

ORIGINAL ARTICLE

Clinical Outcome of Zinc Plus *Saccharomyces Boulardii* versus Zinc Alone in the Treatment of Acute Diarrhea in Children Under 5 Years of Age

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ABSTRACT

OBJECTIVE: To compare the time taken to resolve diarrhea, and the time taken to resolve vomiting in children (under 5 years of age) with zinc plus *Saccharomyces boulardii* (*S. boulardii*) versus zinc alone.

METHODOLOGY: This randomized controlled trial was conducted at the Department of Pediatric Medicine, Children's Hospital and Institute of Child Health, Multan, Pakistan, from February to July 2025. A total of 276 children (138 in each group) aged up to 5 years presenting with acute diarrhea were included with simple random sampling technique. After randomization, Group-A patients received zinc plus *S. boulardii*, while Group-B patients received only zinc. All patients were treated following the institutional treatment protocol. The time taken to resolve diarrhea, and vomiting was noted and compared between the study groups. Data analysis was performed using IBM-SPSS 26.0.

RESULTS: Of 276 children, 141 (51.1%) were males and 135 (48.9%) females, with a median age of 2.2 years (IQR 1.0–3.5). In Group-A, 70 (50.7%) were males and 68 (49.3%) females, while in Group-B, 71 (51.5%) were males and 67 (48.5%) females. Diarrhea resolved earlier in Group-A, 4.3 days (IQR 3.0–5.0) compared with 5.1 days (IQR 4.0–5.5) in Group-B ($p<0.001$). Vomiting resolved in 7.4 hours (IQR 5.0–10.0) in Group-A compared with 11.2 hours (IQR 8.0–14.0) in Group-B ($p<0.001$).

CONCLUSION: The addition of *Saccharomyces boulardii* to zinc supplementation significantly shortened the time to resolution of both diarrhea and vomiting in children under five years of age with acute diarrhea compared with zinc alone.

KEYWORDS: Children, diarrhea, probiotics, *Saccharomyces boulardii*, vomiting, zinc.

Trial Registration: NCT07168304 (www.clinicaltrials.gov)

INTRODUCTION

Globally, around 1.7 billion cases of childhood diarrheal disease occur every year¹. Diarrheal diseases are the 2nd leading cause of mortality among children below 5 years, and cause about 525,000 deaths annually^{2,3}. Pakistan, like other developing countries, is facing a very high burden of diarrheal diseases, with a prevalence of 19%⁴. Pakistan is identified as one of 15 high-burden focus countries, with 39,500 deaths in children below 5 years attributed to diarrhea annually^{5,6}. There are multiple etiological causes of acute diarrhea including infections, drug therapy, food allergies, gastrointestinal problems, and malnutrition⁷. Complications of repeated episodes of diarrhea are malnutrition, retarded growth, weak immunity, and impaired cognitive development, especially in the children of resource-limited countries⁸.

Oral rehydration, breastfeeding, and early refeeding are the most important components in the management of acute childhood diarrhea⁹. Oral rehydration may not minimize the volume or extent of diarrhea which has motivated clinicians to utilize other options like probiotics, anti-peristaltic, and anti-secretory agents^{10,11}. *Lactobacillus GG* and *S. boulardii* are the most common probiotics, as the efficacy of these in the management of gastrointestinal disorders has been shown in the past¹¹. Regarding other approaches, UNICEF and WHO recommend 14 days of zinc supplementation for all children with acute diarrhea¹². Zinc is recommended for treating acute watery ailments in children¹³.

Still, the question of whether the combined therapy of zinc with *S. boulardii* can provide better efficacy in the treatment of acute diarrhea has not been satisfactorily addressed in recent years. For this study, it was hypothesized that there is a difference in the time of resolution of diarrhea and vomiting in patients receiving zinc plus *S. boulardii* versus zinc alone for the treatment of acute diarrhea.

Hence, this study aimed to compare the time to resolution of diarrhea and vomiting in children under 5 years of age with acute diarrhea, treated with zinc plus *S. boulardii* versus zinc alone. If any significant beneficial effect on the combined efficacy of zinc with *S. boulardii* is found, it may add to existing knowledge to provide more effective treatment options.

METHODOLOGY

This randomized controlled trial was conducted at the Department of Pediatric Medicine, The Children's Hospital and Institute of Child Health, Multan, Pakistan, from February 2025 to July 2025, after approval by the institutional ethical review committee (letter number 82, dated 13-01-2025). A sample size of 276 (138 in each arm) was calculated using the OpenEpi calculator based on the expected mean time to resolution of vomiting, estimated as 10.40 ± 8.73 hours in the zinc plus *Saccharomyces boulardii* group versus 13.63 ± 10.33 hours in the zinc-alone group¹⁴, with 80% power, 95% confidence interval, and a significance level of 0.05. Children of either gender aged 1 month to 5 years who presented with acute diarrhea were assessed for eligibility. Children with concurrent acute illnesses such as meningitis, sepsis, or pneumonia, those with severe chronic conditions including cystic fibrosis, endocrinopathies, food allergies, or chronic gastrointestinal diseases, and those with severe undernutrition (weight-for-height z-score < -3 SD or presence of edema of nutritional origin) were excluded. Children who used probiotics, antibiotics, or anti-diarrheal drugs within the past 7 days, or who had the presence of visible blood in stools were also excluded. Acute diarrhea was defined as the passage of three or more loose or watery stools per day (Bristol Stool Form Scale types 5–7) of less than 14 days' duration. Written informed consent was obtained from parents or caregivers¹⁵.

Randomization was performed using a computer-generated simple random sequence. The allocation sequence was placed in sequentially numbered, sealed, opaque envelopes to ensure allocation concealment. As the study involved an additional supplement in one group, blinding of participants and caregivers was not feasible, and the trial was conducted in an open-label manner; however, outcome assessment was performed by an independent investigator blinded to group allocation to minimize assessment bias.

Group A participants received zinc plus *S. boulardii* supplementation according to WHO recommendations, whereas Group B received zinc alone. Both groups received the same standard supportive care, including oral rehydration salts or intravenous fluids of correct dehydration and electrolyte imbalance, as well as antibiotics if clinically indicated. Baseline demographic and clinical characteristics, including age, gender, frequency and consistency of stools, duration of diarrhea, and number of vomiting episodes, were recorded. Patients were monitored daily during hospital stay, and a standardized telephonic evaluation was conducted using a structured symptom-recording checklist after discharge until resolution of symptoms. The primary outcomes were time to resolution of diarrhea, defined as the duration from initiation of treatment until passage of normal stools (Bristol Stool Form Scale types 3–4)¹⁵, and time to resolution of vomiting, defined as the time from the start of treatment to the last episode of vomiting.

All data were analyzed using IBM SPSS version 26.0. Quantitative variables were expressed as means with standard deviation (SD) or medians with interquartile range (IQR), depending on distribution (checked using the Shapiro–Wilk test). Differences between groups were analyzed using the independent-samples t-test or Mann-Whitney U test for quantitative data, and the chi-square test or Fisher's exact test for qualitative data, with $p < 0.05$ considered significant.

RESULTS

In a total of 276 children, 141 (51.1%) were males, and 135 (48.9%) were females. Overall, the median age was 2.2 years (1.0-3.5). In Group A, 70 (50.7%) were males and 68 (49.3%) females, while in Group B, 71 (51.5%) were males and 67 (48.5%) females ($p=0.904$). There were 70 (50.7%) children in Group A with age ≤ 2 years, and 77 (55.8%) in Group B, while 68 (49.3%) and 61 (44.2%) were aged >2 to 5 years ($p=0.398$). Children from rural areas accounted for 171 (61.9%) of the study population, with no statistically significant differences were obtained among participants of both study groups with respect to residence ($p=0.710$). These baseline characteristics confirm that the two groups were comparable at enrollment (Table I).

Table I: Comparison of characteristics of children (N=276)

Characteristics		Group-A (n=138)	Group-B (n=138)	P-value
Gender	Male	70 (50.7%)	71 (51.5%)	0.904*
	Female	68 (49.3%)	67 (48.5%)	
Age groups (years)	≤ 2	70 (50.7%)	77 (55.8%)	0.398*
	>2 to 5	68 (49.3%)	61 (44.2%)	
Age (years), median (IQR)		2.0 (1.0-3.5)	2.4 (1.2-3.8)	0.209^
Duration of diarrhea (days)	≤ 2	102 (73.9%)	105 (76.1%)	0.677*
	>2	36 (26.1%)	33 (23.9%)	
Diarrhea duration, median (IQR)		2.0 (1.0-2.0)	2.1 (1.4-2.2)	0.171^
Nutritional status	Normal	104 (75.4%)	100 (72.5%)	0.583*
	Moderate malnutrition	34 (24.6%)	38 (27.5%)	
Residence	Urban	54 (39.1%)	51 (37.0%)	0.710*
	Rural	84 (60.9%)	87 (63.0%)	

Group-A: Zinc plus *S. boulardii* supplementation; Group-B: Zinc alone; IQR: Interquartile range
*Chi-square test applied; ^Mann-Whitney U test applied.

In terms of treatment efficacy, children in group A (zinc plus *S. boulardii*) demonstrated a significantly shorter time to resolution of both diarrhoea and vomiting; details are given in Table II. The median duration of diarrhea was 4.3 days (IQR 3.0–5.0) in Group A versus 5.1 days (IQR 4.0–5.5) in Group B ($p<0.001$). The median time to resolution of vomiting was 7.4 hours (IQR 5.0–10.0) in Group A compared with 11.2 hours (IQR 8.0–14.0) in Group B ($p<0.001$).

Table II: Comparison of efficacy of treatment (time to resolution of symptoms) in two groups (N=276)

Efficacy in terms of	Group-A (n=138)	Group-B (n=138)	P-value
Diarrhea (Days)	4.3 (3.0-5.0)	5.1 (4.0-5.5)	<0.001
Vomiting (hours)	7.4 (5.0-10.0)	11.2 (8.0-14.0)	<0.001

Group-A: Zinc plus *S. boulardii* supplementation; Group-B: Zinc alone;
Values presented in median (interquartile range).
Mann-Whitney U test applied.

Among male children, the resolution of diarrhea was significantly faster in Group A ($p<0.001$). Similar findings were seen in females ($p<0.001$). In children aged 2-5 years, diarrhea resolved earlier with zinc plus *S. boulardii* (3.9 days [IQR 3.0–5.0]) than with zinc alone (5.2 days [IQR 4.2–6.9]; $p<0.001$). Stratification by initial diarrhea duration showed a clear reduction for episodes ≤ 2 days ($p<0.001$). Significantly better outcomes with zinc plus *S. boulardii* were also seen across nutritional categories, with normal children (4.0 days [IQR 3.1–5.1] vs 4.8 days [IQR 3.9–6.0], $p<0.001$) and those with moderate malnutrition (4.3 days [IQR 3.4–5.7] vs 5.2 days [IQR 4.2–6.7], $p<0.001$) both showing faster recovery. Residence-based analysis revealed that both urban (4.0 vs 4.9 days, $p<0.001$) and rural children (4.4 vs 5.1 days, $p<0.001$) in Group A had significantly shorter resolution times than those in Group B (Table III).

Table III: Stratification of study variables with respect to resolution of diarrhea (N=276)

Variables		Group-A (n=138)	Group-B (n=138)	P-value
Gender	Male	4.0 (3.1-5.2)	4.9 (4.0-6.2)	<0.001
	Female	4.2 (3.3-5.1)	5.1 (4.0-6.3)	<0.001
Age groups (years)	≤ 2	4.2 (3.3-5.4)	4.8 (4.0-6.1)	0.072
	>2 to 5	3.9 (3.0-5.0)	5.2 (4.2-6.9)	<0.001
Duration of diarrhea (days)	≤ 2	3.9 (3.0-5.0)	5.0 (4.1-6.3)	<0.001
	>2	4.3 (3.4-5.5)	4.8 (3.9-6.2)	0.241
Nutritional status	Normal	4.0 (3.1-5.1)	4.8 (3.9-6.0)	<0.001
	Moderate malnutrition	4.3 (3.4-5.7)	5.2 (4.2-6.7)	<0.001
Residence	Urban	4.0 (3.2-5.0)	4.9 (4.0-6.1)	<0.001
	Rural	4.4 (3.3-5.3)	5.1 (4.2-6.8)	<0.001

Group A: Zinc plus *S. boulardii* supplementation; Group B: Zinc alone; Values presented in median (interquartile range). Mann-Whitney U test applied.

In male children, the median time to resolution of vomiting was 8.4 hours (IQR 5.6–11.2) in Group A compared with 10.5 hours (IQR 7.8–13.7) in Group B ($p=0.001$). In females, resolution occurred at 7.1 hours (IQR 5.0–9.3) in Group A versus 12.2 hours (IQR 9.0–15.6) in Group B ($p<0.001$). Younger children (≤ 2 years) in Group A had vomiting resolution in 8.5 hours (IQR 6.1–11.4), significantly shorter than 11.9 hours (IQR 9.1–15.2) in Group B ($p<0.001$), and in those aged >2 to 5 years, 7.0 hours (IQR 5.0–9.1) compared with 10.8 hours (IQR 8.2–14.0), also highly significant ($p<0.001$). Children with diarrhea of ≤ 2 days' duration had vomiting resolution at 8.2 hours (IQR 5.6–10.7) in Group A and 11.3 hours (IQR 8.5–14.5) in Group B ($p<0.001$), while those with >2 days' duration had 7.3 hours (IQR 5.1–9.5) versus 11.4 hours (IQR 8.6–15.0), again significant ($p<0.001$). Nutritional status showed consistent benefit, with normal children recovering in 7.8 hours (IQR 5.4–10.2) compared with 11.0 hours (IQR 8.3–14.1) ($p<0.001$), and those with moderate malnutrition in 8.3 hours (IQR 6.0–11.6) versus 12.0 hours (IQR 9.2–15.4) ($p<0.001$). Both urban (7.9 hours [IQR 5.3–10.5] vs 11.1 hours [IQR 8.4–14.0], $p<0.001$) and rural children (8.2 hours [IQR 6.0–11.0] vs 11.6 hours [IQR 9.0–15.2], $p<0.001$) demonstrated faster resolution of vomiting with the combined therapy (Table IV).

Table IV: Stratification of study variables with respect to resolution of vomiting (N=276)

Variables		Group-A (n=138)	Group-B (n=138)	P-value
Gender	Male	8.4 (5.6-11.2)	10.5 (7.8-13.7)	0.001
	Female	7.1 (5.0-9.3)	12.2 (9.0-15.6)	<0.001
Age groups (years)	≤2	8.5 (6.1-11.4)	11.9 (9.1-15.2)	<0.001
	>2 to 5	7.0 (5.0-9.1)	10.8 (8.2-14.0)	<0.001
Duration of diarrhea (days)	≤2	8.2 (5.6-10.7)	11.3 (8.5-14.5)	<0.001
	>2	7.3 (5.1-9.5)	11.4 (8.6-15.0)	<0.001
Nutritional status	Normal	7.8 (5.4-10.2)	11.0 (8.3-14.1)	<0.001
	Moderate malnutrition	8.3 (6.0-11.6)	12.0 (9.2-15.4)	<0.001
Residence	Urban	7.9 (5.3-10.5)	11.1 (8.4-14.0)	<0.001
	Rural	8.2 (6.0-11.0)	11.6 (9.0-15.2)	<0.001

DISCUSSION

The current study revealed that the time to resolution of diarrhea in the zinc plus *S. boulardii* group was significantly shorter than in the zinc-only group ($p < 0.001$). A meta-analysis of more than 4,000 articles reported that therapeutic zinc supplementation decreased episode duration, stool output, stool frequency, and hospitalization duration in children with diarrhoea.¹⁶ Similar conclusions were drawn in the study carried out by Mateen M et al.¹⁷, showing the mean duration in the zinc supplementation plus probiotics group had a mean time to diarrhea resolution of 24.08 ± 2.50 hours versus 31.35 ± 2.338 hours in the zinc supplementation alone group ($p = 0.0001$). Combined treatment was found to be more effective than zinc-only in another study where Ragavan PSK et al.¹⁸, described the post-treatment mean duration of diarrhea in the study group as 3 days, ranging from 2 to 4 days, vs 4 days in the zinc-alone group, ranging from 4 to 5 days, with $p < 0.05$. In contrast, Abdulah DM 2024¹⁹, found in their study that probiotics plus zinc supplementation had similar outcomes (no gastritis; 100% vs 98.0%, $p = 0.495$) to that of a single drug treatment.

The resolution time for vomiting in Group A was also significantly shorter than in Group B ($p < 0.001$). Somewhat similar findings were obtained by Dalgic and others.¹⁴ In another study conducted at Liaquat University Hospital, Jamshoro, 49 among 50 patients of the case group, who were given *S. boulardii* along with zinc and hypotonic ORS, showed a reduction in the duration¹². A recently published local study comparing WHO treatment with or without *S. boulardii* for acute diarrhea among children concluded that *S. boulardii* was effective when used with zinc to treat acute watery diarrhea among children, as it resulted in a significant reduction in the duration of diarrhea²⁰. Regional data in a single-blind, prospective, randomized controlled trial comparing the efficacy of *S. boulardii* among children with acute diarrhoea showed that the addition of *S. boulardii* resulted in a significant reduction in the duration of diarrhoea and vomiting, which is very aligned with the present findings²¹.

Giles-Vernick T 2016²², in a study of the therapeutic practices of parents and caregivers of children with diarrhea, reported that parents waited more than 5 days, which is significantly longer than the duration of diarrhea observed in the current study. The present study successfully rejected the null hypothesis. Regarding limitations of this study, the single-centre design and modest sample size may limit the generalizability of the present findings. The cost-benefit analysis was not performed, as neither treatment approach is cost-effective and is not provided free of charge in public hospitals either.

CONCLUSION

The addition of *Saccharomyces boulardii* to zinc supplementation significantly shortened the time to resolution of both diarrhea and vomiting in children under five years of age with acute diarrhea compared with zinc alone. The beneficial effect was consistent across most subgroups, including gender, nutritional status, and residence, with the greatest impact observed in older children and those with moderate malnutrition.

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AUTHOR CONTRIBUTION

Raza MH: Conception and design, data collection, drafting, proofreading, responsible for data's integrity, approved for publication.

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