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Original Article

Effect of Phototherapy on Electrolytes, Liver and Kidney Functions during Treatment of Neonatal Hyperbilirubinemia. A Prospective-Analytical Study

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Abstract

Background: Neonatal jaundice is a frequent problem affecting the newborn with various etiologies. Although phototherapy is considered the standard treatment for neonatal hyperbilirubinemia, it has some complications, as erythematous rashes, diarrhea, hyperthermia and electrolyte disturbance. **Objective:** To assess the effect of phototherapy on liver enzymes, renal functions, and serum electrolytes in jaundiced neonates before and after phototherapy and to assess changes in biochemical parameters according to mode of treatment including using Bilisphere then phototherapy, IVIG & Bilisphere then phototherapy and phototherapy only. **Methods:** One hundred neonates with unconjugated hyberbilirubinemia were enrolled. Jaundiced neonates were placed under phototherapy at a distance of 45-50 cm. Laboratory investigations were done before and after phototherapy. **Results:** Mean (± SD) TSB and DSB significantly declined after phototherapy with p value <0.001. Also, Mean (± SD) levels of AST and ALT showed statistically significant decrease after phototherapy (p<0.001). In addition, Mean (± SD) creatinine and urea levels showed statistically significant decrease after phototherapy (p<0.001).We also found statistically significant decrease in potassium and Calcium levels (p-value < 0.001) after treatment. As regards mode of treatment, we found a statistical significant decrease in TSB, creatinine and calcium among the different modes of treatment (p<0.001). **Conclusion:** Neonatal hyperbilirubinemia is considered a treatable condition and much of its ill-effects can be eliminated by proper intervention. However, continuous observation of electrolytes as potassium, sodium and calcium is needed as disturbance in their levels is of concern.

Key words: Neonatal hyperbilirubinemia, Phototherapy, Kidney and liver functions

Introduction

Approximately 80% of preterm infants and 60% of full-term infants during their first week of life suffer from a common disorder which is neonatal hyperbilirubinemia (NH) [1]. Neonatal hyperbilirubinemia exists in two types conjugated and unconjugated. The conjugated type is considered a consequence of an underlying systemic illness whereas the unconjugated type may lead to bilirubin encephalopathy, kernicterus and mental retardation if it is severe [2]. Hyperbilirubinemia in preterm neonates is more prevalent than in their term counterparts as immature infants are more prone to bilirubin-induced brain injury [3]. Phototherapy is the most commonly used therapy for unconjugated hyperbilirubinemia. It's both well tolerated and safe, also it decreases the need for exchange transfusion or drugs as phototherapy transform bilirubin into isomers that are water soluble thus can be easily eliminated through GIT or kidneys in urine, without the need for conjugation in liver [4]. Few side effects of phototherapy were documented such as hyperthermia, dehydration; loose stool feed, intolerance, skin rash, and bronze baby syndrome [5]. Phototherapy can decrease the level of serum electrolytes as serum calcium, sodium, potassium, and chloride [6]. It also affects the serum level of liver enzymes of neonates as it decreases the level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum alkaline phosphatase (ALP) [7]. Some studies about the effect of phototherapy on kidney functions in neonates revealed that phototherapy decrease the level of serum creatinine, serum urea, and serum uric acid [8]. The current study aims to assess the effect of phototherapy on liver enzymes, renal functions, and serum electrolytes in NH patients before and after phototherapy.

Patients and Methods

This observational cross sectional study was performed at the phototherapy neonatal intensive care unit (NICU), Abu El Rich Children's Hospital, Cairo University, Egypt from March 2019 to September 2019. This study included 100 term infants that have received phototherapy for management of neonatal indirect hyperbilirubinemia. Infants were further subdivided into three groups according treatment modalities applied. Group I; infants treated with phototherapy only (66%), Group II: infants treated with Bilisphere then Phototherapy (22%) and Group III; infants treated with IVIG and bilisphere then phototherapy (16%).

Management of hyperbilirubinemia cases relied on American Academy of Pediatrics (AAP) guidelines for hyperbilirubinemia in which a TSB >20-25 mg/dl indicate the need for extensive phototherapy (bilisphere) while levels below that range recommends the use of traditional phototherapy [9]. Intravenous immunoglobulin G (IVIG) is used as an adjuvant for phototherapy in cases with TSB >20-25 mg/dl and suffering from ABO hemolytic disease of the newborn. Inclusion criteria included all full term neonates admitted to the NICU with unconjugated hyperbilirubinemia who received phototherapy. Exclusion criteria included preterm neonates, neonates older than 30 days, neonates with conjugated hyperbilirubinemia, neonates admitted for postoperative care after elective surgery, neonates with any systemic illness such as liver diseases and renal diseases, all neonates who received exchange blood transfusion and all neonates who have sepsis. All included neonates were subjected to detailed maternal, obstetric and neonatal history. Also full clinical data were collected including general and local examination. By following the guidelines of ethical committee of Faculty of Medicine, Cairo University, an informed consent was taken from parents.

Procedure of phototherapy: The conventional phototherapy used includes four blue light lamps (20w) with intensity of 5 $mW/cm^2/nm$ and spectrum of 450-470 nm/cm ^{2}. Neonates were placed naked, 45-50 cm from phototherapy unit while protecting genitalia and eyes by their coverage. The position of the infant was changed periodically.

The intensive phototherapy used was Bilisphere 360 (Novos, Turkey). It includes 16 fluorescent lamps with intensity of 30 mW/cm ^{2} /nm and spectrum of 420-500 nm that encircles the infant 360° and are placed 25 cm from the center of the bed.

Laboratory Investigations: In plain vacutainer tubes, venous blood samples were taken from all infants pre and post phototherapy. Samples were transferred immediately to lab for analysis of total & direct bilirubin, AST, ALT, ALP, urea, creatinine, sodium, potassium and calcium on chemical analyzer Biotechnica (BT 4500) (Italy).

Ethical approval

Ethics approval and consent to participate: The study was approved by the scientific ethics committee of pediatric department, Faculty of Medicine, Cairo University. An informed consent was obtained from parents before enrollment. The consent was verbal, as our research was part of Master thesis of a candidate in our institute so it was performed under Cairo University regulations at the time of performance of the study. In this study, the methods did not include invasive procedure; samples for laboratory investigation done in this study were withdrawn during routine sampling patients during their follow up.

Results

One hundred term infants were included in this study, 51 were males (51.0 %) and 49 were females (49.0 %). Distribution of the studied cases according to maternal disease: 13.0 % had diabetic mothers, 12.0% had mothers suffered from preeclampsia and 75.0% had medically free mothers. According to mode of delivery; 32.0% were delivered normally and 68.0% were delivered by caesarian section (Table 1).

Our patients ranged in age between 2.0 – 23.0 days with a mean age of 4.70 ± 3.35 days. Regarding body weight, mean (± SD) was 3.14 ± 0.49 Kg. The mean length was 49.98 ± 0.68 cm. The mean skull circumference was 34.82 (± 0.45) cm.The mean gestational age was 37.49 (± 0.67) weeks. Phototherapy duration mean was 2.33 (± 1.40) days, while mean age of phototherapy was 4.63 (± 3.31) days (Table 2).

As regards etiology of jaundice, 72% of the included jaundiced infants had physiological jaundice, 18% of the infants suffered from ABO incompatibility and 10% suffered from RH incompatibility (Table 1).

Regarding mode of treatment by phototherapy 66 cases (66.0%) were treated by double LED phototherapy, 34 cases (34.0%) were treated by Bilisphere 360 intensive system. IVIG was given to 22 cases (22.0%) (Table1).

In the present study, TSB significantly decreased from 16.51 ± 2.11 before phototherapy to 7.49 ± 1.23 after phototherapy with p value <0.001. DSB showed statistically significant decrease after treatment (1.05 ± 0.24 before treatment vs 0.31 ± 0.25 after treatment) (p value <0.001) (Table 3).

Also, AST significantly decreased between from 29.84 ± 8.23 before phototherapy to 26.83 ± 6.95 after phototherapy (p value <0.001). In addition, ALT showed statistically significant decrease after treatment (27.79 ± 8.51 before phototherapy vs 24.60 ± 8.49 after phototherapy (p value <0.001) (Table 3).

There was also a decrease in ALP level from 250.0 ± 46.95 before phototherapy to 244.5 ± 44.86 after phototherapy but the difference was not statistically significant (Table 3).

In addition, we observed a statistical significant decrease of serum creatinine after phototherapy as mean (± SD) of creatinine level before phototherapy was 0.56 ± 0.12, while after phototherapy was 0.41 ± 0.12 (p value <0.001). Also a statistical significant decrease of serum urea was observed after phototherapy as mean (± SD) of urea level before phototherapy was 22.73 ± 5.87, while after phototherapy was 20.50 ± 5.40 with p value <0.001.

Regarding effect of phototherapy on electrolytes, we found significant differences in potassium and calcium levels after phototherapy (p value < 0.001) where mean (± SD) level of potassium decreased from 4.48 ± 1.19 before phototherapy to 3.85 ± 0.53 after phototherapy, while mean (± SD) level of calcium decreased from 9.08 ± 0.63 before phototherapy to 7.7 ± 0.9 after phototherapy (Table 3).

There was also a decrease in mean (± SD) level of Na level from 136.5 ± 12.85 before phototherapy to 135.8 ± 2.75 after phototherapy but the difference was not statistically significant (Table 3).

Regarding mode of treatment, the present study revealed a statistically significant difference in TSB in the three groups, where mean (±SD) of TSB showed more decrease in group 2 (group of patients treated with Bilisphere then Phototherapy) than group 3 (group of patients treated with IVIG and bilisphere then phototherapy) and group 1(group of patients treated with phototherapy only) as mean (± SD) decrease of TSB was 11.20 ± 2.22, 9.83 ± 3.15 and 8.37 ± 1.66 mg/dl respectively (p value <0.001) (Table 4).

Also a statistically significant difference in serum calcium level was found in the three groups, where mean (±SD) of serum calcium level showed more decrease in group 2 than group 3 and group 1, where mean (± SD) decrease of calcium level was 1.51 ± 0.55, 1.48 ± 0.39 and 1.19 ± 0.38 respectively (p-value <0.004) (Table 4).

Also a statistically significant decrease in serum creatinine level was found between group2, group 3 and group 1, where mean (± SD) decrease of creatinine level was 0.23 ± 0.12, 0.16 ± 0.11and 0.13 ± 0.13 respectively (p-value <0.017) (Table 4).

Discussion

Various biochemical parameters were evaluated before and after phototherapy, in our study, to find out different effects of phototherapy in infants treated with phototherapy.

In this study, there was a statistically significant decrease of TSB and DSB levels after phototherapy when levels were compared to those before phototherapy. These results were in consistence with Shahriarpanah S et al., [10] who conducted a study on 50 term jaundiced infants receiving phototherapy and the average level of serum bilirubin (total and direct) showed significant decrease after phototherapy ($p < 0.05$).

In the present study, mean (± SD) of serum creatinine and urea levels showed a statistically significant decrease after phototherapy when compared to those before phototherapy ($p < 0.001$). The results of the current study agree with a study done by Suneja S et al., [11] who found that the basal levels of serum creatinine (0.71±0.36 mg/dl) decreased significantly post-phototherapy (0.53±0.46 mg/dl). On the other hand, Asl AS et al., [12], found that Basal serum levels of creatinine and urea at admission showed no significant differences when tested after phototherapy ($p = 0.842$, 0.726 respectively).

In our study, AST and ALT levels showed statistically significant decrease when levels before phototherapy compared to those after phototherapy with p value <0.001. Also, ALP level showed decrease when level before phototherapy compared to level after phototherapy but the difference was statistically non-significant. These results were similar to Suneja S et al., [11] study which revealed that the level of AST was high before phototherapy (75.12±38.9 mg/dl), which can be attributed to the immaturity of the liver functions and decreased significantly after phototherapy (60.94±39.5).

We also observed significant differences in potassium level before and after phototherapy (p value < 0.001). In addition sodium level decreased when level before phototherapy was compared to that after phototherapy but the difference was statistically non-significant (p = 0.605). In consistence to this study, Suneja S et al., [11] observed significant decrease in sodium and potassium levels after phototherapy (p < 0.001). The decrease in sodium and potassium levels were explained by Curtis M et al., [13] who stated that, phototherapy leads to significant impairment of water, potassium and sodium absorption. Also, Jena PK et al., [14] found that the mean (± SD) levels of sodium before and after phototherapy was 141.97±2.795 mmol/L and 140.66±4.751 mmol/L respectively, which was in consonance to Kumar S et al., [15] study that reported similar results when sodium level before phototherapy (139.01± 3.119 mmol/L) compared to levels after phototherapy (138.15± 3.35 mmol/L) (p < 0.001).

Although our results showed non statistical significant decrease of sodium level after phototherapy, other studies reported a significant decrease in mean serum sodium levels after phototherapy. Suneja S et al., [11] found that serum sodium level was 159.38±22.7 before phototherapy and 148.80±10.9 after phototherapy (p > 0.001), Also, Reddy AT et al., [6] revealed a decrease in serum sodium level after phototherapy 138.16±3.36 when compared to levels before phototherapy 139.02±3.12 with (p value > 0.001).

In our study, serum calcium level decreased after phototherapy with statistically significant difference (p value <0.001); This is in agreement with Rozario CI et al., [16] who showed that, about 67% of infants had a statistically significant decrease in serum calcium level from the basal level after phototherapy (p <0.001). As regards degree of reduction, 32% of infants had a 5-9% reduction in serum calcium value and 20% had greater than 10% reduction but only 3% of these infants developed hypocalcemia (serum calcium <7 mg/dl). Also, Asl AS et al., [12] found a decrease in the mean serum calcium levels after phototherapy from 9.37 ± 0.86 to 9.25 ± 0.61 mg/dL, after phototherapy (p value = 0.009). In studies by Karamifar H et al., [17] and Ehsanipour F et al., [18], the incidence of hypocalcemia after 48 h of phototherapy was 15 and 14.4%, respectively.

The etiology of hypocalcemia in infants treated with phototherapy is believed to be caused by increased urinary calcium excretion after exposure to phototherapy. In addition, it can be due to inhibition of melatonin secretion from pineal gland by transcranial illumination. This causes stimulation of corticosterone secretion. Cortisol exerts a direct hypo calcemic effect by decreasing the absorption of Ca and PO_4 ions from the intestine by antivitamin D action and through increasing the renal excretion of these ions and also it accelerates the bone uptake of calcium [18, 19].

Thus, our results are in consistence with the study done by Reddy AT et al., [6] that concluded that infants receiving phototherapy are at risk to develop electrolyte imbalance after phototherapy so close monitoring is recommended.

Regarding mode of treatment, the present study revealed a statistically significant decrease in TSB, creatinine and calcium levels in Group 2 (group of patients treated with Bilisphere then Phototherapy) when compared to group 3 (the group of patients treated with IVIG and bilisphere then phototherapy) and also group 1 (the group of patients treated with phototherapy only) (p = 0.001, 0.017 and 0.009 respectively).

The decrease in TSB in our study was in consistent with Edris AA et al., [20] study who revealed that bilisphere decreased the need for exchange transfusion and shortened the duration of phototherapy. These results are also in agreement with previous studies that show that serum bilirubin levels in neonates may be controlled more effectively with bilisphere (high intensity phototherapy) than with conventional phototherapy [21].

Also the decrease in serum calcium level reported in our study was in agreement with Goyal S et al., [22] who found that the difference between pre and post phototherapy serum calcium levels were found to be statistically significant (p <0.001). Also they found that after Bilisphere, there was hypocalcemia in 35.0% of neonates and hypocalcemia was more in newborns who received Bilisphere for longer time.

In our study, IVIG was used as an adjuvant to phototherapy in cases with ABO incompatibility having high TSB, Also, Al-Lawama M et al., [23] recommended the safe use of IVIG together with phototherapy in neonates with isoimmune hemolytic disorder. Employing phototherapy only produced positive results; this supported the use of selective IVIG administration criteria in newborns with isoimmune hemolytic illness. The Indications for IVIG administration before the newborn reaches the exchange level include rise in Bilirubin despite intensive phototherapy and marked decline of hemoglobin can be used as an indication for administration of IVIG before the newborn approaches exchange level [23].

Also, in the same line with our study, Beken S et al. [24] suggested phototherapy as the initial treatment for hyperbilirubinemia in newborns with ABO hemolytic disorder. If the serum bilirubin level is close to the exchange transfusion level despite phototherapy, IVIG treatment should be considered.

There are some limitations we met in this study as we collected our data from a single hospital, the small size of the studied group which hinders our ability to generalize our findings.

Conclusion

Neonatal hyperbilirubinemia is considered a treatable condition and much of its ill-effects can be eliminated by proper intervention. However, continuous observation of electrolytes as potassium, sodium and calcium is needed during phototherapy as disturbance in their levels is of concern

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Author's contributions

HH conceived of the study, participated in its design and helped to draft the manuscript. YF participated in study design and coordination and helped to draft the manuscript. BF participated in the study design and performed the immunoassays. AK participated in patient selection and data collection. All authors read and approved the manuscript.

Conflict of interest

The authors declare that they have no competing interests

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Table (1): Distribution of the studied neonates according to sex, maternal disease and mode of delivery, cause of jaundice and mode of treatment (n = 100)

Item	No.	%
Sex		
Male	51	51.0
Female	49	49.0
Maternal disease		
Diabetes Mellitus	13	13.0
Preeclampsia	12	12.0
Medically free mothers	75	75.0
Mode of delivery		
Vaginal delivery	32	32.0
Cesarean section	68	68.0
Cause of jaundice		
Non Haemolytic jaundice	72	72.0
ABO incompatibility	18	18.0
RH incompatibility	10	10.0
Phototherapy		
Conventional phototherapy	66	66.0
Bilisphere then conventional phototherapy	34	34.0
IVIG treated infants	22	22.0

Table (2): Descriptive analysis of the studied neonates (n = 100)

Measures	Min. – Max.	Mean ± SD.
Age (days)	2.0 –23.0	4.70 ± 3.35
Body weight (kg)	2.0 –4.10	3.14 ± 0.49
Length (cm)	48.0 –51.0	49.98 ± 0.68
Skull circumference (cm)	33.50 –36.0	34.82 ± 0.45
Gestational age (weeks)	37.0 –40.0	37.49 ± 0.67
Age of receiving photo (days)	2.0 –23.0	4.63 ± 3.31
Phototherapy duration (days)	0.0 –10.0	2.33 ± 1.40

Table (3): Comparison of laboratory investigations before and after phototherapy

Item	Before	After	p
TSB			
Mean ± SD.	16.51 ± 2.11	7.49 ± 1.23	<0.001*
Decrease	**9.03 ± 2.34**		
DSB			
Mean ± SD.	1.05 ± 0.24	0.31 ± 0.25	<0.001*
Decrease	**0.74 ± 0.36**		
Urea			
Mean ± SD.	22.73 ± 5.87	20.50 ± 5.40	<0.001*
Decrease	**2.23 ± 5.25**		
Creatinine			
Mean ± SD.	0.56 ± 0.12	0.41 ± 0.12	<0.001*
Decrease	**0.15 ± 0.13**		
ALT			
Mean ± SD.	27.79 ± 8.51	24.60 ± 8.49	<0.001*
Decrease	**3.19 ± 5.83**		
AST			
Mean ± SD.	29.84 ± 8.23	26.83 ± 6.95	<0.001*
Decrease	**3.01 ± 6.34**		
ALP			
Mean ± SD.	250.0 ± 46.95	244.5 ± 44.86	0.227
Decrease	**5.47 ± 45.01**		
Na			
Mean ± SD.	136.5 ± 12.85	135.8 ± 2.75	0.605
Decrease	**0.70 ± 13.57**		
K			
Mean ± SD.	4.48 ± 1.19	3.85 ± 0.53	<0.001*
Decrease	**0.63 ± 1.15**		
Ca			
Mean ± SD.	9.08 ± 0.63	7.70 ± 0.90	<0.001*
Decrease	**1.38 ± 0.87**		

p: p value for Paired t-test for comparing different parameters between Before and After phototherapy. *: Statistically significant at $p \le 0.05$

TSB: total serum bilirubin, DSB: direct serum bilirubin, ALT: alanine aminotransferase, AST: aspartate transaminase, ALP: alkaline phosphatase, Ca: calcium, Na: sodium, K: potassium

Table (4): Relation between mode of treatment and laboratory investigations for all studied neonates (n = 100)

Item	Treatment			p-value
	Group I	Group II	Group III	
	Only phototherapy (n = 66)	Bilisphere then phototherapy (n = 12)	IVIG and Bilisphere then phototherapy (n = 22)	
Decrease in TSB				
Mean ± SD.	8.37 ± 1.66	11.20 ± 2.22	9.83 ± 3.15	<0.001*
Median	8.0	11.0	10.25	
Decrease in DSB				
Mean ± SD.	0.74 ± 0.32	0.61 ± 0.33	0.83 ± 0.45	0.233
Median	0.80	0.70	0.80	
Decrease in Urea				
Mean ± SD.	1.89 ± 6.10	3.83 ± 3.46	2.36 ± 2.63	0.191
Median	2.0	3.0	2.0	
Decrease in Creatinine				
Mean ± SD.	0.13 ± 0.13	0.23 ± 0.12	0.16 ± 0.11	0.017*
Median	0.10	0.20	0.20	
Decrease in ALT				
Mean ± SD.	3.52 ± 5.85	4.08 ± 5.78	1.73 ± 5.79	0.366
Median	2.0	5.0	3.0	
Decrease in AST				
Mean ± SD.	2.91 ± 6.74	4.25 ± 7.34	2.64 ± 4.41	0.394
Median	2.0	5.50	3.0	
Decrease in ALP				
Mean ± SD.	8.32 ± 45.08	6.25 ± 55.70	3.32 ± 39.05	0.948
Median	3.50	6.0	5.0	
Decrease in Na^+				
Mean ± SD.	0.46 ± 16.39	2.25 ± 3.65	3.34 ± 4.17	0.177
Median	1.0	2.0	2.0	
Decrease in K^+				
Mean ± SD.	0.63 ± 1.29	0.56 ± 0.57	0.67 ± 0.93	0.654
Median	0.30	0.50	0.50	
Decrease in Ca				
Mean ± SD.	1.32 ± 1.02	1.51 ± 0.55	1.48 ± 0.39	0.009*
Median	1.15	1.50	1.30	

p: p value for Mann Whitney test for association between different categories
*: Statistically significant at $p \leq 0.05$
TSB: total serum bilirubin, DSB: direct serum bilirubin, ALT: alanine aminotransferase, AST: aspartate transaminase, ALP: alkaline phosphatase, Ca: calcium, Na: sodium, K: potassium

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