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Original Article

The Effect of Purgative Manna on the Infant Jaundice

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Abstract

Infant jaundice is observed during the first week of life in approximately 60% of term and 80% of preterm infants. Hyperbilirubinemia may lead to the development of kernicterus, hearing loss, and convulsion. The goal of therapy in hyperbilirubinemia is lowering blood bilirubin levels or at least preventing its increase. It is recommended that phototherapy and if unsuccessful, blood exchange transfusion be used to keep bilirubin in the normal levels. In the Iranian traditional medicine, *Cotoneaster* manna (purgative manna) is commonly used in the treatment of infant jaundice. However, no scientific data was available regarding its effectiveness. In this study, purgative manna which was obtained from *Cotoneaster discolor* Pojark from south eastern Iran was used as an oral drop preparation. After standardization of the manna and the drop, clinical study was performed on 200 hyperbilirubinemic newborns. The serum bilirubin was assayed twice a day, using spectrophotometric method. The results showed that 88% of the infants who were treated by purgative manna plus phototherapy were cured during the first 3 days of administration, but only 21% of the infants who were treatment by phototherapy alone were cured.

Keywords: Infant jaundice; Bilirubin; *Cotoneaster*; Purgative manna.
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1. Introduction

Jaundice is one of the most common problems found in newborns, and it occurs in about 60% of term and 80% of preterm newborns [1, 2]. Bilirubin production in human is occurred by heme catabolism. In normal condition, about 80–90% of the total bilirubin is produced from the heme breakage, produced from the old and broken red blood cells [3, 4]. In the normal condition, bilirubin is conjugated with glucuronic acid in the liver and is excreted in bile [4].

Physiologic hyperbilirubinemia is defined as an excessive level of serum bilirubin during impaired liver function in neonates [5, 6]. The causes of physiologic jaundice in human

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newborns are: temporary deficiency in the liver bilirubin absorption, impaired hepatic and intracellular bilirubin transfer, conjugation metabolism disorders, and deficiency in the bilirubin clearance [5, 7].

The newborn jaundice is important because increased levels of bilirubin results in severe and irreversible damage to the brain cells. It leads to mild central nervous system damage and hearing lose in the premature newborns [2, 8]. The incident of mental retardation in babies below two years of age is related to the serum bilirubin levels of neonates [9]. It seems that urgent treatment is necessary in order to decrease the serum bilirubin levels.

There are two usual methods of treatment for neonatal jaundice in the literatures: light therapy and blood exchange [10]. Blood exchange is the last way for decreasing the serum bilirubin levels [2, 11]. The use of light can decrease the need for blood exchange. In children below 2 kg, light therapy can decrease serum bilirubin between 1.6 to 2 mg/dl in 24 hours [4, 10]. Therapy with light has some side effects such as faintness resulted from dehydration, diarrhea, hypokalemia, riboflavin deficit, skin rushes and so on, but it is still the most effective cure for jaundice in neonates [2, 12].

In this study decreasing the unconjugated bilirubin in serum by using a natural medicine was investigated. Purgative manna has been used as laxative, biliousness and tonic for the liver in the Iranian traditional medicine. The manna, known in Iran as Shir-Khesht, is found as dew drops falling on *Cotoneaster* species plants. The manna is white to yellow, round or shapeless pieces with a very sweet taste and cooling properties [13]. *Cotoneaster* genus, Rosaceae family, has 19 species in Iran. The manna is produced by the action of an insect; on some kinds of plants like *C. numularia* and *C. discolor*. *Cotoneaster discolor* is a shrub, 1–1.5 m high, with brown thin branches, elliptical leaves, and red small flowers with triangular sepals [14].

In this research, the purgative manna was prepared as an oral drop formulation, and clinical studies were carried out in order to find out the effect of this formulation on hyperbilirubinemia in neonates.

2. Materials and methods

2.1. Collection of purgative manna

Purgative manna and herbarium sample of its producer plant, *Cotoneaster discolor*

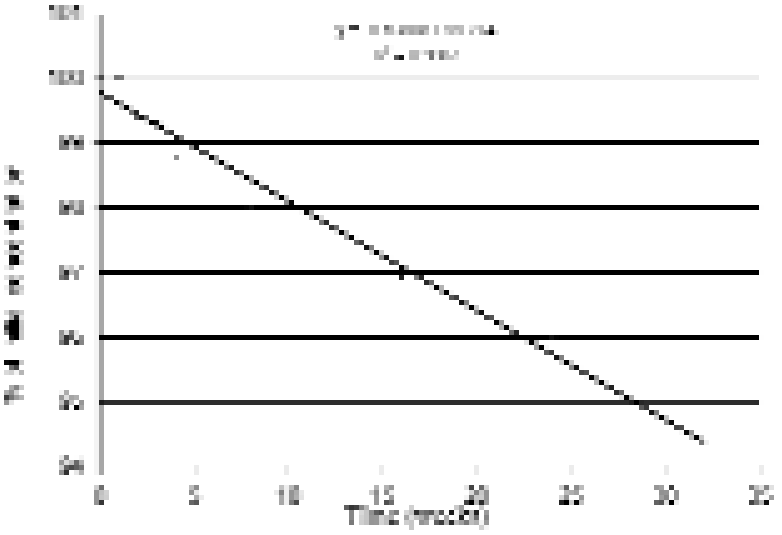

Figure 1. Stability test of the oral drop in room temperature.

Table 1. Abundance of sex, age, and weight of newborns that received the oral drop and phototherapy.

Cases	Phototherapy alone		Treatment with the oral drop and phototherapy	
	Percent	Abundance	Percent	Abundance
Girl	47%	47	47%	47
Boy	53%	53	53%	53
Age (less than 4 day)	24%	24	36%	36
Age (between 4-8 day)	57%	57	52%	52
Age (more than 8 day)	19%	19	12%	12
Weight (less than 2500g)	15%	15	18%	18
Weight (more than 2500g)	85%	85	82%	82
G6PD deficiency	15%	15	18%	18
Hemoglobin (less than 17)	76%	48	56%	40
Hemoglobin (more than 17)	21%	13	44%	32

Pojark, were obtained from the south of Khorasan, a north-eastern province of Iran, in the mid-summer 1997. The plant was authenticated in Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences.

2.2. Identification of the important active materials

Mannitol and manna spots were placed on a paper chromatography (Wattman, No.1). The mobile phase was *n*-propanol, ethyl acetate, and water (2:1:7, v/v/v). The spots were developed using 5% silver nitrate solution.

2.3. Manna extract preparation and standardization

Four hundred grams of the manna was dissolved in 400 ml of distilled water, and the foreign matters such as wood pieces and leaves were separated by filtration. The extract was dried under reduced pressure, and the dry extract was assayed on the basis of mannitol according to British Phrmacopoeia procedure.

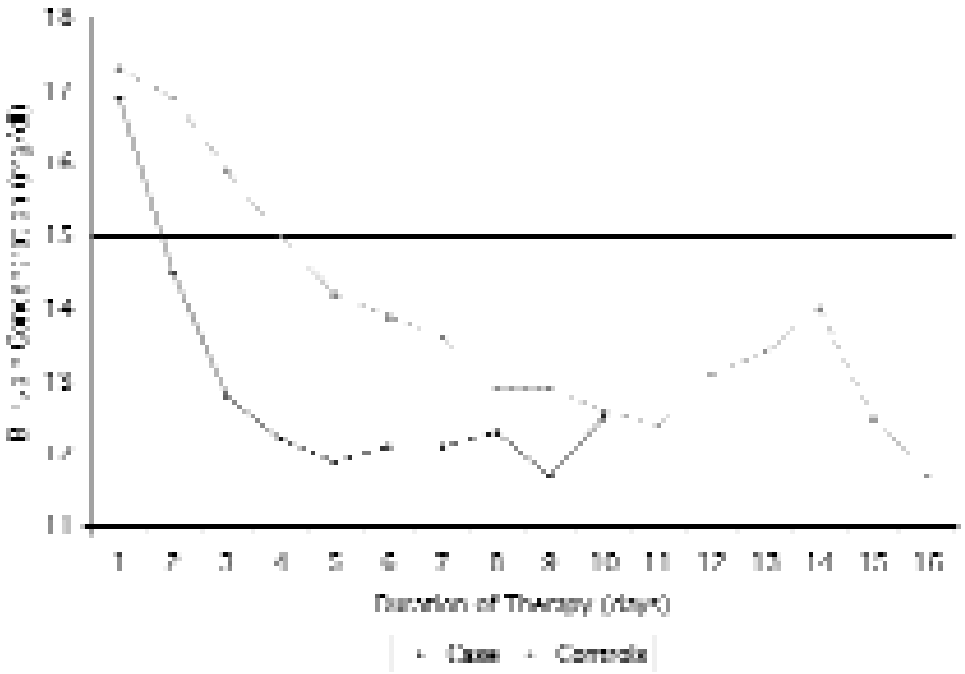

Figure 2. Comparison of bilirubin decrease between case group (treatment with the oral drop and phototherapy) and control group (treatment with phototherapy).

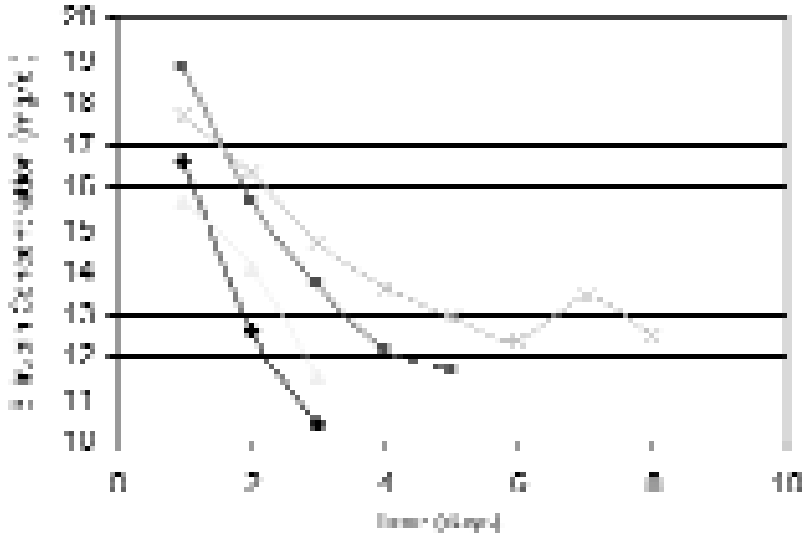

Figure 3. Comparison of hospitalization time between case group (treatment with the oral drop and phototherapy) and control group (treatment with phototherapy).

2.4. Preparation of oral drop

Propyl paraben (0.07 g) and methyl paraben (0.63 g) were dissolved in 150 ml of distilled water at 88 °C, and then 350 g of the dry extract was added to it, and the volume was made up to 350 ml by adding distilled water. The final preparation contained 1 g/ml of the dry extract, 0.02% and 0.18% of propyl paraben and methyl paraben, respectively, as preservative.

2.5. Product control

Microbial limitation and preservative effect tests were performed according to USP XXIII procedure. Periodical procedure was used for stability test.

2.6. Clinical study procedure

Full term neonates, without the background of any other disease, were chosen. A questionnaire was prepared and the infant's information, such as: age, weight, glucose-6-phosphat dehydrogenase condition, direct bilirubin amount, direct Kombs test, and morning and afternoon bilirubin amounts, were recorded. Clinical trail was performed on 200 hospitalized newborns. One hundred newborns received the oral drop and light therapy as the case group, and 100 newborns

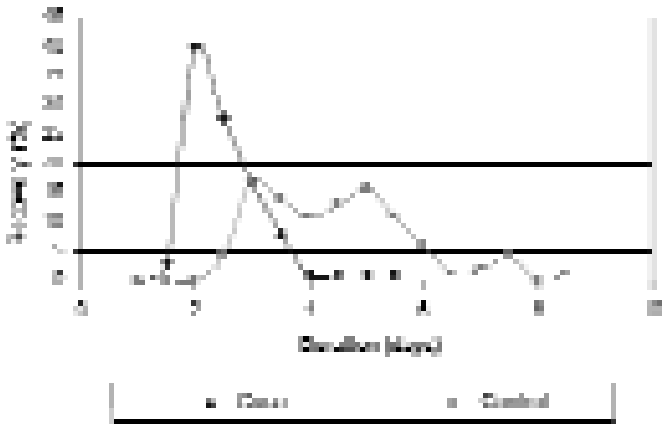

Figure 4. Number of newborn between case group (treatment with the oral drop and phototherapy) and control group (treatment with phototherapy) who were dismissed from hospital before each bleeding.

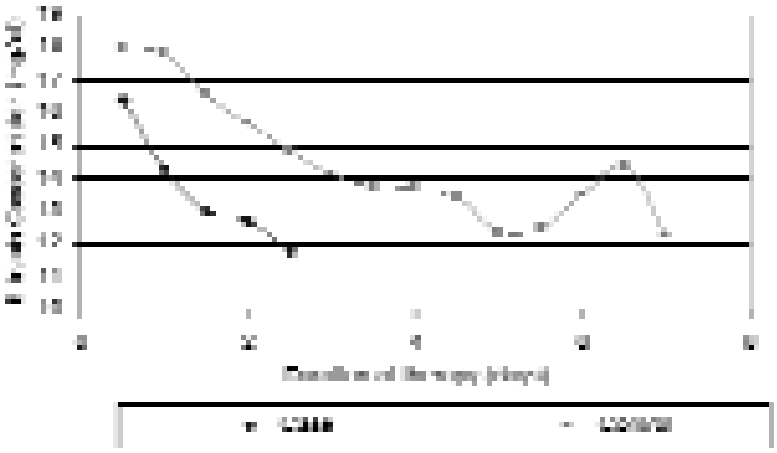

Figure 5. Comparison of the effect of case group (treatment with the oral drop and phototherapy) and control group (treatment with phototherapy) in newborns with G6PD deficiency.

received placebo and light therapy as control group. In each group 5 drops of the drug or placebo were administered three times a day in a double blind study.

2.7. Bilirubin assay

Serum bilirubin level was assayed twice a day by spectrophotometry method with about ± 0.2 mg sensitivity.

2.8. Statistics methods

Student's "t" test used for the comparison of the mean serum bilirubin levels in two groups. One way analysis of variance and EPI6 and SPSS software were used for analysis of the clinical data.

3. Results

The dry extract had 88.3% manna from which 50-60% was mannitol. One ml of the drop contained 610 mg active constituents based on mannitol. Microbial tests of the oral drop revealed no bacterial or fungal contamination. According to Figure 1 the stability of the oral drop was evaluated. The shelf-life of this preparation was assessed 14 months.

The effect of sex, age, and weight of newborns on treatment schedules are shown in Table 1. Although the rate of treatment is the same but the results showed that addition of manna drop to the phototherapy treatment sharply decreased serum bilirubin levels compared to phototherapy alone (Figure 2).

During the first 3 days of treatment, serum bilirubin levels decreased very rapidly, and 88% of the infants receiving the drug plus phototherapy were cured during the first 3 days (Figure 3). Only 21% of the infants in the group who received phototherapy alone were treated in the same period. Majority of the case group were cured in 3 days, but most of the newborn in control group were treated in 6 days (Figure 3). According to Figure 4, most of newborns receiving manna plus phototherapy were dismissed from hospital after the first day of hospitalization. Manna plus phototherapy also decreased the serum bilirubin level in G6PD deficient neonates much faster than phototherapy alone (Figure 5).

4. Discussion

The average of serum bilirubin levels in case and control groups were not significantly different at the beginning of hospitalization, but after start of the treatment the serum bilirubin in neonates who received manna plus phototherapy declined much faster than those who received phototherapy alone, therefore, it could be concluded that rapid

reduction in bilirubin serum concentration in the case group was induced by the manna. Discharge of the case group patients from hospital started after 1.5 days of hospitalization. It means that they were released before the third blood sampling. For the control group, the beginning of release from hospital was after 2.5 days of hospitalization, and most of them were released after 6.5 days.

Some plants such as *Nymphaea stellata* and a poly herbal formulation containing *Berberia aristata, Cordia myxa, Elettaria cardamomum,Glycyrrhiza glabra, Piper longum* and *Zingiber officinale* could also decrease serum bilirubin(15,16). In conclusion; administration of purgative manna (Shirkhesht) could clinically useful for treating infant jaundice.

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