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Incidence of Phototherapy Induced Hypocalcemia in Hyperbilirubinemic Neonates: A Cross Sectional Study

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Abstract

Aim: To study the incidence of hypocalcemia in neonates with hyperbilirubinemia during phototherapy.

Methods: A prospective cross sectional study conducted in pediatric tertiary care hospital. 112 newborns were included in the study and randomized in two equal groups with 56 newborns in each group A(Preterm neonates) and B(Term neonates). Blood samples were drawn from all newborns for measurement of serum ionic calcium, total serum bilirubin and blood group. Total serum bilirubin was measured at the start of phototherapy, 24 hours, 48 hours and then at the end of phototherapy. Serum ionized calcium level was measured at the start of phototherapy and after completion of 48 hours of phototherapy.

Results: The mean serum ionic calcium in group A (preterm neonates) and group B (Term neonates) at 0 hrs and 48 hrs after phototherapy was 4.71 mg/dl, 4.14 mg/dl and4.68 mg/dl, 4.34 mg/dl respectively with a mean difference of 0.57 mg/dl and 0.34 mg/dl with an SD of 0.37and0.24. This decline in serum ionic calcium was statistically significant in both groups. ($p< 0.001$). On comparing the mean decline in serum ionic calcium after 48 hours of phototherapy in group A and group B was 0.57 ± 0.37 mg/dl and 0.34 ± 0.24mg/dl respectively. This decline in serum ionic calcium was significantly higher in group A. ($p<0.001$). Incidence of hypocalcemia found in our study; Group A (Preterm neonates) 26.8% newborns and Group B (Term neonates), 14.3% neonates.

Conclusion: There is a significant decrease in serum calcium levels in neonates with receiving phototherapy and more decrease in serum calcium level in preterm neonates compared to term neonates, but difference of hypocalcemia and symptomatic hypocalcemia was not significant.

Keywords: Serum calcium; Hypocalcemia; Hyperbilirubinemia; Phototherapy.

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Introduction

Hyperbilirubinemia is a common and benign problem in the first week of life in neonates with a prevalence of 60% in full-term newborns who are affected with jaundice.[1] High bilirubin levels can be toxic for central nervous system development and may cause behavioral and neurological impairment.[2],

Phototherapy decreases the serum bilirubin level by transforming bilirubin into water-soluble isomers that can be eliminated without conjugation in the liver.[3] But phototherapy also has some complications like insensible water loss, watery diarrhoea, retinal damage, tanning, bronze baby syndrome in cholestasis, DNA strand break and upsets maternal-infant interaction.[4]

Moreover, one of these complications is hypocalcemia, Neonatal Hypocalcemia is defined as total serum calcium of less than 7 mg/dL or ionized calcium less than 4 mg/dL(1mmol/L) and hypocalcemic symptoms are more likely to occur with an ionized calcium concentration of <1mmol/L in term infants.[5]

It usually manifests as apnea, seizures, jitteriness, extensor tone, clonus, hyperreflexia and stridor (laryngospasm).[5] It was also found that only a few hypocalcemic neonates present clinically and in almost all hypocalcemic neonates serum level of calcium return to normal after 24 hrs of ending phototherapy.[6]

It has been hypothesized that phototherapy inhibits pineal secretion of melatonin, which blocks the effect of cortisol on bone calcium. Therefore, cortisol increases bone uptake of calcium and induces hypocalcemia.[7] There are few other studies also on the hypocalcemic effect of phototherapy.

What is already known?
Conventional phototherapy reduces the serum calcium levels in neonatal hyperbilirubinemia.
What is not known? (Research Question)
To know the incidence of phototherapy induced hypocalcemia and comparision of hypocalcemia in both term and pretem neonates.

Methods

This prospective Cross sectional study was conducted at the Special Care Baby Unit (SCBU), in pediatric tertiary care hospital in north- eastern india, during the period from April 2016 to March 2017. All preterm and term neonates admitted in SCBU with hyperbilirubinemia receiving phototherapy are included in our study. For the purpose of the study, subjects with gestational age of >36 weeks according to New Ballard score was considered 'Term' gestation.

Inclusion Criteria: All Newborns admitted to SCBU with unconjugated hyperbilirubinemia receiving phototherapy. *Exclusion Criteria:* Neonates with

1. Age <24 hrs 2. Congenital hypothyroidism 3. Respiratory distress syndrome or Hyaline membrane disease 4. Clinical sepsis 5. Congenital anomalies 6.Hypoxic ischemic encephalopathy 7. Serum bilirubin in exchange range 8. Maternal diabetes mellitus and hyperparathyroidism. Written and informed consent was taken from parents/guardians of all eligible neonates in their preferred language. Ethical approval was taken from ethical committee.

Group A: 56 Preterm neonates under phototherapy.

Group B: 56 Term neonates under phototherapy.

Clinically suspected and jaundiced neonates who were included in the study as per inclusion and exclusion criteria were given phototherapy on the basis of cut-off values of total serum bilirubin from AAP guideline chart.[8]

Conventional phototherapy equipment, containing four blue light fluorescent lamps with wavelengths of 420–470 nm, was placed at a distance of 30–40 cm from the skin surface of neonates. The irradiance during phototherapy was measured and maintained consistently between the two groups.

Group A Preterm neonates were given phototherapy; while in Group B Term neonates also given phototherapy. In both groups eyes and genitals, were also covered to prevent toxicity. Infants nearing or at exchange level were excluded and acute bilirubin encephalopathy/kernicterus is a more devastating long-term consequence than hypocalcemia.

The neonates were clinically assessed for features of hypocalcemia like jitteriness, irritability, lethargy, and convulsions, as well as for other complications such as rash, loose stools, fever, and dehydration. If any neonate develops these signs of hypocalcemia, they were managed with oral or intravenous calcium.

Data Collection and Laboratory Investigations

The demographic and clinical variables were recorded on a predesigned proforma. It included

name, age in hours, sex, birth weight, gestational age, age at the start of phototherapy in hours, duration of phototherapy, mother's blood group and baby's blood group.

Blood sampling Approximately 4 ml of blood was drawn using aseptic technique by peripheral venous phlebotomy. Approximately 1.5 ml blood was transferred to 2 separate ion free red top vials for measuring serum ionic calcium level and total serum bilirubin (TSB) and 1 ml for Blood Group in EDTA vial if not known; similarly mother blood group was also sent if not known. Total serum bilirubin was measured at the start of phototherapy, 24 hours, 48 hours and then at the end of phototherapy. Serum ionized calcium level was measured at the start of phototherapy and after completion of 48 hours of phototherapy. Ionized calcium level of <4 mg/dL was considered to be hypocalcemia.[5] Bilirubin was measured using the Diazo method with sulfanilic acid and ionized Calcium was measured using Arsenazo III method.

Measurement of total serum bilirubin and calcium level: Serum sodium levels were analyzed in the central laboratory using an Olympus AU640™ discrete chemistry analyzer (Beckman Coulter India Pvt. Ltd.). This chemistry analyzer uses indirect ion-selective electrodes and pre-dilutes the specimen before analysis.

Statistical Analysis

Statistical analysis was performed using SPSS for windows, version 20. Normally distributed continuous variables were compared using the t-test (paired or unpaired). Categorical variables were analyzed using either the chi-square test or Fisher's exact test. All data were expressed as mean ± S.D. For all statistical tests, p-value less than 0.05 was considered to indicate a significant difference.

Results

This cross sectional study was conducted in the SCBU, a level II NICU in Department of Paediatrics, pediatric tertiary care hospital in north eastern india from April 2016 to March 2017. All Newborns admitted to SCBU with unconjugated hyperbilirubinemia receiving phototherapy were eligible for recruitment in the study.112 neonates were recruited in the study, and randomized into two groups of 56 neonates. Group A includes Preterm neonates and group B includes Term neonates. Blood samples were drawn from all newborns for measurement of serum ionic calcium, total serum bilirubin, blood group according to predetermined schedule. Mother blood group was also noted to detect any Rh or ABO incompatibility.

Out of the 56 neonates enrolled in group A, 31 (55.40 %) were male and 25 (44.60 %) were females; and out of 56 in group B, 33 (58.90 %) were male and 23 (41.10 %) were females.

Out of the 56 neonates enrolled in group A, 36 (64.30 %) were NVD and 20 (35.70 %) were LSCS; and out of 56 in group B, 35 (62.50 %) were NVD and 21 (37.50 %) were LSCS.

The mean Serum ionic Ca at the start of phototherapy in Group A was 4.71 mg/dl and 4.14 mg/dl after 48 hours of phototherapy. The mean difference was 0.57 mg/dl with an SD of 0.37. While the mean Serum ionic Ca at the start of phototherapy was 4.68 mg/dl and 4.34 mg/dl after 48 hours of phototherapy. The mean difference was 0.34 mg/dl with an SD of 0.24. By applying paired sample t-test this difference was statistically significant in both the group with a p value of <0.001.

The mean decline in serum ionic calcium after 48 hours of phototherapy in group A was 0.57 mg/dl and 0.34 mg/dl in group B with cap. This difference was analyzed by using unpaired t-test signifying a statistically significant difference with a p value of 0.0001.

A total of 15 newborns (26.8%) from group A developed hypocalcemia while in group B only 8 newborns (14.3%) developed hypocalcemia. This was not found to be statistically significant with p=0.160.

Out of a total of 15 cases of hypocalcemia 5 newborns had symptomatic hypocalcemia in Group A, among them 1 had hypocalcemic seizures with increased extensor tone and hyperreflexia while the rest 4 had jitteriness. While in group B out of total 8 cases of hypocalcemia; 2 newborns had symptomatic hypocalcemia in the form of jitteriness, none had hypocalcemic seizures. P-valve was 1.000 which was not found to be significant which signifies that the difference between the incidence of symptomatic hypocalcemia between the two groups is not significant.

Among symptomatic hypocalcemia, the subject with seizure was treated with iv calcium and others with jitteriness were treated with oral calcium. All of them recovered well and discharged. So there was no significant difference in the outcome.

Table 1: Clinical characteristics of Subjects:

		Group A(without cap)		Group B (with cap)	
		Frequency	percentage	Frequency	percentage
Sex distribution between the two groups	Male	31	55.4	33	58.9
	Female	25	44.6	23	41.10
	Total	56	100	56	100
Mode of delivery between the two groups	NVD	36	64.30	35	62.50
	LSCS	20	35.70	21	37.50
	Total	56	100	56	100

Table 2: Mean, SD, P value, Mean difference of variables

Mean	Group A	Group B	P value
Mean Gestational Age (wks)	37.8+_0.9	37.6+1.0	0.371
Mean Birth Weight (kg)	2.82±0.36	2.77±0.33	0.436
Mean TSB at start of PT (mg/dl)	20.30±2.12	20.34±1.88	0.907
Mean age at start of PT (hrs)	82.70 (SD:22.40)	83.55 (SD:24.15)	0.846
Mean duration of phototherapy (hrs)	49.89 (SD:5.83)	50.80 (SD:7.87)	0.488
Mean difference of phototherapy	0.91		

Table 3: Comparison of mean decline in S. ionic Ca between Group A and Group B

	Mean difference (mg/dl)	S.D	P value
Group A (S. Ionic Ca at 0 hr - 48 hr of PT)	0.57	0.37	0.0001
Group B (S. Ionic Ca at 0 hr - 48 hr of PT)	0.34	0.24	

Discussion

Hyperbilirubinemia is a common and benign problem in most cases in the first week of life in neonates with a prevalence of 60% in full-term newborns who are affected with jaundice.[1]

Phototherapy is widely accepted as a relatively safe and effective method for treatment of neonatal hyperbilirubinemia. Neonates undergoing phototherapy can develop hypocalcaemia as phototherapy leads to inhibition of pineal gland via transcranial illumination, resulting in a decline in melatonin level which blocks the effect of cortisol on bone calcium and cortisol increases bone uptake of calcium and induces hypocalcemia.[9] This phototherapy induced hypocalcaemia can be prevented by supplementing the calcium to the neonates during phototherapy.

Comparison between ionized calcium levels before and after 48 hours of phototherapy in each group was done to detect the change in serum calcium levels induced by phototherapy.

On comparing the mean ± SD decline in serum ionic calcium after 48 hours of phototherapy in

group A without head cover was 0.57 ± 0.37 mg/dl while the mean ± SD decline in serum ionic calcium in group B with head cover was 0.34 ± 0.24 mg/dl. This difference was analyzed by using unpaired t-test (p value< 0.001), denoting a statistically significant difference. The result thus indicates a significant trend towards hypocalcemia in both the groups with a significantly higher decline in serum calcium in the group A without head covering. Pre-phototherapy, there was no statistically significant difference between the two groups; while post phototherapy, there was statistically significant differences between ionized calcium in both the groups. (p<0.001) Our results are in agreement with the following studies: Eghbalian et. al.,[10] in 2002 showed that the difference between pre and post-phototherapy plasma calcium levels were found to be statistically significant (p<0.05). Mean ± SD serum calcium level decreased significantly from a baseline value of 9.85 ± 1.23 mg/dl before phototherapy to 9.09 ± 0.93 mg/dl after phototherapy (p<0.001). Similarly, Durga et. al.,[11] in their study found that in term neonates had a significant fall in serum ionized calcium level (p<0.0001) after exposure to 48 hrs of continuous phototherapy. Prabhakar et. al.,[12] in their study found that 66.67% developed hypocalcemia and there was a significant difference observed between cases and controls (P=0.00016). They concluded that after 48 hours of phototherapy, it causes hypocalcemia in full term born neonate with hyperbilirubinemia.

The incidence of hypocalcemia found in our study in the group A (Preterm neonates), a total of 15 (26.8%) newborns developed hypocalcemia, while in group B (Term neonates), only 8 (14.3%) neonates developed hypocalcemia. Our results in hypocalcemia are consistent with the following studies: Bahbah et. al.,[13] found highly statistically significant decrease in the serum calcium levels after phototherapy, 26% Neonates developed hypocalcemia. Jain BK et al 14 in their study found that 55% of preterm neonates and 30% of full-term neonates with hyperbilirubinemia developed hypocalcemia after 48 hours of phototherapy. Nouh M et. al.,[15] in their study found that a total of 22.2% developed hypocalcemia who received phototherapy. None of the hypocalcemic neonates was symptomatic clinically. Bahawal et al 16in their study found that 16.84% of neonates developed hypocalcemia after 48 hours of phototherapy (P-value 0.01). Khan M et. al.,[17] found that frequency of hypocalcemia in term jaundiced neonates receiving phototherapy was observed in 22.76% and observed that hypocalcemia was not significant among the different age groups, gender, gestational age, duration of jaundice and duration of phototherapy.

Studies with higher incidence of hypocalcemia in comparison to our study are; YadavRK et. al.,[18] in 2012 found that after 48 hours of phototherapy a significant fall in calcium level in 66.6% of term & 80% of preterm neonates in study group was observed. Jain SK[19] in his study found that after 48 hours of phototherapy significant fall in serum calcium level in 39% of term and 53% of preterm neonate was observed. It is suggested that calcium level be assessed in neonates treated with phototherapy for more than 48 hours and managed accordingly.

Studies with incidence of hypocalcemia lower than our study; In 2013 Alizadeh-Taheri et. al.,[20] found that 56% babies had decrease in serum calcium level. Only 7% newborns developed hypocalcemia after 48 hours of phototherapy. There was a significant difference between serum calcium level before and after phototherapy (P=0.03). Tehrani et. al.,[21] in their study found that 7.5% neonates developed hypocalcemia after 48 hours of phototherapy, none of the hypocalcemic neonates were clinically symptomatic. And concluded that although phototherapy induces hypocalcemia in term infants, but the incidence of phototherapy-associated hypocalcemia is not too much. Saravanan et. al.,[22] in 2017 found that in their study population receiving 48 hours of phototherapy, a significant decrease in serum calcium was observed (p<0.03). However, only 7.5% neonates developed hypocalcemia below the acceptable threshold after 48 hours of phototherapy. None of the newborns had symptomatic hypocalcemia. They concluded that although phototherapy lowers serum calcium level in term infants, but the incidence of phototherapy-associated hypocalcemia is not too much.

The difference of hypocalcemia in our study between the two groups when analyzed with Fisher's exact test was not statistically significant (p-value 0.160), signifying that the difference between the hypocalcemia between the two groups is not significant. Among symptoms, in group A out of 15 cases of hypocalcemia 5 newborns developed symptomatic hypocalcemia; out of them 1 had hypocalcemic seizures with increased extensor tone with hyperreflexia while the rest 4 had jitteriness; while in group B out of 8 cases of hypocalcemia 2 newborns had symptomatic hypocalcemia in the form of jitteriness, none had hypocalcemic seizures (p valve = 1.000), which signifies that the difference between the incidence of symptomatic hypocalcemia between the two groups is not significant.

From above discussion, most of the previous studies there was significant difference between the incidences of hypocalcemia between the two group which was similarly found in our study, as preterm are more prone for hypocalcemia due to less store and larger head size.

Limitation of study

Since the study was done at the tertiary care centre, only high-risk patients sent to the hospital were enrolled and this may not be the true reflection of the general population. Smaller sample size; to account for heterogeneity among participant, study must be quite large to realize statistical significance.

Conclusion

From our study, it is concluded that there is a significant decrease in serum calcium levels in neonates with receiving phototherapy. There is more decrease in serum calcium level in preterm neonates compared to Term neonates, but difference of hypocalcemia and symptomatic hypocalcemia was not significant.

Recommendations

Serum ionized calcium level should be monitored in all preterm neonates undergoing phototherapy.

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Conflict of interest: none

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