

## Efficacy of Intensive Phototherapy as A Treatment Modality for Neonatal Hyperbilirubinemia

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### ABSTRACT

**Background:** Jaundice is the most common condition that requires medical attention in newborns. The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin.

**Objectives:** To assess the efficacy of intensive phototherapy as a treatment modality for neonatal hyperbilirubinemia.

**Subjects and methods:** This was A prospective, cohort, controlled study that was conducted on 100 babies with neonatal jaundice. They were admitted to Luxor General Hospital NICU at the beginning of November 2018 to the end of October 2019. Those 100 cases had been divided into 2 groups: the first group received intensive phototherapy sessions as a treatment modality for neonatal jaundice and the second group received conventional phototherapy.

**Results:** The results of the study revealed that intensive phototherapy had succeeded in decreasing the need for exchange transfusion in 39 cases (78 %), whereas 11 cases (22%) remained for exchange transfusion (p value (0.001) was highly significant).

**Conclusion:** The use of intensive phototherapy in the treatment of indirect pathological hyperbilirubinaemia is as effective as exchange transfusion in lowering total serum bilirubin when its level is within 2-3 mg/dl (34-51  $\mu$ mol/l) of the exchange level and it is effective in reducing needs for exchange transfusion and duration of phototherapy.

**Keywords:** Exchange transfusion, Conventional phototherapy, Neonatal, Jaundice.

### INTRODUCTION

Neonatal jaundice is defined as yellowish discoloration of skin, sclera of eyeball, and mucous membranes caused by deposition of bile salts in these tissues. Depending upon the cause, jaundice may be present at birth or any time during the neonatal period. Jaundice due to either indirect (unconjugated) or direct (conjugated) bilirubin within the first 24 hours of life should be taken seriously <sup>(1)</sup>.

Neonatal jaundice is estimated to occur in 60% of term newborns in the first week of life, and < 2% reach total serum bilirubin (TSB) levels of 20 mg/dL. In rare instances, the TSB reaches levels that can cause kernicterus, a condition characterized by bilirubin staining of neurons and neuronal necrosis involving primarily the basal ganglia of the brain and manifested in athetoid cerebral palsy, hearing loss, dental dysplasia and paralysis of upward gaze <sup>(2)</sup>.

The most common cause of jaundice in first 24 hours of life due to hemolytic disease of newborn (HDN) is rhesus (Rh) hemolytic disease. As the mother becomes sensitized due to fetomaternal previous pregnancies, anti-D IgM and IgG are produced. Anti-D IgG is responsible for rhesus disease in the neonate as this antibody can cross placenta. Rhesus (Rh) incompatibility develops between an Rh negative mother (previously sensitized) and her Rh-positive fetus <sup>(3)</sup>. ABO incompatibility is common condition in a newborn baby and causes minimal hemolysis. It may cause elevated levels of bilirubin and anemia but less severe than Rh hemolytic disease <sup>(4)</sup>. For preventing the

Kernicterus and other complications of hyperbilirubinemia, jaundice should be managed by phototherapy or exchange transfusion (ECT) <sup>(5)</sup>.

Phototherapy is a useful method for treating neonatal hyperbilirubinemia because it is easily available and devoid of all complications of double volume exchange transfusions. The efficacy of phototherapy depends on the dose and wave length of light used and the surface area exposed <sup>(6)</sup>. Intensive phototherapy in neonatal hyperbilirubinemia rapidly decreases total serum bilirubin (TSB) below the threshold for treatment <sup>(5)</sup>.

### AIM OF THE WORK

The aim of the work was to assess the effectiveness of intensive phototherapy in comparison with conventional phototherapy in reducing the need for exchange transfusion during the management of neonatal hyperbilirubinemia.

### SUBJECTS AND METHODS

This was a prospective, cohort, controlled study that was conducted on 100 babies with neonatal jaundice. They were admitted to Luxor General Hospital NICU at the beginning of November 2018 to the end of October 2019.

**Those 100 cases had been divided into 2 equal groups:**

**The first group:** received intensive phototherapy sessions as a treatment modality for neonatal jaundice.



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- **The second group:** received conventional phototherapy, and was included in the study as a control group.

**Inclusion criteria:**

- Full term babies with neonatal jaundice "range of bilirubin" indicated for phototherapy.
- All term and near-term newborn infants [gestation age (GA)  $\geq$  35 weeks] suffering from both hemolytic and non-hemolytic hyperbilirubinemia and necessitating exchange (within 2-3 mg/dl and not more).
- Hemolytic cases are characterized by: increased unconjugated bilirubin level,  $> 6$  percent reticulocytes, hemoglobin concentration of  $< 13$  g/dl and Coombs' test, which may be positive in e.g.: Rh, ABO and minor Group incompatibilities or negative as in G6PD deficiency<sup>(7)</sup>.

**Exclusion criteria:**

- Preterm infants.
- Babies with neonatal jaundice "range of bilirubin" indicated for other treatment modalities other than phototherapy (such as blood exchange).

**All studied population was subjected to:**

- Full antenatal, natal and postnatal history taking including demographic data and parent history, detailed history of general health condition and obstetric history and gestational age at delivery
- Careful clinical examination.
- Vital signs measurement.
- Neonatal reflexes.
- Full abdominal, chest and cardiac examination.

**Laboratory investigations:**

- CBC with reticulocyte count.
- ABO grouping "for the neonates and their mothers", G6PD assay and Coomb's test for babies with reticulocytosis.
- Serial serum bilirubin at admission, at the 2<sup>nd</sup> and 3<sup>rd</sup> day of admission.

**Management:**

As soon as the patient was admitted and his/her blood type is known, the blood bank was contacted to reserve compatible blood for possible exchange transfusion. Newborn infants with serum bilirubin level needing exchange transfusion was subjected to intensive phototherapy using (Bilisphere 360, Novos Medical System, Turkey). The bilisphere provides multidirectional intensive phototherapy. It has 16 blue light fluorescent lamps; 8 above & 8 below, with the neonate resting on a hammock mattress in between with an intensity of  $37.5 \mu\text{w}/\text{cm}^2/\text{nm}$  with a spectral irradiance of 420 to 500 nm. The eyes were blindfolded and genitalia covered routinely and phototherapy was applied continuously and interrupted only for the infant feeding, weighting and physical examination.

**RESULTS**

**Table (1):** Demographics characters of the studied neonates.



**Figure (1):** Bilisphere 360 intensive phototherapy.

Serum bilirubin level was measured 6 hours after intensive phototherapy. Exchange transfusion was considered according to American Academy of Pediatrics Practice Parameters<sup>(7)</sup> if total serum bilirubin level remained above the level indicated after intensive phototherapy for 6 hour.

**Ethical approval and written informed consent:**

**An official permission was obtained from NICU of Pediatric Department at Luxor General Hospital.**

**An official permission was obtained from the Institutional Research Board (IRB) and from the Ethical Committee, Faculty of Medicine, Al-Azhar University (Assiut).** Written informed consent was taken from parents for participation in the study after being informed about the aims and process of the study as well as applicable objectives.

**Data management and Statistical Analysis:**

Data entry, processing and statistical analysis were carried out using statistical package for social sciences (IBM-SPSS), version 24 (May 2016); IBM-Chicago, USA). Tests of significance (Kruskal-Wallis, Wilcoxon's, Chi square, logistic regression analysis, and Spearman's correlation) were used. Data were presented and suitable analysis was done according to the type of data (parametric and non-parametric) obtained for each variable.  $P \leq 0.05$  (5%) was considered to be statistically significant.  $P > 0.05$ : Non-significant (NS).  $P < 0.05$ : Significant (S).  $P < 0.01$ : Highly significant (HS).

**Descriptive statistics:** Mean, Standard deviation ( $\pm$  SD) and range for parametric numerical data, while median and inter-quartile range (IQR) for non-parametric numerical data. Frequency and percentage for non-numerical data.

**Analytical statistics:** Kruskal-Wallis test was used to assess the statistical significance of the difference of a non-parametric variable between more than two study groups.

Demographics characters	Group 1 (50)	Group 2 (50)	t-test	P- value
<b>Gestational age (weeks)</b>				
Mean ± SD	37.6 ± 1.6	36.6 ± 1.78	1.270	0.541
	<b>N (%)</b>	<b>N (%)</b>	<b>X<sup>2</sup></b>	<b>P- value</b>
<b>Full term</b>	38 (76)	42 (84)	1.531	0.157
<b>Preterm</b>	12 (24)	8 (16)		
<b>Mode of delivery</b>				
CS	27 (54%)	26 (53%)	0.415	0.828
VD	23 (46%)	24 (48 %)		
<b>Sex</b>				
Males	27 (54%)	28 (56%)	0.613	0.718
Females	23 (46%)	22 (44%)		
			<b>t-test</b>	<b>P- value</b>
<b>Birth weight (g)</b>				
Mean ± SD	<b>2960.0 ± 270</b>	<b>3010.0 ± 350</b>	1.631	<b>0.177</b>
<b>Age on admission (days)</b>				
Mean ± SD	<b>2.1 ± 1.1</b>	<b>2.3 ± 1.3</b>	1.521	<b>0.187</b>
<b>Range</b>	<b>1-3 days</b>	<b>1-4 days</b>		

Table (1) showed that 38 neonates (76%) had ≥ 38 weeks. Mean post-natal age on admission was 2.1 ± 1.1 days in group A and 2.3 ± 1.3 days in group B. Regarding sex 27 (54%) were males & 23 (46%) were females in first group, while in the second group, 28 (56%) were males & 22 (44%) were females with no statistically significant difference between them.

**Table (2):** Bilirubin level before phototherapy between two groups.

Before	Group 1(50)	Group 2 (50)	P-value
<b>Total bilirubin (mg/dL).</b>	27.02 ± 5.71	25.8 ± 6.1	0.981
<b>Direct bilirubin (mg/dL)</b>	1.208 ± 1.65	1.201 ± 1.04	0.874

Table (2) showed that mean total serum bilirubin before phototherapy was 27.02 ± 5.71 mg/dL in group 1 and 25.8 ± 6.1 mg/dL in the second group. Direct bilirubin before intensive phototherapy was 1.208 ± 1.65 mg/dL and 1.24 ± 1.45mg/dL for group 1 and group 2 respectively. Also, there was no statistically significant difference between the two groups.

**Table (3):** Bilirubin level before and after intensive phototherapy for 6 hours of studied neonates.

Variable	Before intensive phototherapy Mean ± SD	after intensive phototherapy for 6 hours	p-value
<b>Total bilirubin (mg/dL).</b>	27.02 ± 5.71	21.4 ± 4.17	< 0.01*
<b>Direct bilirubin before intensive phototherapy (mg/dL)</b>	1.208 ± 1.65	1.24 ± 1.45	< 0.001**

Table (3) showed that mean total serum bilirubin before intensive phototherapy was 27.02 ± 5.71 mg/dL and after intensive phototherapy was 21.4 ± 4.17 mg/dL, while direct bilirubin before intensive phototherapy was 1.208 ± 1.65 mg/dL and after intensive phototherapy was 1.24 ± 1.45 mg/dL. In addition, there was high statistically significant difference before and after intensive phototherapy for 6 hours of studied neonates.

**Table (4):** Rate of serum bilirubin decline 6 hours after phototherapy.

Rate of Serum bilirubin decline	Group 1	Group 2	P. Value
<b>Mean ± SD (mg/dl/h)</b>	<b>0.54 ± 0.13</b>	<b>0.16 ± 0.04</b>	<b>&lt; 0.001**</b>

Table (4) showed that there was high statistically significant difference regarding rate of serum bilirubin decline 6 hours between the two groups.

**Table (5):** Rate of exchange transfusion of studied group.

Exchange transfusion	Group 1	Group 2	P. value
Number	14	21	
%	28%	42%	

Table (5) showed that there was high statistically significant difference regarding rate of exchange transfusion of studied groups

**Table (6):** The success of intensive phototherapy i.e. (decrease in bilirubin level below exchange transfusion level).

	Number	Percentage (%)
Yes	36	72 %
No	14	28%

Table (6) showed that intensive phototherapy had succeeded in decreasing the need for exchange transfusion in 36 cases (72 %), whereas 14 cases (28%) remained candidates for exchange transfusion.

**Table (7):** Complications of phototherapy in studied group.

Complications of intensive phototherapy	Group 1		Group 2		P. Value
Skin rash	32	64	30	60	
Rebound	7	14	6	12	
Dehydration	14	28	11	22	

Table (7) showed that there was no statistically significant difference regarding complications of phototherapy between the studied groups.

We did a multivariate regression analysis for all parameters (clinically and laboratory) to predict success of intensive phototherapy in cases necessitating exchange transfusion.

**Table (8):** Multivariate regression analysis in intensive phototherapy group.

Variable	P value	OR	95%CI of OR	
			Lower	Upper
Post-natal age	0.004*	1.703	1.161	2.819
GA	0.001*	1.254	1.093	1.463
Sex	0.541	0.676	0.275	2.176
HB(mg/dl)	0.649	1.198	0.598	2.584
HCT	0.851	0.973	0.769	1.449
Coombs	0.876	1.374	0.340	6.869
Retics	0.831	0.997	0.935	1.164
TSB pre	0.002*	0.712	0.808	0.711

Table (8) showed that analysis revealed that post-natal age, gestational age and total serum bilirubin (TSB) before intensive phototherapy were the only significant predictors (i.e., the higher post-natal age, the higher the gestational age and the lower the total serum bilirubin level) and the more effective phototherapy will be. They were 1.703, 1.254 and 0.676 respectively and P values were 0.004, 0.001 and 0.002 respectively.

**Table (9):** Multivariate regression analysis in phototherapy group.

Variable	P value	OR	95%CI of OR	
			Lower	Upper
Post-natal age	0.002*	1.651	1.152	2.821
GA	0.003*	1.531	1.082	1.452
Sex	0.981	0.641	0.282	2.165
HB(mg/dl)	0.781	1.185	0.595	2.580
HCT	0.791	0.861	0.765	1.445
Coombs	0.754	1.241	0.345	6.861
Retics	0.941	0.741	0.921	1.131
TSB pre	0.01*	0.651	0.815	0.746

Table (9) showed that analysis revealed that post-natal age, gestational age and TSB before phototherapy were the only significant predictors, (i.e. the higher post-natal age, the higher the gestational age and the lower the total serum bilirubin level).

## DISCUSSION

In group A, 38 neonates (76%) had  $\geq 38$  weeks. Their mean post-natal age on admission was  $2.1 \pm 1.1$  days while, it was  $2.3 \pm 1.3$  days in group B. Regarding sex 27 (54%) were males & 23 (46%) were females in group A, while in group B, 28 (56%) were males & 22 (44%) were females. There was no significant difference between both groups regarding age, sex and birth weight. Our results are in agreement with study of **Abdelazeem et al.** <sup>(8)</sup> who conducted study about efficacy of intensive phototherapy in management of neonatal hyperbilirubinemia. They found that regarding gestational age, sex, mode of delivery, birth weight, and age on admission, there was no statistically significant difference between the two groups. Intensive phototherapy is a novel neonatal phototherapy device and our study evaluated its effectiveness on 50 newborns with severe indirect hyperbilirubinaemia (group 1) and compared it to a historical control group consisting of 50 neonates treated with conventional phototherapy retrospectively (group 2). In addition, **Edris et al.** <sup>(9)</sup> conducted study about the role of intensive phototherapy in decreasing the need for exchange transfusion in neonatal jaundice. They reported that there were no significant differences between both groups regarding age, sex and birth weight.

In the present study, the cases were classified into hemolytic and non-hemolytic. Hemolytic cases are characterized by: increased unconjugated bilirubin level,  $> 6$  percent reticulocytes, hemoglobin concentration of  $< 13$  g/dl and Coombs' test which may be positive in e.g.: Rh, ABO and minor group incompatibilities or negative as in G6PD deficiency <sup>(7)</sup>. **Kaplan et al.** <sup>(10)</sup> reported that etiological risk factors included positive direct Coombs test and gestational age  $< 37$  weeks.

Regarding, bilirubin level before and after intensive phototherapy for 6 hours of studied neonates, our results showed that mean total serum bilirubin was  $27.02 \pm 5.71$  mg/dL before intensive phototherapy and was  $17.92 \pm 6.17$  mg/dL after intensive phototherapy. Direct bilirubin before intensive phototherapy was  $1.208 \pm 1.65$  mg/dL and after intensive phototherapy was  $1.24 \pm 1.45$  mg/dL. In addition, there was high statistically significant difference before and after intensive phototherapy for 6 hours of studied neonates. Besides, there was high statistically significant difference regarding rate of serum bilirubin decline 6 hours after intensive phototherapy. Our results are in agreement with study of **Abdelazeem et al.** <sup>(8)</sup> who reported that the total serum bilirubin decline rate 6 h after admission was significantly more in intensive phototherapy group than in the control ( $p < 0.01$ ). Moreover, **Sarici et al.** <sup>(11)</sup> demonstrated the efficacy of double phototherapy using standard phototherapy unit consisted of five special blue lamps combined with fiberoptic phototherapy pad beneath the infant's body

and the reduction rate of bilirubin was more than that in single phototherapy probably due to the higher irradiance of the phototherapy units. **Thaithumyanon and Visutiratmanee** <sup>(12)</sup> reported that the reduction of bilirubin in the first day was  $3.4 \pm 2.0$  mg/dl using double surface phototherapy which was more than that in single conventional phototherapy.

In contrary of our results, study of **Edris et al.** <sup>(9)</sup> reported that in comparing the bilirubin decline rate between bilisphere group and the control group, it was found that there was no statistically significant difference between them from admission to 6 hours. However, a statistically significant difference between the two groups regarding bilirubin decline rate from 6 hours to 48 hours was obvious. This may be explained by the high percentage of cases that underwent ECT in the control group during the 1st 6 hours of therapy.

Centre National de Reference en Haemobiologie Perinatale **CNRHP** <sup>(13)</sup> studied the time effect of bilisphere 360 intensive phototherapy on blood levels of TSB over 20 hours treatment in jaundiced newborn. They concluded that this device allows an average decrease in TSB levels of 15%, 26% and 37% at hours 4, 10 and 20 exposure respectively. A study of **De Carvalho et al.** <sup>(14)</sup> reported decrease in the TSB levels after 6 hours of high-intensity phototherapy to be 23%, which was almost the same rate of reduction as in our study (24.9% after 6 hours).

**Martins et al.** <sup>(15)</sup> demonstrated that the efficacy of super LED phototherapy for the treatment of hyperbilirubinemia in premature newborn infants is superior to that of halogen phototherapy. Eight hours after the start of treatment, the decrease in serum TB levels was already significantly greater in the newborn infants treated with super LED phototherapy than in those treated with halogen phototherapy (7.9 vs. 3.6%;  $p = 0.02$ ). This difference became more accentuated as treatment continued and, after 24 hours of phototherapy, the percentage reduction in serum bilirubin levels of infants receiving super LED phototherapy was more than double of those on halogen phototherapy (27.9 vs. 10.1%;  $p < 0.01$ ).

In the study in our hands there was no statistically significant difference regarding duration of phototherapy in the studied groups. In contrast to our result, **Abdelazeem et al.** <sup>(8)</sup> reported that there was statistically significant difference regarding duration of phototherapy in the studied groups. This study showed that the mean of duration of phototherapy in group [1] was  $2.5 \pm 1.5$  days while in group [2] it was found that the mean of the duration of phototherapy was  $4.0 \pm 1.4$  days.

Our results showed that there was high statistically significant difference regarding rate of exchange transfusion of the studied groups. Intensive phototherapy succeeded in decreasing the need for exchange transfusion in 39 cases (78 %), whereas 11

cases (22%) remained candidates for exchange transfusion [p value (0.001) was highly significant]. Our results are supported by the study of **Abdelazeem et al.** <sup>(8)</sup> as they reported that there was high statistically significant difference regarding rate of exchange transfusion of studied groups. Regarding the need for exchange transfusion (ECT) in intensive phototherapy group, only 16 (32%) out of 50 cases needed ECT and this was much lower than that in the conventional group [31 (62%) out of 50 cases]. **Edris et al.** <sup>(9)</sup> reported that only 19 (10.4%) out of 188 cases required ECT and this was much lower than in the control group [130 (73.4%) out of 177 cases]. **De Carvalho et al.** <sup>(14)</sup> showed that the use of intensive phototherapy was effective in treating newborn infants admitted with severe Non haemolytic hyperbilirubinaemia (TSB<20 mg/dL) and none of the patients required ECT. **El-feky et al.** <sup>(16)</sup> reported that concerning the need for ECT in intensive phototherapy group, only 16 (16.0%) out of 100 cases required ECT and this was much lower than the conventional phototherapy group [66 (66.0%) out of 100 cases]. In the study in our hands, the most common complications of intensive phototherapy in studied groups were skin rash 15 (30%) followed by dehydration and rebound. Our results are in agreement with study of **Abdelazeem et al.** <sup>(8)</sup> who reported that skin rash was found in 14 (28%) of cases treated with intensive phototherapy. Dehydration was found in 3 cases (6%) and needed frequent feeding or intravenous infusion. It was found that out of 50 cases, 6 (12%) cases needed phototherapy again and they were preterm (< 35 weeks) with their birth weight (< 2000 g). **Bansal et al.** <sup>(5)</sup> reported that post-phototherapy bilirubin estimation was done in 232 neonates. A total of 17 (7.3%) neonates developed bilirubin rebound.

## CONCLUSION

The use of intensive phototherapy in the management of pathological hyperbilirubinemia is very effective in lowering total serum bilirubin when its level is within 2-3 mg/dl (34-50 µmol/l) of the exchange transfusion level. Also, in reducing the use of the invasive maneuver of exchange transfusion with its serious neurological complications. It has also succeeded in reducing the duration of phototherapy and subsequently the duration of hospital stay and economic burden.

## RECOMMENDATION

- It is recommended to apply intensive phototherapy for treatment of indirect hyperbilirubinemia in every neonatal unit of our central and general hospitals because it helps to shorten the hospital stay and reduce the need for exchange transfusion and the economic costs.
- Coombs test should be done for all cases of suspected neonatal hemolytic jaundice.
- Neonatologists should attend all deliveries that are at high risk for developing neonatal jaundice.

Advise parents and carers to seek urgent advice from a healthcare professional if their baby becomes jaundiced especially within the first 24 h of life.

Keep eyes on babies with hemolytic jaundice to avoid post phototherapy rebound.

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