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EFFECT OF PHOTOTHERAPY ON SERUM CALCIUM LEVELS IN NEONATES WITH UNCONJUGATED HYPERBILIRUBINAEMIA

Paediatrics

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ABSTRACT

Jaundice affects about 60% of term newborns and 80% of preterm newborns in the first week of life, when the level of bilirubin rises more than 5-6 mg/dl. Neonatal hyperbilirubinemia is caused by an increase in blood bilirubin levels above the normal range. Phototherapy is the treatment of choice. prevalence of hypocalcaemia in phototherapy treated term and preterm newborns, hence some more studies are required in this direction to find out a definite association between phototherapy and hypocalcaemia in icteric newborns. Therefore, the present study was intended to determine effect of phototherapy on serum calcium levels of neonates with unconjugated hyperbilirubinemia after 48 hours of phototherapy or at the end of phototherapy in case of duration of phototherapy is less than 48 hours. The present 'Prospective observational study' was carried out from August 2022 to June 2024. Total 200 neonate with unconjugated hyperbilirubinemia were enrolled in study. Mean age of neonate with unconjugated hyperbilirubinemia was 4.01 ± 1.29 days with range was from 2-6 days. Among neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy. Among term neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy. Among pre-term neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy ($p < 0.05$). Phototherapy induced hypocalcemia is a significant findings in neonate with jaundice. Serum calcium level falls to a significant level in both phototherapy treated term and preterm newborns. Though fall is more significant in preterm newborns, term newborns are also at risk. Also there is significant fall in serum bilirubin level after phototherapy in neonate with jaundice.

KEYWORDS

Neonatal hyperbilirubinemia, New Bellard score, BIND score

INTRODUCTION:

Jaundice is one of the most frequently encountered medical problems in newborns during their first week of life. It causes significant stress and anxiety to the parents in the immediate neonatal period. Nearly it affects about 60% of term newborns and 80% of preterm newborns in the first week of life.[1] Jaundice in newborns occurs when the level of bilirubin rises more than 5-6 mg/dl.[2] Neonatal jaundice causes yellow discoloration of the skin, mucous membranes and sclerae.[3] Neonatal hyperbilirubinemia is caused by an increase in blood bilirubin levels above the normal range. An increase in the levels of unconjugated bilirubin is the most common manifestation of neonatal jaundice. However, hyperbilirubinemia in the newborn period can be associated with haemolytic disease, metabolic and endocrine disorders, anatomic abnormalities of the liver and infections. Severe unconjugated hyperbilirubinemia can lead to bilirubin encephalopathy with permanent neurodevelopmental handicaps.[4]

Neonatal jaundice may be classed as physiological or pathological.[5] In the majority of cases, jaundice is due to the physiological immaturity of the newborns to manage increased bilirubin production and it usually appears between 24-72 hours of age.[6] Basic pathophysiology of jaundice is same in term and preterm neonates, but premature babies are at a higher risk of developing jaundice. If left untreated, severe unconjugated hyperbilirubinemia may leads to potentially neurotoxic outcomes. Whereas, conjugated hyperbilirubinemia is a consequence of underlying systemic illness. [7]

Most of the time it is physiological and does not need any treatment but about 5-10% of them develop clinically significant jaundice and need intervention in the form of phototherapy.[8] Although there are several treatment schemes available in the clinical setting, phototherapy is generally the preferred choice for preventing the development of bilirubin encephalopathy or nuclear jaundice caused by excessive accumulation of unconjugated bilirubin.[9] A high serum level of free bilirubin may cause neurotoxicity, but mildly elevated bilirubin concentrations are beneficial due to their protective antioxidant role in cell membranes, while markedly low concentrations may also be harmful.[10]

It mostly works by transforming the bilirubin into water soluble isomers that can be eliminated without conjugation in the liver. Although, it is the most affordable and effective way of reducing serum bilirubin level in the newborns, some side effects are also associated with it like loose stools, hyperthermia, dehydration due to fluid loss, skin burn, photo retinitis, low platelet count, increased red cell osmotic fragility, bronze baby syndrome, riboflavin deficiency and DNA damage. A lesser known side effect, but a potential complication of phototherapy is hypocalcaemia.[11] It has been postulated that Melatonin stimulates secretion of corticosterone, which decreases 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, hypocalcaemia develops.[12]

Neonatal hypocalcaemia is defined as total serum calcium concentration < 7 mg/dl or ionized calcium concentration < 4mg/dl. Ionized calcium is crucial for many biochemical processes, including blood coagulation, neuromuscular excitability, and cellular enzymatic activities.[13] The overall prevalence of hypocalcaemia in neonates receiving phototherapy was 8.7% in full-term newborns.[6] As suggested by previous studies, there is a varying prevalence of hypocalcaemia in phototherapy treated term and preterm newborns, hence some more studies are required in this direction to find out a definite association between phototherapy and hypocalcaemia in icteric newborns.[14] Therefore, the present study was intended to determine effect of phototherapy on serum calcium levels of neonates with unconjugated hyperbilirubinemia after 48 hours of phototherapy or at the end of phototherapy in case of duration of phototherapy is less than 48 hours.

Methodology:

The present 'Prospective observational study' was carried out to study effect of phototherapy on serum calcium levels in neonates and to compare effect of phototherapy in term and preterm neonate with unconjugated hyperbilirubinemia after 48 hr hours of phototherapy or at the end of phototherapy in case of duration of phototherapy is less than 48 hours from August 2022 to June 2024. The study population comprised of all neonate with unconjugated hyperbilirubinemia admitted in NICU receiving phototherapy in our tertiary care hospital. Approval was obtained prior to the start of the study from the Institutional Ethics Committee of Medical College. Informed consent

was taken from parents of neonate before enrolling them in study. Sample size was calculated by using Cochrane's formula. Sample size = Z2 *p*q/l2 , p = estimated prevalence of jaundice in neonate 60%.[1] SO, calculated sample size was around 200 taken.

All neonate who were admitted in NICU with unconjugated hyperbilirubinemia requiring phototherapy were included. The neonate with conjugated hyperbilirubinemia or onset of jaundice within 24 hours of life, who developed a complication during course of phototherapy, neonate with co-morbidities like birth asphyxia, respiratory distress, septicaemia, neonate requiring exchange transfusion were excluded. Also the baby of diabetic mother were excluded form study. The parents of neonate were interviewed at the time of hospitalization of neonate. After obtaining Informed consent, data was collected by using predesigned pretested questionnaire. The questionnaire consist of the information like age, gender, gestational age assessed by New Bellard score, Consanguity, mode of delivery, birth weight, times of appearance of icterus in hours, history of excessive BF. Along with this blood sample of neonate for serum calcium and bilirubin level was sent. Severity of jaundice and associated acute bilirubin encephalopathy evaluated by using BIND score. Follow up visit was done at the end of 48 hours of phototherapy or at the end of phototherapy if it is less than 48 hours. Again at this time blood sample of neonate for serum calcium and bilirubin level was sent.

Data was entered in MS excel worksheet and analysed using SPSS (Statistical Package for Social Sciences) trial version 21.0. Data was presented in tabular and graphical format. For qualitative type of data – Chi-square test used. For quantitative data mean, Standard deviation and paired t test were used. All statistical tests considered statistically significant whenever $p < 0.05$.

RESULTS:

Total 200 neonate with unconjugated hyperbilirubinemia who were received phototherapy were enrolled in study. Mean age of neonate with unconjugated hyperbilirubinemia was 4.01 ± 1.29 days with range was from 2-6 days. The mean time of appearance of icterus was 3.91 ± 0.79 days & range was from 3-6 days. The mean duration of phototherapy was 1.99 ± 0.96 days & range was from 1-5 days. The mean duration of hospitalization was 2.99 ± 0.96 days & range was 2-6 days.

Table 1: Distribution Of Neonate With Hyperbilirubinemia According To Clinic-social Parameter

Clinico-social parameter		Frequency	Percentage
Gender	**Male**	117	58.5
	Female	83	41.5
Consanguity	**Yes**	18	9
	No	182	91
Birth weight	**LBW**	50	25
	Normal	150	75
Gestational age	**Term**	127	63.5
	Pre-term	73	36.5
Mode of delivery	**Normal Vaginal Delivery**	139	69.5
	LSCS	61	30.5
Exclusive Breast feeding	**Yes**	131	65.5
	No	69	34.5
Type of feed	**Exclusive BF**	131	65.5
	Formula feed	27	13.5
	Mixed	42	21

About 117 (58.5%) of neonate were male, Only 18 (9%) neonate with unconjugated hyperbilirubinemia had history of Consanguity. The mean birth weight of neonate was 2632.72 ± 362.01gm & range was from 2130 – 3600 gm. About 150 (75%) neonate had normal birth weight. Gestational age of the neonate assessed by using New Bellard Score. The mean GA was 37.45 ± 1.42 weeks and range was 34-40 weeks. About 127 (63.5%) were term neonate followed by 73 (36.5%) were pre-term neonate. Majority of neonate 139(69.5%) were delivered by normal vaginal delivery. About 131 (65.5%) neonate had exclusive breast feeding & 42 (21%) had mixed feeding and 27 (13.5%) had formula feed. (Table 1)

Table 2: Distribution of neonate with hyperbilirubinemia according to Sr. Calcium level

Serum Value		Frequency	Percentage
Sr. Calcium (mg/dl) Before phototherapy	**7-7.9**	37	18.5
	8-8.9	59	29.5
	>9	104	52
Sr. Calcium (mg/dl) After phototherapy	**< 7**	87	43.5
	≥7	113	56.5

Before phototherapy among 104 (52 %) neonate had > 9 mg/dl sr. calcium level followed by 59 (29.5%) had 8-8.9 mg/dl and 37 (18.5%) had 7-7.9mg/dl sr. calcium level. So, before phototherapy none of the neonate had hypocalcaemia. After receiving phototherapy about 87 (43.5%) neonate had <7 mg/dl sr. calcium level & 113 (56.5%) had ≥7 mg/dl sr. calcium level. (Table 2)

Table 3: : Comparison of mean Serum calcium & Bilirubin level before and after of phototherapy

Serum Calcium & bilirubin level among Neonate		Before phototherapy (Mean ±S.D.)	After phototherapy (Mean ±S.D.)	p Value
Neonate	**Serum calcium**	10.12±9.66	7.33±1.33	0.000
	Serum bilirubin	16.58±10.77	11.08±0.58	0.000
Term Neonate	**Serum calcium**	9.91±8.75	7.69±1.31	0.005
	Serum bilirubin	17.07±13.51	11.16±0.58	0.000
Pre-term Neonate	**Serum calcium**	10.49±1.11	6.71±1.12	0.005
	Serum bilirubin	15.73±0.60	10.95±0.57	0.000

Among neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy. Among term neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy. Among pre-term neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy. (Table 3)

DISCUSSION:

Neonatal jaundice or hyperbilirubinemia is a common manifestation among newborns that most frequently is seen in the first week of life. It is the commonest cause of NICU admission & morbidity in newborns worldwide. Phototherapy is widely accepted as a relatively safe and effective method for treatment of neonatal hyperbilirubinemia as described by Cremer et al in 1953 but there are very less number of studies showing the adverse effects of phototherapy. [15] One of these adverse effect is hypocalcaemia. **Romagnoli** was the first who recommended the relation between hypocalcaemia and phototherapy in preterm. [16] The mechanism of hypocalcemic effect of phototherapy was reported by inhibition of pineal gland via transcranial illumination, resulting in decline of melatonin secretion which blocks the effect of cortisol on bone calcium. Cortisol has a direct hypocalcemic effect and increases bone uptake of calcium and induces hypocalcemia.[17,18] **Eghbalian F.** further established this phenomenon in his study, exhibiting a direct relation between duration of phototherapy & the development of hypocalcemia. [19]

In present study total 200 neonate with unconjugated hyperbilirubinemia who were underwent phototherapy were enrolled. Mean age of neonate was 4.01 ± 1.29 days with range is from 2-6 days. **Amneenah AM 2022 [20]** in their study found that mean age of neonate was 4.51 ± 4.46 days. Also the studies conducted by **Jha CB et al 2022 [21] & Shrestha S et al 2021 [22**] found that mean age of neonate was 4.50±3.39 days & 4.12±1.09 days respectively. In present study, about 58.5% were male & 41.5% were female neonate with unconjugated hyperbilirubinemia. Almost similar finding found in study conducted by **Shahriarpanah S. et al 2018 [23], Kale AV et al 2020 [24] & Amneenah AM 2022 [20].** In present study, the history of Consanguity found in only 9% neonate & also almost similar finding found in the study conducted by **Ahmed YA et al 2019. [25].** The studies conducted by **Kale AV et al 2020 [24], Balamkar R et al 2021 [26] & Shrestha S et al 2021 [22**] found that mean BW of neonate was from 2584.04 to 2660 gm.these findings were in line with our study results. In present study, about 63.5% were term neonates & 36.5% were preterm neonates & the mean gestational age was 37.45 ± 1.42 with range was from 34-40 weeks. The mean gestational age found in other study was almost similar to our study findings. [6,22,23,26]. . In the study conducted by **Kale AV et al 2020 [24],** 65% delivered by normal vaginal delivery & 35% delivered by LSCS, in line with our study findings. In present study, the mean time of appearance of icterus was 3.91 ± 0.79 days & range was from 3-6 days. The study conducted by **Kale AV et al 2020 [24],** found that the mean time of appearance of

icterus was 4.7 ± 1.56 days & range was from 4-6 days. In present study, the mean duration of phototherapy was 1.99 ± 0.96 days & range was from 1-5 days. In study conducted by **Balamkar R et al 2021 [26] & Khan M et al 2016 [6]** mean duration of phototherapy was 1.77 ± 0.42 days & 1.74±1.56 days respectively.

In our study, Presents study the overall prevalence of hypocalcemia was 43.5%. Among neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy. Among term neonate, statistically highly significant decrease in serum calcium and bilirubin level after stoppage of phototherapy. Another studies also found similar findings. [20,24,226,27] The prevalence of hypocalcemia in study conducted by **Kumar Shukla A. et al 2022 [28]** was 15.4%. There was significant association between gestational age and developing hypocalcaemia after receiving phototherapy i.e. preterm neonates were more prone to develop hypocalcaemia after receiving phototherapy. In study conducted by **Singh PK et al 2017 [29]** , 70% pre term develop hypocalcaemia & also show that preterm was were more prone to develop hypocalcaemia after receiving phototherapy. . In study conducted by **Singh PK et al 2017 [29],** about 30% term neonates develop hypocalcaemia. Also similar findings found in study conducted by **Karamifar et al. 2015 [12] & Jha CB et al 2022. [21]**

CONCLUSION:

Phototherapy induced hypocalcemia is a significant findings in neonate with jaundice. Serum calcium level falls to a significant level in both phototherapy treated term and preterm newborns. Though fall is more significant in preterm newborns, term newborns are also at risk. Also there is significant fall in serum bilirubin level after phototherapy in neonate with jaundice.

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