Evaluation of Safety and Efficacy of Purgative Manna (Billinaster Drop) and Glycerin Suppository in Icterus of Healthy Term Newborns

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Abstract: *Objective*: The aim of the present study was to investigate safety and efficacy of billinaster drop and glycerin suppository in hyperbilirubinemia of healthy term newborns who had passage of first meconium.

Methods: In a randomized clinical trial, 90 neonates with total plasma bilirubin(TPB) level of 15–20mg/dL, were randomly assigned to be treated with alone phototherapy (control) or 5drop/kg of bilinaster drop every eight hours and phototherapy(B) or half of glycerin suppository every twelve hours and phototherapy(G). The primary outcomes were safety of drugs and efficacy in obtaining TPB of less than 14 mg/dL as measured at the beginning, 12, 24 and 48 hours after intervention. Secondary endpoint was hospitalization days.

Results: After 48 hours of intervention, achieving TPB of less than 14 mg/dL was seen in 50 %(N=15) in control group, 73.3 %(N=22) in B group and 86.7 %(N=26 neonates) in G group (P= 0.01).

Watery stool was seen in two neonates of glycerin group and safety of the treatments was not significantly different.

Mean of TPB 12 hours after beginning of phototherapy(mean±SD:14.38±2.27mg/dL in G, 15.97±1.96mg/dL in B and 16.67±1.77mg/dL in control), 24 hours after intervention(mean±SD:12.56 ±1.59mg/dL in G, 12.57±2.05mg/dL in B and 14.36±2.26mg/dL in control), 48 hours after intervention (mean±SD: 9.34 ± 1.6mg/dL in G, 9.96 ± 2.95mg/dL in B and 12.27 ± 2.4mg/dL in control) and mean of hospitalization days (mean± SD: 1.5 ± 0.4days in G, 1.7 ± 0.4days in B and 2.9 ± 1.1days in control) were significantly lower in glycerin and billinaster groups.

Conclusion: Bilinaster drop and glycerin suppository can be used as hazardless, efficient and cost effective drugs in treatment of neonatal hyperbilirubinemia.

Keywords: Bilinaster, glycerin suppository, jaundice, neonate, purgative manna, term.

INTRODUCTION

Icterus might be seen in 60 percent of full term newborns in the first week of their life and indirect total plasma bilirubin (TPB) of more than 25 to 32 mg/dL can cross blood brain barrier and may be associated with bilirubin induced neurologic dysfunction or kernicterus. Bilirubin neurotoxicity is rare in healthy mature newborns with TPB level of less than 25 mg/dL. Therapeutic interventions such as phototherapy and if unsuccessful, exchange transfusion should be considered for reduction of TPB in neonates with severe hyperbilirubinemia and in prevention of bilirubin encephalopathy. However, phototherapy is considered safe, but, side effects such as erythematous rashes, watery stools, dehydration and hyperthermia might be seen and exchange transfusion is expensive, time consuming and might be associated with increased risk of morbidity, and even mortality. Such harmful adverse effects show the necessity to expand alternative pharmacological methods for treatment of neonatal jaundice [1].

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Based on some experts recommendation for diagnosis of neonates who are at high risk for kernicterus and severe hyperbilirubinemia, all neonates should be screened for hyperbilirubinemia in the first 24-48 hours of life and also, for early detection and prevention of bilirubin induced neurologic dysfunction, all neonates discharged earlier than 48 hours after birth should be followed up within 2-3 days after discharge [2].

Drugs such as metalloporhyrins, clofibrate, bile salts, laxatives and bilirubin oxidase have been used as pharmacological interventions and alternative therapy in neonatal indirect hyperbilirubinemia. However, to allow routine application, they all must be evaluated sufficiently [1, 3]

One of the causes of exaggerated hyperbilirubinemia is persistence of enterohepatic circulation and laxatives can reduce serum indirect bilirubin level by decreasing its enterohepatic circulation [3].

Use of herbal medicines is increasing nowadays [4] and medicinal plants such as Fumaria Parviflora, Cichorium Intybus, Alhagi Pseudoalhagi and Purgative Manna have been used in the treatment of neonatal jaundice as complementary therapies for many years in Iran and south East Asian countries. Purgative manna which is produced by

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the act of an insect on some of plants such as *Cotoneaster discolor* is known as Shir-Khesht in Iran. Its laxative and biliousness effects might interrupt bilirubin enterohepatic circulation and decrease indirect bilirubin. Pharmacologic companies have prepared Purgative Manna as an oral drop formulation which is named Billinaster [5-7].

Meconium (first stool of neonate) is rich in bilirubin and glycerin laxatives which is immediately used after birth can stimulate evacuation of meconium as an osmotic dehydrating and osmotic pressure increasing agent in gut [8] and it can interrupt bilirubin enterohepatic circulation.

A few studies showed that administration of glycerin suppository immediately after birth was effective in evacuation of meconium, but mean total serum bilirubin level 48 hours after treatment was not significantly different in the intervention group compared to controls [9, 10].

In term lower risk neonates, phototherapy should be started with total plasma bilirubin level of 15 mg/dl [2] and concomitant usage of pharmacological drugs might be useful in decreasing of phototherapy duration and hospitalization costs and since, herbal or chemical laxatives might help reach the ambition. The present study was done to investigate efficacy and safety of billinaster drop (as a traditional medicine) and glycerin suppository in hyperbilirubinemia of healthy term newborns who had passage of first meconium.

MATERIALS AND METHODS

We followed a randomized single – blind study which was conducted on the referred and admitted healthy mature newborns with jaundice between September 2012 and February 2013 to Shahid Sadoughi Hospital in Yazd, Iran.

Thirty children were included in parallel single-blinded randomized clinical trial which was conducted on each group to detect a 20% difference in efficacy between the three groups with type one error (alpha) of 0.05 and 80% power based on a study done in the past in our department [1].

Three hundred two neonates in range of 3-7 days were referred to Pediatric Clinic of Shahid Sadoughi Hospital for follow up. Total plasma bilirubin level was measured in all icteric neonates and newborns with TPB level of more than 15 mg/dl were admitted into hospital and phototherapy was started immediately on admission.

Eligible participants included healthy term neonates who:

- Had gestational age of 37-42 weeks
- Had a birth weight of 2500-4000 g
- Were delivered by normal vaginal
- Had total plasma bilirubin level of 15-20 mg/dl
- Were exclusively breast–fed. because breast-fed neonates are more likely to have more icterus than formula-fed neonates) [11].
- Aged more than two days and who had passage of first meconium, as 99% of term neonates evacuate meconium during 48 hours of birth [12].

Newborns with sepsis, anemia, severe birth asphyxia, hemolytic disorders, main congenital anomalies, direct hyperbilirubinemia and underlying hepatic diseases were excluded.

The study used computer generated equal simple randomization by random numbers and allocation ratio was 1:1 for the three groups. Randomisation and blinding were done by a researcher without any clinical involvement in the study. Data collectors, outcome controllers and data analysts were all unaware of the allocation. But, patients and allocated nurse to the evaluation group were aware of the allocated arm. The drug was delivered by the nurse of pediatric ward and primary and secondary outcomes were assessed by the pediatric resident of research who was not informed of the drug group assignment. Ninety neonates were randomly assigned to three groups to be treated with phototherapy alone (group 1) or 5 drop/kg of bilinaster drop (Sobhan Darou Co) every eight hours up to 48 hours and phototherapy (group 2) or half of glycerin suppository every twelve hours up to 48 hours and phototherapy (group 3). "Each phototherapy unit had four special blue lamps (Philips Co of Germany), replaced after 800 h and adjusted to 20 cm above the newborn's cot. Phototherapy was begun just on admission for all newborns in the three groups until TPB reduced to less than 10 mg/dL. In bilirubin level of 25–30 mg/dL, if intensive phototherapy was ineffective, exchange transfusion was done in the newborns. Total and direct serum bilirubin levels of peripheral vein blood samples were assessed by Jendrassik-Grof method. Primary outcomes were safety of drugs, clinical adverse events of treatments and efficacy in obtaining TPB of less than 14 mg/dL as measured at the beginning, 12, 24 and 48 hours after phototherapy. Then TPB was measured daily and when TPB decrease to less than 10 mg/dL, the neonates were discharged. All newborns were assessed for clinical adverse events of treatments during their hospital stay days and on the second day after discharge in the clinic of the hospital [1].

Secondary endpoint was hospitalization days. Analysis of the data was done by SPSS: 18 statistical software. Recorded data were assessed for normal distribution using the Shapiro Wilk test. Analysis of the data of qualitative variables was done by Chi-square test and comparison of mean values were done by two-way ANOVA test and as a significant result was obtained, the Tukey test was applied for post hoc pair wise comparisons. Differences were considered significant at P values of less than 0.05.

Informed consent was taken from patients' parents before administration of the drugs and the study has been approved by the Ethic Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The researchers were not funded by the drugs company. The design and conduct of this study were straightforward, and no loss to follow-up or exclusions was seen.

RESULTS

Ninety neonates including 48 girls (53.3%) and 42 boys (46.7%) with age of 4.04± 1.17 days were evaluated. After application of Shapiro Wilk test, the data had normal distribution. Comparison of some of characteristics of the children is shown in Table **1** which shows that mean of gestational age, birth weight, age, and weight and bilirubin level at the time of admission, number of defecation per day

and sex distribution were not significantly different in the three groups. After 48 hours of treatment, 50% (N=15) in phototherapy alone group, 73.3% (N=22) in phototherapy and billinaster group and 86.7% (N=26 neonates) in phototherapy and glycerin group had TPB of less than 14 mg/dL. (P= 0.01) Table **2** depicts comparison mean of some of variables and indicates that mean TPB levels 12 hours after treatment was lower in both billinaster and glycerin groups than in phototherapy group alone and glycerin was more effective than billinaster in lowering of mean TPB levels 12 hours after intervention. Mean TPB 24 and 48 hours after intervention were significantly lower in both billinaster and glycerin groups; however efficacy of both drugs in lowering of mean TPB levels 24 and 48 hours after intervention were not statistically different. Hospital stay days was statistically significant lower in both billinaster and glycerin groups. Weight in discharge time and number of defecation per day in 24 and 48 hours after intervention were not statistically significant different in the three groups. Only one neonate in each of the three groups required exchange transfusion. No serious clinical side effects were seen in the two groups and only watery stool was seen in two patients of glycerin group. Safety of the treatments was not significantly different in the three groups (p value = 0.14).

DISCUSSION

Based on results of the present study, mean of hospital stay days and mean total serum bilirubin 12, 24 and 48 hours after treatment in healthy term neonates who had passage of first meconium with TPB of 15–20 mg/dL, were significantly lower in glycerin and billinaster groups and glycerin was more effective than billinaster in lowering of mean TPB levels 12 hours after treatment.

Possible reason for more effectiveness of glycerin than billinaster in lowering of mean TPB levels 12 hours after treatment might be in earlier onset of it's laxative effect and glycerin can be used for earlier reduction of bilirubin level in icteric neonates.

In the present study, glycerin suppository significantly reduced TPB level and it was effective in treatment of neonatal unconjugated hyperbilirubinemia which is not in agreement to two other researches [9, 10]. Possible explanation for this discrepancy may be the difference in time of the drug use and age of participants. In this study, glycerin suppository was used in neonates who had passage of first meconium. But, In Bader *et al.,* study, administration of glycerin suppository immediately after birth and then every 4 hours until passing of first stool in healthy term neonates caused faster meconium evacuation but mean serum bilirubin level 48 hours after treatment was not significantly different between the groups. However, boys had significantly lower mean total serum bilirubin, especially if they had type A blood group [9]. Also, systematic review of three randomized clinical trials by Srinivasjois *et al.,* showed that healthy term neonates who used glycerin suppository or glycerin enema had quicker evacuation of meconium but mean total serum bilirubin levels 48 hours after treatment was not significantly different between the groups [10].

This research showed that billinaster (Purgative Manna) can significantly decrease TPB level and it was effective in the treatment of neonatal unconjugated hyperbilirubinemia which is in agreement to other researches [6, 7, 13].

But in a research in Mashhad, Iran, mean total serum bilirubin 12, 24,36,48 and 60 hours after intervention of healthy term neonates with TPB level of 18-29 mg/dl were not significantly different in neonates who received 6 grams (0.21 ounces) of Shir-Khesht or placebo [14].

In a study in Yasoj, Iran, efficacy of 0.5 cc of five herbal drugs (Cichorium intybus, Fumaria parviflora, Zizyphus jujuba, Alhagi pseudoalhagi and Purgative manna) on serum of icteric neonates was assessed and the result showed that only Cichorium intybus extract reduced the bilirubin level significantly [5]. In a study in Sanandaj, Iran, billinaster drop was not effective in prevention of hyperbilirubinemia in term neonates [15].

Possible explanations for these discrepancies are differences in: age, total serum bilirubin and drug dosage.

In present study, mean of hospital stay days was significantly lower in billinaster group which is in agreement to another Iranian study [13].

In the present study, no life-endangering and severe adverse events were seen in neonates who used bilinaster drop or glycerine suppository.

Safety of bilinaster (purgative manna) was reported in other Iranian researches [7, 13, 14, 15].

Table 1. Comparison of Some of Variables in the Three Groups

Data		Phototherapy Alone	Phototherapy and Billinaster	Phototherapy and Glycerine	P Value
Gestational age in week (mean ±SD) *		38.35 ± 1.13	38.6 ± 0.99	37.9 ±1.07	0.13
Birth weight in kg (mean ±SD) *		3.16± 0.52	3.22 ± 0.58	3.13 ± 0.34	0.85
Age in day (mean ±SD) *		4.29 ± 0.63	3.89 ± 1.28	4.19 ± 1.1	0.86
Weight in admission in kg (mean ±SD) *		3.15± 0.51	3.23 ± 0.59	3.16 ± 0.37	0.65
Admission bilirubin level (mean ±SD) *		17.93±1.51	17.67±1.26	17.33±1.44	0.41
Number of defecation per day(mean ±SD) *		3.38±1.64	3.5±1.08	3.35±1.63	0.96
Sex**	Girl	16	18	14	0.63
	Boy	14	12	16	

*The used statistical test: Two-way ANOVA.
**The used statistical test: Chi-square test.

Table 2. Comparison of Mean of Some Variables After Intervention in the Three Groups

Data \ Groups	Phototherapy Alone	Phototherapy and Billinaster	Phototherapy and Glycerine	P Value	
Bilirubin levels in 12 hours after treatment in mg/dL	16.76 ± 1.89	15.97 ± 1.96	14.38 ± 2.27	Ph, Ph +B	0.4
				Ph, Ph +G	0.02
				Ph +B, Ph+ G	0.04
Bilirubin levels in 24 hours after treatment in mg/dL	14.36 ± 2.26	12.57 ± 2.05	12.56 ± 1.59	Ph, Ph +B	0.02
				Ph, Ph +G	0.03
				Ph +B, Ph+ G	0.9
Bilirubin levels in 48 hours after treatment in mg/dL	12.27 ± 2.4	9.96 ± 2.95	9.34 ± 1.6	Ph, Ph +B	0.02
				Ph, Ph +G	0.01
				Ph +B, Ph+ G	0.8
Hospital stays in day	2.9 ± 1.1	1.7 ± 0.4	1.5 ± 0.4	Ph, Ph +B	0.02
				Ph, Ph +G	0.001
				Ph +B, Ph+ G	0.1
Weight in discharge time	3.19± 0.56	3.23 ± 0.58	3.12 ± 0.35	Ph, Ph +B	0.7
				Ph, Ph +G	0.6
				Ph +B, Ph+ G	0.9
Number of defecation per day in 24 hours after intervention	4.05±1.19	4.7±2.02	4.85±1.69	Ph, Ph +B	0.8
				Ph, Ph +G	0.2
				Ph +B, Ph+ G	0.9
Number of defecation per day in 48 hours after intervention	4.6±1.39	5.6±2.11	5.91±1.63	Ph, Ph +B	0.7
				Ph, Ph +G	0.3
				Ph +B, Ph+ G	0.6

*Ph= Phototherapy alone.
**Ph+B = Phototherapy and Billinaster.
***Ph+G = Phototherapy and glycerine.
❖ The statistical test used: Two-way ANOVA for comparing on mean values and Tukey test was applied for post hoc pair wise comparisons.

CONCLUSION

Based on results of the present study, bilinaster drop or glycerine suppository are safe and efficient in treatment of unconjugated hyperbilirubinemia of term healthy newborns during the first week of their birth and they can reduce hospital stay duration and are cost effective as well.

CONFLICT OF INTEREST

The researchers were not funded by the drugs company. The design and conduct of this study were straightforward, and no loss to follow-up or exclusions was seen.

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PATIENT CONSENT

Informed consent was taken from patients' parents before administration of the drugs and the study has been approved by the Ethic Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

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