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Role of Probiotic and Racecadotril as an Adjuvant Therapy in Management of Acute Watery Diarrhea in Children

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Author`s Contribution

[1]Substantial contributions to the conception or design of the work; or the acquisition, [2]final approval of the study to be published [3]Drafting the work or revising it critically for important intellectual content, [4]Data Collection and analysis, [5,6]Manuscript drafting and editing, data interpretation, critical review, [7]Acquisition, analysis and interpretation of data

Funding Source: None

Conflict of Interest: None

Received: Dec 07, 2024

Revised: Mar 28, 2025

Accepted: April 13, 2025

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ABSTRACT

Objective: To see the role of nonspecific antidiarrheal agents as Probiotics and Racecadotril as an adjuvant therapy among children presenting with acute watery diarrhea

Methodology: This cross-sectional comparative study was conducted in Pediatric Department Fatima Memorial Hospital Lahore from July 2023 to December 2023. One hundred and sixty children were included in this study and were equally divided in two study groups. Probiotics was given in Group A and Racecadotril treatment was given in Group B (1.5 mg/kg every eight hours). The effect of both agents was evaluated at 24 hours and 48 hours after admission in terms of improvement in the stool consistency.

Results: Out of 160 children, 97 (60.6%) were male. The mean age was 15.73 ± 9.75 months. The average duration of diarrhea before starting treatment was 2.51 ± 1.21 days, with an average of 13.56 ± 3.85 stools per day. The average number of episodes was significantly lower with Racecadotril (8.08 ± 2.97 on day 1 and 3.68 ± 1.98 on day 2) compared to Probiotics (10.01 ± 3.79 on day 1 and 7.45 ± 2.92 on day 2) with p value 0.000 on both day 1 and day 2 comparison. The result showed that Racecadotril demonstrated better efficacy compared to probiotics with significant improvement in stool grades on the first and second day of treatment (p value 0.000 and 0.001, respectively).

Conclusion: We concluded that Racecadotril is significantly more effective in treating acute watery diarrhea in children.

Keywords: Acute watery diarrhea, Dehydration, Diarrhea grades, Probiotics, Racecadotril

Cite this article as: Asghar L, Usman M, Gul R, Tahir A, Bashir MU, Hussain I, Hashmi FUI. Role of Probiotic and Racecadotril as an Adjuvant Therapy in Management of Acute Watery Diarrhea in Children. Ann Pak Inst Med Sci. 2025; 21(2):424-429. doi. 10.48036/apims.v21i2.1426.

Introduction

Acute diarrhea affects about 2 billion children every year and is a leading cause of mortality in developing countries, accounting for 1.9 million deaths annually.[1] Acute diarrhea is characterized by three or more episodes of loose and watery stools per day, lasting less than 14 days.[2] Symptoms of acute diarrhea include loose or watery stools, often accompanied by fever, vomiting, abdominal pain, and post-diarrheal abdominal distension. Additionally, acute watery diarrhea remains a leading cause of significant morbidity in infants and toddlers.[3] Children with co-morbidity or severe malnutrition require special care since they are at a higher risk of developing complications, including infections, electrolyte imbalances, and potentially death.[4]

The burden of diarrhea is significantly higher in low- and middle-income countries.[5] This is caused by several factors, including the consumption of unsafe drinking water, poor sanitation and hygiene practices, contamination of water sources with fecal coliforms, reliance on leftover food, and overall low public health and nutritional standards. Mortality rates are notably high in these regions, driven by limited access to affordable healthcare and inefficient treatment strategies.[6] Alarmingly, over one billion people lack access to safe

drinking water, and approximately 2.5 billion lack adequate sanitation facilities, underscoring the critical need for improved infrastructure and health interventions in these settings.[7]

Pakistan is one of 15 developing countries that bear the majority of the global diarrhea burden. With over 27 million children under the age of five, the country reports approximately 4.4 million cases of diarrhea annually. Recent studies indicate that diarrhea causes 74 deaths per 1,000 children each year, making it as a critical public health concern.[8]

The pathogenesis of acute diarrhea in children occurs through two primary mechanisms: secretory or osmotic.[9,10] Treatment typically focuses on supportive care, emphasizing rehydration to compensate for the loss of water and electrolytes. Additionally, zinc supplementation is commonly prescribed to aid in recovery and reduce the duration and severity of diarrhea.[10]

Another commonly used class of medications for acute diarrhea is antidiarrheal agents, which function as antisecretory, antimotility, absorbent, or probiotics.[11] Among these, Racecadotril, an antisecretory agent, works by inhibiting the degradation of neutral endopeptidase enzymes, specifically enkephalins—endogenous opioid peptides secreted by myenteric and submucosal neurons in the digestive tract. By activating the sigma opioid receptor, Racecadotril reduces the secretion of chloride ions, thereby decreasing fluid and electrolyte loss associated with diarrhea.[12] Probiotics are another important category of antidiarrheals. According to the WHO, probiotics are defined as "live organisms, which when administered in adequate amounts, confer a health benefit to the host.[13]" Commonly used probiotics include strains such as Lactobacillus and Bifidobacterium, as well as yeast like Saccharomyces boulardii. These probiotics help restore a healthy gut flora balance, enhance the immune response, and support recovery from diarrhea by populating the gut with beneficial bacteria.[14]

Our study aims to identify the most effective agent for relieving diarrhea symptoms in the shortest possible time. In this study, children aged 2 months to 3 years, prescribed an antisecretory agent such as Racecadotril, are compared with those receiving probiotics to evaluate their improvement over the next 48 hours. This comparison will not only help determine the relative effectiveness of these antidiarrheal but also guide the selection of the most appropriate treatment for rapid symptom relief. Ultimately, the findings will improve patient outcomes by reducing complications and mortality associated with diarrhea.

Methodology

This cross-sectional comparative study was planned from July 2023 to December 2023, in Pediatric Department Fatima Memorial Hospital Lahore. It was approved by the ethical committee of the hospital, with IRB certificate No. FMH-19/04/2023-IRB-1208, dated June 16, 2023. The selection of neonates was made subject to the confirmation from their parents/caregivers.

Children passing 3 or >3 loose stools/day for more than 24 hours, dehydrated, aged between 2 months to 3 years, both genders, and no diarrhea in the past 3 months were included in our study. Children were excluded having mucus or blood in stools, comorbidities like third degree malnutrition kidney and liver disease. Children diagnosed as case of cow milk protein allergy or lactose intolerance, with post diarrheal distension, having history of parenteral diarrhea, confirm cases of bacterial infection i.e. neutrophilia and increased CRP, were also excluded from this study.

The sample size of the study was calculated with mean frequency of stool at day 2 of treatment with probiotics 4.54±0.83[15] and mean frequency of stool at day 2 with treatment of Racecadotril 3.12±0.8.[16] Keeping confidence level 95% and power of test, the minimum sample required to conduct this study is 30 in each group whereas we were included 80 cases in each group.

Out of the total 160, patients were equally divided into two study groups using an even-and-odd allocation method. Group A consisted of patients treated with probiotics while Group B included patients treated with the anti-secretory drug i.e. Racecadotril. Racecadotril was given at a dose of 1.5 mg/kg every eight hours, available in granules form packed in 10 mg & 30 mg sachets. The granules were dissolved in a little amount of water and given orally.

The efficacy of the treatment was assessed based on improvement in stool output, specifically focusing on stool consistency, as categorized by the WHO. According to the WHO grading of diarrhea[17] is as follows: Normal formed stools are grade I, Soft stools are grade II, liquid stools taking shape of container are grade III, watery stools with flakes appearing opaque in glass container are grade IV, and watery stools with few flakes appearing translucent in color are grade V.

All patients meeting the study protocols were enrolled through consecutive sampling until the required selection was completed. Data was recorded in a predesigned proforma. Stool consistency and the degree of dehydration were assessed at admission. The effects of both agents were evaluated at 24 and 48 hours, based on improvements in stool consistency using WHO grading for diarrhea. In addition to the prescribed therapy, Oral Rehydration Solution (ORS) and IV fluids were administered as needed. Patients were discharged after complete recovery. Dehydration was categorized as no dehydration, some dehydration, or severe dehydration, based on clinical signs and symptoms at admission and discharge. In no dehydration, the patient is well and alert, the eyes are normal, drinks normally or is not thirsty, and skin turgor goes back quickly. In some dehydration, the patient is restless and irritable, the eyes are sunken, drinks eagerly due to thirst, and skin turgor goes back slowly. In severe dehydration, the patient is lethargic or unconscious, the eyes are deeply sunken, drinks poorly or is unable to drink, and skin turgor goes back very slowly.[18]

Data was entered and analyzed in Statistical package for social sciences (SPSS) version 25. Categorical variables were presented in form of frequency and percentages whereas quantitative variables were discussed in the form of mean ± SD. Descriptive analysis was conducted to summarize the data. Chi square test was used to see association between groups. p-value less than 0.05 was considered significant.

Results

We included 80 cases of diarrhea in each group of the study. Out of the 160 children, 97 (60.6%) were male and the remaining 63 (39.4%) were female. A total of 86 (53.8%) children were aged up to 1 year, with a mean age of 15.73 ± 9.75 months. On initial examination before hospitalization, all children were dehydrated, with 61 (38.9%) experiencing severe dehydration. At the time of admission, 58 (36.3%) children presented with grade 3 stools, 86 (53.8%) with grade 4 stools, and 16 (10%) with grade 5 stools. The average duration of diarrhea before starting treatment was 2.51 ± 1.21 days, with an average of 13.56 ± 3.85 stools per day. A comparison of children before hospitalization is shown in table I.

The result showed that Racecadotril demonstrated better efficacy compared to probiotics with significant improvement in stool grades on the first and second days of treatment (p value 0.000 and 0.001, respectively).

Table I: Comparison of two groups based on the initial condition of the children at admission.

Characteristics/ Variables	Group A	Group B	p value
Gender			
Male	26 (32.5)	37 (46.25)	0.075
Female	54 (67.5)	43 (53.75)	
Age (Months)	13.04 ± 7.4	18.41 ± 11.05	0.000
Weight (Kg)	9.44 ± 3.43	12.83 ± 12.24	0.019
Length (cm)	68.09 ± 19.21	79.44 ± 11.58	0.000
Head circumference (cm)	45.14 ±7.81	45.98 ± 3.11	0.374
Duration of diarrhea (days)	2.44 ± 1.14	2.58 ± 1.28	0.473
Level of Dehydration			
No dehydration	0	0	0.871
Some dehydration	49 (61.25)	50 (62.5)	
Severe dehydration	31 (38.75)	30 (37.5)	
Diarrhea grades (Before treatment)			
Grade I	0	0	0.479
Grade II	0	0	
Grade III	26 (32.5)	28 (35)	
Grade IV	48 (60)	42 (52.5)	
Grade V	6 (7.5)	10 (12.5)	

Similarly, Racecadotril reduced the number of diarrhea episodes more effectively. The average number of episodes was significantly lower in Group B (8.08 ± 2.97) compared to Group A (10.01 ± 3.79) on Day 1 (p = 0.000). On Day 2, the number of episodes in Group B was 3.68 ± 1.98, compared to 7.45 ± 2.92 in Group A(p = 0.000).

On day 3 of treatment, all patients were recovered from watery diarrhea. However, 126 (78.75%) patients were hospitalized for more than 02 days for the treatment of dehydration. (Figure 2)

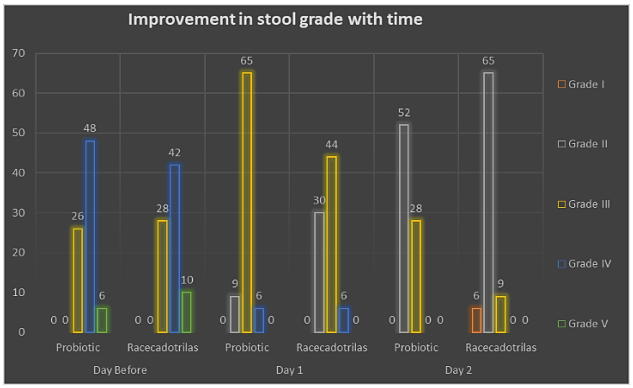

Figure 1. Improvement in stool grade with time in two study groups.

The mean hospitalization duration in Group A was 3.34 ± 0.9 days, compared to 3.05 ± 0.94 days in Group B, with p value 0.05.

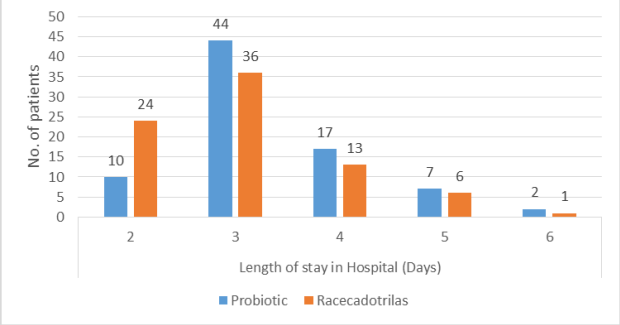

Figure 2. Comparison of hospitalization between two study groups.

Table II: Post-stratification comparison with respect of age groups of Probiotics and Racecadotril.

Time		Stool grades	Group A	Group B	p value
Day 1	Infants	Grade I	0	0	0.972
		Grade II	6 (12)	6 (16.7)	
		Grade III	42 (84)	27 (75)	
		Grade IV	2 (4)	3 (8.3)	
		Grade V	0	0	
	Toddlers	Grade I	0	0	0.000
		Grade II	3 (10)	24 (54.5)	
		Grade III	23 (76.7)	17 (38.6)	
		Grade IV	4 (13.3)	3 (6.8)	
		Grade V	0	0	
Day 2	Infants	Grade I	0	3 (8.3)	0.02
		Grade II	35 (70)	28 (77.8)	
		Grade III	15 (30)	5 (13.9)	
		Grade IV	0	0	
		Grade V	0	0	
	Toddlers	Grade I	0	3 (6.8)	0.000
		Grade II	17 (56.1)	37 (84.1)	
		Grade III	13 (43.3)	4 (9.1)	
		Grade IV	0	0	
		Grade V	0	0	

Post-stratification result showed that children of Group B showed quicker recovery from diarrhea as compared to Group A irrespective of children's age and treatment day.

Discussion

Our study aimed to evaluate the role and efficacy of probiotics vs Racecadotril in managing acute watery diarrhea in children aged 2 months to 3 years admitted to a tertiary care hospital in Pakistan. Although several relevant studies have been conducted in different countries regarding their role in acute watery diarrhea but there has been no published data comparing these two agents. Our results demonstrate that while both treatment modalities are effective, Racecadotril shows a superior efficacy in reducing the severity and frequency of diarrhea episodes, compared to probiotics.

The findings of our study align with previous studies highlighting the anti-secretory effects of Racecadotril in reducing stool output and its rapid onset of action in managing acute diarrhea. A recent study conducted by Tahir R et al[19] in Pakistan demonstrated that Racecadotril's efficacy was higher in treating children with acute watery diarrhea than ORS alone in children under 5 years old. Similarly, Salazar-Lindo E et al[20] demonstrated that Racecadotril significantly reduced stool output and shortened the duration of diarrhea compared to placebo. A systematic review and meta-analysis by Eberlin et al[21] assessed Racecadotril's efficacy in treating acute diarrhea in children. The analysis concluded that Racecadotril effectively reduced the duration of diarrhea and stool output, supporting its use as an adjunct to ORT. These studies support our conclusion that Racecadotril is a highly effective treatment for acute watery diarrhea in Pediatric populations.

In contrast, a randomized clinical trial by Zulfiqar et al[22] compared ORS with and without Racecadotril in children with acute diarrhea. The study found that the addition of Racecadotril to ORS did not significantly reduce the mean duration of illness, suggesting that while Racecadotril may offer benefits, its impact on illness duration may be limited.

In comparison, probiotics have shown moderate efficacy in previous studies. For instance, a meta-analysis by Allen et al[23] reported that probiotics can reduce the duration of diarrhea by approximately one day, particularly in cases caused by viral infections. A randomized controlled trial by Abdullah DM[24] assessed the combined effect of probiotics and zinc supplementation found no significant improvement in clinical outcomes for infants and children with acute infectious diarrhea. The findings of these researchers align with our results.

Conversely, some studies reported benefit of probiotics in decreasing duration of diarrhea. A systematic review and meta-analysis by Haung R et al[25] concluded that probiotics can reduce the duration of diarrhea and hospital stays in pediatric patients, supporting their therapeutic role. These discrepancies may be attributed to variations in probiotic strains, dosages, study populations, and methodologies.

Hospitalization duration was another important outcome in our study. The mean hospitalization duration was slightly shorter in Group B (3.05 ± 0.94 days) compared

to Group A (3.34 ± 0.9 days), although the p-value of 0.05 suggests a marginal statistical significance. Nevertheless, the quicker resolution of diarrhea symptoms in Group B likely contributed to the shorter hospitalization period, reducing the burden on healthcare resources and caregivers.

The strengths of our study include a robust sample size, strict inclusion and exclusion criteria, and the use of standardized WHO grading for stool consistency, which enhances the reliability of our findings. However, some limitations should be noted. The study was conducted at a single center, which may limit the generalizability of the results. Additionally, the relatively short follow-up period may not capture long-term outcomes, such as the recurrence of diarrhea or the impact on gut microbiota.

The observed superiority of Racecadotril in our study aligns with some previous research, indicating its potential as an effective adjunct therapy. However, the variability in study outcomes highlights the need for further large-scale, multicenter trials to establish definitive treatment guidelines.

Conclusion

In conclusion, while both probiotics and Racecadotril are beneficial in managing acute watery diarrhea in children, our study suggests that Racecadotril may offer a more rapid improvement in clinical outcomes. Healthcare providers should consider these findings in the context of individual patient needs and existing clinical guidelines.

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