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A Comparison of Significant Bilirubin Rebound after Discontinuation of Phototherapy in Two Groups of Neonates in Valiasr Hospital: A Randomized Clinical Trial

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ABSTRACT

Introduction: The aim of this study is to compare significant post-phototherapy bilirubin rebound in two groups of neonates, with two levels of bilirubin, at discontinuation of phototherapy.

Materials and Methods: One hundred and fifteen neonates ≥35 weeks of gestationl age (GA), admitted due to hyperbilirubinemia in the Neonatal Ward of Valiasr Hospital, were randomly divided into two groups: group A and group B. In group A, phototherapy was discontinued when bilirubin level reached 11 mg/dl, or the 40th percentile of the Bhutani nomogram, while in group B, it took place at bilirubin level of 13 mg/dl or the 75th percentile. After 24 hr, total serum bilirubin was measured. Significant post-phototherapy rebound was defined as bilirubin increase of more than 2 mg/dl or the 95th percentile.

Results: A total of 13 (11.3%) neonates out of 115 participants developed significant rebound, 9 of which (69%) were in group A , and the rest (21%) were in group B, which was not considered a significant difference (*P*=0.13). Comparison of the two groups showed no significant difference concerning the correlation between rebound and the infant's age, in hr of starting phototherapy. However, the number of neonates in group B, who received phototherapy before 48 hr of age, was too small to draw reliable conclusions. Logistic regression analysis showed that intravenous serum therapy was the only risk factor significantly associated with rebound (*P*=0.005).

Conclusion: According to this study, it is shown that discontinuation of phototherapy in hyperbilirubinemia, at lower bilirubin levels, would not prevent rebound. Moreover, no association was found between the known risk factors and rebound.

Keywords: Bilirubin, Neonate, Phototherapy, Rebound

Introduction

Prevention, diagnosis and treatment of jaundice in otherwise healthy neonates is still an issue, due to its high prevalence; On the other hand, prevalence of kernicterus is extremely low. Although no study has been carried out to show that phototherapy can improve neurodevelopmental outcomes, we know that it prevents the bilirubin from reaching a level which could increase the risk of kernicterus. Many different mechanisms are involved in developing jaundice, some of which do not disappear at discontinuation of phototherapy. As a result, it is probable that after discontinuation of phototherapy, level of bilirubin rises again, and resumption of phototherapy would be necessary. In clinical guidelines for jaundice, including the guidelines of The American Academy of Pediatrics (AAP) for diagnosis and treatment of jaundice, some clear-cut solutions are provided for the onset of phototherapy, according to the presence of risk factors, although this does not apply to discontinuation of phototherapy (1). Bilirubin level of 13-14 mg/dl is suggested for discontinueation of phototherapy in neonates of ≥35 weeks of

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age; though in general this level is variable. Neonates with hemolysis or the ones discharged earlier than 3-4 days of age, are recommended to be checked for jaundice, 24 hr after discharge. It is optional to visit the neonates, who are readmitted, 24 hr after discharge, or measure their bilirubin level (1).

Some cases of recurrent jaundice and readmission after discontinuation of phototherapy raised the necessity to reconsider the bilirubin level to discontinue phototherapy. This led to the assumption that if in the initial admission, therapy is discontinued in lower levels of bilirubin, recurrence of jaundice would be less probable. If we draw the conclusion that discontinuation of phototherapy in lower levels of bilirubin would significantly reduce the risk of rebound, it could be concluded that recommended solutions by the AAP should be reconsidered, based on the particular regional situation. We also can generalize this issue to other treatment measures such as the onset of phototherapy and exchange transfusion level.

Methods

Population

Term and near-term neonates (≥35 weeks of GA) in the Neonatal Ward of Valiasr Hospital, who were under phototherapy from Oct. 2010 to Sep. 2011, were randomly divided into two groups of A and B. Exclusion criteria: neonates with the history of asphyxia, major congenital abnormalities, neurological diseases, hypothyroidism, Crigler-Najjar syndrome, urinary tract infection, lethargy, proven sepsis, acidosis, and admission to NICU, were excluded from the study. Besides, neonates who were discharged before the final sampling and after discontinuation of phototherapy, were also excluded.

Method of data collection: Venous blood sampling method was applied to measure the level of bilirubin in the laboratory of the hospital. Other data was collected either from the medical records, or the history taken from the mothers.

Phototherapy was initiated based on the the physician's decision, and the guidelines of The American Academy of Pediatrics. The following laboratory tests were performed for all neonates: peripheral blood smear; reticulocyte; direct Coombs' test; albumin in case bilirubin was approaching the exchange level; Glucose-6-phosphate dehydrogenase (G6PD) and serum bilirubin every 6 to 24 hr, according to the bilirubin level. To discontinue phototherapy, neonates were randomly divided into two groups. Discontinuation of phototherapy took place according to the following criteria:

Group A: In readmitted neonates, photother-apy was discontinued when bilirubin level was around 10-11 mg/dl in neonates admitted from nursery, with bilirubin level of 11 mg/dl or the 40th percentile of Bhutani nomogram, for the same day, whichever was lower (2).

Group B: In these neonates readmitted, phototherapy was discontinued when bilirubin level reached 12-13mg/dl, and in nursery-admitted neonates with bilirubin level of 13mg/dl or 75% of the risk factor nomogram (Bhutani nomogram) in the same day whichever was lower. If the level of bilirubin decreased more than what had been defined, the neonate would be transferred from group B to group A.

Method of phototherapy

Intensive or conventional phototherapy was performed depending on the level of bilirubin, and neonates were kept in incubators. Type of phototherapy changed through the course of treatment, based on the trend of bilirubin. Phototherapy was discontinued, regardless of the type. Neonates were breast-fed, but in the absence of the mother or shortage of breast milk, formula was used, instead. Some of the neonates received intravenous serum therapy in case of dehydration, or if bilirubin level was near the limit of exchange transfusion.

Measurement of bilirubin

The serum bilirubin level was measured about 24 hr after discontinuation of phototherapy. In case bilirubin measuring was done twice, the higher amount was taken into account. If it was on an increasing pattern, it would be checked again in 36, 48, or 72 hr, after discontinuation of therapy.

Method of sampling and measurement

In this study, intravenous sampling was applied. Total serum bilirubin (TSB) was measured by the auto-analyzer BT-3-000, and the dechloroaniline method, in the laboratory of Valiasr Hospital.

Criteria for significant rebound

Significant rebound was defined as an increase in serum bilirubin of more than 2 mg/dl after discontinuation of phototherapy (4). Resumption of phototherapy was based on physician's decision.

SPSS version 11.5 and X2 method were applied in data analysis.

Table 1. Show the comparison between independent variables, as well as the rate of rebound in both groups.

	Group A (%)	Group B (%)	*P* value
Number of neonates	57	58	
Phototherapy onset less than 48 hr	32 (56.2)	14 (24.4)	0.217
Hg > 17 mg/dl	17 (29.8)	12 (20.6)	0.510
Reticolycite ≥5 %	4 (7)	4 (6.8)	1.000
+ ve direct coombs	2 (3.3)	1 (1.8)	1.000
G6PD deficiency	1 (1.7)	3 (5.0)	0.348
Risk of hemolysis	8 (13.3)	4 (7.3)	0.288
AbNl physical exam	8 (13.3)	4 (7.3)	0.288
IV serum therapy	19 (31)	7 (12.7)	0.132
Caesarean section	37 (61.3)	28 (50.9)	0.245
Admission from the nursery	34 (56.7)	16 (29.6)	0.60
Significant rebound	9 (15)	4 (6.9)	0.13

Results

A total of 115 neonates completed the study, 57 (49%) of which were in group A, and 58 (51%) were in group B. Tables 1 and 2 show the comparison between independent variables as well as the rate of rebound in both groups and Table 3 shows the association of the rate of rebound with the age at onset of phototherapy Moreover, six neonates developed significant rebound more than 24 hr after the discontinuation of phototherapy, which is shown in Table 4.

The association between different factors and rebound in neonates was separately evaluated by regression logistic method. Overall, the only factor which had a significant association with rebound was intravenous serum therapy (p=0.005). Also, neonates with abnormal physical examination (hypotonia, decreased skin turgor, excessive weight loss) were prone to increased rebound (P=0.053).

Table 2. comparison between group A, and group B

	Mean±2SD group A	Mean±2SD group B	Significance (*P* value)
Gestational age	37.55±0.96	37.69±0.83	0.406
Phototherapy onset age	60.24±28.33	78.00±25.29	0.60
Hemoglobin	16.42±2.22	15.90±1.91	0.218
Reticulycite	2.36±1.44	2.37±3.26	0.840
Bilirubin before phototherapy	12.99±4.81	15.49±3.57	0.32
Bilirubin at discontinuation of phototherapy	9.64±1.71	12.34±0.78	0.001
Rebound serum bilirubin	10.37±2.60	10.87±1.83	0.240
Number of days under phototherapy	2.41±0.81	1.56±0.78	0.231

Discussion

In this study we aimed to compare significant rebound in hyperbilirubinemia in two groups of neonates after discontinuation of phototherapy in two different levels.

As a typical solution to deal with jaundice, one of the Middle East countries has suggested that phototherapy should be discontinued when the level of bilirubin reaches 12-13 mg/dl or 40th -75th percentile, which is less than the recommended level by AAP (3).

In this study, the cutoff point for discontinuation of phototherapy was based on the Kaplan's hyperbilirubinemia guidelines (3). In this guideline, the cutoff point for discontinuation of phototherapy is mentioned to be 12-13 mg/dl or between 40th to 75th percentile of Bhutani nomogram; lower percentiles are considered as risk factors for the neonates. In this study, lower percentile is determined for neonates in group A,

Table 3. the association of the rate of rebound with the age of the infant, at onset of phototherapy

Phototherapy onset age (hr)	Group A			Group B			P value
	Total number	Rebound	Percentage	Total number	Rebound	Percentage	
≥48	41	6	%14.6	51	4	%7.8	0.29
<48	16	3	%18	7	0	%0	

Table 4. Charactristics of six neonates developed significant rebound more than within 24 hr after the discontinuation of phototherapy

Risk factor(s)	Time after discontinuation	Bilirubin leve at the time of rebound	Bilirubin after discontinuation of phototherapy	Bilirubin at discontinuation of phototherapy	Group
Intravenous therapy	about 48hs	11.9	8.9	6.5	A
Phototherapy within the first 24hr, Reticolycite 18%, intravenous therapy	3 days	17	9	7	A
Phototherapy within the first 24 hr, Reticolycite 4,5	3 days	17.5	5.9	6	A
Gestational age 37 weeks, phototherapy within the first 24 hr, Reticolycite: 6.7%	48hs	13	8	7.2	A
Gestational age 37 weeks,caesarean section , intravenous serum therapy	48hs	12.8	11.5	10.2	A
Gestational age 35 weeks,caesarean section , intravenous serum therapy	48hs	10	8.5	6.7	A

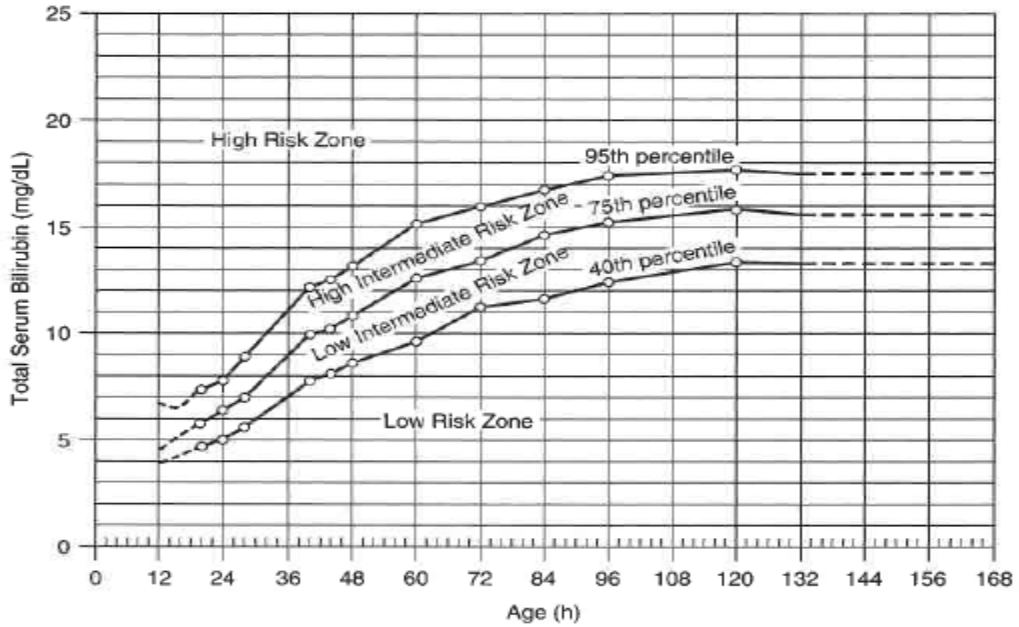

Figure 1. determining the risk in 2840 healthy newborns at 36 or more weeks of gestational age with birth weight of 2000 g or more, or 35 or more weeks ofgestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values (2).

and a higher percentile for neonates in group B.

The overall rate of rebound was 11.3% in our study. In a retrospective study conducted by Measles, the need for repeated phototherapy as an index for significant rebound, varied from 0.7 in infants who first received phototherapy on readmission to 8.2% in infants treated with phototherapy before discharge from the nursery (*P*=0.002) although phototherapy was discontinued in a lower bilirubin level in the second group (total serum bilirubin levels of 10.4±1.8 mg/dL vs. 12.3 ± 1.3 mg/dL). They concluded that for infants who require phototherapy during their birth hospitalization and for those with significant hemolytic disease, it is recommended to obtain a follow-up bilirubin level 24 hr after discharge. (5).

In a study by Anoradha for determining the incidence and magnitude of rebound, phototherapy was stopped when STB levels were less than 14 mg/dL in term neonates (in the hemolytic group 2 consecutive TSB < 14 mg/dl were needed) and if TSB fell 2 mg/dLbelow level at which phototherapy would be indicated for that age in <35GA or < 2500 gr birth weight. A rebound of 7.3% (2.3% to 23% based on absence or presence of the risk factors) has been reported. Risk factors of significant bilirubin rebound included gestation at birth<35 weeks, birth weight<2000 gm and onset of jaundice at <60 hr of postnatal age (7).

The main objective of this study was also to compare rebound in groups A and B, which showed no significant difference. Overall, it seems that discontinuation of phototherapy in lower levels of bilirubin has no significant effect on prevention of rebound. As it is shown in Figure 1, in term and healthy neonates, bilirubin has a rising trend until the fifth day of birth, though it follows a plateau, afterwards. Probably this natural trend is not affected by phototherapy. Significant rebound is defined as more than 2 mg/dl difference in bilirubin level at discontinuation and after discontinuation of phototherapy. For instance, if phototherapy is discontinued after 48 hrs, while bilirubin level is 8 mg/dl (40%), it can reach around 11 mg/dl, based on its natural trend; it is less probable for it to rise more. This type of increase, from our point of view, is defined as significant rebound, but it is neither clinically important or critical, nor does it mean the resumption of phototherapy. However, it might be necessary to monitor the trend of bilirubin. Therefore, the significant rebound which we define, does not necessarily mean the failure of phototherapy or presence of underlying pathology, but it can be the normal trend of bilirubin in a neonate, with or without therapy. According to Kaplan's study, rebound is defined as more than 120% bilirubin increase, bilirubin discontinuation or more than 14 mg/dl, and phototherapy does not resume until bilirubin level reaches 15 mg/dl (4). Although this difference is insignificant, it seems that more rebound in group A in comparison with group B is not justifiable (regarding this issue).

Table 3 shows the comparison of rebound in both groups, according to the time of onset of

phototherapy. As it can be seen in the Bhutani's curve (Figure 1), the normal trend of bilirubin is following an increasing pattern to about 96 hr after birth, reaching a plateau afterwards. Mechanism of hyperbilirubinemia was quite different at these two ages. In the current study, the neonates in the two groups (A and B), who underwent therapy before and after 48 hr of birth were compared separately from each other, and the group which underwent therapy in less than 48 hr of birth showed more rebound in group A. Although due to the small number of neonates in group B, it is not possible to draw a definite conclusion. Despite what was expected according to the results of other studies, no association was found between the known risk factors and bilirubin rebound. Overall, merely intravenous serum therapy had a significant relationship with rebound, which was independent of the effects of other risk factors. A factor in history and clinical examination could have led to the initiation of the intravenous serum therapy, for instance, dehydration or poor sucking/feeding could be a risk factor for hyperbilirubinemia rebound, or even absence of oral feeding via increasing entrohepatic cycle could also have resulted in the increase of jaundice. Some of these neonates received antibiotics due to suspected sepsis. Although number of this variable in neonates is not calculated, the effect of antibiotics on entrohepatic cycle and metabolism of bilirubin is quite probable. In various studies (1-6), presence of a risk factor in neonates is considered as an important factor of rebound, which is an indication for measurement of bilirubin level.

Perhaps, due to the small number of neonates with hemolysis in this study, it was not quite possible to draw the expected conclusion. Six neonates, with at least one risk factor, developed rebound after 24 hr, when rebound evaluation had been terminated. Three of them had blood group or Rh incompatibility, or reticulocyte was more than 5%. It seems that this type of rebound in this group of neonates is the result of ongoing hemolysis, and it could be stated that neonates with hemolysis could develop rebound after 24 hr; therefore, it is necessary to put neonates under longer monitoring. In this study, rebound was developed after 48 and 72 hr. Further studies are needed to determine the exact period for observation.

Conclusion

According to our study, continuation of phototherapy–until significant decrease in bilirubin level is observed– has no effect on decreasing rebound during the 24 hr after discontinuation of therapy.Despite the findings of this study, it is still more preferable to measure bilirubin levels after discontinuation of phototherapy in neonates who have risk factor/s. It is optional to keep the infant hospitalized during this monitoring process. It is important to know that rebound may occur after 24 hr; therefore, parents should be provided with necessary warnings at discharge.

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