

The Effect of Chicory Extract Bath on Bilirubin Levels of Infants: A Randomized Clinical Trial Study

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Abstract

Background: Jaundice is a common problem in infants, particularly premature infants (60-80%). The most common treatment of neonatal jaundice is phototherapy; however, traditional and complementary medicine is preferred due to complications of phototherapy in newborns. This study evaluates the effect of Chicory extract bath on bilirubin levels of infants with jaundice hospitalized in educational hospitals in Isfahan, Iran.

Materials and Methods

This study was a double blind randomized clinical trial in which participants included 64 mature infants with neonatal jaundice admitted to the selected hospitals of Isfahan. The infants were randomly assigned to two groups receiving phototherapy (n=32), and phototherapy with bath with 500ml of chicory extract prepared by hydroalcoholic method and made in Iran (n=32). The infants were bathed by trained nurse with chicory extract before phototherapy as well as 24 and 48 hours after phototherapy; then, the infants received phototherapy. During treatment, serum bilirubin was measured and recorded every 24 hours continuously. Control infants only received phototherapy; during treatment, serum bilirubin was measured and recorded every 24 hours.

Results

The results showed no significant difference in mean bilirubin levels between the two groups on admission (P=0.37); while mean bilirubin level of phototherapy infants was significantly higher than that of infants receiving phototherapy and chicory extract bath in 24 hours after (P=0.014), and 48 hours after intervention (P=0.011).

Conclusion: The results showed that chicory extract bath with phototherapy can be effective in reducing neonatal jaundice.

Key Words: Bilirubin, Chicory extract, Infants, Jaundice, Phototherapy.

*Please cite this article as: Mohammadi Pirkashani L, Asghari Gh, Marofi M, Barekattain B. The Effect of Chicory Extract Bath on Bilirubin levels of Infants: A Randomized Clinical Trial Study. Int J Pediatr 2017; 5(12): 6679-88. DOI: [10.22038/ijp.2017.26069.2226](https://doi.org/10.22038/ijp.2017.26069.2226)

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Received date: Aug.12, 2017; Accepted date: Sep.22, 2017

1- INTRODUCTION

Neonatal jaundice is a common problem, accounting for 60% of term infants and 80% of preterm infants infected during the first week of life. Neonatal jaundice is the most common reason for hospitalization of infants in the first month of birth (1, 2). Neonatal jaundice first onset in eyes; then, it appears on the face and spreads to the chest, abdomen and legs (1, 2). Lack of attention causes symptoms such as decreased activity, somnolence, seizures and eventually mental retardation and deafness (1). Other side effects of indirect bilirubin deposition include inhibition of pulmonary surfactant, coagulation disorders caused by reduction in the factors 2 and 7, reduced life of red blood cells, pancreas Langerhans Cell necrosis and necrosis of testicular cells (3). The goal of the treatment of hyperbilirubinemia is to prevent neurological damage (4).

Therefore, proper diagnosis, treatment and follow-up of jaundice are always one of the major challenges in neonatology (5).

The most common way to treat hyperbilirubinemia is phototherapy. By an irreversible reaction, phototherapy converts natural bilirubin to an isomer called Lumirubin which is excreted from the kidney in a non-conjugated form. Phototherapy reduces the need for blood transfusions (6). Phototherapy is expensive; because infants are limited to incubator and their eyes are covered, mother-infant connections are disrupted, which is followed by later weight gain, increased length of hospital stay, and increased health care costs (7). In most cases, frequent blood sampling is required from newborns during process of jaundice and hospitalization; complications of these blood samplings include the increased risk of nosocomial infection (due to less competent immune system of infants from different aspects), anemia if blood sampling repeated (due to low blood

volume of infants), and pain and stress (8). Thus, efforts to reduce pain and stress of newborns can considerably prevent next damages (8). Other complications of hyperbilirubinemia include hyperthermia, increased blood circulation, increased insensible water loss, fractures in DNA chains, weight loss, hypocalcemia, thrombocytopenia and Patent Ductus Arteriosus (PDA)(9). Due to complications of phototherapy, a less risky alternative treatment can contribute significantly to the health of infants. In various studies carried out both inside and outside the country, phototherapy complications such as decrease of platelet counts and thrombocytopenia and hypocalcemia have been mentioned. Obviously, with the reduction of phototherapy time, it is possible to prevent these complications to some extent (10, 11).

Herbal medicines can be used often as effective and economic supplement along with conventional drugs; moreover, complementary therapies are growing as low-risk, cost-effective, easy treatment with limited side effects in nursing care of many health care centers (7, 12). In this regard, in traditional medicine and supplementation, the use of medicinal plants such as Yin Zhi Huan (YZH) has been proposed whose mechanism of action is by activating the hepatic receptor that causes bilirubin clearance (13, 14). In our culture, we also refer to Shahtare, Jujub, Chicory, Manna and Shirkhesht. These plants, having the effect of laxative and increasing the frequency of defecation or bonding to the bilirubin in the intestine, decrease the intestinal flow of the liver and ultimately excretion of bilirubin intestinal (15). Laxative effect and increased stool frequency or binding to bilirubin in the intestine is one way to reduce liver-intestinal flow and ultimately intestinal excretion of bilirubin. Due to their laxative effect, jujube, cotoneaster and the manna, and chicory can be effective in reducing

bilirubin (15). In Iran, cotoneaster is used to treat neonatal jaundice; moreover, barley flour used on baby's skin experimentally reduced jaundice (6). A review study by Khodashenas et al. (2015) to examine the effect of herbal medicine on neonatal jaundice noted that some herbal medicines as well as phototherapy could be useful in treatment of jaundice (16). In the meantime, chicory is a useful plant with very important therapeutic effects (8). Chicory is liver tonic, bile-inducing, diuretic, laxative and appetizing (17); due to flavonoids such as apigenin, quercetin and luteolin, which stimulate glucuronyl transferase, accelerate excretion of bilirubin. Nabavizadeh et al. (2006) showed that chicory directly influenced liver function and excreted bilirubin (6). In addition to results of some studies on beneficial effect of chicory in reducing jaundice (5, 17), observed no effect of chicory on treatment of jaundice in vitro. Some studies consider bath with herbal medicines as effective treatment and argue that effectively healing ingredients existing in herbs are absorbed through skin and reach the site of disease sometimes faster than internal use (7). Hence, the present study evaluates the effect of chicory extract bath on bilirubin levels of Iranian infants with jaundice.

2- MATERIALS AND METHODS

2-1. Study design and population

This is a double-blind randomized clinical trial was done on neonates with hyperbilirubinemia otherwise normal visited at Beheshti Hospital and Alzahra of Hospital Isfahan city, Isfahan province, Center of Iran, hospitalized only because of indirect hyperbilirubinemia. They were admitted and underwent phototherapy based on the guideline of the American Academy of Pediatrics (AAP) (18) for the treatment of neonatal hyperbilirubinemia, during December 10, 2015 till March 14,

2016. A sample of 32 subjects was selected in each group.

The study protocol registered in IRCT by IRCT Cod: IRCT.2015122225619N2. Measurements were conducted after approving the ethical committee of Isfahan University of Medical Sciences, Isfahan-Iran. Informed consent was taken from all study subjects after describing the objectives of the study and full agreements of neonate's parents.

Sample size was determined as follows:

$$n = \frac{(Z_1 + Z_2)^2 (2S)^2}{d^2} = \frac{(1.96 + 0.84)^2 (2S)^2}{0.7S^2} = 32$$

Where, Z_1 represents 95% confidence interval ($Z_1=1.96$); Z_2 represents 80% confidence interval ($Z_2=0.84$); S represents an estimate of the standard deviation of bilirubin level in each group ($S=0.7$); d represents the minimum difference in mean bilirubin level between groups; this difference is significant. Each group contained 32 infants. It should be noted that the information necessary for determination the sample size was extracted from a pilot study. All the neonates who met the inclusion criteria were selected, informed consent was taken from parents; afterward they were assigned in two groups by simple randomization using computerized random-number table. Both groups were matched for factors including age, gestational age, gender and weight at birth and type of phototherapy (single, double and Intensive).

In single and double phototherapy, white light with an irradiance of 6-12 μ w/cm²/nm is used and Intensive phototherapy with an irradiance of 25 μ w/cm²/nm was used. Sampling continued until the considered number was achieved. Before the start of phototherapy at the baseline, all newborns were tested for Combs, Glucose-6-phosphate dehydrogenase (G6PD), total and direct bilirubin levels and motheral and neonatal Blood Group-Rh (BG-Rh); the results were recorded in patient

records. All these experiments are essential for icterus infants. The infants who were deficient in G6PD and Combs were not included in the study, because the type and duration of phototherapy required for jaundice were different in these infants.

2-3. Measuring tools

A two-part form was used to collect data. The first part included demographic data (gender, gestational age, age-to-date, birth weight, weight at admission), and information on bilirubin level of the infants. The second part included baseline bilirubin, type of phototherapy used (single, double, and intensive), duration of phototherapy and hospital stay, use of chicory extract bath, daily bilirubin tests and complications of interventions.

2-4. Intervention

Hyperbilirubinemia treatment was based on Neonatal Intensive Care Unit (NICU) protocol and based on the guideline of the American Academy of Pediatrics (AAP) monogram for the treatment of neonatal hyperbilirubinemia (18) of the selected hospitals by single, double and full power phototherapy. The intervention was carried out under the supervision of a neonatologist. For the intervention, a group only received phototherapy based on the guideline of the American Academy of Pediatrics (AAP) monogram for the treatment of neonatal hyperbilirubinemia and the other group received both phototherapy and chicory extract bath. Upon admission, the infants were bathed with chicory extract by using sterile cotton before the start of phototherapy and then for 2 days, once a day, after feeding at noon, when phototherapy was interrupted for health care and the rest. The infant's body was washed by a trained nurse in neonatal intensive care unit (NICU) in the presence of mother's infant with chicory extract with sterile cotton. Room temperature was set to 24-28°C; chicory extract was heated to 37.5°C. Then, the

infant was washed for 5 to 7 minutes with 500ml of chicory extract prepared by hydroalcoholic method (19). Before the intervention, body temperature was measured by using a mercury thermometer (Meheconova). Before the intervention, hands were washed completely starting from face to neck, particularly the area behind the ears, chest and upper limbs, abdomen, lower limbs and in the back.

At the end, the body was dried with a clean, soft towel and body temperature was measured again. The infants received single phototherapy (Xhz 90 infant jaundice phototherapy unit) or Intensive phototherapy (Xhz neonate jaundice phototherapy apparatus for which the lamps lasted for 104 days). During treatment, serum bilirubin was measured every 24 hours by photometry in a reliable laboratory at the same hospitals. The results were recorded by trained nurse in research team continuously. Note that the infants were compared only 24 hours and 48 hours after intervention, because majority of infants with jaundice were treated after 48 hours and did not require treatment, as noted in literature. Moreover, this treatment was used as a supplementary treatment for phototherapy. The studied infants were controlled for any allergic complications during the studied period. The infants were excluded from the study in case of any allergies and the doctor in charge was informed about the allergy.

2-5. Ethical consideration

Initially, the researcher obtained the necessary license from the faculty of nursing and midwifery of Isfahan University of Medical Sciences by presenting it to the officials and managers of the research environment. Then, the purpose of the research was explained to the parents of the research units and authorities in the study environment. Neonates in both groups had usual treatments to control jaundice and prevented any damage to them. Research

was consistent with the religious and cultural standards of families and the analysis of the information obtained from the research is unbiased.

2-6. Inclusion and exclusion criteria

Inclusion criteria included absence of anomaly or congenital infection, term infants weighing more than 2,200 grams with no problem except jaundice, hyperbilirubinemia requiring the prescribed phototherapy, no need for blood transfusions and breastfeeding. Exclusion criteria included type of hemolytic jaundice, G6PD and Combs deficiency, increasing jaundice requiring blood transfusions, history of skin allergy in the family, any chicory extract sensitivity, and unwillingness of parents to continue participation, discharge or death of the infant before the end of intervention, worsening newborns during the study for any reason inconsistent with the intervention.

2-7. Laboratory measurements

During treatment, serum bilirubin was measured every 24 hours by photometry in a reliable laboratory at the same hospitals. The results were recorded by trained nurse in research team continuously.

2-8. Data Analyses

The data collected and introduced into SPSS version 18.0 software then following statistical tests were used for analysis: Independent T-test used for compare mean of variables age, gestational age, birth weight, weight on admission, bilirubin level at time of admission, duration of phototherapy and hospitalization in two groups. The ANOVA test was used for mean bilirubin level of controls and intervention group at different times. The Mann-Whitney test was used for compare mean distribution of birth rate and pre-intervention frequency of stool between the two groups. The Wilcoxon test was used for compare pre- and post-

intervention frequency of stool in the two groups. The Chi-square test was used for compare type of delivery, maternal and neonatal blood between the two groups. Also, p-value less than 0.05 were statistically significant.

3- RESULTS

Neonates in this study were divided into two groups: phototherapy (control) and phototherapy with chicory extract bath (intervention). Gender distribution was similar in the two groups and each group contained 17 girls and 15 boys. Chi-square test showed no significant difference in type of delivery, maternal and neonatal blood groups between the two groups ($P > 0.05$). Moreover, Mann-Whitney test showed no significant difference in distribution of birth rate between the two groups ($P = 0.37$).

Independent t-test showed no significant difference in mean age of infants ($P = 0.81$), gestational age ($P = 0.21$), birth weight ($P = 0.71$) and weight on admission ($P = 0.85$) in the two groups (**Table.1**). As shown in **Table.2**, t-test showed no significant difference in mean bilirubin level at time of admission between the two groups ($P = 0.37$), while mean bilirubin level of controls was significantly higher than intervention groups at 24 hours after the intervention ($P = 0.014$), and 48 hours after the intervention ($P = 0.011$).

ANOVA with repeated observations showed that mean bilirubin level of controls and intervention group was not similar at different times ($P < 0.001$). LSD post hoc test showed a significant difference in mean bilirubin level of infants at all times ($P < 0.001$). Independent t-test showed that mean variation in bilirubin level of the intervention group was significant higher than that of controls in 24 hours after intervention compared with admission ($P = 0.01$) and 48 hours after intervention compared with admission ($P < 0.001$).

(Table.3). Based on independent t-test, mean duration of phototherapy and hospitalization of the intervention group was significantly higher than that of controls ($P < 0.001$). Mann-Whitney test showed no significant difference in pre-intervention frequency of stool between the two groups ($P = 0.35$), while post-intervention frequency of stool was

significantly higher in the intervention group than controls ($P < 0.01$). Wilcoxon test showed no significant difference in pre- and post-intervention frequency of stool in the controls ($P = 0.13$), while post-intervention frequency of the intervention group was significantly higher than their pre-intervention frequency ($P < 0.001$).

Table-1: The comparison of mean of background characteristics for the infants in both groups.

Variables	Phototherapy		Phototherapy and chicory extract bath		Independent t-test	
	Mean	Standard deviation	Mean	Standard deviation	t-test	P-value
Infant age (day)	5.47	3.44	5.28	3.77	0.24	0.81
Gestational age (weeks)	37.65	1.53	37.19	1.45	1.26	0.21
Birth weight (gr)	2935.94	439.43	2984.37	600.60	0.37	0.71
Admission weight (g)	2839.37	450.98	2863.12	537.81	0.19	0.85

Table-2: Mean bilirubin level of newborns at admission, 24 and 48 hours after intervention in both groups.

Time	Phototherapy		Phototherapy and chicory extract		Independent t-test	
	Mean	Standard deviation	Mean	Standard deviation	t-test	P-value
Admission	16.15	2.63	16.87	3.68	0.90	0.37
24 hours after intervention	13.15	3.10	11.27	2.86	2.52	0.014
48 hours after intervention	10.60	2.68	8.91	1.54	2.65	0.011

Table-3: Mean variation in neonatal bilirubin level at different times in the two groups.

Time	Control		Intervention		Independent t-test	
	Mean	SD	Mean	SD	t-test	P-value
24 hours after intervention compared to admission	-2.99	1.29	-5.59	2.33	2.64	0.001
48 hours after intervention compared to admission	-5.67	3.08	-9.30	3.22	4.14	<0.001

SD: Standard deviation.

4- DISCUSSION

This study determined the effect of chicory extract bath on bilirubin levels of newborns with jaundice admitted to the

selected hospitals in Isfahan, Iran. The results showed no significant difference in mean of neonatal age, gestational age, birth weight and weight on admission; the two groups were almost identical in terms

of these variables. Moreover, distribution of gender and type of delivery (normal and caesarean section) was similar and no significant difference was found between the two groups ($P>0.05$). Therefore, variables and demographics were controlled; results of interventions cannot be attributed to effect of these variables. The results showed no significant difference in mean bilirubin of control and intervention groups at the beginning of intervention, while mean bilirubin level of controls was higher than the intervention group at 24 and 48 hours after intervention, which can be attributed to positive effect of chicory extract. Because no studies have been done on the effect of using chicory extract on the reduction of neonatal jaundice in a clinical setting, therefore, the results of this study have been compared with other medicinal herbs on neonatal jaundice.

Through a systematic review, Khodashenas et al. (2015), reviewed 23 selected studies to evaluate the effect of herbal medicines on neonatal jaundice. They showed that some herbal medicine used with phototherapy could be helpful and reduce bilirubin level of infants (16). Moreover, Goodarzi et al. (2013) compared the effects of continuous and intermittent phototherapy on reduced level of bilirubin in infants with jaundice. They concluded that bilirubin significantly decreased in 12, 24, 36 and 48 hours after phototherapy (20). This is consistent with the current study and suggests that some herbal medicine such as chicory can be effective in reducing neonatal bilirubin.

Ebrahimi et al. (2009) in Yasooj- Iran, examined the effect of jujube extract with phototherapy in reducing bilirubin level of infants with jaundice. They showed that post-intervention concentration of bilirubin was significantly lower than pre-intervention concentration; this indicates positive effect of jujube extract in reducing bilirubin of infants with jaundice (21).

Similarly, Reyhani and Hadizadeh Talasaz (2000), studied complementary medicine in treatment of neonatal diseases of and claimed that herbal medicines (chicory, manna and cotoneaster) reduce bilirubin in different ways. Moreover, bath with herbal medicine is also an effective treatment (22). Comparison of mean variation in bilirubin of the two groups at 24 and 48 hours after intervention and before intervention showed that the mean variation was significantly higher in the intervention group than the controls, which supports the effectiveness of chicory extract bath on increased excretion of bilirubin in newborns. Najib et al. (2013) found that jujube, cotoneaster, manna and chicory had a laxative effect in reducing bilirubin (15). Ebrahimi et al. (2009) showed that chicory could cause bilirubin excretion (21).

Since bathing with herbal medicines is one of the treatments and in this action, the effective and healing substances found in the plants are absorbed through the skin and lead to treatment the disease (7); therefore, this may help to reduce bilirubin in newborns. On the other hand, given that Indian researchers have shown that Chicory roots have been effective in the treatment of gingivitis (6); it can be deduced that the extract of medicinal herbal is absorbed through the skin and mucus, and in the present study, chicory extract has been absorbed through the skin in the chicory extract bath and has reduced the bilirubin level of the neonates. Azadbakht et al. (2004) examined the effect of cotoneaster extracts on neonatal jaundice. Comparison of post-intervention bilirubin showed a significant difference and reduction in 3-5 days after intervention. This reduction was faster than controls (23). Current results are consistent with these studies. Reduction of bilirubin was higher and faster in 24 and 48 hours after intervention in intervention group than controls. This can be attributed

to positive effect of herbal medicine in reducing bilirubin of infants with jaundice. Saboute et al. (2012) examined the effect of oral Manna of hedysarum with phototherapy in reducing neonatal bilitubin of infants admitted to NICU of Akbarabadi Hospital in Tehran. They found no significant difference in neonatal bilirubin in 24 and 48 hours after intervention between experiment and control groups (24). This is consistent with current results, with the difference that Saboute et al used oral Manna of hedysarum, while current study used chicory extract bath. Therefore, chicory extract bath along with phototherapy can reduce bilirubin of infants with jaundice.

Comparison of mean bilirubin of infants with jaundice before and 24 and 48 hours after intervention in the two groups showed a significant difference in mean bilirubin of the intervention group at all times. This can be attributed to effectiveness of phototherapy with chicory extract bath. Nassirian and Eslami (2008) showed no significant difference in bilirubin level of blood samples to which chicory extract was added compared to the control group (5), this finding is inconsistent with the current study, which may be due to differences in the type of intervention; because this study was conducted in a laboratory environment, while the present study was conducted on the infant's body. The noted positive effect of some medicinal plants such as chicory in stimulating liver function and reducing bilirubin is consistent with the current study. Research showed a significant difference in mean bilirubin level of control newborns before and after intervention. Babaei et al. (2011), also found that phototherapy has a positive effect in reducing neonatal bilirubin (26). Findings showed that interventions had similar complications in both groups; thus, chicory extract had no adverse effects higher than phototherapy. Because of

fewer side effects, cheapness and availability of traditional medicine, this therapy can be used as complementary treatment to phototherapy. Ghotbi et al. (2006) evaluated the effect of cotoneaster in reducing neonatal jaundice. They used cotoneaster and did not observe adverse effects. However, few patients developed lethargy following osmotic diarrhea caused by cotoneaster drops containing mannitol, which was resolved as the lactating increased (27). Tarhani et al. (2004), evaluated the effect of oral manna in reducing physiologic neonatal jaundice. They observed no notable complication in the intervention group compared to the control group. This supports the idea that supplementary medicine and herbal medicine do not cause more complications than phototherapy (28, 29). The mean duration of hospitalization of the controls was significantly greater in the intervention group. Khoshdel and Kheiri (2011) reported the effects of medicinal plants (cotoneaster) along with phototherapy in reducing duration of neonatal hospitalization (30).

Ebrahimi et al. (2009), examined the effect of jujube extract used with phototherapy in reducing bilirubin of icterus infants. They concluded that duration of hospitalization in infants receiving jujube with phototherapy was shorter than infants receiving phototherapy alone. This is consistent with the current study (22). The Most neonatal deaths occur in the first week of life; thus, hospitalization and its complications such as sepsis and nosocomial infections can lead to the increased mortality. Therefore, interventions are required to reduce neonatal hospital stay.

4-1. Strengths and limitation of study

This is the first study done in Iran to evaluate the effect of chicory extract bath on bilirubin levels of Infants. Low sample size in our study and difficulty in intensive care

for neonates were the limitations. Sometimes the presence of IV Line (IV) line and serum therapy or other special care of the infant, prevents timely and accurate perform research. The use of traditional medicine and especially the Chicory extract bath as a new method of nursing care for reducing neonatal bilirubin can be an effective step in improving care provided by nurses. According to the results of this study, it is suggested that in the future studies, the effect of the bath with chicory extract in the prevention of neonatal icter and its effect on premature infants should also be studied.

5- CONCLUSION

The results suggest effectiveness of chicory extract bath in reducing bilirubin, hospitalization and complications of neonatal jaundice. Therefore, it is advisable to use chicory extract bath alongside conventional therapies. Further studies on this subject are recommended with more sample sizes.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

The authors would like to thank the research center of Isfahan University of Medical Sciences. They are also grateful infants and their families who participated in this study. They are Also special thanks to the neonatal intensive care unit in Alzahra Hospital and Beheshti hospital Affiliated to Isfahan University of Medical Sciences that provided the possibility of doing research.

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