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EFFECT OF PHOTOTHERAPY ON SERUM IONIC CALCIUM LEVEL IN NEONATES WITH HYPERBILIRUBINEMIA

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ABSTRACT

Objective: To evaluate the effect of phototherapy on serum calcium level in newborn with hyperbilirubinemia. **Design:** Prospective case-control study. **Material and Methods:** Only healthy term neonates with weight appropriate for gestational age (>2.49kg), of age 3-7 postnatal day included in the study. Newborns with hyperbilirubinemia >15mg/dl and received phototherapy were included as cases and controls were newborns fully matched with cases randomly selected who had hyperbilirubinemia but managed without phototherapy. Both the cases and controls were fully matched with respect to age, sex, period of gestation and birth weight. Serum calcium along with serum bilirubin was measured at the onset and then at 24 and 48 hours of phototherapy by OCPC method. **Results:** Out of 24 cases 66.67% developed hypocalcaemia and there was a significant difference observed between cases and controls(P=0.00016). It was also observed that out of hypocalcaemic cases 81.25% were symptomatic. In symptomatic cases 23% were lethargic, 39% had jitteriness and 38% were irritable. **Conclusion:** After 48 hours of phototherapy, it causes hypocalcaemia in full term born neonate with hyperbilirubinemia.

KEYWORDS: Indirect hyperbilirubinemia, phototherapy, serum calcium level, term neonates.

INTRODUCTION

Jaundice is an important problem in the first week of life. It is a cause of concern for anxiety in parents. High bilirubin level may be toxic to the developing central nervous system and may cause neurological impairment even in term newborns.

Nearly 60% of term newborns become visibly jaundiced in the first week of life.[1] In most of cases, it is benign and no intervention is required. Approximately 5-10% of them have clinically significant hyperbilirubinemia in whom the use of phototherapy becomes mandatory.[2] Phototherapy is the most widely used form of therapy for newborn infants with hyperbilirubinemia in order to decrease the body burden of neurotoxic bilirubin.[3-5] Jaundice is attributable to physiological immaturity of neonates to handle 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 hyperbilirubinemia.

The commonly known side effects of phototherapy are loose stools, Hyperthermia, dehydration fluid loss, skin burn, photoretinitis, low platelet count, increased red cell osmotic fragility, bronze baby syndrome, riboflavin deficiency and DNA damage and hypocalcemia.[6,7] Phototherapy has a negative impact on numerous parts of the oxidant/ antioxidant defense system in newborn hyperbilirubinemic infants and exposes them to potent oxidative stress.[8]

Hakinson[9] and Hunter[7] hypothesizedthat phototherapy inhibits pineal secretion of melatonin which blocks the effect of cortisol on bone calcium. So cortisol increases bone uptake of calcium and induces hypocalcaemia. Kim[10] suggested decreased secretion of parathormone as the cause of hypocalcemia. In Hooman's study the urinary calcium excretion was significantly higher in phototherapy group.[11]

As nearly 60% of term new borns become visibly jaundiced in the first week of life. Out of which 5-10% of them need Phototherapy. Also the Newborn having Hypocalcaemia present with non specific symptoms such as lethargy, poor feeding Jitterness, vomiting, Abdominal distension and seizures. So to find out all above symptom are due to Hypocalcaemia or some other reason we concluded our study.

MATERIAL AND METHODS

The present study was conducted in the department of Pediatrics NSCB Medical College, Jabalpur, MP, India after clearance from the institutional ethical committee. Cases were selected among the neonate admitted in NICU between Oct. 2013 to Oct 2014 with complain of hyperbilirubinemia in neonates > 48 hours of age with weight appropriate for gestational age were taken all infants were >2.49 Kg and term. This study included 84 neonate which are of 3-7 post natal day.

Selection of Cases were as neonate with age 3-7 post natal day. Only healthy term neonate who have serum bilirubin level >15mg/dL and no signs of sepsis or other infection, on Breast feed or formula feed, having no congenital abnormality or deformity were selected. Those neonates who were previously taken as controls and after 48 hours Serum Bilirubin was continuously rising and reached to >15mg/dl are also taken as cases.

Controls were selected as all neonate delivered in Gynecology Labor room or Gynecology Operation-theatre (inborn babies) who were fully matched with the study group with respect to age, sex, period of gestation and birth weight. In the control group babies who had hyperbilirubinemia but were managed without phototherapy.

Exclusion criteria

All neonates having birth wt <2.5 Kg, gestational age <36 wks Babies with Intra Uterine Growth retardation, Inborn error of metabolism, any sign of septicaemia or documented septicaemia, prolonged and difficult labour, respiratory distress, newborn to a diabetic mother, with apgar of less than 7 at 5 minutes of birth, who had exchange transfusion and those receiving cow's milk were excluded.

Pretest and posttest counseling was given to parents. After written consent from the parents those neonates fulfilling the above mentioned criteria were subjected to blood test like serum calcium levels, and serum bilirubin levels at initiation and 48 hours of phototherapy.

Taking all aseptic precaution peripheral vein was puncture and 2-3ml of blood collected in a sample bottle and out of which 1ml of blood wass taken immediately in heparanized syringe for ABG evaluation and rest is for serum Bilirubin. In addion to CBC and blood group, serum bilirubin was estimated by Jendrassik and Grof method. The method is as follows:

1. *(for conjugated bilirubin)* a fasting sample of serum or plasma is collected and acidified by the addition of hydrochloric acid. Ehrlich's diazo reagent is added so that the conjugated bilirubin begins forming blue azobilirubin. After 10 minutes the reaction is stopped and the amount of azobilirubin in the sample is measured.
2. *(for total bilirubin)* to an acidified fasting sample as in the previous method, caffeine benzoate is added as an accelerator for the unconjugated bilirubin to form azobilirubin. When the reaction is stopped, the azobilirubin in the sample thus represents the total of both conjugated and unconjugated bilirubin

Phototherapy of units Bird Meditech with four blue and two white lights with a wavelength of 420-480nm and irradiance of 6-12µw/cm2/nm were used placed at a distance of 20-25cm from skin surface under standard protocol with eyes and genital completely covered. Serum calcium along with serum bilirubin was measured at the onset and then at 24 and 48 hrs of phototherapy by OCPC method. Data was compiled. Cases were given single or double surface phototherapy depending upon serum bilirubin values. Phototherapy was given according to the criteria of American Academy of Pediatrics.

The study was a prospective case control study sample size was 19 by the formula 4pq/2L(Where p=prevalence, q=1-p, and L=level of error. Prevalence was 5% and L=2). We had taken 24 cases to correlate studies associations and outcomes. Controls should be 30 we had taken 60 the increased number of controls doesn't affect the study outcome. Statistical software used was SPSS version 20. Descriptive statistical analysis was done and continuous variables were described as mean and standard deviation and categorical variables in number and percentage(%). Student's t test has been used to assess continuous variables for pair-matched samples with a confidence limit of 95%. Significance was assessed at a level of 5%. For categorical variables chi square test was used.

OBSERVATION AND RESULTS

In our study 84 neonates who were 3-7 postnatal day were divided as cases and controls. Those neonates who were previously taken as control and due to continuously rising serum bilirubin level and reached >15mg/dl included in the case group. So out of 84 healthy term neonates 24 were cases and 60 were controls. It was found that there was no significant difference between cases and controls in terms of age, sex, period of gestation and birth weight (P>0.05). (Table 1-3).

Table No. 1: Distribution according to PND.

	3PND	4PND	5PND	6PND	7PND
CASE	7	11	3	2	1
CONTROL	15	23	13	8	1

Table No. 2: Sex wise Distribution.

Groups	Female	Male
Case	9	15
Control	30	30

Table No. 3: Distribution according to Mode of Delivery.

Group	NVD	LSCS	TOTAL
Case	14	10	**24**
Control	37	23	**60**

Serum calcium in pre-phototherapy and post-phototherapy in both cases and controls were compared and in the study group mean and standard deviation of serum calcium level before and after 48 hours of phototherapy were as 4.67 ± 0.34 and 3.9 ± 0.42 respectively. It was observed that there was a significant reduction in ionized calcium level with p value 0.0016. while in the control group at the time of inclusion mean and standard deviation of ionized calcium was 4.59 and 0.602 respectively which was nearly equal to after 48 hours of phototherapy as 3.9 and 0.42 respectively with p value 0.99 suggesting no significant difference. (Table 4).

Table No. 4: Calcium levels, pre-phototherapy and post-phototherapy in cases and controls.

	Calcium level before phototherapy (Mean ± Standard deviation)	Calcium level after phototherapy (Mean ± Standard deviation)	p value	significance
Cases (n=24)	4.67 ± 0.34	3.9 ± 0.42	0.0016	significant
Controls (n=60)	4.59 ± 0.602	4.59 ± 0.59	0.99	not significant

Among the 24 cases 8 have no effect on serum calcium i.e. normocalcaemic. 3 have hypocalcaemia but no symptoms of hypocalcaemia while 13 have hypocalcaemia with symptoms(Table 5). And jitteriness(5) and irritability(5) were the most common symptoms among the symptomatic cases lesser 3 cases were lethargy. No one had convulsion.(Table 6).

Table No. 5: Distribution of cases post phototherapy

Effect of phototherapy	No. of cases
sympt, hypo. Calc.	13
Asympt. Hypo. Cal	3
normal cal.	8

Table No. 6: Symptoms in study subjects.

SYMPTOMS	STUDY GROUP HAD SYMPTOMS
Jitterness	5
Irritability	5
Lethargic	3
Convulsion	0

Among control group only one newborn had hypocalcaemia who was hypocalcaemic before as well as after phototherapy and was asymptomatic. Treatment for the hypocalcaemia was given and child improved. So it suggest it was not due to phototherapy as the baby was already hypocalcaemic before receiving phototherapy.

DISCUSSION

National Neonatal Perinatal Database Network reported an incidence of Neonatal Hyperbilirubinemia requiring phototherapy 5.7% in Inborn and 32.99% in Out born admitted babies during the period 2002-2003.[12]

Phototherapy is widely accepted as a relatively safe and effective method for treatment of neonatal hyperbilirubinemia. Wide clinical experience suggests that long term adverse biological effects of phototherapy are absent, minimal or unrecognized.[13]

Romagnoli and colleagues in 1979 were the first to suggest an association between hypocalcaemia and phototherapy in preterm neonates and observed hypocalcemia in 52.3% babies This study was in consonance with our study.[17]

Hakanson et al (1981) reported that when young rats were exposed to white fluorescent light, the serum concentration of calcium did decrease. He showed that this calcium drop was accompanied by a decrease in serum melatonin concentration. This effect can be prevented by shielding the occiput, by inhibiting corticosterone synthesis and by administration of exogenous melatonin. They also reported that propranolol could reduce serum calcium by inhibiting synthesis of melatonin. Light-induced hypocalcemia may result from increased calcium uptake by bone when the blocking effect of melatonin decreases after pineal inhibition by transcranial illumination.[9,18]

Zecca et al (1983) reported that administration of 25-hydroxy vitamin D3 was not able to lower the incidence of the phototherapy-induced hypocalcemia in preterm infants. He concluded that vitamin D was unlikely to play an important role in the pathogenesis of phototherapy-induced hypocalcemia.[14]

Sethi et al (1990) has studied the effects of phototherapy in 20 term & 20 preterm hyperblirubinemic neonates. They observed that 75% of term & 90% of preterm neonates developed hypocalcaemia after phototherapy.[15]

In a study done by Jain et al (1998), the prevalence of phototherapy induced hypocalcaemia was 55% in preterm infants and 30% in full-term neonates. Among the affected preterm babies with hypocalcaemia 63.6% had jitteriness and 27.3% had irritability. In the hypocalcaemia full-term neonates 50% had jitteriness and 16.7% were irritable. To prevent hypocalcaemia, they recommended administration of supplemental calcium in the neonates treated by phototherapy.[16]

Karamifar et al (2002) study was performed on 153 jaundiced neonates (62 premature, 91 full-term) that were managed with phototherapy. These neonates were completely normal on physical examination. Serum

calcium was checked on arrival, 48 hours after starting phototherapy. The first samples were considered as controls. Twenty- two neonates (14.4%) developed hypocalcemia. There were significant differences between the prevalence of hypocalcemia in premature (22.6%) and full-term neonates (8.7%) (p=0.018). This study showed that neonates under phototherapy are at high risk of hypocalcemia. This risk is greater in premature neonates.[19] Yadav et al observed that 66% of term and 80% of preterms developed hypocalcemia after phototherapy.[20] In his study 80% of hypocalcaemic term neonates became symptomatic, the most common sign was jitteriness. In Eghbalian's study, one of hypocalcemic newborns had apnea.[21]

Arora et al (2014) study concluded that hypocalcemia was more frequently observed in term neonates as compared to preterm neonates which was in contrast to our study. Higher incidence of hypocalcemia in term group in Arora et al study was probably attributed to higher cut off value of serum calcium level of 8mg/dl as compared to 7mg/dl in preterm babies. The incidence of hypocalcemia in the above study was 43% in preterm neonates which was in consonance with our study.[22] Curtis MD et al (1981) stated that absorption of water, sodium chloride and potassium was significantly impaired in the patients receiving phototherapy.[23] Others also observed change in sodium[24] and potassium.[25] level. Taheri et al observed significant decrease in total serum calcium level.[26]

Hunter et al (2004) hypothesized that phototherapy inhibits pineal secretion of melatonin which blocks the effect of cortisol on bone calcium. Cortisol exerts a direct hypocalcemic effect and increases bone uptake of calcium as well.[27] Medhat et al (2006) of Cairo University observed that 75% of term & 90% of preterm developed hypocalcaemia after phototherapy.[28]

In our study we observed ionic calcium level instead of total serum calcium level which is more reliable marker of hypocalcaemia. We observed a significant decrease in serum ionic calcium level in study group while in control group there was no significant difference observed after 48 hours of phototherapy. We also observed symptoms of hypocalcaemia in study group as jitteriness, lethargy and irritability. No symptomatic cases observed to have convulsions and apnea. These all differentiate our study from previous studies. And comparison with control potentiate that those who are receiving phototherapy should be monitored for hypocalcaemia and prophylactic calcium should be supplemented in them considering them as high risk group.

The findings of our study should be potentiated with other similar longitudinal studies with larger population. Since at higher bilirubin level we had to switch the controls to phototherapy group it is also necessary to correlate higher bilirubin level with serum calcium level without phototherapy to consolidate the findings.

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