Effect of phototherapy on serum level of calcium in infants with hyperbilirubinemia interventional single arm study

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Background
Hypocalcemia may lead to significant symptoms such as convulsions, irritability, apnea, jitteriness and laryngospasm. As a result, phototherapy induced hypocalcemia can be a serious issue in neonates.

Aim
The study's aim was to determine phototherapy effect on serum calcium levels in neonates having unconjugated hyperbilirubinemia after being exposed to phototherapy for 48 h.

Patients and methods
This study is an interventional single-arm study conducted on 40 full-term newborns with jaundice (24 of them are males and 16 are females) who received phototherapy for neonatal indirect hyperbilirubinemia (exaggerated physiological jaundice) in neonatal ICU of Children's Hospital at Assiut University in the period between February 2020 to February 2022.

Results
The total serum Ca levels significantly decreased over admission period from 9.72 ± 0.58 to 9.41 ± 0.47 mg/dl. Similarly, ionized Serum Ca levels significantly decreased over admission period from 1.19 ± 0.11 to 1.07 ± 0.12 mg/dl.

Conclusion
This study concluded that phototherapy decrease serum calcium levels in neonatal jaundice after 48 h of exposure to phototherapy.

Keywords:
calcium, hyperbilirubinemia, infants, phototherapy

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Introduction

Jaundice is a yellow colouring of the skin, sclera and other body tissues caused by deposition of bilirubin in cases of hyperbilirubinemia when bilirubin level exceeds 2 mg/dl or 34.2 μmol/l [1]. It is a major health problem since around 60% of term and 80% of preterm newborns acquire jaundice in the first week of life and 10% of breastfed babies remain jaundiced for 1 month. In addition, jaundice is a common reason for hospital readmission after early discharge of newborns [2].

Types of hyperbilirubinemia include direct (characterized mainly by excess conjugated bilirubin), indirect (characterized mainly by excess unconjugated bilirubin) and mixed hyperbilirubinemia. Unconjugated or unbound bilirubin is the most prevalent cause of neonatal hyperbilirubinemia. It is commonly observed due to newborns' physiological immaturity and their inability to tolerate excessive bilirubin generation during the neonatal period [3].

High unconjugated hyperbilirubinemia is managed by treating the underlying cause if possible, phototherapy provision, immunoglobulin administration in certain cases of hemolytic anemia and in the very severe cases, exchange blood transfusion. If untreated, high levels of unconjugated bilirubin can cause lifelong brain damage (kernicterus) and/or death [3].

Hypocalcemia which is defined as total blood calcium of less than 8 mg/dl (2 mmol/l) in term neonates is one of the findings observed in some studies during phototherapy. However, the results of these studies were not conclusive. Hypocalcemia during phototherapy might be caused by transcranial light inhibiting the pineal gland, resulting in a decrease in melatonin levels. Melatonin increases corticosterone secretion, which lowers calcium deposition in bones. So, when melatonin level is decreased hypocalcemia develops [4].

Hypocalcemia can cause severe symptoms such as convulsions, irritability, apnea, jitteriness, and laryngospasm. Thus, phototherapy-induced hypocalcemia can be a serious problem in neonates [5].

The study aimed to see how phototherapy affects blood calcium levels in newborns with unconjugated hyperbilirubinemia after being exposed to it for 48 h.

Patients and methods

This study is an interventional single-arm study conducted on jaundiced 40 full-term neonates (24 of them are males and 16 are females) who received phototherapy for neonatal indirect hyperbilirubinemia (exaggerated physiological jaundice) in Neonatal ICU of Children's Hospital at Assiut University in the period between February 2020 to February 2022.

The research was examined and approved by Committee of Medical Ethics of Faculty of Medicine, Assiut University on June 15, 2020.

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After approval of the ethical committee, informed consents were acquired from the parents of the selected newborns. Patients whose parents refused their enrollment were excluded and their decision did not affect the medical care of their children.

Inclusion criteria

All cases chosen were icteric, stable full-term neonates managed with phototherapy and were full strength formula fed or breast fed.

Exclusion criteria

We excluded any jaundiced neonate suffering from hypocalcemia, hypothyroidism, congenital abnormalities, requiring exchange transfusion, other severe sickness as perinatal asphyxia, severe RDS, severe sepsis or hemolytic disease of newborn and babies of diabetic mothers.

Control

No control group was taken.

Study tools

Neonatal incubators and Phototherapy source (single, double and capsules).

Intervention

Patients in the studied group were placed naked while covering their eyes and genitalia at a 40–50 cm distance from phototherapy unit receiving continuous phototherapy in neonatal incubators with changes in their positions from time to time. The phototherapy unit used was blue light lamps, 20 W, which supplies spectral irradiance of 5 $mW/cm_2/nm$ at 450–470 nm/cm_2. Type of phototherapy each neonate received (single, double or capsule) was recorded and compared to indicate the relation between phototherapy intensity and serum calcium level changes. Each case was subjected to detailed history taken from the parents (gestational age, mode of delivery, detailed prenatal and natal history, age on admission and day of onset of jaundice and family history of neonatal jaundice) and clinical examination including general and local examination with special emphasis on weight, length, head circumference and manifestations of hypocalcemia (jitteriness, irritability and convulsion). Laboratory investigations included total serum bilirubin before and 48 h after receiving phototherapy, total serum calcium before and after 48 h after phototherapy, blood group to infants and their mothers, reticulocytic count and hemoglobin level. Following that, all data were recorded and statistically analysed to detect hypocalcemia as a complication of phototherapy.

Statistical analysis

We used the Statistical package for social sciences (SPSS) version 24 software for windows (SPSS Inc., Chicago, IL, USA) to analyse the data. Frequencies and percentages were used to describe categorical data while numerical data, when were normally distributed, were described as means and standard deviations. Kolmogrov-Semornov test was used for testing the normality of numerical variables distribution. The association between categorical variables was assessed by Chi square test. Paired sample t-test was used to assess the association between 2 paired numerical variables. Statistical significance was defined by a *P* value less than 0.05.

Results

40 neonates were hospitalised at Neonatal Intensive Care Unit of Children's Hospital, Faculty of Medicine, Assiut University in the period between February 2020 and February 2022 with neonatal jaundice and fulfilling our inclusion criteria. Management via phototherapy was required for all these patients (Table 1 and Fig. 1).

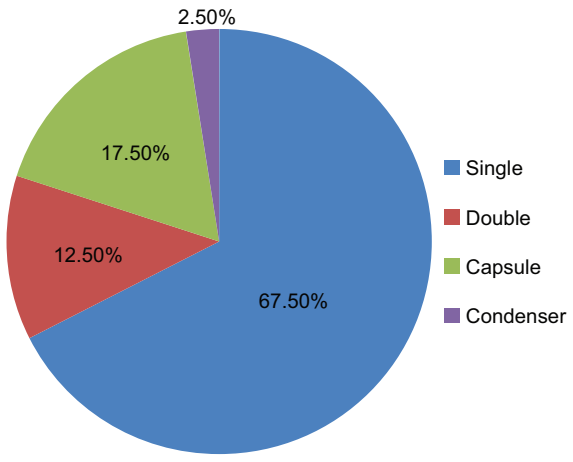
On admission, we found that mean levels of total bilirubin were 13.46 ± 4.77 mg/dl, while their mean indirect bilirubin levels were 12.52 ± 4.17 and mean direct bilirubin levels were 0.94 ± 0.55. Their mean total Ca levels were 9.72 ± 0.58 mg/dl, while their mean ionised Ca levels were 1.19 ± 0.11 mg/dl.

Concerning serum Ca levels, we found that their total serum Ca levels significantly decreased over admission period from 9.72 ± 0.58 to 9.41 ± 0.47 mg/dl. This difference was statistically significant ($P < 0.001$). Similarly, ionized serum Ca levels significantly decreased over admission period from 1.19 ± 0.11 to 1.07 ± 0.12 mg/dl. This was also statistically significant ($P < 0.001$) as shown in Table 2.

A weak positive correlation between Serum Ca level and age on admission was found (Pearson correlation coefficient = 0.02). On the other hand, the correlation was moderately positive between post-treatment Serum Ca level and each of the following; weight, head circumference and baby length (Pearson correlation = 0.02, 0.166, 0.170, 0.205) respectively. However, none of those was statistically significant ($P = 0.901$, $P = 0.307$, $P = 0.293$, $P = 0.212$). We also found that serum total Ca was slightly higher among those neonates fed through a combination between breast milk and formula feeding than those fed via only formula milk (9.55 ± 0.37 vs. 9.39 ± 0.48) respectively as shown in Table 3.

We also analyzed the correlation between post-treatment ionised Serum Ca level and sociodemographic characteristics and noticed that: There was a weak negative correlation between ionised serum Ca level and age on admission (Pearson correlation coefficient =−0.082). This was statistically insignificant ($P = 0.614$). On the other hand, the correlation was moderately negative between post-treatment ionised serum Ca level and each of the following; gestational age, weight, head circumference and baby length (Pearson correlation =−0.139, −0.283, −0.180, −0.298), respectively. However, none of those was statistically significant ($P = 0.391$, $P = 0.077$, $P = 0.268$, $P = 0.065$). We also found that ionised serum Ca level was slightly higher among males compared to females (1.09 ± 0.12 vs. 1.04 ± 0.13) respectively. However, this was also statistically insignificant ($P=0.201$). We also found that ionised serum

Figure 1



Used phototherapy among included patients.

Table 1 Sociodemographic characteristics of included neonates (*n*=40)

Variable	Mean±SD	Minimum–Maximum
Gestational age in weeks	37.8±0.82	37–41
Age in hours	61.03±39.78	12–168
	Number (Percentage)	
Gender		
Male	24 (60%)	
Female	16 (40%)	
Mood of delivery		
Normal vaginal delivery	8 (20%)	
Cesarian section	32 (80%)	
Blood group of Baby		
A-ve	4 (10%)	
A+ve	7 (17.5%)	
AB+ve	1 (2.5%)	
B-ve	2 (5%)	
B+ve	10 (25%)	
O-ve	3 (7.5%)	
O+ve	13 (32.5%)	
Blood group of Mother		
A-ve	1 (2.5%)	
A+ve	9 (22.5%)	
AB+ve	8 (20%)	
B-ve	0 (0%)	
B+ve	13 (32.5%)	
O-ve	0 (0%)	
O+ve	9 (22.5%)	

Table 2 Change in laboratory tests over admission period

Lab test	On admission	48 h post admission	*P*
Total bilirubin	13.46±4.77	9.89±3.62	<0.001
Direct bilirubin	0.94±0.55	0.81±0.43	0.458
Indirect bilirubin	12.52±4.17	9.09±3.47	<0.001
Total Ca	9.72±0.58	9.41±0.47	<0.001
Ionised Ca	1.19±0.11	1.07±0.12	<0.001
Paired sample *t*-test			

Table 3 Correlation between serum total Ca level and sociodemographic characteristics

Variable	Total serum Ca level	*P*
Age on admission (hours)	0.02*	0.901
Gender		
Male	9.52±0.52	0.064
Female	9.24±0.33	
Mode of delivery		
NVD	9.18±0.46	0.122
CS	9.46±0.46	
Gestational age (week)	−0.157*	0.334
Weight (Kg)	0.166*	0.307
Head circumference (Cm)	0.170*	0.293
Length (Cm)	0.205*	0.212
Feeding type		
Formula feeding	9.39±0.48	0.522
Breast & formula	9.55±0.37	

*Pearson correlation coefficient.

Ca level was slightly higher among patients delivered through NVD when compared with those delivered via CS (1.09 ± 0.09 vs. 1.06 ± 0.13), respectively. However, this was statistically insignificant (P = 0.512). We also found that serum total Ca was slightly lower among those neonates fed through a combination between breast milk and formula feeding than those fed via only formula milk (1.04 ± 0.05 vs. 1.07 ± 0.13), respectively. However, this was statistically insignificant (P = 0.561) as shown in Table 4.

Discussion

We enrolled 40 neonates hospitalised in Neonatal Intensive Care Unit (NICU) of Children's Hospital, Assiut University with neonatal jaundice treated via phototherapy; their mean age was 61.03 ± 39.78 h (2.5 ± 1.66 days).

These findings in comparison with many studies that discussed the same topic; as Bahbah *et al.* [6], where the mean postnatal age was 4.26 ± 1.12 days and Khan *et al.* [7], as their mean age was 8.35 ± 6.74 days.

Boskabadi *et al.* [8], found that; the incidence age of newborn jaundice was between 2 and 3 days after delivery in the majority of cases. Yet, the neonate's age of referral was between 6 and 8 days after delivery. The parents seek medical advice about 4 days after they noticed jaundice. Moreover, babies 72 h and older had a statistically significant increased chance to be diagnosed with neonatal jaundice. This corresponds to the natural course of physiological jaundice, which typically peaks between days 3 and 5 after delivery and subsequently returns to normal by day 10 [9].

There was a male predominance among admitted neonates in our study with a prevalence of 60% of admitted neonates, in agreement with Shitran and Abed [10], study as males were predominant (60.4%) with a male to female ratio being 1.54:1, in the same line Boskabadi and Navaei [11], showed that bilirubin level was higher among male neonates, compared to females and Khan *et al.* [12], study that found male predominance also (62.6% males).

Table 4 Correlation between serums ionised Ca level and sociodemographic characteristics

Variable	Ionised serum Ca level	*P*
Age on admission (hours)	−0.082*	0.614
Gender		
Male	1.09±0.12	0.201
Female	1.04±0.13	
Mode of delivery		
NVD	1.09±0.09	0.512
CS	1.06±0.13	
Gestational age (weeks)	−0.139*	0.391
Weight (Kg)	−0.283*	0.077
Head circumference (Cm)	−0.180*	0.268
Length (Cm)	−0.298*	0.065
Feeding type		
Formula feeding	1.07±0.13	0.561
Breast & formula	1.04±0.05	

*Pearson correlation.

Regarding mode of deliveries, we found that most admitted neonates (80%) were delivered via Cesarean section (CS). In harmony with Brits *et al.* [13], where the majority of infants in their research (64.6%) were delivered through cesarean section. Normal vaginal birth, on the other hand, was related with significantly higher newborn jaundice (P = 0.04). Our findings are also in line with Bahbah *et al.* [6], study conducted in Egypt as 60% of neonates with jaundice were delivered by CS however they did not report a significant difference for jaundice when compared with control group.

El-Sayed *et al.* [14], found that the percentage of instances of infant jaundice in CS was 17.4% and 10.2% in normal delivery, with a statistically significant difference (P = 0.004) between the two moods of delivery.

Another study by Chang *et al.* [15], found that bilirubin levels were considerably greater in infants with normal delivery than in those with CS [16].

Our patients' mean gestational age was 37.8 ± 0.82 weeks and their mean weight was 2.92 ± 0.33 kg.

In agreement with Shahriarpanah *et al.* [17], as the mean gestational age was recorded to be 38.14 ± 0.83 weeks and the mean weight during the hospital stay was 3.1 ± 0.3 kg.

Phototherapy is widely known for its usefulness in the treatment of neonatal jaundice.

In the present study, total bilirubin levels have significantly decreased over 48 h of admission from 13.46 ± 4.77 to 9.89 ± 3.62 mg/dl (P < 0.001). Similarly, following 48 h of admission, serum indirect bilirubin levels decreased significantly from 12.52 4.17 to 9.09 3.47 (P < 0.001).

In line with Shahriarpanah *et al.* [17], the average level of serum bilirubin in infants measured at two different times (hospitalisation and discharge) showed a significant decline in the level of bilirubin; the level of bilirubin in those infants after phototherapy had an average value of 8.53 ± 1.6 μmol/l, which was less than that of hospitalisation time 15.19 ± 2.24 μmol/l (P < 0.05).

Before phototherapy the newborns in Jagannath [18], study, included 60 neonates, had a mean serum bilirubin level of 15.2 ± 1.25 mg/dl. After phototherapy, the mean serum bilirubin level was 11.2 ± 2.6 mg/dl. The difference between these before and after phototherapy was also statistically significant ($P = 0.05$).

For serum Ca levels, we noticed that total blood Ca levels significantly decreased over admission period from 9.72 ± 0.58 to 9.41 ± 0.47 mg/dl ($P < 0.001$), as well as ionised serum Ca levels significantly decreased over 48 h from admission and phototherapy from 1.19 ± 0.11 to 1.07 ± 0.12 mg/dl ($P < 0.001$) but no one developed hypocalcemia.

In many studies as Karamifar *et al.* [19], and Ehsanipour *et al.* [20], mentioned 8.7% and 15% hypocalcemia respectively in newborns receiving phototherapy.

Alizadeh-Taheri *et al.* [4], found that out of 147 term neonates, about 56% had a decline in serum calcium level following phototherapy and that 7% developed hypocalcemia after the 48 h of phototherapy.

In our study, we assessed the correlation between serum ca and different variables (age on admission, gender, age of gestation, delivery mood, feeding type, weight, head circumference and length). However, none of these variables had a significant correlation with calcium level. In Khan *et al.* [7], study, stratified analysis was performed revealed that hypocalcemia was not significant regarding the different age groups, sex, gestational age, duration of jaundice and duration of phototherapy.

Suggestions for possibly preventing hypocalcemia in phototherapy-treated neonates include giving them oral calcium as prophylaxis or covering their heads and occipital area with a special hat during phototherapy so that the light of phototherapy do not affect newborns' pineal gland and, as a result, melatonin is not affected and hypocalcemia is prevented [6].

Conclusion

Phototherapy significantly decreases serum calcium level in neonatal jaundice after 48 h of exposure to phototherapy.

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Declarations: I declare that the thesis is an original report of my research, has been written by me and has not been submitted for any other degree or professional qualifications.

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Availability of data and material: Available.

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Conflicts of interest

There are no conflicts of interest.

References

1 Abbas MW, Shamshad T, Ashraf MA, Javaid R. Jaundice: a basic review. Int J Res Med Sci 2016' 4:1313-1319.

2 Amos RC, Jacob H, Leith W. PRACTICE 2017. Jaundice in newborn babies under 28 days: NICE guideline 2016 (CG98). Archives of Disease in Childhood-Education, 102, 207-209

3 Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in neonates: types, causes, clinical examinations, preventive measures and treatments: a narrative review article. Iran J Public Health 2016; 45:558.

4 Alizadeh-Taheri P, Sajjadian N, Eivazzadeh B. Prevalence of phototherapy induced hypocalcemia in term neonate. Iran J Pediatr 2013; 23:710-711.

5 Avery GB, MacDonald MG, Seshia MK. Avery's Neonatology: pathophysiology & management of the newborn. 6th ed. Lippincott Williams & Wilkins: Philadelphia; 2005 . pp. 1748-1755.

6 Bahbah M, Elnemr F, Elzayat R, Aziz E. Effect of phototherapy on serum calcium level in neonatal jaundice. Menoufia Med J 2015a; 28:426-430.

7 Khan M, Malik KA, Bai R. Hypocalcemia in jaundiced neonates receiving phototherapy. Pak J Med Sci 2016a; 32:1449.

8 Boskabadi H, Sezavar M, Zakerihamidi M. Evaluation of neonatal jaundice based on the severity of hyperbilirubinemia. J Clin Neonatol 2020; 9:46.

9 Redfern A. 2010. Coovadia's Paediatrics & Child Health. A manual for health professionals in developing countries

10 Shitran RF, Abed MY. Risk factors and outcomes of neonatal jaundice at al-ramadi teaching hospital for maternity and childhood. Ann Trop Med Public Health 2020; 23:231-228.

11 Boskabadi H, Navaei M. Relationship between delivery type and jaundice severity among newborns referred to Ghaem Hospital within a 6-year period in Mashhad. Iran J Obstet Gynecol Infertil 2011; 14:15-21.

12 Khan M, Malik KA, Bai R. Hypocalcemia in jaundiced neonates receiving phototherapy. Pak J Med Sci 2016b; 32:1449-1452.

13 Brits H, Adendorff J, Huisamen D, Beukes D, Botha K, Herbst H, Joubert G. The prevalence of neonatal jaundice and risk factors in healthy term neonates at National District Hospital in Bloemfontein. Afr J Prim Health Care Fam Med 2018; 10:e1-e6.

14 EL-Sayed YY, Watkins MM, Fix M, Druzin ML, Pullen KM, Caughey AB. Perinatal outcomes after successful and failed trials of labor after cesarean delivery. Am J Obstet Gynecol 2007; 196:583.e1-5. discussion 583.e5

15 Chang P-F, Lin Y-C, Liu K, Yeh S-J, Ni Y-H. Identifying term breast-fed infants at risk of significant hyperbilirubinemia. Pediatr Res 2013; 74:408-412.

16 Huang A, Tai BC, Wong LY, Lee J, Yong EL. Differential risk for early breastfeeding jaundice in a multi-ethnic Asian cohort. Ann Acad Med Singap 2009; 38:217-224.

17 Shahriarpanah S, Haji Ebrahim Tehrani F, Davati A, Ansari I. Effect of phototherapy on serum level of calcium, magnesium and vitamin D in infants with hyperbilirubinemia. Iran J Pathol 2018a; 13:357-362.

18 Jagannath H. Association between phototherapy and serum calcium levels in newborns: A institutional cross-sectional study. Int J Paediatr Geriatr 2020; 3:151-154.

19 Karamifar H, Amir HG, Pishva N. Prevalence of phototherapy-induced hypocalcemia. Iran J Med Sci. 2002; 27:166–168.

20 Ehsanipour F, Khosravi N, Jalali S. The effect of hat on phototherapy-induced hypocalcemia in icteric newborns. Razi J Med Sci 2008; 15:25-29.