Effect of Phototherapy on Liver and Kidney Functions during Treatment of Neonatal Hyperbilirubinemia.

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ABSTRACT:

Background: Neonatal hyperbilirubinemia (NH) affects over 80% of premature babies & 60% of full-term babies in the first week of life. There are two forms of neonatal hyperbilirubinemia: conjugated & unconjugated. Unconjugated forms can cause bilirubin encephalopathy & kernicterus in extreme cases, while conjugated forms are thought to be a result of a systemic sickness. Babies born prematurely are at a higher risk of hyperbilirubinemia due to bilirubin-induced brain damage compared to their term counterparts.

Aim and objectives: The study aims to assess the effect of phototherapy on liver enzymes, renal functions, in NH patients before and after phototherapy .

.**Subjects and methods**: This was an observational cross-sectional study that was performed at neonatal intensive care unit (NICU) Al- Hussein university hospital. It included 100 term infants of both sex that received phototherapy for management of neonatal indirect hyperbilirubinemia. When indicated according to Bhutani Nomogram curve.

Result: There is no statistically significant difference was found between group I that treated by conventional phototherapy only and group II that treated by intensive then conventional phototherapy regarding maternal age , ABO blood groups and Rh status maternal comorbidities like gestational HTN or diabetes , gestational age , onset of jaundice. Also Both therapy groups reduced total and direct bilirubin significantly (Paired sample t test, P = 0.000). Group II had a greater total bilirubin reduction than group I (Independent sample t test, P = 0.001). Both therapy groups had significant ALT, AST, ALP ,urea and creatinine reductions (Paired sample t test, P = 0.000).

Conclusion: As regard the effect of Phototherapy on liver enzymes and kidney functions , our results showed a statistically significant reduction in ALT, AST, ALP ,urea and creatinine in both treated groups.

Keywords: neonatal intensive care unit (NICU), Neonatal hyperbilirubinemia (NH), total serum bilirubin (TSB)

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) (**Olusanya et al., 2015).**

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 (**Bhutani et al., 2010).**

Hyperbilirubinemia in preterm neonates is more prevalent than in their term counterparts as immature infants are more prone to bilirubin-induced brain injury (**Watchko, 2018).**

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 **(Wickremasinghe et al., 2016).**

Few side effects of phototherapy were documented such as hyperthermia, dehydration; loose stool feed, intolerance, skin rash, and bronze baby syndrome **(Gregory et al., 2015).**

Phototherapy affects the serum level of liver enzymes of neonates as it decreases the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum alkaline phosphatase (ALP**) (Chatterje & Shinde 2016).**

Some studies about the effect of phototherapy on kidney functions in neonates revealed that phototherapy decreases the levels of serum creatinine and serum urea. **(Santhanam et al., 2015).**

Aim of the work :

The study aims to assess the effect of phototherapy on liver enzymes, renal functions, in NH patients before and after phototherapy.

PATIENTS AND METHODS:

Ethical consideration:

Ethical Scientific Committee of AL-Azhar University approved the study protocol and informed consents were taken from the parents before their enrollment in the study.

All data and results are kept confidential .

Caregivers of the participants have the right to refuse or withdraw from the study at any time .

The authors declare that they have no conflict of interests regarding the study or the publication .

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The study and the publication are self-funded.

Sample size and equation:

The sample size was calculated according to(Keogh et al .2009). with 31% standard deviation + alpha error of 0.10 & prediction of 90% so our sample size was 100 infants

$$\text{Necessary Sample Size} = \frac{(\text{Z-score})2 \times \text{StdDev} \times (1-\text{StdDev})}{(\text{margin of error})2}$$

Inclusion criteria:

All full-term neonates of both sexes at day one and day two of age who will be admitted to the NICU with unconjugated hyperbilirubinemia and receive phototherapy if indicated according to Bhutani curve .

Exclusion criteria:

1- Preterm neonates.

2- Neonates with conjugated hyperbilirubinemia.

3- Neonates with postoperative care after elective surgery.

4- Neonates with any systemic illness such as liver diseases and renal diseases.

5- Neonates who need exchange blood transfusion.

6- Neonates with sepsis.

Study procedure :

This is an observational cross-sectional study that was performed at neonatal intensive care unit (NICU) Al-Hussein university hospital on 100 term infants of both sex that received phototherapy for management of neonatal indirect hyperbilirubinemia during the period from July 2022 to December 2022 . Infants were subdivided into two groups according to Bhutani Nomogram curve.

Group I: infants treated with conventional phototherapy only.

Group II : infants treated with intensive then conventional phototherapy .

All studied neonates were subjected to the following:

I. Careful history taking regarding:

Prenatal history: maternal age, maternal blood group, gestational diabetes, gestational hypertension, pre-eclamsia, anemia during pregnancy, maternal infection and fever.

Natal history: mode of delivery, single or multiple pregnancies, prolonged labor, birth trauma, asphyxia, need for resuscitation.

Postnatal history:

-Onset of jaundice.

-Type of feeding (breast or formula) .

Family history:

-Previous sibling with jaundice in the neonatal period.

-Previous sibling who needed phototherapy.

- positive Family history of hemolytic disorders like G6PD and spherocytosis.

II. Thorough clinical examination:

Complete general examination :

- Vital signs: heart rate, respiratory rate, Temperature, pulse oximetry
- Complexion: Jaundice, pallor or skin rash.
- Presence of cephal-hematoma and bruising.
- Presence of IUGR.

Systemic examination :

including abdominal , Chest, cardiac and neurological examination.

III. **Laboratory investigations including:**

Timing : at admission and after 24 h of admission.

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:

- Complete blood picture (CBC) that was analyzed on Symex –XN-1000 (Symex Europe GmbH, Bornbarch , Germany)
- Erythrocyte sedimentation rate and C-reactive protein by using Roche/Hitachi Cobas C501 System (Roche Diagnosatics International Ltd, Switerland)
- Total & direct bilirubin (according to Bhutani nomogram)
- AST , ALT , Urea and Creatinine by using ELISA technique .

Phototherapy Procedure :

All studied neonates were classified into two groups according to Bhutani nomogram curve .

group I treated with the conventional phototherapy which 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.

Group II treated with the intensive phototherapy by 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.

Statistical Analysis :

Normality of data distribution was evaluated using Shapiro–Wilk test. Description of means and standard deviation for quantitative variables and frequencies and percentage for qualitative variables were calculated using SPSS Version 22.0 (IBM Corp, Armonk, NY).

Chi-square test was used to detect association between categorical variables.

P value less than 0.05 was considered to declare statistical significance.

Data were analysed using Statistical Package for Social Sciences (SPSS) software program.

Data were expressed as number and percentage for qualitative variables and mean + standard deviation (SD) for quantitative one

Results

Table 1. Maternal demo-clinical Characteristics

Variables	Group I	Group II	*P* value
Age, years	30.9±5.38	31.7±5.69	0.471
Less than 25	6(46.2%)	7(53.8%)	0.91
25 – 35	31(51.6%)	29(48.4%)	
More than 35	13(48.2%)	14(51.8%)	
ABO Blood Group			
Group O	29(48.3%)	31(51.7%)	0.88
Group A	11(55%)	9(45%)	
Group B	9(52.9%)	8(47.1%)	
Group AB	1(33.3%)	2(66.7%)	
Rhesus Factor			
Positive	46(50.5%)	45(49.5%)	0.72
Negative	4(44.5%)	5(55.5%)	

Maternal Comorbidities			
Gestational Diabetes	7(43.75%)	9(56.25%)	0.58
Gestational hypertension	6(60%)	4(40%)	0.50
Preeclampsia	3(60%)	2(40%)	0.64
Anaemia	5(45.5%)	6(54.5%)	0.74
Infection	2(40%)	3(60%)	0.64
Mode of Delivery			
Vaginal	34(50%)	34(50%)	1
Caesarean	16(50%)	16(50%)	
Prolonged labour	15(50%)	15(50%)	1

Table (1) : Summarizes the maternal demographic data, including age, ABO blood group, Rh status, and mode of delivery, prolonged labor, and maternal comorbidities with insignificant difference between mothers of both groups .

Table 2. Demo-clinical Characteristics of studied neonates

Variables	Group I	Group II	*P* value
Gestational Age, weeks	37.8±0.31	38.15±0.54	<0.001
Gender			
Male	23(54.7%)	19(45.3%)	0.41
Female	27(46.6%)	31(53.4%)	
Birth Weight, grams	2999.04± 658.07	2988.18± 630.30	0.92
Normal	43(51.2%)	41(48.8%)	0.58
Low	7(43.75%)	9(56.25%)	
Feeding			
Breastfeeding	26(55.3%)	21(44.7%)	0.34
Formula Milk	5(62.5%)	3(37.5%)	
Mixed	19(42.2%)	26(57.8%)	

Onset of Jaundice	2.64±1.43	2.3±1.28	0.213
Risk Factors of Jaundice			
ABO incompatibility	15(45.4%)	18(54.6%)	0.52
Rh incompatibility	5(55.5%)	4(44.6%)	0.72
IUGR	7(43.75%)	9(56.25%)	0.58
Asphyxia	1(33.3%)	2(66.7%)	0.55
Cephalhematoma	3(60%)	2(40%)	0.64
Congenital Hypothyroidism	0(0%)	1(100%)	0.31
Breastfeeding Jaundice	4(40%)	6(60%)	0.50

Table (2): Summarizes the neonatal characteristics, including gestational age, gender, birth weight, feeding pattern, onset of jaundice, and neonatal risk factors of jaundice with insignificant difference between both studied groups ..

Table 3. Effect of Phototherapy on Bilirubin of both studied groups

Variables	**Group I**	**Group II**	***P* value**
Total Bilirubin, mg/dl			
Pretreatment	24.8 ± 2.9	25.1 ± 2.8	0.803
Posttreatment	16.9 ± 3.1	14.8 ± 2.9	0.001
P value	0.000	0.000	
Direct Bilirubin, mg/dl			
Pretreatment	1.25 ± 0.41	1.24 ± 0.42	0.867
Posttreatment	0.68 ± 0.46	0.69 ± 0.44	0.894
P value	0.000	0.000	

Table (3) : No statistically significant differences were observed between both studied groups regarding pretreatment total and direct bilirubin while a statistically significant reduction in total and direct bilirubin was observed in both treatment groups . However, more significant reduction was found in group II compared to group I in total bilirubin levels .

Table 4. Effect of Phototherapy on Liver Enzymes of both studied groups			
Variables	**Group I**	**Group II**	***P* value**
ALT, U/L			
Pretreatment	33.5 ± 5.8	32.8 ± 6	0.570
Posttreatment	26 ± 6.1	25.3 ± 6.4	0.537
P value	0.000	0.000	
AST, U/L			
Pretreatment	31.1 ± 6.1	30.8 ± 5	0.843
Posttreatment	23.3 ± 6.5	23.3 ± 4.9	0.959
P value	0.000	0.000	
ALP, U/L			
Pretreatment	250 ± 30	252 ± 29	0.931
Posttreatment	149 ± 29	150 ± 31	0.958
P value	0.000	0.000	

Table (4) : No statistically significant differences were observed between groups regarding pretreatment and posttreatment liver enzymes. A statistically significant reduction in ALT, AST, and ALP was observed in both treatment groups.

Table 5. Effect of Phototherapy on Kidney Functions of both studied groups			
Variables	**Group I**	**Group II**	***P* value**
Urea, mg/dl			
Pretreatment	18 ± 4.2	17.1 ± 4.4	0.310
Posttreatment	14.6 ± 4.2	13.7 ± 4.5	0.311
P value	0.000	0.000	
Creatinine, mg/dl			
Pretreatment	0.68 ± 0.11	0.73 ± 0.12	0.154
Posttreatment	0.42 ± 0.15	0.49 ± 0.15	0.115
P value	0.000	0.000	

Table (5) : No statistically significant differences were observed between groups regarding pretreatment and posttreatment kidney functions . A statistically significant reduction in urea and creatinine was observed in both treatment groups .

DISCUSSION

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**) (Olusanya et al., 2015**). 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 if it is severe **(Bhutani et al., 2010).**

Hyperbilirubinemia in preterm neonates is more prevalent than in their term counterparts as immature infants are more prone to bilirubininduced brain injury **(Watchko et al., 2018).**

This study aimed to assess the effect of phototherapy on liver enzymes, renal functions, in NH patients before and after phototherapy.

This study conducted on 100 term infants of both sex that will receive phototherapy for management of neonatal indirect hyperbilirubinemia according to Bhutani nomogram curve **(Bhutani et al., 2010)**

As regard the Democlinical characteristics of studied maternal and neonatal cases in our study it showed that ABO incompatibility was reported in 33%, Rh incompatibility in 9%, IUGR in 16%, neonatal asphyxia in 3%, cephalhematoma in 5%, and breastfeeding jaundice in 10%. Comparing the incidence of neonatal risk factors between both groups there was no statistically significant differences (P > 0.05).

The most common causes of pathologic indirect hyperbilirubinemia were hemolytic anemia (12 ABO and 3 Rh incompatibility) in 15 (25%) patients, neonatal dehydration/feeding problems in 23 (38%), cephalic hematoma in 11 (18.3%), and late preterm delivery in 10 (16.6%). Four patients had urinary tract infections, 2 had maternal diabetes, 2 had suspected sepsis, and 1 had polycythemia. Investigations were normal in six (10%) patients and failed to identify any pathologic cause of jaundice. Ten (16.6%) patients had multiple risk factors **(TUFEKCI et al., 2023)**.

In current study, the mean maternal age was 31.3 ± 5.5 years, ranging from 20 to 40 years, the mean maternal age was 30.9 ± 5.4 years in group I and 31.7 ± 5.7 in group II. No statistically significant difference was found between groups regarding maternal age.

Our results agree with **YU et al. (2021)** who found that the control group received standard phototherapy, and the experimental group received blue phototherapy. The control group had 57 male children and 63 female children. No marked difference was identified by comparing the gestational age, BMI , breastfeeding, gender and place of residence between the two groups of children with jaundice (P>0.05).

Our results agree with **TUFEKCI et al. (2023)** who found that Sixty newborns born between 35 and 42 weeks of gestation and treated with intensive phototherapy were included in the study had no statistically significant differences in terms of mean gestational week, birth weight, day of initiation of phototherapy, gender, or method of delivery.

Our results agree with **SHANKAR et al. (2015)** who found that no statistically significant difference was found between groups regarding onset of jaundice , feeding pattern , birth weight or gender.

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.,**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).

Our results showed that there was no statistically significant differences were observed between groups regarding pretreatment total and direct bilirubin (*P* > 0.05). A statistically significant reduction in total and direct bilirubin was observed in both treated groups (*P* = 0.000). However, more significant reduction was found in group II compared to group I in total bilirubin levels (*P* = 0.001).

Our results compared with **TUFEKCI et al. (2023)** who found that Direct serum bilirubin levels before and after treatment were higher in the conventional phototherapy group than in the intensive phototherapy group (p=0.02, p=00.1) .

Our results agree with **YU et al. (2021)** who found that the control group who received conventional phototherapy, and the experimental group who received blue phototherapy. The control group had 57 male newborn and 63 female newborn; serum total bilirubin levels of the control group before and after treatment were (265.68±34.26) μmol/L and (180.32±34.16) μmol/L, respectively. The serum total bilirubin levels before and after treatment in the experimental group were (271.36±26.00) μmol/L and (115.34±45.87) μmol/L. A significant difference in serum total bilirubin levels before and after treatment was seen in the control group (t=19.327, **P<0.01). The serum total bilirubin levels of jaundiced children in the experimental group were significantly different before and after treatment (t=32.414, **P<0.01). There was a significant difference in serum total bilirubin levels between the control group and the experimental group after treatment (t=12.446, **P<0.01)

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 **(Santhanam et al., 2015).**

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., (2018)** 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, our results not agree with **Asl et al., (2016)** who 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).

Our results agree with **Abohussein et al. (2022)** who found that mean (± SD) of serum creatinine and urea levels showed a statistically significant decrease after phototherapy when compared to those before phototherapy (p <0.001).

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) **(Chatterjea et al.,2017)**.

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.,(2018)** 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).

Our results showed that no statistically significant differences were observed between groups regarding pretreatment and posttreatment liver enzymes (P > 0.05). A statistically significant reduction in ALT, AST, and ALP was observed in both treatment groups (P = 0.000).

Our results agree with with **Abohussein et al. (2022)** who found that AST and ALT levels showed statistically significant decrease when compared before to those after phototherapy with p value <.001 while ALP level showed insignificant decrease when compared before and after phototherapy.

Our results agree with **SUNEJA et al. (2018)** who found that Levels of hepatic enzymes namely AST, ALP and LDH were also elevated significantly in the pre phototherapy group which declined significantly after phototherapy (p<0.05).

Conclusion :

The present study assessed the effect of phototherapy on liver enzymes, renal functions, in NH patients before and after phototherapy. our results showed a statistically significant reduction in ALT, AST, ALP, urea and creatinine in both treated groups probably approaching the normal values as liver and kidney starts resuming the normal functions .

Recommendations :

- ❖ Our study suggest continuous observation and close monitoring of liver enzymes and kidney functions in order to prevent related complications.
- ❖ Further studies with larger sample size are needed to confirm the current results.
- ❖ infants receiving phototherapy are at risk to develop electrolyte imbalance after phototherapy so close monitoring is recommended.

Limitations:

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 and short time follow up period .

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