The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2742-2745

Assessment of Total Serum Bilirubin Level for Neonatal Jaundice after Intensive Phototherapy

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ABSTRACT

Background: Intensive phototherapy in neonatal hyperbilirubinemia rapidly decreases serum total bilirubin (STB) below the threshold for treatment. Intensive phototherapy implies the use of high levels of irradiance to as much of infant's surface area as possible.

Objectives: This study aimed to assess the total serum bilirubin level for neonatal jaundice after intensive phototherapy.

Patients and Methods: This study was conducted on 200 newborns with neonatal jaundice who were admitted to the NICU of Benha Teaching Hospital, Egypt, requiring double surface, and intensive phototherapy treatment during the period of the study from March 2020 till December 2020.

Results: Among the 200 neonates with hyperbilirubinemia, the mean STB measurement at presentation was 12.12 ± 4.6 mg/dl, after phototherapy the mean of STB was 8.4 ± 3.39 mg/dl. After stoppage of phototherapy by 24± 6 hours the mean was 11.34 ± 3.17 mg/dl. The mean STB after phototherapy was 8.4 ± 3.39 mg/dl, while after stoppage by 24 ± 6 hours the mean was 11.34 ± 3.17 mg/dl. There was significant difference between the three measurements regarding present serum total bilirubin, after phototherapy & after stoppage by 24 ± 6 hours (with $P < 0.001$).

Conclusion: Intensive phototherapy in neonatal hyperbilirubinemia rapidly decreases serum total bilirubin (STB) below the threshold for treatment. However, underlying alteration in bilirubin production and excretion may persist and cause bilirubin rebound after stopping phototherapy.

Keywords: NICU, Serum bilirubin, Neonatal jaundice, Phototherapy.

INTRODUCTION

Neonatal jaundice or neonatal hyperbilirubinemia results from elevated total serum bilirubin (TSB) and clinically manifests as yellowish discoloration of the skin, sclera, and mucous membrane. The term jaundice is derived from the French word "jaune", which means yellow. It is the most commonly encountered medical problem in the first two weeks of life and a common cause of readmission to the hospital after birth. Approximately 60% of term and 80% of preterm newborns develop clinical jaundice in the first week after birth **(1).**

In most cases, it is a mild, transient, and self-limiting condition and resolves without treatment referred to as "physiological jaundice." However, it is imperative to distinguish this from a more severe form called "pathological jaundice." Failure to identify and treat this entity may result in bilirubin encephalopathy and associated neurological sequelae. Unconjugated hyperbilirubinemia (UHB) is the cause of clinical jaundice in most neonates, but some infants with jaundice have conjugated hyperbilirubinemia (CHB), which is always pathological and signifies an underlying medical or surgical cause **(2).**

The etiology of pathological UHB and CHB is vast and varied. Preterm infants and those born with congenital enzyme deficiencies are particularly prone to the harmful effects of unconjugated bilirubin on the central nervous system. Severe hyperbilirubinemia can cause bilirubin-induced neurological dysfunction (BIND), which if not treated adequately, may lead to acute and chronic bilirubin encephalopathy **(3).** Phototherapy and exchange transfusions are the mainstay of treatment of UHB, and a subset of patients also respond to intravenous immunoglobulin (IVIG). Treatment of CHB is more complex and depends mainly on the etiology. Despite advances in care and management of hyperbilirubinemia, it remains a significant cause of morbidity and mortality **(4).**

Intensive phototherapy in neonatal hyperbilirubinemia rapidly decreases serum total bilirubin (STB) below the threshold for treatment. Intensive phototherapy implies the use of high levels of irradiance to as much of infant's surface area as possible **(5).** Risk factors for phototherapy neonatal bilirubin rebound include a positive Coombs test, pre-maturity, and treatment at or before 72 hours**.** This study included neonates born at term or pre-term gestation. Those with or without positive Coombs test have concluded that significant bilirubin rebound is rare. Therefore, measurement of bilirubin rebound is not needed. In addition, routine measurement of bilirubin rebound may increase workload to expense and prolong the hospital stay **(6).**

This study aimed to determine the incidence and magnitude of post phototherapy neonatal serum total bilirubin (STB) rebound needing reinstitution of phototherapy.

PATIENTS AND METHODS

This study was conducted on 200 neonatal jaundice who were admitted to the NICU of Benha Teaching Hospital, requiring double surface, and intensive phototherapy treatment during the period of the study from March 2020 till December 2020.

Inclusion criteria: Neonatal hyperbilirubinemia.

Exclusion criteria: Neonatal hyperbilirubinemia with cholestasis or obstructive jaundice, and or due to RH incompatibility.

Received: 10/01/2022
Accepted: 09/03/2022

All patients included in this study were subjected to full history taking (demographic data**,** medical record, birth date, admission date & discharge date), age at presentation, gestational age, sex, maternal drugs, types of feeding and thorough clinical examination.

Measurement of Serum Total Bilirubin: The role of the laboratory in the assessment of hyperbilirubinemia is to provide accurate bilirubin results. A number of methods are available on clinical analyzers [(7)], the Diazo method used for measurement of total bilirubin and its various forms: unconjugated bilirubin and conjugated bilirubin [(8)].

ABO blood grouping system: According to the ABO blood group system there are four different kinds of blood groups: A, B, AB or O (null). Blood typing for the mother's & the jaundiced infant was done for each case [(9)].

Direct Coombs test: The Coombs test is frequently used in the evaluation of jaundiced infant. This test assays for antibody on the RBCs' membrane. A positive result indicates that antibodies are attached to the RBCs, placing it at risk for immune-mediated destruction [(10)].

Reticulocyte count: By using Brilliant Cresyl Blue reagent for counting reticulocyte in 5 fields of 200 RBCs. The normal range depends on the level of hemoglobin, and the range is higher if there is low hemoglobin due to bleeding or red cell destruction in the jaundiced infants [(11)].

Peripheral Blood Smear (PBS): PBS was studied for each case for detection of abnormal red blood cell morphology. The study of the red cell morphology was through the appearance of the erythrocytes on a Wright Giemsa stained smear [(12)].

Serum bilirubin rebound (SBR): SBR is measured 24 ± 6 hrs after stopping phototherapy according to the standard guidelines used for starting and stopping phototherapy [(13)].

Treatment: Including double surface, and intensive phototherapy for 12 hours' treatment to the preterm & term neonates, and at birth with hyperbilirubinemia respectively according to the American Academy of Pediatrics. Significant bilirubin rebound was defined as post-phototherapy bilirubin level needing re-institution of phototherapy [(14)].

Ethical consent:

An approval of the study was obtained from Benha Teaching Hospital Academic and Ethical Committee. Informed written consent was obtained from the parent of every participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Data collected throughout history, basic clinical examination, and outcome measures were coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 25.0) (Armonk, NY: IBM Corp, 2018). Descriptive statistics included Percentage (%), mean and SD. Analytical statistics included chi-square test (χ^2) Student's t-test and Mann-Whitney test (U test). P value ≤ 0.05 was considered statistically significant.

RESULTS

Table (1) showed that the mean GA of cases of neonatal hyperbilirubinemia without SBR (182 cases) was 37.09 ± 3.381, while in cases with SBR (18 cases) mean GA was 37.11 ± 3.689 weeks with no significant difference between the two groups (P > 0.05). The mean age at presentation in cases without SBR (182 cases) was 60.53 ± 44.375 while in cases with SBR (18 cases) it was 52.56 ± 47.384 hours with no significant difference between the two groups (P >0.05).

Table (1): Gestational age among cases with SBR and cases without SBR

		N	Mean ±SD	t	p
Gestational Age (weeks)	No SBR	182	37.09±3.381	0.1	> 0.05
	SBR	18	37.11±3.689		
Presentation AGE in hours	No SBR	182	60.53±44.375	t	p
	SBR	18	52.56±47.384	0.5	>0.05

Table (2) showed that out of 182 cases without SBR, 120 (65.6%) cases their presentation age was < 60 h. & 93 (34.4%) cases was > 60 h. 108 of them were females & 74 were males. Regarding gestation age, 24 (13.3%) cases were < 35 wks. 158 (86.7%) cases were > 35 wks. Concerning the eighteen cases with SBR, 12 (66.7%) cases their age presentation was < 60 h, while in 6 (33.3%) cases it was > 60 h. 8 of them were females & 10 were males, with a total 57.6% females & 42.4% males. Regarding gestation age, 6 (22.2%) cases were < 35 wks. & 12 (77.8%) cases were > 35wks. There was no significant difference between the two groups (P > 0.05).

Table (2): Age in hours, sex and gestational age around 35 wks. among cases with SBR and cases without SBR.

Age	No SBR		SBR		Total		X^2	P
	No.	%	No.	%	No.	%		
<60h	120	65.6%	12	66.7%	132	65.7%	0.1	>0.05
>60h	93	34.4%	6	33.3%	68	34.3%		
Sex								
Female	108	58.9%	8	44.4%	114	57.6%	0.2	>0.05
Male	74	41.1%	10	55.6%	84	42.4%		
Gestational age								
<35w	24	13.3%	6	22.2%	30	15.1%	0.5	>0.05
>35w	158	86.7%	12	77.8%	170	85.9%		

Table (3) showed comparison between cases with SBR and cases without SBR regarding baby ABO. There was no significant difference between the two

groups (P > 0.05) as regards group A. Also, out of the 182 cases without SBR,164 (90.0%) showed negative direct coombs test and 18 cases (10%) showed positive direct coombs test. While in cases with SBR, 8 (44.4%) showed negative direct coombs test and 10 (55.6%) showed positive direct combs test, with a total 172 (85.9%) cases with negative direct coombs test & 28 (14.1%) cases with positive direct combs test. There was significant difference between the two groups with P<0.001.

Table (3): Baby ABO and direct coombs test among cases with SBR and cases without SBR.

ABO	No SBR		SBR		Total		X^2	P value
	No.	%	No.	%	No.	%		
A+	56	31.1%	8	44.4%	64	32.3 %	5.8	0.037
A-	4	2.2%	2	11.1%	6	3.0%		
AB+	2	1.1%	0	.0%	2	1.0%		
B+	60	33.3 %	8	44.4%	68	34.3 %		
B-	4	2.2%	0	.0%	4	2.0%		
O+	52	27.8 %	0	.0%	52	25.3 %		
O-	4	2.2%	0	.0%	4	2.0%		
Total	182	100.0 %	18	100.0 %	200	100.0 %		
Negative	164	90.0 %	8	44.4%	172	85.9 %	13.9	<0.001
Positive	18	10%	10	55.6%	28	14.1 %		
Total	182	100.0 %	18	100.0 %	198	100.0 %		

Regarding reticulocyte in cases without SBR (182), it was 6.29 ± 3.47, while in cases with SBR, the mean reticulocyte count was 11.22 ± 3.41. There was significant difference between the two groups with P < 0.001 (Table 4).

Table (4): Reticulocyte count among cases with & without SBR:

		N	Mean ± SD	t	P value
R.C.	No SBR	182	6.293 ± 3.4748	4.1	< 0.001
	SBR	18	11.222 ± 3.4153		

The mean STB measurement at presentation was 12.12 ± 4.6 mg/dl, after phototherapy the mean of STB was 8.4 ± 3.39 mg/dl. Whereas after stoppage by 24 ± 6 hours, the mean was 11.34 ± 3.17 mg/dl. There was significant difference between the three measurements of present serum total bilirubin, after phototherapy & after stoppage by 24 ± 6 hours with P < 0.001 (Table 5).

Table (5): Present STB compared after phototherapy and after stop:

		Mean ± SD	T test	P value
STB	Present STB	12.12 ± 4.6	8.061	< 0.001
	After phototherapy	8.4 ± 3.39		
STB	Present STB	12.12 ± 4.6	1.59	> 0.05
	After stop	11.34 ± 3.17		
STB	After phototherapy	8.4 ± 3.39	10.63	< 0.001
	After stop	11.34 ± 3.17		

Table (6) showed that 200 neonates' term and preterm with hyperbilirubinemia were treated by exposure to intensive and double surface phototherapy respectively. 91 cases without SBR, the mean STB was 12.22 ± 4.63 mg/dl at presentation, and 8.33 ± 3.38 mg/dl after treatment with phototherapy while it was 11.24 ± 3.143 mg/dl after stoppage of phototherapy by 24 ± 6h. 9 cases with SBR, the mean STB was 10.97 ± 4.65 mg/dl at presentation, 8.87 ± 3.04 mg/dl after treatment with phototherapy and 12.58 ± 3.55 mg/dl after stoppage of phototh.by 24 h ± 6h. There was no significant difference between the three measurements of serum total bilirubin at presentation, after phototherapy, and after stoppage of phototherapy by 24 ± 6 hours.

Table (6): Intensive and double surface phototherapy treatment among cases with SBR and cases without SBR

		Mean ± SD	t	P value
Presentation STB (mg/dl)	No SBR	12.22 ± 4.631	0.8	> 0.05
	SBR	10.97 ± 4.651		
After phototherapy STB (mg/dl)	No SBR	8.333 ± 3.3892	0.5	> 0.05
	SBR	8.878 ± 3.0429		
After stop of phototherapy STB by 24h.± 6h. (mg/dl)	No SBR	11.248 ± 3.1433	1.2	> 0.05
	SBR	12.589 ± 3.5589		

DISCUSSION

In the present study, we re-measured serum total bilirubin for all the cases of neonatal hyperbilirubinemia after discontinuation of intensive phototherapy for detection of significant bilirubin rebound**.** Despite hyperbilirubinemia being a common morbidity among neonates, data about the phenomenon of bilirubin rebound is lacking **[(15)].** Few studies have systematically studied the phenomenon of post-phototherapy rebound **[(16)].** In pooling term as well as premature and low birth weight neonates, it was found that mean bilirubin levels at the time of rebound testing were significantly lower than at discontinuation of phototherapy, but did not supply information regarding peak rebound bilirubin concentrations. Significant rebound was not defined by preset criteria, and only the first serum bilirubin determination performed within 30 hours of phototherapy was included in their analysis **[(17)].**

In this study, we reported the incidence of significant bilirubin rebound after stoppage of phototherapy. In a total of 100 newborns, the proportion

of neonates with significant rebound bilirubin who required phototherapy was 9 % (9/100), 7 of 9 were from the birth hospitalization group (48 hours). Near to our reported cases of significant rebound bilirubin who required phototherapy reinstitution (9% (9/100)), **Bansal *et al.* [(18)]** reported 10% (24/232), however, **Kaplan *et al.* [(19)]** reported13.3% (30/226), but contrary, **Erdeve *et al.* [(16)]** reported 5.1% (19/375) significant rebound bilirubin cases.

In the present study, risk factors for SBR included gestational age < 35 weeks (15.4%, 2/13), birth weight < 2000 g (7.8 %, 1/14), onset of jaundice < 60 hours (10 %, 6/60) & positive direct Coombs test (55.6 %, 5/9). This goes into concordance with **Bansal *et al.* [(18)]** who reported that risk factors for SBR after stoppage of intensive phototherapy, included onset of jaundice < 60 hours (10.8 %), gestational age < 35 weeks (15.6 %) & birth weight < 2000 g (10.8 %), but the positive direct Coombs test (55.6 %, 5/9) is an observation in our study that concur with those of **Bansal *et al.* [(18)]** study as it showed lack of higher SBR in neonates with positive direct Coombs test. **Bansal *et al.* [(18)],** defined SBR as post-phototherapy bilirubin level needing reinstitution of phototherapy. Our current study goes in concordance with **Bansal *et al.* [(18)],** in defining SBR as post-phototherapy bilirubin level needing reinstitution of phototherapy and presetting criteria by using charts recommended by the American Academy of Pediatrics [(14)].

CONCLUSION

Intensive phototherapy in neonatal hyperbilirubinemia rapidly decreases serum total bilirubin (STB) below the threshold for treatment. However, underlying alteration in bilirubin production and excretion may persist and cause bilirubin rebound after stopping phototherapy. Rebound bilirubin level must be obtained in all neonates treated by phototherapy especially high-risk neonates, born at < 35 weeks gestation, birth weight < 2000 g or onset of phototherapy within 60 hours of age18-24 hours after stopping phototherapy.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

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