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Comparison of the Effect of *Purgative manna* and *Alhagi Pseudoalhagi* Usage on Healing Icterus of neonates

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ABSTRACT

Aims Benign neonatal icterus is a common problem in preterm and term neonates. In some countries, traditional medicine is being used to relieve icterus. The aim of this study was to compare the effect of *purgative manna* and *Alhagi pseudoalhagi* usage on healing icterus of neonates.

Materials and Methods In this clinical trial, 171 neonates with physiologic icterus that was referred to the Imam Sadjad hospital of Yasuj in 2016, were selected by simple random sampling method and randomly divided into three groups. The control group (n=57) only received phototherapy. The second group (n=57) received 5 oral drops for 3 times per day of *purgative manna*, and for 3 days along with phototherapy. The third group (n=57) received 1cc/kg of a 30% suspension of *Alhagi pseudoalhagi* oral drop in each 12 hours for 3 days along with phototherapy. Then the rate of reduction in neonatal bilirubin was compared in the three groups. Data were analyzed by SPSS 21 software using Chi-square, one-way ANOVA, Kruskal-Wallis tests and Tukey's post hoc test.

Findings The *Alhagi pseudoalhagi* group had lower total bilirubin mean and direct bilirubin mean in comparison to phototherapy and *purgative manna* groups, and these differences were statistically significant ($p<0.05$). Phototherapy and *purgative manna* had no significant difference ($p>0.05$).

Conclusion Regarding the effect of *Alhagi pseudoalhagi*, its standard products could be used in treatment of icterus in neonates, but *purgative manna* has no significant effect on the treatment of icterus and is not recommended for icterus treatment.

Keywords Hyperbilirubinemia; Icterus; *Alhagi pseudoalhagi*; *Purgative Manna*; Phototherapy

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Introduction

Hyperbilirubinemia is a common –mostly benign- problem in neonates s and is the most common cause of hospitalizing them [1]. The importance of icterus in neonates s is because of its dangerous complications due to bilirubin enhancement in brain that result in severe irreversible mental damages and even death [2].

Approximately 60% of mature neonates s and 80% of immature neonates s will be affected by icterus in the first week of life, which its cause is accumulation of non-conjugated, non-polar, and fat-soluble bilirubin pigments in the skin of neonates (indirect reaction). Skin icterus can also be due to the deposition of pigments in the liver microsomes by uridine di-phosphoglucuronic acid glucuronyl transferase enzyme, in the form of Stargolcoronide bilirubin, which is polar and water-soluble [3]. Totally, 6-7% of mature neonates s have direct bilirubin higher than 12.9 and approximately 3% of them have indirect bilirubin even higher than 15 [4].

Crohn's icterus is an encephalopathy of Bilirubin, which appears as a severe neurological syndrome. Most of the affected neonates s will die due to this sever neurological syndrome and those who survive mostly will suffer of complications such as mental disorders, Seizure, Speech and Hearing Disorders, Hypotonia, Extrapiramidal Symptoms, Bilateral Athetose chorea and Muscle Spasm [4]. Crohn's icterus is seen in 1/3 of neonates s with untreated hemolytic disease and bilirubin levels higher than 25-30mg per dl [5].

Phototherapy is the most common therapeutic and prophylactic method for non-conjugated hyperbilirubinemia that almost in all cases will decrease the concentration of bilirubin [6]. Therapeutic effect of phototherapy depends on the energy rate due to effective wave lengths, distance between light and neonates , the skin surfaces exposed by the light, and the speed of hemolysis, metabolism, and secretion of bilirubin [5]. Transfusion of two times higher than present blood volume will be performed in patients that phototherapy could not decrease their high bilirubin level, as well as those that the danger of Crohn's icterus will be higher than performing this procedure [5].

Other therapies are the administration of non-absorbable materials, which may reduce the serum level of bilirubin and intestinal absorbance of bilirubin, by binding to the bilirubin in the intestine or by reducing the enterohepatic circulation [5]. According to World Health Organization (WHO), 80% of people still believe in conventional herbal medicines [7]. Row extract of herbs from the past were used as medicine for treatment of several diseases [8].

In several areas of Iran such as Kohgiluyeh and Boyer-Ahmad, Fars, and Lorestan provinces, *Alhagi pseudoalhagi* is used for treatment of icterus in neonates s. *Alhagi pseudoalhagi* is one of herbal components that for a long time has been used for treatment of hyperbilirubinemia by Iranian families and Iranian conventional medicine [5]. *Alhagi pseudoalhagi is* a long lasting plant from Papilionaceae family [3]. This substance may decrease the activity of the beta-glucuronidase enzyme and decrease the intestinal-hepatic circulation and result in more bilirubin to be excreted in the stool [9].

Another herbal component that is widely used in treatment of icterus in neonates s is *purgative manna.* Cotoneaster is a white colored substance that is known as *purgative manna.* The substance is extracted of plants of Cotoneaster SPP genus and Rosaceae family [10]. The most important components of *purgative manna* are carbohydrates including mannitol, fructose, glucose, and sucrose [11]. It is believed that *purgative manna* inhibits entering bilirubin into enterohepatic circulation via binding it, and is effective in decreasing icterus [12].

The aim of this study was to compare the effect of *purgative manna* and *Alhagi pseudoalhagi* usage on healing icterus of neonates s.

Materials and Methods

The present study was performed as a clinical trial, on neonates s with physiologic icterus that was referred to the Imam Sadjad hospital of Yasuj in 2016. Sampling performed in the simple random manner. The study was conducted on 171 mature neonates s with 2500 to 4000gr of weight, and 15 to 20mg/dl of bilirubin level. Neonates s that needed to blood exchange and also had the clinical signs of sepsis were excluded from the study. Neonates s that were diagnosed to have icterus were randomly divided into three groups. The first group as the control group (n=57) only received phototherapy. The second group (n=57) received 5 oral drops for 3 times per day of *purgative manna* (bilinaster produced by Barij esans Company; Kashan), and for 3 days along with phototherapy. The third group (n=57) received 1cc/kg of a 30% suspension of *Alhagi pseudoalhagi* (collected from mountains around Yasuj) oral drop in each 12 hours for 3 days along with phototherapy [12]. Then the rate of reduction in neonatal bilirubin was compared in the three groups.

Preparing the extracts of *purgative manna* and *Alhagi pseudoalhagi*: After collecting plants, 2000gr of *purgative manna* powder and 500mgr of *Alhagi pseudoalhagi* were isolated and the desired concentration was prepared. For preparing the extract of *purgative manna* the bilinaster drop (Barij esans Company; Kashan) was used.

Chi-square test was used for comparing the categorical variables. The normal distribution of

variabes was evaluated using Kolmogorov-Smirnov test. The one-way ANOVA test was used in case of normal distributed variables; otherwise, Kruskal-Wallis test was used. Tukey's post hoc test was used for comparing groups two by two. Data analysis was done by SPSS 21 software.

Findings

There was no significant difference among three groups based on gender, age, weight, delivery type, pregnancy age, gravid, and blood groups of mother and neonates (p>0.05; Table 1).

There was significant difference among three studied groups based on the frequency of total and direct bilirubin levels (p=0.001; Table 2).

The means of total (p=0.001) and direct bilirubin (p=0.027) in three studied groups had significant statistical difference (Table 3).

The *Alhagi pseudoalhagi* group had lower total bilirubin mean and direct bilirubin mean in comparison to phototherapy and *purgative manna* groups, and these differences were statistically significant (p<0.05). Phototherapy and *purgative manna* groups had similar results and no significant difference was seen between them (p>0.05).

Table 1) Comparison among 3 studied groups (n=57 in each group) based on frequency of gender, age, weight, delivery type, pregnancy age, gravid, and blood groups of mother and neonates (the numbers in parantheses are percentage)

Variables/Groups	Phototherapy	*Purgative manna*	*Alhagi pseudoalhagi*oral	P. value
Gender				
Male	33 (57.9)	36 (63.2)	31 (54.4)	0.633
Female	24 (42.1)	21 (36.8)	26 (45.6)	
Age (days)				
2-4	31 (54.4)	25 (43.9)	33 (57.9)	0.707
4-6	13 (22.8)	12 (21.0)	12 (21.0)	
6-8	8 (14.0)	12 (21.0)	7 (12.3)	
>8	5 (8.8)	8 (14.0)	5 (8.8)	
Weight (gr)				
2500-3000	19 (33.3)	15 (26.3)	18 (31.6)	0.883
3000-3500	21 (36.8)	24 (42.1)	22 (38.6)	
3500-4000	3 (5.3)	8 (14.0)	6 (10.5)	
4000-4500	10 (17.5)	7 (12.3)	8 (14.0)	
>4500	4 (7.0)	3 (5.3)	3 (5.3)	
Delivery type				
Cesarean	35 (61.4)	38 (66.7)	34 (59.6)	0.273
Normal delivery	22 (38.6)	19 (33.3)	23 (40.4)	
Pregnancy age (weeks)				
36-38	17 (29.8)	17 (29.8)	25 (43.9)	0.275
38-40	20 (35.1)	19 (33.3)	20 (35.1)	
40-42	17 (29.8)	19 (33.3)	8 (14.0)	
>44	3 (5.3)	2 (3.5)	4 (7.0)	
Gravid				
1	12 (21.0)	16 (28.1)	15 (26.3)	0.980
2	23 (40.4)	20 (35.1)	22 (38.6)	
3	10 (17.5)	11 (19.3)	10 (17.5)	
4	12 (21.0)	10 (17.5)	10 (17.5)	
Blood groups of mother				
O+	27 (47.4)	20 (35.1)	25 (43.9)	0.686
O-	2 (3.5)	3 (5.3)	2 (3.5)	
AB+	9 (15.8)	7 (12.3)	7 (12.3)	
AB-	0	0	0	
A-	12 (21.0)	12 (21.0)	11 (19.3)	
A+	0	3 (5.3)	1 (1.7)	
B-	7 (12.3)	8 (14.0)	9 (15.8)	
B+	0	4 (7.0)	2 (3.5)	
Blood groups of neonates				
O+	16 (28.1)	12 (21.0)	12 (21.0)	0.738
O-	4 (7.0)	6 (10.5)	6 (10.5)	
AB+	5 (8.8)	3 (5.3)	6 (10.5)	
AB-	4 (7.0)	3 (5.3)	5 (8.8)	
A-	10 (17.5)	18 (31.6)	12 (21.0)	
A+	2 (3.5)	1 (1.7)	1 (1.7)	
B-	16 (28.1)	11 (19.3)	14 (24.6)	
B+	0	3 (5.3)	1 (1.7)	

Table 2) Comparison among three studied groups (n=57 in each group) based on frequency of total and direct bilirubin levels (the numbers in parantheses are percentage)

Variables/Groups	Phototherapy	*Purgative manna*	*Alhagi pseudoalhagi*
Total bilirubin			
8>	0 (0)	2 (3.5)	11 (19.3)
8-9	12 (21.1)	12 (21.1)	11 (19.3)
9-10	20 (35.1)	26 (45.6)	21 (36.8)
10-11	13 (22.8)	14 (24.6)	11 (19.3)
11<	12 (21.1)	3 (5.3)	3 (5.3)
Direct bilirubin			
<0.3	7 (12.3)	5 (8.8)	6 (10.5)
0.4-0.3	16 (28.1)	22 (38.6)	25 (43.9)
0.5-0.4	11 (19.3)	11 (19.3)	14 (24.6)
0.6-0.5	4 (7)	6 (10.5)	2 (3.5)
0.7-0.6	7 (12.3)	8 (14)	7 (12.3)
0.8-0.7	6 (10.5)	5 (8.8)	2 (3.5)
> 0.8	6 (10.5)	0 (0)	1 (1.8)

Table 3) Comparison of the mean of total and direct bilirubin levels among three studied groups using one-way ANOVA

Variables	Mean±SD	F. value	P. value
Total bilirubin			
Alhagi pseudoalhagi group	11.12±0.36	0.249	0.001
Purgative manna group	14.25±0.11		
Phototherapy group	15.25±0.70		
Direct bilirubin			
Alhagi pseudoalhagi group	0.69±0.08	0.687	0.027
Purgative manna group	0.72±0.16		
Phototherapy group	0.61±0.08		

Discussion

Based on the results of the present study, *Alhagi pseudoalhagi* was more effective in decreasing bilirubin level in comparison to phototherapy and *purgative manna,* and showed better clinical results. Phototherapy and *purgative manna* had similar and close results. So, regarding our results and the effect of oral *Alhagi pseudoalhagi*on on reduction of icterus in neonates s, its usage is recommended for treatment of hyperbilirubinemia in neonates s.

Results of the studies performed by Tarhani *et al.* [13], Nabavizadeh *et al.* [14], and Panjovani *et al.* [5] showed that *Alhagi pseudoalhagi* has no effect on prevention of hyperbilirubinemia in full term neonates s, which is in contrast with our results.

Bandegi in his study showed that though *Alhagi pseudoalhagi* can reduce plasma bilirubin concentration in hyperbilirubinemic mice, the usage of *Alhagi pseudoalhagi* in human depends on the results of clinical trials [8]. However, Kazorani *et al.* showed that receiving *Alhagi pseudoalhagi* with different doses for 10 days, whether oral consumption or intraperitoneal injection, has no significant effect on the serum bilirubin level [15].

Results of this study showed that there is no statistically significant difference between the control (phototherapy) group and the *purgative manna* group based on the speed of serum bilirubin reduction, and in spite of conventional believe, *purgative manna* has no effect on decreasing icterus in hospitalized neonates s. This finding is in concordance with the studies performed by Shahfarahat *et al.* [16] and Mansoori and Ghotbi [17]. On the other hand, in the study of Khoshdel *et al.* [18] bilirubin level reduction in groups that used bilinaster drop was higher than the control group that was used placebo and phototherapy. So, our results is in contrast with the mentioned study. Azadbakht *et al.* showed that the speed of bilirubin reduction due to *purgative manna* drop usage in neonates s that were under phototherapy, was very higher in the first 3 days in comparison to the control group [19], which is also in contrast with our results.

One of the limitations of this study was a small number of samples, which is why the results of the study can not be generalized. Therefore, considering that in Iran this herb is traditionally used in the treatment of neonatal jaundice and also because of the controversial results in reducing neonatal jaundice, it is recommended that supplementary studies be carried out with a larger number of specimens in this regard.

Conclusion

Regarding the effect of *Alhagi pseudoalhagi,* its standard products could be used in treatment of icterus in neonates s via performing supplementary studies. Despite conventional believe that *purgative manna* is effective on the reduction of icterus in neonates s, its prescribing has no significant effect on the treatment of icterus and is not recommended for icterus treatment.

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