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Effect of Phototherapy on Serum Calcium Level in Neonates with Indirect Hyperbilirubinemia

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Abstract

Background: Hyperbilirubinemia is a prevalent neonatal issue, with jaundice occurring in 60% of term neonates and 80% of preterm neonates during the first week of life.

Aim of Study: To assess the effect of phototherapy on serum calcium level in full term neonates with indirect hyperbilirubinemia.

Patients and Methods: This prospective interventional study was conducted on 50 full term neonates with indirect hyperbilirubinemia at the neonatal intensive care unit (NICU) of National Liver Institute, Menoufia University and (NICU) of Al-Mahala Alkobra General Hospital starting from February 2018 till March 2020.

Results: Mean TSB (pre) was 16.87 and ranged from 8.1 to 21, mean TSB (post) was 9.54 and ranged from 5 to 14.3, mean ionized Ca (pre) was 4.92 and ranged from 4.24 to 5.8, mean ionzed Ca (post) was 4.94 and ranged from 4.1 to 6.5, mean Phosphorus (pre) was 6.39 and ranged from 4.7 to 8.4, mean Phosphorus (post) was 7.23 and ranged from 4.5 to 8.9 and mean PTH (pre) was 40.18 and ranged from 15 to 103, mean PTH (post) was 61.52 and ranged from 14.44 to 107.

There was no significant difference between ionized Ca pre and post phototherapy in neonates who received single or double phototherapy $p>0.05$, Significant increase in PTH pre and post phototherapy inneonates who received single and double phototherapy $p<0.05$, no significant difference between phosphorus pre and post phototherapy in neonates who received single phototherapy $p=0.155$ and significant increase in phosphorous post phototherapy in neonates who received double phototherapy $p=0.001$.

Conclusion: Regarding Phototherapy Effects on Neonates, we concluded that there was no significant difference in ionized Ca pre and post Phototherapy and Significant increase in PTH pre and post Phototherapy.

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Key Words: *Phototherapy – Serum calcium level – Neonates – Indirect hyperbilirubinemia.*

Introduction

HYPERBILIRUBINEMIA is one of the most prevalent problems in neonates. Jaundice is observed during the first week of life in approximately 60% of term neonates and 80% of preterm neonates. Jaundice is due to physiological immaturity of the neonates to handle increased bilirubin production. Untreated severe unconjugated hyperbilirubinemia is potentially neurotoxic. No intervention is required in most cases but 5-10% of them have significant hyperbilirubinemia and the use of phototherapy becomes mandatory **[1].**

Phototherapy plays a significant role in the treatment of hyperbilirubinemia in neonates. Phototherapy may also lead to undesired effects including skin rash, diarrhea, body temperature rise, chills, trauma to the eye, nasal obstruction, and bronze baby **[2].**

Hypocalcaemia is one of the lesser known but potential adverse effect of phototherapy. Neonatal hypocalcaemia is defined as total serum calcium concentration of <7mg/dl. Or ionized calcium concentration of <4mg/dl (<1mol/L). Ionized calcium is crucial for many biochemical processes, including blood coagulation, neuromuscular excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity. Hypocalcaemia increases cellular permeability to sodium ions and increases cell membrane excitability **[3].**

Romagnoli et al., **[4]** were the first to suggest an association between hypocalcaemia and phototherapy in preterm neonates and observed hypocalcaemia in 52.3% neonates in their study.

This study aimed to assess the effect of phototherapy on serum calcium level in full term neonates with indirect hyperbilirubinemia.

Patients and Methods

This study was a prospective interventional study conducted on 50 full term neonates with indirect hyperbilirubinemia at the neonatal intensive care unit (NICU) of National Liver Institute, Menoufia University and (NICU) of Al-Inclusion criteria: Full term neonates, weight 2.5kg or more and Bilirubin level which need phototherapy according to (AAP) guideline.

Exclusion criteria: Preterm neonates <36 week, birth wt <2.5Kg, infant of diabetic mother, sick neonates and who needs exchange transfusion, neonates with major congenital anomalies and neonates with hypocalcaemia before starting phototherapy.

Consent: A written informed consent was obtained from all the legal guardian of the participants before inclusion in the study, explaining the value of the study, plus the procedures that were commenced.

Ethical consideration: The whole study design was approved by the local research committee of National Liver Institute at Menoufia, Faculty of Medicine, Confidentiality and personal privacy were respected in all levels of the study, Guardians felt free to withdraw from the study at any time without any consequences and collected data was not and will not be used for any other purpose.

Methods:

All neonates incorporated in this study were subjected to the following (or data were obtained from the legal guardians):

History taking: Gestational age (GA), Sex, birth weight, postnatal age, appropriateness for GA, type of feeding, Onset of jaundice, blood group, duration of phototherapy and Duration of NICU admission. Maternal data including maternal age, blood group, Pregnancy complications, medical diseases, medications, type of delivery and premature rupture of membrane (PROM). Clinical examination: Anthropometric measurements, vital signs and Systemic examination.

Laboratory investigations:

The following investigations were done at time of inclusion in the study: Complete blood picture, total and direct serum bilirubin, Infant and maternal blood group, reticulocytic count, liver enzymes, Serum Ca level (ionized) **[5]**, Serum phosphorus and Parathyroid hormone **[6].**

Sample collection and preparation:

Three milliliters of venous blood was collected using sterile needles, through gentle venipuncture under complete aseptic technique, the collected blood samples were centrifuged at 2000 × g for 10min, after resting for 30 minutes, and the obtained sera were kept at −80 °C until assayed.

Treatment regimen:

All infants received phototherapy in line with the Clinical Practice Guideline Manual of the American Academy of Pediatrics **[7].** There were two groups, First group received single phototherapy and second group received double, Phototherapy was performed in both groups using a Bili-Therapy Spot Type at a distance of 30cm from the infant's surface and at aradiation intensity of 30-40μW/cm^2/nm. Phototherapy side effects include dehydration, diarrhea, hyperthermia, skin rash, abdominal distention.

Follow-up:

72 hours after starting phototherapy, Serum bilirubin (Total & Direct), Serum Ca level (ionized), Serum phosphorus, Parathyroid hormone and total serum bilirubin was followed every 24 hours till phototherapy was be stopped.

Statistical analysis of data (Will be adjusted after the final results):

The study used the Statistical Package of Social Science (SPSS) program for Windows to analyze data. Normality was tested using the Kolmogorov-Smirnov test, and associations between categorical variables were tested using the Chi-square test. Continuous variables were presented as mean ± SD. Comparisons were made using independent *t*-tests, Mann Whitney tests, paired *t*-tests, and one-way ANOVA tests.

Results

Regarding baseline data, 60% of the studied neonates were males and 40% were females. Fifty two percent of studied neonates had double Phototherapy while 48% had single Phototherapy. CRP of 100% of the studied neonates was negative. Ten percent of studied neonates had normal vaginal delivery while 90% had caesarean section. Sixty six percent of the studied neonates had Breast feeding while 14% had Formula and 20% had both. 72% of the studied neonates had Negative Coombs test while 28% had positive Coombs test.

Mean TSB(pre) was 16.87 and ranged from 8.1 to 21, mean TSB (post) was 9.54 and ranged from 5 to 14.3 with significant decrease in TSB pre and post Phototherapy with (*p*. value 0.001*) (Table 1), mean DSB (pre) was 1.02 and ranged from 0.6 to 1.9, mean DSB (post) was 0.58 and ranged from 0.2 to 1.1 with significant decrease in DSB pre and post Phototherapy with (*p*. value 0.001*) (Table 1), mean ISB(pre) was 15.86 and ranged from 7.2 to 19.6, mean ISB (post) was 8.96 and ranged from 4.7 to 13.4 with significant decrease in ISB pre and post Phototherapy with (*p*. value 0.001*) (Table 1), mean Ionized Ca (pre) was 4.92 and ranged from 4.24 to 5.8, mean Ionized Ca (post) was 4.94 and ranged from 4.1 to 6.5 with no statistical significant

difference between ionized Ca pre and post single Phototherapy (*p*. value 0.327) (Table 2), and also no statistical significant difference between ionized Ca pre and post double Phototherapy (*p*. value 0.65) (Table 3), mean Phosphorus (pre) was 6.39 and ranged from 4.7 to 8.4, mean Phosphorus (post) was 7.23 and ranged from 4.5 to 8.9 with statistically significant increase in phosphorous post double Phototherapy *p*=0.001* (Table 4), mean PTH (pre) was 40.18 and ranged from 15 to 103, mean PTH (post) was 61.52 and ranged from 14.44 to 107, with statistically significant increase in PTH pre and post single Phototherapy, *p*=0.043. (Table 5) and statistically significant increase in PTH pre and post double Phototherapy *p*=0.001 (Table 6).

Table (1): Distribution of laboratory Parameters pre phototherapy and post phototherapy of the studied neonates.

	N	Min.	Max.	Mean	SE	SD
TSB pre	50	8.1	21	16.87	0.32	2.29
TSB post	50	5	14.3	9.54	0.30	2.09
DSB pre	50	0.6	1.9	1.02	0.05	0.32
DSB post	50	0.2	1.1	0.58	0.03	0.19
ISB pre	50	7.2	19.6	15.86	0.31	2.20
ISB post	50	4.7	13.4	8.96	0.28	1.97
Ionized Ca pre	50	4.24	5.8	4.92	0.05	0.37
Ionized Ca post	50	4.1	6.5	4.94	0.06	0.43
Phosphorus pre	50	4.7	8.4	6.39	0.12	0.88
Phosphorus post	50	4.5	8.9	7.23	0.15	1.07
PTH pre	50	15	103	40.18	2.85	20.16
PTH post	50	14.44	107	61.52	3.24	22.89

Pre = Pre phototherapy.
Post = Post phototherapy.

Table (2): Comparison between ionized calcium level pre and post single Phototherapy.

	Single	*t*. test	*p*. value
Ionized Ca pre: Mean ± S.D	4.97±0.38	0.9897	0.327
Ionized Ca post: Mean ± S.D	5.08±0.39		

Table (3): Comparison between ionized calcium level pre and post double Phototherapy.

	Double	*t*. test	*p*. value
Ionized Ca pre: Mean ± S.D	4.86±0.37	0.4555	0.65
Ionized Ca post: Mean ± S.D	4.81±0.42		

Table (4): Comparison between phosphorus level pre and post double Photo therapy.

	Double	*t*. test	*p*. value
Phosphorus pre: Mean ± S.D	6.17±0.83	4.7305	0.001*
Phosphorus post: Mean ± S.D	7.39±1.02		

Table (5): Comparison between PTH level pre and post single Phototherapy.

	Single	*t*. test	*p*. value
PTH pre: Mean ± S.D	46.21±23.66	2.0732	0.043
PTH post: Mean ± S.D	59.15±19.37		

Table (6): Comparison between PTH level pre and post double Phototherapy.

	Double	*t*. test	*p*. value
PTH pre: Mean ± S.D	34.60±14.64	4.9876	0.001*
PTH post: Mean ± S.D	63.71±25.91		

Discussion

Neonatal jaundice is a common condition in the neonatal period. Although it is transient, the condition accounts for up to 75% of hospital admissions in the first week after birth. Approximately 5-10% of them have clinically significant hyperbilirubinemia for whom the use of phototherapy becomes mandatory **[8].**

The main results of this study were as follows:

Our results were supported by the study of Goyal et al., as they included 100 neonates, 61 boys (61.0%) and 39 girls (39.0%), with mean gestational age of 38.16±0.95 weeks and mean birth weight of 2.66±0.33 kilograms. 57.0% neonates were delivered by normal vaginal delivery and 43.0% by lower segment caesarean section. Mean time of appearance of icterus and duration of phototherapy was 102.60±48.10 hours and 42.48±10.15 respectively **[8].**

The present study showed that mean TSB (pre) was 16.87, mean ± 2.29 TSB (post) was 9.54, mean± 2.09 DSB (pre) was 1.02, mean ± 0.32 DSB (post)was 0.58, mean ± 0.19 ISB (pre) was 15.86, and mean ± 2.20 ISB (post) was 8.96, mean ± 1.97. There was statistically significant decrease in TSB

pre and post Phototherapy in neonates who received single and double Phototherapy. There was statistically significant decrease in DSB in neonates who received single and double Phototherapy. There was statistically significant decrease in indirect bilirubin pre and post Phototherapy in neonates who received single and double Phototherapy.

The current study showed that the mean Ionized Ca (pre) was 4.92 and ranged from 4.24 to 5.8, means ± 0.37 Ionized Ca (post) was 4.94 and ranged from 4.1 to 6.5 means ± 0.43. There was no statistical significant difference between level of Ionized Ca pre and post Phototherapy in either single or double Phototherapy neonates.

Our results were in disagreement with the study of Shahriarpanah et al., [10] as they revealed that statistical analysis showed that 48 hours after phototherapy, average serum calcium level in the subjects was 9.51±0.54 mg/dL, which was less than that of the hospitalization time (9.85±0.64 mg/dL). This decrease was statistically significant (p<0.001).

Whereas, in the study of Elshenawi et al., [11] mean calcium was 8.63±1.54 pre-phototherapy and was 8.22±1.64 mg/dl postphototherapy. The difference was as statistically significant (p<0.001). Calcium level was lower after phototherapy.

In concordance with our study, Gheshmi et al., they reported a decrease in the serum calcium concentration in 54% of full-term neonates after phototherapy. Gheshmi et al. [12] conducted a crosssectional study on 100 full-term neonates to determine the prevalence of hypocalcemia after phototherapy in two groups, i.e., (1) Those who were more than three days old and (2) Those who were less than three days old, the prevalence was not significantly different in the two age groups (p=0.217).

Moreover, Goyal et al., [9], demonstrated that the mean Serum calcium level before phototherapy in neonates was 9.31mg/dl with standard deviation of 0.69mg/dl. Whereas after phototherapy mean Serum calcium level in neonates was 8.88mg/dl with standard deviation of 0.73mg/dl. There was statistically significant mean difference in Serum calcium level before and after phototherapy in neonates (p<0.001).

Phototherapy can lead to decreased total and ionized calcium levels in neonates, especially in preterm neonates. This effect might be attributable to increased urinary calcium excretion. In addition, light can inhibit pineal secretion of melatonin and consequently leading to hypocalcemia, hypomagnesemia with no significant effect on Vit D levels. Fortunately, only a few hypocalcemic neonates present clinically, and in almost all hypocalcemic neonates serum levels of calcium return to normal 24h after ending phototherapy. Hypocalcaemia in neonates present with tetanus, spasms of the larynx, dysfunction of myocardia and apnoea, myoclonic seizure, jerking, chills, tachycardia, heart failure, and decreased contractility of the heart. Hypocalcaemia is a common cause of seizures in neonates. Neonates should have serial monitoring for serum calcium levels who receive phototherapy for >48 hrs for early identification and treatment [13].

The difference between these studies and ours may be explained by different sample size and different severity of cases. Also all our cases were full term while observed hypocalcemia was more in preterm, Calcium level in our study was measured 72 hours after phototherapy which means that hypocalcaemia may occur and resolved before this time, also in our study we measure ionized calcium while most of the studies measure serum total calcium.

Our results shows that there was increase in phosphorus level post Phototherapy in neonates who received single phototherapy but not statically significance p=0.155 and There was statistically significant increase in phosphorous post Phototherapy in neonates who received double phototherapy p=0.001*.

However, in the study of Suneja et al., [14] there was no statistically significant difference between pre and post phototherapy regarding phosphorus.

Our results showed that there was statistically significant increase in PTH pre and post Phototherapy in single Phototherapy neonates and in double Phototherapy neonates.

Conclusion:

Regarding Phototherapy Effects on Neonates, we concluded that there was Significant decrease in TSB, DSB, and indirect bilirubin pre and post Phototherapy, no significant difference in Ca pre and post Phototherapy in neonates who received single and double phototherapy, Significant increase in phosphorous post double Phototherapy and Significant increase in PTH pre and post Phototherapy.

Limitations:

The present study had some limitations. Lack of control group is the main limitation. The small sample size is another limitation.

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تأثير العلاج الضوئى على معدل الكالسيوم بالدم فى حديثى الولادة المصابون بارتفاع صفراء الدم غير المباشرة

المقدمة: ارتفاع صفراء الدم واحدة من أكثر المشاكل انتشاراً فى حديثى الولادة. وليس هناك حاجة إلى التدخل فى معظم الحالات ولكن ٥-١٠٪ من ارتفاع الصفراء غير المباشرة بالدم شديد واستخدام العلاج الضوئى يصبح إلزامياً.

الهدف من هذه الدراسة: هو تقييم تأثير العلاج بالضوء على مستوى الكالسيوم فى الدم فى حديثى الولادة كاملى النمو المصابون بارتفاع صفراء الدم غير المباشرة.

المرضى وطرق البحث: هذه دراسة تداخلية أجريت على ٥٠ من حديثى الولادة كاملى النمو الذين يعانون من ارتفاع بالصفراء غيرالمباشرة بالدم المعالجة بالضوء وفقا لإرشادات الأكاديمية الأمريكية لطب الأطفال (٢٠٠٤) فى وحدة العناية المركزة لحديثى الولادة بالمعهد القومى للكبد بجامعة المنوفية ووحدة العناية المركزة لحديثى الولادة بمستشفى المحلة الكبرى العام تبدأ من شهر فبراير عام ٢٠١٨ م. وتم الحصول على موافقة كتابية من جميع والدى المرضى قبل المشاركة فى الدراسة.

الطريقة:

جميع الأطفال حديثى الولادة المدرجون فى الدراسة خضعو لما يلى:

أ) أخذ التاريخ المرضى.

ب) الفحص السريرى.

ج) الفحوصات المعملية: مستوى الكالسيوم بالدم (المتأين)، مستوى الفوسفور بالدم، هرمون الغدة الجاردرقية، البيليروبين بالدم (الكلى والمباشر). قبل التعرض للعلاج بالضوء وبعده ب ٧٢ ساعة.

النتيجة: متوسط الكالسيوم المتأين فى الدم قبل التعرض للضوء ٤,٩٢ متراوح من ٤,٢٨ إلى ٥,٨ وكان متوسط الكالسيوم المتأين بالدم بعد التعرض للضوء ٤,٩٤ متراوحاً بين ٤,١ إلى ٦,٥.

متوسط الفوسفور بالدم قبل التعرض للعلاج بالضوء ٦,٣٩ متراوح من ٤,٧ إلى ٨,٤ وكان متوسطة بعد التعرض للضوء ٧,٢٣ متراوح بين ٤,٥ إلى ٨,٩.

متوسط هرمون الغدة الجاردرقية قبل التعرض للعلاج بالضوء كان٤٠,١٨ ويتراوح بين ١٥ إلى ١٠٣ وبعد التعرض للضوء كلن ٦١,٥٢ متراوحا بين ١٤,٤٤ إلى ١٠٧.

الملخص: لايوجد إختلاف ملحوظ بين معدل الكالسيوم المتأين في الدم قبل وبعد التعرض للعلاج الضوئى، بينما كان هناك ارتفاع ملحوظ فى هرومون الغدة الجاردرقية بعد التعرض للعلاج الضوئى.