RESEARCH ARTICLE

Current Treatment Challenge for Neonatal Sepsis

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ABSTRACT

Background & Aim: Probiotics have been known to modulate the immune system and help reduce the risk of infections in infants. This study aims to investigate the impact of probiotics on term babies' health parameters. However, their effectiveness in term babies is still under investigation.

Results: A total of 170 cases were analyzed and reported in the study, focusing on the relationship between probiotics and neonatal sepsis in infants under 28 days old. The analysis involved examining the efficacy of probiotic supplementation in reducing the risk of neonatal sepsis. Parameters such as neutrophil count, CRP levels, and the duration of hospital stay exhibit notable variations between the two groups. However, no significant differences are observed in platelet count and WBC, ultimately indicating the therapeutic efficacy of probiotics.

Conclusion: The findings suggest that probiotics may have a beneficial role in enhancing certain health outcomes in term babies. The significant differences in neutrophil count, CRP levels, and hospital stay duration evidences this. Further research is needed to understand the mechanisms underlying these effects and to optimize probiotic interventions in this population.

Keywords: Probiotics, Neonatal sepsis, Term Babies, NICU, Pediatrics.

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INTRODUCTION

Neonatal sepsis, a critical medical condition affecting infants below 28 days old[1], arises from an exaggerated immune response to infection[2,3], leading to widespread inflammation and organ dysfunction[4]. It can be caused by bacterial[5], viral[6], or fungal[7] pathogens and presents as early-onset[8] (within 72 hours of birth)[9] or late-onset sepsis[10] (after 72 hours of birth)[11]. Symptoms vary widely and include respiratory distress[12], gastrointestinal issues[2], and low blood pressure[10,13,14]

Antibiotics are commonly used to treat neonatal sepsis but face challenges such as resistance due to overuse and incomplete courses.[5,6] Probiotics, live microorganisms with potential health benefits, are being explored as a complementary approach.[3,4] The World Health Organization defines probiotics as microorganisms that confer health benefits when administered adequately.[15,16] Common probiotic genera[17] include Bifidobacterium[4] and Lactobacillus species[4], known for their competitive exclusion of pathogens, enhancement of gut barrier function[16], immunomodulation[2], and synthesis of neurotransmitters.[2] By outcompeting harmful microbes for resources and binding sites in the gut, probiotics help maintain a balanced microbial environment.[3] Our study aims to assess the effectiveness of probiotics in preventing and managing neonatal sepsis by analyzing clinical data from neonates receiving probiotics compared to controls. We seek to contribute valuable insights to neonatal medicine and improve clinical practices for better outcomes in vulnerable infants.

METHODOLOGY

MATERIALS AND METHODS

As part of our study process, we ensure to obtain informed consent from parents or legal guardians, thoroughly explaining the study objectives, procedures, risks, and benefits. This helps in ensuring transparency and understanding among all involved parties.We oversee the collection of baseline data, including demographic information, gestational age, birth weight, hospital stay duration, and relevant medical reports. This data forms the foundation of our study and aids in accurate analysis. For the probiotic interventions, we have selected by alternatively allocating neonates to either Group A (standard care) or Group B (probiotic supplementation). This randomization process is crucial for unbiased results.Throughout the study, we, diligently monitor adherence to interventions and closely observe for any potential adverse effects. This proactive approach helps in maintaining the safety and integrity of our research outcomes. By adhering to ethical guidelines, utilizing a

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Table 1: Analysis of Gender Distribution, Mode of Delivery, Sepsis Types, and Birth Weight in Neonates

Parameters	Group 1		Group2		Total	*P*-value[a]
	Male child (%)	Female child (%)	Male child (%)	Female child (%)		
			Gender			
No of cases	52(61.90)	32(38.09)	38 (44.18)	48(55.81)	170	0.015
			Mode of delivery			
Normal Vaginal Delivery	26(50)	14(43.7)	14(36.8)	10(20.8)	64(37.6)	0.008
Lower Segment Cesarean Section	26(50)	18(56.2)	24(63.1)	38(79.1)	106(62.3)	
Total	52	32	38	48	170	
			Types of Sepsis			
Early-onset sepsis	30(57.6)	20(62.5)	32(84.2)	29(60.4)	111(65.2)	0.120
Late-onset sepsis	22(42.3)	12(37.5)	6(15.7)	19(39.5)	59(34.7)	
Total	52	32	38	48	170	
			Birth weight			
Low birth weight	1(1.9)	1(3.1)	18(47.3)	9(18.7)	29(17)	<0.005
Appropriate for gestational age	51(98.0)	31(96.8)	20(52.6)	39(81.2)	141(82.9)	
Total	52	32	38	48	170	

Independent sample T-test

rigorous study design, and employing standardized data collection methods, the study aimed to provide valuable insights into the efficacy of probiotics in managing neonatal sepsis.

Protocol

Ethical committee approval was obtained before commencing the study. Two groups were formed: Group 1 received sepsis treatment without probiotics, while Group 2 received probiotic supplementation, specifically, Lactobacillus rhamnoses GG, a commercially available probiotic. Patient demographics, including gestational age, birth weight, hospital stay duration, and relevant medical history, were thoroughly collected. Complete blood count (CBC) reports and other essential data were also meticulously gathered. Statistical analysis was conducted using SPSS software to compare various parameters between the groups and evaluate the effect of probiotics in our study. We also employed an independent sample t-test to compare specific parameters between the two groups and further assess the effectiveness of probiotics in neonatal sepsis management.

Study site

The prospective interventional cohort study was conducted at Siddhartha Children's and Multi-specialty Hospital in Rajahmundry, Andhra Pradesh, A Pediatric hospital specializing in the care of infants and children.

Study duration

The study spanned a period of 6 months, running from January 2024 to June 2024.

Study design

This study adopted a prospective cohort design with randomized allocation. It focused on infants as the target population.

Study population

Initially, there were 195 cases considered for the study. After applying inclusion criteria, 170 cases were eligible and included. The remaining 25 cases were excluded due to not meeting the predetermined criteria, ensuring the study's validity.

Data collection method

Data were gathered from different sources such as patient case sheets, parental consent forms, and laboratory reports. Baseline data, physical examination findings, symptoms, and laboratory reports were systematically collected.

Table 2: Comparison of Age in Days and Hospitalization Duration Across Groups

Parameter	Group1	%	Group2	%	Total	%	*P*value[a]
			Age in days				
1-7	51	60.7	62	72	113	66.47	0.237
8-14	9	10.7	3	3.4	12	7.05	
15-21	15	17.8	15	17.4	30	17.64	
22-28	9	10.7	6	6.9	15	8.82	
Total	84		86		170		
			Number of days in the hospital				
3-5days	39	45.3	67	79.7	106	62.3	<0.005
6-7days	24	27.9	1	19.0	40	23.5	
8-10days	17	19.7	3	3.5	20	11.7	
>10days	4	4.6	0	0	4	2.3	
Total	84		86		170		

Independent sample T-test

Table 3: Comparative Analysis of Clinical Parameters

Parameter	Group1	%	Group2	%	P value[a]
White blood cells (cells/µl)					
5000-12000[b]	22	25.5	7	8.3	
>12000	62	72.9	79	94.0	0.990
Mean	15971		15960		
Neutrophils (%)					
<40%	2	2.3	6	7.1	
40-60%	45	52.3	53	63.0	0.005
>60%	37	43.0	27	32.1	
Mean	60		55		
C-reactive protein (mg/dl)					
>10[c]	84	100	86	100	<0.005
Mean	39		25		
Platelet count(cells/µl)					
<150	8	9.3	9	10.7	
150-200	3	3.4	2	2.3	
200-250	13	15.11	17	20.2	0.529
250-300	37	43.0	31	36.9	
2>300	23	26.7	27	32.1	
Mean	261		267		

Independent sample T-test
No Patients Had A WBC Count ≤ 4999 Cells/ml.
No Patients Had A CRP Level ≤ 10 Mg/Dl.

Follow-ups were conducted as per the study requirements.

Study criteria

Inclusion criteria encompassed neonates who are admitted in the neonatal intensive care unit aged less than 28 days and term babies. Exclusion criteria involved neonates with severe congenital anomalies or immune disorders, age exceeding 28 days, non-pediatric patients, those lost to follow-up, preterm babies, outpatients, and cases with inadequate data.

Statistical analysis

we employed Excel for data organization and initial analysis, including basic calculations and visualizations.
Then, we used SPSS v22 for advanced statistical tests like t-tests and, calculating p-values for result significance. This dual approach ensured comprehensive and reliable insights for the study.

RESULTS

Comparative analysis of neonatal demographic and clinical characteristics

Our study undertook a comparative analysis of various parameters between Groups 1 and 2 to discern disparities and potential correlations. Initially, we scrutinized the gender distribution within each group. Group 1 exhibited 52 male infants (61.90%) and 32 female infants (38.09%), while Group 2 consisted of 38 male infants (44.18%) and 48 female infants (55.81%), totaling 90 male (52.94%) and 80 female (47.05%) infants among 170 cases. This gender distribution exhibited statistical significance (*P*-value = 0.015), indicating a slight male predominance.

Subsequently, we assessed the delivery modes across the cases. Out of 170 births, 40 neonates (47.6%) were delivered via normal vaginal delivery (NVD) in Group 1, and 24 neonates (27.9%) were delivered via NVD in Group 2. Moreover, 44 neonates (52.3%) were delivered via lower segment cesarean section (LSCS) in Group 1, and 62 neonates (72%) in Group 2. The statistical analysis revealed a notable difference in delivery modes between the groups (*P*-value = 0.008), with Group 1 having a higher percentage of NVDs (47.6%) and Group 2 having a higher rate of LSCS births (72%).

Our investigation also encompassed the analysis of sepsis types in each group, highlighting a higher prevalence of early-onset neonatal sepsis (EONS) than late-onset sepsis (LOS) overall. Specifically, EONS exhibited a higher prevalence in males (62 cases, 68.8%) than in females (49 cases, 61.2%), while LOS was more prevalent in females (31 cases, 38.7%) than in males (28 cases, 31.1%).

Further dissecting the data by group, in Group 1, EONS predominated in males (30 cases, 35.7%) compared to

Table 4: Comparative Analysis of Neonatal Clinical Parameters: Mean and Standard Deviation

Parameters	Group 1(n = 84)		Group 2(n = 86)	
	Mean	Std. Deviation	Mean	Std. Deviation
Avg White Blood Cells	15,971.10	6,045.87	15960.21	5176.58
Avg Neutrophil	59.64	9.596	55.43	9.75
Avg C-reactive Protein	38.88	33.064	25.12	8.31
Avg Platelet	261.20	60.153	267.36	67.052
Number of Days in The Hospital	6.73	2.566	5.55	1.155

Table 5: Comparative Statistical Analysis of Clinical Parameters

Parameters	Group 1 Mean±std. Deviation	Group 2 Mean±std. Deviation	*P*-value[a]
Age	8.18±8.57	6.69±7.82	0.237
Gender	1.62±0.48	1.44±O.5	0.015
Types of sepsis	1.40±0.494	1.29±0.45	0.120
Mode of delivery	1.52±0.50	1.17±0.45	0.008
Birth weight	1.98±1.53	1.69±046	<0.005
White blood cell	15971.1±6045.8	15960.2±5176.58	0.990
Neutrophil	59.64±9.596	55.43±9.75	0.005
Platelet	261.2±60.15	267.36±67.05	0.529
C-reactive protein	38.88±33.06	25.12±8.31	<0.005
Number of days in the hospital	6.73±2.56	5.55±1.15	<0.005

Independent sample T-test

females (20 cases, 23.8%), whereas LOS was more prevalent in males (22 cases, 26.1%) than in females (12 cases, 14.2%). Conversely, in Group 2, EONS was more prevalent in males (32 cases, 37.2%) than in females (29 cases, 33.7%), and LOS was more prevalent in female children (19 cases, 22%) than in males (6 cases, 6.97%). While these patterns differed, the *P*-value for this comparison was 0.120, indicating a lack of statistical significance.

Additionally, we examined birth weight categories between both groups. Group 1 had one case (1.9%) of low birth weight (LBW) and 51 cases (98.0%) of appropriate for gestational age (AGA), while Group 2 had 18 cases (47.3%) of LBW and 20 cases (52.6%) of AGA. This difference in birth weight groups was highly significant, with a *P*-value below 0.005. For more detailed insights, please refer to the following Table 1

Analysis of age in days and hospitalization duration across groups

The data depicted in Table 2 below provides an analysis of the relationship between Age in days and Number of days in the hospital across different groups. In the age of 1-7 days, there are a total of 113 cases, with 111 cases attributed to EONS, accounting for 66.47% of all cases. Among these, 51 cases (60.7%) are attributed to our group, and 62 cases (72%) belong to the other group. For the age group of 8-14 days, comprising 12 cases (7.05%), our group accounts for 9 cases (10.7%), and the other group has 3 cases (3.4%). In the 15-21 days age range, encompassing 30 cases (17.64%), the distribution is equitable between our group and the other group. Likewise, for the 22-28 days range with 15 cases (8.82%), our group has 9 cases (10.7%), and the other group has 6 cases (6.9%). However, the variance in this age group does not hold statistical significance at the conventional threshold of 0.05.

When examining the hospitalization duration between our group and the other group, where the other group received probiotics, intriguing patterns emerged. In our group, 45.3% of cases had a hospital stay duration of 3-5 days. Conversely, in the other group, this percentage significantly escalated to 79.7%. Conversely, for hospital stay durations of 6-7 days and 8-10 days, our group exhibited higher percentages, implying longer hospitalization periods. This disparity underscores the potential advantages of probiotics in reducing hospital stay durations, particularly in cases with shorter durations, thereby showcasing the efficacy of probiotics in clinical contexts.

Clinical parameter comparison in probiotic intervention

Upon scrutinizing the data, we discern fluctuations in parameters such as White Blood Cell (WBC) counts, neutrophil levels, C-reactive protein (CRP) levels, and platelet counts between Group 1 and Group 2. In our study, we referred to the work of Hussin Attia et al. as a basis for common diagnostic indices and markers used in the assessment of various health conditions. These indices include polymerase chain reaction (PCR), interleukin (IL), tumor necrosis factor (TNF), & a cluster of differentiation (CD) markers. Specifically, we focused on essential markers such as total leukocyte counts, C-reactive protein (CRP), neutrophil count, and platelet count.[10]

Let's delve into the nuanced insights garnered from this comparative analysis: Firstly, regarding WBC counts, both groups showcase diverse distributions across distinct ranges. Group 1 exhibits a significant proportion (72.9%) of cases with WBC counts surpassing 12000, whereas Group 2 registers a higher percentage (94.0%) within this range. The MEAN WBC count for Group 1 stands at 15971, while for Group 2, it slightly dips to 15960, indicating a marginal disparity between the two cohorts. The calculated P-value of 0.009 implies a lack of substantial statistical variance in WBC count distributions.

Transitioning to neutrophil levels, a discernible discrepancy surfaces in the distributions across delineated categories (<40%, 40-60%, and >60%) between the two groups. Group 2, administered with probiotics, manifests a heightened percentage in the 40-60% range compared to Group 1. The *P* -P-value of 0.005 underscores a statistically significant distinction in neutrophil count distributions between these cohorts. In this study, we drew upon the insights from Renato Soibelmann Procianoy et al[18], to explore the significance of serum C-reactive protein (CRP) as a pivotal marker for evaluating illness severity and tracking treatment responses. In terms of CRP levels, a prevalent occurrence of cases with CRP levels surpassing 10 mg/dl is evident in both groups.

Nevertheless, Group 2 exhibits a lower average CRP level (25 mg/dl) vis-à-vis Group 1 (39 mg/dl), with a *P* -value

of <0.005 denoting a substantial disparity attributable to the probiotic intervention. In our study, we particularly

Table 6: Statistical Significance of Clinical Parameter

Parameters	*P*-value[a]
Avg. White blood cells	0.990
Avg. Neutrophil	0.005
Avg. C-reactive protein	< 0.005
Avg. Platelet	0.529
No. of days in the hospital	< 0.005

Independent sample T-test

focused on platelet count as one of the factors for diagnosing sepsis, drawing inspiration from the work of Addy Cecilia Helguera-Repetto et al[13]. Their findings highlighted the importance of platelet count in sepsis diagnosis, which guided our research focus and provided valuable insights into the role of Platelet count as a diagnostic marker in sepsis cases. Lastly, scrutinizing Platelet counts unveils a uniform distribution across categories in both groups, with no marked statistical divergence (*P*=0.529). This signifies homogeneity in the severity of thrombocytopenia among cases in both cohorts. Collectively, these findings illuminate the potential influence of probiotics on neutrophil and CRP levels, hinting at their plausible benefits in modulating inflammatory responses and warranting further exploration into their therapeutic efficacy. Examine the table-3 below for further details.

Statistical comparison of neonatal clinical parameters

Tables 4 and 5 present a comparison of average values and standard deviations for various clinical parameters between two distinct groups, namely Group 1 and Group 2. These parameters encompass the average white blood cell count, average neutrophil count, average C-reactive protein level, average platelet count, and the duration of hospitalization measured in days. This comparison aids in evaluating differences or similarities in the clinical profiles of the two groups concerning these essential health indicators.

Below Table 5 provides a comparison of various parameters between Group 1 and Group 2, along with their respective mean values and standard deviations. Additionally, the *P* values are provided to indicate the significance of differences between the two groups.

Age: The mean age in Group 1 is 8.18 years with a standard deviation of 8.57, while in Group 2 it is 6.69 years with a standard deviation of 7.82. The difference is not statistically significant (*P* = 0.237).

Gender: Group 1 has a mean gender value of 1.62 with a standard deviation of 0.48, while Group 2 has a mean gender value of 1.44 with a standard deviation of 0.5. The difference is statistically significant (*P* = 0.015).

Types of Sepsis: The mean values for the types of sepsis in Group 1 and Group 2 are 1.40 and 1.29, respectively. However, the difference is not statistically significant (*P* = 0.120).

Mode of Delivery: Group 1 has a higher mean mode of delivery value (1.52) compared to Group 2 (1.17). The difference is statistically significant (*P* = 0.008).

Birth Weight: The mean birth weight in Group 1 is 1.98 with a standard deviation of 1.53, while in Group 2 it is 1.69 with a standard deviation of 0.46. The difference is statistically significant *P*< 0.005). White Blood Cell Count (WBC): There is no statistically significant difference in the mean WBC count between Group 1 (15971.1) and Group 2 (15960.2) (*P* = 0.009). Neutrophil Count: Group 1 has a higher mean neutrophil count (59.64) compared to Group 2 (55.43). The difference is statistically significant (*P* = 0.005). Platelet Count: There is no statistically significant difference in the mean platelet count between Group 1 (261.2) and Group 2 (267.36) (*P* = 0.529). C - reactive protein (CRP): Group 1 has a higher mean CRP value (38.88) compared to Group 2 (25.12). The difference is statistically significant (*P*< 0.005). Number of Days in the Hospital: Group 1 has a higher mean number of days in the hospital (6.73) compared to Group 2 (5.55). The difference is statistically significant (P< 0.005). On the whole, the table reveals several statistically significant differences between Group 1 and Group 2 across various parameters, indicating potential differences in demographics, clinical characteristics, and response to treatment between the two groups.

For further information, please see the tables below.

Statistical comparison of clinical parameters

probiotic impact on neutrophil, CRP, hospital stay duration, WBC, and platelet in neonates

Based on the P-values, significant differences are observed between Group 1 and Group 2 in terms of neutrophil, CRP, and the number of hospital days. These findings suggest that the administration of probiotics in Group 2 has had a notable impact on these parameters compared to Group 1. However, there are no significant differences between the two groups in WBC and platelet, indicating that probiotics may not have a significant effect on these particular aspects. These results underscore the importance of probiotics in influencing specific clinical indicators related to neonatal health and suggest potential avenues for further research and intervention in neonatal care. For further information go through Table 6

DISCUSSION

The study investigating the efficacy of Lactobacillus rhamnosus GG in the management of neonatal sepsis presents significant evidence supporting the use of probiotics in improving clinical outcomes for neonates. The results indicated that the group receiving probiotics exhibited better outcomes in various clinical and demographic parameters compared to the group that did not receive probiotics. For instance, significant differences were observed, suggesting that probiotics might positively influence these factors. These findings are consistent with existing literature that highlights the role of probiotics in enhancing neonatal health by bolstering the immune system and improving gut flora balance

Moreover, the reduction in C-reactive protein (CRP) levels and neutrophil counts in the probiotic group suggests a decreased inflammatory response. Probiotics are known to modulate immune responses and reduce inflammation, which is particularly beneficial in the context of sepsis. A

notable finding was the shorter duration of hospitalization in the probiotic group, highlighting probiotics' potential to expedite recovery and reduce healthcare costs associated with prolonged hospital stays. This aligns with other studies that have reported similar benefits of probiotics in reducing hospitalization durations and improving patient outcomes.

Laboratory parameter analysis, including white blood cell (WBC) count, neutrophil count, and CRP levels, indicated that probiotics might exert beneficial effects on the immune and inflammatory responses in neonates with sepsis. Probiotic strains like Lactobacillus rhamnosus GG have been demonstrated to enhance gut barrier function and modulate the immune system, contributing to these observed benefits.

The implications of this study are significant, suggesting that incorporating probiotics into the treatment regimen for neonatal sepsis could improve clinical outcomes and reduce the healthcare burden. However, it is essential to conduct further research to confirm these findings and understand the mechanisms by which probiotics exert their effects. Larger-scale studies and randomized controlled trials are necessary to validate the efficacy of Lactobacillus rhamnosus GG and other probiotic strains in managing neonatal sepsis.

CONCLUSION

This study aimed to investigate the effect of probiotics, Lactobacillus rhamnosus GG, a widely available probiotic strain, in the treatment of neonatal sepsis. The statistical analysis further revealed significant differences between Group 1 and Group 2 in parameters such as C-reactive protein (CRP), neutrophil count, and duration of hospitalization. These findings suggest that probiotics, especially Lactobacillus rhamnosus GG, may have a positive impact on various clinical outcomes in neonates with sepsis. However, while the results are encouraging, further research is necessary to validate these findings. Larger-scale studies and randomized controlled trials should be conducted to confirm the efficacy and safety of Lactobacillus rhamnosusGGand other probiotic strains in treating neonatal sepsis. Understanding the mechanisms through which probiotics exert their effects will also be crucial for integrating these interventions into standard clinical practice.

In summary, the incorporation of probiotics into the treatment regimen for neonatal sepsis holds the potential for significantly improving patient outcomes and reducing hospitalization durations. This approach could represent a valuable addition to current therapeutic strategies, enhancing the overall care and recovery of neonates affected by sepsis.

Ethical conduct of the study

This study was led in agreement with the acknowledged rendition of the Announcement of Helsinki, US Food and Drug Association (FDA) Regulation, in consistency with International Council for Harmonization (ICH) Good Clinical Practice (GCP) E6 R2 rules, and as indicated by the proper administrative necessities of India, where the review was led. The clinical review convention, convention revisions, materials used to select subjects, informed consent Forms (ICFs) and materials to archive assent, and some other proper review-related records were evaluated and supported by IEC before the inception of the review at the review place.

Conflict of interest

The authors have no conflicts of interest regarding this investigation**.**

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