

## Investigating the Efficacy of Zizyphus Jujuba on Neonatal Jaundice

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### Abstract

**Objective:** Neonatal jaundice is a common clinical finding in newborns. The efficacy and safety of phototherapy for neonatal jaundice have been firmly established, but it has some side effects, thus herbal therapy has recently received special attention. Herein we investigated the efficacy of *Zizyphus jujuba* for treatment of jaundice in neonates compared to phototherapy.

**Methods:** In this clinical-trial study, a total of 121 neonates aged 2-14 days hospitalized for jaundice, were randomly assigned into experimental group including 63 patients who received *Zizyphus jujuba*'s fruit extract 1ml/Kg 3 times a day and phototherapy, and control group of 58 cases receiving phototherapy with distilled water. Bilirubin level during hospitalization in both groups was measured daily.

**Findings:** Experimental group stayed in hospital for  $3.47 \pm 0.3$  days. None of the neonates in this group was hospitalized more than 7 days. In controls, hospitalization was  $3.67 \pm 0.4$  days. 2 cases stayed more than 7 days. The bilirubin level had decreased in both groups. Decrease of serum bilirubin in experimental group after 12 hours was statistically significant compared to control group ( $P=0.026$ ). In experimental group, after taking the herb for 1-2 days, 3 children developed slight diarrhea which resolved spontaneously.

**Conclusion:** The results indicate that *Zizyphus jujuba* was effective for the treatment of neonatal jaundice in first 12 hours of treatment compared to controls which could be due to higher effect of *Z. jujuba* extract to reduce bilirubin concentration with different mechanisms.

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**Key Words:** Zizyphus Jujuba; Neonatal Jaundice; Phototherapy; Hyperbilirubinemia; Newborn

### Introduction

Neonatal jaundice is a common clinical finding in newborns seen in 60% of term and 80% of preterm neonates during the first week of life [1]. Jaundice is benign mostly, but if it continues for

prolonged periods of time and if the bilirubin level is markedly elevated, it can lead to kernicterus and permanent brain damage [2]; social costs imposed on society is large [1]. Newborn infants must be monitored to recognize those who might

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develop severe hyperbilirubinemia [1]. Thus, it is important to treat and abate jaundice quickly [3].

Phototherapy is accepted as the primary treatment of hyperbilirubinemia. This treatment also puts the baby at risk of important complications including retinal injury, dehydration, diarrhea and bronze baby syndrome [4]. Therefore, searches in order to reduce the time of phototherapy by a safer treatment have been considered for many years.

Herbal therapy has recently received particular attention in the search for bilirubin-reducing substances [4,5]. It is estimated that about 70-80% of people rely on plant resources in traditional medicine to meet their primary health care needs. WHO proposed the use of medicinal plants due to less side effects and complications [4,6].

Nowadays in various traditional medications a variety of herbal items are being prescribed to jaundiced infants, often in combination with modern treatment such as phototherapy and exchange transfusion. Their medicinal properties have, however, not been investigated by properly conducted studies, so extensive scientific studies to determine the therapeutic efficacy and potential harmful effects as well as to ascertain safety of the various herbal items are warranted [6].

A number of case series have been published showing that herbal treatment using *Zizyphus jujuba* and other herbs resulted in more speedy subsidence of jaundice than those who were treated with western medicines. In the English literature, there is a report on a study investigating the effect of *Artemisia*, *Gardenia*, *Rheum officinale*, and *Scutellaria* on bilirubin metabolism in rats. Findings showed that treatment with these herbs resulted in induction of UDP-glucuronide-transferase and C-glutathione-transferase [7].

Yin Zhi Huang contains extracts from four different plants: *Artemisia capillaris*, *Gardenia jasminoides* Ellis, *Rheum officinale* Baill, and *Scutellaria baicalensis* Georgi, and have been used for centuries in Asia to prevent and treat neonatal jaundice [8]. Several clinical reports in Chinese medical literature indicate that Yin Zhi Huang treatment can enhance bilirubin clearance in newborns [9,10,11]. In Iran, limited studies on the effects of herbal medicines in treatment of hyperbilirubinemia have been conducted.

Medicinal plants were used by the ancient Iranian families for treatment of neonatal jaundice commonly including *Alhagi pseudoalhagi* (Fruit), *Fumaria parviflora* (whole), *Zizyphus jujuba* (Fruit), Purgative *manna*, and *Chicorium intybus* (whole) [12,13].

*Zizyphus jujuba*, a member of the family Rhamnaceae, is used in India for jaundice treatment traditionally; also is in China [14,15]. There are many drug samples from this plant in different areas of Iran. No side effects have been reported, so they seem to be safe to use [16].

Despite common using of this herbal drug in treatment of neonatal hyperbilirubinemia in many parts of Iran especially in Kohkiluyeh-Boyerahmad province, its effectiveness remains doubtful and no convincing evidence, either pharmacological or epidemiological, has demonstrated its usefulness [3]. The evaluation of the role of this herbal treatment in neonatal jaundice requires properly conducted randomized clinical trials. This study investigated and evaluated effects and side effects of *Zizyphus jujuba* on jaundiced neonates.

## Subjects and Methods

This double blind clinical-trial study was carried out at Imam Sajjad Hospital, Yasuj. The protocol used in this study was approved by the institutional ethical committee on human research, and legal representatives of all patients signed an informed consent.

From April 2008 through March 2009, all 2 and 14 day old neonates hospitalized with jaundice, without any other diseases, were randomly assigned into control group (phototherapy with distilled water) and experimental group (*Zizyphus jujuba* fruit extract and phototherapy). No one at the local site was aware of the patient's group assignment. The fruits of *Zizyphus jujuba* were collected from Khorasan Province of Iran. The plants were identified by the herbalist. A voucher specimen (H, No. 622) was deposited at Herbal Research Center Laboratory at University of Medical Sciences, Yasuj, Iran. After collecting, the known species of fruits were dried at 40°C for about 1 week, then drying process continued in

room temperature at  $30\pm 2^{\circ}\text{C}$ . The dried fruits were cored and crushed. This material was ground into powder using mortar and pestle and sieved. The Jujuba fruit extract was provided under sterile conditions and with the quality and microbial control. In brief, the dried and crushed *Zizyphus jujuba* fruit (5 kg) was extracted two times with distilled water in the temperature of  $50^{\circ}\text{C}$  and vacuum conditions to appropriate concentration (1 mg/ml) (with a yield of 10% dried material from 500g of the powdered plant). Material was steeped in 600 ml of distilled water and heated in water bath for 3 hours at  $50^{\circ}\text{C}$ . The mixture was left to cool to room temperature and filtered. The filtrate was later freeze-dried yielding a residue corresponding to 1g/ml.

Concentrated extract was stored in  $-20^{\circ}\text{C}$  temperature until usage. To make it ready for use, this extract was solved in distilled water and sterilized in the autoclave. The extract was given to the baby 0.15 milliliter (150 mg) per kg body weight three times a day.

The serum bilirubin level was measured in both groups prior to the beginning of treatment and 12 hours after and then every 24 hours of treatment till discharge. Free Bilirubin level during hospitalization in both groups was measured in the hospital laboratory by the Diazo Blank method.

Babies who needed exchange transfusion or developed other diseases such as infection in the course of the study were excluded. Demographic data, stool and urine, were also recorded. Data was analyzed by SPSS 16 software using Mann-Whitney test and ANOVA test and results reported as Mean $\pm$ SD.  $P\leq 0.05$  was considered as significant.

## Findings

A total of 121 full term infants (71 [59%] boys and 50 [41%] girls) entered the study. They were divided into two groups, the experimental group including 63 patients of which 40 (63.5%) patients were male and 23 (36.5%) female (male:female ratio 1.74:1) with a mean weight of  $3030\pm 400\text{g}$ .

The control group consisted of 58 newborns, 31 (53.4%) patients were male and 27 (46.6%) were

female (male:female ratio 1.15:1) with a mean weight of  $3193\pm 479\text{g}$ . The mean age was  $5.67\pm 2.7$  days. There was no statistically significant difference regarding age, sex, type of delivery and kind and duration of milk consumption between the two groups. Eighteen patients were excluded from the treatment group and twenty one cases were omitted from the control group due to other illnesses. The change in serum bilirubin level before and after days of treatment is depicted in Table 1.

Data analysis revealed statistically significant differences between the two groups after 12 hours regarding serum bilirubin rates displayed in Diagram 1 ( $P=0.026$ ). Reduction of bilirubin in first four days was faster in the experimental group; especially during first three days it was obvious, but difference was not statistically significant ( $P=0.1$ ). After the fourth day the reduction of bilirubin became slower in less than 8.17% of patients in the experimental group.

Exchange transfusion was not needed in any patient of experimental group but it was necessary in one baby in the control group.

Considering the days of hospitalization, the experimental group stayed in the nursery for average  $3.47\pm 0.3$  days with minimum and maximum of two and six days, respectively; none of the neonates in this group was hospitalized maximum of two and six days, respectively; none of the neonates in this group was hospitalized more than seven days. In the control group, the average of hospitalization was  $3.67\pm 0.4$  days with minimum of two and maximum of nine days, respectively; two cases of controls were hospitalized more than seven days. The average hospitalization days in control group was more than that in experimental group. Seven (15.6%) and five patients from treatment and control group were discharged from the hospital at second day of admission. Thirty seven (82.2%) patients of experimental group and 26 (70.3%) patients of the control group were discharged on 4th day.

Bilirubin continued to decrease in the small group of 8 patients (17.8%) of experimental and 11 patients (29.7%) of control group.

In the control group, the mean defecations per day were  $3.8\pm 1.9$  and  $5.1\pm 2.1$ , before and after the treatment, respectively. In experimental group,



**Table 1:** Mean (SD) of serum bilirubin levels (mg/dl) of both groups before and after treatment

Groups	Before treatment	After 12 hours of treatment	After 4 days of treatment
Treatment group (n=45)	22.3 (2.0)	19.6 (3.0)	13.2 (1.0)
Control group (n=37)	20.9 (2.4)	18.4 (2.8)	13.6 (1.2)

SD: Standard Deviation

day-count stool before treatment was  $3.7 \pm 1.8$  and after treatment  $5.1 \pm 2.1$ . Rate of defecations per day had more increment in experimental group in comparison to the controls with statistically significant difference ( $P=0.001$ ). In experimental group, after taking the herbs for 1-2 days, three children developed slight diarrhea. However, this resolved spontaneously one day after discontinuing consumption of the herb. The difference was not statistically significant between the two groups regarding rate of daily defecations. Urination frequency in experimental group increased in average from  $5.4 \pm 1.45$  to  $7.4 \pm 1.21$ , and in control group reached from  $3.86 \pm 1.93$  to  $4.37 \pm 1.75$  times a day before and after the treatment, respectively. The difference between average increment of urinations was noticeable in experimental compared to the controls ( $P=0.001$ ).

## Discussion

Jaundice is the most common condition that requires medical attention in newborns [17]. During last several decades, phototherapy had been used to treat neonatal jaundice. Recently, however, both older and more recent pharmacological approaches in the field of jaundice have been considered [5].

Herbal therapy has recently received special attention in searches for bilirubin-reducing substances [2]. There are also numerous remedies for jaundice in various traditional medicines. Medicinal plants such as Rhubarb, Licorice and Gardenia are mainly used for neonatal jaundice in China [2,3].

In studies on rats, Yin Zhi Huang, consisting of four plants, had somewhat more potent stimulatory effect on clearance of bilirubin compared with Phenobarbital [7,18]. Yeung et al

reported *in-vitro* effect of a popular Chinese herb, *Artemisia scoparia* [3]. Similar study was done with *Coptis chinensis/japonicum* [19].

Furthermore, traditionally, jujube is used prophylactically for liver diseases. In northern China, the infusion and decoction of *Zizyphus jujuba*'s fruit are asserted as useful natural remedies for management and/or hepatitis control in folks [20]. In the belief of Indian and Chinese system of medicine, *Zizyphus jujuba* has hepatoprotective role in treatment of hepatic diseases [21]. It is also prescribed as a tonic to reinforce liver function and in treatment of jaundice. No studies have been conducted with healthy volunteers. Toxicity has been tested on mice, and doses of 150 g/kg revealed no signs of toxicity [16]. Beside dosage of the extract, characteristics of patients should be considered as limitations of the study.

Due to this study the average level of bilirubin in experimental group was higher which was noticeably different from that in the control group. Results showed higher clearance rate in experimental group; reduction of the amount of bilirubin in first 12 hours in the experimental group was faster than in the control group, which may be due to impact of the *Zizyphus jujuba* extract in reduction of bilirubin concentrations by means of increase in urination frequency and defecation which leads to decrease in entero-hepatic circulation. Results showed that *Zizyphus jujuba* was effective in treatment of neonatal jaundice in the first twelve hours in comparison with control group, but was not effective in consecutive days. Evaluation of the neonates' hospitalization days due to jaundice indicated statistically insignificant decrease in experimental group compared with control group.

*Zizyphus jujuba* fruit contains specific sugars (2.17 to 6.5 percent), protein, vitamin C and minerals [3,17,18], and laxative effect which reduces entero-hepatic circulation due to higher

defecation rate [9,16]. As the experiment was done on humans and no reliable research was found to prove the safety of *Zizyphus jujuba*, high doses of any drug, as well as the herbal agents, cannot be prescribed because of probable side effects and toxicities which make limitations for any treatment.

## Conclusion

We conclude that *Zizyphus jujuba* extract is safe and effective for short time usage but not effective for long time consumption in treatment of neonatal jaundice; also further studies are needed to test the efficacy and safety of the extract and to find possible materials and methods to combine in order to achieve more effective and safer treatments.

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**Conflict of Interest:** None

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