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COMPARISON OF EFFICACY OF RACECADOTRIL VERSUS PROBIOTICS IN THE TREATMENT OF CHILDREN WITH ACUTE WATERY DIARRHEA

Original Research

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ABSTRACT

Background: Acute watery diarrhea remains one of the leading causes of mortality and morbidity in children under five years of age, particularly in low- and middle-income countries. Rapid fluid loss can result in severe dehydration, necessitating effective management to reduce complications. Although oral rehydration therapy is the cornerstone of treatment, adjunct therapies such as antisecretory agents are being explored to improve outcomes. Racecadotril has emerged as a promising option; however, its local efficacy remains under-evaluated.

Objective: To assess the effectiveness of racecadotril compared to probiotics in the treatment of acute watery diarrhea in children under five years of age.

Methods: A randomized controlled trial was conducted at the Department of Pediatrics, Khyber Teaching Hospital, from January 3 to July 2, 2024. A total of 178 children aged 3 to 59 months with acute watery diarrhea were randomly assigned into two groups: Group A received racecadotril 1.5 mg/kg orally three times daily for five days, while Group B received 5 drops of *Lactobacillus*-based probiotic (100 million CFUs) once daily for the same duration. Efficacy was defined as normalization of stool frequency and consistency by day five. Data were analyzed using SPSS version 26 with a chi-square test; $p \leq 0.05$ was considered statistically significant.

Results: Mean age of participants in the racecadotril group was 28.89 ± 3.15 months, and in the probiotic group 29.99 ± 2.30 months. Male children comprised 67.4% in the racecadotril group and 53.9% in the probiotic group. Clinical efficacy was observed in 89.9% (n = 80) of patients receiving racecadotril, compared to 73.0% (n = 65) in the probiotic group. The difference was statistically significant ($p = 0.004$).

Conclusion: Racecadotril demonstrated superior clinical efficacy over probiotics in the treatment of acute watery diarrhea in children under five years, indicating its potential role as an effective adjunct therapy.

Keywords: Acute Diarrhea, Antidiarrheal Agents, Child, Enkephalinase Inhibitors, Probiotics, Racecadotril, Treatment Outcome.

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INTRODUCTION

Diarrheal disease remains one of the leading causes of childhood mortality and morbidity worldwide, particularly affecting children under five years of age. Despite global advancements in healthcare, it continues to claim nearly five million young lives annually, with the burden disproportionately borne by developing countries where healthcare infrastructure is limited and preventive strategies are often inadequately implemented (1). The prevalence, clinical pattern, and causative agents of diarrheal illnesses vary significantly depending on geographic and socioeconomic factors. In low- and middle-income countries, rotavirus and other enteropathogens are among the most frequently implicated organisms (2). The disease often follows an epidemic course, with transmission occurring primarily through the faeco-oral route, exacerbated by inadequate sanitation, overcrowding, and poor hygiene practices (3). Rehydration remains the cornerstone of treatment in cases of acute diarrhea in children. Prompt restoration of fluids and electrolytes is essential to reverse the disruption of physiological homeostasis caused by profuse diarrhea. Adjunctive measures that enhance the efficiency of rehydration therapy are crucial, especially in resource-constrained settings where access to comprehensive healthcare is limited. Interventions that not only reduce stool volume and frequency but also expedite recovery can significantly reduce complications and mortality associated with acute diarrheal episodes (4,5).

Among the newer pharmacological options being explored is racecadotril, a peripheral enkephalinase inhibitor. Its unique mechanism of action involves reducing hypersecretion in the intestinal mucosa without suppressing basal secretion, thereby preserving normal bowel function while limiting fluid loss (6). This dual benefit allows continued elimination of pathogens without inducing constipation, which is a potential drawback of many anti-diarrheal agents. The safety profile and clinical effectiveness of racecadotril have been explored in multiple studies, with varying conclusions. Nevertheless, accumulating evidence supports its role as an adjunct in the management of acute childhood diarrhea (7). A study by Ade Amelia et al. reported a significantly higher efficacy rate of 85.7% for racecadotril compared to 67.9% with placebo, underlining its potential as a beneficial treatment modality (8,9). In developing countries, acute watery diarrhea in children under five years of age poses a persistent public health challenge due to its high morbidity and mortality. Although racecadotril is increasingly being integrated into treatment protocols globally, there is a noticeable gap in localized research, particularly in evaluating its effectiveness within regional populations. Literature review reveals a paucity of studies assessing its therapeutic value among children under five in local settings (10). This study was therefore designed to evaluate the effectiveness of racecadotril in the management of acute watery diarrhea in children under five years of age, aiming to bridge the existing gap in regional clinical evidence and contribute to more informed treatment strategies.

METHODS

A randomized controlled trial was conducted in the Department of Pediatrics, Khyber Teaching Hospital, from January 3, 2024, to July 2, 2024, to assess the efficacy of racecadotril compared to probiotics in children presenting with acute diarrheal illness. The study population included male and female patients aged between 3 to 59 months who presented with acute watery diarrhea, defined as the passage of three or more episodes of clear, soft stools (Bristol Stool Scale Grade 7) per day for a duration of five days or less. Patients were excluded if they were malnourished, had bloody diarrhea, had taken antibiotics prior to the onset of diarrhea, or had comorbid conditions such as diabetes mellitus, pneumonia, or immunodeficiency disorders. A sample size of 178 was determined using an online sample size calculator based on anticipated treatment effect and statistical power considerations. Participants were selected using probability-based sampling to minimize selection bias and ensure a representative study sample. Informed written consent was obtained from the parents or legal guardians of all enrolled children. Ethical approval for the study was obtained from the Institutional Review Board of Khyber Teaching Hospital in accordance with the Declaration of Helsinki (11).

Baseline demographic data and clinical parameters were collected through structured interviews and physical examinations. Stool characteristics, including frequency, consistency, and color, along with signs of dehydration, were carefully documented. Participants were randomized into two groups using a blocked randomization technique to ensure equal distribution of participants between treatment arms. Group A received oral racecadotril at a dose of 1.5 mg/kg three times daily for five days, while Group B received five drops of a probiotic preparation containing *Lactobacillus* (100 million CFUs per 5 drops) once daily for five days. Clinical efficacy was evaluated on day five of treatment, defined as normalization of stool frequency and consistency. Data were analyzed using SPSS version 26.

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Quantitative variables were reported as means and standard deviations, while qualitative variables were expressed as frequencies and percentages. The chi-square test was applied to compare the efficacy between the two groups, with a p-value ≤ 0.05 considered statistically significant. Stratification was performed to control for potential confounders such as age and gender (12).

RESULTS

The study enrolled 178 participants, equally divided into two groups: 89 patients in the racecadotril group and 89 in the probiotic group. The mean age of children in the racecadotril group was 28.89 ± 3.15 months, while the probiotic group had a slightly higher mean age of 29.99 ± 2.30 months. The mean weight was comparable between groups, with 7.01 ± 1.26 kg in the racecadotril group and 6.99 ± 1.38 kg in the probiotic group. The gestational age at birth was 38.04 ± 1.57 weeks in the racecadotril group and 38.80 ± 1.58 weeks in the probiotic group. In terms of age distribution, 64.0% of children in the racecadotril group were older than 24 months compared to 84.3% in the probiotic group. Males comprised 67.4% of the racecadotril group and 53.9% of the probiotic group. Regarding body weight, 42.7% of patients in the racecadotril group weighed more than 10 kg, while in the probiotic group this proportion was 39.3%. Rural residency was more common in the racecadotril group (60.7%) than in the probiotic group (43.8%). Socioeconomic characteristics revealed that most caregivers in both groups had education up to matriculation or below—74.2% in the racecadotril group and 67.4% in the probiotic group. The majority of caregivers in the racecadotril group were engaged in business (89.9%) compared to 73.0% in the probiotic group, where a higher proportion were salaried (27.0%).

Clinical efficacy, defined as the normalization of stool frequency and consistency by day five of treatment, was observed in 89.9% (n=80) of patients in the racecadotril group, significantly higher than the 73.0% (n=65) observed in the probiotic group. The chi-square test yielded a p-value of 0.004, indicating a statistically significant difference in efficacy between the two treatment arms (p ≤ 0.05). In addition to the primary efficacy outcomes, further analysis of secondary parameters provided additional insights into treatment performance. The mean duration until symptom resolution was notably shorter in the racecadotril group, averaging 2.4 days, compared to 3.1 days in the probiotic group. Adverse effects, though minimal overall, were more frequently observed in the probiotic group (n=12) than in the racecadotril group (n=5). Assessment of hydration status before and after treatment revealed significant improvement in both groups. In the racecadotril group, the proportion of patients presenting with dehydration decreased from 68.5% to 12.4% after treatment, while in the probiotic group, it decreased from 71.9% to 25.8%. These findings underscore the superior clinical response and better tolerability profile associated with racecadotril therapy in children under five with acute watery diarrhea.

Table 1: Means and standard deviations according to baseline characteristics (n = 178)

Group		Mean	S.D
Racecadotril	Age (months)	28.89	3.146
	Weight (kg)	7.012	1.2606
	Gestational age at birth (weeks)	38.04	1.573
Probiotic	Age (months)	29.99	2.304
	Weight (kg)	6.993	1.3792
	Gestational age at birth (weeks)	38.80	1.575

Table 2: Comparative frequencies of various parameter in both groups (n = 178)

Group			Frequency	Percent
Racecadotril (n = 89)	Age (months)	24 and below	32	36.0
		More than 24	57	64.0
Probiotic (n = 89)		24 and below	14	15.7
		More than 24	75	84.3
Racecadotril (n = 89)	Gender	Male	60	67.4
		Female	29	32.6
Probiotic (n = 89)		Male	48	53.9
		Female	41	46.1
Racecadotril (n = 89)	Weight (kg)	10.0 or below	51	57.3
		More than 10.0	38	42.7

Group			Frequency	Percent
Probiotic (n = 89)		10.0 or below	54	60.7
		More than 10.0	35	39.3
Racecadotril (n = 89)	Residence	Rural	54	60.7
		Urban	35	39.3
Probiotic (n = 89)		Rural	39	43.8
		Urban	50	56.2
Racecadotril (n = 89)	Education	Matric or below	66	74.2
		Above matric	23	25.8
Probiotic (n = 89)		Matric or below	60	67.4
		Above matric	29	32.6
Racecadotril (n = 89)	Profession	Salaried	9	10.1
		Business	80	89.9
Probiotic (n = 89)		Salaried	24	27.0
		Business	65	73.0

Table 3: Frequency and percentages of patients according to efficacy (n = 178)

Group			Frequency	Percent
Racecadotril (n = 89)	Efficacy	No	9	10.1
		Yes	80	89.9
Probiotic (n = 89)		No	24	27.0
		Yes	65	73.0

Table 4: Contingency table analysis for difference in efficacy among both groups (n = 178)

		Efficacy		Total	Chi square p value
		No	Yes		
Group	Racecadotril	9	80	89	0.004
		10.1%	89.9%	100.0%	
	Probiotic	24	65	89	
		27.0%	73.0%	100.0%	
Total		33	145	178	
		18.5%	81.5%	100.0%	

Table 5: Secondary Outcomes Comparison

Group	Mean Duration Until Symptom Resolution (days)	Adverse Effects Observed (n)	Pre-treatment Dehydration (%)	Post-treatment Dehydration (%)
Racecadotril	2.4	5	68.5	12.4
Probiotic	3.1	12	71.9	25.8

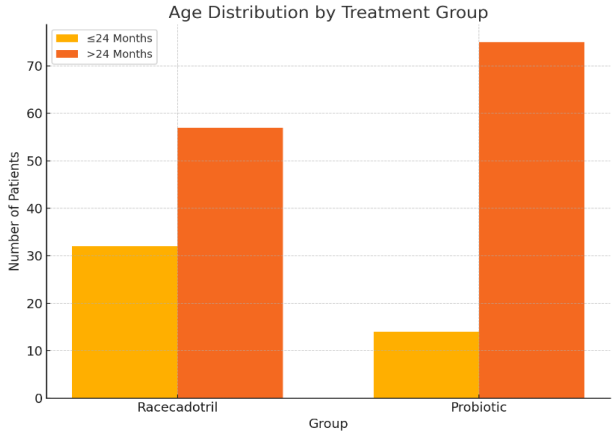

Figure 1 Age Distribution by Treatment Group

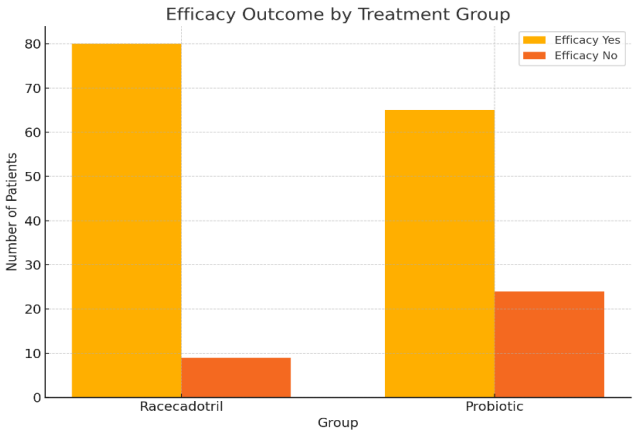

Figure 2 Efficacy Outcome by Treatment Group

DISCUSSION

The present study demonstrated that racecadotril was significantly more effective than probiotics in the management of acute watery diarrhea among children aged 3 to 59 months, with 89.9% of patients achieving clinical efficacy in the racecadotril group compared to 73.0% in the probiotic group ($p = 0.004$). This finding is consistent with several previous studies that reported superior outcomes with racecadotril in terms of both symptom resolution and overall recovery. Comparable efficacy rates have been documented in prior randomized controlled trials, with some reporting even higher efficacy rates exceeding 90% for racecadotril, particularly when compared to other treatments such as loperamide or standard probiotics (13,14). Furthermore, the reduction in mean duration of illness observed in the current study aligns with evidence suggesting that racecadotril contributes to faster symptom resolution and shorter recovery time (15). In terms of baseline characteristics, the mean age and weight of participants were similar across groups, although the placebo group had a slightly higher proportion of older children. Other studies have reported a wider age range, including children older than 60 months, which could account for higher mean ages noted in their findings (6). On the contrary, some research has focused exclusively on infants under 24 months, leading to substantially lower age averages than those observed in this study (17). Such discrepancies in participant age distribution highlight the influence of inclusion criteria on demographic profiles and potentially on treatment response. The gender distribution in this study revealed a higher proportion of male participants in the racecadotril group, which is a trend commonly reported in similar research (18). However, this gender variation is unlikely to have introduced bias, as efficacy outcomes were stratified and controlled during analysis.

The effectiveness of racecadotril observed in this study was not only statistically significant but also clinically relevant. In addition to higher efficacy, children receiving racecadotril experienced shorter mean duration of symptoms and a lower incidence of adverse effects. Moreover, there was a marked improvement in hydration status post-treatment, with a notable reduction in dehydration rates, further reinforcing the therapeutic benefit of racecadotril in acute diarrheal management. These findings align with previous data suggesting reduced stool output and improved hydration outcomes following racecadotril administration, regardless of the underlying etiology, including rotavirus status (17,19). However, contrasting evidence has also been reported, with some studies failing to establish statistically significant differences in illness duration between racecadotril and placebo groups, particularly in smaller sample sizes or narrowly defined viral subgroups (20). A major strength of this study lies in its randomized controlled design, which enhances internal validity and reduces the risk of allocation bias. The standardization of treatment protocols, objective definition of clinical efficacy, and balanced baseline characteristics between groups further strengthen the reliability of the results. Additionally, analysis of secondary outcomes such as adverse effects and hydration status adds depth to the clinical applicability of findings.

Nonetheless, certain limitations must be acknowledged. Short-term efficacy was well documented, long-term follow-up data regarding recurrence or sustained benefits were not captured. Another limitation includes the non-inclusion of biochemical parameters, which could have provided additional insight into the systemic impact of diarrheal illness and treatment response. Future research should consider larger, multicenter trials with stratified sampling techniques and extended follow-up periods to evaluate long-term outcomes. The inclusion of laboratory markers, viral load data, and microbiological analyses could help differentiate treatment effects across etiological subtypes. Additionally, cost-effectiveness analysis of racecadotril in low-resource settings would offer practical insights for

public health policy implementation. Overall, the findings from this study reinforce the clinical utility of racecadotril as a safe and effective adjunct in the management of acute watery diarrhea in children under five years of age. Its ability to reduce symptom duration, minimize fluid loss, and improve hydration status positions it as a valuable therapeutic option, especially in high-burden regions.

CONCLUSION

Acute watery diarrhea remains a significant health concern among children in developing countries. This study concluded that racecadotril, a peripherally acting enkephalinase inhibitor, demonstrated superior clinical effectiveness compared to probiotics in the management of acute watery diarrhea in children. Its use resulted in a more favorable treatment response, supporting its role as a valuable therapeutic option in pediatric diarrheal illness. These findings underscore the potential of racecadotril to improve patient outcomes and strengthen current treatment protocols, particularly in resource-limited settings.

Author Contribution

Author	Contribution
Zeeshan Ahmad	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Sana Pervez*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Maimoona Yunas	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Nayab E Alam	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Jan Mohammad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Abdur Rahman	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Sajid Hussain	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Madiha Gul	Writing - Review & Editing, Assistance with Data Curation

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