Section: Paediatrics

Research

INCIDENCE OF HYPOCALCEMIA IN NEONATES WITH UNCONJUGATED HYPERBILURUBINEMIA AFTER INTIATION OF PHOTOTHERAPY

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Abstract

Background: Neonatal hyperbilirubinemia is a significant concern in the first week of life, affecting roughly 60% of term and 80% of preterm infants. In many cases, neonatal hyperbilirubinemia is just in the physiological range, but it frequently necessitates phototherapy and even exchange transfusion for optimal care. Although hypocalcaemia has been linked to phototherapy in term and preterm neonates, the exact incidence and clinical relevance of the condition has yet to be determined. The aim is to the purpose of this study was to investigate the incidence of hypocalcaemia following the commencement of phototherapy in the treatment of neonatal unconjugated hyperbilirubinemia. **Materials and Methods:** This was a prospective hospital-based comparative study conducted at NRI Institute of Medical Sciences College and Hospital, Neonatal Intensive Care Unit (NICU) from June 1, 2022 to November 30, 2022. This study included 50 newborns with jaundice (25 term and 25 preterm) who were treated with phototherapy for neonatal indirect hyperbilirubinemia (exaggerated physiological jaundice) and neonates in the control group were managed without phototherapy. Before and after 48 hours of phototherapy, serum bilirubin and serum calcium levels were measured. **Result:** A significant drop in calcium level was found in 64 percent of term and 76 percent of late preterm neonates in the study group at the end of phototherapy, but practically all (except one) remained asymptomatic (p value 0.001). The control group, on the other hand, showed no differences. **Conclusion:** Phototherapy exposes neonates to an increased risk of hypocalcaemia. Phototherapy can considerably lower calcium levels in jaundiced term and preterm newborns who are treated for 48 hours. Hypocalcaemia and its repercussions should be closely monitored. However, universal calcium supplementation has yet to be established, but it appears to be feasible.

INTRODUCTION

Jaundice in newborn neonates is observed in almost 60% of term and 80% of preterm babies due to physiological immaturity and it is the common cause for readmission after discharge.[1] Low birth weight neonates were shown to have a greater incidence of jaundice (35.6%) than normal birth weight newborns (16.9%).[2] It's wise to note that neonatal hyperbilirubinemia is a medical emergency that can result in irreparable brain damage or death if not treated promptly.

For the treatment of neonatal hyperbilirubinemia, phototherapy is significantly considered as a relatively safe and successful approach. The efficiency of phototherapy depends on the emission range, peak wavelength of the light source, irradiance and exposed body surface area.[3] However, this treatment modality also has some complications such as insensible water loss, mutation and DNA strand break, hyperthermia, tremor, retinal damage, bronze baby syndrome, maternal infant interaction, hypocalcemia and thrombocytopenia.[4]

The first to suggest a link between infant hypocalcaemia and phototherapy was Romnagoli et al. Due to the release of melatonin by the pineal gland, hypocalcaemia can arise during phototherapy. Melatonin increases corticosterone release, which reduces calcium absorption by the bones.[5,6] Phototherapy causes the pineal gland to be inhibited by transcranial light, resulting in a drop in melatonin levels and hypocalcaemia.

Hypocalcemia has been reported as a reaction to phototherapy in premature and full-term newborns. Some complications of hypocalcemia in newborns

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are apnea, convulsion, muscle cramps, tremors, and tetany. Hypocalcemia causes long-term complications such as mental retardation, physical disability.[7]

Aim of the Study

The aim of this study is to determine the incidence of hypocalcaemia in term and late preterm infants after initiation of phototherapy in treatment of neonatal hyperbilirubinemia.

MATERIALS AND METHODS

This was a prospective hospital based comparative study at NRI Institute of Medical Sciences College and Hospital, Neonatal Intensive Care Unit (NICU) from June 1, 2022 to November 30, 2022 after taking ethical committee approval. The study group includes term and late preterm neonates (35 to 37 weeks GA). All had hyperbilirubinemia. All the neonates included in the study group required phototherapy. The neonates in the control group having hyperbilirubinemia in physiological range and were managed without phototherapy. Serum bilirubin & serum calcium were determined before & after 48 hour of phototherapy. Phototherapy was provided with four blue and two white lights placed at 30 cm from the neonates and delivering at least 20μ W/cm^2/nm.

Healthy term and late preterm neonates (35 to 37 weeks) receiving phototherapy for neonatal jaundice were included in the study. Neonates who were at risk of hypocalcaemia such as perinatal asphyxia, respiratory distress, small for gestational age (< 3rd centile on Fenton's charts), hemolytic conditions like Rh incompatibility and G6PD deficiency, hypothyroidism, infant of diabetic mother and maternal history of consumption of anticonvulsant were excluded. Those babies who were found to hypocalcaemia prior to phototherapy were excluded from the study.

Neonates who were admitted in NICU only for jaundice were assessed and were enrolled in to the study if they satisfied the enrolment criteria. Written informed consent was taken from the parents prior to enrolment.

All the neonates included in the study group had significant hyperbilirubinemia. Evaluation and management with phototherapy were done as per American academy of pediatrics 2004 guidelines.[8] Serum calcium was measured pre and post phototherapy. Convenient sample size of 50 neonates was chosen.

Thorough clinical examination was done for all enrolled neonates Serum bilirubin estimation was done as per the standard guidelines. Total serum calcium was done before and at the end of phototherapy.

Mothers were also examined for their blood group and Rh typing. Total serum calcium level was measured at 0 hour of starting phototherapy and at 48 hours for both groups. Hypocalcemia defined as serum calcium in term neonates less than 8 mg/dl, preterm less than 7 mg/dl on the basis of available literature. All the neonates were clinically assessed for features of hypocalcaemia i.e. jitteriness, irritability/ excitability, letharginess and convulsion, as well as other complication like rash, loose stool, fever and dehydration during phototherapy.

Data Analysis

Analysis of data was done using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two groups, Student t test was performed. Qualitative variables were compared using chi-square (X^2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, A P value < 0.05 is considered significant.

RESULTS

In the present study, 50 neonates were admitted in NICU for phototherapy were evaluated for hypocalcemia. Among them 25(50%) were preterm neonates and 25 (50%) were term neonates. Male neonates were 24 (48%) and 26 (52%) were female neonates. Most of the neonates were exclusively breastfed 23 (46%), 11 (22%) of them were on formula feeds because of inadequate milk let down in mothers, and rest 16 (32%) were under mixed feeding (mothers milk and formula feeds).

None of the neonates developed jaundice before first 24 hours of life; 8 (32%) cases had onset of jaundice between 24 to 72 hours, while majority of cases 17 (68%) had onset of jaundice after 72 hours. In preterm study group, 10 (40%) developed jaundice between 24 to 72 hours and 15 (60%) after 72 hours. In all, 12(48%) of preterm neonates and 7(28%) term neonates developed hypocalcaemia after 48 hrs. of exposure to phototherapy. Symptomatic hypocalcemia was seen in 4(33%) of preterm and 2 (28.5%) of term neonates. Jitteriness was the most common complications observed in both preterm3(75%) and term 1 (50%). Irritability was seen in 1 (25%) of preterm and 1 (50%) of term neonates. Apnea and convulsions were not seen in any of the study groups. The mean total serum calcium levels before the onset of phototherapy were significantly different between groups (term vs late preterm; 9.64±0.68 vs 8.92 ± 0.76; p value <0.01). Post phototherapy mean total serum calcium levels remained statistically significant between groups (term vs late preterm; 7.45 ± 1.87 vs 8.16 ± 1.54; p value <0.01). The fall in total serum calcium

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pre and post phototherapy was statistically significant in both late preterm and term groups.

DISCUSSION

Neonatal jaundice is a frequent cause of morbidity in newborns worldwide and significant cause of hospitalization, mainly in the first week. Efficacy of phototherapy in treatment of hyperbilurubinemia in newborns has been well established.[8] The efforts made around the globe recognize it as a potential complication with variable results, some showing severe hypocalcemia. Romagnoli et al. was the first to suggest the association of hypocalcemia in a newborn following phototherapy.[9] Abrams SA hypothesized that phototherapy inhibits pineal secretion of melatonin which blocks the effect of cortisol on bone calcium. Cortisol unchecked exerts a direct hypocalcemia effect and increases bone uptake of calcium as well.[5,6] The incidence of neonatal hyperbilirubinemia among admitted newborns in NICU was 35% in the present study. Anand VR has reported the incidence of neonatal jaundice in total nursery admission as 54.6 %. In the present study, none of the neonates developed jaundice before first 24 hours of life; 8 (32%) cases had onset of jaundice between 24 to 72 hours, while majority of cases 17 (68%) had onset of jaundice after 72 hours in term neonates. In preterm study group, 10 (40%) developed jaundice between 24 to 72 hours and 15 (60%) after 72 hours.

Our results agreed with study of Chandrashekar, 2014 as they revealed that incidence was 48% in preterm and 14% in term neonates. Incidence of hypocalcemia according to duration of phototherapy being, 2 out of 24 (8%) at 24hrs of PT, 15 out of 73 (21%) at 36 hrs of PT, 45out of 103 (44%) at 48hrs of phototherapy. Out of which incidence was more in preterm than in term neonates, more in SGA neonates then AGA.

The selection method being convenient sampling method is attributed to the present study. The present study showed that there were 48% in preterm neonates, 28% in term neonates developed hypocalcemia after 48 hrs. of use of phototherapy.

In the present study, mean serum calcium concentration in preterm and term neonates (pre study) were similar in both case and control groups. The mean serum calcium level in case group was decreased significantly after giving phototherapy from 8.41 mg/dl ± 0.47 to 7.1 mg/dl ± 0.79 ($p<0.05$) while in control group (after 48 hours), it was from 9.66 mg/dl ± 0.45 to 9.6 mg/dl ± 0.64 ($p=0.82$). The mean serum calcium level in term (pre study) was similar in both cases and control groups. The mean serum calcium level in case group decreased after giving phototherapy from 9.52 mg/dl ± 0.53 to 8.42 mg/dl ± 1.19 ($p<0.05$) and in control group (after 48 hours) it was from 9.64 mg/dl ± 0.45 to 9.7 mg/dl ± 0.48 ($p=0.88$). Statistical analysis showed hypocalcemia was significant in both the groups, preterm and term neonates ($p<0.01$).

Yadav et al. observed that 66% term and 80% preterm neonates developed hypocalcemia after phototherapy.[10] Sethi et al. reported that 90% preterm and 75% term neonates developed hypocalcemia after being subjected to phototherapy.[11]

Similar to the study by Shrivastava J et al. where the serum calcium level before and after phototherapy in preterm babies was 8.82 ± 0.59 mg/dl and 6.64 ± 1.03 mg/dl respectively, whereas in term babies was 9.32 ± 0.99 mg/dl and 7.58 ± 0.83 mg/dl respectively. Hypocalcemia after phototherapy was statistically significant ($p<0.01$).[12] Also in a study by singh PK et al. where the serum calcium level before and after phototherapy in preterm babies was 8.41 ± 0.46 mg/dl and 7.1 ± 0.8 mg/dl respectively, whereas in term babies was 9.52 ± 0.53 mg/dl and 8.42 ± 1.1 mg/dl respectively. Hypocalcemia after phototherapy was statistically significant ($p<0.01$).[13] In a study by Goyal et al. where the mean serum calcium level before and after phototherapy was 9.14 ± 0.78 mg/dl and 8.53 ± 0.77 mg/dl respectively. Hypocalcemia after phototherapy was statistically significant ($p<0.01$).[14] Other study by Alizadeh TP et al. where the mean serum calcium level before and after phototherapy was 9.8 ± 0.8 mg/dl and 9.5 ± 0.9 mg/dl respectively. Hypocalcemia after phototherapy was statistically significant ($p<0.01$).[15]

Similar to the present study where the mean total serum calcium levels before the onset of phototherapy were significantly different between groups (term vs late preterm; 9.64 ± 0.68 vs 8.92 ± 0.76; p value <0.01). Post phototherapy mean total serum calcium levels remained statistically significant between groups (term vs late preterm; 7.45 ± 1.87 vs 8.16 ± 1.54; p value <0.01). The fall in total serum calcium pre and post phototherapy was statistically significant in both late preterm and term groups.

In the present study,19 out of 50 neonates showed hypocalcemia after phototherapy. Among them 31.5% were symptomatic; 4 (33%) of preterm and 2 (28.5%) of term neonates. Jitteriness was the most common complications observed in both preterm 3 (75%) and term 1 (50%). Irritability was seen in 1 (25%) of preterm and 1 (50%) of term neonates. Apnea and convulsions were not seen in any of the study groups. Similar to the study by Yadav RK et al. where 30% of hypocalcemic neonates developed jitteriness, 20% developed irritability, 30% developed letharginess and none of the neonate developed convulsions10. In a study by Jain BK et al. 63.6% of hypocalcemia had jitteriness and 27.3% had irritability in preterm neonates whereas 50% of hypocalcemia had jitteriness and 16.7% had irritability in term neonates.[16]

Our results were supported by study of Gaafar et al. as they reported that evaluation of the average level

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of serum bilirubin in subjects measured at two different times (at hospitalization and after 48 hours of exposure to phototherapy) showed a significant decrease in the level of bilirubin; level of bilirubin in those subjects after phototherapy had an average value of 16.76 ± 2.99 mg/dL, which was less than that of hospitalization time 11.0 ± 2.45 (P<0.001).They showed that showed those 48 hours after phototherapy, average serum calcium level in the subjects was 9.04 ± 0.78 mg/dL, which was less than that of the hospitalization time (9.63 ± 0.79 mg/dL). This decrease was statistically significant.[17]

CONCLUSION

The efficacy of phototherapy in the prevention and treatment of hyperbilirubinemia in newborn infants has been well established. The mean duration of phototherapy in our study was 32 hours. Duration of phototherapy may influence the severity of hypocalcaemia. Hypocalcemia is a significant concern in babies receiving phototherapy but seems to be asymptomatic. Larger studies are warranted to confirm these findings. One needs to be vigilant in dealing neonates in this context while serial monitoring for hypocalcemia and its complications should be considered in institutional policy and research priority. A universal recommendation of oral calcium supplementation in neonates undergoing phototherapy is yet to be established but seems reasonable intervention taking into account the evidence available in existing literature.

Limitations

In the present era of high prevalence of vitamin D deficiency whether phototherapy was the principle reason for the fall in the calcium is debatable. Other limitation of the study was that we did not look in to maternal calcium intake and her calcium status. Duration of phototherapy is not constant for all the neonates which might have affected the results. Also the number of cases taken in the current study is small, larger case number would have given more precise and more reliable results.

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