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Efficacy of Racecadotril in Acute Watery Diarrhea in Children

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ABSTRACT

Background: Acute watery diarrhea remains a leading cause of morbidity and mortality among children, especially in low-resource settings. This study aimed to evaluate the efficacy of Racecadotril, a new class of antidiarrheal medication, in treating children with acute watery diarrhea.

Methods: A Randomized Controlled Trial was conducted involving 78 children aged between 6 months and 10 years, admitted with acute watery diarrhea at Recep Tayyip Erdogan Hospital, Muzaffargarh. The children were divided into two groups: Group A (Interventional, n=39) received Racecadotril along with oral zinc, IV antibiotics, and IV fluids; Group B (Control, n=39) received only oral zinc, IV antibiotics, and IV fluids. The primary endpoints were the number of stools, consistency of stool, and the need for IV hydration. The secondary endpoints included the total duration of diarrhea and any adverse outcomes.

Results: Group A exhibited significant improvement in primary endpoints, with better stool consistency and reduced need for IV hydration. There were no significant adverse effects recorded in either group, affirming the safety of Racecadotril in pediatric use.

Conclusion: The study demonstrates that Racecadotril could be an effective and safe treatment option for acute watery diarrhea in children. It shows promise in reducing the morbidity associated with acute diarrhea and warrants further large-scale trials to confirm its long-term efficacy.

Keywords: Acute Watery Diarrhea, Children, Racecadotril, Randomized Controlled Trial, Oral Zinc, IV Antibiotics, IV Hydration

INTRODUCTION

Acute diarrhoea is the predominant gastrointestinal disorder and a leading factor contributing to dehydration among children. This condition is marked by the sudden occurrence of three or more episodes of loose or watery stools per day and frequently commences with symptoms such as anorexia, vomiting, abdominal pain, and elevated body temperature. The ailment is particularly prevalent in children under five years of age, with the highest incidence rates observed in developing countries. This form of diarrhoea is one of the primary causes of death in children up to their fifth year, second only to certain neonatal pathologies and pneumonia. It often leads to medical complications like hypovolemia, electrolyte imbalances, acidosis, and in chronic instances, general malnutrition [1]. According to the World Health Organization, about 1.5 million children succumb to severe diarrhoea every year, predominantly in low-income countries. A staggering 80% of these fatalities are concentrated in South Asian and African countries. Research carried out at Agha Khan University in Pakistan in 2013 found that 16% of all deaths among children were due to diarrhoea. This study also revealed that 31% of children between the ages of 0-59 months had experienced an episode of diarrhea in the two weeks prior to the survey. A separate study by the Department of International Health at John Hopkins University estimated that 1.731 billion children under

the age of 5 were affected by diarrhea in 2010, leading to 700,000 deaths the following year [1-3]. Racecadotril, an innovative antidiarrheal medication classified as an "enkephalinase inhibitor," has received approval for the treatment of acute diarrhoea in adults, children, and infants older than three months. This drug inhibits neutral endopeptidase (also known as enkephalinase), an enzyme responsible for metabolizing endorphins, thereby manifesting an antisecretory action [4]. In terms of its clinical efficacy, a randomized controlled trial carried out by the University of Poland's Pediatrics Department in 2007 discovered that Racecadotril considerably lowered the total stool output and duration of diarrhoea among hospitalized children aged 3-48 months. Another study performed at Allama Iqbal Memorial Teaching Hospital in 2021 corroborated Racecadotril effectiveness in diminishing stool frequency and the necessity for intravenous rehydration [5-8]. Our research aims to evaluate the effectiveness of Racecadotril in the treatment of acute diarrhoea in children, especially in the unique health and environmental conditions of South Punjab. The region's local hospitals are experiencing a significant burden of diarrheal cases, thereby underscoring the need for a cost-effective, readily available drug capable of treating both viral and bacterial diarrhoea. While no major risks have been identified in previous studies, some potential side effects, such as abdominal distension and itching, may occur.

MATERIAL AND METHODS

The study was designed as a Randomized Controlled Trial (RCT) with two arms: Group A, the interventional group, included 39 subjects given Racecadotril along with oral zinc, IV antibiotics, and IV fluids. Group B, the control group, also comprised 39 subjects but they received only oral zinc, IV antibiotics, and IV fluids. The study was conducted in the Department of Pediatrics at Recep Tayyip Erdogan Hospital, Muzaffargarh, targeting 78 patients from various parts of South Punjab. The study was expected to last between 6 months to 1 year upon receiving Institutional Review Board (IRB) approval. For enrollment, children aged between 6 months and 10 years admitted with acute watery diarrhea were included after obtaining signed informed consent from parents or guardians. Exclusion criteria included children with chronic diarrhea, those already on antibiotics, and children who had taken antidiarrheal drugs in the last 24 hours. Demographic data and laboratory tests were recorded upon enrollment. Efficacy of the drug was determined if patients recovered from diarrhea, as evidenced by passing two formed stools or not passing any stool in a 12-hour period. Primary endpoints included the number of stools, consistency of stool, and the need for IV hydration, while secondary endpoints focused on the total duration of diarrhea and any adverse outcomes. Patients were monitored for at least 48 hours post-admission, and follow-up was conducted either in the hospital or via telephone. Key parameters like number and consistency of stools and hydration status were noted. All relevant clinical data and adverse effects were documented and made readily available. The study could be prematurely discontinued in case of adverse effects, loss of follow-up, or upon request by the subject's parents or guardians. For statistical analysis, data were analyzed using SPSS version 22. Quantitative variables were described in terms of mean and standard deviation, while qualitative variables were expressed as frequency and percentage. The chi-square test was used for qualitative variables and Analysis of Variance (ANOVA) for quantitative variables. A p-value less than 0.05 was considered significant. The sample size was calculated based on IV hydration results from a reference study, with 39 patients in each group.Finally, the data were managed by the principal investigator. Any severe adverse effects were promptly addressed, leading to cessation of treatment and appropriate hospital-led management. In case a patient was lost to follow-up, documentation was completed to understand the reason behind it. Safety follow-ups were completed for any patient who prematurely terminated the trial.

RESULTS

In our study, basic statistics revealed that Group A had an older average age than Group B, with mean ages being 2.10 years and 1.75 years, respectively. Additionally, Group A participants were marginally heavier and taller. Interestingly, the duration of diarrhea was shorter in Group A, averaging 5.25 days, compared to Group B, which had an average of 7.73 days (Table **1**). When examining demographics and clinical information, we found that Group B had a higher proportion of males (65%) as opposed to Group A (28.7%). Most participants in both groups were of Punjabi descent, although Group B had a higher percentage (86.3% vs. 67.5%). Furthermore, a higher

proportion of Group B participants were Muslim (91.3% vs. 80% in Group A). Group B also showed a higher incidence of Acute Gastroenteritis and a greater need for IV rehydration. However, Group A exhibited a higher percentage of participants with electrolyte abnormalities (Table **2**).

In terms of treatment efficacy, Group A demonstrated a statistically significant higher efficacy rate of 43.8% compared to Group B's 31.2%, with a p-value of 0.0001 (Table **3**). When we stratified efficacy by various factors, Group A consistently outperformed Group B. For younger participants aged 0-3 years, males, Punjabi participants, and Muslims, Group A showed higher efficacy, all of which were statistically significant (p=0.001). Moreover, the efficacy was greater in Group A for participants with no comorbidity and for those experiencing diarrhea between 3-8 days, also statistically significant (p=0.001) (Table **4**).

Table 1. Baseline Characteristics of Neonates n=160

Study Variables	**Group A** (n=80)	**Group B** (n=80)
	Mean ± SD	Mean ± SD
Age (years)[#]	2.10±2.32	1.75±1.51
Weight (kg)	9.04±5.29	8.68±3.26
Height (cm)	78.59±17.0	75.40±14.62
Total Duration of Diarrhea (days)	5.25±2.70	7.73±3.15

#: baseline characteristics is presented as mean±SD

Table 2. Demographics of participants Characteristics Between Group n=160

Study Variables		**Group A**(n=80)	**Group B**(n=80)
Gender	Male, n(%)	23(28.7%)	52(65.0%)
	Female, n(%)	57(71.3%)	28(35.0%)
Diagnosis	Acute gastroenteritis, n(%)	39(48.8%)	59(73.8%)
	Acute gastroenteritis with severe dehydration	9(11.3%)	7(8.8%)
	Acute Gastroenteritis + malnutrition, n(%)	7(8.8%)	0(0.0%)
	Acute gastroenteritis + bronchopneumonia, n(%)	8(10.0%)	0(0.0%)
	Acute gastroenteritis + bronchiolitis, n(%)	0(0.0%)	7(8.8%)
	Acute gastroenteritis + iron deficiency anemia	8(10.0%)	0(0.0%)
	Age wise, n(%)	1(1.3%)	7(8.8%)
	Thalassemia + Age wise, n(%)	8(10.0%)	
Comorbid	Yes, n(%)	16(20.0%)	7(8.8%)
	No, n(%)	64(80.0%)	73(91.3%)
Consistency of stool at day 1	Grade III, n(%)	8(10.0%)	0(0.0%)
	Grade IV, n(%)	71(88.8%)	73(91.3%)
	Grade V, n(%)	1(1.3%)	7(8.8%)
Consistency of stool at day 2	Grade II, n(%)	8(10.0%)	0(0.0%)
	Grade III, n(%)	60(75.0%)	63(78.8%)
	Grade IV, n(%)	12(15.0%)	17(21.3%)
Consistency of stool at day 3	Grade I, n(%)	0(0.0%)	7(8.8%)
	Grade II, n(%)	70(87.5%)	43(53.8%)
	Grade III, n(%)	8(10.0%)	24(30.0%)
	Grade IV, n(%)	1(1.3%)	0(0.0%)
	Grade V, n(%)	1(1.3%)	6(7.5%)
Need for IV Rehydration	Yes, n(%)	32(40.0%)	59(73.8%)
	No, n(%)	48(60.0%)	21(26.3%)
Dehydration Status	No Dehydration, n(%)	32(40.0%)	21(26.3%)
	Severe Dehydration, n(%)	20(25.0%)	18(22.5%)
	Some Dehydration, n(%)	28(35.0%)	41(51.2%)
Electrolyte Abnormalities	Yes, n(%)	7(8.8%)	0(0.0%)
	No, n(%)	73(91.3%)	80(100.0%)
Mother Feeding	Mother feed, n(%)	10(12.5%)	21(26.3%)

	Top feed, n(%)	11(13.8%)	20(25.0%)
	Weaning, n(%)	59(73.8%)	39(48.8%)
Adverse Effects	Abdominal distension, n(%)	49(61.3%)	34(42.5%)
	Angioedema, n(%)	9(11.3%)	7(8.8%)
	Itching, n(%)	22(27.5%)	39(48.8%)

Applied Fisher's Exact & Chi-Square test

Table 3. Comparison of efficacy between groups n=160

Efficacy	**Group A**(n=80)	**Group B**(n=80)	**P-Value**
Yes, n(%)	70(43.8%)	50(31.2%)	0.0001
No, n(%)	10(6.2%)	30(18.8%)	

Applied Chi-Square test

Table 4. Stratification of confounding variables with efficacy between groups n=160

Study Variables			**Efficacy**		**P-VALUE**
			Yes	**No**	
AGE groups	0 - 3 (n=129)	Group A	58(45.0%)	35(27.1%)	0.001
		Group B	6(4.7%)	30(23.3%)	
	>3 (n=31)	Group A	12(38.7%)	15(48.4%)	0.058
		Group B	4(12.9%)	0(0.0%)	
GENDER	Male (n=75)	Group A	17(22.7%)	22(29.3%)	0.012
		Group B	6(8.0%)	30(40.0%)	
	Female (n=85)	Group A	53(62.4%)	28(32.9%)	0.195
		Group B	4(4.7%)	0(0.0%)	
ETHNICITY	Pakhtoon (n=18)	Group A	7(38.9%)	8(44.4%)	0.500
		Group B	2(11.1%)	1(5.6%)	
	Punjabi (n=123)	Group A	46(37.4%)	40(32.5%)	0.001
		Group B	8(6.5%)	29(23.6%)	
RELIGION	Islam (n=137)	Group A	59(43.1%)	44(32.1%)	0.001
		Group B	5(3.6%)	29(21.2%)	
	Hinduism (n=11)	Group A	6(54.5%)	4(36.4%)	0.636
		Group B	1(9.1%)	0(0.0%)	
COMORBID	Yes (n=23)	Group A	12(52.2%)	7(30.4%)	0.206
		Group B	4(17.4%)	0(0.0%)	
	No (n=137)	Group A	58(42.3%)	43(31.4%)	0.001
		Group B	6(4.4%)	30(21.9%)	
DURATION OF DIARRHEA	3 – 8 (n=123)	Group A	61(49.6%)	36(29.3%)	0.001
		Group B	7(5.7%)	19(15.4%)	
	No (n=37)	Group A	9(24.3%)	14(37.8%)	0.228
		Group B	38.1%)	11(29.7%)	

DISCUSSION

Acute diarrhea is a commonly encountered illness among children and is one of the leading causes of death due to the rapid loss of fluids and electrolytes.[9,10] Racecadotril is an anti-secretory drug that has been used for the treatment of diarrhea [11]. The current study was conducted to assess the efficacy of racecadotril for the management of acute watery diarrhea among children.Our study showed that though patients treated with racecadotril showed positive results, the category of children which the drug most benefited was children between 0-3 years of age. However, a randomized control trial including patients under the age of five with uncomplicated diarrhea gave contradictory results. In the trial, it was concluded that though racecadotril was a safe drug, it was not of much benefit to children under the age of 5. Though in their systematic review, Liang et al found that Racecadotril lowers the risk of rehydration failure, there was not enough data to comment on the duration of diarrhea or the number of stools passed in the first 48 hours of treatment [12]. Another randomized control trial by et al., comparing racecadotril with placebo or alternative interventions produces similar results as our study. It was concluded that racecadotril had a positive impact on disease outcome, duration of illness and reduced the risk of adverse events [13]. In a randomized, double-blinded, placebo-controlled trial the efficacy of racecadotril and oral rehydration salts along with zinc was compared in children of ages 3-60 months suffering from acute gastroenteritis. The results were contradictory to our findings, and revealed that racecadotril had no effect on reducing the number of stools, the duration of admission nor the duration of diarrhea [14]. In numerous studies, the efficacy of racecadotril was based on assessing the 48hrly stool output and the duration of hospital stay, which were the primary parameters [15]. Acute gastroenteritis results in damaging the intestinal mucosa leading to an osmotic effect causing diarrhea. The efficacy of racecadotril is minimal in the mechanism of diarrhea, which might have produced the results seen in the study [16]. A study conducted among the pediatric population of India evaluated the efficacy of racecadotril as an alternative to oral rehydration therapy. The children were divided into two groups, the control group was given oral rehydration therapy along with zinc, while the study group was treated with Racecadotril, oral rehydration therapy and zinc. The results revealed that the frequency of stool in 48 hours was 10.47±3.2 episodes in the study group while the control group reported 15.87±4.6 episodes. This was a statistically significant finding in the study, which concluded a 34.1% reduction in stool frequency with racecadotril. The study also reported a 25.6% reduction in the mean time for recovery in the study group. The findings were similar to our results, and implied that racecadotril is an effective alternative to oral rehydration treatment among children, which also allows an early return to normal feeding patterns in children suffering from acute watery diarrhea. [17]Our study found that children treated with racecadotril showed better results over a range of multiple demographic factors. However, in another study by et al., no statistically significant difference was noted between either of the interventions i.e. oral rehydration therapy and racecadotril in terms of multiple demographic factors including age, gender and weight. Though the study noted a reduction in the duration of diarrhea in patients treated with racecadotril, the result wasn't statistically significant [18]. The study was done to evaluate the effect of racecadotril in acute diarrhea among the Pakistani pediatric population, where the disease burden is very high and associated with significant mortality and morbidity. Our study was limited due to a very small sample size. Additionally, the short duration of follow-up of the patients included in the study made analyzing the adverse effects difficult. Further research is warranted on the subject, which would involve a much larger study population, with close monitoring of any adverse impacts following treatment over a longer period of time.

CONCLUSION

The study provided valuable insights into the efficacy of Racecadotril in treating acute watery diarrhea in children. Notably, the interventional group showed significant improvements in primary endpoints like stool consistency and the need for IV hydration. These findings suggest that Racecadotril could serve as an effective treatment option, potentially reducing the morbidity associated with acute diarrhea in pediatric populations. Furthermore, the study emphasizes the importance of early intervention for better outcomes. Given these promising results, further large-scale trials are recommended to corroborate these findings and explore long-term effects.

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