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ORIGINAL ARTICLE

Role of Probiotics in Neonates with Hyperbilirubinemia Receiving Phototherapy

BUSHRA TARIQ[1], MUHAMMAD SHAHMAN[2], AMNA MATEEN[3], MOHAMMAD TAHA KAMAL[4], ANUM NAWAZISH ALI[5], SYED AWAIS UL HASSAN SHAH[6]

[1]*FCPS Pediatric Medicine Women Medical officer, DHQ Hospital, Kasur*
[2]*House Officer Shaikh Zayed Hospital, Lahore*
[3]*Senior Registrar, Neonatology Unit, Pakistan Institute of Medical Sciences (PIMS), Islamabad*
[4]*General Surgeon MBBS (Dow) University of Health Sciences, Karachi*
[5]*Operation Theater Technologist, Neurosurgery Department, Lahore General Hospital, Lahore*
[6]*MBBS, FCPS, (Pediatrics) Department of Neonatal Pediatrics Pak-Emirates Military Hospital, Rawalpindi*
Correspondence to: Dr. Bushra Tariq, Email: tariqbushra33@gmail.com, Cell: +92 331 4810532

ABSTRACT

Study Objectives: To compare the mean duration of phototherapy in neonates with hyperbilirubinemia receiving phototherapy with vs. without probiotics.

Study Design and Settings: It was a randomized controlled trial carried at Department of Pediatrics, DHQ Hospital Kasur from Jan 2021 to June 2021.

Patients and Methods: The present research involved 94 neonates of both genders aged between 2 to 28 days of life diagnosed of neonatal hyperbilirubinemia (serum bilirubin level ≥15mg/dL and direct bilirubin level ≤1.5 mg/dL). These neonates were allocated into two groups randomly. Neonates in Group-I were given probiotics along with conventional treatment of phototherapy whereas neonates in Group-II received conventional phototherapy alone. Study outcome was described in terms of mean duration of phototherapy (phototherapy was stopped when serum bilirubin level was less than 10 mg/dl during the first week and less than 11 mg/dl after the first week) which was recorded and compared between the groups. An informed written consent was taken from parents of every neonate.

Results of the Study: The mean age of the neonates was 6.54±4.96 days while the mean gestational age was 37.31±2.04 weeks. There were 55 (58.5%) baby boys and 39 (41.5%) baby girls with a boys to girls ratio of 1.4:1. The mean weight of the neonates was 2.89±0.49 Kg while the mean serum bilirubin level upon admission was 16.73±1.19 mg/dl. The mean duration of phototherapy was significantly shorter in neonates receiving probiotics along with phototherapy as compared to phototherapy alone (3.13±0.92 vs. 3.81±1.12 days; p=0.002). Similar significant difference was observed across various subgroups based on age, gender, gestational age, weight and serum bilirubin level upon admission.

Conclusion: Addition of probiotics to conventional practice of phototherapy alone in jaundiced neonates was found to hasten the recovery evident from significant reduction in the mean duration of phototherapy advocating its routine use in future practice.

Keywords: Neonatal Hyperbilirubinemia, Phototherapy, Probiotics

INTRODUCTION

Among various conditions complicating early neonatal period, neonatal hyperbilirubinemia is a frequent condition requiring visit to neonatologist and hospital admission and management. It predominantly occurs during initial 14 days of life and is seen in as many as 2-15% of neonates. The parents usually complain of yellowish discoloration of sclera and skin which is the result of raised bilirubin levels in the serum.[1] These circulating bilirubin levels are potentially dangerous to developing neonatal brain and may invoke irreversible brain damage resulting in neurological impairment and long-term disability and behavioral problems.[1,2]

Phototherapy is a cheap, readily available and effective treatment option for the management of neonates with hyperbilirubinemia. The mechanism behind phototherapy is the enzymatic conversion of bilirubin into its isomers which are more water soluble and are therefore eliminated without obligatory hepatic conjugation.[2] However, despite routine phototherapy, substantially high bilirubin levels cannot be effectively controlled and necessitate exchange transfusion due to anticipated risk of brain injury.[1,2] Therefore measures which can increase the efficacy of phototherapy and shorten its duration as well as reduce the need for exchange transfusion are actively sought in pediatric practice and clinical research.

During the past decade, probiotics has gained much popularity[3] and their clinical use has seen a significant rise where there are reports of their benefit in patients with acute and chronic diarrhea[4] and pneumonia.[5] There has been studies investigating their role in the clinical management of neonates with hyperbilirubinemia[6,7] but with controversial results.[8-10]

Torkaman et al.[8] (2017) reported that mean duration of phototherapy was significantly shorter in neonates receiving probiotics in addition to phototherapy as compared to neonates receiving phototherapy alone (3.13±0.70 vs. 3.55±0.74 days; p-value<0.001) in Iran. Similar results have also been reported by Demirel et al.[9] in 2015 in Turkish neonates with hyperbilirubinemia receiving phototherapy with and without probiotics (1.9±0.86 vs. 2.6±0.9 days, p-value<0.0001). In the light of this evidence, addition of probiotics to standard phototherapic treatment of neonatal hyperbilirubinemia appears better as it leads to speedy recovery. However, the evidence is not conclusive at the moment as Pasha et al.[10] (2017) in a similar study involving Iranian neonates with hyperbilirubinemia receiving phototherapy with and without probiotics didn't observe any significant difference in the mean duration of phototherapy (3.61±1.17 vs. 3.72±1.18 days; p-value=0.58) and concluded that it would only lead to extra cost to the patient.

Keeping in view these conflicting results in already published research and lack of local such published material; the purpose of the current study was to repeat this trial to further confirm the results with a hope that if addition of probiotics is found to significantly decrease the mean duration of phototherapy, the results of the present study will enable selection of more appropriate treatment for patients presenting with neonatal jaundice in future practice.

MATERIAL AND METHODS

This was a randomized controlled trial which was carried out at the Department of Pediatrics DHQ Hospital Kasur from Jan 2021 to June 2021. A total sample size of 94 cases (47 cases in each group) was calculated with 95% confidence interval (2-sided) and 80% power of test with expected mean duration of phototherapy to be 3.13±0.70 days and 3.55±0.74 days with and without probiotics respectively.[8] 94 cases of neonatal hyperbilirubinemia were included in the study. Patients with neonatal sepsis (respiratory rate >60/minutes), positive Coombs test (acquired on admission), and those who had received exchange transfusion were excluded from the study. We also excluded neonates with ABO incompatibility or Rh incompatibility and birth weight of <2,500

grams. Written informed consent and detailed history was taken from parents of each patient. Patient's demographic details like age, gestational age at delivery, weight and serum bilirubin level at admission were noted. These neonates were then allocated into following two groups randomly using lottery method; Group I: Phototherapy + Probiotics (47 neonates) and Group-II: Phototherapy alone (47 neonates). Patients were admitted to NICU and phototherapy was started using 8-Lamp blue light phototherapy unit 24 hours/day. Neonates in the probiotic group also received half of a capsule of Prokid probiotic (Bifido bacteriumlactis, Lactobacillus acidophilus, Bifidobacterium bifidum, and Lactobacillus rhamnosus) per day until phototherapy was stopped. Serum bilirubin level was acquired every 12 hours and phototherapy was stopped once it was less than 10 mg/dl during the first week and less than 11 mg/dl after the first week. Duration of phototherapy was recorded and logged into a predesigned proforma along with demographic details of the neonate. All the phototherapy sessions and probiotics were administered by a single resident (candidate himself) under supervision and all the serum bilirubin level estimations were acquired from a single lab (hospital lab free for patient) to eliminate bias. Confounding variables were controlled by exclusion. All this information was recorded in a pre-designed proforma (attached). Age, gestational age at delivery, weight, serum bilirubin level at admission and duration of phototherapy have been described by mean ±SD. Independent sample t-test has been used for the comparison of mean duration of phototherapy between the groups taking p≤0.05 as significant. Gender has been described by frequency as well as percentage. Data has been stratified for age, gestational age at delivery (≥37 weeks/ <37 weeks), gender, weight and serum bilirubin level at admission to control effect modifiers. Following stratification, t-test has been used to for the comparison of mean duration of phototherapy across each strata taking p≤0.05 as statistically significant.

RESULTS

Table 1: Demographic features of studied patients

Characteristics	Study Sample n=94
Age (days)	6.54±4.96
• <14 days	83 (88.3%)
• ≥14 days	11 (11.7%)
Gestational Age (weeks)	37.31±2.04
• Preterm	33 (35.1%)
• Full term	61 (64.9%)
Gender	
• Male	55 (58.5%)
• Female	39 (41.5%)
Weight (Kg)	2.89±0.49
• 2.5-3.3 Kg	67 (71.3%)
• 3.4-4.2 Kg	27 (28.7%)
Serum Bilirubin at Admission (mg/dl)	16.73±1.19
• 15-18 mg/dl	69 (73.4%)
• 18-20 mg/dl	25 (26.6%)

Neonatal age ranged from 2 days to 28 days with a mean of 6.54±4.96 days while the gestational age ranged from 34 weeks to 42 week with a mean 37.31±2.04 weeks. There were 55 (58.5%) baby boys and 39 (41.5%) baby girls with boys to girls ratio of 1.4:1. The weight of the neonates ranged from 2.5 Kg to 4.2 Kg with a mean of 2.89±0.49 Kg while the serum bilirubin level upon admission ranged from 15.1 mg/dl to 20.0 mg/dl with a mean of 16.73±1.19 mg/dl as shown in Table 1. There was statistically insignificant difference between the groups regarding mean age (p-value=0.885), mean gestational age (p-value=0.802), mean weight (p-value=0.888) and mean serum bilirubin level upon admission (p-value=0.840) and distribution of different subcategories based on age (p-value=0.748), gender (p-value=0.834), gestational age (p-value=0.829), weight (p-value=0.820) and serum bilirubin level upon admission (p-value=0.815) as shown in Table 2.

Table 2: Demographic features of studied groups n=94

Characteristics	Phototherapy + Probiotics n=47	Phototherapy alone n=47	P-value
Age (days)	6.47±4.75	6.62±5.21	0.885
• <14 days	42 (89.4%)	41 (87.2%)	0.748
• ≥14 days	5 (10.6%)	6 (12.8%)	
Gestational Age (weeks)	37.36±2.02	37.26±2.09	0.802
• Preterm	16 (34.0%)	17 (36.2%)	0.829
• Full term	31 (66.0%)	30 (63.8%)	
Gender			
• Male	28 (59.6%)	27 (57.4%)	0.834
• Female	19 (40.4%)	20 (42.6%)	
Weight (Kg)	2.90±0.51	2.88±0.50	0.888
• 2.5-3.3 Kg	34 (72.3%)	33 (70.2%)	0.820
• 3.4-4.2 Kg	13 (27.7%)	14 (29.8%)	
Serum Bilirubin at Admission (mg/dl)	16.71±1.25	16.76±1.14	0.840
• 15-18 mg/dl	35 (74.5%)	34 (72.3%)	0.815
• 18-20 mg/dl	12 (25.5%)	13 (27.7%)	

Table 3: Comparison of mean duration of phototherapy (days) between the study groups n=94

	Phototherapy + Probiotics n=47	Phototherapy alone n=47	P value
Mean Duration of Phototherapy (days)	3.13±0.92	3.81±1.12	0.002*

observed difference was statistically significant on independent sample t-test

Table 4: Comparison of mean duration of phototherapy (days) between the study groups across various subgroups n=94

Subgroups	Mean Duration of Phototherapy (Days)		P-value
	Phototherapy + Probiotics n=47	Phototherapy alone n=47	
Age			
• <14 days	3.12±0.97	3.80±1.19	0.005*
• ≥14 days	3.20±0.45	3.83±0.41	0.036*
Gestational Age			
• Preterm	3.19±0.98	4.06±0.90	0.012*
• Full term	3.10±0.91	3.67±1.21	0.042*
Gender			
• Male	3.14±0.97	3.78±1.12	0.029*
• Female	3.11±0.88	3.85±1.14	0.028*
Weight			
• 2.5-3.3 Kg	3.15±0.96	3.76±1.09	0.018*
• 3.4-4.2 Kg	3.08±0.86	3.93±1.21	0.046*
Serum Bilirubin at Admission			
• 15-18 mg/dl	3.14±0.91	3.76±1.18	0.017*
• 18-20 mg/dl	3.08±0.99	3.92±0.95	0.042*

* observed difference was statistically significant on independent sample t-test

Observed difference was statistically insignificant on Chi-square and Independent sample t-tests

The mean duration of phototherapy was significantly shorter in neonates receiving probiotics along with phototherapy as compared to phototherapy alone (3.13±0.92 vs. 3.81±1.12 days; p=0.002) as shown in Table 3. Similar significant difference was observed between the groups across various subgroups based upon age, gender, gestational age, weight and serum bilirubin level upon admission as shown in Table 4.

DISCUSSION

Neonatal hyperbilirubinemia or jaundice is a frequent cause of neonatal clinical visits and hospital admission during early life.[1,2] It results from excessive production or accumulation of bilirubin which is the byproduct of heme breakdown. It produces yellow discoloration of sclera and skin. Excessive circulating bilirubin levels may lead to kernicterus that is irreversible secondary brain injury leading to long-term sequela.[11] To counteract this raised bilirubin level phototherapy and exchange transfusion are cost-

effective and routinely used treatment options. The effect of light on reducing the serum bilirubin level was first reported by Cremer et al. in 1958.[12] Since then, phototherapy has been used as a non-invasive and cost-effective therapy in the management of such neonates. Now a day, exchange transfusions is only rarely required and is reserved as a rescue therapy in neonates with severe jaundice when phototherapy alone falls inadequate.[12] Though phototherapy is in practice for more than 50 years, its complications predominantly hypocalcemia put a limit to its prolonged use[12,13]. Therefore measures which can reduce the length of phototherapy are hot focus of research[4-7]. Recent studies claimed that probiotics supplementation of jaundiced neonates significantly reduced the mean duration of phototherapy and advocated its preferred use in future practice[6,7]. However, there was controversy in the existing literature[8-10] while there was no such local published material which necessitated the present study.

In the present study, the mean age of the jaundiced neonates was 6.54±4.96 days. Irshad et al.[14] (2011) observed similar mean age of 5.6±2.3 days in neonates presenting with jaundice at Lady Reading Hospital, Peshawar. A similar mean age of 6.24±2.91 days has been reported previously by Tehrani et al.[15] among Iranian neonates receiving phototherapy for neonatal jaundice. Alizadeh-Taheri et al.[16] (6±3 days) and Karamifar et al.[17] (6.7±3.7 days) also reported similar mean age in Iranian population. While relatively lower mean age of 4.0±1.38 days has been reported by Tandon et al.[18] in Indian such neonates. A comparable mean age of 5.4±1.4 days has been reported by Hassan et al.[19] (2015) in Iraq.

We observed that there was a slight male predominance among jaundiced neonates with male to female ratio of 1.4:1. Irshad et al.[14] in 2011 reported similar male predominance (m:f; 2.3:1) in local population. A similar male predominance has been reported by Taheri et al.[20] in 2014 (1.3:1), Najib et al.[21] in 2013 (1.4:1), Heydarian et al.[22] in 2010 (1.7:1) in Iranian population and Bulbul et al.[23] in 2014 (1.4:1) in Turkish Population. However, Srinivasa et al.[24] observed a female predominance instead with a male to female ratio of 1:1.1 in India.

In the present study, the mean weight of the jaundiced neonates was 2.89±0.49 Kg while the mean serum bilirubin level upon admission was 16.73±1.19 mg/dl. Our observation is in line with other studies where Tandon et al.[18] reported similar mean weight of 2.15±0.15 Kg in India while Karamifar et al.[17] reported it to be 2.08±0.3 Kg in Iran. Alizadeh-Taheri et al.[16] (3.18±0.43Kg) and Tehrani et al.[15] (3.23±3.7 Kg) reported relatively higher mean weight among such neonates in Iran. Similar mean serum bilirubin level of 17.0±2.7 mg/dl has been reported by Torkaman et al.[8] (2017) at admission of jaundiced neonates while Pasha et al.[10] (2017) reported it to be 16.3±1.9 mg/dl in neonates receiving phototherapy.

In the present study, the mean duration of phototherapy was significantly shorter in patients receiving probiotics along with phototherapy as compared to phototherapy alone (3.13±0.92 vs. 3.81±1.12 days; p=0.002). Similar significant difference was observed between the groups across various subgroups based upon age, gender, gestational age, weight and serum bilirubin level upon admission. Our observation is in line with that of Torkaman et al.[8] (2017) who reported that mean duration of phototherapy was significantly shorter in Iranian neonates receiving probiotics in addition to phototherapy as compared to neonates receiving phototherapy alone (3.13±0.70 vs. 3.55±0.74 days; p-value<0.001). Similar results have also been reported by Demirel et al.[9] in 2015 in Turkish neonates with hyperbilirubinemia receiving phototherapy with and without probiotics (1.9±0.86 vs. 2.6±0.9 days, p-value<0.0001).

The current study is first of its kind in local population and augments the unfinished already available research evidence on the subject. In the present study, addition of probiotics to conventional practice of phototherapy alone in jaundiced neonates was found to hasten the recovery evident from significant reduction in the mean duration of phototherapy advocating its routine use in future practice.

A very important limitation to the current study was that we didn't compare the side-effects of probiotics therapy which are also equally important and must be considered before implementing it in routine practice. Such a study is extremely recommended in future research.

CONCLUSION

Addition of probiotics to conventional practice of phototherapy alone in jaundiced neonates was found to hasten the recovery evident from significant reduction in the mean duration of phototherapy advocating its routine use in future practice.

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