The Effect of Purgative Manna and Clofibrate on Neonatal Unconjugated Hyperbilirubinemia

Abolfazl Mahyar[1], Shahrokh Mehrpisheh[2], Bahman Khajeh[2], Parviz Ayazi[1], Sonia Oveisi[3], Shifteh Mahyar[4], Shiva Esmaeili[5]

[1] Department of Pediatrics, Qazvin Children Hospital, Qazvin University of Medical Sciences, Qazvin, Iran

[2] Department of Neonatology, Qazvin Children Hospital, Qazvin University of Medical Sciences, Qazvin, Iran

[3] Metabolic Diseases Research Center, Qazvin University of Medical Sciences, Qazvin, Iran

[4] School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran

[5] Department of Statistics, School of Medicine, Qazvin University of Medical Sciences, Qazvin, Iran

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Abstract- This study was conducted to determine the effect of purgative Manna and clofibrate on unconjugated hyperbilirubinemia of term neonates. In this randomized clinical trial study, sixty neonates suffering from unconjugated hyperbilirubinemia were evaluated. The neonates were divided into three groups using balanced block randomization. Group A (control group-received only phototherapy), group B (intervention group-received purgative Manna and phototherapy) and group C (intervention group-received clofibrate and phototherapy). After the intervention, the amount of serum bilirubin reduction was compared between groups. There was no significant difference among group A, B, and C in terms of serum bilirubin reduction in 24, 48 and 72 hours after starting the intervention ($P>0.05$). The hospital stays in the control group was significantly longer than the intervention groups ($P<0.05$). No side effects were observed related to using purgative Mienna and clofibrate. The present study showed that prescribing of purgative Manna and clofibrate has no effect on reduction of serum bilirubin level in term neonates with unconjugated hyperbilirubinemia. Thus, it seems that the administration of these drugs is not necessary. Further studies in this regard are recommended.

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Keywords: Clofibrate; Hyperbilirubinemia; Purgative manna; Newborn

Introduction

Hyperbilirubinemia is a common disease in neonates and is s observed in 60% of term neonates and 80% of preterm infants in the first week after birth (1). Neonatal hyperbilirubinemia is divided into two types: unconjugated hyperbilirubinemia and conjugated hyperbilirubinemia. Unconjugated hyperbilirubinemia is the most common form of the disease and is a result of increase in unconjugated, nonpolar, lipid-soluble bilirubin pigment. Unconjugated bilirubin is the final product of heme-protein catabolism in reticuloendothelial system (1,2). Among unconjugated hyperbilirubinemia causes, one can refer to the increase in bilirubin production (such as hemolytic diseases, polycythemia), destruction, reduction and blocking of transferase enzyme activity (such as congenital, hypoxia of drugs) and also, decrease in the hepatic absorption of bilirubin (such as congenital, prematurity) (1,2). Although bilirubin has antioxidant properties, increase in unconjugated bilirubin is highly toxic and may lead to neurologically irretrievable damages, which is called kernicterus or bilirubin encephalopathy (1-3). In this dangerous neurologic complication, unconjugated bilirubin sediments in basal ganglia and brain stem nuclei and many of these patients die, and the ones who survive get afflicted with intensive neurologic sequel (1,4). Thus, quick and appropriate treatment of unconjugated hyperbilirubinemia is highly important (1). The goal of treating unconjugated hyperbilirubinemia is to prevent kernicterus regardless of the cause (1). Although phototherapy and blood transfusion are the two main methods of treating unconjugated hyperbilirubinemia, these methods are not without side effects. Blood transfusion is done when phototherapy is not capable of reducing serum bilirubin

Corresponding Author: A. Mahyar
Department of Pediatrics, Qazvin Children Hospital, Qazvin University of Medical Sciences, Qazvin, Iran
Tel: +98 28 13334807-9, +98 939 1823303, Fax: +98 28 13344088, E-mail address: abolfazl473@yahoo.com

to an unthreatening level (1). Guidelines for phototherapy and transfusion have been determined by American Academy for Pediatrics (5). Different lights are used for phototherapy, and maximum light absorption is seen by blue light (range 420-470 mm). Among the side effects of phototherapy, one can refer to diarrhea, cutaneous rash, dehydration, overheating, purpuric rash associated with transient porphyrinemia and bronze baby syndrome (1,2). During phototherapy, in order to prevent damage to the cornea, eyes should be covered, and the temperature should be constantly controlled. Meanwhile, protecting the possibility of bulb breakage and direct measurement of the amount of radiation is necessary (1,2). According to the mentioned contents, it has always been regarded by the researchers to provide a solution for reducing phototherapy time or determine a substitute for it. Some studies mentioned that use of some pharmaceutical agents could help to reduce the time of phototherapy and decrease its side effects (6-11). Such items include using traditional medicines such as purgative Manna and some drugs like clofibrate (7-12). Fallah *et al*., states that the use of purgative Manna along with phototherapy can reduce serum bilirubin level compared to phototherapy alone (8). In Persian traditional medicine, purgative Manna is called as a Mellin, anti-bilious and tonic for the kidney (13). This substance has a white to yellow color with a sweet taste and is related to the plants of *Cotoneaster spp* and of *Rosacea* family (7,8,13,14). In some reports, it has been mentioned that prescription of clofibrate in 50 and 100 mg/kg dose as a single dose along with phototherapy reduces serum bilirubin level and decreases duration of phototherapy (9,11). Clofibrate is one of the fibric acid derivatives (fibrates), and it is believed that this drug accelerates the excretion of bilirubin (9,14,15). This study was carried out according to the paradoxes in this field.

Materials and Methods

Population study

This single-blind randomized controlled clinical trial was conducted on 60 term neonates with unconjugated hyperbilirubinemia. This study was conducted in the neonatal department of Qazvin children's hospital in 2017-18. This hospital is the only children's referral hospital in the Qazvin province and is affiliated to Qazvin University of Medical Sciences (Qazvin, Iran). Neonates with the following conditions entered the study (inclusion criteria's):

1-Term (gestational age of between 37-42 weeks)

2-Weight between 2500-4000 grams

3-Age 2-10 days

4-The presence of nonhemolytic unconjugated hyperbilirubinemia

5- Only breast-fed

6-Candidate for phototherapy based on the instruction of American Academy of Pediatrics (AAP) (1,5).

The neonates with the following condition were excluded (exclusion criteria):

1-Hemolyric unconjugated hyperbilirubinemia (such as ABO and Rh incompatibility deficiency, glucose-6-phosphate dehydrogenase and etc.).

2-Presence of risk factors and concomitant and underlying diseases such as asphyxia, acidosis, hemorrhage, hypothyroidism, sepsis, polycythemia and etc.).

3-Neonates fed with non-breastfeeding

4-Mother's disease (such as eclampsia, diabetes, chorioamnionitis, hypertension, and etc.).

5-Conjugated hyperbilirubinemia

The 6-Colic escalation followed by taking purgative Manna

Study design

Based on the previous study that was conducted on the term neonates with unconjugated hyperbilirubinemia (8), the sample size (60 patients) was calculated according to:

1-α =0.9(power) $Z_{1-\beta/2}$=1.28 β=0.05 1-α=0.95 $Z1-_{\alpha}/2$=1.96 β=0.1

(S1=2.26) Standard deviation in control group

(S2=2.05) Standard deviation in the trial group

μ_1=14.36 mg/dL (The mean of bilirubin level in control group)

μ_2=12.57 mg/dL (The mean of bilirubin level in the trial group) (8).

The neonates were divided into three groups using balanced block randomization (groups A, B, and C- each group 20 neonates). In this method, at first, 20 blocks (ACB-BCA-CAB-BAC-ABC-CBA, …) were set based on a random table. Then cards were prepared in the order of the above letters, and they were put in homochromatic envelopes. The referring patients entered the above groups in the mentioned order. The entry of the patients into the study was balanced and did not have the capability of being disclosed. Group A (control group) received the only phototherapy; Group B (intervention group) received phototherapy along with purgative Manna, and Group C (intervention group) received phototherapy along with clofibrate. The

conditions for phototherapy were the same for all groups (1,9). The groups were similar in terms of background and confounding variables. Phototherapy was done by intensive phototherapy device of Tosan model, made in Iran with eight blue-light lamps (Philips bulb, made in Germany, each lamp was 20 watt with lifetime of 2500 hours and wavelength of 420-470 nm). For prescribing purgative Manna we used Bilineaster drop with a dose of 3 drops/kg three times per day (Sohan Darou Company, Rasht Industrial City, Rasht, Iran, and Batch No: 122802337). Bilineaster drop is prepared from aqueous extract of purgative Manna and contains mannitol (40-60% -300 mg mannitol/ml), sucrose, dextrose, fructose, and polysaccharide. Microbial tests of the oral drop revealed no bacterial or fungal contamination (7,16). Clofibrate was prescribed with the dose of 30 mg/kg as a single oral dose (Zahravi pharmacy company, Tabriz, Iran, Batch No: 218, registration number 1228098598). Phototherapy was done equally for all the groups based on the protocol of American Academy of Pediatrics (1,5). Discontinuation of phototherapy was when the bilirubin reached to less than 10 mg/dl (1,5). The neonates were visited in the hospital clinic 48 hours after discharge to control their jaundice recurrence. Bilirubin was measured by DCA method (Prestige device of model 24I, Japan) in the laboratory department of Qazvin children hospital.

Statistics

The chi-square test, t-test (mean±SD) and Mann-Whitney U test [median (IQR) (Interquartile Range)] were used to compare variables between groups. All statistical analyses were performed using SPSS for Windows 16.0 (SPSS Inc., Chicago, IL). $P<0.05$ were considered as statistically significant.

Ethics statement

This project was approved by the ethics committee of Qazvin University of Medical Sciences (IR.QUMS.REC.1395.116). Also, the project was registered at the IRCT (IRCT2016110412897N2). All parents were provided information regarding the research method in simple language. Neonates were included in the study after their parents agreed and signed the informed consent form.

Results

The male/female ratio in the groups A (receiving the only phototherapy), B (receiving phototherapy and purgative Manna) and C (receiving phototherapy and clofibrate) was 12/8, 12/8 and 9/11, respectively ($P=0.54$). The median (IQR) of the neonates' age in the three groups of A, B and C were, 4.5 (3), 4.5 (2) and 5 (2), respectively ($P=0.83$). There was no significant difference between groups in terms of background and confounding variables ($P<0.05$) (Table 1). After starting of the intervention, no significant difference was observed among the groups in terms of decrease of serum bilirubin level in 24, 48 and 72 hours after the beginning of treatment ($P>0.05$) (Table 2). The duration of hospitalization was significantly longer in the control group A (receiving only phototherapy) than the other two groups (B, C) ($P<0.05$). After the intervention, no significant difference was observed among the three groups in terms of jaundice recurrence, side effects and Jaundice recurrence ($P<0.05$) (Table 2).

Table 1. Comparison of variables between groups before intervention

Variables	Group A (Phototherapy alone)	Group B (intervention group) (Phototherapy and purgative Manna)	Group C (intervention group) (Phototherapy and clofibrate)	*P*
Gender(male/female) [1]	12/8	12/8	9/11	0.54
Age (day) [3]	4.5(3)	4.5(2)	5(2)	0.83
Birth weight (gr)[2]	3238±340	3248±461	3196±390	0.90
Weight on admission(gr) [2]	3115±352	3155±487	3087±351	0.86
Gestational age (week) [3]	39(1)	39(1)	38.5(2)	0.56
Defecation (per day) [3]	5(3)	5(2)	4(2)	0.07
Labor(cesarean/vaginal) [1]	14/6	9/11	14/6	0.17
Total bilirubin (mg/dL)[2]	17.9±3.1	17±1.7	18±2.4	0.43
Indirect bilirubin (mg/dL)2	17.3±3.1	16.3±2	17.4±2.3	0.31
Direct bilirubin (mg/dL)[2]	0.52±0.12	0.51±0.1	0.55±0.16	0.67

[1]Frequency (Chi-square test), [2]Mean±SD (*t*-test), [3]Median (IQR) (Mann–Whitney *U* test

Table 2. Comparison of variables between groups after intervention

Groups/ Variables	Group A (control group) (Phototherapy alone)	Group B (intervention group) (Phototherapy and purgative Manna)	Group C (intervention group) (Phototherapy and clofibrate)	*P*	
Bilirubin levels in 24hours after treatment (mg/dL) [1]	2.4±14.4	1.4±14	13.25±3.5	A, B A,C B,C	0.89 0.32 0.64
Bilirubin levels in 48 hours after treatment (mg/dL) [1]	2.6±10.2	9.47±1.6	9.92±3	A, B A,C B,C	0.58 0.91 0.84
Bilirubin levels in 72 hours after treatment (mg/dL) [1]	10.4±2.4	-	1.1±9.9	A, B A,C B,C	- 0.73 -
Hospital stays(day) [2]	3(1)	2(0)	2(0)	A, B A,C B,C	0.00 0.00 0.97
Jaundice recurrence(yes/no) [3]	1/19	0/20	0.20	A, B A,C B,C	1 1 1
Defecation (per day)[2]	6(3)	7(1)	7.5(1.5)	A, B A,C B,C	0.074 0.068 0.66
Complications (yes/no)[3]	11/9	16/4	14/6	A, B A,C B,C	0.17 0.51 0.71

[1]Mean±SD (*t-test*), [2]Median (IQR) (Mann–Whitney *U* test, [3]Frequency

Discussion

This study showed that purgative Manna and clofibrate have no effect on reduction of serum bilirubin level in neonates suffering from unconjugated hyperbilirubinemia. The results of studies in these fields are contradictory (7,8,17-21). The study by Fallah *et al*., on 90 neonates with neonatal unconjugated hyperbilirubinemia with bilirubin level of 15-20 mg /dl has revealed that consumption of purgative Manna leads to a significant reduction in serum bilirubin level in comparison with the control group during 24 and 48 hours after starting the treatment (8). The study of Khoshdel *et al*., on 120 neonates with unconjugated hyperbilirubinemia has shown that purgative Manna induces significant reduction of serum bilirubin and also shortens hospitalization period (17). The role of purgative Manna in rapid decline of the bilirubin has been confirmed in other studies (7,18). In return, other studies have indicated that purgative Manna has no effect on treating neonatal jaundice (19-21). The study conducted by Shah Farhat *et al*., on 104 neonates with jaundice has shown that administration of 6 gr purgative Manna has no effect on the reduction of serum bilirubin concentration in comparison with the control group. In this study 50 neonates received purgative Manna and 54 neonates' placebo) (19). These findings have been confirmed by Mansouri *et al*., study (20). The in-vitro study by Nabavizadeh *et al*., has shown that purgative Manna has no effect on unconjugated hyperbilirubinemia. In this study, initially 0.5 ml of extracts of five common herbal drugs including *Cichorium intybus*, *Fumaria arviflora*, *Zizyphus jujube*, alhagi pseudoalhagi and purgative Manna were prepared by hydro alcoholic distillation and were added to the 1 mL of the serum of the neonates suffering from unconjugated hyperbilirubinemia. Then the level of serum bilirubin was measured and compared with the control group. These researchers have indicated that only the extract of *Cichorium intybus* significantly reduces the serum bilirubin level (21). 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 dewdrops falling on *Cotoneaster* species plants. The Manna is white to yellow, round or shapeless pieces with a very sweet taste and cooling properties. *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 Cotoneaster *numularia* and Cotoneaster *discolor*. *Cotoneaster discolor is* a shrub, 1-1.5 m high, with brown thin branches, elliptical leaves, and red small flowers with triangular sepals. Except diarrhea no complication was reported for this drug (7).The proponents of the effect of purgative Manna believe that this substance reduces jaundice with two mechanisms. The first mechanism is attributed to mannitol which forms 40-60% of purgative Manna and the second is

activating of the hepatic receptors (17,22). It is believed that mannitol reduces serum bilirubin level by creating osmotic diarrhea, increase the frequency of stools, decrease enterohepatic cycle and increase of bilirubin excretion through stool (17). Regarding the second mechanism, it is believed that the activation of hepatic receptors increases bilirubin clearance through kidney (22). Our study showed that there is no significant difference between the group receiving purgative Manna and the group receiving only phototherapy. The result of our study are similar to the results of Shah Farhat *et al.*, Mansouri *et al.*, and Nabavizadeh *et al.*, studies (19-21). The effect of clofibrate with different doses on neonatal jaundice has been shown in some studies (9,23-26). Habibi *et al.*, study on 52 neonates suffering from pathologic unconjugated hyperbilirubinemia have revealed that administration of clofibrate caused a significant reduction of serum bilirubin level in 24 hours after the beginning of the treatment. In this study, 26 neonates treated by phototherapy and clofibrate with the dose of 100 mg/kg as single dose and the 26 neonates in the control group received only phototherapy (9). The study by Kumar *et al*., has shown that prescribing clofibrate with dose of 50 mg/kg as a single dose before the phototherapy causes the reduction of phototherapy duration (23). A study by Eghbalian *et al*., showed that the prescription of 25 mg/kg clofibrate as a single dose like the dose of 50 mg/kg as a single dose results in significant reduction of serum bilirubin. These researchers recommend using a low dose of clofibrate for the treatment of neonatal unconjugated hyperbilirubinemia (24). Also, the administration of fenofibrate with the dose of 10 mg/kg as a single dose has been induced reduction in serum bilirubin in neonates with unconjugated hyperbilirubinemia due to ABO or Rh incompatibility (25). Although, most researchers have mentioned the effect of clofibrate on unconjugated hyperbilirubinemia (23-26) but, Gholitabar *et al*., believe that the existing data has been insufficient to absolutely confirm the effect of clofibrate on neonatal jaundice, and more studies are needed to be conducted on this issue (27). Advisers to use of clofibrate for neonatal jaundice believe that this drug increases hepatic conjugation by activation of peroxisome receptors and stimulation of e glucuronyl transferase (27-28). The results of mentioned studies were different from those of our study. In our study, we did not find any significant difference between clofibrate recipient group and the control group. The difference in the results may be related to different variables such as neonatal age, sample size, drug dose, methodology of the study and the type of used phototherapy. After the discharge, only in one case of the control group, jaundice recurrence was observed. During intervention period and subsequent follow up, we did not observe any side effect related to purgative Manna and clofibrate. The only side effect that observed among the groups during intervention was cutaneous rash. The frequency of rash among the groups was not significant. The rashes was related to phototherapy and disappeared after the interruption of phototherapy. With regard to the results obtained from our study, the cancerous state of clofibrate in animals (29) and also lack of recommendation of using clofibrate by Food and Drug Administration (FAD) (29). It seems that prescription of these drugs in neonatal jaundice is not necessary. Our limitation was small sample size. We recommend that this study be carried out in a larger volume.

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