Original Article

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Effect of Addition of Probiotics to Standard Treatment on Neonatal Jaundice

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ABSTRACT

Objective: To compare the mean change in the bilirubin levels with the addition of probiotics to standard treatment for the management of neonatal jaundice.

Methodology: The randomized controlled trial was undertaken at the Neonatal Intensive Care Unit of the Paediatrics Department, Federal Government Polyclinic (Post Graduate Medical Institute), Islamabad from 1st April to 30th September 2019. Neonates with hyperbilirubinemia requiring phototherapy were randomly divided into two groups, each having 30 patients. Group A received probiotics along with phototherapy while group B received phototherapy alone. The primary outcome was serum total bilirubin, which was calculated on 0, 1, and 3 days of treatment. Duration of phototherapy and patient's outcome was also recorded. Data was analyzed statistically using SPSS v. 23.

Results: The mean serum bilirubin level after 24 hours was 14.27 ± 4.35 mg/dl in the combination group while 16.43 ± 4.36 mg/dl in the phototherapy group ($p > 0.05$). After 48 hours, the mean serum bilirubin level was 12.37 ± 3.33 mg/dl in the combination group while 14.09 ± 3.60 mg/dl in the phototherapy group ($p > 0.05$). After 72 hours, /the mean serum bilirubin level was 11.09 ± 2.87 mg/dl in combination group while 11.72 ± 2.96 mg/dl in phototherapy group ($p > 0.05$). The mean time required of blue light phototherapy was 43.47 ± 20.71 hours in the combination group while 61.53 ±28.27 hours in the phototherapy group ($p < 0.05$). All neonates were discharged.

Conclusion: The addition of probiotics to standard treatment decreased the time required for phototherapy in neonatal jaundice. However, no statistically significant difference was seen in the bilirubin levels between the two groups.

Keywords: *Neonates, Neonatal jaundice, Phototherapy, Probiotics, total bilirubin*

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Introduction

Neonatal jaundice is one of the most common problems encountered in early neonatal life.[1] Around 60% of term and 80% of preterm babies develop jaundice in the first week of life.[2] Jaundice is unconjugated in most cases with physiological jaundice being the most common cause of jaundice.[3] Other causes of unconjugated hypebilirubinemia include ABO incompatibility, Rh incompatibility, G6PD enzyme defect, hereditary spherocytosis, cephalhematoma, breast milk jaundice, breastfeeding jaundice, Crigler Najjar syndrome, and Gilbert syndrome.[4] In the neonatal period, there is decreased conversion of conjugated bilirubin into stercobilirubin due to a lack of bacterial flora in the intestine. Conjugated bilirubin then converts into unconjugated bilirubin by increased activity of beta glucuronidase that causes unconjugated hyperbilirubinemia.[5]

The main options for the treatment of neonatal jaundice are phototherapy, exchange transfusion, and pharmacological therapies.[6] Depending upon the age, weight, and bilirubin level of the baby, treatment modality is selected. Phototherapy is commonly used for the treatment of unconjugated jaundice. It converts bilirubin into photo isomers that are then excreted from

the body.[7] However, it can also cause some undesirable effects in newborns such as hyperthermia, erythematous rashes, burns, and diarrhea if the treatment is prolonged.[8] Extreme levels of bilirubin in the body can cause kernicterus or even death. If bilirubin levels are not reduced with phototherapy, exchange transfusion is the treatment for severe hyperbilirubinemia in order to prevent kernicterus.[9]

Probiotics have been recently studied as an adjunct in the treatment of neonatal jaundice. It reduces the activity of beta glucuronidase and decreases enterohepatic circulation that decreases hyperbilirubinemia.[10] Various studies suggested that probiotics may protect against breast milk jaundice and hyperbilirubinemia by affecting intestinal motility and intestinal microbial flora.[11]

The effectiveness of the probiotics to treat neonatal hyperbilirubinemia is the new area of interest for researchers[12]. Apart from phototherapy, medicines, and exchange transfusion, supplementation of probiotics can be helpful in neonatal hyperbilirubinemia by improving the immune system of neonates primarily through regulation of the microbial colonies. There are little data available regarding the effectiveness of the probiotics on serum bilirubin levels among neonates.[13]

The aim of the study is to determine the role of probiotics in neonatal jaundice as this can help to reduce the admission rate and burden in the neonatal units of developing countries. Probiotics can help to reduce the duration of treatment resulting in a reduction in the cost of treatment.

Methodology

A randomized controlled trial was conducted in the Paediatrics Department, Federal Government Polyclinic (PGMI), Islamabad for six months from 1st April 2019 to 30th September 2019. Assuming confidence level= 95%, power = 80%, anticipated population mean 1 (Serum bilirubin levels) = 195[14], standard deviation for population 1 = 40, anticipated population mean 2 (Serum bilirubin levels) = 155[14] and standard deviation for population 2 = 37, the total number of samples required for this study was 52 (26 samples in each group). To avoid a loss to follow patients, four extra patients were enrolled in each group so the total sample size was 60.

All neonates of both genders which were more than 1.5 kg with indirect hyperbilirubinemia requiring phototherapy presenting in the first 7 days of life were included in the study. Neonates less than 1.5kg, direct hyperbilirubinemia, indirect bilirubin in exchange transfusion range, and taking phenobarbital were excluded from the study. All neonates with congenital anomalies or any life-threatening disease were also excluded from the study.

The study was conducted after the approval of the ethical committee. Informed written consent from parents of each neonate was taken. A structured proforma was used to record the patient's demographic data like patient's name, age, weight, and gender. Patients that fulfilled the inclusion criteria were randomly divided into two groups each having 30 patients. Group A received 2.5ml of Enterogermina ampule containing *Bacillus clausii* given orally, twice a day for 3 consecutive days while Group B received 2.5ml of saline orally, twice a day for 3 consecutive days. Phototherapy was given to both groups by phototherapy devices (ARDO Amelux Infant phototherapy lamps) according to the normograms of the American Academy of Pediatrics. The primary outcome was serum total bilirubin determined on 0, 1, and 3 days of treatment. The duration of phototherapy and patient's outcome were also observed.

Data was entered and analyzed using SPSS version 23. Qualitative variables like gender and cause of neonatal jaundice were presented as frequency and percentages. Quantitative variables like age, gestational age, age at which jaundice develops, weight and mean change in bilirubin were presented as mean and standard deviation. Both groups were compared for mean serum bilirubin levels and mean duration of phototherapy by using independent samples t-test. The patient's outcome was recorded using the chi - square test. P - value of 0.05 or less was taken as statistically significant.

Results

In the combination group, there were 16 (53.3%) male neonates and 14 (46.7%) female neonates. In the phototherapy group, there were 22 (73.3%) male neonates and 8 (26.7%) female neonates. In the combination group, the mean weight of neonates was 2.59 ± 0.94 kg and 2.52 ± 0.61 kg in the phototherapy group. In the combination group, the mean gestational age at birth was 36.47 ± 1.74 weeks and 36.30 ± 2.72 weeks in the phototherapy group. In the combination group, the most common reason of neonatal jaundice was hemolytic [9 (30%)], followed by breast feeding [6 (20%)], breast milk [5 (16.7%)] and infections [1

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(3.3%)]. In the phototherapy group, the most common reason of neonatal jaundice was hemolytic [14 (46.7%)], followed by infections [6 (20%)], breastfeeding [3 (10%)], and breast milk [3 (10%)]. Table I

The mean serum bilirubin level was compared in both groups on different follow-ups. The mean serum bilirubin level after 24 hours was 14.27 ± 4.35 mg/dl in the combination group while 16.43 ± 4.36 mg/dl in the phototherapy group ($p > 0.05$). After 48 hours, the mean serum bilirubin level was 12.37 ± 3.33 mg/dl in the combination group while 14.09 ± 3.60 mg/dl in the phototherapy group ($p > 0.05$). After 72 hours, the mean serum bilirubin level was 11.09 ± 2.87 mg/dl in the combination group while 11.72 ± 2.96 mg/dl in the phototherapy group ($p > 0.05$). The mean time required of blue light phototherapy was 43.47 ± 20.71 hours in the combination group while 61.53 ±28.27 hours in the phototherapy group ($p < 0.05$). All neonates were discharged in both groups. Table II

Table I: Demographics of neonates at presentation

	Group	
	Probiotics + phototherapy (N-30)	Phototherapy alone (N-30)
Gender		
Male	16 (53.3%)	22 (73.3%)
Female	14 (46.7%)	8 (26.7%)
Weight (kg)	2.59 ± 0.94	2.52 ± 0.61
Gestational age at birth (weeks)	36.47 ± 1.74	36.30 ± 2.72
Cause of neonatal jaundice		
Hemolytic	9 (30%)	14 (46.7%)
Infections	1 (3.3%)	6 (20%)
Breast feeding	6 (20%)	3 (10%)
Breast milk	5 (16.7%)	3 (10%)
Others	9 (30%)	4 (13.3%)

Discussion

Neonatal jaundice that requires phototherapy and hospital admission is associated with a significant socioeconomic burden.[15] Finding a way to decrease the hospital stay has several benefits including decrease expenses and more emotional contact between the mother and the child. Administration of probiotics might help in the treatment of neonatal jaundice. However, there is inadequate data regarding the effectiveness of probiotics on serum bilirubin levels among neonates.[16]

A systematic review of randomized controlled trials by Deshmukh et al showed that there was a significant reduction in phototherapy time when probiotics are used along with phototherapy[15]. In our study, the mean time required for blue light phototherapy to reduce significant bilirubin level was 43.47 ± 20.71 hours in the combination group while 61.53 ± 28.27 hours in the phototherapy group. The difference was significant ($p < 0.05$). This showed that the combination group required less time for phototherapy as compared to the phototherapy alone group. Another study conducted by Chandrasekhar also showed that the time required for phototherapy reduced significantly in the probiotics group.[5]

Liu W et al concluded that serum bilirubin decreased on day 1 of treatment but there was no intergroup difference ($P<0.05$) however on day 4 and day 7 serum bilirubin levels significantly decreased more in the phototherapy and probiotics group than in the phototherapy group alone[14]. In our study, there was a decrease in bilirubin levels after day 1,2, and 3 however no intergroup difference was seen ($p>0.05$). The same results were reported in other studies.[15-17] This could hint towards the effectiveness of probiotics on serum bilirubin levels after three days. One study also suggested that bilirubin does

Table II: Comparison of outcome during follow-up

	Group		P - value
	Probiotics + phototherapy (N-30)	Phototherapy alone (N-30)	
Serum bilirubin at 0 hour	16.74 ± 2.46	17.90 ± 4.43	
Serum bilirubin at 24 hours	14.27 ± 4.35	16.43 ± 4.36	0.119
Serum bilirubin at 48 hours	12.37 ± 3.33	14.09 ± 3.60	0.093
Serum bilirubin at 72 hours	11.09 ± 2.87	11.72 ± 2.96	0.724
Time of blue light phototherapy (hours)	43.47 ± 20.71	61.53 ± 28.27	0.012
Outcome			
Discharged	30 (100%)	30 (100%)	NA
Expired	0 (0%)	0 (0%)	

not significantly fall in probiotics group after 24 hours however it does after 36 hours of treatment with probiotics group.[18] Hamed et al also concluded that the addition of probiotics significantly decreased the serum total bilirubin levels and the time required for phototherapy.[19] A study conducted in Iran also showed that probiotics can reduce the serum total bilirubin levels when used as an adjunct to standard therapy.[20]

A meta-analysis conducted by Chen Z et al provided evidence that the combination of routine treatment with probiotics including *Bifidobacterium, S. boulardii, C. butyricum*, probiotic oligosaccharides and *B. subtilis* had more efficacy in neonatal jaundice. Moreover, it was also helpful in reducing total bilirubin levels, time of jaundice fading, duration of phototherapy and hospitalization[21]. Various studies have demonstrated the role of probiotics prophylactically in newborns for the prevention of neonatal jaundice.[10,22] Mu et al reported that neonatal hyperbilirubinemia in the intervention group (probiotic group) was 33.33% while it was 57.14% in the control group.[22]

Serce et al concluded that probiotics do not decrease the bilirubin level significantly and have no considerable effect on neonatal jaundice[12]. It was shown that the serum bilirubin levels did not fall significantly even after 4 days of treatment with *Saccharomyces boulardi.*[12] Pasha et al showed that there was no significant effect of oral probiotics on the bilirubin levels between the two groups at the end of three days.[24] This was also consistent with our study that showed that bilirubin levels do not significantly fall till 3 days.

One of the main concerns in the study was the choice of probiotics. We choose bacillus clausii which was also studied by various other researchers. However other strains like *Saccharomyces boulardii*, *Bifidobacterium* and *Lactobacillus reuteri* have also shown efficacy in the treatment of neonatal jaundice.[16] More extensive researches are required as the effect may get altered according to the dose of probiotic bacteria strains, their ability to survive, and proliferation in the intestinal environment. In our study, all neonates were discharged in both groups and no further complication developed to increase the hospital stay.

Conclusion

The addition of probiotics to phototherapy decreased the time required for the treatment in neonatal jaundice. However, no statistically significant difference was seen in the reduction of bilirubin levels between the two groups.

Limitations of the study: The study was conducted in a single setup with limited patients over a short duration of time.

Suggestions: It is suggested that further trials should be done on large scale to get authentic and more reliable results. Financial constraints must be resolved before initiating new trial

References

1. McKiernan P. Neonatal jaundice. Clin Res Hepatol Gastroenterol. 2012;36(3):253-6. https://doi.org/10.1016/j.clinre.2012.03.018
2. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297-316. https://doi.org/10.1542/peds.114.1.297
3. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med (Lond). 2017;78(12):699-704. https://doi.org/10.12968/hmed.2017.78.12.699
4. Ansong-Assoku B, Ankola PA. Neonatal Jaundice. In: StatPearls. Treasure Island (FL): StatPearls Publishing;2020.
5. Chandrasekhar J, Varghese T, Gopi A, Raj M, Sudevan R, Jayakumar H. Treatment effect of probiotic Bacillus clausii on neonatal jaundice in late preterm and term newborn babies: An experimental study. Pediatr Ther. 2017;7(3):326-31. https://doi.org/10.4172/2161-0665.1000326
6. Wan A, Daud S, Teh SH, Choo YM, Kutty FM. Management of neonatal jaundice in primary care. Malays Fam Physician. 2016;11(2-3):16-9.
7. Itoh S, Okada H, Kuboi T, Kusaka T. Phototherapy for neonatal hyperbilirubinemia. Pediatr Int. 2017;59(9):959-66. https://doi.org/10.1111/ped.13332
8. Makhoul G, Mardini J, Ojaimi MA, AbiFares G, Hanna P, Alameddine A, et al. Effect of Probiotic "L.Reuteri" Association on the Reduction of Serum Bilirubin in Neonatal Jaundice. ESJ. 2018;14(12):384. https://doi.org/10.19044/esj.2018.v14n12p384
9. Wusthoff CJ, Loe IM. Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes. Semin Fetal Neonatal Med. 2015;20(1):52-7. https://doi.org/10.1016/j.siny.2014.12.003
10. Suganthi V, Das AG. Role of Saccharomyces boulardii in Reduction of Neonatal Hyperbilirubinemia. J Clin Diagn Res. 2016;10(11):SC12-SC15. https://doi.org/10.7860/JCDR/2016/20115.8878
11. Tuzun F, Kumral A, Duman N, Ozkan H. Breast milk jaundice: effect of bacterias present in breast milk

and infant feces. J Pediatr Gastroenterol Nutr. 2013;56(3):328-32. https://doi.org/10.1097/MPG.0b013e31827a964b

12. Serce O, Gursoy T, Ovali F, Karatekin G. Effects of Saccharomyces boulardii on neonatal hyperbilirubinemia: a randomized controlled trial. Am J Perinatol. 2015;30(2):137-42. https://doi.org/10.1055/s-0034-1376390
13. Ohland CL, MacNaughton WK. Probiotic bacteria and intestinal epithelial barrier function. Am J Physiol Gastrointest Liver Physiol. 2010;298(6):G807-G819. https://doi.org/10.1152/ajpgi.00243.2009
14. Liu W, Liu H, Wang T, Tang X. Therapeutic effects of probiotics on neonatal jaundice. Pak J Med Sci. 2015;31(5):1172-5. https://doi.org/10.12669/pjms.315.7921
15. Deshmukh J, Deshmukh M, Patole S. Probiotics for the management of neonatal hyperbilirubinemia: a systematic review of randomized controlled trials. J Matern Fetal Neonatal Med. 2019;32(1):154-63. https://doi.org/10.1080/14767058.2017.1369520
16. Chen K, Yuan T. The role of microbiota in neonatal hyperbilirubinemia. Am J Transl Res. 2020;12(11):7459-74.
17. Xiong T, Chen D, Duan Z, Qu Y, Mu D. Clofibrate for unconjugated hyperbilirubinemia in neonates: a systematic review. Indian Pediatr. 2012;49(1):35-41. https://doi.org/10.1007/s13312-012-0012-x
18. Mutlu M, Aslan Y, Kader S, Acar F. Preventive Effects of Probiotic Supplementation on Neonatal Hyperbilirubinemia Caused by Isoimmunization. Am J Perinatol. 2020;37(11):1173-6. https://doi.org/10.1055/s-0039-1692690
19. Hamed A, Abdelmeguid M, Omar S. The Effect of Probiotics on Reducing Duration of Hospitalization in Infants with Indirect Hyperbilirubinemia. The Egyptian Journal of Hospital medicine. 2019;77(6):5900-5. https://doi.org/10.21608/ejhm.2019.64968
20. Ahmadipour S, Baharvand P, Rahmani P, Hasanvand A, Mohsenzadeh A. Effect of Synbiotic on the Treatment of Jaundice in Full Term Neonates: A Randomized Clinical Trial. Pediatr Gastroenterol Hepatol Nutr. 2019;22(5):453-9. https://doi.org/10.5223/pghn.2019.22.5.453
21. Chen Z, Zhang L, Zeng L, Yang X, Jiang L, Gui G, et al. Probiotics Supplementation Therapy for Pathological Neonatal Jaundice: A Systematic Review and Meta-Analysis. Front Pharmacol. 2017;8(6):432. https://doi.org/10.3389/fphar.2017.00432
22. Mu-Xue Y, Dong-Ping C, Zhong-Jiao Y, Yeu-Xin L. The effect of probiotics on the incidence of neonatal hyperbilirubinemia. Chinese J Microecol. 2013;5:16.
24. Pasha Y, Ahmadpour-kacho M, Jazi A, Gholinia H. Effect of Probiotics on Serum Bilirubin Level in Term Neonates with Jaundice: A Randomized Clinical Trial. Int J Pediatric. 2017;5(10)5925-30.

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