Original Article

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Comparison of Two Phototherapy Methods (Prophylactic vs Therapeutic) for Management of Hyperbilirubinemia in Very Low Birth Weight Newborns

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Abstract

Objective: Preterm and low birth weight (LBW) infants are at greater risk of developing bilirubin-associated brain damage compared with term infants. Certainly, phototherapy, if used appropriately, is capable of controlling the bilirubin levels in LBW infants; but there is not a unique phototherapy treatment strategy in LBW infants. This study was designed to compare the prophylactic phototherapy and late treatment of jaundiced newborns weighing 1000-1500 grams.

Methods: Sixty newborns with birth weight 1000–1500 g were studied. They were divided into two groups: the "Prophylactic" group, in which phototherapy started within six hours after birth and continued for at least 96 hours, and the "Treatment" group, which received phototherapy when indicated according to birth weight and suspended when bilirubin level fell below 50% of bilirubin level for blood exchange. Mean value of daily transcutaneous bilirubin (TCB), duration of phototherapy, the need for blood exchange, and the highest TCB value in both groups were analyzed.

Findings: In the prophylactic group, the highest daily mean rate of TCB was 7.71±1.84 mg/dl, which happened on the third day. In the treatment group, it was 8.74±1.72 mg/dl on the fourth day after birth. The TCB values in prophylactic group were significantly less than those of the treatment group only on the fourth and fifth days after birth (P<0.001). Although the median duration of phototherapy in the treatment group was shorter than that of the prophylactic group (137.60±57.39 vs 168.71±88.01 hours, respectively), this difference was not statistically significant. Only one neonate needed blood exchange in the treatment group.

Conclusion: The prophylactic phototherapy treatment for babies weighing 1000–1500 g significantly decreases bilirubin levels on the fourth and fifth days after birth but the clinical course of hyperbilirubinemia does not alter in LBW infant, as indicated by the non-significant change in the duration of phototherapy.

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Key Words: Phototherapy; Neonatal jaundice; Preterm Neonate; VLBW infant

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Introduction

Neonatal jaundice is a common problem and one of the most prevalent clinical conditions requiring evaluation and management within the first few days of life [1]. About two-thirds of neonates become clinically jaundiced (serum bilirubin concentration >5mg/dl) and more than 97% of full-term and preterm babies demonstrate a biochemical hyperbilirubinemia (serum bilirubin level >1 mg/dl)[2]. Although indirect hyper-bilirubinemia is a benign (physiologic) condition for most infants, in minority of cases it can become severe and lead to hyperbilirubinemic encephalo-pathy or kernicterus[3].

In the full-term newborns, physiologic jaundice is characterized by a peak serum bilirubin concentration of 5 to 6 mg/dl (86 to 103 µmol/L) on the third to fourth day of life.

Furthermore, term healthy newborns whose total serum bilirubin (TSB) levels exceed this threshold (7 to 17 mg/dl or 104 to 291 µmol/L) are identified as having exaggerated physiologic jaundice. TSB levels higher than 17 mg/dl in healthy full-term infants are not considered physiologic [4,5]. Such infants should be evaluated and monitored carefully.

The premature newborn infant has an exaggerated form of physiologic jaundice with mean serum bilirubin concentrations reaching peaks of 10 to 12 mg/dl (171 to 205 µmol/L) or more with delay in reaching the maximum concentration as compared with full-term neonates (on the fifth and sixth day of life).

Although this could be considered physiologic because of its occurrence in all preterm infants, the mean peak of unconjugated bilirubin concentrations higher than 10 mg/dl may be associated with acute bilirubin encephalopathy or kernicterus in certain high-risk, very low birth weight neonates [5,6]. Thus, many neonatologists aggressively approach hyperbilirubinemia in very low birth weight (VLBW) neonate and use prophylactic or early phototherapy to prevent TSB levels from ever becoming sufficiently great to require exchange transfusion [7].

Although phototherapy is the standard method of treatment in neonatal hyperbilirubinemia with minimal side effect, it is not completely safe. Some possible side effects reported for phototherapy are: dehydration, persistent ductus arteriosus, and interruption of maternal-infant interaction[8,9]. On the other hand, bilirubin is a powerful antioxidant and may have a physiologic role. It has been suggested that maintaining very low TSB levels with aggressive phototherapy might be associated with development of retinopathy of prematurity due to reducing antioxidant levels[10]. Thus, some researchers believe that treatment with phototherapy in very low birth weight infants initiate when the TSB level is raised enough, and that phototherapy immediately after birth (prophylactic) is not suitable.

Therefore, although guidelines for management of hyperbilirubinemia in term and near term neonates are clear, there is a controversy in premature neonates and especially in VLBW infants. The aim of this study was to compare the prophylactic phototherapy and late treatment of jaundiced newborns weighing 1000-1500 g.

Subjects and Methods

During three months, sixty jaundiced premature neonates who were admitted to the neonatal ward of Shahid Beheshti Hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, were prospectively enrolled in this study.

The Research Committee in Isfahan University of Medical Sciences approved the study, and informed written consents were obtained from the parents.

These neonates were all of Iranian race, healthy, breastfed, delivered before the 35th week of gestation, had birth weight between 1000 and 1500 gram, and were appropriate for gestational age (AGA) following an uneventful pregnancy.

The exclusion criteria were major congenital malformations, hemolytic disease (Rh or ABO incompatibility and a positive Coombs' test), infection (congenital or acquired), G6PD deficiency, sepsis, asphyxia, dehydration, conjugated (>15% of the total serum bilirubin levels) hyperbilirubinemia, and prolonged jaundice persisting beyond the 14th day of life, and maternal or neonatal use of phenobarbital.

The enrolled infants were randomly assigned to two groups, either phototherapy initiated during the first six hours after birth and continued up to

96 hours regardless of their TSB (prophylactic group), or phototherapy started when the TSB level reached higher than 8 mg/dl and discontinued with the TSB level lower than 5 mg/dl (treatment group). In the prophylactic group phototherapy continued after 96 hours if TSB level was higher than 8 mg/dl and discontinued when the level fell below 5 mg/dl.

All phototherapy units contained four special blue lamps (Philips TL18/54, Philips lighting, Rosendale, Netherlands) and were adjusted to be 20cm above the infants. Lamps were changed regularly after 1500 hours of utilization.

Total serum bilirubin levels were measured at the beginning, and then every 24 hours.

Laboratory investigations included complete blood count, blood group typing of neonates and their mothers, direct and indirect Coombs' tests, reticulocyte count, total serum bilirubin level, and erythrocyte G6PD level. Bilirubin was measured by Bilicheck bilirubin analyzer (SpectRx Inc. Norcross, Georgia, USA). Serum bilirubin level (total and direct) was also measured for control of Bilicheck measurements.

TSB was measured by Unistate® Bilirubinometer (Reichert-Jung, Germany), and determination of direct bilirubin was made by the colorimetric method of Lathe and Ruthven.

Other tests were performed accordingly by the standard laboratory methods.

The obtained data were transferred to coding sheets in a computer database. All analyses were performed using SPSS version 10.5 (Chicago Inc., USA). Values were expressed as mean (standard deviation). Numeric variables were compared between the two groups using the independent Student's test. The Chi-square test was used to compare sex and type of delivery between the two groups. A *P*-value of less than 0.05 was considered statistically significant.

Findings

Table 1 shows the basic demographic data of the two groups. There were no significant differences between the two groups regarding the mean birth weight, mean head circumference, mean length, mean gestational age, gender distribution, and mode of delivery. Thus, the prophylactic and treatment groups were comparable.

As shown in Table 2, the maximum mean bilirubin levels in the phototherapy and treatment groups were observed on the third and fourth day of life, respectively. The total bilirubin levels were significantly lower in the prophylactic group on the fourth and fifth days of life (Table 2).

Total bilirubin levels exceeded 8 mg/dl in 29 (96.6%) and 18 (60%) newborns of the treatment and prophylactic groups, respectively (*P*=0.01).

In the prophylactic group, the minimum and maximum duration of phototherapy was 96 and 356 hours, respectively. Minimum and maximum duration of phototherapy in the treatment group was 72 and 312 hours, respectively. The required mean duration for phototherapy in the treatment

Table 1: Demographic data of infants in the prophylactic and treatment groups

Demographic data	Prophylactic n=30	Treatment n=30	95% CI	*P*-value
Birth weight (g) [mean (SD)]	1262.66 (181.71)	1283.66 (174.48)	-113.06 _ 71.06	NS
Length (cm) [mean (SD)]	39.96 (2.56)	40.25 (3.17)	-1.77 _ 1.20	NS
Head circumference (cm) [mean (SD)]	27.95 (1.74)	27.88 (1.62)	-0.80 _ 0.93	NS
Gestation (weak) [mean (SD)]	30.23 (2.48)	30.90 (2.17)	-1.87 _ 0.53	NS
Sex				
Male (n)	15 (50%)	17 (56.7%)		NS
Female (n)	15 (50%)	13 (43.3%)		
Delivery				
Vaginal (n)	13 (43.3%)	7 (23.3%)		NS
Cesarean (n)	17 (56.7%)	23 (76.7%)		

SD: Standard Deviation / CI: Confidence Interval / NS: Non-significant

Table 2: Daily mean (standard deviation) of total bilirubin of the prophylactic and treatment groups in the first week of life

Total Bilirubin (mg/dl)	Prophylactic n=30	Treatment n=30	95% CI	*P*-value
1st day	4.91 (0.30)	4.35 (0.29)	-0.29 _ 1.40	NS
2nd day	6.76 (0.37)	7.57 (0.40)	-1.90 _ 0.29	NS
3rd day	7.71 (0.33)	8.29 (0.19)	-1.36 _ 0.19	NS
4th day	6.90 (0.24)	8.74 (0.31)	-2.64 _-1.04	<0.001
5th day	6.90 (0.31)	8.63 (0.30)	-2.6, -0.84	<0.001
6th day	6.95 (0.41)	7.47 (0.26)	-1.49 _ 0.47	NS
7th day	6.68 (0.46)	6.57 (0.31)	-1.02 _ 1.20	NS

CI: Confidence Interval

and prophylactic groups was 137.60±57.39 and 168.71±88.01 hours, respectively (*P*=0.1).

The mean age of neonates at the beginning of phototherapy was significantly lower in the prophylactic group, but the mean age at discontinuation of phototherapy was not significantly different (Table 3).

One neonate in the treatment group and none in the prophylactic group required blood exchange transfusion and all were discharged in good general condition.

Discussion

In this study, the mean bilirubin concentration was significantly higher in the treatment group, compared with that in the prophylactic group on the fourth and fifth day of life. However, the mean duration of phototherapy was not different between the two groups. Our data also revealed that although the number of neonates with bilirubin concentration >8 mg/dl was more in the treatment group (*P*=0.01), the mean age of neonates at the time of discontinuation of phototherapy in the prophylactic and treatment groups was not statistically different.

In a similar study, conducted by Leite et al in Brazil, 81 infants with birth weight of less than 2000 grams were divided into two groups. In the first group (early phototherapy group), phototherapy was started 12 hours after birth and continued for at least 96 hours. In the second group (late phototherapy), phototherapy started only when bilirubin levels reached 8 mg/dl, and it stopped when bilirubin reached 5 mg/dl [11]. The results showed that the mean bilirubin levels in the early phototherapy group on the seventh day and in the late phototherapy group on the second day had significant difference (*P*<0.01). Leite et al showed the median duration of phototherapy in the early and late phototherapy groups were 96 hours (minimum of 96 and maximum of 156 hours) and 51 hours (minimum of zero and maximum of 120 hours), respectively. In this study, none of the infants needed blood transfusion. The results of our study have some similarities with and some differences from those found by Leite et al. in Brazil. The duration of phototherapy was longer in the early

Table 3: Age of patients at the beginning and the end of phototherapy in both groups

Age of patients (hour)	Prophylactic		Treatment		95% CI	*P*-value
	Mean (SD)	Range	Mean (SD)	Range		
At the beginning of phototherapy	3.23 (1.41)	1-6	62.40 (18.56)	24-96	-65.97 _ -52.36	<0.001
At the end of phototherapy	174.61 (91.03)	97.5-360	200 (51.52)	122-352	-63.61 _ 12.84	NS

SD: Standard Deviation / CI: Confidence Interval / NS: Non-significant

phototherapy group in both studies, but the difference was not significant in our study. The reason for longer phototherapy duration might be the fact that bilirubin level reach its peak on the third day in term infants and in a week in preterm infants and perhaps starting phototherapy when bilirubin has not reached its peak cannot have any effect on decreasing the bilirubin level. Therefore, in early phototherapy, besides receiving prophylactic phototherapy within the first days, infants need phototherapy when bilirubin increases, but in the therapeutic group, infants only receive phototherapy when bilirubin increases and when the indication of phototherapy exists. Hence, the infants did not receive prophylactic phototherapy within the first days in the therapeutic group, which shortened the duration of phototherapy. In the Brazilian study, bilirubin level of late phototherapy group reached its maximum on the second day after birth, but in the present study bilirubin level of the therapeutic group (late phototherapy) reached its maximum on the fourth day after birth. Actually, in the present study prophylactic phototherapy has changed the time of reaching the bilirubin level to the peak from the fourth day (in the therapeutic group) to the third day (in the prophylactic group), but in the Brazilian study prophylactic phototherapy has changed it from the second day (in the therapeutic group) to the seventh day (in the prophylactic group). This difference in the two studies is not reasonable but it could be due to differences in the range of infants' weight in the two studies and the difference in the time of starting and stopping phototherapy based on different bilirubin levels. However, it seems that the results of the present study is more reasonable, because prophylactic phototherapy prevented the increase of bilirubin after first three days and peak level of bilirubin occurred in the third day. In other words, this result shows that prophylactic phototherapy can prevent increase of the bilirubin level in following days.

In another similar study conducted by Curtis-Cohen et al in 1985 [12], 22 preterm infants (birth weight 850±220 grams) were divided into two groups of receiving phototherapy after birth and receiving phototherapy if bilirubin reached 5 mg/dl. In contrast with our and the Brazilian studies, the mean bilirubin concentrations were not different in the two groups. This discrepancy in efficacy of prophylactic phototherapy maybe due to the time of starting phototherapy in the treatment group (5mg/dl) which is considered as too soon and this level was close to the bilirubin level in prophylactic group.

On the other hand, duration of phototherapy was longer in prophylactic phototherapy group[12]. However, in our study the length of phototherapy was longer in prophylactic group but in contrast to Curtis-Cohen et al[11] and Leite et al[12] studies, this difference was not significant.

This discrepancy maybe due to differences in study design and perhaps by increasing sample size in the present study, this difference would become significant because this result was common in all three studies. Although the duration of phototherapy is longer in the prophylactic group, none of the infants was hospitalized solely because of phototherapy; all of them were preterm infants who were hospitalized for prematurity and longer phototherapy caused no longer hospitalization. In any case, longer duration of phototherapy in infants receiving prophylactic phototherapy exposes them to its side effects.

In another study conducted by Tripathi et al, 50 neonates were randomly assigned to two groups of control and prophylactic phototherapy. They showed that there was no significant difference in the age of reaching peak bilirubin levels in either group[13]. This result is consistent to the findings of Curtis-Cohen et al [12] indicating that prophylactic phototherapy in preterm babies is not beneficial.

There is no similarity among all studies regarding the mean bilirubin concentration during phototherapy in early and late phototherapy groups. Probably, it is because of the different study designs, weight range of infants, environments, and race. Also, the time of starting phototherapy in late phototherapy group can be an affective factor on the decrease of bilirubin and patient's clinical improvement.

Conclusion

In conclusion, our results indicate that although prophylactic phototherapy in preterm infants,

who weigh between 1000-1500 grams, can significantly decrease jaundice in the fourth and fifth day after birth compared with the control group, the prophylactic phototherapy in preterm neonates is unnecessary, because duration of prophylactic phototherapy is longer than late treatment group and the neonates in late phototherapy group had desirable control of bilirubin without any complications and with shorter duration of phototherapy.

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Conflict of Interest: None

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