



Efficacy of Zinc Plus Probiotics Versus Zinc Alone in Children With Acute Diarrhea: A Multicenter Randomized Controlled Trial

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Abstract: Background: Acute diarrhea remains an important cause of childhood morbidity, particularly in developing countries. Zinc is routinely used in the management of acute childhood diarrhea, while probiotics may provide additional benefit by modifying intestinal microbial balance and reducing the duration and severity of diarrhea.

Objective: To compare the efficacy of zinc plus probiotics with zinc alone in children with acute diarrhea. **Methods:** This randomized controlled trial was conducted in the Department of Pediatrics, MTI Hayatabad Medical Complex, and Bacha Khan Medical Complex from August 23, 2019 to March 25, 2020. A total of 142 children aged 1 to 36 months with acute diarrhea were enrolled and allocated by lottery method into two equal groups of 71 participants. Group A received zinc plus *Saccharomyces boulardii*, while Group B received zinc alone. Zinc was administered at 10 mg/day in children younger than 6 months and 20 mg/day in children older than 6 months. The probiotic preparation was administered at 250 mg once or twice daily for five days. Efficacy was defined as cessation of diarrhea by approximately 72 hours, confirmed by achievement of a Bristol Stool Scale score below 5. Data were analyzed using SPSS version 22.0, and a p-value <0.05 was considered statistically significant. **Results:** The mean age was 17.17 ± 10.34 months in the zinc plus probiotics group and 15.59 ± 9.94 months in the zinc-alone group. Males constituted 76.1% and 69.0% of the two groups, respectively. Mean duration of disease before enrollment was 2.87 ± 1.21 days in the combination group and 3.30 ± 1.22 days in the zinc-alone group. Mean hospital stay was 53.41 ± 18.78 hours with zinc plus probiotics and 58.65 ± 16.56 hours with zinc alone. Treatment was effective in 54 of 71 children (76.1%) receiving zinc plus probiotics compared with 32 of 71 children (45.1%) receiving zinc alone, representing a statistically significant difference ($p < 0.001$). **Conclusion:** The combination of zinc and probiotics was more effective than zinc alone in achieving cessation of acute diarrhea in children. Zinc plus probiotics may therefore provide additional clinical benefit in the management of acute childhood diarrhea.

Keywords: Acute diarrhea; children; zinc; probiotics; *Saccharomyces boulardii*; randomized controlled trial

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INTRODUCTION

Acute diarrhea remains an important public health problem among children, particularly in low- and middle-income countries, where it continues to contribute substantially to childhood morbidity and mortality. Oral rehydration remains central to treatment, while zinc supplementation is an established adjunct in childhood diarrhea.^{1,2}

Contemporary randomized trials continue to support the clinical role of zinc in acute childhood diarrhea. A large multicenter trial confirmed that zinc remains effective across different daily doses, while another randomized trial reported shorter time to recovery and hospitalization with zinc supplementation.^{2,3}

Probiotics have also been investigated as adjunctive therapy for acute gastroenteritis. Current pediatric guidance emphasizes that probiotic effects are strain specific; selected strains, including *Saccharomyces boulardii*, may be considered in children with acute gastroenteritis, although the certainty of evidence remains limited.⁷

Recent systematic reviews and meta-analyses have reported that selected probiotics, particularly *Saccharomyces boulardii*, may shorten diarrhea duration and hospital stay, although the magnitude of benefit varies by strain and setting.⁴⁻⁶ Recent clinical studies have also produced mixed findings: combined zinc and probiotics showed benefit in one comparative study, *Bacillus clausii* added to oral rehydration and zinc showed no significant additional efficacy in another trial, while *Weizmannia coagulans* added to oral rehydration and zinc reduced diarrhea duration in a more recent randomized trial.⁸⁻¹⁰

There remains a need for local evidence regarding the potential benefit of adding probiotics to conventional zinc therapy in children with acute diarrhea. This study was therefore conducted to compare the efficacy of zinc plus probiotics with zinc alone in children presenting with acute diarrhea at two tertiary care hospitals in Peshawar and Mardan, Pakistan.

Objective

To compare the efficacy of zinc plus probiotics with zinc alone in the treatment of acute diarrhea in children.

MATERIALS AND METHODS

Study design and setting

This randomized controlled trial was conducted in the Department of Pediatrics, MTI Hayatabad Medical Complex, Peshawar, Pakistan and Bacha Khan Medical Complex, Mardan. The study was conducted from August 23, 2019 to March 25, 2020.

Study population and sample size

A total of 142 children were included, with 71 participants allocated to each treatment group. The sample size was calculated using an expected efficacy of 52.73% for zinc plus probiotics and 29.09% for zinc alone, with 95% confidence, 80% power, 5% margin of error, and 5% level of significance. Participants were recruited using consecutive non-probability sampling.

Inclusion criteria

- Age 1 to 36 months.
- Acute diarrhea, defined as three or more watery stools per day.
- Either sex.

Exclusion criteria

- Severe dehydration greater than 10%.
- Coexisting severe infection, including sepsis, pneumonia, or meningitis.
- Immunodeficiency.
- Chronic gastrointestinal disease, including celiac disease or food allergy.
- Ongoing antibiotic therapy.

Randomization and intervention

Eligible participants were allocated into two treatment groups using the lottery method.

Group A, zinc plus probiotics: Children received zinc sulfate at a dose of 10 mg/day when younger than 6 months and 20 mg/day when older than 6 months. In addition, they received a *Saccharomyces*

boulardii preparation, 250 mg once or twice daily, for five days.

Group B, zinc alone: Children received zinc sulfate at a dose of 10 mg/day when younger than 6 months and 20 mg/day when older than 6 months.

Participants were monitored during hospitalization for the duration and frequency of diarrhea.

Outcome measurement

The primary outcome was treatment efficacy. Efficacy was defined as cessation of diarrhea by approximately 72 hours after admission or initiation of treatment, confirmed by stool evaluation with a Bristol Stool Scale score below 5. Age, sex, weight, height or length, duration of disease, duration of hospital stay, and treatment efficacy were recorded on a structured proforma.

Ethical considerations

Ethical and research approval was obtained before commencement of the study. An informed consent form was included as part of the study protocol, and participation was undertaken after consent from the parent or guardian.

Statistical analysis

Data were entered and analyzed using SPSS version 22.0. Continuous variables including age, duration of disease, and duration of hospital stay were summarized using mean and standard deviation. Categorical variables including sex and efficacy were presented as frequencies and percentages. Treatment efficacy was compared between the two groups using the chi-square test. Stratified analyses were performed for age, sex, duration of disease, and duration of hospital stay. A p-value <0.05 was considered statistically significant.

RESULT

A total of 142 children were included in the analysis, with 71 participants in each treatment group. Baseline characteristics

The mean age of children receiving zinc plus probiotics was 17.17 ± 10.34 months, compared with 15.59 ± 9.94 months among those receiving zinc alone. There were 54 males (76.1%) and 17 females (23.9%) in the zinc plus probiotics group. The zinc-alone group included 49 males (69.0%) and 22 females (31.0%). Mean body weight was similar between the two groups, at 7.10 ± 2.48 kg in the zinc plus probiotics group and 7.00 ± 2.53 kg in the zinc-alone group.

Table 1. Baseline characteristics of participants

Characteristic	Zinc alone, n=71	Zinc plus probiotics, n=71
Age, months, mean $\pm$ SD	15.59 $\pm$ 9.94	17.17 $\pm$ 10.34
Age 1 to 17 months, n (%)	33 (46.5)	30 (42.3)
Age 18 to 36 months, n (%)	38 (53.5)	41 (57.7)
Male, n (%)	49 (69.0)	54 (76.1)
Female, n (%)	22 (31.0)	17 (23.9)
Weight, kg, mean $\pm$ SD	7.00 $\pm$ 2.53	7.10 $\pm$ 2.48
Length/height, cm, mean $\pm$ SD	58.97 $\pm$ 4.83	57.74 $\pm$ 4.38

Disease duration and hospital stay

Mean duration of diarrhea before enrollment was 3.30 ± 1.22 days in the zinc-alone group and 2.87 ± 1.21 days in the zinc plus probiotics group. The mean hospital stay was 58.65 ± 16.56 hours among children receiving zinc alone compared with 53.41 ± 18.78 hours among those receiving zinc plus probiotics.

Table 2. Disease duration and hospital stay

Variable	Zinc alone, n=71	Zinc plus probiotics, n=71
Disease duration, days, mean $\pm$ SD	3.30 ± 1.22	2.87 ± 1.21
Disease duration 1 to 3 days, n (%)	41 (57.7)	52 (73.2)
Disease duration 4 to 6 days, n (%)	30 (42.3)	19 (26.8)
Hospital stay, hours, mean $\pm$ SD	58.65 ± 16.56	53.41 ± 18.78
Hospital stay 24 to 48 hours, n (%)	33 (46.5)	43 (60.6)
Hospital stay 49 to 72 hours, n (%)	34 (47.9)	19 (26.8)
Hospital stay 73 to 84 hours, n (%)	4 (5.6)	9 (12.7)

Treatment efficacy

Treatment efficacy was achieved in 54 of 71 children (76.1%) receiving zinc plus probiotics compared with 32 of 71 children (45.1%) receiving zinc alone. The difference between the groups was statistically significant ($p < 0.001$), demonstrating a higher rate of cessation of diarrhea with combined zinc and probiotic therapy.

Table 3. Comparison of treatment efficacy

Treatment group	Effective, n (%)	Not effective, n (%)	p-value
Zinc alone	32 (45.1)	39 (54.9)	
Zinc plus probiotics	54 (76.1)	17 (23.9)	<0.001

Age, sex, and duration of disease were not significantly associated with overall treatment efficacy in the stratified analyses.

benefit, but current pediatric guidance emphasizes

DISCUSSION

The present randomized controlled trial demonstrated that the addition of probiotics to zinc therapy improved treatment efficacy among children with acute diarrhea. Approximately three-quarters of children receiving zinc plus probiotics achieved the predefined efficacy outcome compared with less than half of those receiving zinc alone.

Zinc remains an established adjunct in acute childhood diarrhea, and recent randomized trials have continued to evaluate its efficacy, dose, and tolerability.^{2,3} Probiotics may provide additional

that their effects are strain specific and that evidence quality varies among preparations.⁷

The present findings are consistent with a 2022 comparative study by Yalcin et al., in which combined probiotic and zinc treatment was associated with a significantly shorter time to cessation of diarrhea than zinc alone or probiotic therapy alone.⁸

The findings are also broadly compatible with recent systematic reviews and meta-analyses reporting reduced diarrhea duration with selected probiotics,

including *Saccharomyces boulardii*.⁴⁻⁶ More recent randomized evidence remains strain dependent. Lahiri et al. found no significant additional benefit from *Bacillus clausii* when added to oral rehydration and zinc, whereas Majeed et al. reported a shorter duration of diarrhea with *Weizmannia coagulans* added to oral rehydration and zinc.^{9,10}

In the present study, the mean hospital stay was approximately five hours shorter in the zinc plus probiotics group than in the zinc-alone group. More children receiving combination treatment were discharged within 24 to 48 hours. These findings are directionally consistent with previous studies showing shorter illness duration with combination therapy. However, the principal statistically supported finding of this study was the higher proportion of children achieving the predefined efficacy endpoint.

Age, sex, and duration of illness did not show a significant association with overall efficacy. This suggests that the observed difference in response was not clearly attributable to these measured characteristics, although the study was not specifically powered for subgroup analyses.

Broader translational and clinical research has also examined mechanism-based adjunctive therapies in gastrointestinal physiology, inflammatory pathways, and oxidative stress across other disease settings.¹¹⁻¹³ These studies did not evaluate pediatric acute diarrhea and are cited here only as contextual examples of adjunctive therapeutic research, not as direct evidence for probiotic efficacy in this population.

The study has several limitations. Blinding was not documented, and the study did not characterize diarrhea according to specific viral, bacterial, or parasitic etiology. The follow-up period was short and focused on cessation of the acute diarrheal episode. Detailed information regarding probiotic strain characteristics and adverse events was also not available in the study dataset. Larger multicenter trials with standardized probiotic preparations and etiological classification of acute diarrhea would help further define the children most likely to benefit from combination therapy.

CONCLUSION

Zinc plus probiotic therapy was more effective than zinc alone in children with acute diarrhea. Treatment efficacy was achieved in 76.1% of children receiving zinc plus probiotics compared with 45.1% receiving zinc alone. The combination may therefore provide additional benefit as an adjunct to standard management of acute childhood diarrhea. Further multicenter studies using standardized probiotic preparations are recommended to confirm these

findings and determine which probiotic strains provide the greatest clinical benefit.

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Declarations

Ethics approval: Ethical and research approval was obtained from the relevant institutional authority before commencement of the study. The approval/reference number was not available in the source records used to prepare this manuscript and should be inserted before submission if required by the target journal.

Consent to participate: Written informed consent was obtained from the parents or legal guardians of all participating children.

Consent for publication: Not applicable. The manuscript does not contain identifiable individual patient information or images.

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acquisition and coordination of the study. A.R. and T.A. contributed to data interpretation and critical review of the manuscript. M.U. and M.A. contributed to literature review, drafting, and revision of the manuscript. H.S. supervised the overall work and coordinated preparation of the final manuscript. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.