

Prebiotics in Management of Neonatal Jaundice: Open Label Randomised Control Trial

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Abstract

Background: Approximately 5-35% of neonates develop jaundice requiring treatment during the 1st week of life. Prebiotics, a mixture of Galacto-oligosaccharides (GOS) and Fructo-oligosaccharides (FOS), has been postulated to reduce serum bilirubin levels on principle of interruption of entero-hepatic circulation. **Objective:** To evaluate the effect of oral supplementation with prebiotics (Fructo-oligosaccharides) in the management of neonatal jaundice. **Subjects and Methods:** Design & Setting: Open Label, Randomized Control Trial at Level II NICU in public hospital over one year. Participants: Term exclusively breast-fed neonates with Jaundice requiring phototherapy. Intervention: Randomisation of Sixty eligible neonates into Control and Prebiotic groups (n= 30 each). Both groups received phototherapy, and Prebiotic group received additional oral prebiotics. Outcome: Primary outcome measure was a reduction in total serum bilirubin levels (TSB) and duration of phototherapy. The secondary outcome measure was the change in the frequency of stools. **Results:** Baseline Features were similar in both groups. Overall serum bilirubin levels decreased significantly from enrolment till the omission of phototherapy (17.24 + 1.16 vs. 12.74 + 0.48; P: 0.00). ANOVA depicted no statistical difference between the groups in 12 hourly reductions of TSB (F [3, 232] = 0.14, P: 0.94). Mean duration of phototherapy (in hours) required in prebiotic and control group was similar (50.40 + 9.66 vs. 47.60 + 8.62; P = 0.24). Secondary outcome measures were also similar in both groups. **Conclusion:** Prebiotics, containing only fructo-oligosaccharides, administered for upto three days, do not have any additional effect on reduction of serum bilirubin levels in neonates with jaundice receiving conventional treatment.

Keywords: Inulin, Oligo-saccharides, Phototherapy, Bilirubin.

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Introduction

Approximately 60% of term neonates develop jaundice during the first week of life.^[1] It occurs due to physiological transition process resulting from increased bilirubin production (due to breakdown of red blood cells), its defective uptake and decreased clearance by the immature liver. In term neonates, total serum bilirubin level usually rises to a peak of 6-8 mg/dl by 3 to 5 days of age and then falls. Levels <2 mg/dL may not be seen until 1 month of age.^[2]

Severe neonatal jaundice, defined as total serum bilirubin (TSB) above the 95th percentile for age on the hour specific nomogram, is seen in 5 to 35% of neonates.^[3-5] It can lead to substantial morbidity and mortality.^[6] Therefore; its proper and timely treatment is of critical importance. Phototherapy is the mainstay of management of neonatal jaundice.^[7]

Phototherapy does not cause serious side effects, but recently it has been observed in some clinical trials on neonates that phototherapy (both conventional and intensive

types) is associated with DNA damage.^[8,9] Clinical trials on various add on pharmacological therapies for reducing the requirement of phototherapy with insufficient evidence for their use in clinical practice.^[10-12]

Use of Prebiotics is a promising and novel strategy in the management of neonatal jaundice. Prebiotics are "non-digestible food components that affect the host beneficially by selectively stimulating the growth and/ or activity of one or a limited number of bacteria in the colon, thereby improving host health".^[13] Oral administration of specific mixture of short-chain galacto-oligosaccharides (GOS) and long-chain fructo-oligosaccharides (FOS) in 9:1 ratio in the dosage of 0.4-0.8 grams/100ml of enteral milk has a proven benefit in the development of early microbiota, increased stool frequency and stool softness.^[14,15]

The hypothesis suggests that enteral supplementation of prebiotics leads to decrease in bilirubin levels by reducing entero-hepatic circulation (by mechanism of reducing conversion of conjugated bilirubin to unconjugated bilirubin). Few Randomised control Trials have shown benefits of enteral administration of Prebiotics (GOS & FOS

mixture) in prevention and management of jaundice in neonates.^[16-18] Studies in neonates on Prebiotics preparation containing only FOS are also available.^[19]

FOS supplement is available in India and not GOS & FOS mixture. Hence, this study was conducted to evaluate the effect of FOS (Inulin) on TSB in term neonates with jaundice.

Subjects and Methods

Trial Design:

It was an Open-Label, Randomized, Control Trial conducted at level II NICU in public hospital over one year. The institutional ethics committee approved the trial.

Participants:

All term neonates admitted with Jaundice requiring phototherapy were assessed for eligibility by a neonatologist. Exclusion criteria were Newborn with birth weight < 2500 grams, Formula fed, those requiring exchange transfusion, sick neonates (with hypotension, temperature instability, acidosis, sepsis, dehydration) and Congenital GIT malformations. Parental Informed Consent before enrollment.

Sample size:

The Sample size was calculated as total 60 (30 in each group) considering 80% power and Type 1 error of 5 %. Calculations were based on an expected effect size of at least 0.8mg/dl TSB as observed in a previous Randomized Control Trial,^[17] with an estimated 10% drop-out rate.

Randomization sequence generation:

Block randomization was done using a web-based random number generator using permuted blocks of two. Randomization of the enrolled patients into two groups (Prebiotic group and Control group). Allocation concealment was done using sequentially numbered, opaque, sealed envelopes. Blinding was not intended in this study.

Interventions:

Total Serum Bilirubin (TSB) documentation on age-specific bilirubin nomogram at enrolment. Both the groups received Phototherapy (Single surface, LED Phototherapy with Spectral Irradiance: 20 microwatt cm⁻² nm⁻¹ at 30 cm from the light unit). Prebiotic Group received additional supplement of long-chain fructo-oligosaccharide FOS (inulin) in powder form, administered at a dosage of 1.5 grams/kg/day divided into three doses.^[18] Each part of the preparation was dissolved in 10 ml of mother's own expressed breast milk and was administered three times a day using cup & spoon. Babies immediately breastfed after prebiotic administration. The endpoint was the omission of phototherapy according to age-specific bilirubin nomogram.

Data collection:

Demographic data was collected. Serial TSB was recorded at enrollment and 12 hourly till the endpoint. Frequency of stools was documented at registration and then at an interval of 24 hours till endpoint. Side effects if any documented. Epi-info software version 7.2 was used to facilitate data collection.

Outcomes:

The primary outcome measure was the reduction in serum bilirubin levels and the required duration of phototherapy. Change in frequency of stools was the secondary outcome measure.

Statistical methods:

Statistical analysis was done using Microsoft excel 2010 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social science Inc. Chicago, IL, USA) VERSION 19. 0. Continuous variables presented as mean & standard deviation. Chi-Square test was for applied for qualitative variables. The continuous data compared between the groups using unpaired Students t-test for normally distributed data and Mann –Whitney U test for skewed data. Continuous variables with multiple measures obtained over time were analyzed using ANOVA for between-group differences. P-Value of ≤ 0.05 was considered statistically significant.

Results

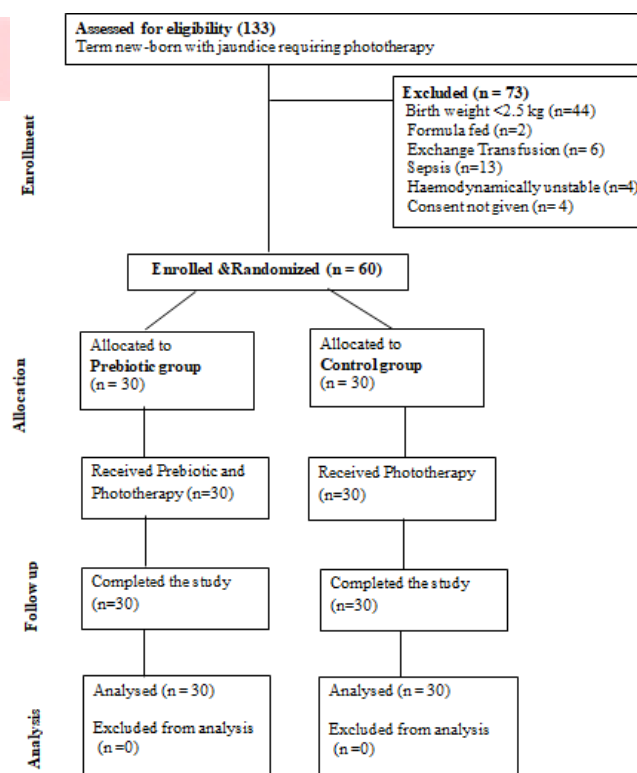


Figure 1: Patient flow diagram

Table 1: Baseline characteristics

| Characteristics | Prebiotic group (n=30) | | Control group (n=30) | | P-Value |
|--|--------------------------|--------|--------------------------|--------|---------|
| | Mean | SD | Mean | SD | |
| Continuous variables At enrolment | | | | | |
| Weight (grams) | 2827 | 238 | 2843 | 233 | 0.78* |
| Age (Hours) | 57 | 14 | 58 | 18 | 0.78* |
| TSB (mg/dl) | 17.03 | 1.34 | 16.77 | 1.58 | 0.14* |
| Stool frequency | Median 4 (Min. 3, Max.8) | | Median 5 (Min. 2, Max.7) | | 0.47# |
| Dichotomous variables | | | | | |
| Gender | Male | Female | Male | Female | 0.80\$ |
| | 14 | 16 | 13 | 17 | |
| Mode of delivery | Vaginal | LSCS | Vaginal | LSCS | 1\$ |
| | 17 | 12 | 17 | 12 | |
| Risk factors for jaundice | | | | | |
| ABO Incompatibility | 15 | | 17 | | 0.77\$ |
| Birth asphyxia | 02 | | 01 | | |
| Maternal oxytocin | 09 | | 08 | | |

TSB: Total Serum Bilirubin, SD: Standard Deviation, * Unpaired Student T-Test, # Mann Whitney U test, \$ Pearson Chi-Square Test

Total 133 neonates with jaundice requiring phototherapy admitted over one year. After excluding seventy-three neonates, sixty randomized into Prebiotic group and Control group (n=30 each). All neonates completed the study and included in analysis. [Figure 1]

The mean age of presentation of enrolled neonates was 58 + 16 hours of life. The average weight of the enrolled neonates was 2835+ 233 grams. There were 27 (45%) male and

33(55%) female new-borns. Baseline data were comparable in both the groups. [Table 1]

Change in serum bilirubin levels: The mean total reduction in TSB at the endpoint was similar in both Prebiotic and Control groups [Table 2]. Overall serum bilirubin levels decreased significantly from enrolment till the omission of phototherapy (17.24 + 1.16 vs. 12.74 + 0.48; mean difference 4.5; 95% Confidence interval [CI] 4.17, 4.82; P: 0.00). Serum bilirubin levels decreased significantly in both the Prebiotic (from 17.42 + 0.80 to 12.77 + 0.48; mean difference 4.47; 95% CI 4.12, 4.81; P = 0.00) and control (from 17.07 + 1.43 to 12.72 + 0.48; mean difference 4.35; 95% CI 3.80, 4.90; P = 0.00) groups. At end of intervention, the serum bilirubin levels were similar between the groups (12.77 + 0.48 vs. 12.72 + 0.48; mean difference 0.05; 95% [CI] -0.20, 0.30; P = 0.68). TWO WAY ANOVA with repeated measures analysis depicted, that the difference in 12 hourly reductions of TSB amongst Prebiotic and Control group was not statistically significant (F [5, 348] = 0.27, P: 0.93). [Figure 2]

Duration of phototherapy: Mean duration of phototherapy in prebiotic and control group was similar (50.40 + 9.66 vs. 47.60 + 8.62; mean difference 2.8; 95% [CI] -1.932, 7.532; P = 0.24). [Table 2]

Frequency of stools: There was no significant difference in frequency of stools at 24 hours and 48 [Figure 3].

Side effects: Side effects of prebiotics not observed.

Table No. 2: Observed Outcome measures in the study groups

| Parameter | Prebiotic group(n=30) | | Control group (n=30) | | Mean difference | 95% CI | P-VALUE* |
|---|-----------------------|------|----------------------|------|-----------------|-------------|----------|
| | Mean | SD | Mean | SD | | | |
| Mean Serum Bilirubin at the endpoint (mg/dl) | 12.77 | 0.48 | 12.72 | 0.48 | 0.05 | -0.20, 0.30 | .68 |
| Mean Total reduction in serum bilirubin (mg/dl) | 4.65 | 0.80 | 4.35 | 1.36 | 0.3 | -0.28, 0.88 | 0.30 |
| Mean duration of Phototherapy required (hours) | 50.40 | 9.66 | 47.60 | 8.62 | 2.8 | -1.93, 7.53 | 0.24 |

SD: Standard Deviation, CI: Confidence Interval, * Unpaired Student T Test

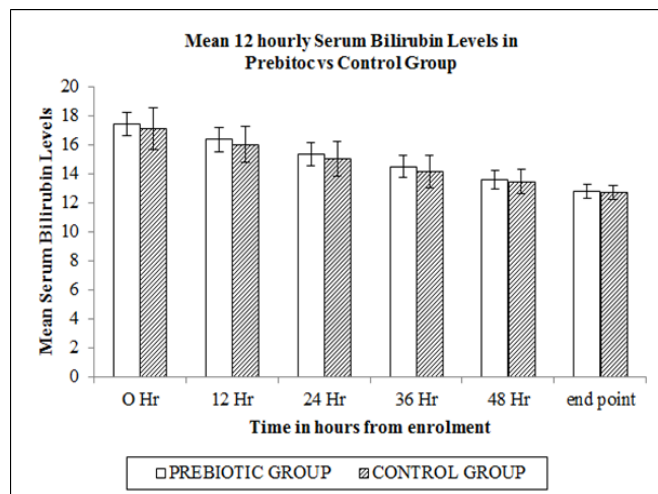


Figure 2: Mean serum bilirubin levels from enrolment until the end of intervention

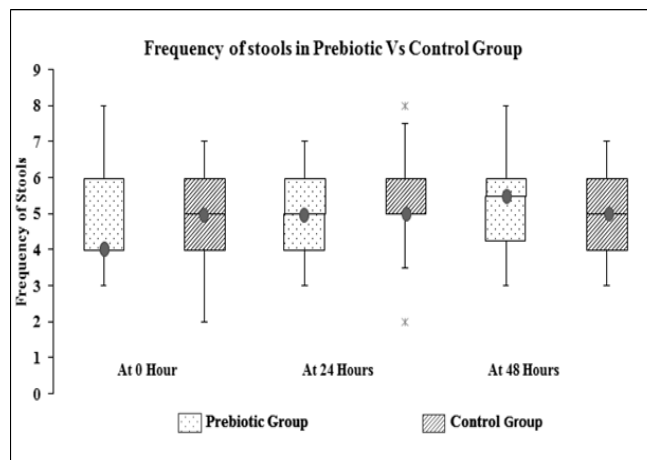


Figure 3: Box Plot showing Frequency of stools in Prebiotic VS Control Group from enrolment until the end of the intervention

Discussion

ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology, and Nutrition) committee recommends the addition of prebiotics to formula milk.^[20] Recommended prebiotics are short-chain galacto-oligosaccharide (GOS) and long-chain fructo-oligosaccharides (FOS) in 9:1 ratio. Bisceglia M et al.^[17] used GOS - FOS supplemented milk formula in term neonates over 28 days, and reported it to be safe & effective in management of mild jaundice in new-borns. Armanian A. M et al.^[18] also reported beneficial effects of GOS - FOS preparation added to the expressed breast milk in preterm neonates. Authors of both these trials attributed this beneficial effect of prebiotics to interruption of entero-hepatic circulation due to increased gastrointestinal motility. They documented significant increase in frequency of stools in participants. This effect is also associated with reduced stool viscosity and facilitated growth of Bifidobacterium and Lactobacilli.^[13] Dose and duration-dependent accelerated gastrointestinal transit time reported with GOS - FOS use for more than two weeks.^[21,22] Euler AR et al.^[19] reported increase in stool frequency with high dose FOS supplemented for seven days. In our study also, FOS - only preparation was used, and such beneficial effect was not demonstrated, probably due to shorter duration of FOS administration (2-3 days).

There is limited evidence to suggest the benefit of Prebiotics through facilitated growth of intestinal microflora capable of reducing bilirubin to urobilinoids and its elimination in stool.^[23-25]

Limitations of the study include GOS & FOS mixture 9:1 not used, optimal dose and duration not defined, exclusion of pre-terms, stools not evaluated for viscosity and microflora.

Further research recommended, after fulfilling these limitations.

Conclusion

Supplementation of Prebiotics, containing only fructo-oligosaccharides for upto three days, does not have any additional effect on reduction of serum bilirubin levels in neonates with jaundice receiving conventional treatment.

‘What is Already Known?’

Prebiotic supplemented formula milk containing mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides in 9:1 ratio shows enhanced gastrointestinal motility and lowers bilirubin levels in neonates with jaundice.

‘What this Study Adds.’

Prebiotics supplementation with only Fructo-oligosaccharides at a dose of 1.5 gram/kg/day for shorter duration does not show any change in gastrointestinal

motility or bilirubin levels in neonates with Jaundice.

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