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ORIGINAL ARTICLE

Comparison of probiotics and placebo in preventing necrotizing enterocolitis in preterm babies.

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ABSTRACT… Objective: To compare the probiotics with placebo in preventing the necrotizing enterocolitis (NEC) in preterm newborns. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Pediatrics Unit-1, Bahawal Victoria Hospital, Bahawalpur, Pakistan. **Period:** May 2022 to April 2023. **Material & Methods:** A total of 92 pre-term neonates with gestational age between 28-32 weeks gestation were included. Patients were randomly assigned to either probiotics or placebo groups (46 in each group). In probiotics group, probiotics named Bifidobacteria (hiflora/gutcare one sachet daily) were given for 5 days while in placebo group, neonates were given placebo for 5 days. All neonates were observed for feeding intolerance, abdominal distension, grossly bloody stools (naked eye blood in stool) and change in colour of skin of abdomen (erythema). Patients having three or more of these features in first 7 days of life were labeled as having NEC. **Results:** In a total of 92 newborns, maternal age ranged between 18 to 40 years with mean age of 29.30±5.27 years. The mean gestational age was 30.88±2.08 weeks while the mean weight was 2.06±0.71 kg. The NEC was found in 3 (6.52%) neonates in probiotics groups versus 11 (23.9%) in placebo group (p=0.020). In the probiotics group, NEC was found to have significant association with gestational age between 31-32 weeks (p=0.012), spontaneous vaginal delivery (p=0.028) and maternal educational status as educated (p=0.006). In the placebo group, NEC had significant association with birth weight between 1-1.5 kg (p=0.007). **Conclusion:** This study concluded that probiotics are better in preventing NEC in preterm neonates than placebo.

Key words: Bifidobacteria, Necrotizing Enterocolitis, Neonate, Preterm, Probiotics.

INTRODUCTION

Preterm labor is the condition that develop before 37th weeks of gestation when regular contraction of the uterus related to the change in cervix takes place.[1] The risk factors associated with preterm labor include current multi-fetal pregnancy, smoking, previous history of preterm labor and/or shortening of the cervical canal but previous premature birth is not necessarily related to preterm labor.[2] Among pregnancy related complications, preterm labor is a critical condition but it can be prevented if detected at early stage that.[3] In order to suppress uterine contractions, a wide range of medications have been recommended. Currently, beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donors, and oxytocin receptor antagonists are being used.[4] Considering gastrointestinal health, necrotizing enterocolitis (NEC) is the most frequently occurring emergency state among preterm neonates.[5,6]

To prevent NEC, researchers and health providers recommend probiotics, which ultimately improve child health significantly and prevent NEC development or at least reduce its risk, most importantly in those neonates who are preterm or with low birth weight (LBW).[7,8] Probiotics are live organisms, naturally found in the intestine and capable of producing lactic acid. Bifidobacteria and Lactobacilli are the most common bacteria mentioned in the literature to produce lactic acid. Mainly, these are responsible for the prevention of stomach against damaging effects of the acid and low surface tension of the bile as well.[9,10] Bin-Nun and colleagues conducted a randomized

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controlled trial on infants having very low birth weight (VLBW) and administered B. infanitis, S. thermophilis and B. bifidus in one group, whereas other was controlled. They noted that among infants who received probiotics supplementation, NEC incidence was reduced to 4% from 16.4% while the overall incidence was between 20-30% less.[11] A local study from Lahore among LBW preterm newborns revealed the prevalence of NEC in probiotics group as 4.7% versus 24.7% in placebo group.[12]

We performed this study to evaluate the role of probiotics among preterm babies regarding prevention of NEC. To the best of our knowledge, for Southern population of Punjab, no previous research is published to evaluate the benefits of probiotics for preventing NEC in preterm newborns. Local research and data was thought to be beneficial for developing the future protocols to prevent NEC in preterm neonates. The objective of this study was to compare the probiotics with placebo in preventing NEC in preterm newborns.

MATERIAL & METHODS

This randomized controlled trial was performed at the Department of Pediatrics Unit-1, Bahawal Victoria Hospital, Bahawalpur, Pakistan from May 2022 to April 2023. Approval from "Institutional Ethical Committee" (2094/DME/QAMC Bahawalpur) was obtained. Informed and written consents were acquired from parents or guardians of neonates studied. By using open epi software, the calculated sample size was 46 preterm neonates in each group considering 95% level of significance, 80% power of study and the frequency of NEC as 4.7% in probiotics group as compared to 24.7% in controlled group.[12] Simple random sampling technique was adopted.

Inclusion criteria were pre-term newborns of both genders, gestational age between 28-32weeks (on the basis of ballard scoring chart) having LBW (< 2.5 kg). All newborns presenting and admitted on day-1 of life and using both NG feed and/or bottle feed were included. Exclusion criteria were neonates weighing < 1 kg, on mechanical ventilatory support or those with congenital cyanotic heart diseases or having birth asphyxia, and/or persistent cyanosis and need of oxygen inhalation (as per clinical assessment).

At the time of enrollment, physical and clinical examination were performed and strict adherence to inclusion/exclusion criteria was performed. Gestational age and weight of each neonate was noted. Detailed medical history of the mother was also taken. Feeding started when the infant had stable vital signs, active bowel sound (no abdominal distension) and no bile/blood in the nasogastric tube. In cases that tolerated trophic feeding for the first 24 hours, gradual increase in the feeding volume was performed. Standard care was given to all admitted neonates. Neonates were randomly divided in two groups. Probiotics group was given probiotics named Bifidobacteria prophylactically (hiflora/gutcare one sachet daily) for 5 days and placebo group neonates were given placebo for 5 days. Probiotics group was given probiotics (one sachet) dissolved in 6 ml breast milk and then 3 ml given once daily for 5 days. Placebo group was given only breast milk. Patients were included in this study on first day of life. After 5 days of treatment, all neonates were evaluated for feeding intolerance, abdominal distension, grossly bloody stools (naked eye blood in stool) and change in colour of skin of abdomen (erythema) by consultant pediatrician having at least three years post fellowship experience of neonatology. Neonates having three or more of these features in first seven days of life were labeled as having NEC. A special proforma was developed to record study data.

Data was done using "Statistical Package for Social Sciences (SPSS)", version 26.0. Quantitative variables such as gestational age, weight and age of mother were presented as mean and standard deviation (SD) whereas qualitative variables like feeding intolerance, abdominal distention and baldy stools change in skin color of abdomen, mode of delivery, area of living and educational status of mother were presented in the form of frequency and percentages. Chi square test was used to compare the frequency of NEC in both groups. Effect modifiers like mode of delivery, gestational age, weight, age of mother, area of living and educational status of mother were

controlled through stratification. Post-stratification chi-square test was applied to see their effect on outcome (frequency of NEC) and p-value<0.05 was considered as significant.

RESULTS

In a total of 92 newborns, 50 (54.3%) were male. The mean maternal age and gestational age were 29.30±5.27 years and 30.88±2.08 weeks. The mean weight was 2.06±0.71 kg. Place of living was urban among 61 (66.3%) newborns. Table-I is showing comparison of baseline characteristics between both study groups and no statistically significant differences were observed (p>0.05).

The frequency of NEC was noted in 3 (6.5%) neonates of probiotics group versus 11 (23.9%) in placebo group while the difference was statistically significant (p=0.020) as shown in Figure-1.

Details about the stratification of study variables with respect to NEC in both study groups are shown in Table-II. In the probiotics group, NEC was found to have significant association with gestational age between 31-32 weeks (p=0.012), spontaneous vaginal delivery (p=0.028) and maternal educational status as educated (p=0.006). In the placebo group, NEC had significant association with birth weight between 1-1.5 kg (p=0.007).

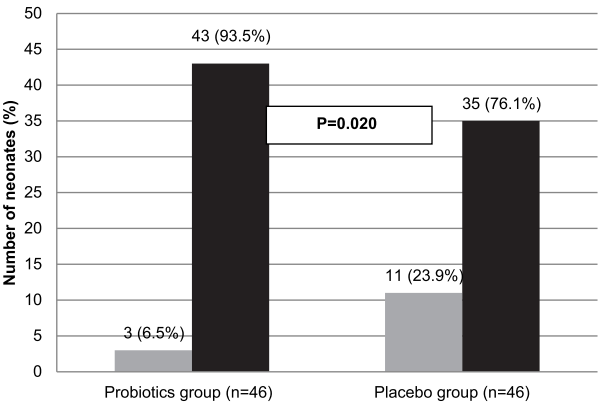

Figure-1. Necrotizing enterocolitis (NEC) in both study groups (N=92)

DISCUSSION

Preterm neonate lacks in the microbial diversity of the gut flora as compared to healthy term newborn baby while gastrointestinal abnormalities are more evident in the initial days of neonatal period.[13] In Cincinnati USA, the analysis of data of NEC patients collected for a period of more than 8 years revealed that occurrence of NEC was 18% presenting 12 temporal clusters.[14] We conducted this study to compare the probiotics with placebo in preventing NEC in preterm babies. In our study, frequency of NEC was found in 6.5% of the cases in probiotics group versus 23.9% in placebo group (p=0.020).

Characteristics		Probiotics Group (n=46)	Placebo Group (n=46)	P-Value
Gender	Male	26 (56.5%)	24 (52.2%)	0.676
	Female	20 (43.5%)	22 (47.8%)	
Maternal age (years)	18-30	27 (58.7%)	29 (63.0%)	0.669
	31-40	19 (41.3%)	17 (37.0%)	
Gestational age (weeks)	28-30	14 (30.4%)	13 (28.3%)	0.819
	31-32	32 (69.6%)	33 (71.3%)	
Weight (kg)	1-1.5	13 (28.3%)	10 (21.7%)	0.470
	1.6-2.5	33 (71.3%)	36 (78.3%)	
Place of living	Rural	14 (30.4%)	17 (37.0%)	0.508
	Urban	32 (69.6%)	29 (63.0%)	
Mode of delivery	Spontaneous vaginal delivery	31 (67.4%)	29 (63.0%)	0.662
	Cesarean section	15 (32.6%)	17 (37.0%)	
Maternal education	Uneducated	13 (28.3%)	9 (19.6%)	0.328
	Educated	33 (71.7%)	37 (80.4%)	

Table-I. Comparison of baseline characteristics (N=92)

Study Variables		Necrotizing Enterocolitis		P-Value
		Probiotics Group (n=3)	Placebo Group (n=11)	
Gender	Male	2 (66.7%)	5 (45.5%)	0.181
	Female	1 (33.3%)	6 (54.5%)	0.053
Maternal age (years)	18-30	1 (33.3%)	7 (63.6%)	0.029
	31-40	2 (66.7%)	4 (36.4%)	0.296
Gestational age (weeks)	28-30	1 (33.3%)	1 (9.1%)	0.957
	31-32	2 (66.7%)	10 (90.9%)	0.012
Weight (kg)	1-1.5	1 (33.3%)	6 (54.5%)	0.007
	1.6-2.5	2 (66.7%)	5 (45.5%)	0.282
Place of living	Rural	-	3 (27.3%)	0.098
	Urban	3 (100%)	8 (72.7%)	0.065
Mode of delivery	Spontaneous vaginal delivery	2 (66.7%)	8 (72.7%)	0.028
	Cesarean section	1 (33.3%)	3 (27.3%)	0.349
Maternal education	Uneducated	1 (33.3%)	1 (9.1%)	0.774
	Educated	2 (66.7%)	10 (90.9%)	0.006

Table-II. Stratification of study variables with respect to necrotizing enterocolitis in both study group (N=14)

Hoyos AB investigated NEC incidence in NICU among infants after administering B. infantis and L. cidiphilius.[15] Significantly better outcome was observed in the probiotic prophylaxis group (P <0.0002) as compared to the historic control group. Mortality rate in probiotic prophylaxis group (p<0.005) was also significantly lower than historic control group. Samanta et al analyzed 186 preterm VLBW neonates for a period of 6 months. The prevalence of NEC in probiotic group was 5.5% versus 15.8% in control group (p=0.032).[16] Significant reduction in NEC by probiotics was observed in a meta-analysis but it did not reduce the incidence of intraventricular hemorrhage.[17]

A study from Dhaka showed the incidence of NEC as 6% in prebiotics group when compared to 18% in control group (p<0.05).[18] In accordance to the findings of our study, Lin et al reported that the occurrence of NEC was lower in the probiotics group than in control group (1.1% vs. 5.3%; p=0.04).[19] Contrary to the findings of this study, Sari et al found insignificant difference in the prevalence of NEC between probiotics group and control group (5.8% vs. 9%, p=0.447).[20] Probably, this could have been because of the fact that the probiotics used in that study was of single strain while the present study included multiple strains of probiotics. As neonates with extremely LBW (ELBWs) are the population at highest-risk for developing NEC, therefore the effectiveness of probiotics to reduce NEC in VLBW neonates still needs further evaluation.

Among preterm neonates, there are numerous factors such as gestational age, delivery mode, diet, and antibiotic coverage, which affect gut microbiota development.[21] These factors have significantly confounding prospective in probiotics and NEC correlation. It is already established that NEC development risk among those neonates who take breastfeeding (mother or donor) is lower in comparison with the neonates who take formula feed, while gut microbiota is affected by caesarean delivery.[22]

The present study along with others discussed above show that probiotic prophylaxis has an important role to play in NEC prevention. Among preterm babies, benefits of probiotic prophylaxis are evident so by using probiotics in such neonates, we may decrease NEC incidence and its associated morbidity and mortality.

CONCLUSION

This study concluded that probiotics are better in preventing necrotizing enterocolitis in preterm neonates when compared to placebo. Prophylactic probiotics should be used routinely in preterm neonates for reducing the incidence of necrotizing enterocolitis.

REFERENCES

1. Samuel TM, Sakwinska O, Makinen K, Burdge GC, Godfrey KM, Silva-Zolezzi I. **Preterm birth: A narrative review of the current evidence on nutritional and bioactive solutions for risk reduction.** Nutrients. 2019; 11(8):1811. doi:10.3390/nu11081811

2. Halimi AA, Safari S, Parvareshi HM. **Epidemiology and related risk factors of preterm labor as an obstetrics emergency.** Emerg (Tehran). 2017; 5(1):e3.

3. Munim S, Islam Z, Zohra N, Yasmin H, Korejo R. **Guidelines on prevention of preterm birth.** J Matern Fetal Neonatal Med. 2022; 35(25):9527-9531. doi:10.1080/14767058.2022.2045582

4. da Fonseca EB, Damião R, Moreira DA. **Preterm birth prevention.** Best Pract Res Clin Obstet Gynaecol. 2020; 69:40-49. doi:10.1016/j.bpobgyn.2020.09.003

5. Chekole TB, Aynalem MA, Tefera ZB, Fisha AG, Kassaw A, Walle BG, et al. **Necrotizing enterocolitis and its predictors among preterm neonates admitted in neonatal intensive care units of Gurage Zone Public Hospitals, Southwest Ethiopia, 2021.** Pediatric Health Med Ther. 2022; 13:95-102. doi:10.2147/PHMT.S353663

6. Ergenekon E, Tayman C, Özkan H. **Turkish neonatal society necrotizing enterocolitis diagnosis, treatment and prevention guidelines.** Turk Arch Pediatr. 2021; 56(5):513-524. doi:10.5152/TurkArchPediatr.2021.21164

7. Beghetti I, Panizza D, Lenzi J, Gori D, Martini S, Corvaglia L, et al. **Probiotics for preventing necrotizing enterocolitis in preterm infants: A network Meta-Analysis.** Nutrients. 2021; 13(1):192. doi:10.3390/nu13010192

8. Patel RM, Underwood MA. **Probiotics and necrotizing enterocolitis.** Semin Pediatr Surg. 2018; 27(1):39-46. doi:10.1053/j.sempedsurg.2017.11.008

9. Gray KD, Messina JA, Cortina C, Owens T, Fowler M, Foster M, et al. **Probiotic use and safety in the neonatal intensive care unit: A matched cohort study.** J Pediatr. 2020; 222:59-64.e1. doi:10.1016/j.jpeds.2020.03.051

10. Underwood MA, Umberger E, Patel RM. **Safety and efficacy of probiotic administration to preterm infants: Ten common questions.** Pediatr Res. 2020; 88(Suppl 1):48-55. doi:10.1038/s41390-020-1080-6

11. Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M, et al. **Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates.** J Pediatr. 2005; 147(2):192-196. doi:10.1016/j.jpeds.2005.03.054

12. Hussain M, Jabeen S, Subhani RH. **Role of probiotics in prevention of necrotizing enterocolitis in preterm low birth weight neonates.** Pak J Med Health Sci. 2016; 10(2):455-457.

13. Yao Y, Cai X, Ye Y, Wang F, Chen F, Zheng C. **The Role of Microbiota in Infant Health: From Early Life to Adulthood.** Front Immunol. 2021; 12:708472. doi:10.3389/fimmu.2021.708472

14. Meinzen-Derr J, Morrow AL, Hornung RW, Donovan EF, Dietrich KN, Succop PA. **Epidemiology of necrotizing enterocolitis temporal clustering in two neonatology practices.** J Pediatr. 2009; 154(5):656-661. doi:10.1016/j.jpeds.2008.11.002

15. Hoyos AB. **Reduced incidence of necrotizing enterocolitis associated with enteral administration of Lactobacillus acidophilus and Bifidobacterium infantis to neonates in an intensive care unit.** Int J Infect Dis. 1999; 3(4):197-202. doi:10.1016/s1201-9712(99)90024-3

16. Samanta M, Sarkar M, Ghosh P, Ghosh Jk, Sinha Mk, Chatterjee S. **Prophylactic probiotics for prevention of necrotizing enterocolitis in very low birth weight newborns.** J Trop Pediatr. 2009; 55(2):128-131. doi:10.1093/tropej/fmn091

17. Sun J, Marwah G, Westgarth M, Buys N, Ellwood D, Gray PH. **Effects of probiotics on necrotizing enterocolitis, sepsis, intraventricular hemorrhage, mortality, length of hospital stay, and weight gain in very preterm infants: A meta-analysis.** Adv Nutr. 2017; 8(5):749-763. doi:10.3945/an.116.014605

18. Mannan MA, Shahidullah M, Barua CC, Nahar Z, Barua S. **Effect of probiotics on necrotizing enterocolitis in very low birth weight infants.** J Chittagong Med Coll Teacher Assoc. 2010; 21(1):30-33. doi:10.3329/jcmcta.v21i1.7667

19. Lin HC, Su BH, Chen AC, Lin T, Tsai C, Yeh T, et al. **Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants.** Pediatrics. 2005; 115(1):1-4. doi:10.1542/peds.2004-1463

20. Sari FN, Dizdar EA, Oguz S, Erdeve O, Uras N, Dilmen U. **Oral probiotics: Lactobacillus sporogenes for prevention of necrotizing enterocolitis in very low-birth weight infants: A randomized, controlled trial.** Eur J Clin Nutr. 2011; 65:434-9.

21. Fouhy F, Watkins C, Hill CJ, O'Shea C, Nagle B, Dempsey EM, et al. **Perinatal factors affect the gut microbiota up to four years after birth.** Nat Commun. 2019; 10(1):1517. doi:10.1038/s41467-019-09252-4

22. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. **The infant microbiome development: Mom matters.** Trends Mol Med. 2015; 21(2):109-117. doi:10.1016/j.molmed.2014.12.002

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4	Muhammad Anwar	Supervision, Methodology, Critical Revisions.	
5	Asif Javeed	Literature Review, Discussion.	