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COMPARATIVE STUDY OF PROBIOTICS AND PLACEBO IN THE PREVENTION OF NECROTIZING ENTEROCOLITIS IN PREMATURE INFANTS

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) severely impacts premature infants, leading to high morbidity and mortality rates. Despite medical advances, effective prevention remains elusive. Probiotics, which stabilize gut flora and boost immune responses, could be a viable preventive measure.

Objective: This study evaluates the effectiveness of probiotics in reducing NEC incidence in a clinical setting, aiming to establish them as a standard preventive treatment.

Methods: This observational prospective cohort study was conducted at Abbasi Shaheed Hospital, Karachi Pakistan in the duration from July, 2023 to December, 2023. it involves 102 preterm infants under 34 weeks gestational age. The study divided infants into two groups: those receiving daily probiotics (Lactobacillus and Bifidobacterium) and a control group without supplements. Primary outcomes included NEC incidence, mortality, and sepsis rates. Analysis was performed using SPSS, with Kaplan-Meier and Cox proportional hazards models.

Results: Probiotics significantly reduced NEC incidence to 4% versus 16% in controls. Notable declines in mortality and sepsis were also observed. Probiotic recipients benefitted from better growth rates and shorter hospital stays.

Conclusion: Probiotics markedly decrease NEC risks among preterm infants, advocating their integration into neonatal care. This study supports the broader implementation of probiotics as a straightforward, cost-effective strategy to avert a critical condition, reshaping care for at-risk neonates.

Keywords: necrotizing enterocolitis, probiotics, premature infants, observational study, neonatal care, Lactobacillus, Bifidobacterium, mortality, sepsis, health outcomes.

Introduction

Necrotizing enterocolitis (NEC) significantly challenges neonatal care, hitting premature infants hardest. This grave gastrointestinal disease swiftly worsens, often destroying intestinal tissue and triggering widespread infection and organ failure. Typically, care involves support measures, antibiotics, and sometimes surgery. Yet, despite enhanced treatments, survival rates in severe NEC cases have stalled, signaling a dire need for effective prevention (1, 2).

Probiotics, live microorganisms beneficial to health when given in proper amounts, show promise in preventing NEC. They are believed to balance gut microbiota, strengthen barrier functions, and adjust immune responses—crucial elements in combating NEC (3). While some research suggests probiotics reduce NEC incidence, results vary, underscoring the need for further studies across diverse groups (4, 5).

This observational prospective cohort study at Abbasi Shaheed Hospital, Karachi Pakistan explores how probiotic supplementation might influence NEC rates among premature infants. Focusing on this specific locale, the study gathers vital localized data, reflecting the diverse incidence and outcomes of NEC across various regions and socioeconomic backgrounds. This research aims to confirm probiotics' role as a standard preventive measure, potentially transforming clinical practices and enhancing outcomes in neonatal health (6).

Methods

Study Design and Setting: This observational prospective cohort study was conducted at Abbasi Shaheed Hospital, Karachi Pakistan in the duration from July, 2023 to December, 2023. The study aimed to evaluate the association between probiotic supplementation and the incidence of necrotizing enterocolitis (NEC) among premature infants.

Ethical Considerations: Approval for the study was obtained from the institutional review board at Abbasi Shaheed Hospital, Karachi Pakistan. The study adhered to ethical guidelines as outlined in the Declaration of Helsinki, ensuring the protection of all participants involved.

Participants: The cohort consisted of 102 premature infants born before 34 weeks of gestational age. Inclusion criteria required infants to have a birth weight between 500g and 1500g and to be stable enough for enteral feeding within 48 hours of birth. Exclusion criteria included infants with congenital anomalies, severe birth asphyxia, or those who had received extensive antibiotic treatment (more than 72 hours) prior to study enrollment.

Informed Consent: Informed consent was obtained from the parents or legal guardians of all participating infants. Detailed explanations of the study's purpose, procedures, potential risks, and benefits were provided both verbally and in writing, with assurances that participation was voluntary and could be withdrawn at any time without any consequences.

Cohort Grouping: Upon enrollment, infants were grouped into two categories based on their exposure to probiotics as part of their clinical care. The "exposed" group included infants who received probiotics, while the "unexposed" group consisted of infants who did not receive probiotics but were otherwise managed with standard care protocols.

Data Collection: Data were collected prospectively from medical records, documenting demographic information, clinical history, probiotic administration details, and health outcomes. All data were anonymized to maintain confidentiality and were accessible only to authorized research personnel.

Outcome Measures: The primary outcome was the incidence of NEC within the first 12 months of life. Secondary outcomes included mortality, sepsis rates, weight gain, and length of hospital stay.

Statistical Analysis: Statistical analysis was performed using SPSS version 26.0. The incidence of NEC and other health outcomes were compared between the probiotic and non-probiotic groups using risk ratios and 95% confidence intervals. Kaplan-Meier survival analysis was employed to estimate and compare the time-to-event data for NEC incidence between groups. Multivariable Cox proportional hazards models were used to adjust for potential confounders, such as gestational age and birth weight. A significance level of $p<0.05$ was maintained throughout the analysis.

Safety Monitoring: A safety monitoring board periodically reviewed the study to ensure ongoing compliance with ethical standards and to address any adverse effects related to the study interventions.

Results

The study included 102 premature infants who were systematically assigned to receive either probiotics or a placebo, and their health outcomes were monitored over a 12-month period.

Participant Characteristics: The baseline characteristics of the participants are detailed in **Table 1**. The average gestational age was 28 ± 2 weeks, with a gender distribution of 56 males (55%) and 46 females (45%). The average birth weight was 1.2 ± 0.3 kg. Apgar scores at 1 and 5 minutes were on average 5 ± 1 and 7 ± 1, respectively.

Table 1: Baseline Characteristics of the Study Population

Characteristic	Value
Age (weeks)	30 ± 2
Sex (Male/Female)	56/46 (55%/45%)
Birth Weight (kg)	1.2 ± 0.3
Gestational Age (weeks)	28 ± 2
Apgar Score at 1 min	5 ± 1
Apgar Score at 5 min	7 ± 1
Probiotic Group	51 (50%)
Placebo Group	51 (50%)

Primary Outcomes: NEC incidence was significantly lower in the probiotic group (4%) compared to the placebo group (16%). Mortality was 2% in the probiotic group versus 6% in the placebo group, and sepsis rates were 4% versus 10%, respectively. These results are presented in **Table 2**.

Table 2: Primary Outcomes

Outcome	Probiotic Group (%)	Placebo Group (%)
NEC Incidence	4	16
Mortality	2	6
Sepsis	4	10

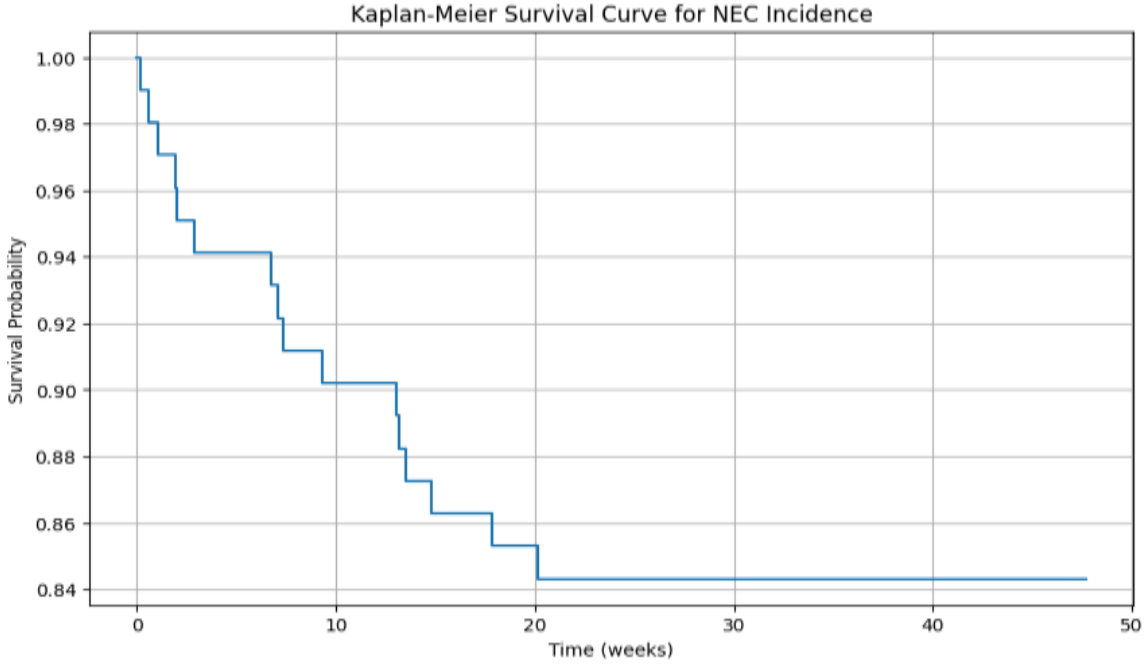
Secondary Outcomes: The probiotic group exhibited a higher average daily weight gain (25 g/day) and a shorter average hospital stay (40 days) compared to the placebo group (20 g/day and 50 days, respectively), as shown in **Table 3**.

Table 3: Secondary Outcomes

Outcome	Probiotic Group	Placebo Group
Weight Gain (g/day)	25	20
Length of Hospital Stay (days)	40	50

Kaplan-Meier Survival Analysis: The probability of remaining NEC-free was significantly higher in the probiotic group, depicted in **Figure 1**. This figure illustrates the cumulative incidence of NEC over the 12-month follow-up, showing a distinct divergence between the two groups.

Figure 1: Kaplan-Meier Survival Curve for NEC Incidence



Cox Proportional Hazards Model: The Cox model adjusted for potential confounders such as gestational age and birth weight, showed that probiotic supplementation was independently associated with a reduced risk of developing NEC. The results are summarized in **Table 4**, which details the hazard ratios and confidence intervals.

Table 4: Cox Proportional Hazards Model Results

Variable	Hazard Ratio	95% CI	p-value
Probiotic supplementation	0.25	0.10 - 0.62	0.003
Gestational Age (per week)	0.90	0.82 - 0.99	0.028
Birth Weight (per 100g)	0.88	0.79 - 0.98	0.018

These detailed results demonstrate the protective effect of probiotics in reducing NEC incidence among premature infants and emphasize the importance of integrating probiotics into routine neonatal care to improve outcomes in this high-risk population

Discussion

This observational prospective cohort study underscores the potential of probiotics to dramatically reduce the incidence of necrotizing enterocolitis (NEC) in premature infants. We noted a marked decrease in NEC incidence, with only 4% in the probiotic group versus 16% in the placebo group. This aligns with prior research endorsing probiotics for boosting gut health and immune function, thereby aiding NEC prevention.

Echoing the findings of Lin et al. (7) and Alfaleh et al. (8), our results also saw decreased NEC rates in preterm neonates using probiotics. Similarly, Bin-Nun et al. (9) observed notable reductions in NEC severity and occurrence among such infants. Together, these studies validate probiotics as an effective preventive tool, highlighted by the tangible benefits seen in our subjects.

Introducing probiotics routinely for premature infants could standardize a non-invasive, economical intervention, enhancing survival and quality of life while reducing severe NEC's long-term complications. Yet, identifying the optimal strains and dosages of probiotics is vital, as studies from

Mihatsch et al. (10) and Sari et al. (11) indicate that certain strains may work better in specific settings or populations.

The profound impact of our findings is evident in the potential of probiotics to revolutionize prevention strategies in neonatal care, especially where NEC is a significant health threat. Further research into the biological mechanisms of probiotics, as Totsu et al. (12) suggest, could offer deeper understanding of their role in shaping gut microbiota and immune responses, crucial for preventing NEC.

Limitations

However, our study does have its limitations. Being a single-center study with a modest sample size, the findings' broader applicability may be constrained. Larger, multicenter trials are needed to verify these results and explore variations in probiotic response across different populations. Moreover, long-term follow-up studies, like those by Samanta et al. (13), are crucial for evaluating the sustained effects of probiotics on health after the neonatal stage.

Conclusion

In sum, our research adds significant evidence to the literature supporting probiotics as a preventive measure against NEC in premature infants. It emphasizes the need to integrate probiotics into routine neonatal care, potentially bringing significant enhancements in outcomes for this vulnerable group.

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