Effect of Phototherapy on Biochemical Markers of Neonates with Unconjugated Hyperbilirubinemia

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ABSTRACT

BACKGROUND
Hyperbilirubinemia is one of the commonest clinical problems encountered in the neonatal period, especially during the first week of life which can be classified into unconjugated & conjugated hyperbilirubinemia. Phototherapy plays an important role in the treatment of neonatal hyperbilirubinemia. The study intended to evaluate changes in serum electrolyte levels in neonates undergoing phototherapy for exaggerated physiological hyperbilirubinemia.

METHODS
A prospective cross-sectional observational study was conducted in a tertiary care teaching hospital from April 2020 to March 2021 on neonates born after achieving gestational age of 28 weeks.

RESULTS
A significant incidence of hypocalcaemia was noted in neonates post phototherapy (19.2 %; P-value < 0.001). The incidence of hypocalcaemia was higher in preterm (31.7 %) than the term (8.6 %) and at low birth (41.7 %) than in normal-weight (10.6 %). It was also found to be much more when the duration of PTH was > 24 hours (28.6 %) as compared to the duration of PTH when less than 24 hours (12.2 %). No adverse events due to hypocalcaemia were noted. The incidence of hyponatraemia and hypokalaemia after phototherapy was found to be non-significant (P values 0.371 and 0.301 respectively) before and after phototherapy.

CONCLUSIONS
The study thus does not recommend any calcium supplementation over and above the prescribed guidelines recommended by AAP and NNF. However, in view of higher incidence, LBW and preterm neonates may be considered for monitoring and calcium prophylaxis on an individual basis.

KEY WORDS
Hyponatraemia, Hypocalcaemia, Hypokalaemia, Phototherapy, Low Birth Weight.
BACKGROUND

Hyperbilirubinemia is one of the commonest clinical problems encountered in the neonatal period, especially during the first week of life. Studies suggest a prevalence of neonatal hyperbilirubinemia as high as 90 % in preterm infants & 60 % of term infants in the first week of life. The commonest manifestations are yellowish discoloration over the skin and the scleral portion of the eye with some mothers also reporting high coloured urine. The condition can be classified as unconjugated and conjugated hyperbilirubinemia. Unconjugated hyperbilirubinemia is a normal physiological condition that manifests due to increased breakdown of neonatal red cells along with relatively immature conjugation reaction in the neonatal liver, potentiated by increased enterohepatic circulation. The rise of this unconjugated bilirubin above a certain level crosses over the blood-brain barrier leading to neurotoxicity unless treated in time. Conjugated hyperbilirubinemia is less neurotoxic as it does not cross the blood-brain barrier but it usually represents a potentially serious underlying illness requiring further evaluation.

Unconjugated hyperbilirubinemia is treated with phototherapy (PTH), exchange transfusion (ET) or pharmacological agents. PTH plays a significant role in the treatment of unconjugated hyperbilirubinemia. It transforms lipid-soluble unconjugated bilirubin into water-soluble isomers which are capable of being excreted even without conjugation reaction in the liver. Effectivity of PTH mainly depends on the kind of light source used (i.e., dose, spectral release curve, depth of infiltration), body surface area exposed to light, underlying aetiology and bilirubin level at the onset of PTH. The ultimate goal of PTH is to prevent the rise of bilirubin to levels to cause bilirubin induced neurological dysfunction (BIND) & kernicterus and reduce the need for ET. As with any treatment, PTH also has its side effects like hyperthermia, bronze baby syndrome, feed intolerance, loose stools, skin rashes, retinal changes, dehydration, hypocalcaemia, electrolyte imbalance, and redistribution of blood flow & genotoxicity.

A very small number of studies are currently available that describe the effect of PTH on biochemical parameters like serum sodium, potassium, calcium, blood urea and creatinine. These abnormalities have the potential of aggravating the documented adverse effects of PTH.

METHODS

This prospective hospital-based observational study was conducted in the Department of Paediatrics in a tertiary care referral and teaching hospital in Lucknow for a period of one year from April 2020 to March 2021. All eligible neonates born after completing 28 weeks of gestation and receiving phototherapy during this period were recruited for the study after written informed consent. Permission for the study was granted by the Institutional Ethics Committee. Conditions affecting hyperbilirubinemia such as perinatal asphyxia, respiratory distress syndrome, meconium aspiration syndrome, persistent pulmonary hypertension, congenital adrenal hyperplasia, and Rh/AO incompatibility, sepsis, conjugated or pathological hyperbilirubinemia, or mothers with a history of diabetes, hypothyroidism and on anticonvulsant use were excluded from the study.

Socio-demographic factors such as age and gender were noted. Complete maternal history was obtained to rule out gestation related morbidities & chronic illness. The neonatal history was obtained from caregivers and a detailed examination of neonates was carried out. The first venous blood sample of the neonates was obtained before PTH for baseline data. A second venous blood sample was subsequently obtained after 48 hours or after the termination of PTH if it was employed for less than 48 hrs. In case PTH continued beyond this period, samples were obtained every 48 hours till its cessation. These samples were analysed to determine the changes in various biochemical markers.

Statistical Analysis

The sample was calculated taking a Z value of 1.96 for a two-tailed sample, the precision of 5 %, and the proportion of neonates requiring phototherapy for hyperbilirubinemia at 10 % (determined by a pilot study of fifty neonates conducted in the department), and was determined to be 130 patients. The two-sample t-test (Student's t-test) was used for analysing the quantitative variables with normal distribution. The chi (χ²) square test was used where distribution was skewed and for categorical variables. In comparisons using the Student’s t-test, 80 % confidence intervals for the mean difference in response provided a range of likely values to assess the clinical significance and for all tests of significance, P-values < 0.05 were considered statistically significant.

RESULTS

A total of 130 neonates were enrolled in this study. 71 babies (54.6 %) were males and the remaining 59 (45.4 %) were females with M: F ratio being 1.2:1. Of the majority of the studied neonates, 70 (53.8 %) were term while 54 (27.7 %) neonates were late preterm (34 to 36[6/7] weeks) and 6 (18.5 %) neonates were moderate preterm (all between 33[1/7] to 36[6/7] weeks). The mean gestational age in the study group was 36.99 ± 2.02 weeks. The reason for a high number of preterm deliveries requiring phototherapy in the study was the lower threshold for PTH requirements in these neonates due to physiological immaturity.

Moreover, our hospital being a tertiary care centre with a level III NICU, a relatively higher number of preterm deliveries were recorded as compared to other hospitals. The majority of the studied neonates had normal birth weight with only 36 (27.7 %) neonates being recorded with weights less than 2500 grams. Mean birth weight was noted to be 2.90 ± 0.51 kg. The majority of the 74 (58.5 %) neonates were born by normal vaginal delivery (NVD) and the rest 54 (41.5 %) neonates by Caesarean section (CS). Gender wise distribution shows that 30 (42.3 %) females and 41 (57.7 %) males were born by NVD; the rest 24 (44.4 %) female and 30 (55.6 %) male neonates by caesarean section. The baseline serum values are noted in table 1.
The baseline serum levels are depicted in Table 2. Only serum total bilirubin and unconjugated bilirubin components were significantly different when measured for babies presenting before or after 5 days of birth. Rest parameters were largely comparable.

The incidence of hyponatremia following phototherapy was more in LBW babies (11.1%) than in normal babies (3.2%), however, the relationship was insignificant in statistical comparison. The incidence of hypocalcaemia following phototherapy was more in low-birth-weight babies (41.7%) than in normal babies (10.6%) which was significant (P < 0.001). Thus, the study showed that low-birth-weight babies were at more risk of hypocalcaemia following phototherapy than normal babies. The incidence of hypokalaemia after phototherapy was found to be non-significant (P = 0.981) in both pretermers and term neonates. The incidence of hyponatremia and hypokalaemia was deemed insignificant between groups receiving PTH for less and more than 24 hours (P-values 0.519 and 0.413 respectively). But the incidence of hypocalcaemia was 28.6% when the duration of phototherapy was ≥ 24 hrs as compared to a duration of < 24 hrs (12.2%). By using the chi-square test, the p-value was 0.019, thus it was statistically significant. Thus, babies were at higher risk of hypocalcaemia when kept under phototherapy for more than 24 hrs.

**DISCUSSION**

Phototherapy is the safest and most commonly used treatment option for unconjugated neonatal hyperbilirubinemia. In our study, 130 neonates with gestational age higher than 28 weeks were enrolled and evaluated. 26 (44.1%) female and 33 (46.5%) male neonates were given PTH for 12 hours while another 5 (8.5%) female and 10 (14.1%) male neonates received PTH for 18 hours. Longer duration PTH for 24 hours was given in another 26 (44.1%) female and 26 (36.6%) male neonates. Only 2 (3.4%) female and 2 (2.8%) male neonates had a PTH time of 36 hours. The biochemical parameters of serum total and unconjugated bilirubin, urea/ creatinine, sodium, potassium and calcium were compared against gender distribution, age less than 5 days or more, LBW babies against normal birth weight and term and preterm neonates. No significant difference was found in the baseline biochemical parameters between the two sexes. On scrutiny of all the biochemical parameters against neonatal age of 5 or more days against those lesser than that, there was no significant difference found except for baseline unconjugated and total bilirubin levels (P-values 0.001 each). The mean values of all biochemical parameters in babies less and more than 2.5 kg were comparable and statistically insignificant. Periods of gestation wise distribution of biochemical parameters were comparable for neonates born before and after 37 weeks of gestation.
Similar studies have been published by other authors in the past decade. Krishna et al.\(^6\) Subhashini et al.\(^7\) Bezboruah et al.\(^8\) and Suneja et al.\(^9\) have reported prospective hospital observational comparative studies of phototherapy induced electrolyte imbalance in hyperbilirubinemia of newborns and concluded that neonates undergoing phototherapy are at a higher risk of electrolyte changes. The various authors have highlighted preterms and LBW babies to be at higher risk for electrolyte changes. Similarly, other authors like Karamifar et al.\(^10\) Zecca E et al.\(^11\) Taheri et al.\(^12\) and Eghbalian F et al.\(^13\) have reported on hypocalcaemic changes in neonates post phototherapy. Many of these authors have concluded prematurity and low birth weight to be significant risk factors for post phototherapy hypocalcaemia noted in these babies.

The incidence of hypocalcaemia in several studied neonates after phototherapy was in a significantly greater number of 25 (19.2 %) neonates than the before phototherapy (P < 0.001). The incidence of hypocalcaemia following phototherapy was more in low-birth-weight babies (41.7 %) than in normal babies (10.6 %) which was significant (P < 0.001) on applying the chi-square test. Incidence of hypocalcaemia following phototherapy was also found to be more in preterm neonates (31.7 %) than in term neonates (8.6 %), (P-value 0.0012) suggesting that low birth weight and prematurity were risk factors for hypocalcaemia following phototherapy. Incidence of hypocalcaemia was 28.6 % when the duration of phototherapy was ≥ 24 hrs as compared to a duration < 24 hrs (12.2 %). By using the chi-square test, the p-value was 0.019, thus it was statistically significant. Thus, we can conclude that babies were at higher risk of hypocalcaemia if kept under phototherapy for more than 24 hrs.

In a similar study Krishna et al.\(^6\) reported that 13.1 % (33) cases were hypocalcemic after phototherapy which was comparable to our study. Their reported incidence of hypocalcaemia following phototherapy was more in LBW babies (36.2 %) as against normal babies (6.2 %); in preterm neonates (41.2 %) compared to term neonates (6.2 %) and the incidence of hypocalcaemia was 18.8 % after phototherapy duration of > 48 hrs as compared to duration < 48 hrs (10.9 %). Subhashini et al.\(^7\) reported a higher incidence of hypocalcaemia in preterm neonates 28.6 % than in term neonates (24.1 %) and when the duration of phototherapy was more in phototherapy greater than 48 hrs. Our reported incidence was much higher at 41.7 %. Suneja et al.\(^9\) reported that 25.34 % of preterms became hypocalcemic following phototherapy as compared with term neonates, in which only 10.24 % became hypocalcemic. They also found that the incidence of hypocalcaemia was more in LBW babies (26.25 %) than in normal-weight neonates (7.94 %). Karamifar et al.\(^10\) study observed a significant fall in serum calcium levels in preterms and term babies after phototherapy. Zecca E et al.\(^11\) study also suggested an association between hypocalcaemia and phototherapy in preterm neonates and observed hypocalcaemia in 52.3 % of babies. Jain et al.\(^14\) have found that 55 % of preterm neonates and 30 % of full-term neonates developed hypocalcaemia after phototherapy. There was a statistically significant (P < 0.05) difference in the serum calcium level. Eghbalian et al.\(^13\) study found a statistically significant difference (P < 0.05) between pre-and post-phototherapy plasma calcium levels in term neonates. Yadav RK et al.\(^15\) found a significant fall (P < 0.05) in calcium levels in 66.6 % of term and 80 % of preterm neonates after 48 hours of phototherapy. 20 Taheri et al.\(^12\) studied the prevalence of phototherapy induced hypocalcaemia in 147 term neonates and found a decrease in serum calcium level in 56 % of babies out of which 7 % developed significant hypocalcaemia (P=0.03) after 48 hours of phototherapy. Arora et al.\(^16\) study conversely concluded that hypocalcaemia was more frequently observed in term neonates as compared to preterm neonates which was in contrast to our study. The higher incidence of hypocalcaemia in the term group in Arora et al.\(^16\) study was probably attributed to a higher cut off value of serum calcium level of 8 mg/dl as compared to 7 mg/dl in preterm babies. 22 The incidence of hypocalcaemia in the above study was 43 % in preterm neonates which was in consonance with our study.

The incidence of hyponatremia and hypokalemia after phototherapy was found to be non-significant (p values 0.371 and 0.301 respectively) before and after phototherapy. The incidence of hyponatremia following phototherapy was more in LBW babies (11.1 %) than in normal babies (3.2 %), however, the relationship was insignificant in statistical comparison. The incidence of hyponatremia and hypokalemia was deemed insignificant between groups receiving PTH for less and more than 24 hours (P-values 0.519 and 0.413 respectively). The incidence of hyponatremia following phototherapy was more in preterm neonates (6.7 %) than in term neonates (5.7 %), but the p-value obtained was insignificant at 0.639. The incidence of potassium after phototherapy was found to be non-significant (P=981) in both preterms and term neonates. Krishna et al.\(^6\) Subhashini et al.\(^7\) Bezboruah et al.\(^8\) and Suneja et al.\(^9\) have reported post-PTH hyponatremia and hypokalemia which was not observed in our study.

**CONCLUSIONS**

The study brings out a higher incidence of hypocalcaemia in babies managed with phototherapy for unconjugated hyperbilirubinemia, the incidence being substantially more in LBW and preterm neonates. No adverse effects of hypocalcaemia were noted in these children. The study thus does not recommend any calcium supplementation over and above the prescribed guidelines recommended by AAP and NNF. However, in view of higher incidence, LBW and preterm neonates may be considered for monitoring and calcium prophylaxis on an individual basis.

**REFERENCES**


