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A Randomized Controlled Trial of Probiotic Supplementation in Antibiotic-Associated Diarrhea

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ABSTRACT

Background: Bacterial infections account for approximately 525,000 deaths annually among children worldwide, as estimated by the World Health Organization (WHO). Although antibiotics are essential for the treatment of bacterial infections, their use can disrupt the normal gut microbiota by reducing beneficial bacteria and promoting the growth of opportunistic pathogens. This imbalance increases the risk of antibiotic-associated diarrhea (AAD). **Objective:** To evaluate the effectiveness of probiotic therapy in reducing the incidence and severity of antibiotic-associated diarrhea in pediatric patients. **Study Design:** Multicenter, single-blinded randomized controlled trial. **Settings:** Isra Hospital, Hyderabad Pakistan. **Duration:** April 2021 to July 2024. **Methods:** A total of 208 children aged 6–12 years receiving antibiotic therapy were enrolled and randomly allocated into probiotic and placebo groups using computer-generated randomization. The primary outcome was the occurrence of antibiotic-associated diarrhea, assessed using the Bristol Stool Form Scale (BSFS), defined as a score of 5–7 stools per day over a 24-hour period. Data were analyzed using SPSS software. **Results:** Antibiotic-associated diarrhea was observed in 13.6% of participants in the probiotic group and 17.1% in the placebo group, yielding a relative risk (RR) of 0.71 (95% CI: 0.39–1.22). Severe AAD occurred in 10.4% of the probiotic group compared to 11.3% of the placebo group (RR: 0.83; 95% CI: 0.51–1.69). The incidence of mild AAD was comparable between the probiotic and placebo groups (24.3% vs. 23.5%, respectively; RR: 1.01; 95% CI: 0.60–1.41). **Conclusion:** Probiotic supplementation may lead to a modest reduction in the incidence and severity of antibiotic-associated diarrhea in children; however, the observed differences were not statistically significant.

Keywords: *Antibiotic-associated diarrhea, Probiotic, Pediatric, Antibiotic.*

INTRODUCTION

In the last decade, probiotics have received much attention as a potential therapeutic intervention for pediatric acute diarrhea, mainly in conjunction with antibiotic therapy.[1] Diarrheal disease is among the most common causes of morbidity and mortality in children globally and is largely caused by bacterial infections.[2] The mainstay of treatment for most bacterial infections is the use of antibiotics; however, their administration impacts the gut microbiota, with potential complications including antibiotic-associated diarrhea (AAD).[3] AAD results in prolonged hospital stay, dehydration, and malnutrition in children, thereby increasing the overall burden of disease. Restoration of the gut microbiota, which demonstrates promise in the prevention of AAD, is achieved through the use of probiotics.[4] These live microorganisms have potential health benefits when given in adequate amounts.

The gastrointestinal tract holds a complex and dynamic microbial community that plays a crucial role in digestion, immune regulation, and protection against pathogens. Antibiotic therapy, while essential for treating infections, can disrupt this delicate balance by reducing beneficial bacterial populations and allowing

opportunistic pathogens to proliferate. This dysbiosis increases the risk of AAD, characterized by frequent, loose stools occurring in association with antibiotic use.[5,6] Many meta-analyses and systematic reviews have examined the role of probiotics in preventing AAD in children; mixed results appear. Probiotics have been shown to significantly reduce the rate of occurrence of diarrhea and its duration, while others show minimal or no effect. Such discrepancies may be due to some heterogeneity in study populations, differences in antibiotic regimens, and differences in probiotic formulations.[7-8] In addition, the optimal time of administration of probiotics, whether at initiation of antibiotics or after discontinuation, is relatively unknown.

Bacterial infections are said to be a cause of death in approximately 525,000 children annually, as estimated by WHO.[9] The current cornerstone of the management of diarrheal disease is oral rehydration therapy combined with zinc supplementation.[10] However, adjunct therapies with probiotics present a potential means of reducing the incidence and severity of AAD. Probiotics, presumably competing for adhesion sites with pathogenic bacteria in the intestinal mucosa, producing antimicrobial substances, and having an enhancing effect on mucosal immunity, reduce the risk of AAD.[11]

The effectiveness of probiotics may be patient-specific. For example, the age and nutritional status of a patient could influence the effects of probiotics. Malnourished children or those suffering from weakened immunity may respond to probiotic supplementation differently than well-nourished individuals. Finally, the colonization and activity of administered probiotics are influenced by the gut microbiota composition that varies among different individuals. Given these complexities, an RCT designed to evaluate probiotic efficacy in a well-defined pediatric population receiving antibiotics for acute diarrhea is essential. The choice of probiotic strain is particularly important, as some strains have been associated with greater risks than others. Hence, the current study investigates the efficacy and safety of probiotic supplementation among pediatric patients with AAD.

METHODS

This single-blinded, multicenter randomized controlled trial was carried out at Isra University between April 2021 and July 2024. The study was accepted and approved by the Ethical Review Committee of the Isra University on Oct 3, 2022. The study followed CONSORT guidelines for reporting results. A total of 208 children, with 104 allocated to each group, were estimated as the required sample size based on a 16% incidence of AAD in the pediatric population, with a 5% significance level and 80% power.

Children within the age bracket of 6-12 years, on oral or intravenous antibiotic therapy for the last 24 hours, with parental written consent, were recruited. Participants who had a prior antibiotic use in the last four weeks, consumption of probiotics, laxatives, and a history of intensive care unit admission due to critical conditions such as cancer or gastrointestinal disorders in the previous month. Afterwards, the allocation of participants was initiated using a computer-generated random sequence method. The allocation was then concealed in an envelope, which was stored at the research site. Participants were blinded before data collection. The probiotic and placebo were identical in packaging, appearance, taste, and odor. Parents were instructed to administer two sachets per day of the assigned study product, beginning within 24 hours of the first antibiotic dose and continuing throughout antibiotic therapy plus an additional seven days. The intervention consisted of a multispecies probiotic (Ecologic AAD 612; Winclove Probiotics B.V.) containing eight bacterial strains, delivering a total of 10 billion CFU daily (5 billion CFU per sachet). The primary outcome was the occurrence of AAD, defined as three or more episodes of loose or watery stools per day, scoring between 5 and 7 on the Bristol Stool Form Scale (BSFS) within 24 hours.

RESULTS

The table shows the baseline characteristics of participants, each with 104 individuals (total n=208). The mean age was comparable between groups, being 8.54±1.80 years in the probiotic group and 8.76±1.74 years in the placebo group. Both groups had more males than females, at 59.6% in the probiotic group and 61.5% in the placebo group. The majority of participants were inpatients (60.6% in probiotic vs. 62.5% in placebo). The most common reason for antibiotic treatment was upper respiratory tract infections (30.8% in probiotic vs. 44.2% in placebo), followed by gastrointestinal infections (28.8% vs. 30.8%). Nervous system infections were reported in 10.6% and 11.5% of probiotic and placebo groups, respectively. The route of antibiotic administration was significantly different, with more participants in the probiotic group receiving only oral (39.4%) or intravenous (40.4%) antibiotics compared to 24.0% and 19.2% in the placebo group, respectively. On the other hand, a higher percentage in the placebo group received intravenous followed by oral antibiotics (56.7%) compared to the probiotic group (20.2%). Findings show that a relatively balanced profile exists for most demographic and clinical characteristics, albeit with variations as observed in types of infections and antibiotic routes administered.

Table 1: Baseline characteristics of participants

Characteristics	Probiotic (n=104)	Placebo (n=104)	Total (n=208)
Age (Mean ± SD)	8.54±1.80	8.76±1.74	
Sex			
Female	42 (40.4%)	40 (38.5%)	82 (39.42%)
Male	62 (59.6%)	64 (61.5%)	126 (59.13%)
Setting			
Inpatient	63 (60.6%)	65 (62.5%)	128 (61.53%)
Outpatient	41 (39.4%)	39 (37.5%)	80 (38.46%)
Reason for antibiotic treatment			
Lower respiratory tract infection	21 (20.2%)	14 (13.5%)	35 (16.82%)
Upper respiratory tract infection	32 (30.8%)	46 (44.2%)	78 (37.5%)
Nervous System Infection	11 (10.6%)	12 (11.5%)	23 (23%)
Gastrointestinal infection	30 (28.8%)	32 (30.8%)	62 (29.80%)
Other	10 (9.6%)	-	10 (4.80%)
Antibiotic administration route			
Only Oral	41 (39.4%)	25 (24.0%)	66 (31.73%)
Only intravenous	42 (40.4%)	20 (19.2%)	62 (29.80%)
Intravenous followed by oral	21 (20.2%)	59 (56.7)	80 (38.46%)

Comparing outcomes between the probiotic and placebo groups. Antibiotic-associated diarrhea was observed in 13.6% of the probiotic group and 17.1% of the placebo group, with a relative risk (RR) of 0.71 (95% CI: 0.39–1.22), indicating a possible but statistically nonsignificant decrease in AAD with probiotics. Severe AAD was observed in 10.4% of the probiotic group and 11.3% of the placebo group (RR: 0.83, 95% CI: 0.51–1.69), while mild AAD rates were almost comparable between groups (24.3% vs. 23.5%; RR: 1.01, 95% CI: 0.6–1.41). No cases of antibiotic discontinuation due to diarrhea were reported in either group. Adverse events were slightly higher in the probiotic group (9.2%) compared to the placebo group (5.5%), with an RR of 1.23 (95% CI: 0.66–2.9), and this was not statistically significant. Overall, it appears that probiotics do have the potential for reducing AAD, though confidence intervals suggest a level of uncertainty surrounding the size of the effect, with no actual adverse event differences seen between the groups. (Table 2)

Table 1: Case analysis of the target population

Outcome	Events, No. (%)		Relative Risk (95% CI)
	Probiotic Group	Placebo Group	
AAD	22 (13.6)	27 (17.1)	0.71 (0.39-1.22)
Severe AAD	17 (10.4)	18 (11.3)	0.83 (0.51-1.69)
Mild AAD	29 (24.3)	37 (23.5)	1.01 (0.6-1.41)
Antibiotic cessation owing to diarrhea	0	0	N/A
Adverse events	15 (9.2)	9 (5.5)	1.23 (0.66-2.9)

DISCUSSION

The findings indicated a slight decrease in AAD incidence among participants receiving the probiotic compared to those in the placebo group. The lower relative risk (RR = 0.71, 95% CI: 0.39–1.22) suggests a potential trend favoring probiotics in reducing AAD occurrence. Additionally, the degree of severity of AAD was slightly less severe in the probiotic group, with fewer occurrences of severe diarrhea. However, mild AAD was similar between groups, meaning that while probiotics might decrease the overall risk of AAD, they might not influence milder presentations of the disease. More importantly, no antibiotic treatment was discontinued because of diarrhea in either group, indicating that, although AAD was indeed present, it did not interrupt treatment. Adverse events were slightly more frequent in the probiotic group, although this difference was not significant, emphasizing the importance of careful strain selection and safety evaluations in pediatric populations.

A meta-analysis by Szajewska and Kolodziej[12] reported that probiotic supplementation, particularly with Lactobacillus rhamnosus GG and Saccharomyces boulardii, reduced the risk of AAD in pediatric patients. Their pooled analysis suggested a significant protective effect, particularly when probiotics were administered at higher doses. Another review of 33 articles, encompassing 6,352 participants with follow-up periods ranging from five days to twelve weeks, reported an AAD incidence of 8% in the probiotic group compared to 19% in the control group.[13] Additionally, another study found that probiotics reduced the incidence of AAD by 38%, with a pooled relative risk of 0.62 (95% CI: 0.51–0.74).[14] However, the present study did not observe as substantial a reduction, which could be attributed to differences in probiotic strains, dosages, or study populations. Another review focuses on the best possible efficacy among all available probiotics agents for AAD. A total of 51 studies with a sample of 9569 were identified. The findings showed that in terms of effectiveness, Lactobacillus rhamnosus GG (LGG) had the best chance of being rated first, with an odds ratio of 0.28.[15] In contrast, another study, with 10 RCTs and 4692 participants, showed better results for L. casei.[16]

One of the strengths of this study is the randomized controlled trial design, which reduces bias and strengthens the validity of findings. The study used a standardized tool in measuring the severity of AAD; thus, it offers a proper comparison between groups. The relatively large sample size enhances the reliability of findings and adds useful data to the growing body of evidence regarding probiotics in pediatric populations.

CONCLUSION

The findings suggest that while probiotics may contribute to a modest reduction in the incidence and severity of antibiotic-associated diarrhea (AAD), their effect is not statistically significant. The lower relative risk (RR=0.71) indicates a potential trend favoring probiotics, but the similarity in mild AAD cases between groups suggests that probiotics may not significantly impact less severe forms of the condition.

LIMITATIONS

Although the study has strengths, there are certain limitations that need to be stated. One of them includes antibiotic regimens that varied across participants, which might have produced a different influence on gut microbiota and consequently probiotic efficacy. The study also did not conduct analyses of the microbiome to assess alterations in gut flora before and after probiotic supplementation, which could provide mechanistic insights to explain the observed effects. Another limitation is the lack of long-term follow-up to determine whether probiotics have lasting benefits beyond the acute treatment phase.

SUGGESTIONS / RECOMMENDATIONS

Future studies should incorporate microbiota profiling and extended follow-up periods to evaluate the sustained impact of probiotics on gut health.

CONFLICT OF INTEREST / DISCLOSURE

There is no any conflict of interest in this study.

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