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POST-PHOTOTHERAPY HYPOCALCEMIA IN FULL-TERM ICTERIC NEONATES AT TERTIARY CARE HOSPITAL

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ABSTRACT

Neonatal jaundice affects approximately 60% of term and 80% of preterm infants requiring medical intervention shortly after birth. Phototherapy is a convenient and economical modality for the treatment of neonatal hyper-bilirubinemia but it has some side effects e.g. hypocalcemia. In this cross-sectional study, we aimed to determine the frequency of post phototherapy hypocalcemia. A total 117 full-term, icteric neonates who were exposed to photo-therapy for ≥48 hours were enrolled and hypocalcemia was assessed from serum calcium level before and after exposure to phototherapy. Phototherapy induced hypocalcemia was present in twenty icteric neonates (17.1%) and affecting more female (n=12, 60%) as compared to male (n=8, 40%). Serum calcium levels were significantly reduced from 9.25 ± 0.56 mg/dL to 8.39±0.92 mg/dL after 48 hours of phototherapy (*P*-value ≤ 0.001). Moreover, a significant difference was also observed in Serum bilirubin level from baseline values 17.74 ± 1.986 mg/dL to 9.69 ± 1.29 mg/dL after 48 hours of phototherapy (*P*-value ≤ 0.001). Although the prevalence of hypocalcemia was not much higher but there is a need for calcium assessment for all neonates undergoing phototherapy.

KEYWORDS: Icteric neonates, hypocalcemia, phototherapy

INTRODUCTION

Jaundice is a very common physiological phenomenon but, in most cases, benign condition in neonates (Alizadeh-Taheri, *et al.*, 2013, Rennie, *et al.*, 2010). Neonatal jaundice affects approxima-tely 60% of term and 80% of preterm infants requiring medical intervention shortly after birth (Cohen, *et al.*, 2010). Jaundice refers to yellowish staining of the skin and sclera in neonates due to degradation of haem from normal RBC turnover (Rennie, *et al.*, 2010). In most neonates, un-conjugated hyperbilirubinemia reveals a normal physiological phenomenon (Singh, 2010), while untreated severe indirect hyperbilirubinemia is potentially neurotoxic and can lead to adverse behavioural and neurodevelopmental outcomes or permanent brain damage (Sgro, *et al.*, 2012). Pathological neonatal hyperbilirubinemia remains a major problem in developing countries, where the burden goes largely unrecognized and lives unaddressed (Parkash, *et al.*, 2005). Overall detected rate of hyperbilirubinemia in Pakistani population varies from 11.4%–22.7% (Khan, *et al.*, 2016).

Phototherapy is a convenient and economical modality for the treatment of neonatal hyper-bilirubinemia and it has revolutionized the treatment of jaundice thereby reducing the number of exchange transfusions drastically (Xiong, *et al.*, 2011). Despite the benefits of phototherapy, it may also lead to some adverse effects such as skin rash, dehydration, hyperthermia, diarrhoea, trauma to eye, bronze baby syndrome DNA damage (Kliegman, 2011, Xiong, *et al.*, 2011). However, no phototherapy-induced change in blood ions has been reported except for a reduction in serum calcium level (Singh, 2010, Xiong, *et al.*, 2011). Ionized calcium is a very important factor for numerous biochemical processes such as blood coagulation, cellular enzymatic activity, cell membrane integrity and neuromuscular excitability (Tehrani, *et al.*, 2014). Hypocalcemia is one of the little known but potential hostile side effects of phototherapy (Rozario, *et al.*, 2017). Almost 43% of preterm and 56% of full-term neonates develop hypocalcemia after being subjected to phototherapy (Alizadeh-Taheri, *et al.*, 2013, Arora, *et al.*, 2014). Phototherapy induced hypocalcemia can be symptomatic or asymptomatic in the form of lethargy, poor feeding, jitteriness, apnea or convulsions (Hakanson, *et al.*, 1987). The underlying mechanism for phototherapy induced hypocalcaemia is not well understood yet, but it appears that hypocalcaemia is accompanied by a reduction in serum melatonin concentration and is consecutively regulated by the pineal gland (Maisels, *et al.*, 1995).

The present study aimed to investigate the effect of phototherapy on serum calcium levels in full-term icteric neonates. This may provide useful insights to address phototherapy induced hypocalcemia in the long run.

MATERIALS AND METHODS

This cross-sectional study was conducted at Ziauddin University Hospital, Karachi. After taking written informed consent from parents or guardian, a total of 117 neonates with jaundice were recruited from the neonatal intensive care unit of the hospital. All the neonates who were born at full-term gestational age of ≥ 37 weeks with an age of ≥ 48 hours, with jaundice having serum bilirubin of ≥ 13 mg/dL and required phototherapy were included in

this study. Whereas, neonates diagnosed as a case of birth asphyxia, congenital malformations, septicemia, hypothyroidism, infant of diabetic mothers, hemolytic anaemia, neonatal hypocalcemia, ABO or Rh incompatibility, conjugated hyperbilirubinemia, intrauterine growth retardation, newborn needing exchange transfusion or onset of jaundice < 24 hours of age were excluded from the study. Prior ethical approval was obtained from the university ethical review committee.

Gestational age was confirmed by last menstrual period and dating ultrasound ± 1 week. Neonates were selected for phototherapy according to guidelines of the American Academy of paediatrics subcommittee on hyperbilirubinemia American Academy of Pediatrics,2004. LED phototherapy with the blue light of wavelength 420 nm ± 2% and irradiance of 33-120 mw/cm^2/nm (± 10%) was used. All the naked neonates, while covering their eyes and genitalia, were kept under LED phototherapy at a distance of 45-50 cm from phototherapy and were managed in an incubator under continuous phototherapy. The position of the recruited neonates was changed after every 2 hours and I/V fluids were given. Laboratory investigations including serum bilirubin level and total serum calcium level were evaluated at the time of admission in Neonatal Care Unit and after 48 hours of continuous phototherapy. Serum calcium level < 7 mg/dL was considered as hypocalcemia.

All the data were collected on structured proforma containing the information about gestational age, mode of delivery, age at admission and onset of jaundice, family history of neonatal jaundice and clinical examination like weight, length and head circumference. Data were entered and analyzed in SPSS v. 20. Mean and the standard deviation was calculated for continuous variables whereas, frequency and percentages represented categorical variables. Chi-square test was used to see the association of gender, weight at admission, gestational age and age at jaundice with hypocalcemia. Paired *t*-test was used to calculate the difference in laboratory investigations before and after phototherapy. *P*-value of <0.05 was considered as significant.

RESULTS

This study included 117 full-term neonates with a mean gestational age of 38.1±1.15 weeks and the mean neonatal age of 3.81±0.91 days. The age at the time of jaundice was 3.2 ± 0.66 days and the mean serum bilirubin and serum calcium level at the time of admission were 17.7±1.9mg/dL and 9.3 ±0.56 mg/dL respectively. There were 62 (53%) male neonates and 55 (47%) female neonates. The demographic details of recruited neonates are given in table 1.

Table-1: Clinical and Demographic Information of Jaundiced Neonates

Variables	**Mean ± SD**
Age (days)	3.81 ± 0.91
Age at jaundice diagnosis (Days)	3.2 ± 0.66
Gestational age at delivery (Weeks)	38.1 ± 1.15
Gender	**n (%)**
Male	62 (53%)
Female	55 (47%)
Mode of delivery	**n (%)**
SVD	49 (41.9%)
LSCS	68(58.1%)
Hypocalcemia	**n (%)**
Yes	20 (17.1%)
No	97 (82.9%)

Abbreviations are as follow: SVD Spontaneous vaginal delivery; LSCS, Lower segment Cesarian section. Data were entered and analyzed in SPSS v. 20. Mean and the standard deviation was calculated for continuous variables whereas, frequency and percentages represented categorical variables.

Our data showed that the prevalence of phototherapy induced hypocalcemia was 17.1% (95% CI, 11.3-24.9) which affected more female (n=12, 60 %) as compared to male (n=8, 40%). Moreover, hypocalcemia was developed more in those neonates who delivered between 37-38 weeks of gestation (n=11, 55%) and in whom jaundice was developped at an earlier age from 2-3 days of life (n= 11, 55%) but they were statistically not significant (Table 2).

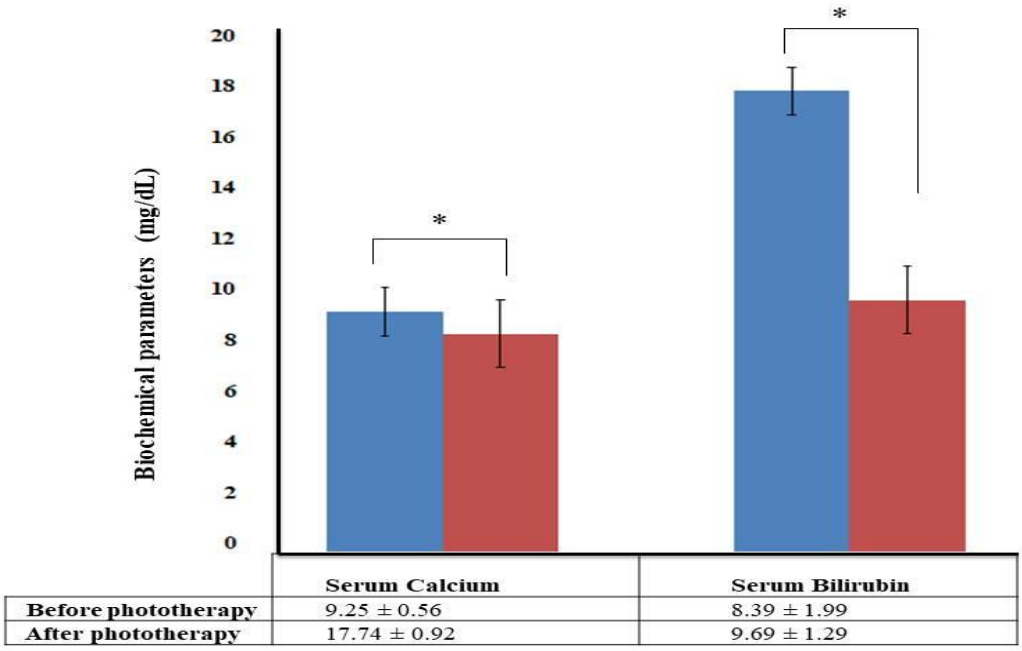
Table-2: Frequency of hypocalcemia with respect to gender, weight at admission, gestational age and age at jaundice.

	Hypocalcaemia		***P*-value**
	Yes (n = 20)	**No (n = 97)**	
Gender			
Male	8 (40%)	54 (55.7%)	0.201
Female	12 (60%)	43 (44.3%)	
Weight at admission (Kg)			
2.5-3.0	10 (50%)	59 (60.8%)	0.37
3.1-3.5	10 (50%)	38 (39.2%)	
Gestational age (Weeks)			
37-38	11 (55%)	68 (70.1%)	0.189
39-41	9 (45%)	29 (29.8%)	
Age at Jaundice (Days)			
2-3	11 (55%)	70 (72.2%)	0.13
4-5	9 (45%)	27 (27.8%)	

Corresponding *P* values were measured by the Chi-square test.

The mean duration of phototherapy was 48.64 ± 1.04 hours. After 48 hours of phototherapy, the

serum bilirubin levels were significantly declined from baseline values 17.74±1.986mg/dL to 9.69± 1.29mg/dL, *P*-value ≤ 0.001. However, significant difference was observed in serum calcium level before and after 48 hours of phototherapy 9.25 ± 0.56 mg/dL *vs.* 8.39±0.92 mg/dL, *P*-value ≤ 0.001 (Figure 1).



	Serum Calcium	Serum Bilirubin
Before phototherapy	9.25 ± 0.56	8.39 ± 1.99
After phototherapy	17.74 ± 0.92	9.69 ± 1.29

Figure-1: Effect of phototherapy on serum calcium and serum bilirubin level.
The serum calcium and serum bilirubin levels were evaluated at the time of admission in the Neonatal Care Unit and after 48 hours of continuous phototherapy. The p values were determined with Paired *t*-test. Error bars represent the standard error of the mean ($^{*}P$<0.001).

DISCUSSION

Phototherapy is a safe treatment for hyperbilirubinemia with high indirect bilirubin levels in newborns (Tan, 1991). Hypocalcemia is one of the little known but potential hostile side effects of phototherapy (Rozario, *et al.*, 2017). The main causes of hypocalcemia in newborns undergoing phototherapy is believed to be caused by a decrease in melatonin and corticosterone levels secretion (Hakanson, *et al.*, 1987) and an increase in urinary excretion of calcium (Hooman, *et al.*, 2005). Corticosterone secretion stimulated by melatonin decreases the calcium absorption by bones. Phototherapy leads to inhibition of pineal gland by transcranial illumination, resulting in a decline in melatonin level and as a result, hypocalcemia develops (Hakanson, *et al.*, 1987).

In the present study, full-term neonates with jaundice were treated with 48 hours of phototherapy with bilirubin levels of 17.7±1.9mg/dL and hypocalcemia was assessed as a complication of phototherapy. Phototherapy has shown a significant effect in reducing the serum calcium levels after treatment. We found a significant reduction of serum calcium after 48 hours of phototherapy as compared to baseline values at the time of admission to the hospital. Similar results were observed by other authors as well showing a reduction in serum calcium after 48 hours of phototherapy (Alizadeh-Taheri, *et al.*, 2013, Bahbah, *et al.*, 2015, Nouh, *et al.*, 2013). The severity of hypocalcemia in infants receiving phototherapy also depends on many factors like duration of exposure, gestational age and whether doubles surface or single surface phototherapy is used as shown by Arora *et al.*, in his study (Arora, *et al.*, 2014).

The prevalence of phototherapy induced hypocalcemia showed variable results according to different reports, in the present study, it was 17.1% which is consistent to 17.6% reported by Nouh *et al*, (2013) but is slightly lower than 22.7% reported by Khan *et al.*, (2016). Sidiqqui *et al.*, (2018) reported 22.76% and Aslam *et al.*, reported 22.6% of term neonates developing hypocalcemia after phototherapy. However, many other studies reported 9%, 11.4% and 13.5% phototherapy induced hypocalcemia which is considerably lower as compared to our findings (Arif, 1982, Karamifar, *et al.*, 2002, Parkash, *et al.*, 2005). Furthermore,

Arora, *et al*., (2014) reported a much higher prevalence of hypocalcemia i.e. 56%.

There was also a significant reduction in serum bilirubin after 48 hours of phototherapy in our results which showed that jaundice had been well treated with the effect of phototherapy. Bahbah, *et al.*, (Bahbah, *et al.*, 2015) and Goyal, *et al.*, (2018) also reported a significant reduction of serum bilirubin after phototherapy of the same duration.

In our study, the mean neonatal age of jaundice was 3.2±0.66 days and which is consistent with reported by Alizadeh *et al*., (2013). In our study, females have a higher frequency of hypocalcemia than males (60% vs. 40%). A study by Khan *et al.*, (2016) from the same region also reported a higher frequency of hypocalcemia among females (30.4% vs. 18.2%). However, Alizadeh, *et al.*, (2013) reported that females had a lower frequency of hypocalcemia as compared to males (4.2% vs. 10.4%). In the present study, no significant association of hypocalcemia with factors like age, gender and birth weight was found, which is consistent with already reported studies (Arif, 1982, Karamifar, *et al.*, 2002, Manoj, *et al.*, 2016).

CONCLUSION

Based on our findings it is recommended that even though the prevalence of hypocalcemia is much lower in full-term neonates undergoing phototherapy but must not be neglected. It seems necessary to monitor the serum calcium levels in newborns undergoing phototherapy for 48 hours or more and identify the reason. Further data from a large set of population representing various populations is required to establish proper guidelines for the need of calcium supplementation to infants receiving phototherapy.

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