

Efficacy Of Probiotic With Phototherapy Versus Phototherapy Alone For Treatment Of Neonatal Hyperbilirubinemia

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Abstract

Introduction: Neonatal jaundice or hyperbilirubinemia is the result of alterations in the bilirubin metabolism. Phototherapy is recommended but its effects are limited and adverse reactions can occur. **Aims:** Current project was aimed to compare the efficacy of probiotics with phototherapy versus phototherapy alone for treatment of neonatal Hyperbilirubinemia. **Methodology:** This RCT was held at Pediatrics Department Ittefaq Hospital, Lahore. It enrolled 308 patients following ethical approval from hospital. In group-A (n=154) all patients was treated with probiotic and standard phototherapy and in Group-B (n=154) all patients was treated with standard phototherapy alone. With the help of trained staff nurses a blood sample of 5 ml in aseptic measures was drawn at 4th and 7th day of treatment to assess serum bilirubin levels. Data were analyzed using SPSS version 26, with significance set at $p \leq 0.05$. **Results:** Group-A demonstrated a significantly higher efficacy (94.8%) compared to Group-B (78.6%) with p-value of <0.001 . Baseline variables, including age, gender and gestational age, were comparable between groups. **Conclusion:** It was concluded that addition of Probiotics with Phototherapy had higher efficacy as compared to Phototherapy alone. Thus it is recommended that Probiotics may be added to reduce the risk of bilirubin-induced neurological dysfunction and reduce the risk of probability of death.

Author Details

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Introduction

Neonatal jaundice or hyperbilirubinemia is the result of alterations in the bilirubin metabolism.¹ Hyperbilirubinemia though a common benign occurrence in the 1st week of life can sometimes progress to critical levels.^{2,3} The hospital based prevalence of Hyperbilirubinemia in term and preterm neonates is 60% during early weeks of life.^{4,5} According to one study, it has been reported that relative lack of bacteria in the gut during the first week of life, conjugated bilirubin cannot be converted to stercobilin thus leading to hyperbilirubinemia in a newborn.⁶ Both mildly alkaline pH of the proximal intestine and the over-activity of the beta-glucuronidase enzyme in the sterile gut are involved in this process according to previous literature.^{4,7} Severe hyperbilirubinemia if improperly treated can cause long-term, irreversible and devastating, neurological impairment, or sometimes death.²

Phototherapy is gold standard and an effective treatment for hyperbilirubinemia.^{6,8} Number of sessions needed to treat varies widely depending on different variables like age of onset, neonatal gender and gestational age.³ Exchange transfusion of phototherapy leads to complications in about 5% of treated infants.³ Recently the role of Probiotics is one the hot debate to treat neonatal jaundice as it is considered to lower the serum bilirubin levels.⁹

Probiotics have been utilized to boost immunity in addition to blue light phototherapy, touching, and medications, primarily via controlling bacterial colonies. They create a biological barrier by using teichoic acid to precisely bind intestinal epithelial cells. Consequently, its use to treat newborn jaundice has received special consideration.^{1,8}

One previous study evaluated the therapeutic effects of probiotics on Hyperbilirubinemia with combination of probiotics and phototherapy (treatment group) and placebo (phototherapy only). They reported the efficacy rate in treatment group was 91.18% and 79.41% in placebo group, $p=0.002$.¹

Due to lack of local data and high frequency of Hyperbilirubinemia in neonates, it is necessary to find a way to reduce the bilirubin level and to minimize the duration of hospitalization.⁵ If it is not corrected in time then prolonged and uncontrolled high levels of bilirubin can lead to bilirubin-induced neurological dysfunction and it also increase the probability of death. Thus, current project was aimed to compare the efficacy of probiotics with phototherapy versus phototherapy alone for treatment of neonatal Hyperbilirubinemia.

METHODOLOGY:

This RCT was held at Pediatrics Department Ittifaq Hospital, Lahore. Total of 308 was calculated as sample size by using percentage of efficacy as 91.18% in probiotic and phototherapy group and 79.41% in phototherapy group while keeping 90% power of test, 5% level of significance and 95% confidence level.¹ All neonates of either gender having age of 0-28 days who were diagnosed as Hyperbilirubinemia as per operational definition were included. Any sick newborn who required NICU admission, had buffalo or cow's milk feeding history while mothers of neonates with history of anticonvulsants medicine during pregnancy or post-partum were excluded.

All patients were enrolled following ethical approval from hospital through Non-probability consecutive sampling. In group-A (n=154) all patients was treated with probiotic and standard phototherapy for 05 days and in Group-B (n=154) all patients was treated with standard phototherapy alone for exact same duration. With the help of trained staff nurses a blood sample of 5 ml in aseptic measures was drawn at 4th and 7th day of treatment to assess serum bilirubin levels. The efficacy of both

treatments was labeled as per operational definition. All basic and related data was collected by researcher herself on attached proforma.

DATA ANALYSIS:

SPSS version 26 analyzed all collected data. Quantitative data like age (days), birth weight and gestational age (weeks) was presented as Mean \pm standard deviation. Qualitative data like gender and efficacy of treatments was presented in form of frequencies and percentages. To compare efficacy of treatment in both treatments Chi-square test was applied. P-value ≤ 0.05 was considered as significant. To address effect modifiers data was stratified for gender, age and gestational age. Post stratification Chi-square test was applied taking p-value ≤ 0.05 as significant.

RESULTS:

In combined group there were 86 (55.8%) male and 68 (44.2%) female. In Phototherapy alone group, there were 85(55.2%) male and 69(44.8%) female cases. Mean age of cases in combined (Probiotics + Phototherapy) was 14.14 ± 6.54 days and in Phototherapy alone group was 16.53 ± 7.84 days while other parameters like mean birth weight and mean gestational age were represented as mean \pm SD in table-1.

		Mean	S.D	Minimum	Maximum
Age (days)	Probiotics + Phototherapy	14.14	6.54	1.00	27.00
	Phototherapy	16.53	7.84	1.00	28.00
Birth weight (g)	Probiotics + Phototherapy	2915.27	505.38	2206.00	3798.00
	Phototherapy	2954.86	502.80	2210.00	3793.00
Gestational age (weeks)	Probiotics + Phototherapy	37.60	2.16	35.00	41.00
	Phototherapy	37.83	2.15	35.00	41.00

Group-A demonstrated a significantly higher efficacy (94.8%) compared to Group-B (78.6%) with value of <0.001 as shown in table-2. However, in combined and alone group 8(5.2%) and 33(21.4%) cases did not had efficacy of the treatment.

		Study group		P-value
		Probiotics + Phototherapy	Phototherapy	
Efficacy	Yes	146(94.8%)	121(78.6%)	0.001*
	No	8(5.2%)	33(21.4%)	
Total		154(100.0%)	154(100.0%)	308(100.0%)

*Statistically significant; Chi-square

When data was stratified for age for age, in age group of < 14 days the frequency of efficacy was statistically higher in combined group (93.3%) as compared to Phototherapy alone group (81.5%), p-value <0.05 . In 14-28 days of age, the frequency of efficacy of was higher in combined group (96.2%) as compared to alone group (76.4%), (table-3).

Age (day)			Classes		p-value
			Group-A	Group-B	
< 14 days	Efficacy	Yes	70(93.3%)	53(81.5%)	0.033*

		No	5(6.7%)	12(18.5%)	
<i>14-28 days</i>	<i>Efficacy</i>	Yes	76(96.2%)	68(76.4%)	<0.001**
		No	3(3.8%)	21(23.6%)	

*Statistically Significantly

In males the frequency of efficacy was statistically higher in combined group (93.0%) as compared to Phototherapy alone group (81.2%), p-value <0.05. In female cases, the frequency of efficacy of was higher in combined group (97.1%) as compared to Phototherapy alone group (75.4%), (table-4).

Table-4: Efficacy between groups with respect to Gender					
Gender			Classes		p-value
			Group-A	Group-B	
<i>Male</i>	<i>Efficacy</i>	<i>Yes</i>	80(93.0%)	69(81.2%)	0.021*
		<i>No</i>	6(7.0%)	16(18.8%)	
<i>Female</i>	<i>Efficacy</i>	<i>Yes</i>	66(97.1%)	52(75.4%)	<0.001**
		<i>No</i>	2(2.9%)	17(24.6%)	

*Statistically significant

In cases with gestational age < 37 weeks the frequency of efficacy was statistically higher in combined group (87.7%) as compared to Phototherapy alone group (60%), p-value <0.05. In cases with gestational age > 37 weeks, the frequency of efficacy of was higher in combined group (10) as compared to Phototherapy alone group (88.9%) as shown in table-5.

Table-5: Efficacy with respect to Gestational age among Groups						
Gestational age (weeks)			Study group		Chi-square	p-value
			Group-A	Group-B		
<i>< 37 weeks</i>	<i>Efficacy</i>	Yes	57(87.8%)	33(60.0%)	12.185	<0.001*
		No	8(12.3%)	22(40.0%)		
<i>37 weeks or more</i>	<i>Efficacy</i>	Yes	89(100.0%)	88(88.9%)	10.503	0.001*
		No	0(0%)	11(11.1%)		

*Statistically significant

DISCUSSION:

In neonatal medicine, jaundice is the most prevalent clinical symptom. According to previous study, about 60% of healthy term babies and 80% of preterm babies experience clinically noticeable jaundice during the first week of life. Thus, it remains the most frequent cause of readmission to hospital among neonates.¹⁰ Various treatment options are there but most popular treatment for severe hyperbilirubinemia is phototherapy. In order to prevent exchange transfusion, it causes the concentration of total bilirubin to decrease.¹¹ Despite being a safe therapeutic option, phototherapy has drawbacks of its own. Its adverse effects like hyperthermia, a shift in the infant's thermal environment cause increased peripheral blood flow and insensible water loss as reported previously.¹⁰

Similarly, diarrhea and darker, greenish-tinged stools are more common in infants undergoing routine phototherapy for hyperbilirubinemia. One previous study has demonstrated a connection between phototherapy and type-1 diabetes mellitus and asthma.¹² Bronze baby syndrome and infrequent purpuric and bullous eruptions in a baby with severe cholestatic jaundice have been documented. Thus it should only be used after careful consideration and justification because it disrupts mother-infant

connection.^{13,14} Probiotics have been utilized to boost immunity in addition to blue light phototherapy, touching, and medications, primarily via controlling bacterial colonies. They create a biological barrier by using teichoic acid to precisely bind intestinal epithelial cells. Consequently, its use to treat newborn jaundice has received special consideration^{1,8} One previous study was designed to evaluate the therapeutic effects of probiotics on Hyperbilirubinemia with combination of probiotics and phototherapy (treatment group) and placebo (phototherapy only). They reported the efficacy rate in treatment group was 91.18% and 79.41% in placebo group, $p=0.002$.¹ Another study was carried out to assess the impact of probiotics on lowering the total bilirubin level in the serum of newborns suffering from jaundice. When comparing the probiotic group to the control group, it was reported that there was a more significant difference in bilirubin on days 1 ($p=0.000$), 2 ($p=0.000$), and 3 ($p=0.000$) of treatment. Therefore, they concluded that probiotics as an adjuvant to phototherapy caused a more quick and significant decrease in bilirubin.¹⁴ Another study's main findings showed that the intervention and control groups' mean SBL before to probiotic intervention was 16 ± 1.9 and 16.9 ± 1.9 mg/dl, respectively ($P>0.05$). However, there was no significant difference ($P>0.05$) in the two groups even after treatment with probiotics. Therefore, SBL and the length of phototherapy are not significantly affected by oral probiotics in newborns with jaundice. Longer-term follow-up investigations are required.¹⁵

LIMITATIONS:

Single-center design limited external generalizability and lack of genetic work up followed by limited financial and human resources.

CONCLUSION:

It was concluded that addition of Probiotics with Phototherapy had higher efficacy as compared to Phototherapy alone. Thus it is recommended that Probiotics may be added to reduce the risk of bilirubin-induced neurological dysfunction and reduce the risk of probability of death.

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