

Research

Localized impact of zinc and probiotics on antibiotic-associated diarrhea in children: a perspective from southern Iran

Mohammad Bagher Rahmati¹ · Razie Khodadadzade¹ · Mehran Ahmadi¹ · Saeed Hoseini Teshnizi¹

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Abstract

Background Antibiotic-associated diarrhea (AAD) is a frequently encountered complication that arises from the administration of antimicrobial agents.

Objective The aim of this study was to evaluate the efficacy of zinc and probiotics in reducing antibiotic-associated diarrhea (AAD) incidence, hospitalization, and treatment duration.

Patients and methods This is a randomized clinical trial involving 165 children referred to Bandar Abbas Children's Hospital, which necessitated antibiotics for any given reason. They were randomly assigned to three groups of equal size, exclusively receiving the standard antibiotic regimen or the zinc and probiotics groups. Age, sex, length of hospital stays, treatment duration, type of antibiotic, and incidence AAD were documented for all patients.

Results Among the 165 children who participated in the survey, AAD occurred in 12.7% of the zinc group, 9.1% of the probiotics group, and 10.9% of the control group; however, the difference among the groups was not statistically significant ($P=0.829$). There was no significant association between AAD and age, sex, hospital length of stay, type of antibiotic, or patient grouping.

Conclusions Despite the lower incidence of AAD, duration of hospital stay and duration of treatment in children in the probiotic group, these findings were not statistically significant.

Clinical trial number: Retrospectively registered ClinicalTrials.gov Identifier: NCT06665503, 2024-10-29.

Keywords Antibiotic-associated diarrhea · Children · Zinc · Probiotics

1 Introduction

Over the past two decades, numerous studies have elucidated the clinical benefits and safety profiles of a diverse array of probiotics in the prevention and management of gastrointestinal diseases [1–3]. The use of probiotics as preventive interventions against antibiotic-associated diarrhea (AAD) in pediatric populations has gained considerable traction. AAD is a prevalent adverse effect associated with antibiotic therapy, leading to significant discomfort and complications [4]. Specifically, two probiotic strains, *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, are recommended for the prevention of AAD in children [5]. *Lactobacillus rhamnosus* GG has demonstrated efficacy in reducing both the incidence and duration of AAD among pediatric patients. A previous study indicated that children administered *Lactobacillus rhamnosus* GG exhibited a significantly lower risk of developing AAD compared to those receiving a placebo [6]. Similarly, *Saccharomyces boulardii* has been identified as another effective probiotic strain for preventing AAD in children [6, 7].

✉ Mohammad Bagher Rahmati, mbrahmati@gmail.com | ¹Department of Pediatric, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.



Regarding dosage, clinical trials have reported that a higher dose range of 5–40 billion colony-forming units per day is associated with optimal efficacy [6]. While probiotics are typically regarded as safe for healthy children, it is important to note that rare but serious adverse events have been documented in severely debilitated or immunocompromised pediatric populations [8]. In conclusion, probiotics—specifically *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*—have shown effectiveness in preventing antibiotic-associated diarrhea among children [5].

Zinc supplementation has demonstrated promising outcomes in the prevention and treatment of antibiotic-associated diarrhea (AAD) in pediatric populations [9]. AAD is a prevalent adverse effect associated with antibiotic use, and numerous studies have investigated the role of zinc in mitigating the severity and duration of diarrhea [10]. Zinc is an essential micronutrient that plays critical roles in immune response, cellular proliferation, and protein synthesis. Research indicates that zinc enhances the absorption of water and electrolytes in the intestines, contributing to a reduction in both the duration and severity of diarrhea [11]. Furthermore, zinc supplementation has been shown to prevent subsequent infections for 2–3 months post-administration. The acceptability of zinc supplementation among both children and caregivers is generally high, and its efficacy appears to be consistent regardless of the specific zinc salt used (e.g., zinc sulfate, zinc acetate, or zinc gluconate) [12].

2 Objectives

The objective of this study was to evaluate and compare the effects of zinc and probiotics on children aged 3 months to 12 years diagnosed with AAD in southern Iran. While zinc supplementation and probiotics have shown promising outcomes in managing diarrhea, further research is necessary to determine their efficacy, particularly in the prevention and treatment of AAD in pediatric populations.

3 Materials and methods

3.1 Study design

The study included a zinc group, a probiotics group, and a control group. The zinc group received oral zinc supplementation, specifically 2.5 ml every 12 h for children under 1 year of age and 5 ml every 12 h for older children. The probiotics group received one sachet of KidiLact daily, which contained *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Bifidobacterium infantis*, and other strains, totaling 5 billion CFU. The control group received the standard antibiotic regimen without any additional supplementation.

Interventions commenced within 24 h of antibiotic initiation and continued for seven days. AAD was defined as the occurrence of three or more loose stools per day for two consecutive days during or within 2 weeks of antibiotic use. The Bristol stool scale was employed to classify stool consistency [13]. The incidence of AAD was assessed and compared among the three groups, along with the evaluation of other parameters such as hospitalization and treatment. The probiotics group received one sachet of KidiLact daily (containing *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Bifidobacterium infantis*, and other strains, total CFU: 5 billion). The control group received the standard antibiotic regimen without additional supplementation. Interventions started within 24 h of antibiotic initiation and continued for seven days. AAD was defined as three or more loose stools per day for two consecutive days during or within 2 weeks of antibiotic use. The Bristol stool scale was used to classify stool consistency. The incidence of AAD was assessed and compared among the three groups.

3.2 Data collection and statistical analysis

After the desired information was collected, it was entered into SPSS software version 26 and subsequently analyzed using descriptive statistics. Chi-square tests and Fisher's exact tests were employed to compare qualitative variables between the study groups. Due to the non-normality of the distribution of quantitative variables, as indicated by the Kolmogorov–Smirnov test, the Kruskal–Wallis and Mann–Whitney tests were utilized to compare quantitative variables across groups. Additionally, logistic regression was applied to identify the factors influencing the incidence of AAD.

3.3 Ethical considerations

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was ethically approved by the Ethics Committee of Hormozgan University of Medical Sciences (Approval ID: IR.HUMS.REC.1399.579). Informed consent was obtained from the children and their parents. Clinical trial number is not applicable.

4 Results

In this study, a total of 165 children aged between 3 months and 12 years were investigated. The participants had an average age of 45.65 ± 41.46 months (Table 1). Among the total sample, 84 (50.9%) were boys, and 81 (49.1%) were girls (Table 2). AAD incidence was 12.7% in the zinc group, 9.1% in the probiotic group, and 10.9% in the control group ($P=0.829$). Hospitalization and treatment durations were significantly shorter in the probiotic group than in the zinc group ($P<0.001$) (Table 3 and 4). Ampicillin consumption was observed in 16.4% of the probiotics group, 3.6% of the control group, and 1.8% of the zinc group ($P=0.013$). Additionally, vancomycin consumption was observed in 10.9% of the control group and 7.3% of the zinc group, whereas no patients in the probiotics group received vancomycin ($P=0.037$) Table 5. No significant differences were found among the groups in terms of the consumption of ceftriaxone, meropenem, cefotaxime, or clindamycin. There was no significant association between AAD and age, sex, hospital length of stay, type of antibiotic, or patient grouping.

5 Discussion

The present study observed that probiotic supplementation was associated with a lower incidence of AAD and reduced hospitalization and treatment durations compared to zinc; however, these differences did not reach statistical significance. These findings contrast with prior studies that reported zinc as more effective in accelerating diarrhea recovery [14, 15]. This discrepancy may be attributed to contextual factors in Southern Iran, including regional dietary patterns, healthcare practices, and the specific multi-strain probiotic formulation utilized in this trial. The inclusion of diverse bacterial strains in the probiotic intervention (e.g., *Lactobacillus* and *Bifidobacterium* species) may have enhanced its efficacy, consistent with evidence suggesting that synergistic probiotic combinations yield broader therapeutic effects than single strains [16].

Table 1 Comparison of age between study groups

Variable	Groups			P-value
	Control (55 persons) (IQR)*	Probiotic (55persons) (IQR)	Zinc (55 persons) (IQR)	
Age (months)	41.(19–96)	20.(6–42)	40.(14–80)	0.001
*IQR Rinterquartile range				

Table 2 Comparison of gender between study groups

Sex	Groups			P-value
	Control (55 persons) %	Probiotic (55 persons) %	Zinc (55 persons) %	
Male	(45/5) 25	(54/5) 30	(52/7) 29	0/601
Female	(54/5) 30	(45/5) 25	(47/3) 26	

Table 3 Comparison of the incidence of diarrhea between study groups

Diarrhea	Groups			P value
	Control (55 persons) %	Probiotic (55 persons) %	Zinc (55 persons) %	
No	(89/1) 49	(90/9) 50	(87/3) 48	0/829
Yes	(10/9) 6	(9/1) 5	(12/7) 7	

Table 4 Comparison of hospital stay and treatment duration between study groups

P-value	Groups			Variables
	Control (55 persons) (IQR)	Probiotic (55 persons) (IQR)	Zinc (55 persons) (IQR)	
0/001	3 (2–5)	2 (1–3)	4 (2–5)	Hospital stay (day)
0/001	3 (2–5)	2 (1–3)	4 (2–5)	Treatment Time (day)
P-value	Groups			Antibiotic
	Control (55 persons) %	Probiotic (55 persons) %	Zinc (55 persons) %	
0/171	(85/5) 47	(83/6) 46	(94/5) 52	Ceftriaxon
0/013	(3/6) 2	(16/4) 9	(1/8) 1	Ampicillin
0/137	(10/9) 6	(0) 0	(7/3) 4	Vancomycin
0/128	(7/3) 4	(0) 0	(1/8) 1	Meropenem
0/117	(7/3) 4	(16/4) 9	(5/5) 3	Cefotaxim
0/178	(14/5) 8	(10/9) 6	(94/5) 52	Clindamycin

Table 5 Comparison of antibiotic type between study groups

P-value	Adjusted OR (95% CI)	P-value	Crude OR (95% CI)	Variables	
0/466	0/995 (0/981–1/009)	0/635	(0/985–1/010) 0/997	Age	Sex
				Male	
0/313	0/591 (0/213–1/641)	0/362	0/628 (0/231–1/709)	Female	Groups
				Control	
0/916	1/067 (0/321–3/544)	0/768	1/191 (0/373–3/802)	Zinc	Antibiotic
0/501	0/635 (0/321–2/385)	0/751	0/817 (0/234–2/852)	Probiotic	
1/000	1/158 (0–?)	0/382	2/523 (0317–20/069)	Ceftriaxon	
0/999	189,797,070/6 (0–?)	0/767	0/727 (0/088–5/988)	Ampicillin	
0/675	1/771 (0/122–25/641)	0/924	0/902 (0/108–7/764)	Vancomycin	
1/000	0 (0–0)	0/999	0 (0–0)	Meropenem	
1/000	0 (0–0)	0/536	0/518 (0/064–4/170)	Cefotaxim	
0/975	1/023 (0/250–4/194)	0/971	1/025 (0/275–3/816)	Clindamycin	
0/714	0/962 (0781–1/184)	0/881	0/987 (0/836–1/166)	Hospital stay	

The comparative effectiveness of zinc and probiotics remains a topic of ongoing debate. Cai J et al. [17] assessed the efficacy of zinc, probiotics, and their combination in children with AAD, concluding that the combined regimen was more effective than monotherapies—an assertion that contrasts with the findings of the current study. Similarly, Azim et al. [18] demonstrated that the combination of zinc and probiotics was more effective in reducing the severity of acute gastroenteritis compared to zinc alone. Discrepancies in study design, including variations in inclusion criteria (such as diarrhea etiology and patient demographics), differing zinc dosage forms (e.g., sulfate vs. acetate), and diverse probiotic compositions, likely contribute to these conflicting results. Additionally, the objectives of earlier studies—whether aimed at diarrhea prevention or treatment—may influence the observed outcomes. For example, Tai et al. [19] found that zinc supplementation shortened the duration of AAD in hospitalized children but did not affect disease severity, whereas Zarin Far et al. [20] reported that *Lactobacillus* probiotics did not reduce the incidence of AAD but alleviated symptoms of colitis. This heterogeneity highlights the necessity of standardizing interventions and outcomes in future research endeavors.

Notably, neither zinc nor probiotics in this study significantly reduced hospitalization or treatment duration compared to the control group. This finding contrasts with the conclusions of Huang et al.'s meta-analysis [16], which indicated that probiotics effectively shortened diarrhea duration and hospitalization. The null effect observed in this study may reflect regional differences in baseline microbiota, variations in antibiotic prescribing practices, or differences in pathogen prevalence. Furthermore, the relatively small sample size and the non-uniform probiotic formulations across studies complicate direct comparisons.

Emerging evidence suggests that combination therapies may offer synergistic benefits. Xiang et al. [9] reported that the administration of zinc in conjunction with probiotics was more effective than probiotics administered alone in managing pneumonia-related antibiotic-associated diarrhea (AAD). Additionally, Hassan et al. [16] and Azim et al. [18] both emphasized the superiority of dual therapy. These findings imply that zinc and probiotics may target distinct biological pathways—zinc enhances intestinal immunity while probiotics restore microbial balance—thereby justifying further exploration of their combined use.

5.1 Conclusion

The present study underscores the potential efficacy of multi-strain probiotics in managing AAD while emphasizing the need for larger, context-specific trials to address inconsistencies in prior research. Future investigations should include a combination therapy arm (zinc plus probiotics) alongside monotherapy and control groups. Standardizing probiotic strains, zinc formulations, and outcome measures will enhance comparability across diverse populations. Additionally, research should stratify results according to the etiology of diarrhea, as pathogen-specific responses may influence treatment efficacy. Until conclusive evidence is obtained, clinical decision-making should consider regional practices, patient demographics, and available formulations.

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Data availability “The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request”.

Declarations

Ethics approval and consent to participate This study was conducted in accordance with the tenets of the Declaration of Helsinki and was ethically approved by the Ethics Committee of Hormozgan University of Medical Sciences (Approval ID: IR.HUMS.REC.1399.579). Written informed consent was obtained from a legally authorized representative(s) for the anonymized patient.

Consent for publication The authors declare that they have no conflict of interest.

Competing interests The authors declare no competing interests.

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