Original Research Article

Evaluation of incidence of phototherapy induced hypocalcaemia in term newborns with neonatal hyperbilirubinemia and its clinical significance: a cross sectional study with controls

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ABSTRACT

Background: Neonatal hyperbilirubinemia in many of the cases is only in physiological range, but quite often it requires phototherapy and even exchange transfusion for proper management. Although hypocalcemia is often proposed to be associated with phototherapy in term and preterm newborns, its exact incidence and clinical significance still remains to be elucidated.

Methods: Current study was carried out in a tertiary care center in North India with 29 term neonates in test group receiving single surface phototherapy and 29 age, sex and gestational age matched neonates in control group, who did not receive phototherapy. Serum calcium levels at 0 and 48 hours of starting phototherapy were determined in both the groups and compared.

Results: Mean difference of Serum ionized calcium between two groups was statistically significant at 48 hours with mean for test group was 4.58 mg/dl compared to 4.94 mg/dl for control group ($p < 0.001$). 10 newborns (47%) in test group had hypocalcemia according to standard definitions and 3 out of them (30%) had were clinically symptomatic with jitteriness and poor feeding, which resolved after calcium supplementation

Conclusions: Term neonates undergoing phototherapy are at increased risk for hypocalcemia. A universal recommendation regarding calcium supplementation in neonates undergoing phototherapy is yet to be established but seems like a reasonable intervention.

Keywords: Hyperbilirubinemia, Hypocalcemia, New Delhi, Phototherapy, Term

INTRODUCTION

Neonatal hyperbilirubinemia is one of the most common developmental peculiarities, which often reaches pathological range especially after first 24 hours of life, without definitive evidence of hemolysis in the body.¹ Jaundice usually becomes apparent in a cephalocaudal

progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Hyperbilirubinemia in infants ≥ 35 weeks gestation is defined as total bilirubin $>95^{\text{th}}$ percentile on the hour-specific Bhutani normogram.^{2,3}

The term "Bilirubin induced neuronal damage" is used to

describe neurological clinical manifestations of bilirubin induced neurological dysfunction.⁴ Appropriate intervention is important to consider in every infant with severe hyperbilirubinemia.⁴ Phototherapy and, if it is unsuccessful, exchange transfusion remains the primary treatment modality to keep the maximal total serum bilirubin below pathologic levels.⁵ Infants under phototherapy have long been proposed to be at risk for developing hypocalcemia, especially preterm newborn.¹

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but in a large series, kernicterus occurred only in infants with a bilirubin >20 mg/dL.⁶ Ninety percent of the infants, in whom kernicterus developed, were previously healthy, predominantly breast-fed term and near-term infants.⁷ The duration of exposure to high bilirubin levels needed to produce toxic effects are unknown.⁸ The more immature the infant is, the greater is the susceptibility to kernicterus.²

A number of studies are available on this regard in literature, but with conflicting results and moreover the mechanism for this hypocalcemia is also not clearly elucidated till now, although increased urinary calcium excretion is one of the most promising theoretical hypothesis till now. Although few studies have demonstrated hypocalcemia in neonates receiving phototherapy, a study with adequate sample size in Indian population to determine the exact prevalence of hypocalcemia and its etiopathogenesis in terms of urinary calcium excretion is required to make recommendations of calcium supplementations in neonates during phototherapy.

METHODS

Accordingly, one observational analytic study was planned with similar objectives and was carried out at Neonatal Intensive Care Unit (NICU) of Department of Paediatrics, Mata Chanan Devi Hospital, New Delhi, between November 2013 to June 2015 to determine the effect of phototherapy on ionized serum calcium level in term new-borns. Since preterm new-borns have also associated confounding factors, which predisposes them for hypocalcemia, so to study the isolated effects of phototherapy induced hypocalcemia, only term new-borns were included in the study.

The study population not only included inborn new-borns with hyperbilirubinemia, but also all new-borns admitted in hospital, including male and female, for phototherapy and observation due to hyperbilirubinemia, after obtaining informed consent from the primary caregiver. The required data was recorded in a predesigned case record form and later on shifted to Microsoft excel spread sheet for statistical analysis.

The participants were divided into test and control group, with 50 new-borns were enrolled in each group. The test

group included the new-born babies with neonatal hyperbilirubinemia, with serum bilirubin levels above the minimum value which mandates phototherapy; irrespective of the fact whether they also required exchange transfusion of blood during the course of illness. Phototherapy and exchange transfusion chart given by American academy of paediatrics in 2004 for term babies (AAP 2004) guidelines were followed. Initially the newborns were started on single surface phototherapy if the serum bilirubin value was not touching the exchange transfusion level. The controls included term new-borns, who had neonatal hyperbilirubinemia, but their level was not high enough to need phototherapy. These controls were enrolled in such a way to match the test group with respect to age, sex, period of gestation and birth weight. These babies were managed without phototherapy.

All those babies who were at known risk of developing hypocalcemia such as small for gestation, infants of diabetic mothers, exposed to asphyxia, having respiratory distress, neonatal sepsis, sodium bicarbonate therapy, haemolytic conditions like Rh incompatibility and G6PD deficiency and hypothyroidism were excluded. All enrolled neonates were evaluated with detailed history and thorough physical examination.

A relevant antenatal, natal, post-natal and family history was inquired, and a detailed general and systemic examination was performed in each case. Every case investigated for serum ionized calcium, serum bilirubin, blood group, and Rh typing, haemoglobin, peripheral blood smear, urinary calcium, urinary creatinine, Erythrocyte Glucose-6-Phospho Dehydrogenase enzyme deficiency, serum thyroid stimulating hormone, C-reactive protein, micro erythrocyte sedimentation rate, total leukocyte count, absolute neutrophilic count and immature to mature neutrophil ratio.

Mothers were also examined for their blood group and Rh typing. Serum ionized calcium level was measured at 0 hour of starting phototherapy and at 48 hours for both groups. Normal serum ionized calcium in term neonates were taken as 4.8 mg/dl on the basis of available literature.

Symptoms and signs of neonatal hypocalcemia rarely occur unless total serum calcium is <7 mg/dL (<1.75 mmol/L) or the ionized calcium is <3.0 mg/dL (<0.75 mmol/L). Signs include hypotonia, tachycardia, tachypnea, apnea, poor feeding, jitteriness, tetany, and seizures. Those new borns who were found to have hypocalcemia, were screened for clinical symptoms.^{9,10}

Data analysis

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables are presented as mean $\pm$ SD, and categorical variables are presented as absolute numbers

and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's *t* test.

Nominal categorical data between the groups were compared using Chi-squared test.

Spearman correlation was also used to see the relationship between Serum ionized calcium and urinary calcium/creatinine ratio at 0 hour and 48 hours. For all statistical tests, a *P* value less than 0.05 was taken to indicate a significant difference.

RESULTS

Total number of newborns enrolled in the current study was 58, out of which 29 cases (50%) were included in test group and 29 cases (50%) were included in control group. The mean difference of serum ionized calcium between the two groups was found statistically significant at 48 hours with mean for test group was 4.58mg/dl compared to 4.94 mg/dl for control group (*p* value <0.001) (Table 1).

Table 1: Comparison of serum ionized calcium (mg/dl) between control and test group.

Serum ionized calcium	Control Group (n=50)		Test Group (n=50)		P value
	Mean±SD	Min-Max	Mean±SD	Min-Max	
0 Hours	4.95±0.18	4.40-5.21	4.96±0.23	4.20-5.20	0.873
48 Hours	4.94±0.20	4.38-5.24	4.58±0.47	3.59-5.12	<0.001*

Table 2: Serum Bilirubin level of Control and Test Group at 0 and 48 hours.

Serum Bilirubin	Control Group (n=50)		Test Group (n=50)		P value
	Mean±SD	Min-Max	Mean±SD	Min-Max	
0 hours	8.42±1.00	6.6-10.4	17.10±2.35	10.80-22.10	<0.001
48 hours	10.00±0.81	8.10-11.30	10.18±1.01	6.90-11.60	0.323

Table 3: Comparison of U. Ca/U. Crt ratio (mg/mg) between two groups.

U. Ca/U. Crt ratio	Control Group (n = 50)		Test Group (n = 50)		P value
	Mean±SD	Min-Max	Mean±SD	Min-Max	
0 hours	0.26±0.03	0.21-0.34	0.25±0.04	0.15-0.38	0.459
24 hours	0.25±0.04	0.19-0.40	0.39±0.17	0.21-0.94	<0.001

The percentage change in mean Serum ionized calcium in test group at 48 hours from baseline (0 hour) was found statistically significant with a value of -7.76% (*p* value <0.001) (Table 2). According to the standard definition 10 term new borns (47%) in the test group developed hypocalcemia, but none of the term newborns developed hypocalcemia according to definition of <7 mg/dl total level or ionized calcium <3 mg/dl (Table 3). Out of the 10 term newborns with hypocalcemia, 3 were symptomatic with excessive jitteriness in two children and poor feeding in one child respectively. Rest of the seven children were asymptomatic. All of these 10 newborns were provided calcium supplements as per standard recommendations, following which the symptoms resolved in all the three symptomatic newborns.

DISCUSSION

The current study showed incidence of hypocalcemia was significantly higher in term newborns, undergoing phototherapy for neonatal hyper bilirubinemia and also

brings out the fact that that around 30% of the children with hypocalcemia had clinical symptoms, which were reversible after supplementing with calcium, thereby indicating the importance of routine surveillance of serum calcium levels in newborns undergoing phototherapy. Phototherapy may lead to other 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. Romagnoli was the first to suggest the association of hypocalcaemia and phototherapy in preterms.¹¹

Hakinson and Hunter hypothesized that phototherapy inhibits pineal secretion of melatonin which blocks the effect of cortisol on bone calcium.¹² So cortisol increases bone uptake of calcium and induces hypocalcaemia.¹³ Kim suggested decreased secretion of parathormone as the cause of hypocalcemia. In Hooman's study the urinary calcium excretion was significantly higher in phototherapy group. Sethi et al studied sixty neonates with hyperbilirubinemia including 20 preterm (Group A)

and 20 full term (Group B) neonates undergoing phototherapy.¹³ Ten neonates from each group formed the control group. They noticed that ninety per cent preterm neonates and seventy-five per cent full term neonates developed hypocalcemia after being subjected to phototherapy, consistent with our study results. They recommended that neonates under Phototherapy should be supplemented with calcium to prevent hypocalcemia. Jain et al showed similar results in 40 newborn babies with hyperbilirubinemia.¹³

In their study the prevalence of phototherapy-induced hypocalcemia was 55% in preterm infants and 30% in full-term neonates. They noticed that 63.6% had jitteriness and 27.3% had irritability in preterm babies with hypocalcemia. In the hypocalcemic full-term neonates 50% had jitteriness and 16.7% had irritability. They also recommended administration of supplemental calcium in phototherapy exposed neonates, to prevent hypocalcemia.

They have also found the prevalence of hypocalcemia to be higher in patients with high level of serum bilirubin, although this difference was not statistically significant. They concluded that the phototherapy-induced hypocalcemia in premature neonates was due to higher penetration of light in premature neonates. They also suggested that although phototherapy induces hypocalcemia in new-born infants, no calcium supplement seems to be required except in symptomatic cases.¹⁴

Habibzadeh F et al showed similar results and also proposed that hypocalcemia might be due to changes in serum melatonin concentration which is regulated by the pineal gland.^{15,16} The pineal gland influences diurnal light-dark cycle in normal human. Karamifar et al also noticed that none of hypocalcemic neonate became clinically symptomatic and the serum calcium level was in normal range 24 hrs after discontinuation of phototherapy.¹⁷

Zarkesh et al in also showed a statistical significant difference in Urinary calcium/creatinine ratio (mg/mg) at commencement and after 48 hours of phototherapy in icteric term newborn.¹⁸ They also recommended further investigation for clarifying the importance of this phenomenon.

CONCLUSION

In conclusion it is suggested that calcium level be assessed in new-borns treated with phototherapy for 48 hrs or more and managed accordingly. Hypocalcaemia in new-borns undergoing phototherapy still remains a mystery. Various previous studies and the current study, although unequivocally proves its existence, but its clinical relevance in the form of symptomatology and underlying pathomechanism like increased urinary calcium excretion and even other proposed mechanisms needs to be studied in more studies with larger sample size. A universal recommendation regarding calcium

supplementation in neonates undergoing phototherapy is yet to be established but seems like a reasonable intervention taking into account the evidence available in existing literature.

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