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The Effect of Probiotics on Reducing Duration of Hospitalization in Infants with Indirect Hyperbilirubinemia

Amira Mohammed Mohammed Hamed[1], Mona Mohamed Abdelmeguid[2], Shehab Ahmed Abdel Maksoud Omar*[1]

[1]Department of Pediatric, [2]Department of clinical pathology, Faculty of Medicine, Al-Azhar University

***Corresponding author:** Shehab Ahmed Abdel Maksoud Omar**,**

E-mail: shihabahmed2017@gmail.com**, Mobile:** (+20) 01156276379

ABSTRACT

Background: In recent years, the tendency to use drugs has been increasing in the treatment of neonatal jaundice. Several drugs have been used since then, but the effect of probiotics on serum bilirubin level (SBL) is not so clear. This study was conducted to evaluate the effect of probiotics on SBL and the duration of phototherapy in term neonates with hyperbilirubinemia.

Objective: The aim of this study was to evaluate effects of probiotics on neonatal jaundice in reducing hospitalization duration.

Patients and Methods: In this randomized clinical trial, we studied 100 term neonate with jaundice hospitalized for phototherapy in AL Azhar Hospital, during August 2017 till January 2018. Eligible neonates were randomly divided into two groups; probiotic group and control group. Both groups received standard conventional phototherapy, but the intervention group received sachet on 10 ml of probiotic containing formula until hospital discharge. The outcome variables were SBL and the duration of phototherapy.

Results: The 1st group had a significantly lower hospitalization stay in comparison to the 2nd group. The first group showed 3.34 ± 0.70 days and the second group showed 3.7 ± 0.74.

Conclusion: Oral probiotics in neonates with jaundice have significant effect on SBL and the duration of phototherapy. Further studies are needed with longer time follow up.

Keywords: Bilirubin, Jaundice, Newborn, Phototherapy, Probiotic.

INTRODUCTION

General data: Jaundice is a yellow discoloration of the skin and mucus membrane. Jaundice is not a disease, but is a symptom of an elevated blood bilirubin level. Jaundice is a marker used to identify those infants who may be at risk for developing severe hyperbilirubinemia. Severe hyperbilirubinemia can be toxic to the nervous system of infants, potentially causing brain damage **(1).**

One of the most prevalent clinical conditions in hyperbilirubinemia is neonatal hyperbilirubinemia, which is a common clinical problem encountered during the neonatal period, especially in the first week of life **(2).** Hyperbilirubinemia is the most common cause of hospitalization in infancy. Physiological icterus is a common cause of infantile hyperbilirubinemia, which is diagnosed by ruling out other important etiologies such as hemolysis, infections and metabolic disorders **(3)**.

Hyperbilirubinemia is the most common cause of readmission in early infancy **(4 & 5)**. In 2% of mature infants, bilirubin levels can reach more than 20 mg/dL, which requires therapeutic action and may result in complications such as kernicterus and neurological damage **(6)**. The aim of managing hyperbilirubinemia is to prevent neurological damage. The most prevalent therapeutic method form an aging infantile icterus and preventing its complications is phototherapy, which has been applied for decades as a safe method **(7)**.

Probiotics are defined to be non pathogenic strains of organisms that are incorporated into the diet to modify gut microbial ecology leading to beneficial structural and functional changes in the gut. Probiotics are microorganisms, which can decrease the transit time of materials in the intestines **(8)**. A few studies assessing the eff ect of probiotics on decreasing bilirubin levels have reported decreases in the required length of phototherapy **(9 & 10)**. In addition, some may carry metabolic functions such as helping the fermentation of non-digestible fibers, and storing energy in the form of short-chain fatty acids. Bifidobacteria and Lactobacilli are considerd the two most essential bacteria beneficial to human health **(11).** The role of probiotics in human body has been explained by different pharmacological mechanisms. For example, they can rapidly increase the number of anaerobic bacterial colonies, promote the recovery of intestinal microflora balance, and resist infections in some cases **(12).**

AIM OF THE STUDY

The aim of this study was to evaluate effects of probiotics on neonatal jaundice in reducing hospitalization duration.

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PATIENTS AND METHODS

This randomized, controlled clinical trial included 100 patients with hyperbilirubinemia 50 case as 1st group (probiotic group) and 50 as 2nd group (control group) who were admitted to the Neonatal Intensive Care Unit of AL Azhar Hospital from August 2017 to January 2018.

The patients according to inclusion criteria were randomly assigned to two groups 1st group (probiotic group) and 2nd group (control group) using a random number tabulation. The probiotic group was treated with probiotic-contained sachets (Lactobacillus acidophilus) and probiotics-contained milk (Bifidobacteriumlactis, Lactobacillus acidophilus, Bifidobacterium bifidum, and Lactobacillus rhamnosus).

The patients' bilirubin levels were measured using serum samples prior to admission and after treatment. All of the patients with bilirubin underwent phototherapy. Those with bilirubin levels between 14 mg/dL and 18 mg/dL underwent 8-lamp phototherapy. Those with bilirubin levels less than 14 mg/dL were treated with 4-lamp phototherapy.

The duration of the phototherapy, the blood groups of infants, the patients' bilirubin levels before and after phototherapy, direct Coombs test results and levels of hemoglobin and reticulocytes were recorded. The normal distributed variables were compared.

Ethical approval and written informed consent:

An approval of the study was obtained from Al- Azhar University Academic and Ethical Committee.

Every patient signed an informed written consent for acceptance of the study. The steps of the study, the aims, the potential benefits and hazards were discussed to the probiotic and control group parents. The probiotic and control groups have the right to withdraw from the study at any time without giving any reasons.

Inclusion criteria:

Neonates with physiological jaundice, hemolytic jaundice and sepsis.

Exclusion criteria:

- Other causes of jaundice:
  1-Hepatic causes (hepatocellualr diseases)
  2-Metabolic disorders

Examination:

- **General Examination:** apperarance, vital signs, measurements, gestational age assessment.
- **Local Examination:** head, ear, nose, throat, neck, eye, cardiopulmonary, chest, skin, abdomen, gentalia, musculoskeletal, neurologic.

Statistical analysis

- Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non parametric distribution.
- ***Chi-square test*** was used in the comparison between two groups with qualitative data and ***Fisher exact test*** was used instead of the Chi-square test when the expected count in any cell found less than 5.
- ***Independent t-test*** was used in the comparison between two groups with quantitative data and parametric distribution and ***Mann-Whitney test*** was used in the comparison between two groups with quantitative data and non parametric distribution.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
  - $P > 0.05$: Non significant (NS)
  - $P < 0.05$: Significant (S)
  - $P < 0.01$: Highly significant (HS)

RESULTS

Table (1): Comparison between 1st group & 2nd group as regards demographic data

		Probiotic group (No.=50)		Control group (No.=50)		Chi square test	
		No.	%	No.	%	X^2/t*	P value
Sex	Male	33	66.0%	30	60.0%	0.386	0.534
	Female	17	34.0%	20	40.0%		
Age (days)	Mean ± SD	3.5 ± 1.2		4 ± 1.7		1.699*	0.092
	Range	2.5 - 5		2.1 - 5.15			
Gestational age (weeks)	Mean ± SD	34.5 ± 2.3		33.8 ± 3.5		-1.182*	0.240
	Range	33.2 - 35.6		32.1 - 35.7			
Weight (KM)	Mean ± SD	2.8 ± 0.89		3± 0.6		1.318*	0.190
	Range	2.5 - 3.5		2.3 - 3.3			

* Independent t test

This table showed that there was no statistically significant difference in demographic data between the studied groups**.**

Table (2): Comparison between 1st group &2nd (control) group as regards blood group and consanguinity

		1st group (N0.=50)		2nd group (N0.=50)		Chi square test	
		No.	%	No.	%	X^2	P value
Blood group	AB	15	30.0%	13	26.0%	2.145	0.542
	B+	18	36.0%	13	26.0%		
	O+	12	24.0%	17	34.0%		
	A+	5	10.0%	7	14.0%		
Consanguinity	Positive	5	10.0%	3	6.0%	0.543	0.461
	Negative	45	90.0%	47	94.0%		

This table showed that there was no statistically significant difference concerning blood group and consanguinity between the studied groups.

Table (3): Comparison between 1st group & 2nd group as regards HB and causes of jaundice

		1st group (N0.=50)		2nd group (N0.=50)		Chi square test	
		No.	%	No.	%	X^2/t*	P value
HB level	Mean ± SD	13.5 ± 2.6		13.8 ± 2.4		0.600*	0.550
	Range	10.4 - 17.6		10.4 - 18.1			
Jaundice	Septicemia	5	10.0%	3	6.0%	6.328	0.096
	Abo	15	30.0%	15	30.0%		
	RH	13	26.0%	5	10.0%		
	Unknown	17	34.0%	27	54.0%		

This table showed that there was no statistically significant difference in HB, sucking power and jaundice between the studied groups.

Table (4): Comparison between 1st group & 2nd group as Coomb's test and CRP.

General signs		1st group (N0.=50)		2nd group (N0.=50)		Chi square test	
		No.	%	No.	%	X^2	P value
Coomb's test	Positive	31	62.0%	25	50.0%	1.461	0.226
	Negative	19	38.0%	25	50.0%		
CRP	Positive	5	10.0%	3	6.0%	0.543	0.461
	Negative	45	90.0%	47	94.0%		

This table showed that there was statistically non-significant difference comparing 1st group with 2nd group concerning Coomb's test and CRP at the 1st day.

Table (5): Comparison between 1st group & 2nd group as regards bilirubin level on admission (1st day)

	1st group (No.=50)	2nd group (No.=50)	Independent t-test	
	Mean ± SD	Mean SD	T	P-value
1st day	17.63 ± 1.53	17.46 ± 2.33	2.968	0.003

This table showed that there was statistically non-significance in comparing 1st group with 2nd at 1st day of admission regarding.

Table (6): Comparison between 1st group &2nd group as regards bilirubin level at 3rd day

	1st group (No.=50)	2nd group (No.=50)	Independent t-test	
	Mean ± SD	Mean SD	T	P-value
3rd day	10.41 ± 1.24	10.91 ± 1.88	1.570	0.119

This table showed that there was no statistically significant difference in bilirubin level trend at 3rd day between probiotic group & control group.

Table (7): Comparison between 1st group & 2nd group as regards bilirubin level at 4th day

	1st group (No.=50)	2nd group (No.=50)	Independent t-test	
	Mean ± SD	Mean SD	T	P-value
4th day	9.25 ± 1.15	10.15 ± 1.49	3.381	0.001

This table showed that there was statistically significant increase of bilirubin level in control group in comparison with probiotic group at 4th day.

Table (8): Comparison between 1st group & 2nd group as regards bilirubin level at 5th day

	1st group (No.=50)	2nd group (No.=50)	Independent t-test	
	Mean ± SD	Mean SD	T	P-value
5th day	8.49± 1.09	10.29±1.41	7.142	0.001

This table showed that there was statistically significant increase of bilirubin level in control group in comparison with probiotic group at 5th day.

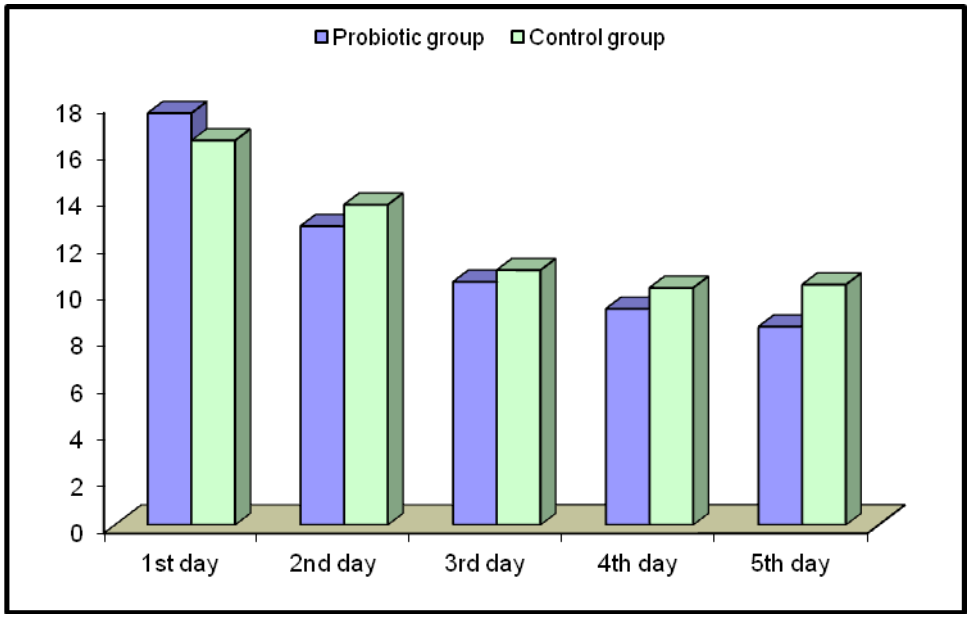

Figure (1): Bilirubin level trend at regarding probiotic group and control group

Table (9): Duration of hospitalization

	1st group	2nd group	Independent t test	
	Mean ±SD	Mean ±SD	T	P value
duration of hospitalization	**3.34±0.70**	**3.7 ±0.74**	2.499	0.014

The average duration of hospitalization was 3.34 ± 0.70 days overall, with an average of 3.7 ± 0.74 days for the 2nd group and 3 ± 0.70 days for the 1st group. Table (9) showed that the 1st group had a significantly lower hospitalization stay in comparison with the 2nd group (P < 0.00, [CI=95%,-1.31to-0.64**]).**

DISCUSSION

In this study, there were 66 % male and 34% female in the probiotic group and in the control group, there were 60 % male and 40 % female, which has no significant or need other studies to confirm that hyperbilirubenemia is more in male than in females.

Mean age was 3.5 ±1.2 days in the probiotic group and 4 ± 1.7 days in the control group that were within the average age of appearance of Jaundice. The gestational age was 34.5 ± 2.3 weeks in probiotic group and 33.8 ± 3.5 weeks in the control group, which need more studies to create the relation between the gestational age and Jaundice. Weight 2.8 ± 0.89 kg in probiotic group and 3 ± 0.6 kg in control group.

Regarding blood groups, Ab was 30%, B +ve was 36 %, O +ve was 24% and A +ve was 10%. These results disagree with other studies in number of cases and distribution on the blood groups.

Consanguinity was 10% positive in probiotic group and 6% negative in control group that disagree with the other studies which have very low consanguinity relative to the higher in our country because of our traditions.

Hemoglobin level was 13.5 ± 2.6 gm/dL in probiotic group and 13.8 ± 2.4 gm/dL in control group which may need other studies to create the relation between level of Hb and probiotic effect in Jaundice.

Regarding causes of jaundice in the study 10% was due to septicemia and 30% was due to Abo incompatibility, 26% due to Rh incompatibility and 34% due to unknown causes in probiotic group which disagree with Liang [13] who reported that more than 40 % of jaundice was due to Abo incompatibility. We need studies, which measure the mode and cause of blood destruction and effect of probiotic in each cause of jaundice.

Regarding general signs 46% of probiotic group have pallor, 26% have edema, 62% have positive Coomb's test and 10% have positive CRP. These results agree with other studies. General signs have no significance in comparing between the two groups but it may let us to deal with every case separately.

Bilirubin level in the 1st day in the 1st group was 17.63 ± 1.53 and 17.46 ± 2.33 in the 2nd group. In the 3rd day, it was 10.41 ± 1.24 1st group and 10.91 ± 1.88 in 2nd group. In the 4th day the bilirubin level was 9.25 ± 1.15 in 1st group and 10.15 ± 1.49 in 2nd group. In the 5th day, bilirubin was 8.49 ± 1.09 and 10.29 ± 1.41 in the 1st and 2nd group successively. These results agree with study of **Torkaman *et al.*** [14].

Data from 92 patients with a mean age of 5.25 ± 2.35 days underwent analysis. Most of the infants (52.2%) weighed between 3000 and 3500grams. There was nonsignificant difference between the two groups for distribution of birth weight (P=0.18). Most of the infants in both the probiotic (74%) and control (79%) groups were born by normal vaginal delivery. Eighty-five of the infants (92.4%) were breastfed and 7 of the infants (7.6%; 2 in the probiotic group and 5 in the control group) received both breast milk and formula. There was no significant difference between the two groups with respect to the type of nutrition (P = 0.43). The mean bilirubin level trend in the patients before and after intervention. On the first day of the study, 92 infants had a mean bilirubin level of 16.70 ± 3.07 mg/dL, with a mean of 16.46 ± 2.33 mg/dL in the control group and 16.95 ± 2.67 mg/dl in the probiotic group (P = 0.35). The day after intervention, the probiotic group had a significantly lower bilirubin level (P =0.001). The mean bilirubin level decrease was 4.80 ± 1.76 in the probiotic group and 2.76 ± 1.29 in the control group the day after intervention (P < 0.001). Most of the infants (84.7%) in the probiotic group were discharged two days after intervention, but 32of the infants (69.5%) in the control group were still under treatment on the third day. At the time of discharge, infants had a mean bilirubin level of 9.72 ± 0.96mg/dL in the probiotic group and9.38 ± 0.71 mg/dL in the control group (P=0.053).

The aim of hyperbilirubinemia management was to prevent the indirect bilirubin levels from reaching the point at which neurotoxicity may occur. Possible complications

of hyperbilirubinemia include deafness and kernicterus. Phototherapy is the treatment of choice for infant hyperbilirubinemia and was administered equally for the infants in both groups in the present study. The prescription of a variety of drugs such as clofibrate and Phenobarbital has been proposed for reducing hospitalization duration. The purpose of probiotics is to increase the number of beneficial bacteria in the bowels. No adverse effects from the administered probiotics were found in the present study. Recently, probiotics have been shown to be useful for treating gastroenteritis by slowing bacterial growth. They can decrease the passing time of materials in the bowels.

CONCLUSION

We concluded that this randomized controlled trials involving 100 cases assessed the clinical value of probiotics supplementation therapy for the treatment of neonatal jaundice.

It provided evidence that the combination of routine complementary treatment with probiotics supplementation therapy, including Bifidobacterium, S. boulardii, C. butyricum, probiotic oligosaccharides, *B. subtilis*, had an obvious increase of efficacy rate in neonatal jaundice.

Moreover, it did not only significantly improve neonatal jaundice by reducing total bilirubin, time of jaundice fading, but also decreased the duration of phototherapy and hospitalization.

RECOMMENDATIONS

We recommend using milk formula has probiotics and probiotic sachets in addition and give probiotic to all newborn with hyperbilirubinemia because of its benefits on gastrointestinal system.

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