

Phototherapy Induced Hypocalcemia in Neonates with Unconjugated Hyperbilirubinemia

Amna Khan, Anila Farhat, Hamayun Anwar, Sajid Shamim, Mujeeb Ur Rehman, Irfan Khan

ABSTRACT:

Objective: To determine the frequency of hypocalcemia in neonates with unconjugated hyperbilirubinemia receiving phototherapy.

Study design and setting: Cross sectional study conducted at neonatal intensive care unit, King Abdullah Teaching Hospital, Manshehra for one year from December 2017 to November 2018.

Methodology: Total 213 full term stable neonates of either gender with jaundice were studied in this study. Out of which, 143 with unconjugated hyperbilirubinemia were exposed to phototherapy while 70 neonates with exaggerated physiological hyperbilirubinemia taken as control were not exposed to phototherapy. Serum calcium level was determined through blood test before and after 24 hours of phototherapy. SPSS version 22 was used to analyze the data. Frequency and percentages were used to describe categorical variables like gender and hypocalcemia. Hypocalcemia was stratified by age and gender to see effect modifiers. Post stratified chi-square test was applied in which p value = 0.05 was considered as significance value.

Results: In study group, 143 neonates who received phototherapy had mean age of 7 days \pm 2.62 SD. Total 65% neonates were male and 35% neonates were female. Mean serum calcium level of neonates before and after provision of phototherapy was 9.28 mg/dl \pm 0.23 and 8.54 mg/dl \pm 0.68 respectively, which is statistically significant. The frequency of hypocalcemia was 40% in neonates with unconjugated hyperbilirubinemia after 24 hours of phototherapy.

Conclusion: Hypocalcemia is an important complication in neonates with unconjugated hyperbilirubinemia after continuous phototherapy. Hypocalcemia has clinical impact and adds to morbidity, and if left untreated, can lead to mortality.

Key words: Hypocalcemia, Neonates, Patent ductus arteriosus (PDA), Phototherapy, Unconjugated hyperbilirubinemia.

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INTRODUCTION:

Hyperbilirubinemia is one of the most frequent and benign problem in neonates. During first week of life, around 80%

of preterm neonates and 60% of full term neonates have hyperbilirubinemia. Severe unconjugated hyperbilirubinemia, if not treated timely, can lead to permanent brain damage in the newborn.¹ Hyperbilirubinemia can be managed either by phototherapy, exchange transfusion or pharmacological agents.² Phototherapy is the most effective therapy for management of neonatal hyperbilirubinemia which lowers serum bilirubin level by converting bilirubin through structural photo isomerization and photo-oxidation into non-toxic form that is excreted out of the body.³

Complications of phototherapy are dehydration, diarrhea, skin rash, hyperthermia, retinal degeneration, DNA damage to lymphocytes, patent ductus arteriosus (PDA), bronze baby syndrome, and hypocalcemia.⁴ Melatonin concentration is reduced in newborns with phototherapy which in turn leads to hypocalcemia.⁵ First of all the association between phototherapy and hypocalcemia was reported by Shafiq MB et al. in preterm infants.⁶

The pathophysiology and the underlying mechanism by which phototherapy causes Hypocalcemia was suggested by Hayat⁷ and Hunter⁸ and reported that phototherapy inhibit the secretion of melatonin by pineal gland and this results

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in blockage of the effect of cortisol on bone calcium.⁸ Study by Husain et al suggested that neonates receiving phototherapy have reduced level of parathyroid hormone which leads to hypocalcemia.⁹ While Hooman in a study reported that urinary excretion of calcium was significantly higher in patients exposed to phototherapy.¹⁰

Hypocalcemia is a significant problem in neonates subjected to phototherapy and its prevalence in full term neonates is 8.7%.¹¹ Complications of hypocalcemia in newborns include apnea, convulsion, muscle cramp, tremor, and tetanus.⁵ Hypocalcemia developed in 39% of term and 53% of pre-terms after being subjected to phototherapy for more than 48 hours.¹² Hypocalcemia, being a major complication of phototherapy, is associated with poor prognosis in terms of high mortality rate as compared to babies with normocalcemia, if not diagnosed timely and treated accordingly.^{12,13} The treatment of hypocalcemia includes intravenous 10% calcium gluconate by slow intravenous infusion over 30 minutes and when oral feeding begins, calcium supplementation are provided for few days.^{12,14} Therefore, the objective of this study was to evaluate the frequency of phototherapy induced hypocalcemia in full term neonates with neonatal hyperbilirubinemia.

METHODOLOGY:

This cross sectional study was carried out at neonatal intensive care unit, King Abdullah Teaching Hospital, in Mansehra for one year from 1st December 2017 to 30th November 2018 after approval from the ethical committee of King Abdullah Teaching Hospital, Mansehra (ERC# 1766-08/EC). Sample size was calculated by WHO software formula to estimate a population proportion with specific absolute precision is used with the following assumptions: Confidence level = 95%, Anticipated proportion of hypocalcemia after phototherapy = 39%, absolute precision = 8%. Samples were collected by using non-consecutive sampling technique. Written consent was taken from parents/guardians before enrolling the patients into this study.

Total 213 full term stable neonates (37 to 41 weeks) of either gender with jaundice were assessed in this study. Among them 143 neonates (93 males and 50 females) with neonatal jaundice were enrolled in study group who were exposed to phototherapy. Total 70 stable neonates (45 males and 25 females) with physiological hyperbilirubinemia were enrolled in control group who were not exposed to phototherapy. All the full term stable neonates delivered at 37 to 41 weeks of gestational age, of either gender with unconjugated hyperbilirubinemia were included in the study. Newborns with jaundice in first 24 hours of life, neonates of a diabetic mother, who already had exchange transfusion, babies with prolonged jaundice for more than 14 days, neonates with conjugated hyperbilirubinemia were excluded from study.

Hypocalcemia was defined as serum calcium level less than 8mg/dl whereas hyperbilirubinemia was defined as total

serum bilirubin level above 95th percentile for age on hournomogram. A 4cc venous blood sample for serum calcium level and bilirubin level was sent to laboratory before starting conventional phototherapy and after 24 hours of continuous phototherapy. All the information including gestational age, gender, weight, age, mode of delivery, and serum calcium levels (pre and post phototherapy) were recorded on a pro-forma. SPSS version 22 was used to analyze data. Quantitative variables like age and serum calcium were described in terms of mean \pm standard deviation. Frequency and percentages were used to describe categorical variables like gender and hypocalcemia. Hypocalcemia was stratified by age and gender to see effect modifiers. Post stratified chi-square test was applied in which p value = 0.05 was considered as significance value.

RESULTS:

Among 143 neonates in the study group that received phototherapy, 93 (65%) neonates were male and 50 (35%) neonates were female while among 70 neonates of control group, 45 (64%) neonates were male and 25 (36%) neonates were female (Table 1). The frequency of hypocalcemia in neonates of the study group after 24 hours of phototherapy was 57 (40%), out of which 37 were male patients and 20 were female patients (Table 2). Distribution of hypocalcemia after phototherapy in different age groups is illustrated in (Table 3). 41 children out of 103 in age range of 1-10 days, 14 children out of 36 in age range of 11-20 days and 2 children out of 4 in the 21-28 days age range had hypocalcemia. The serum calcium levels of neonates before phototherapy of studied group and control group were 9.28 mg/dl \pm 0.23 and 9.14 mg/dl \pm 0.87 respectively (Table 4). There was no statistically significant difference between these two groups regarding serum calcium level on arrival ($P>0.05$). Mean serum calcium levels of neonates of the studied group before and after provision of phototherapy were 9.28 mg/dl \pm 0.23 and 8.54 mg/dl \pm 0.68 respectively (Table 5). There is statistically significant decrease of serum calcium after phototherapy in the study group ($P<0.001$).

Table : Gender distribution of neonates in studied group with hypocalcemia and control group

	Gender	Frequency	Percentage
Studied Group (n=143)	Male	93	65%
	Female	50	35%
Control Group (n=70)	Male	45	64%
	Female	25	36%

Table 2: Frequency of hypocalcemia in neonates with respect to gender of the studied group (n=143) after phototherapy

Hypocalcemia	Frequency			Percentage		
	Male	Female	Total	Male	Female	Total
Yes	37	20	57	26%	14%	40%
No	56	30	86	39%	21%	60%
Total	93	50	143	65%	35%	100%

Table 3: Distribution of hypocalcemia after phototherapy in the neonatal age-group

Hypocalcemia	1-10 days	11-20 days	21-28 days	Total
Yes	41	14	2	57
No	62	22	2	86
Total	103	36	4	143
Mean ± SD (days)	7 ± 2.62			

Table 4: Comparison between studied group and control group regarding results of serum calcium on arrival

	Studied Group (n=143) (mean ± SD)	Control Group (n=70) (mean ± SD)	t-test	P-Value
Serum calcium (mg/dl)	9.28 ± 0.23	9.14 ± 0.87	1.28	>0.05

Table 5: Comparison between serum calcium levels before and after phototherapy treatment among studied group

	Before Phototherapy	After Phototherapy	Paired t-test	P-Value
Serum calcium (mg/dl)	9.28 ± 0.23	8.54 ± 0.68	8.25	<0.001

DISCUSSION:

Neonatal jaundice is one of the very common conditions with which pediatrician deal with and presents especially during the 1st week of life¹³ and it is highly prevalent and dangerous during this stage of life.¹⁴

Jaundice is present in 60% of term and 80% of preterm infants and in most of cases it is benign condition. In Pakistan it affects 39.7% babies per 1000 live birth.¹⁵ Unconjugated bilirubin is potentially neurotoxic and can cause neurologic and behavioral impairment. Thus main aim of therapy for neonatal jaundice is to prevent neurotoxic effect of unconjugated bilirubin.¹⁶ The management options for newborn jaundice include phototherapy which can be divided into conventional phototherapy or intensive phototherapy, exchange transfusion and pharmacologic options like phenobarbitone, metalloporphyrins and intravenous immunoglobulin (IVIG).¹⁷

Phototherapy is the most effective therapy for management of neonatal hyperbilirubinemia which lowers serum bilirubin level by converting bilirubin into non-toxic excretable form.³ Phototherapy converts unconjugated bilirubin to more polar stereoisomer by a process called photo isomerization. The substance formed cannot cross the blood brain barrier and is not neurotoxic and later on excreted out of the body via urine and bile.¹⁷

Blue fluorescent light with wavelength in the band of 460-490 nm are widely used for phototherapy and babies are kept at distance of 15-20 cm from light with eye pads for protection of eyes. Phototherapy reduces bilirubin level and

also the risk of exchange transfusion. Although phototherapy is safe way of treating neonatal jaundice but has some side effects like skin burn, diarrhea, hyperthermia, fluid loss, retinitis, thrombocytopenia, bronze baby syndrome. One of the important side effect but infact a complication of phototherapy is hypocalcemia.

Post phototherapy prevalence of hypocalcemia is 8.7% in this study. It results due to inhibition of pineal gland via transcranial illumination which decreases melatonin which in turn inhibits cortisol effect on bone calcium. Cortisol induces hypocalcemia by increasing calcium uptake by the bones.

Hypocalcemia leads to apnea, convulsion, muscle cramp, tremor, tetanus and increased mortality rate.⁵ Therefore, it should be timely diagnosed by monitoring serum calcium level in neonates receiving phototherapy and appropriately treated with intravenous 10% calcium gluconate along with calcium supplementation. Our study will help pediatricians to plan prompt interventions to avoid complications of hypocalcemia in neonates receiving phototherapy.

In our study, the frequency hypocalcemia was 40% in neonates with unconjugated hyperbilirubinemia after completed continuous phototherapy for at least 24 hours. Study conducted by Jain SK et al¹² showed that hypocalcemia was developed in 39% of term and 53% of preterm neonates after being subjected to phototherapy for more than 48 hours. Analogous results were observed in another study conducted in Karachi by M et al²⁰ in which the frequency of hypocalcemia in term jaundiced neonates receiving phototherapy was 22.76% (28/123). Another study conducted by Rozario CI et al²¹ had comparable results with our study, in which 67% of babies developed hypocalcemia after phototherapy. Alike results were also observed in another study conducted by Arora S et al¹¹ in which the frequency of hypocalcemia was found to be 42% in neonates with unconjugated hyperbilirubinemia after completed continuous phototherapy for at least 24 hours. In a study conducted in Iran,²² the frequency of hypocalcemia was 7.5% after phototherapy which is contradictory to our study. In an Indian study by Goyal S et al,²³ the frequency of hypocalcemia was 35% in neonates after receiving phototherapy. Shrivastva et al²⁴ in a study observed that the frequency of hypocalcemia was 30% in term neonates while Haq et al²⁵ reported hypocalcemia to be present in 75% of the neonates exposed to phototherapy.

A study conducted in Egypt in 2015 by Bahbah et al²⁶ showed post phototherapy hypocalcemia was present in 26% of term neonates, in which 50 term neonates received phototherapy and 25 neonates were taken as control with physiological jaundice needing no phototherapy. This is analogous to our study in which we took 70 neonates as control with physiological jaundice needing no phototherapy and among 143 neonates exposed to phototherapy for 24 hours, 40% developed hypocalcemia.

In our study, the mean calcium level before and after 24 hours of continuous phototherapy was 9.28 ± 0.23 mg/dl and 8.54 ± 0.68 mg/dl respectively.

Mean calcium level before and after phototherapy in the local study conducted by Khan M et al²⁰ was 8.73 ± 0.68 mg/dl and 7.47 ± 0.8 mg/dl which is comparable with our study. Similarly, mean calcium level before and after phototherapy in the study conducted by Bahbah et al²⁶ was 9.36 ± 0.29 mg/dl and 8.58 ± 0.76 mg/dl which is also comparable with our study.

Phototherapy is also one of the effective therapies for neonatal hyperbilirubinemia with potential complication of hypocalcemia.²⁷

This study is conducted on small group of subjects so further studies on larger scale should be conducted so that results can be extrapolated to larger population. Our study also explains this effect on calcium levels of neonates receiving phototherapy. Further studies are required to elaborate this aspect further, and to find out ways to avoid hypocalcemia after phototherapy either by using calcium supplements or refining application of phototherapy. Hence, results of this study will be useful for practitioners to devise meaningful early interventions to avoid complications of hypocalcemia in neonates receiving phototherapy at neonatal intensive care units.

CONCLUSION:

Hypocalcemia is an important complication in neonates with unconjugated hyperbilirubinemia after continuous phototherapy. Hypocalcemia has clinical impact and adds to morbidity, and if left untreated, can lead to mortality.

Authors Contribution:

Amna Khan: Conception and design, collection and assembly of data, final approval and guarantor of the article

Anila Farhat: Conception and design, collection and assembly of data, statistical expertise, final approval and guarantor of the article

Hamayun Anwar: Analysis and interpretation of data, drafting of article, statistical expertise

Sajid Shamim: Drafting of article, critical revision of the article for important intellectual content

Mujeeb Ur Rehman: Analysis and interpretation of data, statistical expertise

Irfan Khan: Drafting of article, critical revision of the article for important intellectual content

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