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# Effect of *Cotoneaster tricolor* Pojark Manna on Serum Bilirubin Levels in Neonates

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**Abstract:** The effect of *Cotoneaster discolor* pojark manna known as Shirkhesht in Iran (a remedy used in traditional medicine for the treatment of neonatal jaundice) in a double blind placebo controlled trial in subjects with neonatal jaundice was evaluated. One hundred and four neonates (50 and 54 in case and control groups, respectively) with jaundice who had bilirubin level of 18-29 mg $dL^{-1}$ were included in the trial. Newborns with weight less than 2.5 kg, renal failure, systemic infectious diseases, prior use of Cotoneaster manna, high bilirubin level who required transfusion were not included in the study. Patients received either a single dose of manna (6 g) or placebo (starch in distilled water, 0.1%) in the first hour of trial in addition to phototherapy. The bilirubin level was determined in blood samples every 12 h until bilirubin level reduced to less than 15 mg $dL^{-1}$ and 24 h after phototherapy discontinued. Phototherapy was discontinued when bilirubin levels fell below 15 mg $dL^{-1}$. The results indicated that the bilirubin level drops from 23 mg $dL^{-1}$ on the first day of trial to 14 mg $dL^{-1}$ on third day of trial in both case and control groups in a similar manner. Therefore, it could be suggested that the administration of *Cotoneaster* manna did not have any effect on bilirubin level providing no basis for use of the drug in neonate jaundice.

**Key words:** Neonatal jaundice, *Cotoneaster discolor* manna, bilirubin level

## INTRODUCTION

One of the most common problems in neonates in the first few days of life is icter also known as jaundice and is caused by elevated bilirubin levels in blood (Stoll and Klieman, 2004). In severely jaundiced infants, this can cause acute bilirubin encephalopathy or even Kernicterus (Dai *et al*., 1997). Phototherapy and exchange transfusion are the therapeutic modalities used most widely in infants with neonatal jaundice (Maisels, 1999; Halamek and Stevenson, 2002). As Phototherapy seems harmless, most pediatricians would use this form of treatment for bilirubin levels of 15 mg $dL^{-1}$ or more, which means separating 20% of newborns from their mothers and interrupting nursing for 2-3 days. Development of a medication as an alternative to phototherapy would be desirable provided that it is safe and effective. In modern medicine, several drugs have been used in sever bilirubenimia. They include phenobarbital (Hansen and Tommarello, 1998), cholestyramine (Nicolopoulos *et al*., 1978), agar (Li *et al*., 1984) and clofibrate (Mohammadzadeh *et al*., 2005) and tin mesoporphyrine (SnMP) (Kappas, 2004). There are various traditional remedies in various parts of the world for the treatment of neonatal jaundice. For example, a herbal decoction containing four different plants namely *Artemisia capillaries*, *Gardenia jasminoides*, *Rheum officinalis* and *Scutellaria baicalensis* has been used for the treatment of neonatal jaundice in Asia (Huang *et al*., 2004). In Iranian folk medicine, two herbal-derived preparations for the treatment of neonatal jaundice are being used

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throughout the country namely, Taranjebin (manna of *Alhagi cameolorum*) and Shirkhest also known as purgative manna, (manna of *Cotoneaster* sp.). Both manna have high content of sugar and are used as mild laxative (Aynehchi, 1986). Several compounds have been isolated from *Cotoneaster* species including dibenzofuran derivatives (Kokubun *et al*., 1995), flavonoids, arbutin and chlorogenic acid (Palme *et al*., 1996, 1994). Major components of Shirkhesht are mannitol, fructose, glucose and sucrose (Mirheydar, 1992). Our previous study involving 185 newborns indicated that Tranjebin (manna of *Alhagi cameolorum*) was not effective in preventing hyperbilirubinemia in normal term newborns (Panjvani *et al*., 1995).

In the present study, the effect of oral administration of manna of *Cotoneaster tricolor* pojark, Rosaceae family, (Shirkhesht) in combination with phototherapy in lowering bilirubin level was investigated in newborns with level of bilirubin of 18-23 mg $dL^{-1}$. Shirkhesht contains sugar such as fructose, glucose and sucrose and polysaccharide fraction.

## MATERIALS AND METHODS

The manna of *Cotoneaster tricolor* pojark was prepared from Qaien, a southern city in Khorasan province, Iran.

During the period of May 2001 to December 2003, 104 neonates with jaundice who were admitted to the neonatal Unit of Imam-Reza Hospital, Mashhad, Iran were enrolled in a prospective, double blind study. The inclusion criteria for enrolling neonates in the study were bilirubin level of 18-29 mg $dL^{-1}$. The neonates with low weight (<2.5 kg) at birth, renal failure, systemic infections and those who had already taken Shirkhest were excluded form the study. Neonates were divided into two treatment and control groups. During the course of study, neonates were given phototherapy simultaneously to prevent any damage due to high level of bilirubin. The phototherapy unit was constructed so that three neonates at a time can be treated. All neonates were given phototherapy in the same phototherapy unit. Phototherapy unit lamps were exchanged every 500 h of working.

During the first hour of trial, the neonates in treatment group were given a single dose of six grams of Shirkhest dissolved in distilled water (8 mL) by their mothers while the control group was given a starch solution (0.1%, 8 mL) colored with one drop of caramel solution to make the appearance as the same as Shirkhest solution. The bilirubin level was determined just before taking the drug and then every 12 h for three days using diazo method (Abel and Palmer-Toy, 2002) and phototherapy was discontinued after the total serum bilirubin declined to less than 15 mg $dL^{-1}$. All neonates were breastfed during the study. All neonates were examined 24 h after phototherapy discontinued for evaluation of their rebound hyperbilirubinemia and any side effects of the Shirkhest. The data was analyzed with statistical Package for Social Sciences (SPSS, version 10.05). Differences between groups were determined using Student's t-test. Statistical significance was assumed if $p<0.05$.

## RESULTS

One hundred and four newborns with neonatal jaundice were enrolled in the study of which 50 and 54 were assigned into either treatment or control group, respectively. As shown in Table 1, although the mean TBS in either treatment or control group decreased from 23 mg $dL^{-1}$ at the time of enrollment to around 14 mg $dL^{-1}$ at 72 h of treatment, but the mean TBS in treatment group was not significantly different from those of control group during 72 h of study.

Table 1: Serum bilirubin concentrations in neonates

| | Bilirubin mg $dL^{-1}$ (mean±SD) | | | | | | |
|---|---|---|---|---|---|---|---|
| Time (h) | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
| Treatment group | 23.7±3.0 | 20.5±3.3 | 17.6±3.3 | 15.6±2.7 | 14.7±1.7 | 14.9±0.5 | 14.1±0.0 |
| Control group | 23.2±3.2 | 20.1±4.0 | 16.9±2.7 | 15.2±2.9 | 14.7±2.0 | 14.6±2.1 | 14.2±0.0 |
| p-value | 0.45 | 0.31 | 0.22 | 0.63 | 0.8 | 0.83 | 0 |

Table 2: The characteristics of study and control groups

| | BUN[1] (mg $dL^{-1}$) | | | Sodium (meq/L) | | | No. Stools per day | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (h)2 | 0 | 24 | 48 | 0 | 24 | 48 | 24 | 48 | 72 |
| Treatment group | 13.5±4.0 | 13.4±3.9 | 13.4 ±4.0 | 137.9±6.2 | 138.0±5.9 | 139.7±6.0 | 5.7±1.8 | 5.5±1.6 | 5.0±1.4 |
| Control group | 14.4±4.9 | 14.4±5.6 | 14.2±5.3 | 136.6±4.9 | 137.2±5.1 | 138.3±4.7 | 5.7±2.0 | 4.7±2.3 | 1.0±0.0 |
| p-value | 0.26 | 0.28 | 0.63 | 0.48 | 0.45 | 0.49 | 0.99 | 0.19 | 0.26 |

[1]Blood urea nitrogen, [2]Hours after single dose administration of either Shirkhesht or placebo

The number of stools per day and the mean weight of neonates were not significantly different in either group. Likewise, while the mean of BUN and sodium in either treatment or control group remain in the normal range during 3 days of trial, there were no significant differences between these parameters in treatment group compared to those of control group (Table 2).

## DISCUSSION

Shirkhest is a manna obtained from *Cotoneaster discolor* which is indigenous to Iran. The major components of the manna are fructose, glucose, sucrose and polysaccharide fraction. The manna has mild laxative activity (Aynehchi, 1986) and used in traditional medicine in treating neonatal jaundice (Mirheydar, 1992). It is believed that shirkhesht increases the frequency of stool thereby increasing the excretion of bilirubin and decreasing its enterohepatic circulation. Agents that sequester bilirubin in the gut have been used in the newborn to interrupt its enterohepatic circulation and thus influence the course of neonatal hyperbilirubenimia. A reduction of 30% in peak serum bilirubin was observed in term infants fed activated charcoal at 4 h of life but no effect was observed if it is given at 12 h of life (Valaes and Harvey-Wilkes, 1990). Agar, a colloidal laxative, is a polysaccharide extracted form seaweed which binds unconjugated bilirubin in the gut, preventing its absorption and increasing its excretion in the stool. When fed to newborns starting at 20 h of age and continued for 4 days, it prevented the expected rise in bilirubin level that occurs on the 3rd to 5th day of life (Poland and Odell, 1971). Shirkhesht which is a laxative might act similarly but our results indicated no differences in the mean number of stools per day and neonates weight in infant fed with either shirkhesht or placebo. Bilirubin in stool was not determined and it is possible that shirkhesht might increase the excretion of bilirubin in stool without increasing the quantity of stool.

The plasma bilirubin levels in treatment group was not significantly different from those of control group while bilirubin levels fell constantly in either group in a similar manner indicating no additional effect from shirkhesht to phototherapy. Due to ethic problem, our trial strategy included phototherapy, as a well-established treatment strategy for treating newborns with neonatal jaundice, in conjunction with either shirkhsht or placebo group. Therefore, it is difficult to rule out the effect of shirkhesht on bilirubin levels and further study has to be conducted to confirm the proposal that shirkhesht does not contribute to bilirubin levels.

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