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ORIGINAL ARTICLE

Comparison of Continuous and Intermittent Phototherapy in the Treatment of Toxic Neonatal Jaundice: A Double-blind Clinical Trial

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KEYWORDS

Neonatal Jaundice;
Phototherapy;
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ABSTRACT: Hyperbilirubinemia is most common cause of readmission after early hospital discharge for healthy newborns. Phototherapy is the first line for treating neonate jaundice and preventing any complications. There is a lack of general agreement on whether continuous phototherapy is more effective than intermittent phototherapy. Traditional phototherapy is continuous phototherapy witch causes emotional disorder and inadequate breast feeding. In this research, we are trying to answer this question and also developing quality and quantity of neonatal jaundice treatment. In this clinical trial study, 82 healthy term neonate with jaundice admitted in the neonatal ward of Hajar hospital of Shahrekord city, Iran, were randomly designated into two groups (N=41): the first group treated with 1 hour turn on and 1 hour turn off phototherapy and the second group treated with 0.5 hour turn on and 3 hours turn off phototherapy. In both groups, total and direct bilirubin levels were measured per 12 hours. Serum sodium and potassium levels were measured before and after phototherapy. The average of phototherapy duration and admission duration was 2±0.8 days, and 2.9±1.4 days in the first and second groups, respectively. Mean admission duration in intermittent phototherapy was significantly lower than continuous phototherapy (P<0.0001). There was a significant reduction (P<0.0001) of serum sodium and potassium levels after intermittent phototherapy. Intermittent phototherapy decreases the admission duration and total sodium and potassium concentrations. Intermittent phototherapy (1 hour turn on and 1 hour turn off) is recommended.

INTRODUCTION

Hyperbilirubinemia is a prevalent and in most of the times benign neonatal problem [1-5] which is the most common cause of hospitalization of infants after discharge from the hospital [6-8]. Neonatal jaundice caused by indirect hyperbilirubinemia has still remained as the main cause of infant hospitalization [8]. Severe indirect Hyperbilirubinemia is highly neurotoxic for infants if proper actions aren't taken on time and hence diagnosis and treatment to prevent complications are very important [4, 8]. Diagnosis of Hyperbilirubinemia needs treatment based on total serum bilirubin measurements [6]. Jaundice occurs in the first week of birth in more than 60% of infants (gestational age greater than 37 weeks) and 80% of preterm infants (gestational age less than 35 weeks) [1, 2, 5, 9]. It is caused by the accumulation of non-conjugated (indirect), non-polar, and fat-soluble bilirubin in the skin. This non-conjugated bilirubin is the final product of protein catabolism in a series of enzymatic reactions by both oxygenase and biliverdin reductase, as well as the reduction of non-enzymatic components in reticuloendothelial cells.

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It may also be caused by conjugated bilirubin deposition. Non-conjugated bilirubin is conjugated by Uridine diphosphate glucuronic acid transferase in the liver and is converted into polar and water-soluble form [1].

Although bilirubin acts as an antioxidant, increased indirect and non-conjugated bilirubin levels increase the toxicity of neuronal cells. The conjugated bilirubin form is not neurotoxic, but direct hyperbilirubinemia causes serious liver disorders and systemic diseases [1]. A non-conjugated bilirubin that passes through a placenta and is toxic to the nervous system, is not soluble in water, and therefore difficult to dispose of, it becomes a conjugated bilirubin to be soluble in water [1]. Non-conjugated hyperbilirubinemia occurs as a result of disruption of the balance between bilirubin production and excretion. When the amount of bilirubin produced increases in comparison to its excretion (for reasons such as hemolytic anemia, polycythemia, shorter red cell life in newborn infants, infection, increased intra circulation of liver), bilirubin is increased in the body [1, 10,11]. Sometimes due to damage or reduced activity of the transferase enzyme and other related enzymes (for reasons such as genetic defects, oxygen deficiency, infection, thyroid failure), the competition of some drugs with transferase enzyme or the reduction or absence of the amount of the required enzyme, bilirubin excretion fails and the bilirubin through the body increases [1].

Jaundice may be present at birth or at any other time during the infancy. Jaundice usually starts from the face and expands depending on the bilirubin level to the abdomen and then to the legs, so that at levels of bilirubin up to 5 mg/dl jaundice is observed at the face, at concentration of 15 mg/dl, jaundice extends to the abdomen and at concentration of 20 mg/dl, jaundice observed to the foot. Visible jaundice signifies an increase in the amount of bilirubin, but a precise estimate of the concentration of bilirubin in circulation and other tissues in the body is difficult [1, 10, 12].

The first line and the most commonly used treatment for healing neonatal jaundice and prevention of its complications, as well as a significant reduction needs replacement of blood or phototherapy [1, 7, 10, 13]. Although photo-toxicity occurs with this method, but it has been shown that there are few clinical complications and a safe method that has been used in the treatment of neonatal jaundice for decades [1, 3,7].

The most rate of light absorbed by bilirubin is in the range of blue light spectra [470-420 nm] [1, 3, 10]. The only one that can penetrate the skin has the ability to make changes in the bilirubin molecules. The light penetration increases with increasing wavelength, so the light with maximum energy at wavelength (490-460 nm) is most effective [3].

Bilirubin absorbs light energy in the skin, and several light-chemical reactions occur. One of the main products derived from phototherapy as a result of "reversible" photos-isomerization is the reaction of the conversion of non-conjugated toxic 15Z and 4Z bilirubin to non-conjugated bilirubin isomers, 15E and 4Z, which can be secreted in the bile. The main products of phototherapy are Lumirubin, an irreversible construction isomer of bilirubin and can be secreted and repelled by the kidneys [1, 3,7].

Phototherapy effects are typically evaluated by measuring the reduction in each unit of TSB per unit time. Of course, in cases where the TSB is rising rapidly, the slower rate of this increase also suggests effective phototherapy [3].

The treatment of fluorescent lamps, especially blue light (with a range of 400 nm to 500 nm apart), the distance between the lamps and the baby in the range of 15 and 20 cm, and the location of fibro-optic patches underneath the baby are conducted to increase contact [1,7,10, 20]. Phototherapy of neonates with blue light is widely and successfully used to treat neonatal jaundice, as well as the reduction of serum bilirubin concentrations and subsequent prevention of kernicterus [14]. Infants are relocated continuously for maximum contact. Phototherapy should be discontinued to reduce the indirect concentration of bilirubin to safe levels according to the age of the baby and his condition [1].

Some researchers have argued that the total light energy needed to reduce TSB levels may be less frequent in continuous phototherapy [7, 14], and alternate phototherapy can allow the baby to be evaluated during the period of inactivity. Similarly, in a laboratory study, mouse

lymphoma cells were used to compare the cytotoxic effects of continuous, continuous phototherapy, which in this study did not increase the cell death to continuous or intermittent exposure, and a high level of necrosis in the cells under phototherapy It was seen intermittently [7]. In all of these cases, it may be argued that these effects may also be due to a decrease in bilirubin levels [7].

In contrast to these studies, some other studies have proposed continuous phototherapy [1, 10, 15]. In the studies, the rate of formation of photo-isomers was investigated, in some 17 to 18% of photo-isomers, after 2 hours of phototherapy, while in others, about 40% of photo-isomers were developed after phototherapy after 3 hours [3, 16]. In this research, we are trying to answer this question and also developing quality and quantity of neonatal jaundice treatment.

MATERIALS AND METHODS

Studied Population

The study population included infants with Hyperbilirubinemia who were hospitalized to infants Unit of Hajar hospital in Shahrekord, Iran. This work were operated under supervision of SKUMS research deputy and approved by the ethical research committee by number: IR.SKUMS.REC.1391/8.

Inclusion criteria included healthy infants (with no signs of infectious diseases or any kind of metabolic syndrome) with total serum bilirubin higher than 12 and less than 18 mg/dl, age over 3 days, weight between 2500 to 4000 g and fed by breastfeeding, no direct bilirubin increase of more than 2 mg per deciliter, no risk symptoms such as lethargy, nausea, fever, maternal and neonatal complications, polycythemia, anemia, and a history of neonatal jaundice extreme conditions. The outflow conditions included clinical and laboratory symptoms of infection, any abnormality, dehydration, glucose-6-phosphates deficiency, incompatibility blood groups (ABO), Coombs positive test, indirect bilirubin more than 2 mg / dl and total bilirubin more than 18 mg/dl.

Sample size and sampling method

Assuming that the mean hospitalization time of infants is 2.5 ± 0.8 days and at least 0.5 days of difference in the time of admission of newborns in two groups, with 95% confidence and 80% probability of testing in each group was 41 and the total study was 82. Neonates were randomly assigned to two groups using random numbers (Tables 1 and 2).

Table 1. Eligible infants exposed to phototherapy for 1 hour ON and 1 hour OFF (alternate phototherapy)

		Group 2		Group 1	
TSB	***P* value**	**Mean±Standard deviation**	**Number**	**Mean±Standard deviation**	**Number**
12	0/05	13.4±1.3	41	13.5±1.8	41
24	0/36	12.5±1.4	41	12±2.4	41
36	0/11	10.3±4.4	41	10.5±3.4	41
48	0/005	9.1±5	41	5.9±5.6	41
60	0/01	6.9±5.9	41	5.2±3.5	41
72	0/0001	6±5.4	41	3.7±1.3	41
84	0/0001	5.5±4.3	41	2.5±0.6	41
96	0/0001	4.9±2.7	41	2.3±0.5	41
108	0/0001	4.3±1.9	41	1.6±0.2	41
120	**0/0001**	**3.8±1.4**	**41**	**0/0±0/0**	**41**

Table 2. Qualified infants exposed to phototherapy for half an hour OFF and 3 hours ON in a regular basis (continuous phototherapy)

DSB	*P* value	Group 2		Group 1	
		Mean±Standard deviation	Number	Mean±Standard deviation	Number
12	0/67	0.6±0.2	41	2±0.6	**41**
24	0/21	0.6±0.2	41	0.5±0.1	**41**
36	0/60	0.5±0.3	41	0.5±0.2	**41**
48	0/40	0.5±0.3	41	0.3±0.3	**41**
60	0/02	0.3±0.3	41	0.3±0.2	**41**
72	0/0001	0.3±0.3	41	0.7±0.2	**41**
84	0/0001	0.3±0.2	41	0.15±0.03	**41**
96	0/0001	0.3±0.2	41	0.14±0.03	**41**
108	0/0001	0.3±0.1	41	0.09±0.01	**41**
120	0/0001	0.3±0.2	41	0/0±0/0	**41**

The infants of the two groups also were similar in terms of variables such as gestational age, birth weight, delivery method, sex, hospitalization age, hemoglobin levels, and bilirubin levels at entry.

Method of data collection and its tools

Data was collected using a questionnaire by the pediatric intern during the period of admission of each neonate, total bilirubin and serum levels were measured every 12 hours and serum sodium and potassium concentrations were measured at the time of arrival and after treatment and completed using a blood sample taken Honored Nurse, and then the experiments were done at the Hajar Hospital Laboratory, shahrekord university of medical sciences.

Study method

This double-blind clinical trial was conducted from July to October 2017 on 82 healthy and infants with jaundice admitted to infants unit of Hajar hospital in Shahrekord. Newborns were randomly assigned to 2 groups of 41 patients under phototherapy according to the mentioned conditions of entry and exit from the study, and first of all their parents were taken informed consent for this research. The first group under phototherapy was switched on for 1 hour ON and 1 hour OFF, and the second group was exposed to phototherapy for half an hour ON and three hours OFF. Phototherapy was discontinued if the bilirubin reached 10 mg /dl. Phototherapy was performed by the 4 standard TL 20W/52 SLV/25 light (Philips Co) with blue light and the distance to the baby's surface 30 cm, and the bulbs of the device were replaced every 2000 hours of use. Naked babies were treated with phototherapy with the eyes and genital tract covered. Breast feeding continued throughout the stay. Blood sampling interval (To determine the level of amber, Bilirubin was administered every 12 hours). Serum sodium and potassium concentrations in neonates treated with alternate phototherapy were measured before and after the phototherapy period.

Neonates in two groups were similar in terms of variables such as gestational age, birth weight, and mode of delivery, sex of infants, hospitalization age, hemoglobin levels, and bilirubin levels at entry. The information was completed in a questionnaire by an intern and checked by a specialist in the Neonatal Department of Hajr Hospital. The required blood samples were taken by the nursing staff of the neonatal department and sent to the hospital laboratory for the results.

RESULTS

In the study, a total of 82 patients were included in two groups of 41 patients. The first group of eligible infants were exposed to phototherapy for 1 hour ON and 1 hour OFF (alternate phototherapy). The second group of eligible babies underwent phototherapy for half an hour ON and three hours of light OFF (continuous phototherapy). Out of 82 neonates, 54 were boys and 28 were girls. From 54 neonates, 26 ones were in the first group and 28 ones in the second group. The mean age of the first group was 9.5 days (4 to 13 days) and the mean age of the second group was 5.9 days (4 to 14 days). In general, there was no significant difference between the two groups in terms of sex, age of infants, birth weight and total bilirubin (referring to P. Value).

The minimum duration of hospitalization was 12 hours in the first group and 1 day in the second group (24 hours). The maximum duration of this period in the first group was 4.5 days (108 hours) and the second group was 6 days (156 hours). There was a significant difference between the two groups during the hospitalization period, so that the average number of hospital days in the first group was 2.0 ± 0.8 and in the second group 2.9 ± 1.10 days (P. Value = 0.0001).

There was no significant difference between the two groups in the reduction of serum bilirubin level and serum levels from the time of admission until 48 hours after admission. After 48 hours of phototherapy and admission, the first group was significantly faster than the second group. Information on these data is presented in Table 3.

Table 3. Total serum bilirubin in two groups every 12 hours during admission

Sodium concentration after treatment (mEq/l)		Sodium concentration at the time of entry (mEq/l)		P value
Mean±Standard deviation	**Number**	**Mean±Standard deviation**	**Number**	
141±5.0	41	142.9±4.2	41	0.0001

Table 4. The mean of direct serum bilirubin in two groups every 12 hours during the period of admission

Sodium concentration after treatment (mEq/l)		Sodium concentration at the time of entry (mEq/l)		P value
Mean±Standard deviation	**Number**		**Number**	
4.9±0.6	41	4.6±0.4	41	0.0001

Considering that after 120 hours of phototherapy and admission, there were only 3 patients in the groups, there was no statistical analysis after 120 hours.

Intermittent phototherapy in infants with hospitalized jaundice has a good effect on serum sodium level and a statistically significant difference in serum sodium concentration after phototherapy (P value 0.0001) (Tables 4). The mean sodium content of newborns under intermittent phototherapy at the time of entry was 142.9 ± 4.2 mA/L, and 141 ± 5 mA/L when treatment was completed. Similar results were observed in the serum potassium level of these infants, so that the mean serum potassium concentration was 4.6 ± 0.4 mm/ (P value 0001/0) (Tables 3).

DISCUSSION

Neonatal jaundice caused by indirect hyperlipidemia still remains the main cause of infant admission [8]. Jaundice is seen in the first week of birth in more than 60% of infants and is close to term (gestational age greater than 37 weeks) and 80% premature infants (gestational age less than 35 weeks) [1, 2, 5, 9]. Yellowish is caused by the accumulation of non-conjugated (indirect), non-polar, and lipid-soluble bilirubin in the skin [1]. This non-conjugated bilirubin is the final product of protein catabolism in a series of enzymatic reactions. It may also be caused by conjugated bilirubin deposition. Bilirubin in the skin absorbs light energy and, through several chemical-optical reactions, converts to products that can be excreted through the bile and kidneys [1, 3, 7]. The first line of treatment and

the most commonly used treatment for the treatment of neonatal jaundice caused by indirect hyperbilirubinemia and the prevention of its complications is phototherapy [1, 7, 10, 13]. The therapeutic effects of phototherapy depend on the amount of energy emitted in the range of effective wavelengths, the distance between the bulbs of the baby, the level of exposure to the skin of the baby's body with light, the age of the baby, and the level of TSB and hemolysis [1, 3]. Despite the increasing use of phototherapy, there are still gaps and shortcomings in various studies about this therapist [17]. These include the lack of efficacy and efficacy of current phototherapy in the expected range [18], duration of treatment and admission, and efforts to reduce it [19], the need for less frequent use of electricity for treatment [18], reduction of separation period mother and baby during phototherapy and subsequently avoid interference in the emotional relationship between mother and infant, as well as intermittent infant feeding, which causes inadequate breast feeding and subsequently weight loss and hyperextension in newborn infants [20]. Therefore, the aim of this study was to determine the efficacy of intermittent phototherapy and its comparison with current persistent phototherapy in reducing serum bilirubin levels and duration of admission in healthy and infants with Hyperbilirubinemia. In previous studies, different results were obtained. The results of a study suggested the effect of continuous phototherapy more than intermittent, and Lau and Fung presented the effects of continuous and alternate phototherapy as 1 hour of brightness and 3 hours of silence, identical and similar [15, 21]. However, the findings of this study showed that the duration of hospitalization in newborns treated with intermittent phototherapy was significantly lower than that of neonates undergoing continuous phototherapy, so that the mean days of admission of newborns in the first group was less than 1 day, less than the second group. Also, the reduction in total bilirubin and serum direct levels in neonates in the first group was much faster than that of the second group. The results showed that the effect of alternate phototherapy was 1 hour of brightness and 1 hour off more than continuous phototherapy as 3 hours of light and 0.5 hour of silence. Since one of the questions and concerns in the treatment of neonatal jaundice is maternal and infant separation under phototherapy, followed by inadequate breastfeeding and weight loss as well as hyperthermia hypothermia, in addition to the study, the effect of intermittent and continuous phototherapy was investigated and the serum sodium and potassium levels of newborns treated with intermittent phototherapy before and after phototherapy were compared. In previous studies, the serum sodium and potassium levels were evaluated in neonates under continuous phototherapy before and after phototherapy. The results indicated a significant difference in sodium concentration before and after continuous phototherapy and a significant increase in serum potassium levels after 72 hours of continuous phototherapy, which, with the discontinuation of phototherapy, returned to normal range [22]. The results of this study showed that sodium and potassium levels of serum decreased significantly after the completion of intermittent phototherapy.

An important issue in neonates with jaundice is increased level of oxidative stress in which lead to reduction in level of antioxidants such as ascorbic acid and glutathione (GSH). This weakens the ability of these antioxidants to challenge the growing stress. Reduced antioxidants and increased oxidative stress can cause neural cell death [23]. In this condition there would be change in lipid per-oxidation which is evidenced by increase in MDA level [24-26]. This also shows presence of enhanced oxidative stress. The increase in the MDA level might be due to enhanced production of free radicals resulted from increase in oxidative damage in these patients. Increase in free radicals and oxidative stress cause oxidization of other biomolecules such as membrane lipids [24]. Increase in MDA level in neonatal jaundice also causes the oxidative damage, which is attributed to free radical formation, causing lipid per-oxidation and increase in MDA which is the main product of lipid peroxidation [26-29]. Through Lipid peroxidation, the phospholipids of the membrane are converted to MDA and increased MDA level has been reported in patients' erythrocytes of neonatal jaundice [30].

A significant reduction in levels of non-enzymatic antioxidant defense system including in vitamin E, glutathione and ascorbic acid has been reported in neonatal jaundice patients [23]. The non-enzymatic antioxidants are responsible for scavenging important free radicals and reduction of peroxidation in cell membranes [30]. The reduction of non-enzymatic antioxidants is resulted from enhanced turnover, suggesting an enhanced defense against oxidant damage in these patients.

The superoxide which is an important antioxidant enzyme is also increased in these patients which is indicative of enhanced superoxide production. The enhanced activity of antioxidant enzymes and increased MDA might be compensatory regulation in these patients in response to enhanced oxidative stress. This suggests than the use of antioxidants might be useful in these, at least for reduction of the side effects of jaundice. In this regard, the use of natural antioxidants should be more beneficial [31-34]. Natural antioxidants have been shown to be less toxic and more reliable [33-36]. They also mostly have effects on various diseases [35-38]. Therefore, these natural antioxidants can be useful for other infants' problems, too.

According to the findings of this study, phototherapy is recommended for 1 hour and 1 hour off for treatment of infants with Hyperbilirubinemia. Because in addition to decreasing hospitalization time, it decreases serum sodium and potassium levels, decreases the separation time of mother and infant during the period of hospitalization, and reduces the consequences and complications, including interference in the emotional relationship between mother and infant. The inadequate nutrition of the infant and consequently the reduction of hyperhidrosis, which is considered a serious threat to life, is also reduced. Alternate phototherapy, along with effective treatment, also reduces energy consumption and helps maintain energy resources.

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Ethical considerations

All procedures were approved by the ethics committee of Shahrekord University of Medical Sciences, Iran (IR.SKUMS.REC.91-7-15).

Conflict of interests

The authors declare no conflict of interest.

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