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Original Article

The Effect of Intensive Phototherapy on Management of Hyperbilirubinemia in Neonates with the Gestational Age of 34 Weeks and More

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ABSTRACT

Background: Neonatal hyperbilirubinemia is one of the most common causes of neonatal morbidity and a global health priority. This study aimed to evaluate the effect of intensive phototherapy on management of hyperbilirubinemia with different etiologies.

Methods: This retrospective cohort study was conducted on 219 neonates with indirect hyperbilirubinemia, who had the indication for phototherapy, admitted to neonatal intensive care unit of Akbar-abadi Hospital, Tehran, Iran, during 2014-2016. The levels of total bilirubin, hemoglobin, reticulocyte, and glucose 6-phosphate dehydrogenase (G6PD) enzyme were examined and direct Coombs test was performed during hospital stay. The participants were assigned to four groups based on the etiology of hyperbilirubinemia and underwent intensive phototherapy. Finally, the level of total bilirubin was compared among the groups to assess the effect of intensive phototherapy.

Results: According to the results of this study, nonhemolytic jaundice was the most frequent cause of hyperbilirubinemia (82.19%). The mean bilirubin levels after 6 and 24 hours of intensive phototherapy were 4 and 6.2 mg/dl, respectively. Intensive phototherapy after 6 hours led to more significant reduction in the total bilirubin level of the neonates with total bilirubin level of higher than 14 mg/dl in comparison to those with the total bilirubin level of 14 mg/dl or less. The total bilirubin level was significantly decreased in all the groups after 6 and 24 hours of intensive phototherapy. Comparison of the rate of decrement of the total bilirubin level among the groups demonstrated that the neonates with ABO incompatibility showed the greatest decline after 6 and 24 hours of treatment (the rate of bilirubin decline: -5.16; P<0.001, the rate of bilirubin decline: -8.48; P<0.001, respectively).

Conclusion: Intensive phototherapy could efficiently lower the total bilirubin level in the neonates with gestational age of 34 weeks and more with hyperbilirubinemia of different causes. Moreover, the efficacy of intensive phototherapy was more significant in the subjects with higher levels of total bilirubin.

Keywords: Hyperbilirubinemia, Intensive phototherapy, Neonate

Introduction

Neonatal hyperbilirubinemia (jaundice) is a common disorder leading to serious complications such as kernicterus (bilirubin encephalopathy) (1, 2). About 50-70% of the neonates with gestational age of more than 35 weeks experience jaundice during the first week of life (3). With implementation of hyperbilirubinemia guidelines of the Canadian Pediatric Society, the incidence of severe neonatal hyperbilirubinemia has decreased in Canada from 1 in 2480 newborns to 1 in 8352 newborns (4).

Clinical manifestations of hyperbilirubinemia vary from yellowing of the skin and conjunctiva to encephalopathy (5). The major causes of hyperbilirubinemia are physiologic jaundice, ABO or Rh incompatibility, glucose 6-phosphate

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dehydrogenase (G6PD) deficiency, medications, congenital illnesses, birth trauma, excessive neonatal weight loss, infections, polycythemia, and prematurity (6-9).

Serial measurements of total bilirubin level and identifying the risk factors play a crucial role in prevention of serious complications of hyperbilirubinemia (1, 6, 10). Phototherapy, intravenous immunoglobulin therapy, and exchange transfusion are therapeutic modalities for neonatal jaundice (11). Phototherapy is the main treatment protocol to treat the moderate to severe hyperbilirubinemia, which facilitates the conjugation and excretion of bilirubin in the bile and urine.

The exposure of the skin to the light of wavelength 400 to 500 nm during phototherapy is more effective (12, 13). Intensive phototherapy implies usage of high levels of irradiance (more than 30 $mW/cm^2/nm$) in the 430 to 490 nm wavelength range. The light irradiance in intensive phototherapy is much higher in comparison to the conventional method (14, 15). The neonatal hyperbilirubinemia is one of the most common causes of neonatal morbidity and a global health priority (16). This study sought to evaluate the leading causes of neonatal hyperbilirubinemia and the effect of intensive phototherapy on lowering the total bilirubin level to decrease the morbidity rate.

Methods

This retrospective cohort study was carried out in the neonatal intensive care unit of Akbarabadi Hospital affiliated to Iran University of Medical Sciences, Tehran, Iran, from 2014 to 2016. The sample size was computed as 40 cases per group based on Zahedpasha et al. study (17). Considering the proposed sample size of 219, the power of the study was 80% and the alpha error was 0.05. A total of 219 neonates with indirect hyperbilirubinaemia, who had the indication for phototherapy, were entered into the study. The exclusion criteria included gestational age of less than 34 weeks, congenital anomalies, conjugated hyperbilirubinemia, sepsis, or dehydration.

The participants' demographic data and history of congenital diseases were extracted from their medical records. All the findings of the neonates' physical examination entailing primitive reflexes, level of consciousness, symptoms of cephalohematoma, seizure, and cyanosis were recorded. The levels of total bilirubin, hemoglobin, reticulocyte, and G6PD enzyme were evaluated and direct Coombs test (by IgG specific antiglobulin reagent) was performed during hospital stay.

To determine the effect of intensive phototherapy on lowering the level of total bilirubin, the subjects were assigned to two groups of neonates with the bilirubin level of more than 14 mg/dl and those with bilirubin level of 14 mg/dl or less. Additionally, the subjects were categorized into four groups based on the etiology of hyperbilirubinemia including nonhemolytic jaundice, ABO incompatibility, Rh incompatibility, and G6PD deficiency.

The neonates were treated based on the guidelines of American Academy of Pediatrics (18). All the subjects were naked, except for their eyes and genitalia, laid on a gauze hammock, and received intensive phototherapy (Tosan Co., Iran, model 022 with eight disk shaped, blue-light lamps; 220 V AC, 2002 A370 W). High levels of irradiance (30 $mW/cm^2/nm$ or higher) in the domain of 430 to 490 nm were continuously used; however, the treatment was paused during feeding, routine nursery care, and blood sampling. The level of total bilirubin was measured 6 and 24 hours after the therapy initiation.

Regarding the significant differences in the number of subjects in each group, the participants were randomly assigned to four groups. Out of 150 cases in the jaundice group, 15 subjects were randomly selected using SPSS software, version 18, to conform the number of the members in all groups. Thereafter, the total bilirubin levels, which were measured 6 and 24 hours after the therapy initiation, were compared among the four groups to assess the effect of intensive phototherapy on the management of hyperbilirubinemia. Moreover, the total bilirubin level was compared between the two groups with respect to the bilirubin level; upper and lower than 14 mg/dl.

Statistical analysis

Data analysis was performed using descriptive statistics (including frequency distribution and mean and standard deviation), mood's median test, which is a special case of Pearson's chi-squared test, Mann-Whitney U, and Wilcoxon signed-rank tests in SPSS, version 18. In all the measurements, P-value less than 0.05 was considered statistically significant.

Ethical considerations

In compliance with Declaration of Helsinki, this study was approved by the Institutional Review Board of Iran University of Medical

Sciences. Confidentiality of the personal data was assured and no extra cost was imposed on the subjects.

Results

Out of the 219 icteric subjects, 120 (54.79%) neonates were male and 132 (61.7%) were born through cesarean section. The mean age, gestational age, birth weight, and total bilirubin level on admission were 6.04±4.46 days, 37.78±1.44 weeks, 3116.17±489.30 g, and 16.1435±3.39 mg/dl, respectively. The main causes of hyperbilirubinemia were nonhemolytic jaundice (180 cases; 82.19%), G6PD deficiency (18; 8.21%), Rh incompatibility (11; 5.02%), and ABO incompatibility (10; 4.56%).

The total bilirubin level was less and more than 14 mg/dl in 42 (19.6%) and 172 (80.4%) neonates, respectively. It is worth mentioning that positive direct Coombs test was observed in one subject. Detailed demographic data of all the participants are shown on tables 1 and 2.

According to the results, there was no significant difference among the four groups' demographic data, except for the level of hemoglobin and reticulocyte count (P<0.05).

The medians of bilirubin decline rate after 6 and 24 hours of the intensive phototherapy were 4 and 6.2 mg/dl, respectively (Table 1). It was confirmed that the total bilirubin level after 6 hours of intensive phototherapy was decreased more significantly in the neonates with total bilirubin level of higher than 14 mg/dl in comparison to those with bilirubin levels of 14 mg/dl or less (the rate of bilirubin decline: 3.90 and 1.88, respectively (P=0.00); Table 3).

After 6 and 24 hours of intensive phototherapy, the total bilirubin level had significantly decreased in the groups with different causes of hyperbilirubinemia (Table 4). Comparison of the groups in terms of the rate of decrement in total bilirubin level demonstrated that the neonates with ABO incompatibility had the greatest decline after 6 and 24 hours of therapy (the rate of bilirubin decline: -5.16; P<0.001, -8.48, P<0.001; Figure 1).

Furthermore, the route of delivery was significantly different among the four groups (P=0.01). Given the results of repeated measures analysis of variance (ANOVA), intensive phototherapy significantly affected the total bilirubin level, while there was no significant

Table 1. Comparison of demographic data among the four groups

Variables	Median	IQR*	P- value
Gestational age (week)	38	37-39	0.939
Weight at the time of admission (g)	3170	2885-3415	0.295
Total bilirubin level on admission (mg/dl)	16.2	14.4-18.7	0.726
Total bilirubin level after 6 hours of therapy (mg/dl)	12.2	9-15.2	0.234
Total bilirubin level after 24 of therapy (mg/dl)	10	7.9-12.15	0.527
Hb** level	15	13.3-16.3	0.001
Ret***	1	0.5-2	0.029

* Interquartile range, ** Hemoglobin, *** Reticulocyte

Table 2. Demographic data of the subjects of each group

Variables	Nonhemolytic jaundice N=15		ABO incompatibility N=10		Rh incompatibility N=11		G6PD* deficiency N=18	
	Median	IQR**	Median	IQR	Median	IQR	Median	IQR
Gestational age (week)	38	36-39	38	37.25-40	38	38-40	38	38-39
Weight on admission	3250	3000-3550	3480	2510-3880	3180	3050-3350	3130	3017-3375
Total bilirubin level on admission	15.8	15-17.6	20.5	14.9-23	16.2	15-18.7	17.3	14.875-19.725
Total bilirubin level after 6 hours of therapy	13.2	11.8-14.4	17	7.775-18.4	13.9	12.3-16.5	14.2	11.05-15.95
Total bilirubin level after 24 hours of therapy	9.3	7.4-11.5	10	6.725-13.9	10.6	8.6-12.325	10.8	7.95-14.3
Hb*** level	15.6	14.9-16.6	10.2	9.15-11	10.5	14-16.8	14.3	12.55-16.05
Reticulocyte count	0.7	0.5-1.6	1.6	0.775-2.525	0.5	0.5-0.7	1.75	0.675-2.6

* Glucose 6-phosphate dehydrogenase, ** Interquartile range, ***Hemoglobin

Table 3. The effectiveness of intensive phototherapy after 6 and 24 hours

Variables	Bilirubin≤14	Bilirubin >14	P-value
On admission	13.06	18.13	
After 6 hours	11.18	14.23	0.00
After 24 hours	10	10.79	0.672
P-value	0.00	0.00	

Table 4. The effectiveness of intensive phototherapy in the four groups after 6 and 24 hours

Groups		Bilirubin basis – bilirubin level after 6 hours of therapy	Bilirubin after 6 hours - bilirubin level after 24 hours of therapy	Bilirubin basis -bilirubin level after 24 hours of therapy
Nonhemolytic jaundice	Z	-3.067[b]	-3.068[b]	-3.235[b]
	Asymp. Sig. (2-tailed)	.002	.002	.001
jaundice due to ABO incompatibility	Z	-2.812[b]	-2.505[b]	-2.812[b]
	Asymp. Sig. (2-tailed)	.005	.012	.005
jaundice due to Rh incompatibility	Z	-2.491[b]	-2.803[b]	-2.803[b]
	Asymp. Sig. (2-tailed)	.013	.005	.005
G6PD* deficiency	Z	-3.413[b]	-3.042[b]	-3.180[b]
	Asymp. Sig. (2-tailed)	.001	.002	.001

a: Wilcoxon Signed Ranks Test, b: Based on negative ranks, * Glucose 6-phosphate dehydrogenase

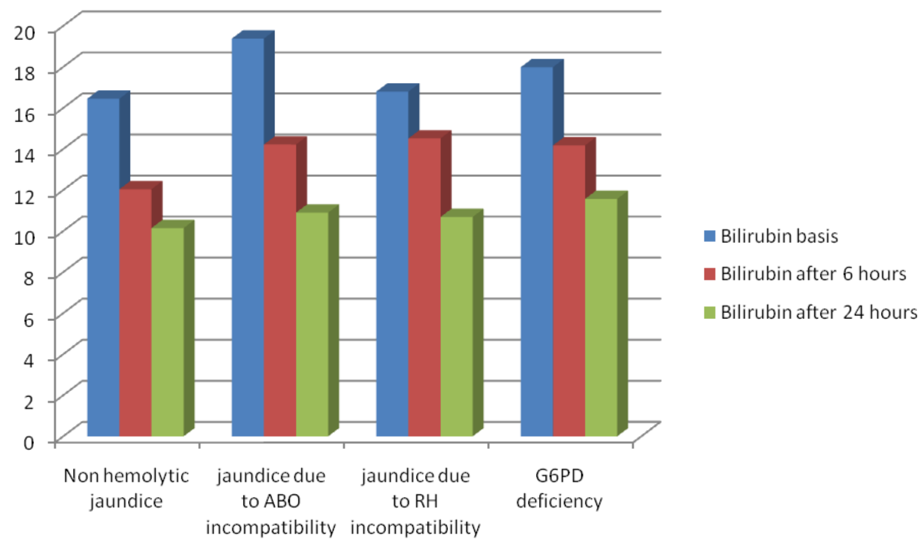

Figure 1. The comparison of the rate of total bilirubin level reduction among the four groups

Table 5. Effects of bilirubin in different groups

Variables	Effect	F	P-value
Bilirubin	Greenhouse-Geisser	29.934	<0.001
Bilirubin and groups	Greenhouse-Geisser	1.572	0.215

difference between the four groups in this respect (Table 5, Figure 1).

Discussion

Various studies exhibited the positive effects and safety of phototherapy as the main treatment modality in term and near-term infants with jaundice (7, 12, 19); however, its efficacy depends on some factors such as wavelength and irradiance of light and the level of total bilirubin (12).

According to the results of the present study, intensive phototherapy (with irradiance of more than 30mW/cm^2/nm, within the range of 430 to 490 nm wavelength) could efficiently and promptly reduce the total bilirubin level. After 6 to 24 hours of intensive phototherapy, the median of total bilirubin level was decreased by 4 and 6.2 mg/dl, respectively. Zahedpasha et al. confirmed the effect of intensive phototherapy on decreasing the mean total bilirubin level (4.35 mg/dl after 12 hours) and showed its safety regarding the stability of body temperature in comparison to single or double phototherapy (18). In addition, Edris et al. determined the efficacy of intensive phototherapy in rapid decline of total bilirubin level (6.7 mg/dl after 6 hours and 6.1 mg/dl after 12 to 48 hours of intensive phototherapy) among 188 newborns with hyperbilirubinaemia. Moreover, the results of the mentioned study revealed that the bilirubin decline rate during the first two days of hospital admission was significantly greater in subjects of intensive phototherapy group compared to those in conventional phototherapy group (7).

Regarding the results of this study, after 6 to 24 hours of intensive phototherapy, the total bilirubin level had significantly decreased in all the groups with ABO and Rh incompatibility, G6PD deficiency, or nonhemolytic jaundice. The decline rate in total bilirubin level was 2.49 to 3.41 mg/dl among the four groups during 6 hours of phototherapy. In comparison to the obtained results, Porter et al. indicated a lower range (about 1 to 2 mg/dl) and Edris et al. showed a higher range (6.7 mg/dl) of decrement within 4-6 hours of intensive phototherapy (9, 7).

Given the results of this study, the effectiveness of intensive phototherapy reduced with decline in total bilirubin level within 6 hours. Consistent with the results of he current study, De Carvalho revealed that the initial total bilirubin levels were significant factors for the efficacy of phototherapy; more pronounced and faster decline was observed in subjects with higher total bilirubin levels (20).

In addition, we noted that the rate of decrease in total bilirubin among the neonates with ABO incompatibility was more significant in comparison to the other three groups. Because the subjects with ABO incompatibility had higher total bilirubin levels in comparison to the other cases, it was assumed that neonates in this group responded more promptly to intensive phototherapy than their counterparts in the other groups.

In this study, the most common causes of hyperbilirubinemia were nonhemolytic jaundice (82%) and G6PD deficiency (8.21%). Based on a report by Kaplan, the causes leading to the hyperbilirubinemia vary among different geographic regions (21). Regarding the results of a study conducted in the neonatal intensive care unit of a teaching hospital in India (from January to August, 2008), G6PD deficiency (7%), ABO incompatibility (2%), and Rh incompatibility (0.8%) were determined as the most frequent etiologies of hyperbilirubinemia (22). The rate of nonhemolytic neonatal hyperbilirubinemia was 0.7% among the non-Asian full-term neonates of normal birth weight, who were delivered via vaginal method by nonobese and multiparous mothers (23). Abo El Fotoh showed that out of 202 neonates, 18 neonates (8.9%) had G6PD deficiency as an important cause of neonatal jaundice (18).

In this study, higher prevalence of G6PD deficiency was indicated (8.21%) in comparison to the previous reports of our center (5.7%) and another center in Tehran, Iran (7.5%) (24, 25).

Despite the availability of Rh immunoglobulin in Iran, 5.02% of the subjects were suffering from hyperbilirubinemia due to Rh hemolytic disease. This disorder was significantly more prevalent in the neonates with immigrant mothers, especially Afghans, who did not receive appropriate prenatal care.

In the current study, the rate of cesarean section among icteric subjects was higher than normal vaginal delivery. Furthermore, it was found that the route of delivery was significantly different among the four groups (P=0.01). In consistent to our result, Mansouri et al. and Mahmodi et al. reported no correlation between the route of delivery and prevalence of neonatal jaundice (26, 27). However, Bertini et al. demonstrated that cesarean section led to lower risk of neonatal hyperbilirubinemia (28).

Limitations of the study

We did not follow the subjects 24 hours after the therapy to monitor the bilirubin rebound after terminating the intensive phototherapy and side effects of this procedure. Further, we did not consider the other etiologies of hyperbilirubinemia including hypothyroidism or inflammatory diseases, which could provide informative and beneficial data.

Conclusion

According to the results of this study, 6 to 24 hours of intensive phototherapy could efficiently lower the total bilirubin level in neonates with gestational age of 34 weeks or more with hyperbilirubinemia of different causes. Moreover, the efficacy of intensive phototherapy was more significant in the subjects with higher total bilirubin levels. Further studies are recommended with larger sample sizes.

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Conflicts of interest

None declared.

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