	0	0%
12--24	3	3.1%	91	96.8%	3	3.1%
24--48	36	38.2%	55	58.5%	39	41.5%
Total	39	41.5%	55	58.5%	39	41.5%
P<0.001						

On applying Kappa Statistics, the kappa value between serum calcium and ionic calcium testing was found to be 0.91. [Table 6]

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Table 6: Kappa statistics for comparison of prevalence of Post phototherapy hypocalcemia based on total serum calcium and ionized calcium level estimation

Serum Calcium Post	Ionic Calcium Post			
	Hypocalcemia		Normal	
	Count	%	Count	%
Hypocalcemia	39	90.7%	0	0.0%
Normal	4	9.3%	51	100.0%
Total	43	100.0%	51	100.0%
Kappa value = 0.91;P<0.001				

Table 7: Sensitivity and specificity of serum calcium estimation compared to ionic calcium estimation.

Statistic	Value	95% CI
Sensitivity	90.70%	77.86%to 97.41%
Specificity	100.00%	93.02%to 100.00%
Positive Predictive Value	100.00%	-
Negative Predictive Value	92.73%	83.37%to 97.01%
Accuracy	95.74%	89.46%to 98.83%

It was found that ionized calcium testing had higher sensitivity for detecting hypocalcemia. The sensitivity of serum calcium testing with respect to ionized calcium testing was found to be 90.70%. The serum calcium test had an accuracy of 95.74% as compared to ionic calcium testing. [Table 7]

DISCUSSION

One of the most frequent reasons for NICU hospitalizations is neonatal hyperbilirubinemia, also known as neonatal jaundice. Neonatal hyperbilirubinemia can be treated reasonably safely and successfully with phototherapy. Hypocalcemia is one of the side effects of electrolyte imbalances in neonates, which have been documented in earlier research. The objective of this cross-sectional research was to determine how phototherapy affected serum and ionized calcium levels. The effects of hypocalcemia brought on by phototherapy were also evaluated.

In the present study 51.1% were male neonates and 48.9% were female neonates. Similarly in the study done by Kale AV et al,[13] 53% were males and 47% were females. However, in the study done by Khan A et al,[14] 65% were male neonates and 35% were female neonates. In our study 57.4% of neonates were delivered through normal vaginal delivery route and 42.6% through lower segment caesarean section (LSCS). Similar findings were reported by Goyal S et al,[15] The mean birth weight of neonates in the present study was 2.6 ± 0.3 kgs which was similar to the study done by Kale AV et al,[13] where the mean birthweight was 2.5 ± 0.4 kgs.

Also, in the our study 67% of neonates were having birthweight of >2.5kgs and 33% were of birthweight <2.5 kgs whereas in the study conducted by Kale AV et al,[13] 62% of neonates birthweight was found to be between 2.5 to 3.5 kgs and only 1% of neonate had birthweight >3.5 kgs. In the present study the mean Serum Total Bilirubin level before phototherapy in neonates was15.05 ± 1.51 mg/dl. Whereas after phototherapy exposure, mean Serum Total Bilirubin level in neonates was 12.18 ±1.78 mg/dl. This decrease in Serum Bilirubin was statistically significant (p<0.001). Similarly, Gupta R et al,[16] in their study reported decrease in Serum bilirubin level from 17.10 ± 2.35mg/dl to 10.18±1.01mg/dl after 48 hours of phototherapy exposure. This difference was found to be significant.

In the present study, we found that majority (47.9%) of the babies needed phototherapy for 24 to 48 hours for adequate response. About 41.5 % babies were administered phototherapy for 12 to 24 hours. Similarly in study conducted by Sreeram S et al,[17] in 2018, they found that the mean duration of phototherapy administered was 32 ± 14 hours. The mean Total Serum calcium levels before phototherapy in neonates was9.09 mg/dl with standard deviation of 0.50 mg/dl. Whereas after phototherapy mean Serum calcium level in neonates was 8.39mg/dl with standard deviation of 0.55 mg/dl. There was statistically significant difference in the mean Serum calcium level between before and after phototherapy values(p<0.001).Similar findings were observed inthestudydonebyKale AV et al.[13]

In a study by Goyal S et al,[15] the mean serum calcium levels before phototherapywas9.14±0.78 mg/dl and it was decreased to (8.53±0.77 mg/dl) after phototherapy treatment. The difference between pre and post phototherapy serum calcium levels were found to be statistically significant (p<0.001).In the our study, the mean Ionized Calcium level before phototherapy was 1.3 mmol/L with standard deviation of 0.05 mmol/L. Whereas post phototherapy, mean Ionized Calcium level was 1.18 mmol/L with standard deviation of 0.13 mmol/L. There was statistically significant mean difference before and after phototherapy in neonates (p<0.001).Similarly in the study done by Pal S et al(18) the mean Serum Ionized Calcium level immediately after birth in neonates was 1.26±0.14 mmol/L. The mean ionized calcium after 24 h of phototherapy was 1.13±0.20 mmol/L. Gupta R et al,[16] also reported decrease in Serum Ionized Calcium level,48hrs after administering phototherapy which was also found to be statistically significant.

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Contrary to our study finding, in the study conducted by Rastogi D et al,[19] total serum calcium levels decreased significantly however decrease in serum ionized calcium was not found to be statistically significant.

On applying Kappa Statistics, the kappa value between serum calcium and ionic calcium testing was found to be 0.91 ($p<0.001$) suggesting excellent inter-test agreement.

In the present study, hypocalcemia was found in 45.7% of neonates, which was comparable to the studies conducted by Pal S et al,[18] and Durga T et al,[20] who found 39 % and 46% of neonates had hypocalcemia post phototherapy respectively. Study done by Khan A et al,[14] also reported 40% prevalence of hypocalcemia inneonatesexposedtophototherapy.InastudybyArora et al,[21] it was reported that 56% term babies developed hypocalcemia post phototherapy.

In some studies, like Gheshmi et al,[22]&Alizadeh-Taheri et al,[23] lower prevalence of hypocalcemia was observed. In their studies, 54% and 56% of neonates showed decline in calcium levels compared to their pre phototherapy levels respectively. However, only 7% and 9% of their neonates developed hypocalcemia respectively. Although patients developing hypocalcemia was low, there was a statistically significant decline in the calcium levels after 48hours of phototherapy, which was comparable to our study.

In our study, it was seen that as the duration of phototherapy increased, the incidence of hypocalcemia increased, with the highest incidence (40.4%) of hypocalcemia seen in the neonates who underwent phototherapy for 24 to 48 hours. In neonates who received phototherapy for 12 to 24 hours 5.3% developed hypocalcemia. None of the infants who received phototherapy for less than 12 hours developed hypocalcemia. These results were similar for both - total serum calcium and ionic calcium levels. Similar findings were observed in studies conducted by Pal S et al,[18]Srinivasa et al,[24] and Eghbalian F et al,[25] who found a decline in calcium levels as the duration of phototherapy increased.

In the present study, 17% of the neonates developed irritability and 21.3% developed Jitteriness. 6.4% of the neonates had rashes, 4.3% had purpuric eruptions and none of the neonates had convulsions. Similarly in the study done by Rashi Aryan Et al,[26] among neonates having hypocalcemia 21% developed symptoms. About 16% of the neonates developed irritability and 33% developed jitteriness. None of them developed convulsions. In contrast, in a study conducted by Pal S et al,[18] only 3% of the neonates developed irritability and jitteriness.

CONCLUSION

It was concluded in our study that total serum & ionic calcium levels were significantly reduced post phototherapy. Ionic calcium was observed to be more sensitive predictor of hypocalcemia compared to total serum calcium. The kappa value between total serum calcium and ionic calcium testing was found tobe 0.91 ($p<0.001$) - suggesting excellent inter-test agreement. As the serum ionized calcium test is more expensive to perform and not easily available in all setups, serum calcium levels can be used routinely for monitoring hypocalcemia among neonates exposed to phototherapy.

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