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Original Research Article

Prevalence of hypocalcemia in term newborns requiring phototherapy

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ABSTRACT

Background: Neonatal hyperbilirubinemia in the first week of life is one of the most prevalent clinical entity observed, affecting 60% of term-babies and 80% of preterm newborn babies, many requiring intervention in the form of phototherapy. The effect of phototherapy on serum calcium levels has not been studied much in Indian literature. The objectives of this study was to evaluate the prevalence of hypocalcemia in healthy, term newborn babies receiving phototherapy for unconjugated hyperbilirubinemia and to determine the association, if any between serum calcium and birth weight, postnatal age at start of phototherapy, weight at enrolment, gestational age at birth, maternal age and duration of phototherapy.
Methods: This was a prospective observational study conducted over a period of 10 months among 80 term neonates admitted to the inpatient department at a tertiary care centre in Mumbai**.** Total serum calcium and ionised calcium levels were measured at the start of phototherapy and on stopping phototherapy/discharge. Data were analysed using statistical package for social sciences (SPSS) version 21 software.
Results: Two (2.5%) out of the 80 neonates were found to have hypocalcemia after phototherapy with serum ionic calcium levels less than 1 mmol/l. Even though a larger proportion of neonates showed a decrease in the serum total calcium (56.25%) and serum ionic calcium (58.75%) levels after phototherapy, none of the neonates developed symptomatic hypocalcemia at those levels. A statistically significant association was found between maternal age in years with the serum total calcium levels after phototherapy and age at starting phototherapy (in hours) with the serum ionic calcium levels after phototherapy.
Conclusions: The present study concludes that there is significant decrease in the levels of ionised calcium after phototherapy, however there was no significant decrease in the total serum calcium levels and none of the neonates were symptomatic**.** Hence, we do not recommend regular serum calcium monitoring in healthy term neonates receiving phototherapy and find no indication for the prophylactic use of calcium supplementation in these neonates.

Keywords: Phototherapy, Neonates, Hypocalcemia

INTRODUCTION

Phototherapy is the commonest and the most-effective mode of therapy used in the management of pathological indirect hyperbilirubinemia. It works through the mechanisms of photoisomerisation, structural isomerisation and photo-oxidation.[3] Though effective, it is has adverse effects like insensible water loss, watery diarrhea and increased fecal water loss, dehydration, retinal damage, bronze baby syndrome, opening of patent ductus arteriosus (PDA) in the low-birth weight (LBW) babies, mutations, sister chromatid exchange and DNA strand breaks.[2] Hypocalcemia, which can be associated with jitteriness, irritability, convulsion, apnoea and stridor, is one of its lesser studied side-effects. [1] Inhibition of the pineal gland, inhibition of parathormone secretion and increased urinary excretion are the supposed mechanisms for the causation of hypocalcemia following

phototherapy.[4,6,7] The reported prevalence of hypocalcemia in term babies receiving phototherapy has a wide range (3-75%).[8,9,11,17]

Considering the uncertainty about its prevalence globally, we embarked on this study to determine the prevalence of hypocalcemia in healthy, term newborn babies receiving phototherapy for unconjugated hyperbilirubinemia and to determine the association, if any between serum calcium and birth weight, postnatal age at start of phototherapy, weight at enrolment, gestational age at birth, maternal age and duration of phototherapy.

METHODS

Various details regarding the performance of the research study are enumerated below.

Study site

This single-center prospective observational study was carried out at a private tertiary care hospital in a metropolitan city of India. The hospital has a 105- bedded neonatal intensive care unit (NICU) and is affiliated to National Board of Examination and the State Health University. The NICU has approximately 900 admissions annually and is equipped with 14 phototherapy units of GE Lullaby LED phototherapy system, 24V.

Study population

Term newborn babies (gestational age: 37-41 weeks) with unconjugated hyperbilirubinemia requiring phototherapy were included in the study. Infants born to mother on anti-convulsant drugs or with diabetes, infants with onset of jaundice within 24 hours of age, perinatal asphyxia (APGAR score <7 at 5 min), congenital anomalies, sepsis or serum calcium (total) less than 7 mg/dl at the initiation of phototherapy were excluded from the study.

Methodology

After confirming eligibility for participation in the study based on history, examination and review of medical records, the enrolled babies were administered phototherapy (initiation, continuation, discontinuation) as per the clinical practice guidelines on management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation provided by the American Academy of Pediatrics (AAP)[5] using GE Lullaby LED phototherapy system, 24V which used blue light with a wavelength of 420-465 nm with a high irradiance of 45 μw/cm^2/nm and low irradiance of 22 μw/cm^2/nm.

Serum calcium (total and ionic) levels were determined at the initiation and discontinuation of phototherapy. No separate blood collection/ venepuncture was done for the purpose of the study. Sample for the determination of serum calcium was obtained from the sample collected for the determination of bilirubin (total and direct) level. Levels of calcium (total) in the serum were estimated by O-cresolphthalein complexone (OCPC) method on COBAS C 111 analyzer machine, while those of ionic calcium were measured by ion-selective electrode method. For the purpose of the study, hypocalcemia was defined as the total serum calcium concentration of <7 mg/dl or ionized calcium concentration of <4 mg/dl (<1 mmol/l).[3]

Study duration

The study conduct was planned for a period of 10 months.

Sample size

The sample size was calculated by using the formula for 1 proportion with 95% confidence interval.[18] The sample size was estimated as 80.

$$n = z^2{}_{1-\alpha/2} p\ (1-p)]/d^2$$

Wherein, $z_{1-\alpha/2} = 1.96;\ p = 0.3\ (30\%); 1 - p = 0.7\ (70\%); d - margin\ of\ error\ of\ 10\% = 0.1$

Outcome measures

Proportion of term-babies receiving phototherapy for neonatal hyperbilirubinemia (indirect) developing hypocalcemia was the primary outcome measure. The secondary outcome measures included association of post-phototherapy serum calcium levels with the following factors: birth weight, gestational age at birth, postnatal age at enrolment, maternal age, duration of phototherapy and weight at enrolment.

Data management

Data was collected on enrolment from the maternal and infant medical records and entered in the case record forms. The information of the case record form was entered in an excel master-sheet and was analysed by independent statistical analyser, not involved in the study.

Statistical analysis

Data was analysed using IBM statistical package for social sciences (SPSS) version 21 software. The baseline characteristic which were on continuous scale, for them mean and standard deviation (SD) were calculated. The association between total and ionic calcium before and after phototherapy was analysed using the paired 't' test. A p value of less than 0.05 was considered statistically significant. Linear regression analysis was performed using analysis of variance (ANOVA) for assessing the association between birth weight, gestational age at birth, postnatal age at enrolment, maternal age, weight at enrolment and duration of phototherapy and serum total calcium and serum ionic calcium after phototherapy. Analysis of variance was performed by putting dependent variable (outcome variable) as serum total and ionic

calcium after phototherapy and predictor variables as birth weight, gestational age at birth, postnatal age at enrolment, maternal age, weight at enrolment and duration of phototherapy.

Ethics

The study was approved by the institutional ethics committee and the participants were enrolled after obtaining written informed consent from a parent or guardian.

RESULTS

The participants were enrolled over a 10-month period beginning January 2019. On screening 84 participants, 80 babies (male infants 42, 52.5%) were found eligible and were enrolled. The baseline characteristics of the study population are shown in Table 1.

Table 1: Baseline characteristics of study population.

Variables	Unit	Mean± SD	Range
Gestational age	Week	37.93±0.93	37-40.42
Birth weight	Gram	2969.05±525.04	1850-5080
Maternal age	Year	31.11±4.28	21-44
Age at start of phototherapy	Hour	76.21±30.49	32-152
Weight at enrolment	Gram	2802.70±488.61	1800-4875

Twenty-one (26.25%) were delivered vaginally. Forty (50%) were exclusively breastfed, while the rest had received at least one formula feed in addition to the breastmilk. Seventy-nine mothers received calcium supplementation during pregnancy. Co-morbid conditions in the mothers included hypothyroidism 11 (13.75%), pregnancy-induced hypertension (PIH; 5, 6.25%) and bronchial asthma, psoriasis and ANA positivity (1 each, 1.25% each). One mother had hypothyroidism and PIH.

As shown in Table 2 there was a significant difference between the ionic levels of calcium in the serum before and after phototherapy. The serum total calcium levels after phototherapy were lower than those at the initiation of phototherapy in 45 (56.25%) babies, while they were increased in 34 (42.5%) babies. The levels of ionic calcium after phototherapy were lower than those prior to phototherapy in 47 (58.75%) babies. No change in the levels of ionic calcium in the serum was noted in one (1.25%) baby. Thirty-two babies (40%) had an increase in the levels of ionic calcium in the serum following phototherapy. Two (2.5%) out of the 80 babies developed hypocalcemia with serum ionic calcium levels less than 1 mmol/l. However, none of the babies developed clinical manifestations of hypocalcemia.

Table 2: Mean levels of total and ionic calcium levels before and after phototherapy.

Variables	Before phototherapy	After phototherapy	P value
Serum total calcium (mg/dl)	9.97±0.76	9.90±0.68	0.26
Serum ionic calcium (mmol/l)	1.23±0.10	1.20±0.10	0.025*

* Statistically significant

There was a significant association between maternal age and post-phototherapy total calcium levels in the serum (p=0.010) and between age at the initiation of phototherapy and post-phototherapy ionic calcium levels in the serum (p=0.004).

DISCUSSION

The study demonstrated that there was a drop in the serum levels of both total calcium and ionic levels following phototherapy and that the reduction in ionic calcium levels was statistically significant. The post-phototherapy total calcium levels in the serum were lower than pre-therapy levels in 45 (56.25%) babies while the post-phototherapy ionic calcium levels in the serum were lower than the pre-therapy levels in 47 (58.75%) babies. Two (2.5%) infants developed ionic hypocalcemia, but were asymptomatic. There was a significant association between maternal age and post-phototherapy serum total calcium levels and between infant's age at starting phototherapy and post-phototherapy serum ionic calcium levels.

Several investigators who have studied the relationship between phototherapy and serum calcium levels have noted that levels of total and ionized calcium in the serum fall at 48 hours of phototherapy (Table 3).[8,14,16,17] Our study also noted these findings and the fall in the ionic levels was statistically significant. The differences arise regarding the prevalence of hypocalcemia following phototherapy. Several studies (all published in 2016 or earlier) have noted high prevalence (25-75%) of hypocalcemia following 48-hours of phototherapy.[8,9,14,15] In contrast, there are investigators who reported lower prevalence of hypocalcemia (sub-10%) in their study populations.[11,12,16,17] Our study has reported the lowest levels for prevalence of hypocalcemia among the studies listed in Table 3. The exact reason for the wide range of prevalence reported has not been probed and could be a research question for future studies. Our study found a significant association between post-phototherapy total calcium level and maternal age and between post-phototherapy serum ionic calcium level and infant's age at initiation of phototherapy.

However, considering the small numbers, these observations need to be probed further. Studies exploring the association with type of light used for phototherapy and maternal calcium levels may have to be undertaken. Various investigators, especially those reporting higher prevalence of hypocalcemia have described symptomatic infants with jitteriness, irritability, lethargy and even convulsions. Similar to Sarvanan et al, none of the babies enrolled in our study developed any symptoms.[11] The studies with lower prevalence have reported children with similar symptoms but at much lower frequencies. Measures such as monitoring of calcium levels, head covering and calcium supplementation have been proposed by investigators. However, studies reporting lower prevalence rates have not suggested any such measures.

Table 3: Summary of studies regarding serum calcium levels after phototherapy.

Study details	Remarks
Sethi et al[8] India, 1993	Enrolled 60 neonates (term and pre-term) in study and control groups. Significant fall in the total and ionic calcium levels. 75% of the term neonates developed hypocalcemia. Recommendation: supplemental calcium to neonates requiring phototherapy
Jain et al[9] India, 1998	Enrolled 60 (term and pre-term) neonates in study- and control-groups. Hypocalcemia in 6 (30%) term neonates. Manifestations: jitteriness 3, irritability 1. Recommendation: supplemental calcium supplementation
Karamifer et al[12] Iran, 2002	153 jaundiced (term: 91) infants enrolled. Hypocalcemia in 8 (8.70%) term neonates. No one symptomatic.
Yadav et al[15] India, 2012*	Enrolled: study group 30 (15 term) infants; control group 20 (10 term). Ten (66.6%) of the term neonates developed hypocalcemia. Eight (53.33%) term infants were symptomatic: jitteriness (3), irritability (2), lethargy (3). Suggestion: consider calcium supplementation
Jain et al[13] India, 2015*	200 (term: 155) enrolled. Ionic hypocalcemia in 61 (39.3%) term neonates at 48-hours of phototherapy. Symptomatic: 13 (8.39%), lethargy in 6 (3.87%), jitteriness 7(4.52%)
Bahbah et al[14] Egypt, 2014	Study group: 50 term neonates, control: 25 term neonates. Significant decrease of serum calcium levels after phototherapy in study group. Hypocalcemia in 13 (26%). Jitteriness (7, 14%) and convulsions (5, 10%). Suggestions: head covering or calcium supplementation to prevent phototherapy induced hypocalcemia
Prabhakar et al[10] India, 2016*	84 term neonates (24 cases, 60 matched controls) enrolled. Hypocalcemia in 16 (66.67%) infants in the study group. Symptoms of hypocalcemia in 13 (54.17%): jitteriness (5, 20.83%), irritability (5, 20.83%), lethargy (3, 12.5%).
Saravanan et al[11] India, 2017	198 term infants enrolled, 15 (7.50%) developed hypocalcemia. None was symptomatic
Rozario et al[17] India, 2017	100 term infants enrolled, 67 showed decrease in serum calcium levels after phototherapy. Three (3%) developed hypocalcemia. None were symptomatic.
Goyal et al[16] India 2018*	Study group: 52 (35 term) infants, control group: 26 (18 term) infants. Significant fall in serum calcium (total, ionic) levels in the study group (that included preterm babies as well) after phototherapy. Hypocalcemia in 3 (8.50%) term-neonates. Recommendation: calcium supplementation
Present study, 2019	Enrolled 80 term neonates. Decrease in serum total calcium levels after phototherapy was not statistically significant. 2.50% developed ionic hypocalcemia. No one developed symptoms

*Studied ionic as well as total calcium levels in the serum. Others studied only serum total calcium levels

The study has certain strengths and unique features. We enrolled adequate number of participants calculated as per the sample size estimation and the sample studied was larger than that studied by some other investigators.[8,9,14,15] Also, in contrast to various studies that have only studied the total calcium levels; we studied total as well as ionic calcium levels.[11,12,14,17] The importance of estimating ionic calcium levels cannot be over-emphasized, since it is the component that is primarily responsible for maintaining the integrity of neuromuscular functioning, blood coagulation and cell enzymatic and secretory activities. It is also not influenced by factors such as serum protein levels. Most studies have chosen to determine serum calcium levels after only 48- hours of exposure to phototherapy.[9-15,17] As it has been observed that the degree of reduction in serum calcium levels is related to the duration of exposure to phototherapy, we have included babies who received phototherapy at least for 48 hours and have determined the serum calcium levels on the day, the phototherapy was discontinued.[16] Thus, it can be assumed that the study, by determining the calcium levels after the maximum possible period of exposure to phototherapy, has recorded the nadir of serum calcium levels in the enrolled babies. The absence of a control group may be construed to constitute a limitation. Some studies did have a control group of normal or mildly jaundiced babies, who

did not require phototherapy. Many of them have not specified the timing of sampling in controls, corresponding to post-exposure sample of the study group. As the healthy babies are generally discharged at 48 hours of birth, it would have been difficult to obtain sufficient number of age- matched controls. Also, it would have been logistically difficult to subject normal term babies to a planned blood collection only for the purpose of the study.

Although, the overall evidence appears to suggest that term infants have lower levels of serum total and ionic calcium after exposure to phototherapy; definitive conclusions cannot be reached, as there is a paucity of robust studies with control population. The importance of controls cannot be over-emphasized, as normally, the serum calcium levels which are higher than the maternal levels at birth decrease progressively over 24-48 hours after birth and achieve normal levels by the tenth post-natal day.[1] Our study adds to the evidence that the prevalence of hypocalcemia following phototherapy is quite low. In view of the low prevalence (2.5%) of hypocalcemia found in our study with none of the babies developing any symptoms of hypocalcemia; recommending calcium supplementation to term babies requiring phototherapy would not be appropriate. Considering the wide range of prevalence reported, it may be prudent to find more definitive evidence by conducting studies with age-matched controls and by designing studies to determine factors (maternal calcium status, socioeconomic status of families) that are associated with occurrence of hypocalcemia in term infants exposed to phototherapy.

CONCLUSION

Hypocalcemia was found in 2.5% of the term jaundiced neonates receiving phototherapy. There was no statistical significance in the decrease of serum total calcium levels after phototherapy. However, a statistically significant decrease in serum ionic calcium was noted post phototherapy. A statistically significant association was found between maternal age (in years) and serum total calcium after phototherapy and age at starting phototherapy (in hours) and serum ionic calcium after phototherapy. Hence, we do not recommend regular serum calcium monitoring in healthy term neonates receiving phototherapy and find no indication for the prophylactic use of calcium supplementation in these neonates.

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