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Original Article

Do We Have to Obtain Rebound Bilirubin Levels and What is the Optimal Time?

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ABSTRACT

Aim: We aimed to determine the frequency of rebound hyperbilirubinemia (RHB) needing treatment and therefrom, to clarify the clinical importance of routinely checking serum total bilirubin (STB) levels after the cessation of phototherapy and to define an optimal time to check STB levels for the detection of RHB.

Materials and Methods: Term and late preterm babies who received phototherapy were included in this study. The demographic and clinical features, time of onset of jaundice, phototherapy time and results to determine the etiology of jaundice were recorded for all babies. Serum "rebound" bilirubin measurements were performed two times at 12 and at 24 hours after the cessation of phototherapy. The re-initiation of phototherapy according to the 12th and 24th hour STB levels was accepted as "early rebound" and "late rebound", respectively. IBM SPSS 22 was used for statistical analyses.

Results: Data was available for 110 infants. The rebound rate requiring phototherapy was 9.1% (n=10) and all had a risk factor. Most of the babies (9/10) rebounded at the 12th hour after the termination of phototherapy. Hemolysis and prematurity were found to be statistically significant for RHB (p=0.008; p=0.048).

Conclusion: Post-phototherapy bilirubin follow-up may be incorporated using a combined approach of individualization, evaluation of risk factors, and application of common sense before discharge. Our study showed that STB levels could be measured after the cessation of phototherapy, especially in patients with a risk factor, at the 12th hour before discharge. Randomized controlled studies with larger sample sizes are still needed for definitive recommendations.

Keywords: Hyperbilirubinemia, newborn, phototherapy, rebound bilirubin

Introduction

Phototherapy is the most effective method to lower serum total bilirubin (STB) levels in newborns with hyperbilirubinemia. A sudden increase in bilirubin levels, depending on the cause of hyperbilirubinemia, may be observed after the cessation of phototherapy (1,2). This situation brings forth a discussion on whether to re-check bilirubin levels after phototherapy has been stopped. As the results of the studies about this dilemma are assessed, there is still no consensus about this subject (2-11). The American Academy of Pediatrics (AAP) recommends to measure bilirubin levels within 24 hours after cessation of phototherapy only in cases caused by hemolysis or in those who needed phototherapy in the first three to four days of life (2).

The incidence of hyperbilirubinemia varies with ethnicity and geography and our country is located in this high-risk area (12). Sarici et al. (13) reported the incidence of hyperbilirubinemia as 10.5% for term and 25.3% for near-

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term infants in Turkey, which is much higher than the incidence reported from European countries and the United States (14,15). Thus, guidelines developed from those countries may not apply to our country.

The primary aim of our study is to determine the frequency of rebound hyperbilirubinemia (RHB) needing treatment and therefrom, to clarify the clinical importance of routinely checking STB levels after the cessation phototherapy and to define an optimal time to check STB levels for the detection of RHB.

Materials and Methods

Term and late-preterm babies, who received phototherapy due to hyperbilirubinemia in the Neonatal Intensive Care Unit of Marmara University Medical Faculty between January 2015 and December 2015, were enrolled in this prospective study. Newborns with congenital anomalies or any disease accompanying hyperbilirubinemia (sepsis, pneumonia, perinatal asphyxia, etc.) were excluded. The study was approved by the Ethics Committee of Marmara University Medical Faculty (approval number: 09.2016.231). Informed consent was obtained from the parents of the infants. Infants with RHB and without RHB were compared in terms of their demographic and clinical characteristics, at the 12th and 24th hour STB levels after inpatient phototherapy, time of onset of jaundice, phototherapy period and in terms of the results of all tests performed to determine etiology (blood type of the mother and the baby, reticulocyte count, direct Coombs test, peripheral smear, glucose-6 phosphate dehydrogenase enzyme levels, thyroid function tests, reducing substances in urine). Late preterm infants are defined as those born at 34-0/7 to 36-6/7 weeks' gestational age (16). Phototherapy and exchange transfusion decisions were made according to the AAP's guidelines and high-density light-emitting diode phototherapy was initiated on all patients (2).

The "early treatment group" consisted of the infants who received phototherapy before the 72nd hour of life and the "late treatment group" consisted of the infants who received phototherapy after the 72nd hour of life. Phototherapy was discontinued when STB levels dropped below 13-14 mg/dL in the late treatment group and 3 mg/dL or more below the phototherapy threshold level according to postnatal age in the early treatment group (17,18). RHB was defined as the return of TSB to the phototherapy threshold within 72 hours of phototherapy. Serum rebound bilirubin levels were measured twice; at the 12th hour and 24th hour after the cessation of phototherapy. The need for the re-initiation of phototherapy at the 12th or 24th hour STB levels were accepted as "early rebound" and "late rebound", respectively.

Statistical Analysis

The distribution of the data was determined by Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U tests were used to compare normally-distributed (parametric) and not normally-distributed (non-parametric) data, respectively. Results were expressed as "mean ± standard deviation" for parametric data and "median (minimum-maximum)" for non-parametric data. Fisher's exact test and chi-square test was performed for non-parametric variables between groups where appropriate. IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, ABD) was used for statistical analyses. For all statistical analysis, p values <0.05 were considered significant.

Results

One hundred and ten infants who were treated due to hyperbilirubinemia were included in the present study. Ninety-one infants (83%) were term and 19 (17%) were late-preterm with mean birth weights of 3.273±462 g and 2.513±534 g; respectively. When the cases were assessed for jaundice etiologies, the number of cases with hemolysis due to ABO or Rh incompatibility, excessive weight loss (loss of ≥10% of birth weight) and prematurity were 17 (15%), 20 (18%) and 19 (17%), respectively. No etiological factor could be detected in 59 (53%) infants (Table I). Six babies received exchange transfusion (n=1, Rh incompatibilities and n=5, ABO incompatibilities).

The rebound rate was 9.1% (10/110). There were no significantly statistically differences between rebound and non-rebound groups in terms of birth weight, gestational weeks, gender, prematurity, delivery route, history of jaundice in sibling or excessive weight loss after birth (Table 2). The presence of hemolysis and early phototherapy were found to be statistically significant between the groups, (p=0.008, p=0.034) respectively (Table II). When the two groups were compared according to the rebound frequency, the number of RHB cases in the early phototherapy group was significantly higher (8/10; p<0.001). Nine of the 10 infants (90%) with RHB were detected at testing of STB levels at the 12th hour. Hemolysis and being late-preterm were found to be statistically significant higher for those babies with RHB (p=0.008, p=0.048) (Table II). The clinical features of those infants with RHB are shown in Table III.

Discussion

The necessity of rebound STB measurements in newborn jaundice cases is controversial (2,5,9,10). In our research, the RHB rate was calculated at 9.1%. In recent studies, the occurrence of RHB was reported to be between 0.7%-19.6% (7,19). The wide range of the reported frequencies could be

Table I. Demographic and clinical features of the study population

	Study group (n=110)
Male, n (%)	68 (61.81)
Late preterm, n (%)	19 (17.27)
Birth weight, (g)	
Term/late-preterm	3.273±462/2.513±534
Cesarean delivery, n (%)	53 (48.18)
Family history of jaundice, n (%)	11 (10.00)
Etiology, n (%)	
Hemolysis, n (%)	17 (15.45)
Late-preterm, n (%)	19 (17.27)
Excessive weight loss, n (%)	20 (18.18)
No etiological factor, n (%)	59 (53.63)
Exchange transfusion, n (%)	6 (5.45)
Early-treated hyperbilirubinemia, n (%)	56 (50.90)
Time of initiation of phototherapy (hours)	97 (3-192)
Serum total bilirubin level at the beginning of phototherapy (mg/dL)	17.63±5.52
STB level at the end of phototherapy (mg/dL)	11.33±1.87
Duration of phototherapy (hours)	24 (8-72)
12^{th} hour rebound STB (mg/dL)	11.53±2.42
24^{th} hour rebound STB (mg/dL)	11.38±2.30

Data of variables are expressed as mean ± standard deviation or median (minimum-maximum) or absolute number and its frequencies n (%); STB: Serum total bilirubin

Table II. The comparison of the demographic and clinical features of the ınfants with and without rebound hyperbilirubinemia

	Rebound group (n=10)	No-rebound group (n=100)	p value
Birth weight (g)	3045±536	3201±508	0.358
Gestational weeks	37.61±2.01	38.32±1.43	0.144
Male, n (%)	5 (50.00)	63 (63.00)	0.501
Term, n (%)	6 (60.00)	85 (85.00)	-
Late-preterm, n (%)	4 (40.00)	15 (15.00)	0.048
Vaginal delivery, n (%)	5 (50.00)	52 (52.00)	1.000
Hemolysis, n (%)	5 (50.00)	12 (12.00)	0.008
Weight loss of ≥10% of birth weight, n (%)	3 (30.00)	17 (17.00)	0.385
No etiological factor, n (%)	0 (0)	59 (59)	<0.001
Early phototherapy, n (%)	8 (80.00)	48 (48.00)	0.034
STB level at the beginning of phototherapy (mg/dL)	19.48±7.29	17.70±5.11	0.315
STB level at the end of phototherapy (mg/dL)	11.24±2.13	11.10±2.01	0.822
12^{th} - hour rebound, n (%)	9 (90)	0	<0.001
24^{th} - hour rebound, n (%)	1 (10)	0	0.001

Data of variables are expressed as mean ± standard deviation (range) or median (minimum-maximum) or absolute number and its frequencies n (%); STB: Serum total bilirubin

Table III. Clinical features of the patients with rebound hyperbilirubinemia

	Early treatment group	Late treatment group	12^{th} rebound	24^{th} rebound	Hemolysis	Excessive weight loss	Late preterm infant
Case 1	+	-	+	-	-	+	+
Case 2	+	-	+	-	-	+	+
Case 3	-	+	+	-	-	+	-
Case 4	+	-	+	-	+	-	-
Case 5	+	-	+	-	-	-	+
Case 6	+	-	+	-	+	-	-
Case 7	-	+	-	+	-	-	+
Case 8	+	-	+	-	+	-	-
Case 9	+	-	+	-	+	-	-
Case 10	+	-	+	-	+	-	-

explained by the differences in the definitions of RHB, sample sizes, jaundice etiologies and risk factors (3-5,8-10,19). Chang at al. (18) reported a 4.6% rate of RHB; whereas, Barak et al. (19) found a higher rate (19.6%) and this increased rate was attributed to the discontinuation of phototherapy in cases with higher STB levels (18). In another study, the rebound frequency was recorded as 0.7% and the exclusion of risk groups was held accountable for this low prevalence (7). The RHB rate has been reported as 5.1% in Turkey, which is lower than our study (5). The lower mean bilirubin levels at which to start and stop phototherapy and the lower number of cases with blood group incompatibility and hemolysis, compared to our study group, might explain the difference.

Waiting for a rebound STB level measurement prolongs hospital stay; therefore, AAP recommends rebound measurements only in babies with certain risk factors (2). In one study, gestational and postnatal age, and STB levels at the time of cessation of phototherapy were reported as the three most important risk factors for RHB (18). It has been reported in many studies that late-preterm infants, who have the highest risk for newborn jaundice, also have a high "rebound" rate (5,10). In our study, RHB developed in 4 of the 19 late-preterm babies (21%), which was higher compared to term babies (6%). Two of these "rebounding" late preterm babies were in the early treatment group, both having excessive weight loss. Kaplan et al. (9) reported that the majority of their rebound cases were late-preterm infants and all had hemolysis.

Those infants who received phototherapy before their initial discharge after birth (in the first three days of life) were reported to have a higher rate of being hospitalized for a second course of phototherapy (7,9). In our study, 9 of the infants with RHB (90%) were in the early treatment group. Kaplan et al. (9) stated that neonates with hemolysis, late prematurity and onset of phototherapy within 72 hours should be regarded as high risk. In our study, all of the cases with RHB had at least one of these risk factors (hemolysis, excessive weight loss or prematurity).

In the literature, the measurements of rebound STB levels were performed between 8 to 36 hours after the cessation of phototherapy (3,5,7,9,10). AAP recommends the measurement of rebound STB levels within 24 hours of phototherapy cessation, without specifying an exact period (2). "The National Institute for Health and Clinical Excellence", and the "Canadian Paediatric Society Fetus and Newborn Committee" do not refer to the evaluation of rebound STB levels in their guidelines (17,20). In our study, rebound STB levels were measured in two-time sections (12th hour and 24th hour) and it was detected that most of the "rebounds" had developed by the 12th hour measurement and all of them had risk factors. Nine of 10 infants with RHB were detected with the measurement of 12th hour rebound STB levels, thus enabling an early initiation of treatment. Even though AAP recommends outpatient evaluation for rebound STB level, in our country, as we are concerned about the lack of follow-up, we suggest checking rebound STB levels at the 12th hour, before discharge.

Conclusion

Post-phototherapy bilirubin follow-up may be incorporated using a combined approach of individualization, evaluation of risk factors, and application of common sense before discharge. Our study showed that STB levels can be measured after the cessation of phototherapy, especially in patients with a risk factor, at the 12th hour before discharge. Randomized controlled studies with larger sample sizes are still needed for definitive recommendations.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Marmara University Medical Faculty (approval number: 09.2016.231).

Informed Consent: Informed consent was obtained from the parents of the infants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ö., A.M., Z.A.Ü., Concept: H.Ö., H.S.B., Design: H.Ö., H.S.B., Data Collection or Processing: H.Ö., A.M., Z.A.Ü., Analysis or Interpretation: H.Ö., H.S.B., E.Ö., Literature Search: H.Ö., H.S.B., Writing: H.Ö., H.S.B.

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