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THE PROPHYLACTIC EFFECT OF LACTULOSE ON NEONATAL HYPERBILIRUBINEMIA BY ACCELERATION OF MECONIUM PASSAGE

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ABSTRACT

One of the causes of neonatal hyperbilirubinemia is increased reabsorption of bilirubin from meconium in the gastrointestinal tract. This occurs when the conjugated bilirubin which is excreted into the colon is unconjugated by beta glucuronidase activity, present in the neonatal intestine, which hydrolyzes bilirubin diglucuronide into unconjugated bilirubin, which subsequently is reabsorbed into the portal circulation, contributing to the bilirubin overload on hepatic excretory pathways. Thus, delayed passage of meconium can cause an elevation in the serum bilirubin level.

We accelerated meconium transit by lactulose and evaluated the relationship between meconium passage, neonatal jaundice and bilirubin level.

150 newborns were selected after birth in Tabriz Al-zahra Hospital with special criteria. Half of them were given 4.5-5 mL lactulose by gavage 2 hours after birth. Time of meconium passage, appearance of jaundice and level of bilirubin were studied in both groups. Results showed that 40% of neonates in the study group and 26.6% in the control group were non-icteric. Bilirubin level more than 12 mg/dL was seen in 28% of the study group and 53.4% of neonates in the control group. There was a statistically significant correlation between lactulose receivers and the control group (p=0.0028).

This investigation showed that acceleration of meconium passage in newborns decreases the incidence of jaundice and hyperbilirubinemia.

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INTRODUCTION

It has been traditionally a custom in East Azarbaijan to give butter to neonates after birth. They believed that butter will cause accelerated passage of meconium. This investigation is based upon this belief and we used lactulose for acceleration of meconium transit.

Lactulose is one of the most frequently used agents in the treatment of constipation and hepatic encephalopathy because of its efficacy and good safety profile.[1,2] The key to understand the possible modes of action by which lactulose achieves its therapeutic effects in these disorders lies in certain pharmacological phenomena: lactulose is a synthetic disaccharide that dose not occur naturally, there is no disaccharidase on the microvillus membrane of enterocytes in the human small intestine to hydrolyze lactulose, so it is not absorbed from the small intestine, and it increases intestinal permeability by causing a hyperosmolar condition and small bowel transit leading to increased passage of feces.[2,3,4] Lactulose is readily fermented by the colonic bacterial flora with the

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production of short-chain fatty acids and various gases.[2,5]

Adverse effects of lactulose are flatulence, abdominal discomfort, diarrhea, nausea and vomiting.[6]

The etiologic factors of neonatal hyperbilirubinemia are:

1-Increased destruction of red blood cells.

2-Decreased conjugation in the glucuronidase system.

3-Decreased albumin binding.

4-Increased reabsorption from the gastrointestinal tract.[7,8,9,10]

Reabsorption of bilirubin from meconium in the GI tract can increase the bilirubin level. This occurs when the conjugated bilirubin that was excreted into the colon is unconjugated by beta glucuronidase activity, present in the neonatal intestine, which hydrolyzes bilirubin diglucuronide into unconjugated bilirubin.[5] This substance is subsequently reabsorbed into the portal circulation, contributing to bilirubin overload on hepatic excretory pathways. Thus, delayed passage of meconium can cause elevation in the serum bilirubin level.[9,10]

There is around 450 mg bilirubin in the meconium of the intestinal tract in the newborn infant, and accelerated passage of meconium is critical to avoid the deconjugation and reabsorption of this bilirubin from the gut into the serum.

Failure to pass meconium is associated with elevated serum bilirubin, and time of the first stool passage correlates with the level of serum bilirubin.[9,11]

MATERIAL AND METHODS

Neonates born in Al-zahra hospital during a 2 month period (23rd Sep, 99 -21st Nov, 99) with the following criteria were chosen and studied.

1-Full term (gestational age of 38-42 weeks)

2-Birth weight of 2.5-4 kg.

3-No meconium staining.

4-No need for resuscitation at birth.

5-Uncomplicated delivery and no problem after birth.

6-No congenital or genetic anomaly, intrauterine infection.

7-Absence of jaundice during the first 24 hours of life.

8-No ABO or Rh incompatibility.

9-Breast feeding started as soon as possible.

10-Availability of parents for follow up.

2 hours after birth half of the neonates were randomly given 4.5-5 mL of lactulose by NG tube. In icteric neonates bilirubin level, Hb, Hct, reticulocyte count and Coombs' test were requested. If there was any evidence of a hemolytic process the neonates were omitted from the study. Finally 150 neonates were chosen, lactulose was given to half of them and the other half was considered as the control group.

The time of meconium passage in both groups was recorded. The mothers were requested for follow up on the 3rd, 5th and 7th day of life for re-examination. All of the babies were visited by the same resident and lab studies were done in Al-zahra laboratory center. Finally all the neonates were divided in to 3 groups of non-icterics (serum bilirubin level equal or less than 4mg/dL), icterics with bilirubin less than or equal to 12mg/dL and those with bilirubin more than 12 mg/dL.The database was analyzed by using SPSS.

RESULTS

From 75 neonates who had received lactulose, 30 neonates (40%) were non-icteric and 45 icteric, 20 neonates (26.6%) from the control group were without icter and 55 neonates (73.4%) had icter on one or all the days of the examination.This shows that icter in the study group was13.4% less than the control group (Table I), which is not a statistically significant difference between the two groups (p=0.08).

A bilirubin level more than 12 mg/dL was found in 28% of the study group,and 53.4% of the control group (Table I). This shows a statistically significant difference between the two groups (p=0.0028).

In the study group 73.3% of neonates had meconium passage in the first 6 hours of life and 26.7% in 6-12 hrs. In the control group 37.3% of neonates passed meconium in the first 6 hours of life, 42.6% in 6-12 hrs,16% in 12-24hrs and 4% after 24 hours (Table II). This study shows that meconium transit was rapid in the study group and all of them passed meconium in the first 12 hours of life, while meconium passage lasted even more than 24 hours in some of the control group (p=0.0029).

As shown in Fig. 1 the incidence of icter was lower in those who passed meconium in a short period of time, while in those who had delayed meconium passage

Table I. Effect of lactulose on jaundice and bilirubin level.

	Non-icteric		Bilirubin<12mg/dL		Bilirubin>12mg/dL		Total	
	No.	%	No.	%	No.	%	No.	%
Lactulose	30	40	24	32	21	28	75	50
Control	20	26.6	15	20	40	53.4	75	50
Total	50	33.3	39	26	61	40	150	100

Table II. Effect of lactulose on meconium passage.

Passage time	0 - 6hr		6 -12hr		12 - 24hr		> 24hr		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Lactulose	55	73.3	20	26.7	0	0	0	0	75	100
Control	28	37.3	32	42.6	12	16	3	4	75	100
Total	83	55.4	52	34.6	12	8	3	2	150	100

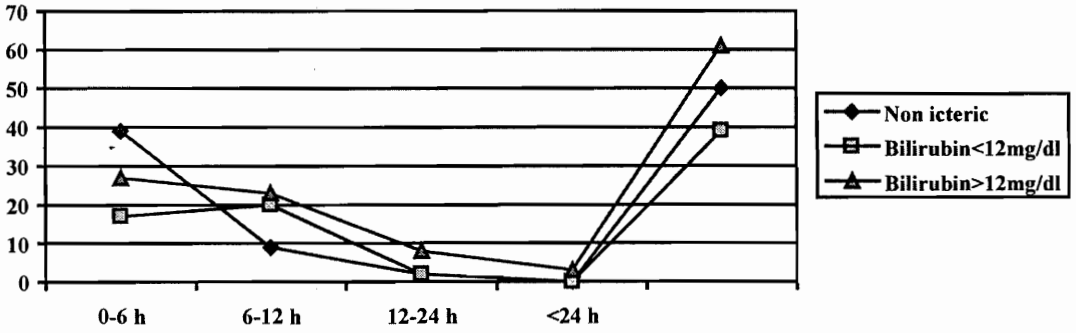

Fig. 1. Correlation between meconium passage, appearance of jaundice and bilirubin level.

the incidence of icter was higher, so that 100% of neonates who had passed meconium after 24 hrs were icteric.These results show a meaningful relationship between meconium passage and incidence of jaundice (p= 0.0003).

Serum bilirubin more than 12 mg/dL was present respectively in 32.5%, 44.2%, 66.6% and 100% of neonates who had passed meconium in the first 6, 6-12, 12-24 and after 24 hours of life. This study shows that there is a direct relationship between time of meconium passage and bilirubin level (p=0.010), such that delayed meconium passage is accompanied with higher bilirubin level (Fig.1).

DISCUSSION

The enterohepatic circulation of bilirubin has been shown to play an important role in many cases of neonatal jaundice.[9,13] Acceleration of meconium passage reduces the enterohepatic circulation of bilirubin, decreases the incidence of jaundice, hyperbilirubinemia and need for hospitalization.[10]

This study was done for the first time with lactulose to accelerate meconium passage and to study its effect on neonatal hyperbilirubinemia. In the first step the amount of lactulose used was half of the present study, but since this dose of lactulose had no effect on meconium passage, the second step of the study was done by a double dose of lactulose and showed that in neonates who had acceleration of meconium passage there were lower levels of bilirubin. With this dosage of lactulose there was no side effect seen in the study groups.

A similar study has been done by Panjvani et al. in Iran using Toranjabin. This material is obtained from Alhagica melorum fish or Canel's thornmanna and contains saccharose, but in this study Toranjabin had no effect on neonatal hyperbilirubinemia, possibly because the amount of effective material in this substance was not known and it was not clear whether it had any effect on meconium passage.[12] Another study with agar has been done by Caglayon et al. in Turkey which had good results in decreasing neonatal hyperbilirubinemia. Agar binds to bilirubin and reduces bilirubin absorption leading to a shortened enterohepatic circulation of bilirubin without having any effect on meconium passage.[13]

Study with lactulose and agar shows that if the enterohepatic circulation of bilirubin is reduced it will lead to decreased neonatal hyperbilirubinemia.

There is a wrong belief in our society that colostrum causes jaundice in neonates. Considering the importance of breast feeding in our society from the immunological, nutritional, economical and emotional point of view and the fact that breast milk especially colostrum has laxative properties, it seems that any failure in proper breast feeding after birth causes delayed meconium passage resulting in hyperbilirubinemia. So for improvement of breast feeding and rapid meconium passage the followings are recommended:

1-In order to change the wrong belief that colostrum causes jaundice it is better to explain the importance of

breast milk and colostrum to mothers before their babies are born.

2-As soon as possible breast feeding must be started, given frequently and avoiding dextrose/water, which is given unfortunately in some private hospitals.

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