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Prophylactic Versus Therapeutic Phototherapy in Very Low Birth Weight Infants

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Abstract

Background: Preterm and very low birth weight (VLBW) infants are at great risk of hyperbilirubinemia and bilirubin-associated brain damage.

Objectives: The aim of this study was to compare the efficacy of prophylactic versus therapeutic phototherapy in VLBW infants.

Patients and Methods: Fifty VLBW infants were randomly assigned to receive either phototherapy from the first day of life regardless of their serum bilirubin level for up to five days (prophylactic group) or phototherapy when their bilirubin level reached half the exchange transfusion level (therapeutic group). All data, including gestational age, gender, birth weight, serum bilirubin level on the first day, peak serum bilirubin concentration, the age at which the peak serum bilirubin level was reached, duration of phototherapy, and the number of exchange transfusions, were studied and analyzed.

Results: The mean bilirubin level on the first day in both groups exhibited no significant difference. The peak serum bilirubin was 7.7 ± 1.4 and 8.5 ± 2.1 mg/dL in the prophylactic and therapeutic group, respectively, and there was no significant difference in the age at which the peak serum bilirubin levels were reached in both groups (2.4 ± 1.2 vs. 2.1 ± 1 days in the prophylactic and the therapeutic group, respectively). The mean duration of phototherapy in the prophylactic group was 84 ± 43 hours, while for the therapeutic group it was 72 ± 39 hours, and hence the difference was not significant. The need for an exchange transfusion was lower in the prophylactic group compared to the therapeutic group (33% vs. 7%), although the difference was not statistically meaningful ($P < 0.112$).

Conclusions: According to our study, phototherapy should not be used as prophylactic therapy for all VLBW infants, but rather it should be individualized in order to maintain low bilirubin levels.

Keywords: Hyperbilirubinemia, Phototherapy, Prophylactic, Newborn

1. Background

Hyperbilirubinemia is a common clinical problem in neonates during the first few days of life. The most common form of hyperbilirubinemia observed in neonates is due to unconjugated bilirubin, which is fat soluble and able to cross the cell membranes. If not adequately monitored and treated, a high level of unconjugated bilirubin is potentially neurotoxic, resulting in acute bilirubin encephalopathy and potentially progressing to conditions including kernicterus and/or death (1-3).

Preterm infants, especially very low birth weight (VLBW) newborns, are more likely to be subject to hyperbilirubinemia due to various physiologic conditions such as short red blood cell (RBC) lifespan, low albumin level and the related limited binding capacity, deficiency in hepatic conjugation, and an increase in enterohepatic circulation. Associated diseases such as infection, hemolysis, hypoalbuminemia, asphyxia, acidosis, and hyperosmolarity that increase bilirubin production, reduce albumin binding, or compromise the permeability of the blood-brain barrier could place VLBW newborns at a greater risk of neurological sequelae (4-6).

As a safe and effective method of treatment for neonatal hyperbilirubinemia, phototherapy has been used in clinical practice for more than 50 years (4, 7, 8). Phototherapy leads to the configurational and structural photoisomerization of the bilirubin into a water soluble form, which can then be excreted through biliary and urinary routes without the need for hepatic conjugation (9).

Phototherapy can be used as a prophylactic from the first day of life and such treatment can continue for four or five days (10). It can also be used for therapeutic purposes, in which case it is implemented when the biliru-

bin level reaches half that of the exchange transfusion level (10).

2. Objectives

As there is no common agreement regarding which treatment (prophylactic or therapeutic) is the most efficient in very low birth weight infants, the present randomized clinical trial was carried out to compare the serum bilirubin concentration on the first day of life, the peak serum bilirubin level, the age at which the maximum bilirubin level was reached, and the number of exchange transfusions among the prophylactic and therapeutic groups.

3. Patients and Methods

A randomized clinical trial was carried out at the neonatal unit of Shahid Beheshti Hospital, Kashan University of Medical Sciences, over a one-year period on neonates with a birth weight of less than 1500 gr. Those neonates who exhibited hemolysis (ABO, Rh, minor group incompatibility, and a positive direct Coombs test), G6PD deficiency, major congenital anomalies, maternal use of phenobarbital, and conjugated hyperbilirubinemia were excluded. The study was approved by the Research Ethics Committee of Kashan University of Medical Sciences. After informed parental consent was obtained, the eligible VLBW infants were randomly assigned to receive either phototherapy from the first day of life regardless of their serum bilirubin concentration for up to five days (prophylactic group) or phototherapy from when their bilirubin level reached half that of the exchange transfusion level until the bilirubin level fell to 5 mg/dL (therapeutic group). The random allocation of the neonates into either the prophylactic or the therapeutic phototherapy group was achieved by using sealed opaque envelopes for allocation concealment.

The phototherapy units contained four special blue lamps (Philips TL18/54, Philips Lighting, Rosendale, The Netherlands).

The first measurement of serum bilirubin was performed prior to the start of phototherapy in both groups and then repeated every day at indicated intervals during the hospital stay. All data, including gestational age, gender, birth weight, serum bilirubin level on the first day, peak serum bilirubin concentration, age at which the peak serum bilirubin level was reached, duration of phototherapy, and number of exchange transfusions, were studied and analyzed using Fisher's exact test.

4. Results

During the study period, a total of 50 VLBW infants participated in this study. Of the two groups, seven babies from the prophylactic group and three babies from the therapeutic group died. Therefore, the final analysis included data from 18 infants in the prophylactic group and 22 infants in the therapeutic group. The Consolidated Standards of Reporting Trials (CONSORT) diagram of the study is shown in Figure 1.

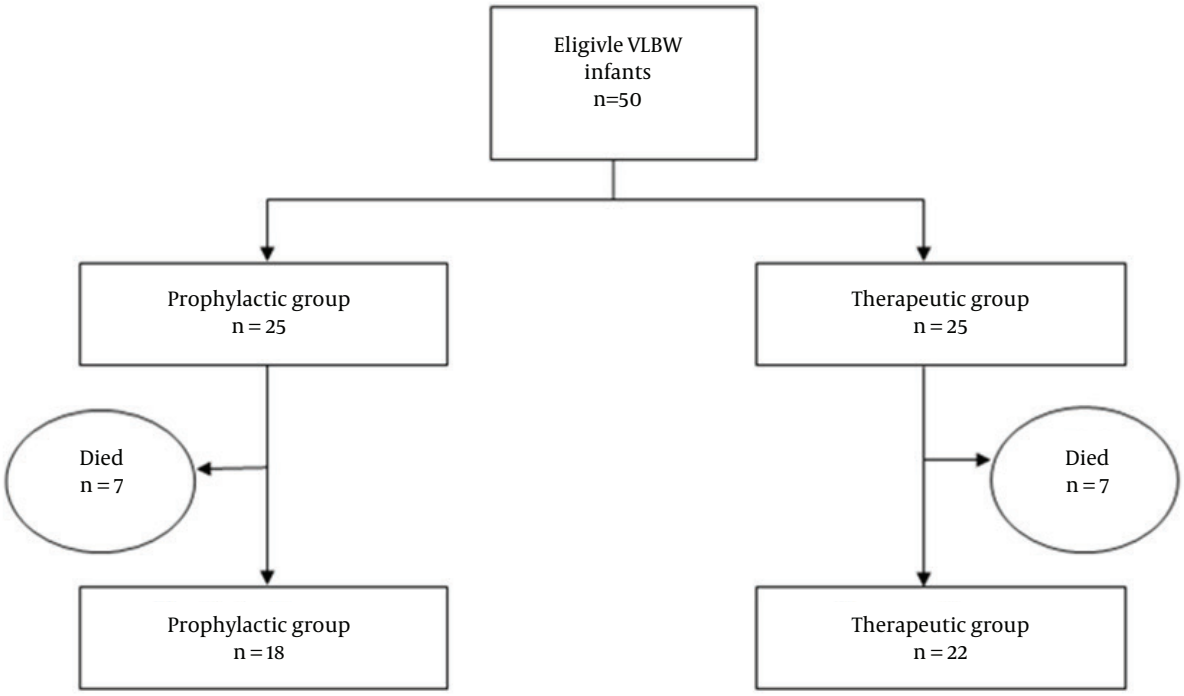

Figure 1. Consort Diagram of the Study

Table 1. Characteristics of VLBW Infants Enrolled in the Study[a,b]

Variables	Study	Control
GA	31.17 ± 1.8	31 ± 2.3
BW	1284 ± 214	1254 ± 242
Male	11	13
Female	7	9
Cesarean	12	14
NVD	6	8
Death	7	3

[a]P Value are not significant.
[b]Data are presented as mean ± SD or number.

Table 2. Bilirubin level, Duration of Phototherapy, and Number of Exchange Transfusions in the Prophylactic and the Therapeutic Group[a]

Variables	Study	Control	P Value
Serum bilirubin on the first day, mg/dL	5 ± 2	4.6 ± 1.6	.486
Age at which peak serum bilirubin level was reached, days	2.4 ± 1.2	2.1 ± 1	.393
Peak serum bilirubin level, mg/dL	7.7 ± 1.4	8.5 ± 2.1	.228
Duration of phototherapy, hr	84 ± 43	72 ± 39	.179
Exchange transfusions, No	5	2	.112

[a]Data are presented as mean ± SD or number.

The mean gestational age (GA) in the prophylactic and the therapeutic group was 31.7 ± 1.8 weeks and 31 ± 2.3 weeks, respectively, while the mean birth weight (BW) was 1284 ± 214 and 1254 ± 242 in the prophylactic and the therapeutic group, respectively. There were no differences in terms of gender or mode of delivery between the groups (Table 1).

There was no significant difference in the mean bilirubin level on the first day of life in both groups. Despite the early initiation of phototherapy in the prophylactic group, there was no significant difference between the groups in terms of the peak serum bilirubin level. In addition, there was no significant difference in the age at which the peak serum bilirubin level was reached in both groups.

The mean duration of phototherapy in the prophylactic group was 84 ± 43 hours, while for the therapeutic group it was 72 ± 39 hours.

Exchange transfusions were performed in five (33%) and two (7%) babies in the prophylactic and the therapeutic group, respectively. The need for an exchange transfusion was significantly lower in the latter group, although the difference did not reach statistical significance (Table 2).

5. Discussion

The management of hyperbilirubinemia in VLBW infants is a major concern. Brain growth and development are not yet complete in VLBW infants, which places them at greater risk of neurological sequelae than their full-term counterparts (11, 12). As unconjugated hyperbilirubinemia is very common in preterm and low birth weight infants, and because there is no way to predict a safe level of bilirubin in VLBW infants, the prophylactic use of phototherapy has been suggested.

The efficacy of prophylactic phototherapy was previously evaluated by Curtis-Cohen et al. (13). In their study, 22 preterm infants were randomly assigned to receive phototherapy either soon after birth or when the serum bilirubin level reached 5 mg/dl. No decrease was found in the peak bilirubin level in either group, which is similar to the results of our study. In a study conducted on newborns weighing less than 2000 gr who did not suffer from hemolytic disorders, early treatment implemented at 12 hours of life was safer when compared to late treatment that was implemented when the bilirubin level was equal to or greater than 8mg/dl, which suggested that early treatment with phototherapy is a good option for low birth weight infants even if treatment is required for a longer duration (14). Iranpour et al. studied 60 neonates with a birth weight of 1000-1500 g and, comparing the two methods, they found that the serum bilirubin levels were significantly lower than those in the treatment group on only the fourth and fifth days of life, but that the median duration of phototherapy was longer than that of the treatment group (15). Photo-

therapy acts on bilirubin in the capillaries of the skin or interstitial space and its efficacy is directly proportional to the serum bilirubin level. If phototherapy is initiated when the bilirubin concentration is not high enough, it is not efficient and the duration of treatment is lengthened (4).

Researchers who suggest the use of prophylactic phototherapy believe that if it is implemented early enough, it may prevent larger increases in the serum bilirubin level and so may reduce the need for exchange transfusions, although Morris and Tripathi did not identify any significant difference in the rate of exchange transfusions (16, 17). In the present study, despite phototherapy being introduced very early in the prophylactic group, we found a higher rate of exchange transfusions in that group compared to the therapeutic group (33% versus 7%). This higher rate may be due to the clinical status of the infants or the severity of the underlying illness, but this finding needs further evaluation with a larger sample size.

Premature and very low birth weight infants are at great risk of oxygen toxicities (18) and bilirubin is considered to have antioxidant properties (4). Hence, it has been suggested that phototherapy be used as a prophylactic rather than as a therapeutic agent at a predetermined bilirubin level in VLBW infants.

The effect of prophylactic phototherapy on neurodevelopmental impairment raises a major concern. Jangaard et al. evaluated 95 VLBW infants who received prophylactic phototherapy at 12 hours of life or therapeutic phototherapy when the serum bilirubin reached 8.8 mg/dl or greater. The infants were followed up to 12 - 18 months of corrected gestational age. There was a trend toward poor neurodevelopment outcomes such as cerebral palsy in infants receiving prophylactic phototherapy. Jangaard et al. concluded that a low bilirubin level may be associated with a better prognosis in VLBW infants (18). Moreover, Morris et al. found a higher mortality rate in infants with a birth weight of less than 750 gr when they received aggressive phototherapy. This higher rate of mortality due to aggressive phototherapy might be due to oxidative injury to cell membranes. Such injury is probable in preterm infants whose thin and gelatinous skin readily transmits light and so subjects them to phototoxicity (16).

Our study may have been limited by the small sample size and lack of follow-up regarding the long-term adverse outcomes for newborns who received the two phototherapy regimens.

While phototherapy is relatively safe and effective in reducing the bilirubin level, the risks of such treatment could be significant for preterm infants, leading to dehydration, temperature instability, and electrolyte imbalance. According to our study, phototherapy should not be used as a prophylactic therapy for all VLBW infants, but rather it should be individualized to maintain low bilirubin levels.

Further studies to evaluate the effects of prophylactic phototherapy on neurodevelopment and other the long-term outcomes for VLBW infants are warranted.

Footnote

Authors' Contribution: Study concept and design: Ziba Mosayebi; analysis and interpretation of data: Ziba Mosayebi, Mahboubeh Homayounfar, and Amir Hossein Movahedian; drafting the manuscript: Ziba Mosaybi, Mahboubeh Homayounfar, and Amir Hossein Movahedian; critical revision of the manuscript: Shahin Nariman and Setareh Sagheb; statistical analysis: Mahboubeh Homayounfar.

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