ORIGINAL ARTICLE

REBOUND HYPERBILIRUBINEMIA AFTER INTENSIVE PHOTOTHERAPY: CROSS SECTIONAL STUDY

Ahmed Monir Ali *, Hanan Mohamed Abd El-moneim, Magda Farghali Gabri

Pediatric department, Faculty of medicine, Aswan University

ABSTRACT

Keywords: Rebound hyperbilirubinemia, phototherapy, blood exchange, neonate.

***Corresponding author:** Ahmed Monir Ali

E-mail: ahmed170466@aswu.edu.eg

Phone number: 01120749335

Background: Rebound hyperbilirubinemia is the return of total serum bilirubin to phototherapy threshold within 72 hours of phototherapy termination. **Objective**: to determine the prevalence and magnitude of post-phototherapy bilirubin rebound needing reinstitution of phototherapy.**pateints and Methods:** observational cross-sectional study in NICU department of Aswan University Hospital from January 2021 to December 2021.**Results**: It included 101 neonates with hyperbilirubinemia at age of 71.5 ± 46.1 hours, 50 male, and 51 females. The most common cause of jaundice is ABO incompatibility in 58.4% of cases. Exchange transfusion was done to 16% of cases and blood transfusion to 6%. The incidence of rebound is 12.9%. The Mean (95% CI) bilirubin after 24 hours was 8.71 [8.27- 9.14], and after 72 hours were 6.82 [5.77- 7.87]. There were statistically significant differences between the rebound and non- rebound neonate in term of hemoglobin, MCH and total bilirubin after 72 hours. The results showed highly statistically significant effect of blood transfusion on rebound occurrence. Our findings suggest that if the cause of the jaundice was hemolytic, then it is more likely to develop rebound hyperbilirubinemia. **Conclusion**: the prevalence of rebound hyperbilirubinemia is high .so repeated follow up after discharge is mandatory

INTRODUCTION

Neonatal Hyperbilirubinemia, presenting as jaundice, is a global and frequently condition in newborn babies (1). Jaundice affects at least 60% of full-term and 80% of preterm neonates (2) and it is a leading cause of hospitalization in the first week of life (3). Although most cases of neonatal jaundice are benign, there is still potential toxicity of bilirubin, therefore, newborn infants must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy (ABE), or kernicterus (4).

Neonatal jaundice was a major contributing cause for cerebral palsy in Egyptian children and Kernicterus was the third most common cause of developmental delay in Egyptian children composing 9% of the whole etiologies (5).

The primary goal for the management of neonatal jaundice is to avoid bilirubin induced mortality and neurotoxicity in otherwise healthy newborn babies by preventing serum bilirubin from reaching potentially neurotoxic concentrations (1). A Transcutaneous bilirubin (TcB) and/or total serum bilirubin (TSB) measurement should be performed on every infant who is jaundiced in the first 24 hours after birth, together with the use of intensive phototherapy and/or exchange transfusion (ET) as indicated (6)

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As hyperbilirubinemia may be resolved by the time phototherapy is discontinued, post-phototherapy rebound may occur (7). Rebound is defined as the return of total serum bilirubin to phototherapy threshold according to AAP guidelines within 72 hours of phototherapy termination (8). It may be necessary for outpatient to repeat total serum bilirubin measurement 24 hours after discharge (9).

And so, aim of this study was to determine the prevalence of post-phototherapy bilirubin rebound needing reinstitution of phototherapy.

PATIENTS AND METHODS

This study was an observational cross-sectional study that conducted in Neonate intensive care unit (NICU) of Aswan University Hospital, from January 2021 to December 2021. IRP approval of was taken, and written consent obtained from all case's parents before getting them involved in the study. All neonates admitted to NICU with indirect hyperbilirubinemia in the first 15 days of age with gestational age ≥ 35 week were included. Neonates with neonatal sepsis, shock, surgery, or direct hyperbilirubinemia were excluded.

Full history taking including perinatal, family history, and physical examination was done. Investigation including complete blood count **(**CBC) with reticulocytes, blood groups, Rhesus (*Rh*) for both mothers and neonates, total and indirect serum bilirubin level were done.

Total bilirubin & indirect bilirubin was investigated at admission, 24, 48 and 72 hours after discharge. Phototherapy was stopped when TSB decreased 2 mg/dL below level at which phototherapy was indicated for that age (10)

All statistical analysis was performed using R version 4.1.1 software (R Core Team) and SPSS 25. Descriptive statistics: Mean, Standard deviation (± SD), Median, range and Interquartile range (IQR) for numerical data. Frequency and percentage of categorical data.

RESULTS

This observational cross-sectional study included 101 patients, 50 of them were males. The mean age was (71.5 ± 46.1) hours, mean of weight at birth was (2701 ± 511) gram. About 30.7% born vaginally. Regarding the type of feeding, half of them used mixed, 25% were exclusive breast feed and 25% used artificial milk. There were 2 cases with down syndrome, 1 with polydactyly, 1 with ASD and the reset has no anomalies **table 1**

Table 2 shows the prevalence of rebound was 12.9%. Regarding to the neonate blood group, the percentage of groups A, B, O, and AB was 34.7%, 54%, 10%, and 2% respectively. In addition, 95% of them were Rh +ve. 20 % of cases had previous blood transfusion. Only 4 cases had history of previous NICU admission while only 2 cases had similar condition. Mortality rate was 0.9%.

Table 3 the mean maternal age at delivery was 28 ± 4.85 years. Regarding maternal blood group, percentage of A, B, O, and AB was 13.9%,12.9%,72.3% and 0% respectively. 78.2% were RH +ve. 6% of mothers had hypertension, 6 % had DM and 1% had thalassemia. Thirty-eight were +ve Coombs.

Table 4 shows the laboratory investigation of studies cases. Mean (SD) of haemoglobin (g/dl) was 15.5 (3.09), mean (SD) of Haematocrit 43.43 (7.81) %, mean (SD) of RBCS (Million cells/mcL) was 4.34 (0.64), mean (SD) of reticulocytes was 7.52 (4.54), mean (SD) of MCV 101 (12.7), mean (SD) of MCHC 33.7 (1.7), and Total bilirubin 19.6 ± 5.15.

Table 5 shows that the most common cause of jaundice is ABO incompatibility the presented in 58.4% of cases. Exchange transfusion was done to 16% of cases and blood transfusion to 6%. Regarding type of phototherapy used intensive phototherapy, triple, double and single phototherapy were 56.4%, 3%, 28.7% and 11.9% respectively

Table 6 shows that the incidence of rebound occurrence is 12.9%. the mean ± SD of bilirubin (mg/dl) after 24 hours was 8.58±2.1, after 48 hours was 8.7±4.3, and after 72 hours was 7.14 ± 5.66.

Table 7 shows the mean age of neonates with rebound hyperbilirubinemia was 59.4 ± 42.8 hours, and the mean weight of those neonates was 2738 ± 528 gram. Eight of them was male, and 5 of them born vaginally. Ten neonates had breast feeding, and all of them were vaccinated. Only 4 of them had history of blood transfusion and no one of them died. Moreover, one infant had ASD, and one was infant of diabetic mother. Eleven baby was blood group B, 1 was blood group A, 1 was blood group O and non was AB, while 12 was Rh +ve. ABO incompatibility was the cause of jaundice in 10% of the neonates.

Table 8:Laboratory results of neonates with rebound hyperbilirubinemia the mean Hb was 13.9± 3.67 g/dl. The mean of haematocrit was 40.11 ± 0.77 %, the mean of Retics was 7.83± 4.23 %, the mean of MCV was 97.4± 6.64, and the mean of MCHC was 34.1± 2.13. Nine children needed intensive phototherapy, and 4 needed only double phototherapy. The phototherapy duration was 72.9± 34.1 hours.

TABLES AND FIGURES

Table 1: demographic data of studied cases

Variables	Cases
Age (hours)	
• Mean ± SD	71.5 ± 46.1
• Median (IQR)	72 (36- 96)
• Range	[2- 240]
Gestational Age (weeks)	
• Mean ± SD	37.4 ± 1.34
• Median (IQR)	38 (37- 38)
• Range	[33- 40]
Gender	
• Male	50 (49.5%)
• Female	51 (50.5%)
Weight (gram)	
• Mean ± SD	2701 ± 511
• Median (IQR)	38 (37- 38)
• Range	[1200- 4000]
Type of delivery	
• Vaginal	31 (30.7%)
• C-section	70 (69.3)
Type of feeding	
• Breast feeding	25 (25 %)
• Artificial	26 (25.9%)
• Mixed	50 (50%)
Congenital Anomaly	
• Down syndrome	2 (2%)
• Polydactyly	1 (1%)
• ASD	1 (1%)
• No anomaly	96 (95.7%)

ASD: atrial septal defect.

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Table 2: Clinical data of studied cases

Variables	N (%)
Cases with rebound	13 (12.9%)
Neonate blood group • A • B • O • AB	 35 (34.7%) 54 (53.5%) 10 (9.9%) 2 (2%)
Neonate Rh • +ve • -ve	 96 (95%) 5 (5%)
History of previous NICU admission	4 (4%)
History of similar condition	2 (2%)
History of Blood transfusion	22 (21%)
Outcomes • Deaths • Alive	 1 (0.9%) 100 (99.1)

Table 3: Baseline characteristics of the mothers of studied cases

Variable	101
Maternal age at delivery (years) Mean ±SD Median (IQR) Range	 28 ± 4.85 28 (24- 31) [19- 43]
Blood group A B O AB	 14 (13.9%) 13 (12.9%) 73 (72.3%) 0
Rh +ve -ve	 79 (78.2%) 21 (20.8%)
Gestational disease HTN DM Thalassemia	 6 (5.9%) 6 (5.9%) 1 (1%)
Direct Coombs +ve	 38 (37.7%)

Table 4: laboratory investigations of studied cases

Variables	
CBC at admission	
Hemoglobin (gm/dl) • Mean (SD) • Median (IQR) • [Min- Max]	 15.5 (3.09) 17.4 (13.7- 15.7) [7.7- 25.9]
Hematocrit % • Mean (SD) • Median (IQR) • [Min- Max]	 43.43 (7.81) 39.95 (44- 46) [22.2- 65.9]
RBCS (Million cells/mcL) • Mean (SD) • Median (IQR) • [Min- Max]	 4.34 (0.64) 4.35 (3.9- 4.832) [3.01- 5.7]
Reticulocytes % • Mean (SD) • Median (IQR) • [Min- Max]	 7.52 (4.54) 6 (4.5- 10) [0.4- 23.4]
MCV • Mean (SD) • Median (IQR) • [Min- Max]	 101 (12.7) 100 (97.8- 105) [1.7- 139]
MCHC • Mean (SD) • Median (IQR) • [Min- Max]	 33.7 (1.7) 33.9 (32.4- 34.6) [29.4- 39.5]
Total bilirubin at admission • Mean (SD) • Median (IQR) • [Min- Max]	 19.6±5.15 20(16- 23) [6- 32]

Table 5: Management of studied cases

Variable	N (%)
Cause of Jaundice • RH incompatibility • ABO incompatibility • ABO incompatibility+ RH incompatibility • Hereditary spherocytosis • Autoimmune • Exaggerated physiological jaundice • Subgroup • Unknown	 11 (10.9%) 59 (58.4%) 7 (6.9%) 1 (1%) 2 (2%) 1 (1%) 1 (1%) 19 (18.8%)

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Blood transfusion • Blood transfusion • Exchange transfusion • No blood transfusion	 6 (6%) 16 (16%) 79 (79%)
Phototherapy type • Single • Double • Triple • Intensive	 12 (11.9%) 29 (28.7%) 3 (3%) 57 (56.4%)

Table 6: **Rebound occurrence and follow up**

Variables	
Number of cases	13 (12.9%)
After 24 hours • Mean ± SD • Median (IQR) • [Min- Max]	 8.58±2.1 9(7- 10) [3- 12]
After 48 hours • Mean ± SD • Median (IQR) • [Min- Max]	 8.7±4.3 8(7- 9) [2- 22]
After 72 hours • Mean ± SD • Median (IQR) • [Min- Max]	 7.14± 5.66 5(4- 9.5) [1- 22]

Table 7: Baseline characteristics of the neonates with rebound

Variables	
Age at presentation (hours) • Mean ± SD • Median (IQR) • [Min- Max]	 59.4 ± 42.8 48 (36- 72) [12- 144]
Gestational age (weeks) • Mean ± SD • Median (IQR) • [Min- Max]	 37.5 ± 1.2 38 (36- 38) [36- 39]
Weight (gram) • Mean ± SD • Median (IQR) • [Min- Max]	 2738 ± 528 2800 (2300- 3000) [2100- 3500]
Gender • Male • Female	 8 % 5 %

Type of delivery • Vaginal • C-section	 5 % 8 %
Breast feeding	10 %
Vaccination	13 %
History of Blood transfusion	4 %
History of previous NICU admission	2 %
History of surgery	0
Death	0
ASD	1 %
Gestational DM	1 %
Neonate blood group • A • B • O • AB	1 % 11 % 1 % 0 %
• Rh +ve	12 %
Cause of jaundice • RH incompatibility • ABO incompatibility • Unknown	 2 % 10 % 1 %

Table 7: Laboratory results of neonates with rebound hyperbilirubinemia

laboratory test after 72 hours	
Hemoglobin (gm/dl) • Mean ± SD • Median (IQR) • [Min- Max]	 13.9 ± 3.67 16 (11.7- 13.1) [8.3- 22.9]
Hematocrit % • Mean ± SD • Median (IQR) • [Min- Max]	 40.11 ± 9.33 38.6 (33.5- 45) [25.6- 63.0]
RBCS (Million cells/mcL) • Mean ± SD • Median (IQR) • [Min- Max]	 4.09 ± 0.77 4 (3.34-4.50) [3.01- 5.42]
Reticulocytes • Mean ± SD • Median (IQR) • [Min- Max]	 7.86 ± 4.23 5 (7- 10) [0.4- 16)
MCV • Mean ± SD • Median (IQR) • [Min- Max]	 97.4 ± 6.64 99 (94.3- 104) [83- 104]
MCHC • Mean ± SD	 34.1 ± 2.13

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• Median (IQR) • [Min- Max]	34.3 (33.9- 35.1) [30- 36.7]
Type of phototherapy • Double • Intensive	 4 % 9 %
Phototherapy Duration (hours) • Mean ± SD • Median (IQR) • [Min- Max]	 72.9 ± 34.1 72 (48- 96) [24- 144]

DISCUSSION

Hyperbilirubinemia is a clinical condition that occur when the rate of bilirubin production exceeds the rate of elimination. The end result is a rise in total serum bilirubin which manifest as yellow discoloration of skin, sclera and mucosa. Phototherapy is the current treatment of choice for neonatal hyperbilirubinemia and has almost replaced exchange transfusions because of its efficacy and safety (10).

As hyperbilirubinemia may be resolved by the time phototherapy is discontinued, post-phototherapy rebound may occur (**Kaplan et al.**, **2006**). Rebound is defined as the return of total serum bilirubin to phototherapy threshold within 72 hours of phototherapy termination (8). It may be necessary for outpatient to repeat total serum bilirubin measurement 24 hours after discharge (9).

So, our study aimed to determine the magnitude of post-phototherapy bilirubin rebound needing reinstitution of phototherapy. Our study was observational cross-sectional study carried out in NICU at Aswan University Hospital from January 2021 to December 2021.

Our study included 101 neonates with hyperbilirubinemia at age of 71.5 ± 46.1 hours with gestational age mean was 37.4 ± 1.34 weeks. Similar to **Singh et al.**, (**2020**) in his study that conducted in India, they reported that the mean gestational age of their cases was 36.96 + 1.71 weeks. Moreover, **Chang et al.**, (**2017**b) in their study that conducted in California and **Valinjkar**, (**2017**) found that gestational age in their study was 38 ± 1.7 weeks and 36.5 ± 5.1 weeks respectively. In **Al-Saedi**, (**2002**) study that conducted in Jeddah, Kingdom of Saudi Arabia, the gestational age was 39.4 ± 1.4 week. Moreover, **Elhawary et al.**, (**2018**) in their study that conducted in Zhejiang university school of medicine, the median (IQR) gestational age of cases was 38 (30–40) weeks and birth weight of 2.900 (1.3–4.7) kg. **Hassanein et al.**, (**2019**) in their study that conducted in Benha, the mean gestational age was 36 weeks.

Regarding to the neonate blood group, most of our cases (54%) blood groups were blood group B followed by A (34.7%), then O in 10% of cases, and only 2% were blood group AB. In addition, 95% of cases were Rh +ve, and 20 % of cases had previous blood transfusion. Only 4 cases had history of previous NICU admission while only 2 cases had similar condition. Mortality rate was 0.9 %. Regarding maternal obstetric history, 22.8% of our cases were RH -ve. 6% of mothers had hypertension, 6 % had DM and 1% had thalassemia. Thirty-eight were +ve for Coomb's test.

Regarding laboratory investigation of studies cases, mean (SD) of hemoglobin (g/dl) was 15.5 (3.09), mean (SD) of hematocrit 43.43 (7.81) %, mean (SD) of RBCS 4.34 (0.64) (Million cells/mcL), mean (SD) of reticulocytes 7.52 (4.54) %, mean (SD) of MCV 101 (12.7), mean (SD) of MCHC 33.7 (1.7), and mean (SD) of total bilirubin was 19.6 ± 5.15 mg/dl. Similar to **Hassanein et al.**, (**2019**), they found that mean hemoglobin level ± SD was 14.5 ±1.9, mean hematocrit level ± SD was 43.4 ±4.9. But, against to our results, they found that median reticulocyte count in their cases was 3% and ranged from 0.3 to 8.8.

The most common cause of jaundice reported in our cases was ABO incompatibility in 58.4% of cases, RH incompatibility found in 10.9 % of cases and both ABO and RH incompatibility were found in 6.9 % of them. This result were simliar to **Elhawary et al., (2018)**, as they reported that

56.6% of their cases developed neonatal hyperbilirubinemia due to hemolytic causes. In contrast to our results, **Al-Saedi, (2002)** reported that the ABO incompatibility was responsible for hyperbilirubinemia in 16% of their cases, Rh incompatibility in 3% and minor sub-blood group incompatibility in 1.3%. in addition, **Bansal et al., (2010)** in their study in India reported that the most common assigned etiology of jaundice was prematurity in 22.5% of their cases followed by G6PD deficiency in 7%, ABO incompatibility in only 2%, and Rhesus incompatibility in 0.8%.

Regarding line of treatment, we used intensive phototherapy in 59.4% of cases, double and single phototherapy were used in 28.7% and 11.9% of cases respectively. Exchange transfusion done to 16% of cases and blood transfusion to 6% of them.

Rebound hyperbilirubinemia were reported in 12.9 % of our cases. The mean ± SD of bilirubin after 24 hours was 8.58 ± 2.1, after 48 hours was 8.7±4.3, and after 72 hours were 7.14 ± 5.66. Similar to **Niknafs et al.**, (**2014**), they found in their study that rebound hyperbilirubinemia occurred in 11.3% of their neonates out of 115 participants, in Iran neonatal population.

Other study showed comparable results such as **Singh et al.**, (**2020**), **Swain et al.**, (**2017**), **Bansal et al.**, (**2010**), and **Kaplan et al.**, (**2006**). They stated that rebound hyperbilirubinemia were reported in 11.3%, 11.1%, 7.3%, and 13.2% of their cases. In contrast to our results, **Chang et al.**, (**2017**b) found only 4.6% of neonates developed rebound hyperbilirubinemia; while **Elhawary et al.**, (**2018**) found that 24.9% of studied neonates developed rebound hyperbilirubinemia. This wide range of variability in results of serum bilirubin range in various study may be due to study plan not being uniform with regard to timing of measurement of serum bilirubin rebound, prematurity, birth weight and presence of other risk factors.

RECOMMENDATIONS

We recommend to: 1) Assess different proven risks in selecting neonates to be tested for rebound hyperbilirubinemia. 2) Neonates with history of blood transfusion and hemolytic causes should be regarded as high-risk factors. 3) New studies with larger sample size and investigating the rebound causes should be conducted

LIMITATION

The study's limitations include the presence of several confounding factors, such as hemolysis, high admission TSB, and intensive phototherapy treatment, all of which have associated effects, the inability to perform a routine glucose-6-phosphate dehydrogenase test in all neonates, and the high proportion of neonates whose causes of bilirubin rebound are still unknown.

CONCLUSION

In conclusion, our study revealed that the prevalence of rebound hyperbilirubinemia is high .so repeated follow up after discharge is mandatory.

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