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To evaluate the effect of phototherapy on serum calcium levels in newborns requiring phototherapy according to AAP guidelines

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Abstract

Aim: The present study was aimed to evaluate the effect of phototherapy on serum calcium levels in newborns requiring phototherapy according to AAP guidelines.

Methods: The present study was conducted at GSL MEDICAL COLLEGE AND GENERAL HOSPITAL, Rajahmundry, A.P and inborn Neonates admitted to NICU with hyperbilirubinemia who met the inclusion and exclusion criteria were included in the study. 150 neonates meeting the inclusion criteria were included in the study.

Results: In our study, 80 (53.3%) were males and 70 were females (46.7%) with M: F ratio being 1.14:1. The mean age of presentation of jaundice in the study population in hours of life was 84.17 ± 16.69 hrs. Most of the presented neonates were 60-90 hours of life (78%) next after 90 hours of life (59%) in the study. The most common presentation was jaundice in our study (100%), followed by a refusal to feeds (12%), fever, and lethargy by (10.7%) and (6%), respectively. The mean \pm SD of bilirubin was 17.22 ± 1.93 mg/dl and 7.75 ± 1.44 mg/dl before and after phototherapy respectively with significant p-value (<0.05). The mean \pm SD of calcium was 9.09 ± 0.66 mg/dl, and 8.63 ± 0.80 mg/dl before and after phototherapy, respectively, and the p-value was significant (<0.05). In our study, there was a reduction in calcium levels in 78.0% neonates, but significant fall to the hypo-calcemic range was seen only in 3 cases (2%). All three neonates were symptomatic. The chi-square/Fisher exact test with p-value being 0.0785, i.e., not significant. The decrease in calcium was not associated with or affected by the post-natal age of the neonate. The chi-square/Fisher exact test, with p-value being 0.481, i.e., not significant. The decrease in calcium was not associated with or affected by the sex of the neonate.

Conclusion: The study shows that neonates under phototherapy for unconjugated hyperbilirubinemia are at higher risk of reduction in serum calcium levels occasionally even to the hypocalcemic range and development of symptoms of hypocalcemia. Hence, babies should be closely monitored for variations in calcium and should be treated accordingly.

Keywords: Hypocalcemia, phototherapy, serum calcium, neonates

Introduction

Jaundice is an important problem in the neonatal period. High bilirubin levels may be toxic to the developing central nervous system and may cause irreversible neurological impairment even in term newborns. Nearly 60% of term newborns and 80% of preterms become visibly jaundiced in the first week of life. In most of the 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 ^[1]. The main reason for neonatal hyperbilirubinemia is liver's immature excretory pathway for bilirubin and is the commonest reason for readmission of neonates in first week of life in current era of postnatal discharge from hospital ^[2].

Jaundice in newborns is a cause of concern for the parents as well as for the paediatricians ^[3]. Elevated levels of unconjugated bilirubin can lead to bilirubin encephalopathy and subsequently kernicterus, with devastating, permanent neurodevelopmental handicaps ^[4]. Conjugated hyperbilirubinemia indicates potentially serious hepatic disorders or systemic illnesses. Hence appropriate management of neonatal hyperbilirubinemia is of paramount importance. Phototherapy, exchange transfusion and pharmacological treatment are the main modalities of treatment.

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Phototherapy plays a significant role in the treatment of hyperbilirubinemia in neonates.

Phototherapy may also lead to undesired side effects including skin rash, diarrhea, rise in body temperature, retinal degenerations, nasal obstruction, bronze baby syndrome etc. [2]. Nonetheless, no change in blood It is hypothesized that phototherapy inhibits pineal secretion of melatonin which blocks the effect of cortisol on bone calcium. Unchecked cortisol exerts a direct hypocalcemic effect and increases bone uptake of calcium as well [5]. Calcium is essential for many biochemical processes including blood coagulation, cell membrane integrity and function, cellular enzymatic activity and neuromuscular excitability. Hypocalcemia increases cellular permeability to sodium ions and increased cell membrane excitability. The signs are usually non-specific like apnea, seizure, jitteriness, irritability, increased extensor tone, hyperreflexia, and stridor (laryngospasm) [6].

The present study was aimed to evaluate the effect of phototherapy on serum calcium levels in newborns requiring phototherapy according to AAP guidelines.

Materials and Methods

The present study was conducted at GSL medical college and general hospital,

Rajahmundry, A.P and inborn Neonates admitted to NICU with hyperbilirubinemia who met the inclusion and exclusion criteria were included in the study. 150 neonates meeting the inclusion criteria were included in the study.

Inclusion criteria

Term AGA neonates with unconjugated hyperbilirubinemia requiring phototherapy according to AAP guidelines

Exclusion criteria

Newborns with,

- Jaundice in first 24 hr of life
- Born to a diabetic mother
- Birth asphyxia
- Neonatal sepsis
- Jaundice lasting more than 14 days
- Babies who had exchange transfusion or were on TPN.

Written consent was taken from the parents. Ethical clearance was taken from the ethical clearance committee, GSL medical college & general hospital, rajahmundry. Sepsis screening is done wherever required. Doctors with aseptic precautions drew the blood samples, and no squeezed samples were used, and the samples were analyzed immediately within 15 minutes after drawing blood.

Bilirubin Measurement: Total and direct bilirubin is measured by Diazo method (Diazotized sulfanilic test). Principle: Bilirubin reacts with diazotized sulfanilic acid in presence of ethyleneglycol and dimethyl sulfoxide to produce an intensely coloured diazo dye i.e, azobilirubin. The intensity of colour is proportional to quantity of bilirubin. **Calcium measurement:** Calcium is measured by Arsenazo III method.

Principle: Arsenazo III combines with calcium ions at Ph6.5 to form coloured chromophore, the absorbance of which is measured at 650 nm and is proportional to calcium concentration. Both calcium and bilirubin were measured by a semi-automated analyser ERBA Chem 7. The sample were

analysed immediately within 15 minutes after drawing blood.

Phototherapy: Phototherapy was given by blue fluorescents lamps (410-470nm) placed at a distance of 30 to 40 cms from the neonates who required phototherapy according to AAP guidelines. The eyes and genitalia were covered with the head exposed to phototherapy.

Statistical analysis

Neonatal and Maternal data were collected in predesigned proforma. Data shall be analyzed using SPSS 22.0, and R environment ver.3.2.2 was used for the analysis and evaluation of the data, and Microsoft Word and MS Excel have been used to generate graphs, tables, etc. For quantitative data, mean and standard deviation (SD) were calculated for qualitative data percentages calculated. A chi-square test was used for comparing differences between categorical variables. For comparison between the means, Wilcoxon matched test was used, and the students t-test used. For interpretation of results, significance shall be adopted at p-value < 0.05 at a 95% confidence interval.

Results

Table 1: Demographic details

Gender	No. of neonates	%
Female	70	46.7
Male	80	53.3
Hours of Life		
<60	13	8.7
60-90	78	52.0
>90	59	39.3
Symptoms		
Icterus	150	100
Refusal of Feed	18	12.0
Fever	16	10.7
Lethargy	9	6.0
Seizures	0	0

In our study, 80 (53.3%) were males and 70 were females (46.7%) with M: F ratio being 1.14:1. The mean age of presentation of jaundice in the study population in hours of life was 84.17 ± 16.69 hrs. Most of the presented neonates were 60-90 hours of life (78%) next after 90 hours of life (59%) in the study. The most common presentation was jaundice in our study (100%), followed by a refusal to feeds (12%), fever, and lethargy by (10.7%) and (6%), respectively.

Table 2: Comparison of mean serum bilirubin and mean serum calcium before and after phototherapy by wilcoxon matched test

Time point	Mean	SD	Mean diff.	SD diff	T-value	p-value
Before treatment	17.22	1.93	9.469	0.5	55.613	<0.001
After treatment	7.75	1.44				
Mean serum calcium						
Before treatment	9.09	0.66	0.455	- 0.14	9.834	<0.001
After treatment	8.63	0.80				

The mean \pm SD of bilirubin was 17.22 ± 1.93 mg /dl and 7.75 ± 1.44 mg/dl before and after phototherapy respectively with significant p-value (<0.05). The mean \pm SD of calcium was 9.09 ± 0.66 mg/dl, and 8.63 ± 0.80 mg/dl before and after phototherapy, respectively, and the p-value was significant (< 0.05).

Table 3: Variations in calcium level after phototherapy

Variation in Serum Calcium	No. of neonates	%
Decreased	117	78.0
Increased	26	17.3
Same	7	4.7
Total	150	100.0

In our study, there was a reduction in calcium levels in 78.0% neonates, but significant fall to the hypo-calcemic range was seen only in 3 cases (2%). All three neonates were symptomatic.

Table 4: Comparison of decrease in calcium with age and sex of presentation

		Decrease		Total
		Yes	No	
Age	<60HOL	6	7	13
	60-90HOL	68	10	78
	>90HOL	43	16	59
		117	33	150
		Decrease		Total
		Yes	No	
Sex	Males	65	15	80
	Females	52	18	70
		117	33	150

The chi-square/Fisher exact test with p-value being 0.0785, i.e., not significant. The decrease in calcium was not associated with or affected by the post-natal age of the neonate. The chi-square/Fisher exact test, with p-value being 0.481, i.e., not significant. The decrease in calcium was not associated with or affected by the sex of the neonate.

Table 5: Signs and symptoms of hypocalcemia

Symptoms of Hypocalcemia	No. of neonates	%
J, IR	3	2.0
No	147	98.0
Total	150	100.0

In our study, the most common symptoms suggestive of hypocalcemia with the three hypocalcemic neonates include irritability (100%) and jitteriness (100%). There were no other symptoms like apnea, lethargy, convulsions, etc.

Discussion

In our study a total of 150 cases were included, and all were term babies, all were appropriate for gestational age, other studies like Eghbalian *et al.* [7] where 63 cases were included, in Taheri *et al.* [8] 147 cases were included, Mohammed Hamed Bahbah [9] 50 term babies were included, Gheshmi *et al.* [10] included 100 neonates. In our study, the mean gestational age is 38.22±0.96 weeks, while in similar studies conducted by Tehrani *et al.* [11], it is 38.14±0.83, and that of Mohammed Hamed Bahbah [9] was 38.28±0.99. In the same way, a study conducted by Goyal S *et al.* [12] and Rekha Kumari [13] on full-term neonates took into consideration, and their mean gestational age is 38.16±0.95 and 38.12±0.078 respectively.

The age of onset of icterus is a vital entity and is required to differentiate from physiological or pathological jaundice. Tehrani *et al.* [11] did research, the mean age of onset of icterus is 132.4±58.8, the age of onset in more as compared to other studies is attributed to smaller sample size. Other

studies include Mohammed Hamed Bahbah, [9] the start of icterus is around 102.2±26.8 hours of life, similar results seen with Goyal S *et al.* [12] and Rekha Kumari [13] with the age of onset of jaundice at 102.60±48.10 and 118.4±50.2 hours of life respectively. In our study, 80 were males and 70 were females with ratio being 1.14:1, with ratio in other studies being 0.6, in Prabhakar *et al.* [14], in Arora *et al.* [15] the ratio is 0.8, 1.22 was in Gheshmi *et al.* [10]

Mean total serum bilirubin (TSB) in our study group after phototherapy is 7.75±1.44 mg/dl compared to a similar study by Karamifar *et al.* [16] which showed 8.53±1.6 mg/dl in term babies and research by Taheri *et al.* [8], mean TSB in term neonates was 12.41±2.10 mg/dl and also similar to other studies done by Mohammed Hamed Bahbah [9] and Goyal S *et al.* [12] with mean Total serum bilirubin 11.18±3.11 mg/dl and 9.69±1.29 mg/dl respectively. In all of the studies, there is a definitive decrease in the mean Total serum bilirubin values similar to that of ours but needs to be compared using the t-test and p-value to know whether the reduction is significant or not. Phototherapy is an appropriate and commonly used measure to reduce indirect bilirubin levels in newborns. Romagnodi *et al.* [17] was the first to suggest the association of hypocalcemia in the newborn with treatment using phototherapy. The mean serum bilirubin before and after phototherapy in our study was 17.22±1.93 and 7.75±1.44 respectively and the difference was significant with p-value being < 0.0001 which was similar to other studies Mohammed Hamed Bahbah [9] like where the mean TSB was 15.48±1.94 and 12.41±2.10 with before and after phototherapy with significant p-value.

Mean Serum calcium level in our study group were 9.09±0.66 mg/dl compared to a similar study by Karamifar *et al.* [16] which showed 9.53±0.92 mg/dl in term babies and in a study by Taheri *et al.* [8], mean Sr calcium in term neonates was 9.8±0.80 mg/dl and also similar to other studies done by Mohammed Hamed Bahbah [9] and Goyal S *et al.* [12] with total serum bilirubin 9.36±0.29 mg/dl and 9.14±0.78 mg/dl respectively. Rozario CI *et al.* [18] showed 9.27±0.73 mg/dl while Rekha Kumari [13] showed 9.70±1.45 mg/dl of mean serum calcium level. The mechanism of the hypocalcemic effect of phototherapy was reported by inhibition of the pineal gland via transcranial illumination, resulting in a decline of melatonin secretion, which blocks the effect of cortisol on bone calcium. Cortisol exerts a direct hypocalcemic impact by decreasing the absorption of Calcium and Phosphate ions from the gut by antivitamin D action and by increasing the urinary excretion of these ions and also accelerates the bone uptake of calcium. In addition, renal calcium excretion is increased after exposure to phototherapy, as shown by Hooman and Honarpisheh [19]. The mean serum calcium levels before and after phototherapy in our study were 9.09±0.66 and 8.63±0.80, respectively. The difference was significant with p-value being < 0.001 which was similar to other studies like Eghbalian *et al.* [7] where the mean serum calcium levels before phototherapy was 9.85±1.23 and after phototherapy is 9.09±0.93 with significant p-value, even in studies like Karamifar *et al.* [16] and Taheri *et al.* [8] there was significant fall in serum calcium values with p-value being < 0.05. Similarly in studies of Mohammed Hamed Bahbah [9], Rozario CI *et al.* [18], Goyal S *et al.* [12] there is significant fall in serum calcium levels before and after phototherapy, in a similar study conducted by Rekha Kumari [13] in the year

2019 the difference of serum calcium level before and after phototherapy was 0.749 (>0.05) which is nil significant but mentioned that monitoring of serum calcium regularly is necessary for all babies who are receiving phototherapy for non-hemolytic hyperbilirubinemia.

In our study we found that out of 80 males and 70 female neonates 65 males and 52 females had decrease in serum calcium levels with nil significant p-value (>0.05), similarly in another study by Kanwal Mahadev^[20] out of 62 males and 55 female neonates 8 males and 12 females had decrease in serum calcium levels with nil significant p-value (>0.05). In our study we found that out of 117 neonates with decreased serum calcium levels, 74 cases are below 4 days, and 43 cases are above 4 days of age which showed nil significant p-value (>0.05), similar study conducted by Kanwal Mahadev^[20] exhibited nil considerable p-value of 0.13, and hence indicates that the incidence of reduction in serum calcium levels after phototherapy was not affected by the age of neonate.

In our study, out of 3 hypocalcemic neonates, both were having irritability (100%) and jitteriness (100%). Phototherapy itself could cause irritability to the baby. Symptomatic hypocalcemia was observed in Yadav *et al.*^[21], Jain *et al.*^[22], and Arora *et al.*^[15]

Conclusion

The study shows that neonates under phototherapy for unconjugated hyperbilirubinemia are at higher risk of reduction in serum calcium levels occasionally even to the hypocalcemic range and development of symptoms of hypocalcemia. Hence, babies should be closely monitored for variations in calcium and should be treated accordingly.

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