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Treatment Effect of Probiotic *Bacillus Clausii* on Neonatal Jaundice in Late Preterm and Term Newborn Babies: An Experimental Study

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Abstract

Objective: To evaluate the effect of prophylactic probiotic *Bacillus clausii* treatment on the need and duration of phototherapy in new born babies.

Design: Open labeled clinical trial.

Setting: Level II obstetric ward of a teaching hospital in Southern India.

Participants: A total of 1043 babies with a gestational age of more than 35 weeks were enrolled in the study. There were 510 babies in the probiotic *Bacillus clausii* intervention group and 533 babies in the control group.

Intervention: Intervention group babies < 37 weeks received 2 ml of *Bacillus clausii* (2.5 ml for those >37 weeks) twice a day for 3 days.

Main outcome measure: The outcome measures were (i) Need of phototherapy and (ii) Duration of phototherapy.

Results: A total of 32 babies in control group and 17 in intervention group required phototherapy. This difference in need for phototherapy was statistically significant between the two groups (p 0.04). Treatment with probiotic reduced the risk of need for phototherapy by 44% (RR 0.56, 95% CI 0.32, 0.99).The median duration of phototherapy in the intervention group was 18 hrs(IQR 16.50, 24.00) and that of control group was 24 hrs (IQR 18.00, 48.00). This difference in duration of phototherapy was statistically significant (p=0.027). No adverse drug reactions were noticed in the intervention group.

What is already known: The management of neonatal jaundice depends on phototherapy and exchange transfusion.

What this study adds: Prophylactic probiotic therapy appears to reduce the need and duration of phototherapy in neonatal jaundice.

Conclusion: Prophylactic treatment of probiotic *Bacillus clausii* for three consecutive days reduced both the need as well as the duration of phototherapy in newborn babies.

Keywords: Probiotic *Bacillus clausii*; Neonatal jaundice; Phototherapy

Introduction

Neonatal Jaundice is a critical illness in the newborn period [1]. It is one of the leading causes of admissions in new born nurseries throughout the world [2]. Neonatal jaundice is considered when the total serum bilirubin (TSB) rises above the 95th percentile for age during the first week of life [3,4]. Approximately 60%-80% of healthy infants are expected to present with idiopathic neonatal jaundice [5].

The lack of bacteria in the gut during the newborn period has an impact on the enterohepatic circulation of conjugated bilirubin [6,7]. The low bacterial load during this first week of life results in decreased conversion of conjugated bilirubin to stercobilin. The resultant high levels of conjugated bilirubin get converted to unconjugated bilirubin in the intestine by the enzyme beta-glucoronidase. The resultant high levels of unconjugated bilirubin gets absorbed and reaches the blood stream resulting in unconjugated hyperbilirubinemia during this period [6,7]. A significant proportion of babies both term and preterm demand intervention due to neonatal jaundice [8]. The main treatment options for neonatal jaundice are phototherapy (conventional or intensive), exchange transfusion and pharmacological treatment [9]. The pharmacological treatment options include Phenobarbitone, Intravenous immunoglobulins (IVIG), and Metalloporphyrins [9]. Probiotic administration prevents the action of β glucoronidase responsible for the deconjugation of the bilirubin diglucoronide and

enterohepatic circulation thus reducing bilirubin levels [10,11]. Several studies have shown a therapeutic benefit for various probiotics in the management of neonatal hyperbilirubinemia [12-14].

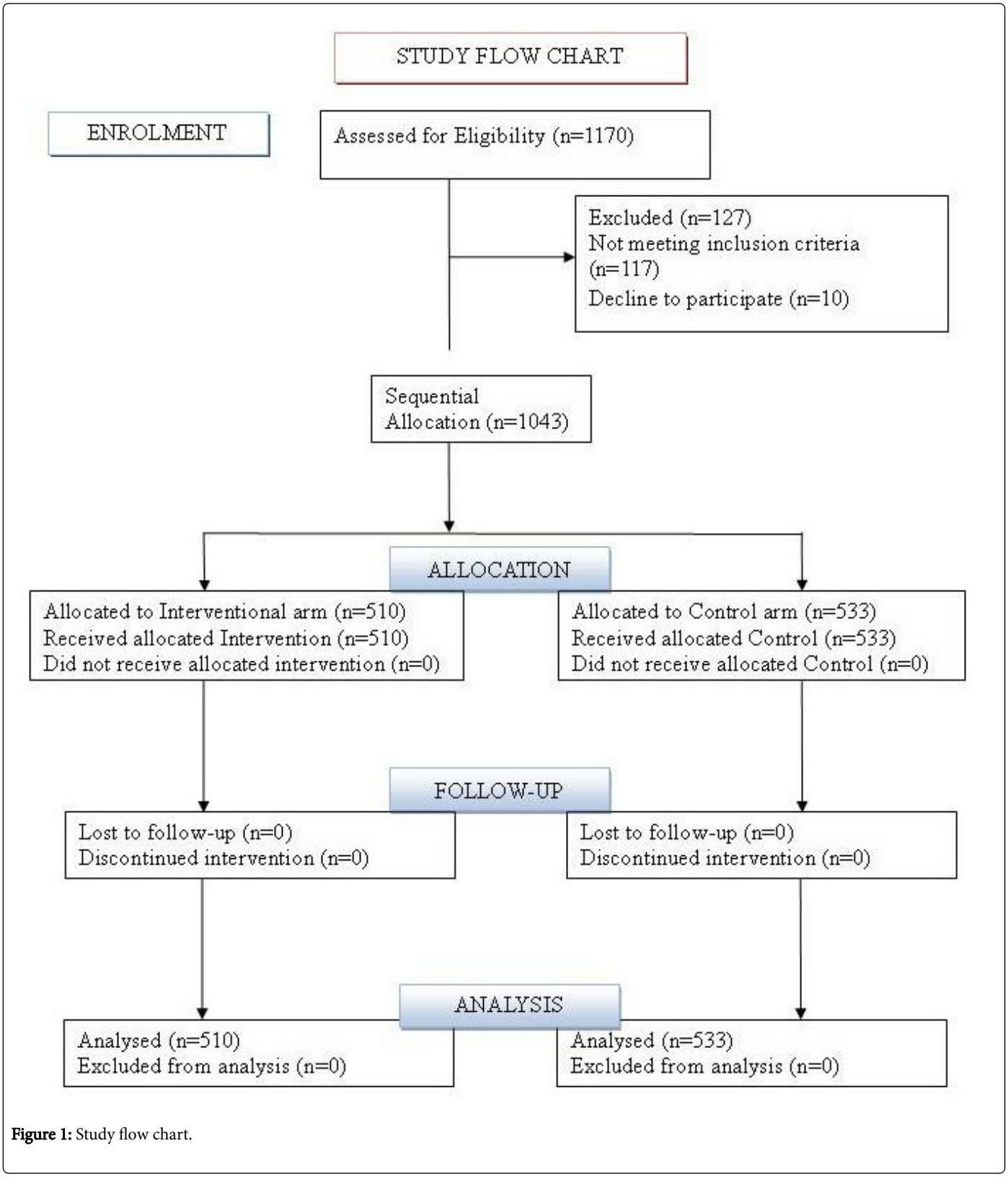

Figure 1: Study flow chart.

The primary objective of this study was to examine the therapeutic efficacy of prophylactic probiotic administration to reduce the need and duration of conventional phototherapy in babies more than 35 weeks of age.

Methods

This study was done in the Department of Pediatrics, Government Medical College, Kottayam, India. The study was initiated after obtaining clearance from the Institutional Ethical Committee. The sample size was calculated based on the assumption of 3% absolute reduction in the need of photo therapy for the intervention group compared to the control arm (2% in the intervention arm vs. 5% in control). We selected an alpha of 0.05 and 80 percent power giving us a sample size of 588 newborns per arm (Total 1176 babies).

The study recruited newborn babies from the obstetric ward of study institution. All newborns whose parents provided written informed consent and satisfied the inclusion and exclusion criteria mentioned below were taken for the study.

Inclusion criteria included (i) all neonates born in Govt. Medical College, Kottayam, (ii) gestational age of >35 weeks. The exclusion criteria included (i) neonates with hypothyroidism, trisomy 21, cephalhaematoma (ii) proven hemorrhages, (iii) direct hyperbilirubinemia and (iv) formula fed babies. We intended to recruit 588 newborns in the intervention arm in the first two months of the study followed by the same number in the control arm in the subsequent months. We were able to sequentially recruit 510 newborns in the intervention arm after screening 580 newborns and 533 in the control arm after screening 590 newborns during the study period (February 2012 to May 2012) (Figure 1).

The intervention group (510 newborns) received Prophylactic *Bacillus clausii* (Enterogermina) batch number (10456 and 10448 Sanofi Aventis). The dose was 2,000 million spores of multi antibiotic-resistant *Bacillus clausii* (excipient: purified water) per 5 ml available in the liquid form orally, at a dose of 2.5 ml twice a day for term newborns and 2.0 ml twice a day for preterm newborns, after the first feed, for 3 consecutive days. All *Bacillus clausii* administrations were supervised by the principal investigator (PI). Newborns in the control group were not given prophylactic *Bacillus clausii*. All newborns in both groups were exclusively on demand breast feed during the intervention period. All babies were observed for jaundice by clinical examination, twice daily by 2 paediatric residents, independently. These residents were given proper training to assess jaundice at the start of the study by the PI for uniformity in measurement. Jaundice was assessed using a trans-cutaneous bilirubinometer (May and Becker). A blood draw for serum bilirubin was done if trans-cutaneous bilirubin (Tcb) values were equal to/more than/within 2 mg/dl of the photo-therapy cut off range for risk category as per the AAP chart [15]. Serum bilirubin estimation (both total and direct) was done using Van den Bergh's method [16]. The serum bilirubin estimations were repeated at an interval of 24 hrs for a minimum of 3 days. All estimations were done by the same technician who was blinded to group status.

Continuous single surface photo therapy was given with routine precautions for photo therapy to all indicated newborns as per the AAP chart. Total duration of photo therapy was documented in minutes and converted to hours. All babies were monitored for adverse effects of probiotic like vomiting, feed intolerance, loose stools and abdominal distension [17].

Statistical analysis

All continuous variables are reported as mean (SD) and categorical variables as percentages. Chi square test was used to find out the association between the probiotic administration and need for phototherapy among the two groups. The relative risk with 95% confidence intervals and NNT (number needed to treat) for the need of photo therapy was also calculated. Duration of photo therapy in the two groups was compared using Mann Whitney U test.

Results

We recruited 510 newborns in the intervention (probiotic) group and 533 newborns in the control group. All newborns in the intervention group completed the full course of probiotic therapy (2 doses per day, total 6 doses in three days). There were 37 preterm newborns (0.07%) in the intervention group vs. 28 (0.05%) in the control group. The mean birth weight of newborns in the intervention group was 2.78 kg (SD 0.46) vs. 2.73 kg (SD 0.44) in the control group. The mean transcutaneous bilirubin in the intervention group was 5.02 mg/dl (SD 2.61) and in the control group was 5.15 mg/dl (SD 2.77). The mean birth weight, gestational age status (preterm/term), gender distribution and transcutaneous bilirubin levels were comparable between the two groups. The details related to the baseline comparison of the study groups are presented as Table 1 below.

	Intervention group (n=510)	Control group (n=533)	p value
Birth status			
Pre-term babies (<37 weeks)	37 (0.07)	28 (0.05)	0.181
Term babies (≥ 37 weeks)	473 (0.93)	505 (0.95)	
Mean birth weight (kg)	2.78 ± 0.46	2.73 ± 0.44	0.062
Gender			
Male	270 (52.9)	286 (53.7)	0.816
Female	240 (47.1)	247 (46.3)	
Trancutaneous bilirubin level (mg/dl, Day 1)	5.02 ± 2.61	5.15 ± 2.77	0.428

Table 1: Baseline comparison of study sample.

Group	Photo therapy not needed n (%)	Needed n (%)	p value
Intervention group (probiotic)	493 (96.7)	17 (3.3)	0.04
Control group	501 (94.0)	32 (6.0)	

Table 2: Need for photo therapy-intervention group vs. control group.

A total of 49 newborns required photo therapy in the study. In the intervention group 17 newborns (3.3%) required photo therapy compared to 32 newborns (6%) in the control group. This difference in proportion of subjects requiring photo-therapy was significant between the two groups (p=0.04). Treatment with probiotic reduced the risk of need for photo therapy by 44% (RR 0.56, 95% CI 0.32, 0.99).

Among the newborns requiring photo therapy as per AAP guidelines, the median duration of photo therapy was 18 hours (IQR 16.50, 24.00) in the probiotic group versus 24 hours (IQR 18.00, 48.00) in the control group (Table 2). The difference in duration of photo therapy between the two groups was statistically significant (p=0.027). A graphical representation of the comparison related to duration of photo therapy between the two groups is presented as Figure 2 below.

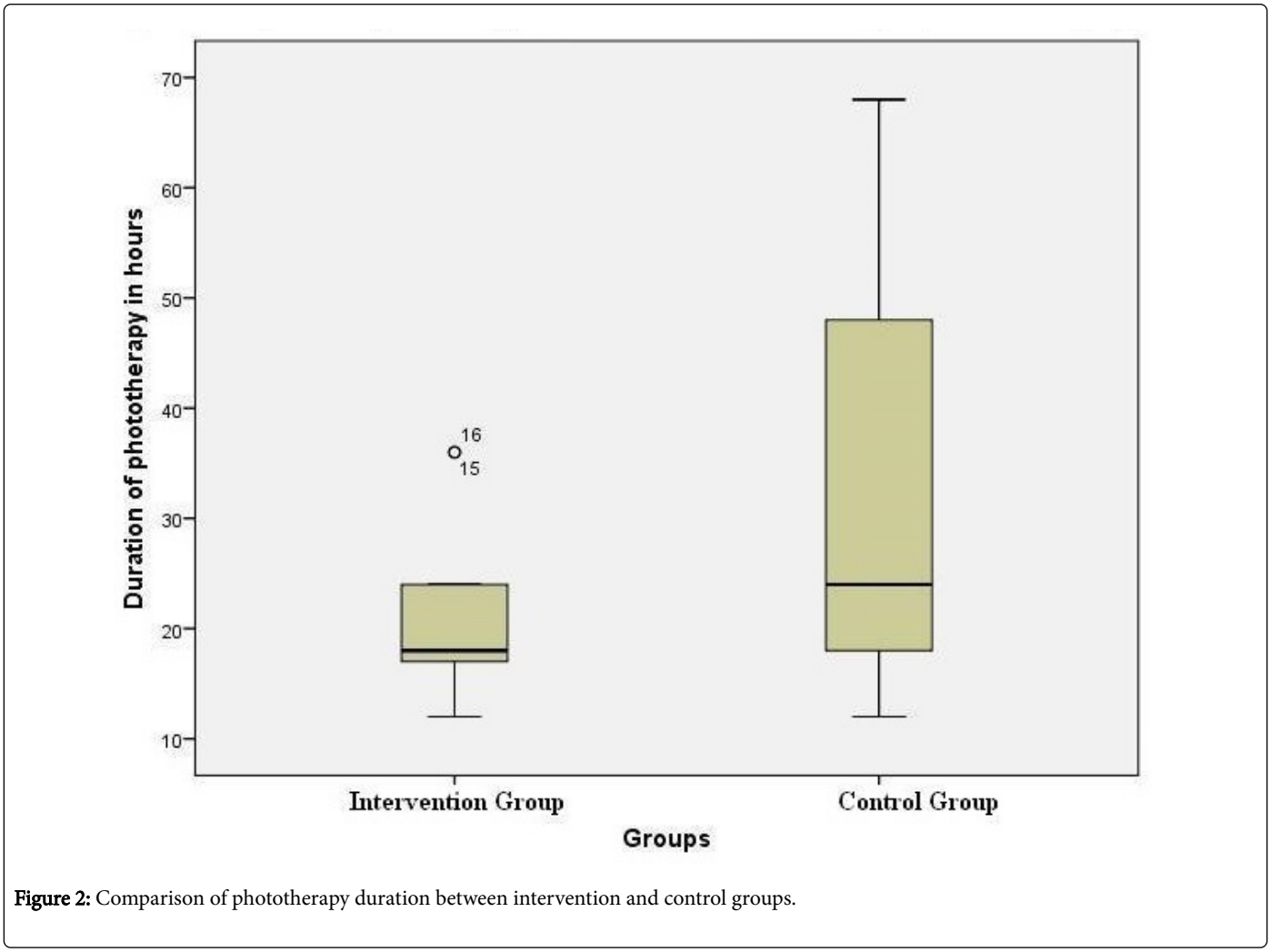

Figure 2: Comparison of phototherapy duration between intervention and control groups.

All newborns (both groups) were monitored for predefined adverse effects including vomiting, abdominal distension, intolerance to feeds and loose stools. In addition all newborns were monitored for any signs of sepsis. None of the babies from the two groups reported the above mentioned adverse effects or features suggestive of sepsis.

Discussion

This open label clinical trial examines the clinical efficacy of probiotic *Bacillus clausii* as a prophylactic therapy during the first three days of life, aimed at reducing the incidence of neonatal jaundice. The same also examines the impact of probiotic therapy on duration of phototherapy in indicated newborns as per the AAP guidelines. The study findings suggest that prophylactic *Bacillus clausii* therapy during first three days of life is effective in reducing the incidence of neonatal jaundice requiring phototherapy. There is a significant reduction in incidence of jaundice requiring phototherapy as per study results (44%).

Our study results are in agreement with four studies reported earlier that examined the therapeutic efficacy of probiotic in the management of neonatal jaundice [12-14,18].

Demirel et al. reported that the administration of probiotic (Saccharomyces boulardii) is effective in reducing the duration of phototherapy in very low birth weight (VLBW) newborns of gestational age ≤ 32 weeks with jaundice [12]. Liu et al. reported that therapy with probiotic (bifid triple viable) in term newborns (gestational age 38-42 weeks) with jaundice lowered the serum bilirubin levels significantly in the treatment group compared to the control group during assessments done on day four and seven of treatment [13]. Similarly Suganthi et al. reported significant differences in serum bilirubin levels between intervention group and control group on day three when term newborns were treated with probiotic ((Saccharomyces boulardii) for the first two days of life [14].

Mu-xue et al. reported that neonatal hyperbilirubinemia in the intervention group (probiotic group) was 33.33% while it was 57.14% in the control group [18]. The incidence of neonatal

hyperbilirubinemia in the intervention group was significantly lower than in the control group ($p<0.05$) in the study by Mu-xue et al. [18].

The current study results also suggest that prophylactic *Bacillus clausii* treatment in approximately 38 newborns (Number needed to treat, NNT 37.45) will prevent the occurrence of one episode of hyperbilirubinemia requiring phototherapy. This suggests that treating 1000 newborns with prophylactic *Bacillus clausii* will prevent the need for phototherapy in approximately thirty newborns. The study centre caters to approximately 5500 newborn babies every year [19]. Extrapolating the study results, we can expect approximately 147 newborns to avoid the need for phototherapy every year if exclusive prophylactic treatment of *Bacillus clausii* is instituted at the study centre. Approximately 6% of newborns require phototherapy in the community setting if no interventions are attempted to reduce the occurrence of hyperbilirubinemia. The study suggests that we can reduce the burden of hyperbilirubinemia significantly and save millions of newborn babies from the after effects and nuances of both hyperbilirubinemia and phototherapy.

Among newborns who required phototherapy as per the cut-offs stipulated by the AAP guidelines, prophylactic *Bacillus clausii* demonstrated a significant efficacy by means of reduction in the duration of phototherapy. The duration of phototherapy between the two groups was significantly different with lower values in the intervention (probiotic) group. Our results suggest that the short term and long term side effects of phototherapy including disruption of maternal infant interaction and risks associated with the exchange transfusion can be nullified with the prophylactic supplementation of probiotic *Bacillus clausii*. A shorter hospital stay and economic benefits due to avoidance of phototherapy/exchange transfusion are other probable advantages of this prophylactic probiotic therapy.

Study Limitations

The limitations of our study were the lack of simple randomization and data from a single centre. Simple randomization was not attempted due to concerns regarding" Herd effect". Alternatively, sequential allocation was done to overcome the "Herd effect". There are some possible confounding factors to the reported results like diet of the mother, amount of breast milk and the duration of lactation. Such variables were not measured in the study due to feasibility issues and limited time frame.

Conclusion

The study results have shown that administration of probiotic *Bacillus clausii* during neonatal period in term and preterm newborns with physiological jaundice is beneficial in reducing both need and duration of phototherapy. This prophylaxis should be considered in all newborns to reduce the burden of phototherapy related issues during this period.

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