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Effect of Bilineaster Drop on Neonatal Hyperbilirubinemia

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Abstract

Background: Hyperbilirubinemia is considered one of the most prevalent problems in newborns. Phototherapy, exchange transfusion, and herbal medicine are common therapeutic approaches for preventing any neurologic damage in infants with neonatal jaundice. However, herbal **medicine** is less commonly used.

Aim: This study aimed to investigate the effect of bilineaster drop on neonatal hyperbilirubinemia.

Method: This study was a randomized clinical trial conducted on 98 term neonates (aged 2-14 days) with neonatal jaundice admitted to Ghaem Hospital of Mashhad, Iran, during 2015. These newborns were randomly assigned into intervention (phototherapy and bilineaster drop) and control (only phototherapy) groups. Total and direct serum bilirubin levels were measured at the time of admission and then 12, 24, 36, and 48 h after treatment. Data were analyzed using independent t-test and repeated measures ANOVA through Stata software (Version 12).

Results: The mean ages of the newborns at the time of admission were 6.2 ± 2.5 and 6.04 ± 2.4 days in the intervention and control groups, respectively. The intervention group showed higher reduction in mean duration of hospital stay, readmission rate, and bilirubin levels 12 and 24 h after the intervention, compared to the control group ($P > 0.001$). However, the two groups demonstrated no statistically significant difference 36 h and 48 h after the intervention ($P = 0.06$, $P = 0.22$, respectively). Repeated measures ANOVA indicated that the intervention had no significant effect on the reduction trend of bilirubin levels ($P = 0.10$ [total], $P = 0.06$ [indirect]) in both groups. Nonetheless, bilirubin levels significantly diminished in both groups over time ($P < 0.001$).

Implications for Practice: The results of this study demonstrated that the use of bilineaster drop along with phototherapy could cause a significant decrease in the levels of total and direct bilirubin; however, the intervention had no effect on the downward trend of bilirubin.

Keywords: Hyperbilirubinemia, Neonatal, Phototherapy, Bilineaster drop

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Introduction

Hyperbilirubinemia is a condition caused by excessive level of bilirubin in the blood, resulted from an imbalance between the rate of bilirubin production and bilirubin elimination. This disease manifests itself with a yellowish discoloration of the infants' skin and eyes (1, 2). Neonatal hyperbilirubinemia is one of the leading causes of hospitalization and readmission in the first few weeks of life throughout the world. Timely and appropriate implementation of phototherapy, exchange transfusion, and pharmacologic therapy is effective in controlling high bilirubin levels among newborns with hyperbilirubinemia. In addition, taking these measures can prevent severe complications such as severe hyperbilirubinemia, acute bilirubin encephalopathy, and kernicterus (3, 4).

Although phototherapy is the most commonly applied treatment for neonatal jaundice, it has numerous side effects including disconnection of mother-infant bonding, ambient temperature imbalance, dehydration, electrolyte disorders, transient erythematous rash, loose stool, hyperthermia, bronze baby syndrome, and circadian rhythm disorders (5, 6). Likewise, exchange transfusion may lead to complications such as blood-borne infections, thrombocytopenia, coagulation disorders, graft-versus-host disease, necrotizing enterocolitis, portal vein thrombosis, electrolyte disorders, apnea, bradycardia, cyanosis, vasospasm, hypoxic-ischemic encephalopathy, acquired immunodeficiency syndrome, cardiac arrhythmias, and sudden death (3 deaths per 1000 cases) (7, 8).

Although some medications (e.g., phenobarbital, oral zinc sulfate, oral activated charcoal, metalloporphyrins, and clofibrate) have been proposed for the treatment of neonatal jaundice (9-12), more studies are needed to confirm the safety and effectiveness of these drugs (9, 10, 12-14). Purgative manna is one of the most common medicinal plants used for the treatment of hyperbilirubinemia in many parts of Iran, which is suggested in traditional medicine (15-17).

Different studies have reported various results on the effectiveness of purgative manna on hyperbilirubinemia. For example, Mansoori et al. (2013) and Nabavi Zadeh et al. (2006) showed that purgative manna has no effect on reducing neonatal jaundice (15, 18), whereas Khoshdel et al. (2012) and Ghotbi et al. (2007) concluded that the use of purgative manna could decrease bilirubin level and duration hospital of stay (19, 20). The study by Azad Bakht et al. was the first attempt to investigate the impact of pharmaceutical product of purgative manna (bilineaster drop) on 100 infants with hyperbilirubinemia. Sobhan Pharmaceutical Company marketed this product after confirming its positive impact and receiving permission from the Ministry of Health (21). Bilineaster drop is prepared from aqueous extract of purgative manna and contains 300 mg/ml of mannitol (22).

There are a number of studies examining the pharmaceutical forms of purgative manna; however, these studies have reported conflicting results and bear some limitations. Despite the fact that purgative manna has been commonly used for the treatment of neonatal jaundice in traditional medicine, pediatricians hold different views regarding the prescription of this herbal medicine. In this regard, conducting further studies investigating the effectiveness of bilineaster drop seems quite essential. Therefore, this study aimed to investigate the effect of bilineaster drop on neonates with hyperbilirubinemia admitted to the Pediatric Emergency Department of Ghaem Hospital of Mashhad, Iran.

Methods

This randomized clinical trial was performed on 98 term neonates (aged 2-14 days) with gestational age of 35-42 weeks suffering from jaundice who were admitted to the Pediatric Emergency Department of Ghaem Hospital of Mashhad, Iran, during June 22, 2015-March 5, 2016. The newborns were selected based on convenience sampling method and were randomly assigned to intervention and control groups. Regarding the results of Ghotbi et al. (23), the maximum sample size was 49 cases for each group with type-I error probability of 5%, type-II error probability of 20%, and standard deviation of 1.5 for both groups. Data analysis was performed through G*Power software.

The inclusion criteria were 1) gestational age of 35-42 weeks, 2) birth weight more than 2000 g, 3) birth Apgar score higher than 7, 4) exclusive breastfeeding, 5) no severe birth defects, 6) no birth asphyxia, 7) no maternal eclampsia or pre-eclampsia, 8) no treatment with phototherapy or other treatment before hospitalization, 9) nonpathologic jaundice, 10) direct bilirubin less than 2 mg/dl, and 11) total serum bilirubin more than 17 mg/dl or to the extent recommended by the American Academy of Pediatrics (8).

The exclusion criteria consisted of 1) indication for exchange transfusion, 2) mild or transient respiratory distress, 3) sepsis, 4) hemolytic hyperbilirubinemia (reticulocyte more than 5% in peripheral blood

smear), 5) Rh or ABO incompatibility, 6) positive direct Coombs test, and 7) decreased G6PD. In total, six cases were excluded from the study because of observing indications for exchange transfusion (2 cases), decreased G6PD (1 case), positive direct Coombs test (2 cases), and positive blood cultures (1 case).

For the purpose of data collection, the bilirubin levels, hematocrit, direct and indirect Coombs, reticulocytes, CBCT, G6PD, blood group, and Rh in the infants were measured. Besides, the direct and total bilirubin levels were evaluated on admission and 12, 24, 36, and 48 h after starting the treatment. The bilirubin measurements continued until the infant was discharged based on the physician advice.

Additionally, the demographic information was extracted from the medical records of the mothers and newborns. Phototherapy was performed based on the principles defined by the American Academy of Pediatrics (8). To this end, all infants were bare and only their eyes and genital area were covered during phototherapy. Phototherapy was interrupted only for breastfeeding, changing diapers, and taking blood samples. The infants' age at the onset of phototherapy and the level of total serum bilirubin were recorded at the beginning and end of this procedure.

The control group received the routine treatment, whereas the intervention group received both the conventional treatment and bilineaster drop (Sobhan Pharmaceutical Company, according to the manufacturer's instruction and approval of pediatrician) as much as five drops per kg of body weight three times a day. All the infants were fed exclusively with breast milk. The phototherapy was carried out under the same conditions for all the infants. Each ship phototherapy unit had eight blue light therapy lamps and their distance was 30-40 cm from the baby. Lamp power was measured at the end of each month through photometry. If the power was less than $17 \mu\text{W}/\text{cm}^2/\text{nm}$, the lamp would be replaced. Sometimes the lamps were switched earlier than one month due to frequent use of the device. The bilirubin levels were determined in the hospital laboratory through AutoAnalyzer. The person performing the test was blinded about the groups. In addition, researchers examined the effects of treatment one month after hospital discharge by calling the infants' mothers.

The researchers submitted a written introduction letter from Nursing and Midwifery School of Sabzevar, Iran, to the officials of the research environment. Afterwards, the researchers explained the study objectives and process to the parents of neonates and obtained their informed consent for participating in the study. Subsequently, the patients' parents were assured of the confidentiality of the data. Furthermore, they were informed about the therapeutic intervention along with its success rate, complications, and benefits. In addition, the study phases were explained to the parents and their written consent was obtained. Based on the ethical codes proposed by the Deputy of Research of the university, the parents were reminded of arbitrariness of participating in the study. Thereafter, the researchers presented some information regarding the method of application and purpose of the investigation, possible losses, benefits, nature, and duration of the research and answered their questions. The parents were also given some information on the employed medication (drop). Moreover, researchers' phone number was registered on the drop package for quick access of the intervention group, and the parents were assured that they could call whenever needed. The researchers made follow-up phone calls one or two months later by phone to seek the health status of the newborns.

The data were analyzed using Shapiro-Wilk and Chi-square tests for qualitative variables and paired t-test for quantitative ones through Stata software (Version 12). Furthermore, for the purpose of comparing the bilirubin mean score, independent and paired t-test, ANCOVA, and repeated measures ANOVA were performed. P-value less than 0.05 was considered statistically significant.

Results

The results of the Chi-square test revealed that there was no significant difference between the intervention and control groups regarding male: female ratio ($P=0.84$), vaginal birth and cesarean-section ratio ($P=0.83$), history of jaundice in the first child ($P=0.1$), birth rank ($P=0.89$), distribution of blood groups in the mothers ($P=0.20$), and distribution of blood groups in the newborns ($P=0.20$). Similarly, t-test showed no significant difference between the two groups in terms of mean age on admission, age at the onset of jaundice, birth weight, maternal age, hemoglobin level, and gestational age.

The results of t-test demonstrated a statistically significant difference between the intervention and control groups regarding mean weight at the time of admission ($P=0.03$). This difference in admission weight between the two groups led us to conduct ANCOVA for controlling the effect of this variable. The mean duration of hospital stay was 35.9 and 49.5 h in the intervention and control groups,

respectively. In other words, the intervention group was discharged from the hospital 13.6 h earlier, which explains the significant difference between the two groups ($P < 0.001$; Table 1). According to the independent t-test, the mean levels of total and indirect bilirubin indicated no significant difference between the two groups before the intervention ($P = 0.18$). The results of repeated measures ANOVA reflected an interaction effect between the intervention and time. Consequently, receiving bilineaster drop over time was found to have a significant effect on the reduction of total and indirect bilirubin levels in the intervention group, compared to the control group ($P < 0.001$ for both). Furthermore, the main effect of time was statistically significant ($P < 0.001$). Indirect bilirubin level at baseline was not significantly different between the two groups; however, the intervention group showed higher reduction of indirect bilirubin levels after 24 h, compared to the control group (8 mg/dl vs. 5.9 mg/dl), and this accounts is caused that the time factor in this study to be statistically significant.. No significant main effect was found for the intervening factor on the reduction in total ($P = 0.06$, $F = 2.6$) and indirect ($P = 0.06$, $F = 3.4$) bilirubin levels. As can be noted, regardless of the time factor, indirect bilirubin level was lower in the intervention group than the controls in general. Despite the non-significant difference between the two groups at baseline, the difference increased over time. However, the effect size of the intervening factor ($\eta^2 = 0.02$) was insignificant.

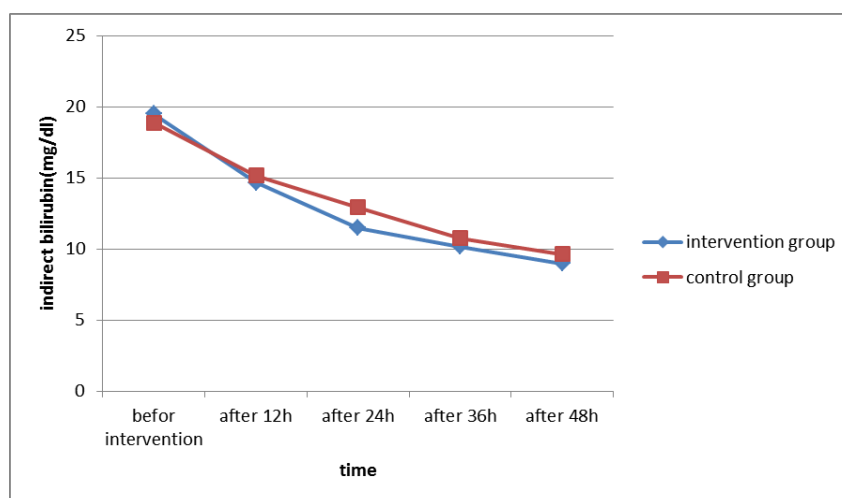
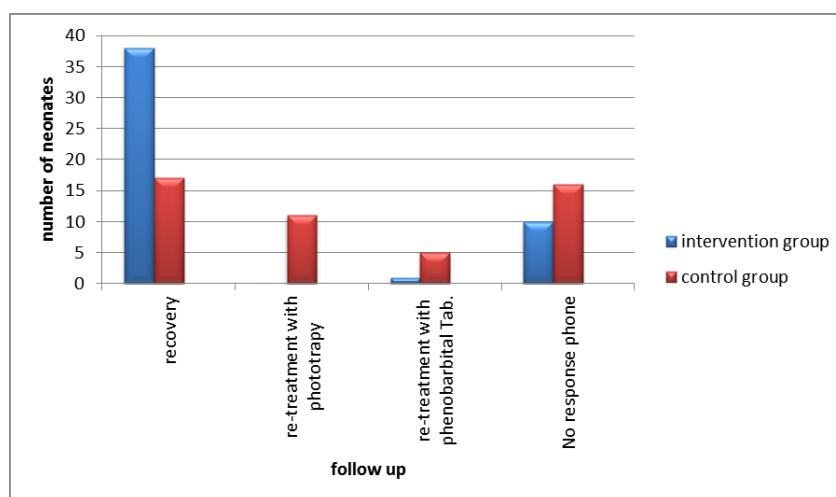
Based on the results of independent t-test, the mean score of total and indirect bilirubin levels were not significantly different between the two groups before the intervention and 12, 36, and 48 h after the intervention ($P > 0.05$). However, this difference was statistically significant 24 h post-intervention ($P < 0.001$). The results of paired t-test indicated no significant difference regarding the mean score of total and indirect bilirubin levels 12, 24, 36, and 48 h after the intervention in the both groups ($P < 0.001$). Nonetheless, the differences were greater in the intervention group. Based on the ANCOVA results, there was a significant difference between the two groups 12 and 24 h after the intervention ($P < 0.001$); nevertheless, no significant difference was observed in the mean score of indirect bilirubin level 36 and 48 h after the intervention between the two groups ($P = 0.06$ and $P = 0.23$, respectively; Table 2, Figure 1). In the follow-up phone calls, no problem was reported by the intervention group one and two months after discharge in terms of the need for readmission and other possible adverse events. Out of the 39 cases responding to the phone calls, only one case required to receive phenobarbital tablets due to skin complications following phototherapy (because the mother had stopped giving the infant the remaining doses of the drop). In the control group, out of 33 cases who responded to the telephone calls, 17 cases had improved without the need for other treatment; five infants were prescribed phenobarbital tablets by their physician, and 11 cases underwent phototherapy again (Figure 2).

Table 1. Distribution of the quantitative variables of the intervention and control groups

Variables	Mean \pm SD		P-value (t-test)
	Intervention	Control	
Neonate age on admission (day)	6.2 \pm 2.5	6.04 \pm 2.4	0.74
Neonate age at the onset of jaundice (day)	3 \pm 0.8	3.2 \pm 1	0.32
Maternal age (year)	28 \pm 5.5	27 \pm 5.5	0.37
Birth weight (g)	3249 \pm 360.2	3141 \pm 425.6	0.18
Admission weight (g)	3203 \pm 343.2	3036 \pm 420.9	0.03
Hemoglobin level (g/dl)	15.7 \pm 2.3	16.3 \pm 2.4	0.14
Gestational age (weeks)	38.7 \pm 1.1	38.5 \pm 1.3	0.45
Duration of hospital stay (h)	35.9 \pm 11.6	49.5 \pm 14.5	<0.001

Table 2. Mean comparison of neonatal indirect bilirubin level before and several hours after the intervention in the intervention and control groups

Indirect bilirubin	Mean \pm SD		Independent t-test		ANCOVA		Paired t-test			
	Intervention	Control	t	P-value	f	P-value	Intervention t	Intervention P-value	Control t	Control P-value
Pre-intervention	19.5 \pm 2.4	18.9 \pm 2.8	1.2				0.23			
After 12 h	14.7 \pm 2.3	15.1 \pm 2.1	-1.5	0.14	11.9	<0.001	21.3	<0.001	16.9	<0.001
After 24 h	11.5 \pm 2.2	12.9 \pm 2.2	-3.2	<0.001	31.6	<0.001	30.2	<0.001	19.7	<0.001
After 36 h	10.2 \pm 1.8	10.7 \pm 1.6	-1.4	0.17	3.6	0.06	31.2	<0.001	20.7	<0.001
After 48 h	8.9 \pm 1.5	9.6 \pm 1.5	-1.2	0.23	1.5	0.23	19.8	<0.001	17.8	<0.001
Repeated measures ANOVA	Interaction between time and intervention							p=0.06	f=3.4	
								p<0.001	f=46.8	
								p=0.3	f=3.7	

**Figure 1. Mean comparison of neonatal indirect bilirubin level before and several hours after the intervention in the intervention and control groups****Figure 2. Comparison between the intervention and control groups in terms of the need for re-treatment of neonatal jaundice**

Discussion

The results of this study showed that the use of bilineaster drop alone did not significantly reduce the total and indirect bilirubin levels. However, with the interference of time, the total and indirect bilirubin levels exhibited a significant reduction in both groups, compared to baseline levels. The indirect and total

bilirubin levels were significantly lower in the intervention group 24 h post-intervention, compared to the control group.

In general, the level of bilirubin was significantly diminished in both groups during the study period due to the identical effect of phototherapy that used in both groups. In this study, the reduction of bilirubin in the first 24 hours was higher, especially in the intervention group, since higher levels of bilirubin are more affected by phototherapy and probably bilineaster drop. But in the second 24 hours, downward trend of bilirubin level was less due to lower bilirubin level. Nevertheless, the obtained results in the second 24 h may not be reliable because of discharging a large number of newborns and reduced sample size.

The results of the present study are consistent with the findings of Azad Bakht et al. (21), Ghotbi et al. (20), and Khoshdel et al. (19). In the study of Khoshdel (19), the bilirubin level significantly reduced in all four groups during the study. This reduction was greater in the treatment group receiving purgative manna and phototherapy, compared with the control group receiving placebo and phototherapy.

In the mentioned study, there was a significant decrease in bilirubin levels during the study; besides, the downward trend was different in the treatment groups. However, there was no significant difference between the groups 48 and 72 h after the intervention. There were no clear boundaries in terms of bilirubin difference between treatment groups. Nevertheless, the results of current study are not consistent with those of Nabavi Zadeh et al. (15) and Shah Farhat et al. (23).

Nabavi Zadeh et al. (2005) conducted an experimental study in Imam Sajjad Hospital of Yasouj, Iran, on the head of infants with hyperbilirubinemia. They found that only chicory extract could significantly reduce the serum levels of indirect bilirubin, whereas the extracts of jujube, purgative manna, and manna were not effective in reducing neonatal serum bilirubin (15). In the mentioned study, oral purgative manna had not been given to babies, and an in-vitro study was conducted on the blood serum of newborns by adding purgative manna extract in their serum, the action mechanism of which was different from that of the current study.

Shah Farhat et al. (2005) conducted a study entitled as “the effect of shirkhesht on newborns' indirect hyperbilirubinemia” in Imam Reza Hospital of Mashhad, Iran, on 104 newborns admitted to the neonatal intensive care unit. In that survey, the bilirubin level was not significantly different between the groups in terms of duration of hospital stay. The bilirubin level showed no significant difference after treatment in the two groups. The results of the mentioned study showed that consumption 6 g of purgative manna was not as effective as placebo for neonatal jaundice (23). In the mentioned study, no standard level was considered for purgative manna. In the mentioned study, one group received only 6 g of purgative manna on admission, and another group took a placebo (0.1% starchy water and a drop of caramel); as a result, the mean levels of serum bilirubin after 72 h were 14.1 and 14.2 in the intervention and comparison groups, respectively.

Medicinal plants that have recently attracted the interest of researchers are acknowledged as a treatment option for neonatal jaundice, and their effectiveness is confirmed in clinical studies. The Chinese have always used herbs with efficient therapeutic effects (22, 24). In the Iranian traditional medicine, purgative manna has been used to treat neonatal jaundice (9).

The present study used bilineaster drop containing purgative manna extract (300 mg/ml of mannitol, which is active ingredient of purgative manna). The purgative manna obtained from cotoneaster contains mannitol, sucrose, dextrose, fructose, and multiple polysaccharides. The level of mannitol is about 40-60% in purgative manna.

Mannitol has minor oral absorption in the gastrointestinal tract and causes osmotic diarrhea in the intestines. This property of mannitol available in purgative manna may lead to excretion of optical and structural isomers of bilirubin (which are produced under the influence of light or are imported into the intestine through heme metabolism) through feces and reduce the levels of bilirubin (22). The present study demonstrated that bilineaster drop could lower neonatal bilirubin levels and improve jaundice without showing any side effects or the need for re-treatment.

A limitation of this study was the discharge of most infants before 48 h, which resulted in conducting 36 and 48 h bilirubin measurements on a smaller sample size. However, it should be noted that most of the cases, particularly those in the intervention group, were discharged due to observing acceptable level of bilirubin based on the treating physician' opinion and in some cases, due to personal desire.

Implications for Practice

According to the results of the present study, the use of bilineaster drop along with phototherapy significantly reduced the total and indirect bilirubin levels in the first 24 h after intervention, compared to the use of phototherapy alone. However, the intervention did not change the downward trend. Taking into account the reduction of the total and indirect bilirubin levels and duration of hospital stay, it is recommended to use this drop along with phototherapy in treating neonatal hyperbilirubinemia. Using results of this research can prevent and reduce the effects of long-term phototherapy or the readmission Baby.

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Conflict of interest

The authors declare that there is no conflict of interest.

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