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The Effect of Manna on Blood Bilirubin Level in Neonates with Hyperbilirubinemia and Identification of Its Constitutes

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MRM, MRK, MH and ARR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SK managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Hyperbilirubinemia is the most common problems in 60% of term infants and 80% of preterm infants. In the case of severe indirect hyperbilirubinemia, it can cause neurotoxic disorders, however, the direct hyperbilirubinemia is considered as severe or systemic problems of liver. Phototherapy and in more severe condition the exchange transfusion are the main treatments that can be used to treat infant jaundice. In traditional medicine manna is also used orally to treat jaundice in infants. The aim of this study was to determine the effect of manna on blood bilirubin levels in neonates with hyperbilirubinemia.
Materials and Methods: In this clinical-trial study, a total of 124 neonates with non-hemolytic indirect hyperbilirubinemia, were randomly assigned into four groups (three experimental groups

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and one control group). The experimental groups were: (A) both mother and neonate respectively recipient 30 cc and 1 cc/kg of the 25% manna solution and phototherapy, (B) only mother recipient of the manna and phototherapy and (C) only neonate recipient of the manna and phototherapy. Control group receiving phototherapy with distilled water. Bilirubin levels were measured at the baseline of experiment and then daily during the experimental period.
Results: The results showed that the amount of bilirubin and days of hospitalization had no significant difference among different groups ($p > 0.05$) and the administered manna solution at these doses had no effect on neonatal bilirubin.
Conclusion: According to the results of the project, the prescribed doses of manna solution had no effect on neonatal bilirubin. Therefore, it must be used cautiously in infants.

Keywords: Bilirubin; neonatal hyperbilirubinemia; manna; taranjabin.

1. INTRODUCTION

Hyperbilirubinemia is one of the most common problems in newborns, as 60% of term infants and 80% of preterm infants are suffering from this disorder in the first week of life [1]. Bilirubin is the yellow breakdown product that is produced from catabolism of hemoglobin in the reticuloendothelial system. During the catabolism of 1 g of hemoglobin approximately 35 mg bilirubin can be produced. The amount of bilirubin in infants is 2 to 3 times greater than that of older children. This is probably due to the increase in production of Red Blood Cells (RBC) mass and the short life span of RBC in infants (70 to 90 days) compared with that of adults (120 days) [2]. Bilirubin is a lipophilic molecule that is conjugated in the liver to make it water-soluble, and eliminated by excretion into bile. The fetus conjugates only a small amount of produced bilirubin and conjugated bilirubin is transported across the placenta very poorly. In contrast, unconjugated fetal bilirubin is easily transported from the fetal circulation, across the placenta, for elimination by the mother's liver. Immediately after birth, the liver of neonates is the only way to eliminate bilirubin, but it has poor functionality in the first week of life and it is unable to eliminate all of produced bilirubin [3]. Jaundice is not a disease by itself, but a sign that results from hyperbilirubinemia. Hyperbilirubinemia at high levels can however have toxic effects on the body, such as kernicterus syndrome [4]. Kernicterus especially in severe levels can cause nerve deafness, seizures, stupor, muscle imbalance and even death [5]. Jaundice is usually generated due to Erythroblastosis fetalis, hidden bleeding, polycythemia or intrauterine infections such as syphilis, cytomegalovirus disease, rubella and congenital toxoplasmosis. Regardless of the cause of this disorder, the aim of treatment is to prevent indirect bilirubin levels to reach neurotoxic doses. Phototherapy is most commonly used method to change unconjugated bilirubin into forms that can be eliminated rapidly through the urine. Exchange transfusion is used when the bilirubin level is very high and continues to rise despite use of intensive phototherapy. This treatment can rapidly decrease bilirubin from the bloodstream below the critical level [5]. Phototherapy can cause several side effects such as damage to the retina, retinal disease, dehydration, diarrhea and etc. [6,7]. So, it has always been necessity to develop a solution to reduce the time required for phototherapy or substitution it with other methods. *Manna (Taranjabīn* in persian*)* has been used in traditional medicine for the treatment of neonatal jaundice. *Manna* is a semiliquid resinous compound exuded by the leaves and branches of some species of Alhagis mainly *Alhagi mannifera* and *A. persarum* from the Papilionaceae family [8,9]. The plant is called kar-e sotor, kar-e Taranjabin in Persian and it is called camel's thorn in English [10,11]. The manna or *Taranjabīn* is used as a treatment for glandular tumors, nasal polyps, and ailments related to the bile ducts. It is also used as a medicinal herb for its gastroprotective, diaphoretic, diuretic, expectorant, laxative, antidiarrhoeal and antiseptic properties, and in the treatment of rheumatism and hemorrhoids [5,10]. Studies conducted on the effects of manna or *Taranjabīn* on hyperbilirubinemia in laboratory animals have shown positive results. However, the effect of manna in the treatment of neonate's hyperbilirubinemia is not clear exactly [11,12]. So, the aim of this study was to determine the effect of manna on blood bilirubin levels in neonates with hyperbilirubinemia.

2. MATERIALS AND METHODS

This clinical-trial study was carried out at Hajar Hospital of Shahrekord from October 2012 to June 2013. It was approved by the ethics

committee of the Medical University of Shahrekord, Iran and has been recorded in the Iranian clinical trial center with registration number IRCT201012042085N6. The sample size was calculated based on a 95% confidence and a power of 80% to see a change of 0.5±0.7 day in hospitalization days between groups. The sample size obtained as 31 patients in each group. A total of 124 neonates with non-hemolytic indirect hyperbilirubinemia, were randomly assigned into four groups (three experimental groups and one control group). The experimental groups were: (A) both mother and nenonate respectively recipient 30 cc and 1 cc/kg of the 25% manna solution and phototherapy, (B) only mother recipient of the manna and phototherapy and (C) only nenonate recipient of the manna and phototherapy. Control group received phototherapy with distilled water. Bilirubin levels were measured at the baseline of experiment and then daily during the experimental period.

The criteria for selection of neonates in this study were as follow: Non-hemolytic indirect hyperbilirubinemia, the total bilirubin levels of serum in the baseline of study ranging from 14 to 20 milligrams per deciliter, the beginning of jaundice between the third and tenth days after birth, term infant with 2.5 – 4 kg at the time of birth, the neonate must not have a history of illness or drug consumption and breast milk must be the only infant nutrition. Informed consents were obtained from the legal representatives of children prior to study. The protocol used in this study was approved by the institutional ethical committee on human. The exit of neonate from the hospital for any reason before reaching the bilirubin levels less than 12 mg / dl, lack of parental consent to proceed with the project and the need of neonates to other drugs were of criteria that excluded from the study. The manna was obtained from trusted groceries of Medicinal Plants Research Centers of Shahrekord University of Medical Sciences. Based on the routine method of aplication of manna in treatment of neonatal jaundice in previous studies, a solution of manna was prepared with a concentration of 25 g per 100 ml of distilled water. The obtained solution was passed through Buchner funnel flowed by filter paper, so that the transparent solution was obtained of which the mother and neonates recipient respectively 30 cc and 1 cc/kg three times a day. Phototherapy was done for all groups in the same circumstances. 6 lamps with wavelengths of 420 - 460 nm and an average lamp life less than 2,000 hours at a distance of 40 – 45 cm from the infant body were used for phototherapy. For all babies, the blood bilirubin level was measured prior to the beginning of treatment and then every 24 hours during experimental period till discharge. The criteria for discharge of neonates from hospital were the total bilirubin levels less than 12 mg/dl. All babies were reviewed daily by business projects and the amount of bilirubin and their general condition were recorded in related questionnaires. Preparation and maintenance of manna was carried out under hygienic conditions and the solution was refrigerated up to 5 days. For continuous variables (bilirubin, hospitalization, infant's age), data were presented as mean ± SD and for categorical ones, as frequency with percent. Comparisons between two groups were done using the Chi-square test for categorical variables (gender, childbirth) and analysis of variance for continuous ones. The parametric analysis of variance was used for distributed normal variables (infant's age, birth weight, hospitalization, bilirubin at arrival, bilirubin at day 1 and 2) and Kruskal-Wallis test was used for non-distributed variables (bilirubin at day 3 and 4). Statistical analysis was performed by SPSS (Ver. 11) and P-values <0.05 were statistically significant.

Due to the differences between the consumption of manna in traditional medicine and that mentioned in this study, some of the constitutes were separated by the filtration of manna solution (Table 1).

The amount of constitutes identified in manna solution passed through the filter paper were measured and the result are presented in Table 2.

Table 1. The main constitutes separated by filtration of manna solution

Constitutes	**N**	**P**	**K**	**Ca**	**Mg**	**Zn**	**Fe**	**Mn**	**Cu**	**Cd**
Unit	**%**	**%**	**%**	**%**	**%**	**$mg.kg^{-1}$**	**$mg.kg^{-1}$**	**$mg.kg^{-1}$**	**$mg.kg^{-1}$**	**$mg.kg^{-1}$**
Amount	2.147	0.982	1.352	1.235	0.981	101.28	352.79	156.03	35.17	0.82

Table 2. The main constitutes identified in manna solution after passing through filter paper

Constitutes	N	P	K	Ca	Mg	Zn	Fe	Mn	Cu	Cd
Unit	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$	$mg.lit^{-1}$
Amount	645.93	98.37	876.91	121.84	69.34	1.04	0.61	1.12	0.55	0.05

3. RESULTS

In this study, the effect of *manna* on serum bilirubin of neonates with hyperbilirubinemia was investigated in the Hajar Hospital of Shahrekord and following results were obtained. The age of infants was from 3 to 10 day with mean of 5.8±2.19 day. According to the Analysis of variance, there was no significant difference in age of neonatal among different groups (P > 0.05). In terms of gender distribution, of the total 124 neonates, 73 patients (58.9 percent) were boys and 51 patients (41.1%) were girls (P>0.05). Table 3 shows the distribution of gender in different groups.

Table 3. Gender distribution of neonates in different groups

Gender \ Group	A	B	C	D
Boy	19	18	17	19
Girl	12	13	14	12
Total	31	31	31	31

The mean for birth weight of neonates was 3087±377.1 g, and the analysis of variance showed no significant difference among different groups (P > 0.05). In term of type of childbirth, of 124 studied neonates 59 cases (47.6%) and 65 cases (52.4%) had natural childbirth and Caesarean section, respectively (P> 0.05). Table 4 shows the distribution of the type of childbirth in different groups.

The amount of total bilirubin in the time of enrolment was from 14 to 20 mg/dl with mean of 16.6±1.75 mg/dl. The result of analysis of variance showed no significant difference among different groups in total bilirubin of subjects prior to experiment (P> 0.05). Changes in bilirubin during the study period are shown in Table 5.

Table 4. The distribution of the type of childbirth in different groups

Type \ Group	A	B	C	D
NVD	15	16	15	13
C/S	16	15	16	18
Total	31	31	31	31

NVD: Natural Vaginal Delivery
C/S: Caesarean Section

Based on the significant levels presented in Table 5, it can be seen that the amount of bilirubin among different groups had significant difference only at day one of experiment. The group A with a mean of 13.5±1.96 mg/dl had the lowest and the group C with mean of 14.9±1.99 mg/dl had the highest amount of bilirubin. In other days of hospitalization, it was not seen any significant difference in bilirubin levels of neonates' blood among different groups. Fig. 1 shows the levels of bilirubin in different groups during the study.

In the view of duration of treatment, duration of hospitalization ranging from 1 to 5 days with mean of 2.5±0.84 days. The analysis of variance test showed no significant difference in the duration of treatment or hospitalization among different groups (P > 0.05). Fig. 2 shows the duration of hospitalization in different groups. Thus, it can be said that the prescribed doses of manna solution in this study showed no effect on the duration of hospitalization of patients among different groups (p > 0.05).

Table 5. Changes in bilirubin levels of neonates' blood of different studied groups

Group	A		B		C		D		p
Time	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	
Arrival	31	16.6±1/71	31	17.1±1.58	31	16.8±1.94	31	16±1.64	0.07*
Day 1	31	13.5±1.96	31	14.4±1.90	31	14.9±1.99	31	13.8±1.60	0.019*
Day 2	27	11.2±1.69	31	11.5±1.49	31	12.1±1.81	29	11.1±1.81	0.138*
Day 3	10	11.3±1.35	14	11.6±1.26	15	12.2±1.54	14	11±0.94	0.124**
Day 4	3	11.1±0.70	5	11.1±0.74	6	11.9±1.51	2	11±0.00	0.94**

**: ANOVA Test; **: Kruskal Wallis Test*

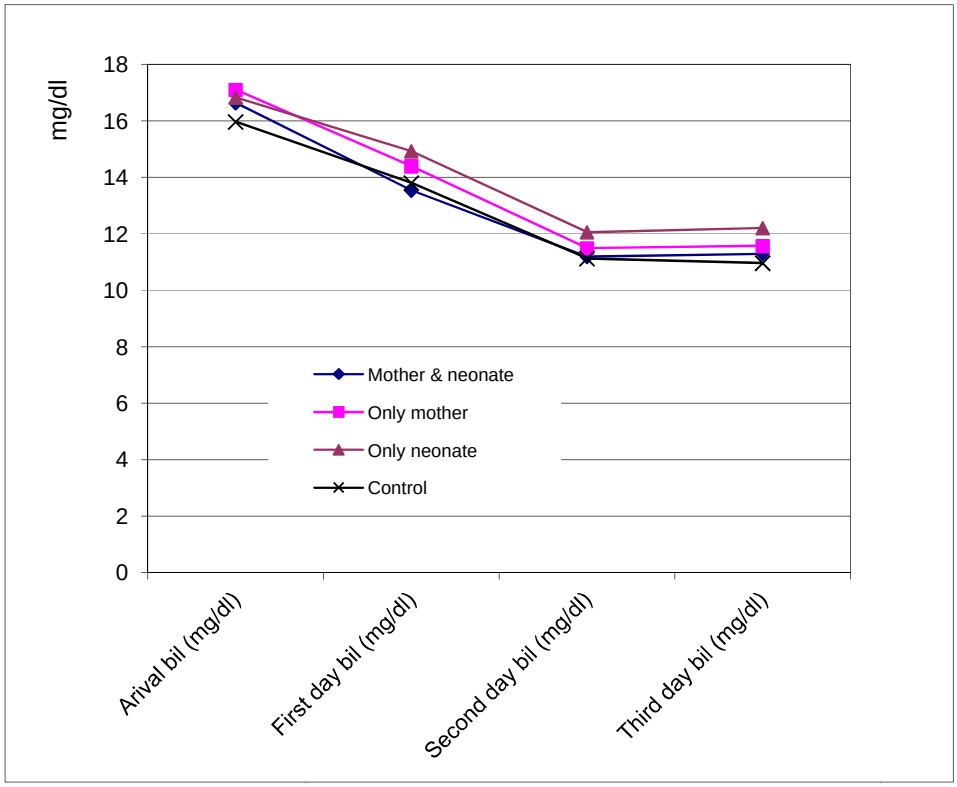

Fig. 1. Changes of bilirubin levels in different groups during the study

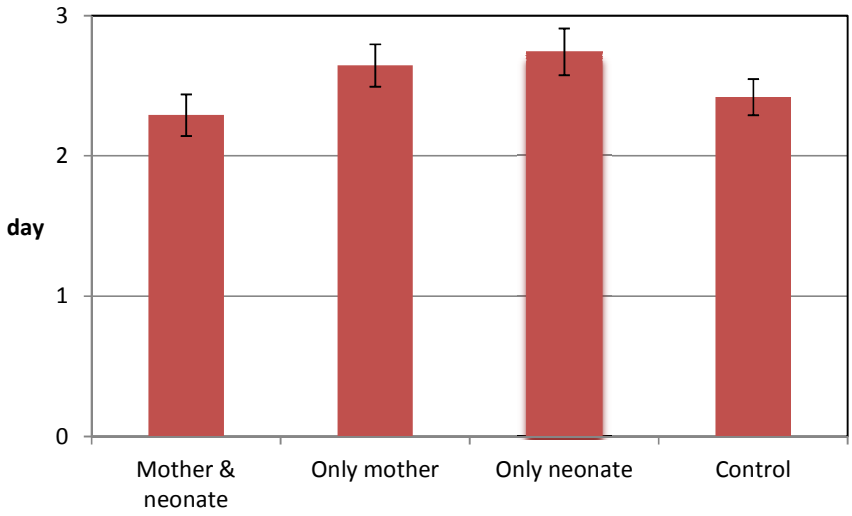

Fig. 2. The mean of hospitalization days in different groups

4. DISCUSSION AND CONCLUSION

Neonatal bilirubin at day one of hospitalization had significant difference among different groups ($p < 0.05$). Because the amount of bilirubin of control group is located between those of other groups, this difference cannot be attributed to the intervention. Except day one, the amount of bilirubin of neonates had no significant difference among different groups ($p > 0.05$). The results of this study showed that the prescribed doses of manna solution in this study had no effect on the

bilirubin level of neonates' blood. According to the statistical analysis which did not show any significant difference among different groups in terms of age of neonates, gender of neonates, age of mothers, type of childbirth and the amount of early bilirubin as well as the place of birth, It can be said that the administered doses of manna solution to the mother and baby, mother or newborn babies individually had no effect on bilirubin levels of neonates' blood compared with that of control group.

The findings of this study showed that, contrary to popular belief, oral administration of manna had no effect in reducing neonatal bilirubin level. Nabavizadeh et al. [13] also reported that the addition of manna extracts could not cause any direct effect on blood bilirubin of neonates suffered from hyperbilirubinemia. Tarhany et al. (2004) also concluded that the manna administration had no positive effect on neonatal jaundice compared with controls. During their study, the effect of oral administration (1 cc/kg) of manna solution 30% in reducing the physiological jaundice in newborns with hyperbilirubinemia was studied. The result indicated that manna solution did not reduce neonatal jaundice in treated group compared with control group so it cannot be recommended as a treatment for neonatal jaundice [14]. In traditional medicine and in regard with how manna is used to treat neonatal jaundice, after soaking and filtering the resulting solution is used for both mother and baby without passing through filter paper. In this study the prepared manna solution was passed through a Buchner funnel to separate the remaining parts of the plant. It is passed through a filter paper again, and in this passing phase through the filter a remarkable amount of compounds including N, P, K, Ca, Mg, Zn, Fe, Mn, Cu and Cd were separated from the extract. In fact, these materials are taken by the mother and newborn in traditional medicine. These materials appear to play important roles in increasing the peristaltic movements of intestine, faster disposal of meconium and prevention of re-absorption of bilirubin from the intestinal wall. These materials were excluded from the consumption of mother and baby, because of the method of extract preparation used in this study. The study of Saboute et al. [15] indicated that the total bilirubin levels in neonates in the baseline of study (arrival), 24 and 48 hours after intervention had no significant difference between these two groups. All of the above mentioned studies are in accordance with the present study. Bandegi [16] in conducted study on Wistar rats concluded that the oral administration of 100 µl of 30% manna solution every 2 hours could decrease significantly the bilirubin levels in jaundice Wistar rats during 24 hours after hyperbilirubinemia compared with control group which was not in accordance with the result of our study. In fact, it seems that the difference in the findings of Bandegi's study and those of other studies may be due to the high dose of manna solution that was used per body weight of studied rats [16]. According to the results obtained in this study and also the results of previous studies as well as due to the ineffectiveness of oral administration of manna solution in lowering blood bilirubin in infants, it should be required to inform that the manna solution must be used with caution. On the other hand, because this drug is used along with phototherapy it cannot be identified its therapeutic effects clearly. In addition, the results of our study suggest that the prescribed doses of manna solution have no effect on the duration of hospitalization of patients among different groups most likely due to the significant decrease of the soil residue containing the above mentioned minerals (N, P, K, Ca, Mg, Zn, Fe, Mn, Cu and Cd) on Manna.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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