

Evaluating Association of Hypocalcemia with Duration of Phototherapy in Neonates with Unconjugated HyperbilirubinemiaAjit Kumar Singh¹, Sachin Kumar², Nagendra Prasad Gupta³¹Senior Resident, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India²Senior Resident, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India³Professor, Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India

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Abstract**Aim:** The aim of the present study was to assess the prevalence of hypocalcemia in neonates with unconjugated hyperbilirubinemia receiving phototherapy and to observe association of hypocalcemia with duration of phototherapy.**Material & Methods:** A prospective observational study conducted over a period of 18 months among 100 neonates (both term and preterm) in the Department of Paediatrics**Results:** The mean age of preterm and term neonates was 116.14±44.88 and 124.26±43.17. There were more males as compared to females in preterm and term neonates. Mean birth weight of preterm and term in this study were 2614.12±248.42 grams and 3264.82±372.98 grams respectively. Similarly, 10 term neonates had hypocalcemia 48 hours after starting of phototherapy. None of the preterm neonates enrolled in the study experienced hypocalcemia after starting of phototherapy. It was observed that occurrence of hypocalcemia was not significantly associated with the duration of phototherapy. On comparing the 0 hours calcium level with subsequent hours, the mean difference in total serum calcium levels in both term, and preterm babies were found to be statistically significant and the difference was seen to be more significant in term babies. Correlation analysis of a duration of phototherapy with hypocalcemia showed a negative but insignificant correlation with a coefficient (r of -0.045 and a p=0.95).**Conclusion:** A reduction in the serum calcium with increased duration of phototherapy, however, it does not fall to the level where treatment is required. Hence it is not recommended to monitor serum calcium levels in neonates receiving phototherapy.**Keywords:** Hypocalcemia, Jaundice, Neonates Phototherapy.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Hyperbilirubinemia is one of the most frequent and benign problem in neonates. Hyperbilirubinemia is the most common abnormal physical finding in the first week of life in neonates and is observed in ~60% of term neonates and 80% of preterm infants. [1] Jaundice is the yellowish coloration of the skin, sclera, and mucus membrane resulting from the accumulation of bilirubin. [2] Incidence of jaundice was found to be higher in low birth weight neonates (35.6%) compared with normal birth weight infants (16.9%). [3] High bilirubin level may be toxic to the developing central nervous system and may elicit neurological impairment in newborns. [4] Jaundice is attributable to physiological immaturity of neonates to manage increased bilirubin production. Visible jaundice

usually appears between 24-72 hours of age. Basic pathophysiology of jaundice is same in term and preterm neonates, but premature babies are at a higher risk of developing jaundice. [5]

There are various modalities of treatment for neonatal hyperbilirubinemia and, phototherapy is one of them. It reduces the risk of exchange transfusion. [6] This relatively common therapy lowers the serum bilirubin level by transforming bilirubin into water-soluble isomers that can be eliminated without conjugation in the liver. [7] It blunts the rise of bilirubin level regardless of the etiology of jaundice. [8] Though it is considered safe, a few side effects encountered in phototherapy are loose stools, hyperthermia, dehydration due to fluid loss, skin burn, photo retinitis, low platelet

count, increased red cell osmotic fragility, bronze baby syndrome, riboflavin deficiency and DNA damage. A lesser known side effect, but a potential complication of phototherapy is hypocalcemia. [9] Phototherapy may lead to complications including skin rash, diarrhea, hyperthermia, chills, dehydration, DNA damage to lymphocytes, retinal degeneration, bronze baby syndrome especially in cholestatic jaundice and PDA opening in LBWs and Hypocalcemia. [10]

Besides the useful effects of phototherapy, some complications like hypocalcemia can be seen during the treatment with phototherapy. [10] It leads to inhibition of pineal gland by transcranial illumination, resulting in a decline in melatonin level and as a result, hypocalcemia develops. [11] Hypocalcemia refers to total serum calcium level less than 8 mg/dl in term neonates and less than 7 mg/dl in preterm neonates. [12] Hypocalcemia may cause cardiac and neurological dysfunctions. It may be symptomatic in the form of jitteriness, apnea, lethargy, stridor, irritability, and seizures. [13]

Hence, this study was undertaken to see occurrence of hypocalcemia in preterm and term neonates with hyperbilirubinemia receiving phototherapy, as phototherapy induced hypocalcemia can be a significant problem.

Material & Methods

A prospective observational study conducted over a period of 18 months among 100 neonates (both term and preterm) in the Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India.

Inclusion Criteria

All preterm (34 to less than 37 weeks) and term (37 to 40 weeks) neonates with jaundice and receiving phototherapy were included in the study.

Exclusion Criteria

Neonates with jaundice requiring exchange transfusion, birth asphyxia, sepsis, respiratory distress, ABO and Rh incompatibility, neonatal seizure, IUGR (Intrauterine growth retardation) babies, infants of diabetic mother and neonates with conjugated hyperbilirubinemia and prolonged jaundice were excluded from the study.

Methodology

The socio-demographic and clinical details of the neonates were recorded and entered in pre-designed proforma. In the enrolled neonates, serum total bilirubin and serum calcium levels at 0 hours, 12 hour and after 48 hours were sent in all cases. The serum calcium level estimated just before starting of phototherapy was considered as control and serum calcium level less than 7 mg/dl in preterm neonates and less than 8 mg/dl in term neonates is considered as hypocalcemia.

Statistical Analysis

Data were analyzed using statistical package for social sciences version 21 (SPSS). Continuous variables were described as mean and standard deviation and categorical variables in number and percentage. Hypocalcemia in term and preterm was compared using Fischer exact test. Pearson correlation was applied to see an association between hypocalcemia and the duration of phototherapy. Paired sample t-test was used to compare the means of calcium level before (0 hours) and after (12 hours, 48 hours) phototherapy; with a 95% confidence limit and $p < 0.05$ was considered statistically significant.

Results

Table 1: Demographic profile of neonates admitted for neonatal hyperbilirubinemia

Variables	Preterm	Term
Age in hours (Mean \pm SD)	116.14 \pm 44.88	124.26 \pm 43.17
	Male	33
	Female	37
Sex	15	37
Gestational age in weeks (Mean \pm SD)	36.12 \pm 0.72	37.93 \pm 0.82
Birth weight in grams (Mean \pm SD)	2614.12 \pm 248.42	3264.82 \pm 372.98
TSB in mg/dl at 0 hours (Mean \pm SD)	17.4 \pm 2.32	18.04 \pm 1.92
Serum calcium in mg/dl at 0 hours (Mean \pm SD)	9.42 \pm 0.96	9.64 \pm 0.82
Duration of phototherapy in hours (Mean \pm SD)	65 \pm 9.48	64.56 \pm 9.75

The mean age of preterm and term neonates was 116.14 \pm 44.88 and 124.26 \pm 43.17. There were more males as compared to females in preterm and term neonates. Mean birth weight of preterm and term in this study were 2614.12 \pm 248.42 grams and 3264.82 \pm 372.98 grams respectively.

Table 2: Serum calcium level at 12 hours and, after 48 hours

Duration of phototherapy	Serum calcium level	Preterm, n (%)	Term, n (%)	P value
At 12 hours	Hypocalcemia present	0	5	1
	Hypocalcemia absent	30	70	
	Total	70	62	
After 48 hours	Hypocalcemia present	0	10	0.12
	Hypocalcemia absent	30	60	
	Total	30	70	

5 term neonates experienced hypocalcemia at 12 hours after starting of phototherapy. Similarly, 10 term neonates had hypocalcemia 48 hours after starting of phototherapy. None of the preterm neonates enrolled in the study experienced hypocalcemia after starting of phototherapy. It was observed that occurrence of hypocalcemia was not significantly associated with the duration of phototherapy.

Table 3: Comparison of serum calcium at 0 hour with subsequent hours (at 12 hours and after 48 hours) in term and preterm neonates receiving phototherapy

Gestational age (Weeks)	Comparison of serum calcium (Hours)	Mean paired difference (mg/dl) \pm SD	P value
Preterm (34-37)	0 and at 12	0.512 \pm 0.600	0.003
	0 and after 48	0.710 \pm 0.854	0.004
Term (38-41)	0 and at 12	0.525 \pm 0.713	<0.001
	0 and after 48	0.912 \pm 0.770	<0.001

On comparing the 0 hours calcium level with subsequent hours, the mean difference in total serum calcium levels in both term, and preterm babies were found to be statistically significant and the difference was seen to be more significant in term babies.

Table 4: Correlation of hypocalcemia in term neonates with duration of phototherapy

Correlation	R	CI for r	P value
Negative	-0.045	-0.740 to 0.773	0.95

Correlation analysis of a duration of phototherapy with hypocalcemia showed a negative but insignificant correlation with a coefficient (r of -0.045 and a p=0.95).

Discussion

Jaundice is the yellowish coloration of the skin, sclera, and mucus membrane resulting from the accumulation of bilirubin. [14] It is a common morbidity observed in the neonate during the first week of life in approximately 60% of term and 80% of preterm neonates. In most of the neonates no intervention is required however, 5-10% of the cases have clinically significant jaundice, which requires treatment. [15,16] High level of unconjugated bilirubin may cause permanent neurological damage. [17,18] There are various modalities of treatment for neonatal hyperbilirubinemia and, phototherapy is one of them. Besides the useful effects of phototherapy, some complications like hypocalcemia can be seen during the treatment with phototherapy. [19] Hypocalcemia is a significant problem in neonates subjected to phototherapy and its prevalence in full term neonates is 8.7%. [20] Hypocalcemia developed in 39% of term and 53% of preterms after being subjected to phototherapy for more than 48 hours. [21] Hypocalcemia, being a major complication of phototherapy, is associated with poor prognosis in terms of high mortality rate as compared to babies with normocalcemia, if not diagnosed timely and treated accordingly. [21,22]

The mean age of preterm and term neonates was 116.14 \pm 44.88 and 124.26 \pm 43.17. There were more

males as compared to females in preterm and term neonates. Mean birth weight of preterm and term in this study were 2614.12 \pm 248.42 grams and 3264.82 \pm 372.98 grams respectively. In a study done by Taheri et al mean birth weight in term neonates was 3182 \pm 430 grams which were agreed with the term neonates of our study. [23] Hypocalcemia refers to total serum calcium level less than 8 mg/dl in term neonates and less than 7 mg/dl in preterm neonates. [24] Hypocalcemia may cause cardiac and neurological dysfunctions. It may be symptomatic in the form of jitteriness, apnea, lethargy, stridor, irritability, and seizures. [25]

Similarly, 10 term neonates had hypocalcemia 48 hours after starting of phototherapy. None of the preterm neonates enrolled in the study experienced hypocalcemia after starting of phototherapy. It was observed that occurrence of hypocalcemia was not significantly associated with the duration of phototherapy. In the study by Chandrashekhara [26] prevalence of hypocalcemia was seen in 11%, 27%, and 68.5% at 24 hours, 36 hours, and 48 hours of phototherapy in preterm neonates and 6%, 14%, and 16% at 24 hours, 36 hours and 48 hours of phototherapy in term neonates respectively however, in this study serum calcium level of less than 7 mg/dl was considered as hypocalcemia in both term and preterm which is in contrast to this study. Phototherapy is the most effective therapy

for management of neonatal hyperbilirubinemia which lowers serum bilirubin level by converting bilirubin into non-toxic excretable form. [27] Phototherapy converts unconjugated bilirubin to more polar stereoisomer by a process called photo isomerization. The substance formed cannot cross the blood brain barrier and is not neurotoxic and later on excreted out of the body via urine and bile. [28]

On comparing the 0 hours calcium level with subsequent hours, the mean difference in total serum calcium levels in both term, and preterm babies were found to be statistically significant and the difference was seen to be more significant in term babies. Correlation analysis of a duration of phototherapy with hypocalcemia showed a negative but insignificant correlation with a coefficient ($r = -0.045$ and a $p=0.95$). This indicates that the duration of phototherapy causes little or no significant hypocalcemia in term neonates before the discharge. However, no similar studies have been published to date which could indicate or determine the correlation between the duration of phototherapy and hypocalcemia before discharge i.e., after 48 hours.

Conclusion

The present study concluded that though there is a reduction in the serum level of calcium with increasing duration of phototherapy, it does not fall to the level where treatment is required. Hence it is not recommended to monitor serum calcium levels in neonates receiving phototherapy.

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