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Randomized Clinical Trial Comparing The Effect Of Oral Rehydration Therapy With And Without Racecadotril In The Management Of Acute Diarrhea In Children

Sughra Zulfiqar[1], Hifza Zeb[2], Nadia Mumtaz[3], Ammara Mushtaq Khan[4], Taimur Khalil Sheikh[5], Tariq Saeed[6]

Abstract

Objective: This study aimed to investigate the beneficial effect of racecadotril in children with acute diarrheal illness.
Methods: This randomized case-control study was conducted at Watim General Hospital over four months from April to July 2023. A total of 120 children aged 3 months to 12 years with acute diarrhoea were included and randomly allocated to two groups. Group A (n=60) received standard treatment with oral rehydration therapy, while Group B (n=60) received oral rehydration therapy, zinc, probiotics, and racecadotril. The primary outcome measured was the mean duration of illness, and the secondary outcome was the number of stools 48 hours after the start of treatment. Data were collected using a pre-designed proforma and analyzed using SPSS version 24.
Results: The study population had an average age of 50.35±41.52 months, with equal gender distribution. The mean duration of illness in Group A was 2.72±1.34 days, while in Group B, it was 2.70±1.29 days. There was no statistically significant difference in the mean duration of illness between the two groups (p=0.945).
Conclusion: This study did not demonstrate a significant reduction in the mean duration of illness for children with acute gastroenteritis using standard treatment with or without racecadotril. Further investigations and large-scale studies may be needed to establish the efficacy of racecadotril in the management of acute diarrhoea in children.
Keywords: Acute diarrhoea, ORS, Racecadotril.

[1] Assistant Professor, Watim Medical College, Rawalpindi; [2] Medical Officer, DHQ, Attock; [3] Senior Registrar, Holy Family Hospital, Rawalpindi; [4] Senior Registrar, Riphah International Hospital; [5] Assistant Professor, Al-Nafees Medical College, Islamabad; [6] Professor, Watim Medical College, Rawalpindi.
Correspondence: Dr. Sughra Zulfiqar, Assistant Professor, Watim Medical College. **Email:** drsughrazulfiqar@gmail.com
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1. Introduction

Acute diarrhoea poses a significant global health challenge, especially for children. Diarrhea affects around 2.5 billion people annually, with approximately 1.5 million deaths reported.[1] Children constitute 40% of the morbidity and 30% of the mortality, especially those in their first two years of life[2]. Oral rehydration therapy (ORT) is the primary treatment for acute watery diarrhoea, and dehydration prevention is crucial in reducing mortality and morbidity[2,3]. Recently, researchers have focused on anti-secretory agents like racecadotril to address the mechanisms causing water and electrolyte loss during diarrhoea. This study aims to assess the efficacy of racecadotril as an additional therapy in children with acute diarrhoea.

ESPGHAN recommends the utilization of anti-secretory agents, such as racecadotril and diosmectite, in managing acute diarrhoea in children to reduce the frequency of diarrheal episodes, although these agents do not impact the overall mortality of the illness.[4,5]

Racecadotril, a relatively newer anti-secretory agent, operates through a distinct mechanism of action. It functions by inhibiting the enzyme endopeptidase located at the epithelium of intestinal cells, thereby prolonging the life of the anti-secretory agent enkephalin. This process helps curtail the hypersecretion of water and salts from the intestinal epithelium, effectively preventing dehydration[6]. While racecadotril has been employed in developed countries, its incorporation into guidelines for routine use in children with acute diarrhoea is yet to be definitively established.[8]

According to a study conducted in Malaysia, the combination of ORS and racecadotril is reported to be more advantageous and cost-effective than using ORS alone[7]. Additionally, Sreeni vas et al. observed a significant 34.1% reduction in stool frequency at 48 hours.

Numerous previous studies have consistently demonstrated the efficacy of racecadotril in reducing both stool output and the mean duration of illness in children with acute diarrhoea. A comprehensive meta-analysis, which included a total of 11 studies, reaffirmed that racecadotril administration, when compared to placebo, significantly decreases the duration of diarrhoea.[12] It is important to note that all these studies were conducted in developed countries, and no local investigations on this subject are available in Pakistan, where acute diarrhoea is a commonly encountered issue among children. Considering Pakistan's status as a resource-limited country, the potential effectiveness of racecadotril presents an opportunity for a cost-effective intervention in reducing the duration of illness in children presenting with acute diarrheal illness. By doing so, it not only alleviates the burden on healthcare facilities but also provides relief to affected families.

2. Materials & Methods

This study utilized a randomized case-control clinical design with a convenience sampling technique. It was conducted at Watim General Hospital over four months, starting from April 2023 to July 2023. A total of 120 children aged 3 months to 12 years of either gender, presenting with at least three episodes of loose stools in 24 hours lasting up to 7 days, were included in the study. Children with chronic diarrhoea, blood in stools, suspected sepsis, malabsorption syndrome, or shock due to dehydration were excluded. The children were randomized into a control group (Group A) or a case group (Group B). Written consent was obtained from parents before randomization. Group A received standard treatment comprising ORT, zinc, and probiotics, while Group B received the same treatment plus racecadotril.

The primary outcome measured was the mean duration of illness, and the secondary outcome was the number of stools at 48 hours post-treatment.

Randomization was done by computer-generated sequencing in blocks of varying sizes. Attrition bias was reduced by the provision of 10% extra for the sample size. The outcomes measured were pre-designed so the selective reporting bias would be eliminated. The sample size was calculated by the WHO sample size calculator using the outcome of a total number of stools at 48 hours. Study power was taken at 90% with a 95% significance level. After providing 10 % for attrition the sample size of 120 (60 in each group) was finalized.

Data was collected in the form of variables and entered and analyzed on SPSS version 24. Frequencies and percentages calculated for qualitative data. Mean and standard deviation of quantitative data i.e. age, episodes of diarrhoea at 48 hours post-treatment, and duration of illness was calculated. A two-sided t-test was used to compare the difference between the duration of illness in the two groups. Variables like age, gender, duration of symptoms, and the number of episodes of diarrhoea at 48 hours between the two groups were corrected by stratification analysis. A p-value < 0.05 was considered statistically significant.

3. Results

The study comprised 60 children in each group, with an equal distribution of male and female participants as shown in Figure 1. The mean age of the participants was 50.35 months. In Group A, the mean duration of illness was 2.72±1.34 days, while in Group B, it was 2.70±1.29 days. There was no statistically significant difference in the mean duration of illness between the two groups (p=0.945).

Table 1: Descriptive Statistics of Characteristics of Study Patients

Variables	Group A n=60		Group B n=60		Overall n=120	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Age(months)	50.12	43.67	50.58	39.63	50.35	41.52
Duration of illness (Days)	2.72	1.34	2.7	1.29	2.71	1.31
Number of Episodes	5.5	1.19	5.35	1.1	5.43	1.14

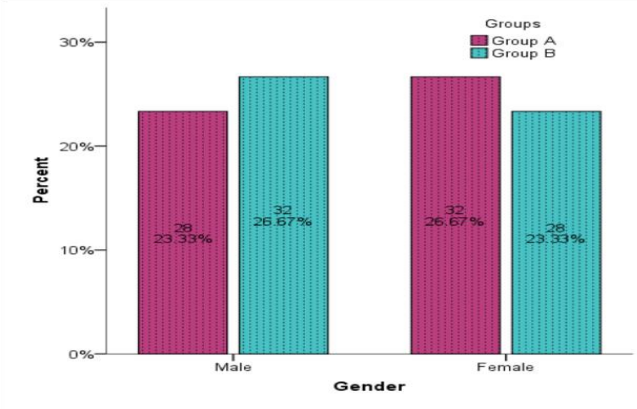

Figure 1: Gender Distribution of The Patients N=120

Figure 2 presents a comparison of the mean duration of illness between groups of acute diarrhea in children. Notably, the case and control groups did not exhibit a statistically significant difference in the mean duration of illness (p-value 0.945).

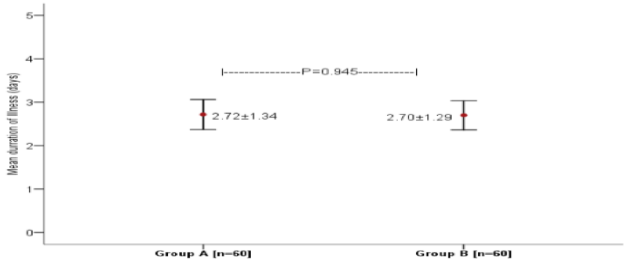

Figure 2: Comparison of mean duration of illness between groups of acute children

Moreover, a stratification analysis was conducted, indicating that the mean duration of illness in both groups, when stratified by variables of age, gender, duration of illness, and number of episodes at 48 hours, remained nearly identical, with none of the p-values falling within the statistically significant range, as illustrated in Table 2.

Table 2: Comparison of mean duration of illness in children with acute diarrhea, stratified by age, gender, number of episodes, and duration of illness

Variable	Groups	n	Mean	Standard Deviation	95% confidence interval		P-value
					Lower bound	Upper bound	
Age							
12 months or <	Group A	21	3.05	1.32	2.45	3.65	0.72
	Group B	19	2.89	1.44	2.2	3.59	
> 12 to 60 months	Group A	20	2.85	1.66	2.07	3.63	0.87
	Group B	22	2.95	1.29	2.8	3.53	
> 60 months	Group A	19	2.21	0.78	1.83	2.59	0.99
	Group B	19	2.21	1.03	1.71	2.71	
Gender							
Male	Group A	28	2.5	1.171	2.05	2.95	0.85
	Group B	32	2.56	1.413	2.05	3.07	
Female	Group A	32	2.91	1.46	2.38	3.44	0.88
	Group B	28	2.86	1.14	2.41	3.38	
Number of episodes of diarrhoea in 48 hours							
4 to 5	Group A	26	1.6	1.03	1.54	2.8	0.26
	Group B	38	2.32	1.35	1.87	2.76	
6 to 8	Group A	34	3.29	1.26	2.85	3.74	0.82
	Group B	22	3.26	0.84	2.9	3.74	
Duration of illness							
3 and < days	Group A	45	2.04	0.7	1.83	2.26	0.68
	Group B	45	2.11	0.85	1.8	2.37	
>3 days	Group A	15	4.73	0.45	4.48	4.99	0.14
	Group B	15	4.47	0.51	4.18	4.7	

4. Discussion

In this randomized clinical trial, we investigated the efficacy of racecadotril as an additional therapy in children with acute diarrhea. Contrary to our expectations, the study did not demonstrate a significant reduction in the mean duration of illness for children treated with racecadotril in addition to standard oral rehydration therapy, zinc, and probiotics. The mean duration of illness was comparable between the two groups, suggesting that racecadotril did not provide an additional benefit in terms of reducing illness duration.

These findings are consistent with the results reported by Gharial J and Motahari et al in their respective studies.[5,11] However, it is important to note that in Motahari's study, a reduction in the number of stools was observed in the racecadotril group after the first 24 to 48 hours, although the difference between the treatment and control groups did not reach statistical significance. In our study, out of the 60 children in the treatment group, 22 (36.6%) still had 6 to 8 episodes of stools at 48 hours, compared to 34 (56.6%) of children in the control group. Racecadotril was assessed as a less effective intervention compared to the superior treatments of zinc and probiotics combination or zinc and smectite combination in children with acute diarrhea, particularly in terms of its impact on the duration of diarrhea, which was the primary outcome of the study.[13] The findings of this study contrast with some previous research from other parts of the world, which reported a reduction in the duration of illness with racecadotril administration. Notably, a study from Malaysia claimed that ORS combined with racecadotril was more effective and cost-effective than ORS alone.[7] Similarly, Sreeni vas et al. indicated a noticeable reduction in stool frequency at 48 hours and reduced time for recovery with racecadotril use.[9]

However, it is worth noting that these studies were conducted in different populations, and regional variations in response to treatment may play a role. Additionally, the presence of a longer duration of diarrhoea in our participants might have influenced the results, as children having diarrhoea for up to 7 days were included in our study whereas most of the other studies included children with a history of diarrhoea up to 5 days[8]. A longer duration of diarrhoea could lead to osmotic diarrhoea, which may not be effectively targeted by racecadotril, potentially reducing its efficacy.

Furthermore, in our study, we did not include racecadotril's safety profile as an outcome although previous research does support its relatively good tolerability in children with acute gastroenteritis.[10]

All the children included in our study regardless of their allocation to the control group or case group were treated with ORS, Zinc, and probiotics whereas most of the trials on the subject used ORS as standard treatment. The only other study where zinc was included as part of standard treatment is the Gharial J study in Kenyan children with acute gastroenteritis. In his study racecadotril did not affect any of the study outcomes. i.e. number of stools at 48 hours, duration of hospital admission, or duration of diarrhea.[5]

The main limitation of our study is that we did not assess the baseline hydration status of the participants, which could have influenced treatment outcomes. Future research should consider including assessments of hydration status, such as Vesikari scoring, to better understand its impact. Secondly, relying on parental recall for stool output may have introduced some recall bias, and more accurate methods of measurement should be considered in future studies.

5. Conclusion

In conclusion, this study did not find a significant beneficial effect of racecadotril on either the mean duration of illness or the number of stools at 48 hours in children with acute gastroenteritis when combined with standard oral rehydration therapy, zinc, and probiotics. Further research is warranted to explore the efficacy of racecadotril in different populations and settings, considering baseline hydration status and duration of diarrhoea. Understanding the regional variations in response to treatment will be crucial in optimizing its use and reducing the burden of acute diarrhoea in children.

CONFLICTS OF INTEREST- None

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Contributions:
S.Z - Conception of study
H.Z - Experimentation/Study Conduction
N.M, T.K.S - Analysis/Interpretation/Discussion
S.Z - Manuscript Writing
T.S - Critical Review
N.M, A.M.K - Facilitation and Material analysis

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