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Brief Report

Effect of Common Chicory Essence and Phototherapy on Serum Bilirubin Levels in Preterm Infants Admitted to Neonatal Intensive Care Unit: An In Vitro Study

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Abstract

Jaundice is a common neonatal disorder that occurs in most term and preterm infants. Chicory or dandelion flower has long been used in the treatment of jaundice. This study aimed to investigate the effect of common chicory essence and phototherapy on serum bilirubin levels in preterm infants admitted to the neonatal intensive care unit (NICU) of Valiasr Hospital in Birjand, Iran. This in vitro study was conducted on preterm infants with gestational age of less than 37 weeks and weight less than 2500 g. Bilirubin levels in blood samples from 21 infants were measured before and after the addition of chicory essence or distilled water. Then, phototherapy was performed, and bilirubin levels were measured again. Data were analyzed using SPSS (version 21). The mean weight of infants was 1542.8 $\pm$ 453.5 g. In the chicory essence group, the mean total serum bilirubin was 5.29 $\pm$ 1.55 and 0.18 $\pm$ 0.07 mg/dL before and after the intervention, respectively ($P < 0.001$). The mean indirect serum bilirubin was 4.96 $\pm$ 1.59 and 0.18 $\pm$ 0.07 mg/dL before and after the intervention, respectively ($P < 0.001$). The mean changes in total bilirubin in the distilled water and chicory groups were 5.15 $\pm$ 1.70 and 5.43 $\pm$ 1.99 mg/dL, respectively ($P = 0.62$). The results showed that both distilled water and chicory essence decreased direct and total serum bilirubin concentrations. The indirect bilirubin changes were not significant, and there was no difference in the total bilirubin changes between the two groups. Totally, the chicory essence had no effect on reducing the serum bilirubin level in preterm infants.

Keywords: Jaundice, Preterm Infants, Chicory Essence, Phototherapy

1. Introduction

Hyperbilirubinemia is a common and often benign problem during infancy (1). Jaundice occurs in about 60% of term neonates and 80% of preterm infants during the first weeks of life (2). Overall, the causes of hyperbilirubinemia include: (a) Increased bilirubin load that needs to be metabolized by the liver; (b) reduced activity of bilirubin-metabolizing enzymes; (c) competition and inhibition of glucuronyl transferase activity; and (d) factors enhancing serum levels of free bilirubin, such as hypoproteinemia, which increases the unconjugated (indirect) bilirubin toxicity (2, 3).

Indirect hyperbilirubinemia is commonly associated with hemolysis due to blood type incompatibility (ABO and Rh and other less common blood groups) or non-hemolytic causes such as physiologic jaundice, breast milk jaundice, internal bleeding, and polycythemia vera (4).

The manifestations and the onset of hyperbilirubinemia differ according to the cause. Based on causes, hyperbilirubinemia may develop at birth or during infancy. The most common manifestation is jaundice, which is characterized by bright yellow to orange skin in indirect hyperbilirubinemia, and yellow to green skin in direct hyperbilirubinemia. Failure to treat hyperbilirubinemia not only causes jaundice, but also is associated with clinical symptoms such as lethargy, encephalopathy, and poor feeding (2).

Distinguishing physiologic from non-physiologic hyperbilirubinemia is associated with some problems. Therefore, the neonatal jaundice is considered as non-physiologic variant and needs urgent examination in the following cases: (a) The onset of jaundice within the first 24 hours after birth; (b) increased serum bilirubin levels (greater than 0.5 mg/dL per hour); (c) signs of disease such as vomiting, poor feeding, impaired weight gain, lethargy, apnea, tachypnea, and body temperature instability; and (d) stable jaundice for more than eight days in term infants and over 14 days in preterm infants (5).

Generally, regardless of the cause of jaundice, treatment in all newborns is aimed at preventing neurotoxic effects caused by indirect bilirubin. Some of the early lines of jaundice treatment include phototherapy and exchange transfusion in the absence of response to treatment or high severe jaundice, which are used to maintain bilirubin levels below the pathological levels (6, 7). Other treatments mentioned in this field are the use of high-dose venous immunoglobulin (8), metalloporphyrins (9), and phenobarbital (10).

Given that conventional treatments of jaundice in newborns require hospitalization, physicians always seek alternative therapies to treat neonatal jaundice with the least complication and for the shortest period, and at the lowest cost. Among these, medicinal plants have attracted further attention. Chicory essence has been used to treat neonatal jaundice for a long time.

Common chicory, *Cichorium intybus L.*, is a plant of order Asterales, family Asteraceae and genus Cichorium. There are two cultivated species and four to six wild species of this plant. The wild species grows up to one meter, and the cultivated species up to two meters. Chicory has different species, three of which are known: Berry chicory is known as tansy that does not grow in Iran; Yellow chicory known as dandelion that, has been used in ancient medicine in most parts of the country; and common chicory (11). Common chicory is a perennial herb with blue or purple flowers. It is originally native to the old world and later on the American continent as a wild plant on the roadside. The origin of this plant is Central Europe, the western and central parts of Asia, and North Africa, and it has a huge distribution in various parts of Iran, especially the cities of Eqlid, Azerbaijan, and the mountainous regions of Khorasan. Several studies have evaluated the effects of common chicory on the indirect serum bilirubin level in newborns and suggested further studies on the term infants (12).

2. Objectives

The aim of this study was to determine the effect of common chicory essence, and phototherapy on serum bilirubin levels in preterm infants admitted to the neonatal intensive care unit (NICU).

3. Methods

The current in vitro study was performed on 21 preterm infants with a gestational age of 30 - 36 weeks and 6 days (weight: 1500 - 2500 g). The babies were diagnosed with jaundice during the NICU admission. The sample size was estimated as 14 subjects using the equation of $N = Z(1-\alpha/2)+Z(1-\beta)^2 \partial 1^2 + \partial 2^2/(\mu 1 - \mu 2)^2$ based on the study by Nabavizadeh et al. (13) and six other studies (the mean indirect bilirubin was 8.93 $\pm$ 1.3 in the common chicory group and 10.79 $\pm$ 2.11 in the distilled water group) and regarding α = 0.05 and β = 0.2. Considering the dropout, 21 patients were enrolled in the study.

Exclusion criteria were indications of intensive phototherapy, the presence of any clinical or laboratory signs of hemolysis or infection, any congenital anomalies of the infant, dehydration, G6PD deficiency, ABO incompatibility, positive Coombs test, history of maternal phenobarbital reception, IUGR, mechanical ventilation, and inability to use oral medication. To exclude the causes of withdrawal, examinations were conducted to determine the maternal and infant blood group, hemoglobin, CBC, reticulocyte count, peripheral blood smear, Coombs test, thyroid function tests, and G6PD for all neonates. The indication of starting phototherapy for infants was based on the criteria regarding the maximum acceptable levels of indirect serum bilirubin (mg/dL) in preterm infants.

Before enrolling the patients, the sampling method, probable side effects, and standard treatment method were explained to the legal guardians of all babies, and informed written consent was obtained. All newborns received routine treatments of neonatal jaundice to prevent the disease complications. In this study, considering the inclusion and exclusion criteria, all newborns were enrolled from 1 January 2018 until the sample size was completed.

After obtaining permission from the parents, blood samples (2 cc) were taken from 21 infants, and their baseline bilirubin levels were measured. Each sample was then divided into two parts in equal volume, and each part was added with half of its volume of chicory essence or distilled water. The bilirubin level was re-evaluated. In this way, we had 42 samples, and serum bilirubin levels were re-evaluated in these specimens. The chicory essence used was prepared from Golchekan Zamani Company with an essential oil concentration of 1.1 to 1.5 mg per 100 mL. Next, all specimens underwent phototherapy by Tosan phototherapy device with four PHILIPS fluorescence lamps for 3 hours, so that the distance between the lamps and the level of the specimens was 30 cm. Radiation was in the blue-green spectrum (wavelength of about 430 - 490 nm) with irradiance of 10 μw/cm^2/nm at the center of phototherapy. The bilirubin levels were reassessed after adding distilled water/chicory essence before and after phototherapy. For all samples, direct and total bilirubin levels were checked. Then, the indirect level was obtained by subtracting the direct level from the total level. All experiments were performed at the reference laboratory of the Birjand University of Medical Sciences in accordance with the method of the Diazo of Pearlman and Lee on the Cobas Integra Autoanalyzer.

The collected data were inserted into SPSS version 21 software. Descriptive analysis was performed by mean, standard deviation, frequency, and percentage. Wilcoxon and Mann-Whitney tests were used for indirect bilirubin in the common group, and paired *t*-test and independent *t*-test for other cases. A P-value ≤ 0.05 was considered as the significance level.

4. Results

We included 21 infants (12 boys vs. nine girls) with a mean weight of 1542.8 ± 453.5 g and a mean gestational age of 30.9 ± 2.9 weeks (Table 1). Family history of jaundice was found in 9.5% of infants. The mean total and indirect bilirubin levels at the baseline and before adding chicory essence and distilled water were 7.29 ± 2.46 and 7.16 ± 2.55 mg/dL, respectively. Since we divided one sample into two parts, the bilirubin level was equal for both groups before adding distilled water and chicory essence. Adding distilled water and chicory essence to the samples could decrease the bilirubin level in the pre-phototherapy test. This decrease in bilirubin level was statistically significant in each group, but the comparison of bilirubin showed no significant decrease between the two groups (Tables 1 and 2).

Table 1. Comparison of Baseline Bilirubin Level with Bilirubin Level Immediately After Adding Distilled Water and Common Chicory Essence and Before Phototherapy [a]

Groups and Bilirubin (mg/dL)	Before	After	Statistical Test
Distilled water			
Total	7.29 ± 2.46	5.38 ± 1.72	P < 0.001
Indirect	7.16 ± 2.55	5.10 ± 1.79	P < 0.001
Direct	0.39 ± 0.14	0.32 ± 0.11	P = 0.005
Common chicory essence			
Total	7.29 ± 2.46	5.29 ± 1.55	P < 0.001
Indirect	7.16 ± 2.55	4.96 ± 1.59	P < 0.001
Direct	0.39 ± 0.14	0.32 ± 0.12	P = 0.005

[a] Values are expressed as mean ± SD.

The mean total bilirubin level was 5.38 ± 1.72 in the distilled water group and 5.29 ± 1.55 in the chicory essence group, with no significant difference (P = 0.85). This was also true for the direct and indirect bilirubin levels between the two groups.

Table 2. Comparison of Bilirubin Levels After Adding Chicory Essence and Distilled Water and Before Phototherapy [a]

Bilirubin (mg/dL)	Distilled Water	Common Chicory Essence	Statistical Test
Total	5.38 ± 1.72	5.29 ± 1.55	P = 0.85
Indirect	5.10 ± 1.79	4.96 ± 1.59	P = 0.78
Direct	0.32 ± 0.12	0.32 ± 0.11	P = 1

[a] Values are expressed as mean ± SD.

As seen in Tables 1 and 3, the augmentation of chicory essence and distilled water separately in each group significantly reduced the bilirubin level (P < 0.001), and phototherapy after this stage reduced bilirubin levels in each group separately, which was statistically significant. There was no significant difference between the two groups regarding the total and indirect bilirubin levels. To measure the changes in the bilirubin level, the mean total bilirubin after phototherapy was subtracted from the mean total bilirubin in each group before phototherapy. The results showed that the decrease in bilirubin between the two groups was not statistically significant. In other words, although the augmentation of distilled water and chicory essence decreased the bilirubin level, none of the two substances had a significant effect on decreasing bilirubin levels. Thus, the chicory essence had no effect on reducing bilirubin levels in vitro.

Table 3. Determination and Comparison of Mean Serum Bilirubin (Total and Indirect) in Samples Before and After Phototherapy [a]

Common chicory essence (mg/dL)	Before	After	Statistical Test
Bilirubin			
Total	5.29 ± 1.55	0.18 ± 0.07	P < 0.001 [b]
Indirect	4.96 ± 1.59	0.18 ± 0.07	P < 0.001 [c]
Distilled water bilirubin			
Total	5.33 ± 1.75	0.18 ± 0.07	P < 0.001 [b]
Indirect	5.05 ± 1.83	0.18 ± 0.07	P < 0.001 [b]

[a] Values are expressed as mean ± SD.
[b] Paired *t*-test
[c] Wilcoxon test

5. Discussion

In line with the results of this study, Khalid et al. showed that administration of common chicory extract at doses of 100 mg/kg and 250 mg/kg did not affect serum bilirubin levels (14). Contrary to the results of this study, Nabavizadeh et al. in Yasuj (Iran) investigated the direct effects of plant extracts on the serum bilirubin levels in neonates and showed that the total serum bilirubin levels were significantly decreased only in the presence of chicory essence, and the indirect bilirubin levels had a significant difference only in these samples (containing chicory essence) (13). In agreement with the results of this study, Nassirian and Eslami examined the effect of chicory essence on neonatal hyperbilirubinemia among 30 infants and reported that the differences in direct and indirect bilirubin levels were not significant in any of the groups. In addition, no significant difference was observed in the examination of term and preterm infants (15-17).

One reason for the difference between the results of the present study and those of previous studies might be related to the difference in the method of prescribing common chicory extract and the dosage. For example, in the study by Khalid et al. while doses of 100 mg/kg and 250 mg/kg of common chicory extract did not affect the serum bilirubin level, a dose of 500 mg/kg caused a significant reduction in bilirubin (14). Because the volume of serum obtained from the taken blood sample was different considering the hemoglobin level in our study, we tried to pay more attention to the volume of liquid added, and we used volume equal to the serum volume of the neonates (14). In an animal model, Naderi et al. prescribed common chicory extract to rat mothers and measured the effects of secretion of chicory essence through the milk on rat bilirubin (18). The results indicated a significant decrease in total and direct bilirubin levels in the neonates with hyperbilirubinemia following the administration of common chicory to the mother (18). Another approach, recently proposed by Mohammadi Pirkashani et al., was chicory extract bath combined with phototherapy (19). The results showed that co-treatment of phototherapy and chicory extract bath significantly decreased the bilirubin level over a period of 24 to 48 hours more than the phototherapy alone (19).

In conclusion, this study showed that both distilled water and chicory essence decreased indirect and total serum bilirubin concentrations, but chicory essence together with phototherapy could not reduce the serum bilirubin levels in vitro.

One limitation of this study was sampling the proper volume of blood from preterm infants. If we could have more blood volumes, we would be able to evaluate different doses of chicory essence. If we could use more infants for sampling, we would have achieved more accurate results. As the study was performed as in vitro, the results cannot be generalized to clinical conditions.

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Footnotes

Authors' Contribution: Study concept and design: G. F.; acquisition of data: M. S.; analysis and interpretation of data: B. B., G. F.; drafting of the manuscript: G. F., M. S.; critical revision of the manuscript for important intellectual content: G. F.; statistical analysis: G. F., B. B.

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Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

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