ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Electrolyte Imbalances in Preterm and Term Hyperbilirubinemic Neonates Following Phototherapy

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Article History:

Received on: 16 Sep 2020
Revised on: 16 Oct 2020
Accepted on: 21 Oct 2020

Keywords:

Calcium,
Hyperbilirubinemia,
Hypocalcemia,
Hyponatremia,
Jaundice,
Phototherapy

ABSTRACT

Neonatal hyperbilirubinemia is the most frequently occurring disorder in neonates. Phototherapy is the most common treatment strategy practiced routinely in the management of neonatal unconjugated hyperbilirubinemia. Reviews on electrolyte variations post phototherapy are highly variable. Therefore our study was aimed to evaluate the effect of phototherapy on calcium, sodium, potassium, magnesium and liver enzymes in physiologically hyperbilirubinemic neonates before and after phototherapy. The study was carried out on 100 (45 preterm, 55 term) hyperbilirubenimic neonates who underwent phototherapy. The overall prevalence of hypocalcemia was found to be 7%, none in preterm, 12.73% in term, 12.12% in males, 13.64% in females, 2.56% in low birthweight and 11.11% in normal birthweight neonates. The incidence of hypomagnesemia was found to be 4.45% in preterm, 7.27% in term, 5.2% in males, 13.64% in females, 5.13% in low birthweight and 7.4% in normal birthweight neonates. We found the incidence of hyponatremia to be 12%, 11.11% in preterm, 12.73 % in term, 12.12% in males, 18.6% in females, 5.13% in low birthweight and 14.8% in normal birthweight neonates. Monitoring of serum calcium and electrolyte levels in neonates undergoing phototherapy will help to identify hypocalcemia and electrolyte imbalances to prevent complications.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.3585

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INTRODUCTION

Neonatal hyperbilirubinemia is the most frequently occurring disorder in neonates in their first week of life (Schwartz *et al.*, 2011). Approximately 80% of preterm and 60% of term neonates are found to be affected by hyperbilirubinemia. In India, the prevalence of hyperbilirubinemia in preterm neonates is found to be about 54.6 - 77% (Khan *et al.*, 2017).

Physiological jaundice is a transient, mild benign form of unconjugated hyperbilirubinaemia which usually starts on the second day of life and reaches a peak by a third to the fifth day in term babies and fifth to the sixth day in preterm babies. The hyperbilirubinaemia usually resolves within seven to ten days in term neonates and by three weeks in preterm neonates. Increased breakdown of red blood cells (RBC) & haemoglobin causes accumulation of unconjugated bilirubin in the blood, which being lipid-soluble can cross the blood-brain barrier resulting in neurotoxicity or kernicterus. (Queensland Clinical Guidelines, 2019). In clinical practice, the total bilirubin concentration in neonates usually reflects the serum level of unconjugated bilirubin. The risk of kernicterus increases proportionately as the bilirubin concentration increases (Kirk, 2008).

Phototherapy is a safe, non- invasive and well-tolerated therapy for mild to severe neonatal hyperbilirubinemia (Taksande and Selvam, 2018). Bilirubin absorbs maximum light from the blue-green region of the spectrum near 460 nm wavelength, which is used for treating neonatal jaundice (Suneja *et al.*, 2018). The risk factors associated with phototherapy may include hyperthermia, feed intolerance, loose stools, skin rashes, temporary skin tanning, bronze baby syndrome, retinal changes, erythema, dehydration, mineral imbalance and increased blood flow to the skin (Singh *et al.*, 2017). Studies have shown that neonates receiving phototherapy are found to have changes in serum calcium, sodium, potassium and magnesium levels which require close monitoring and treatment (Rangaswamy *et al.*, 2019).

Previous studies showed the incidence of hypocalcemia following phototherapy in preterm neonates as 22.6% by Karamifar *et al.* (2002), 80% by Yadav *et al.* (2012), 41.2% by Reddy *et al.* (2015) and term neonates as 8.7% by Karamifar *et al.* (2002), 66.6% by Yadav *et al.* (2012), 6.2% by Reddy *et al.* (2015), 7% by Alizadeh-Taheri *et al.* (2013) and 22.76% by Khan *et al.* (2016). Literature review on sodium and potassium variations post phototherapy has shown significant changes in potassium levels by Tan and Jacob (1981), sodium levels by Reddy *et al.* (2015), both sodium and potassium levels by Suneja *et al.* (2018) and Rangaswamy *et al.* (2019). In contrast, no change was observed by Usharani (2018). Therefore our study was aimed to evaluate the effect of phototherapy on Calcium, sodium, potassium and magnesium in physiologically hyperbilirubinemia neonates before and after phototherapy.

MATERIALS AND METHODS

This comparative study was conducted on 45 preterm and 55 term hyperbilirubinemia neonates who were considered for the treatment of phototherapy at NICU of SRM Medical College Hospital & Research Centre, Kattankulathur, Potheri, Chengalpattu district, Tamilnadu, India. The study protocol was performed under the approval of the Institutional ethics committee (Ethical approval number: 1602) and informed written consent was taken from parents of all the neonates participating in the study.

The sample size of 100 was calculated based on the prevalence mentioned in the previous reports (Suneja *et al.*, 2018). A detailed history including NICU admission of a neonate, visual examination of a neonate, gender and birth weight of neonate, type and duration of phototherapy for both preterm and full-term babies were noted. Hyperbilirubinemia neonates are undergoing phototherapy for Rh/ABO incompatibility, undergoing exchange transfusion, congenital malformations, infants of maternal diseases such as eclampsia, diabetes, bone, kidney, liver diseases, perinatal asphyxia and a low Apgar score of less than seven at the first and fifth minute after birth were excluded from the study.

Under aseptic precautions, 2 ml of venous blood was collected in plain vacutainers for serum separation from neonates. Pre-therapy samples were collected before initiation of phototherapy, and post-therapy samples were collected 48hours after phototherapy. All the biochemical estimations were carried out using Beckman Coulter Auto analyser on the day of sample collection in the Central Laboratory of Biochemistry Department of SRM Medical College Hospital and Research Centre.

Estimations of bilirubin (3, 5- dichlorophenyldiazonium tetrafluoroborate method), sodium and potassium (Ion-selective method), Calcium and magnesium (IFCC method) were carried out using commercial kits of Beckman coulter. SPSS version 22 was used for statistical analysis. All the data obtained in this study was used for 't' test and correlation analysis. The significance level was calculated with $p \leq 0.05$.

RESULTS AND DISCUSSION

The study participants consisted of 100 neonates, among them, 45 were preterm, and 55 were term neonates. All the neonates included in the study underwent phototherapy due to increased serum unconjugated bilirubin levels which is an indication of physiological jaundice. Among the 45 preterm neonates, 24 were males, and 21 were females. Among the 55 term neonates, 33 were males, and 22 were females.

The bodyweight of neonates was categorised as low birth weight (<2.5kg), normal birth weight (2.5-4 kg) and high birth weight (>4 kg). Among the 45 preterm babies, 22 were of low birth weight, 18 were normal, and five were of high birth weight. Among the 55 term babies, 17 were of low birth weight, 36 were normal, and two were high of birth weight.

Analysis based on the gestation period

We found the mean levels of bilirubin and indirect bilirubin to be significantly less in term neonates than in preterm neonates (Table 1).

Analysis of study parameters in preterm neonates

The mean levels of Bilirubin, Indirect bilirubin, Sodium and Calcium in preterm neonates were found to be significantly declined after phototherapy when compared with values before phototherapy (Table 2)

Analysis of study parameters in term neonates

The mean levels of Bilirubin, Indirect bilirubin, and Calcium in term neonates were found to be significantly declined after phototherapy when compared with values before phototherapy (Table 3).

Status of electrolyte imbalance

All the preterm neonates were found to have calcium level in the normal range of 7 – 12 mg/dl, whereas hypocalcemia was observed in 12.73% of term neonates following phototherapy (Table 4). Hyponatremia was found in 11.11% of preterm and 12.73% of term neonates (Table 5). Hypokalemia was observed in 4.44% preterm neonates only (Table 6). Hypomagnesemia occurred in 4.45% of preterm and 7.27% of term neonates (Table 7). The status of electrolyte imbalance following phototherapy based on gender and birth weight has been summarised in Table 8.

Pearson correlation analysis of bilirubin with the various study parameters pre and post-therapy

A significant positive correlation of bilirubin with magnesium [r (0.3325), P (0.0256)] was found in preterm pretherapy neonates. A significant positive correlation of bilirubin with Sodium [r (0.475), P (0.001)] was found in preterm posttherapy neonates. A significant positive correlation of bilirubin with magnesium [r (0.3317), P (0.0134)] was found in term pretherapy neonates. A significant positive correlation of bilirubin with Calcium [r (0.514), P (0.000)] and Magnesium [r (0.464), P (0.000)] was found in term posttherapy neonates.

In our present study among the 100 neonates, 57% were males, and 43% were females. Among the preterm neonates, 24 (53.33%) were males, and 21(46.67%) were females. Among term neonates 33 (60%) were males, and 22 (40%) were females. Many studies have established that jaundice is more common among male neonates through the underline cause is known (Boskabadi *et al.*, 2011). $ in his study involving 273 infants with jaundice at Ghaem hospital, Iran from 2008 to 2012 also observed similar findings.

The development of hypocalcemia as a consequence of phototherapy has been attributed to pineal gland inhibition through transcranial illumination (Hakanson *et al.*, 1984). The resultant decrease of melatonin secretion from pineal gland has an inhibitory effect of cortisol on bone calcium. Thus hypocalcemia results due to increased calcium uptake by the bone (Cardinali *et al.*, 2003).

Hypocalcemia following phototherapy was first reported in 1979 by Romagnoli and colleagues in preterm neonates (Romagnodi *et al.*, 1979). Hakanson and Bergstrom (1981) in the year 1987 studied calcemic responses to manipulation of serum melatonin and demonstrated that hypocalcemia during phototherapy results from transcranial photic inhibition of melatonin synthesis. Occipital shielding and usage of blue light, which has a low degree of cranial penetrance prevents hypocalcemia (Sisson, 1977). Administration of phototherapy parallel to a circadian rhythm may help to ameliorate the development of hypocalcemia following phototherapy (Wan *et al.*, 1981).

Our study findings reveal a significant decrease in blood calcium levels following phototherapy in both preterm (P - 0.0001) and term (P - 0.0007) neonates. These findings are similar to that of Reddy *et al.* (2015); Suneja *et al.* (2018), in her study involving 119 neonates (64 males, 55 females) has also reported a significant decline in serum calcium levels after phototherapy.

The incidence of hypocalcemia in our study was found to be 7%. None of the preterm neonates was found to develop hypocalcemia following phototherapy when a cut-off of <7mg/dl was used. The prevalence of hypocalcemia as a consequence of phototherapy in preterm neonates was found to be 22.6% by Karamifar *et al.* (2002), 80% by Yadav *et al.* (2012), 43% by Arora *et al.* (2014) and 41.2% by Reddy *et al.* (2015).

Our study shows that 12.73% of term neonates developed phototherapy induced hypocalcemia. The incidence of hypocalcemia following phototherapy in term neonates was reported as 8.7% by Karamifar *et al.* (2002), 66.6% by Yadav *et al.* (2012), 7% by Alizadeh-Taheri *et al.* (2013), 56%

Table 1: Comparison of study parameters between preterm and term neonates

Parameters	Preterm (N=45)	Term (N=55)	P-Value	Significance
Bilirubin (mg/dl)	16.37 ± 1.69	14.44 ± 2.92	0.0002***	Significant
Indirect Bilirubin (mg/dl)	15.47 ± 1.66	13.62 ± 2.92	0.0003***	Significant
Sodium (mmol/l)	150.95±15.08	151.11±12.42	0.9537	Not significant
Potassium (mmol/l)	5.33 ± 1.47	5.35 ± 1.52	0.9472	Not significant
Calcium (mg/dl)	9.97 ± 0.84	9.77 ± 0.87	0.2483	Not significant
Magnesium (mg/dl)	2.59 ± 0.36	2.57 ± 0.44	0.8069	Not significant

Significant: *P-value< 0.05, **P-value < 0.01, ***P-value <0.001

Table 2: Comparison of study parameters pre and post-therapy in preterm neonates

Parameters	Pre-treatment	Post-treatment	P-value	Significance
Bilirubin (mg/dl)	16.37 ± 1.69	12.41 ± 1.70	0.0001***	Significant
Indirect bilirubin (mg/dl)	15.47 ± 1.66	11.46 ± 1.72	0.0001***	Significant
Sodium (mmol/l)	150.95 ± 15.08	142.49 ± 22.58	0.0395*	Significant
Potassium (mmol/l)	5.33 ± 1.47	5.13 ± 0.95	0.4454	Not Significant
Calcium (mg/dl)	9.97 ± 0.84	9.22 ± 0.73	0.0001***	Significant
Magnesium (mg/dl)	2.59 ± 0.36	2.52 ± 0.41	0.3918	Not Significant

Significant: *P-value< 0.05, **P-value < 0.01, ***P-value <0.001

Table 3: Comparison of study parameters pre and post-therapy in full-term neonates

Parameters	Pre-treatment	Post-treatment	P-value	Significance
Bilirubin (mg/dl)	14.44 ± 2.92	11.29 ± 2.93	0.0001***	Significant
Indirect bilirubin (mg/dl)	13.62 ± 2.92	10.47 ± 2.91	0.0001***	Significant
Sodium (mmol/l)	151.11 ± 12.42	146.04 ± 17.75	0.0855	Not Significant
Potassium (mmol/l)	5.35 ± 1.52	5.10 ± 1.10	0.3253	Not Significant
Calcium (mg/dl)	9.77 ± 0.87	9.12 ± 1.08	0.0007***	Significant
Magnesium (mg/dl)	2.57 ± 0.44	2.40 ± 0.52	0.0669	Not Significant

Significant: *P-value < 0.05, **P-value < 0.01, ***P-value<0.001

Table 4: Status of calcium levels inpreterm and term neonates following phototherapy

Calcium (mg/dl)	Preterm neonates	Calcium (mg/dl)	Term neonates
<7	0 (0%)	<8	7 (12.73%)
7 – 12	45 (100%)	8 – 12	47 (87.45%)
>12	0 (0%)	>12	1 (1.82%)

Table 5: Status of sodium levels in preterm and term neonates following phototherapy

Sodium (mmol/l)	Preterm neonates	Sodium (mmol/l)	Term neonates
<135	5 (11.11%)	<135	7 (12.73%)
135 – 150	27 (60%)	135 – 150	37 (67.27%)
>150	13 (28.89%)	>150	11 (20%)

Table 6: Status of potassium levels in preterm and term neonates following phototherapy

Potassium (mmol/l)	Preterm neonates	Potassium (mmol/l)	Term neonates
<3.5	2 (4.44%)	<3.5	0 (0%)
3.5 – 5.5	30 (66.67%)	3.5 – 5.5	42 (76.36%)
>5.5	13 (28.89%)	>5.5	13 (23.64%)

Table 7: Status of magnesium levels in preterm and term neonates following phototherapy

Magnesium (mg/dl)	Preterm neonates	Magnesium (mg/dl)	Term neonates
<1.8	2 (4.45%)	<1.8	4 (7.27%)
1.8 – 2.6	28 (62.22%)	1.8 – 2.6	38 (69.09%)
>2.6	15 (33.33%)	>2.6	13 (23.64%)

Table 8: Status of electrolyte imbalance inhyperbilirubinemia neonates following phototherapy based on gender and birthweight

Electrolyte abnormalities	Number of Neonates	Gender of neonates		Birthweight of neonates		
		Male	Female	Low birth weight	Normal birth weight	High birth weight
Hypocalcemia	7 (7%)	4 (12.12%)	3 (13.64%)	1 (2.56%)	6 (11.11%)	-
Hyponatremia	12 (12%)	4 (12.12%)	8 (18.6%)	2 (5.13%)	8 (14.8%)	2 (28%)
Hypokalemia	2 (2%)	2 (3.5%)	-	-	1 (1.85%)	1 (14%)
Hypomagnesemia	6 (6%)	3 (5.2%)	3 (13.64%)	2 (5.13%)	4 (7.4%)	-

by Arora *et al.* (2014), 6.2% by Reddy *et al.* (2015) and 22.76% by Khan *et al.* (2016).

Most of the observations regarding the development of hypocalcemia following phototherapy show a greater prevalence in preterm than in term neonates. Arora *et al.* (2014) found that hypocalcemia was more frequently noticed in term neonates as compared to preterm neonates who are similar to the finding of our study.

Analysis based on gender revealed that 12.12% of males and 13.64 % of females term neonates developed hypocalcemia. We observed that 2.56% of low birth weight and 11.11% of normal weight term neonates developed hypocalcemia. Reddy *et al.* (2015) observed incidence of hypocalcemia to be 36.2% in low birth weight babies and 6.2% normal-weight babies.

Bilirubin binds with and activates N-methyl-D-aspartate (NMDA) receptors of the plasma membrane causing neuronal injury. NMDA receptor antagonists can block the neurotoxic effect of bilirubin. Mg2+ ions are found to close the NMDA channels in a voltage-dependent manner. Magnesium acts as an NMDA antagonist which can counteract the neurotoxicity of bilirubin (Khosravi *et al.*, 2011). Levels of magnesium did not differ significantly following phototherapy among the neonates of our study. Our results are contrary to the findings of Mosayebi *et al.* (2020).

A significant positive correlation between serum bilirubin and magnesium levels was found in the preterm and term neonates of this study before phototherapy. Choudhury and Borkotoki (2018) demonstrated a positive correlation between plasma magnesium and severity of hyperbilirubinemia. We observed similar findings in our study before phototherapy in preterm neonates r (0.3325) P (0.0256) and term neonates r (0.3317) P (0.0134).

The incidence of hypomagnesemia was found to be 4.45% in preterm, 7.27% in a term, 5.2% in males, 13.64% in females, 5.13% in low birth weight and 7.4% in normal birth weight neonates. The release of intracellular magnesium may be due to the destruction of neurons and erythrocytes. Thus magnesium may provide a defence mechanism to alleviate the neurological effects of bilirubin (Sarici *et al.*, 2004). Therefore, the role of serum magnesium estimation and its supplementation in the setting of neonatal hyperbilirubinemia needs for the evaluation.

Among the various side effects of phototherapy, the development of diarrhoea due to irritation of bowel has been well documented. Curtis *et al.* (1989) demonstrated significant impairment of absorption of water, sodium, chloride and potassium in patients receiving phototherapy. Electrolyte disturbances due to inadequate fluid replacements are also of concern in neonates on phototherapy (Beresford and Boxwell, 2006).

Our study findings reveal a significant decrease in sodium levels following phototherapy in preterm neonates. We did not observe any significant change in sodium levels following phototherapy in term neonates which is similar to the findings of Usharani M, 2018 in her analysis of a group of 30 term jaundiced neonates. The overall incidence of hyponatremia was found to be 12 % in our study group, 11.11 % in preterm and 12.73 % in term neonates. Reddy *et al.* (2015) has documented an overall incidence of hyponatremia as 6% in their study group, 17.6% in preterm and 3.1% in the term. Our analysis based on gender has revealed that 12.12% of males and 18.6 % of females neonates developed hyponatremia. We observed that 5.13% of low birth weight and 14.8% of normal weight neonates developed hyponatremia. Reddy *et al.* (2015) has reported an incidence of hyponatremia of 17.2% and 2.6% in low birth weight and normal-weight babies, respectively.

We did not observe a significant difference in potassium levels following phototherapy. Our results are similar to the findings of Reddy *et al.* (2015) whereas Rangaswamy *et al.* (2019) and Suneja *et al.* (2018) have reported a significant decrease in both sodium and potassium levels and Tan and Jacob (1981) observed increased levels of potassium following phototherapy.

In our study, the overall prevalence of hypocalcemia was found to be 7%, and we did not observe hypocalcemia among the preterm neonates. Studies with a larger number of neonates may help to assess the exact prevalence. The limitation of our study is the single post-therapy estimation of the blood parameters. Also, systematic analysis of parameters the following phototherapy along with clinical correlation of symptoms may help to identify the importance of the electrolyte imbalances following phototherapy.

CONCLUSIONS

Our study findings indicate that phototherapy induced hypocalcemia is more commonly observed in term neonates. The overall prevalence of hypocalcemia was found to be 7%, none in preterm, 12.73% in the term, 12.12% in males, 13.64% in females, 2.56% in low birth weight and 11.11% in normal birth weight neonates. The sodium levels are significantly reduced in preterm neonates following phototherapy. We found the incidence of hyponatremia to be 12%, 11.11% in preterm, 12.73 % in the term, 12.12% in males, 18.6% in females, 5.13% in low birth weight and 14.8% in normal birth weight neonates. Monitoring of serum calcium and electrolyte levels in neonates undergoing phototherapy will help to identify hypocalcemia and electrolyte imbalances to prevent complications.

ACKNOWLEDGEMENT

We gratefully acknowledge the support extended by the paediatric department and the parents of the neonates involved in the study.

Conflict of interest

The authors declare that they have no conflict of interest for this study.

Funding support

The authors declare that they have no funding support for this study

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