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EFFICACY OF RACECADOTRIL IN CHILDREN (LESS THAN FIVE YEARS OF AGE) WITH ACUTE WATERY DIARRHEA AT TERTIARY CARE HOSPITAL

Ayesha Almas[1*], Kausar Keerio[2], Mameeta Kumari[3], Fiza Syed Shah[4], Muhammad Touseef[5], Faiza[6]

[1*]MBBS, FCPS, Woman medical officer, Department of pediatrics, Liaquat University Hospital Hyderabad. ayesha.almas79@gmail.com. 03352447783
[2]MBBS, FCPS, senior registrar, pediatric department, Liaquat University of Medical and Health Sciences Jamshoro. kausarkeerio@gmail.com. 03313681574
[3]MBBS (FCPS trainee), pediatric department, Liaquat University of Medical and Health Sciences Jamshoro. mumeeta10@gmail.com. 03363073017
[4]MBBS, MPH (UK), FCPS, Woman medical officer, Department of pediatrics, Liaquat University Hospital Hyderabad. fiza.shah@hotmail.com. O3453532474
[5]MBBS, FCPS, senior registrar, pediatric department, Liaquat University of Medical and Health Sciences Jamshoro. ttlumhs@hotmail.com. 03332614213
[6]MBBS, DCH, MD (Pediatrics), Woman Medical Officer, Department of Pediatrics, Sindh Government Hospital, Hyderabad. faizazizullah@gmail.com. 03332684705

[*]**Corresponding author:** Ayesha Almas
[*]MBBS, FCPS, Woman medical officer, Department of pediatrics, Liaquat University Hospital Hyderabad. ayesha.almas79@gmail.com. 03352447783

ABSTRACT

Introduction: Acute diarrhea in children is a serious public health concern. In both industrialized and developing countries, it considerably raises morbidity in infants and early children despite advancements in oral rehydration therapy and recently introduced immunizations. Acidosis and dehydration due to excessive fluid and electrolyte losses are the main causes of acute watery diarrhea-related fatalities. In order to treat acute gastroenteritis in children, this study assessed the efficacy of oral rehydration solution alone versus racecadotril, an adjuvant to it and zinc Sulphate.

Objective: - The aim of this research was to assess the effectiveness of Racecadotril in treating acute diarrhea in children in a tertiary care hospital in comparison to oral rehydration solution alone.

Study design: Randomized controlled trial

Place and Duration: Pediatric Department of University Hospital, from 12 March 2021 to 12 September 2021

Methodology: A total of 252 children were assigned at random. Overall 126 patients in group B (the treatment group) received Racecadotril in addition to ORS and Zinc Sulphate, while 126 patients in group A (the placebo group) received only ORS and Zinc Sulphate. The frequency of stools during the first 72 hours following admission served as the main efficacy criterion. The length of time it took for diarrhoea to go away after starting Racecadotril was the main outcome indicator. Every piece of data was kept in a pre-made proforma.

Results: The children ranged in age from 23.31±14.05 months. Group B was found to be substantially more effective than Group A in treating acute diarrhoea in children (97.6% vs. 81.7%; p=0.0005).
Conclusion: In this trial, Racecadotril considerably outperformed the control group in terms of effectiveness in treating acute diarrhoea. In infants and children with acute diarrhoea, it demonstrated that Racecadotril is an efficient, well-tolerated supplement to oral rehydration therapy.

Key Words: Acute diarrhea, Racecadotril, ORS and Zinc Sulphate

INTRODUCTION

A loose stool is one that would resemble a container, and diarrhoea is described as passing three or more of these in a 24-hour period [1]. Precisely 2 billion cases annually, acute diarrhea in children is a worldwide health concern. An estimated 1.9 million children, mostly in developing countries, pass away from the illness every year; this represents 18% of all pediatric mortality. 78 percent of these deaths occur in Southeast Asia and Africa combined [2].

It was 32% prevalent in Karachi [3]. Despite improvements in oral rehydration therapy and newly launched vaccinations, it significantly increases morbidity in newborns and young children in both developed and developing nations [4]. Dehydration and acidosis are the results of substantial fluid and electrolyte losses, which account for most acute watery diarrhea deaths.

Although illnesses that cause acute diarrheal illness are frequently self-limiting, reducing the length of the illness can have important advantages in terms of hydration and eventual morbidity. Although it is still underutilized in some places, oral rehydration therapy is now the standard treatment for acute diarrheal disease [5].

In contrast to current antidiarrheal medications, racecadotril is an anti-secretory agent. It is an enkephalinase inhibitor that increases enkephalin's ability to suppress secretory activity in the submucous myenteric neurons. This reduces stool production while not affecting intestinal transit time [6, 7].

The primary goal of treatment with Racecadotril is to stop the intestine from losing fluid and electrolytes as a result of acute diarrhoea. Racecadotril has been proven to be a powerful and secure anti-secretory drug for usage in children with diarrhoea in numerous preclinical and clinical trials. [8, 9]

Racecadotril significantly reduced the length of time that symptoms lasted compared to placebo, according to a meta-analysis of three studies with 642 participants (mean difference: 53.48 h, 95% CI: 65.64 to 41.33) [10]. One hundred twenty children were enrolled in a global study. Each group's 60 participants were analyzed individually. While the other group received ORS and Zinc Sulphate, the first group received ORS and Racecadotril. Between the two groups, the results were identical. Stools at 48 hours: 5 (3–7) and 5 (2.5–7.5) on a median (IQR) scale, respectively; p=0.63. [11] In a different trial, the Racecadotril group demonstrated 88% efficacy whereas the control group demonstrated 76%. [6]

Despite the fact that racecadotril has been used for over 20 years, there is a paucity of data from Pakistan about its efficacy. In treating acute gastroenteritis in children, this trial examined the efficacy of oral rehydration solution alone vs racecadotril, an adjuvant to it and zinc Sulphate. Because there is inconsistent information regarding the effectiveness of racecadotril in compared to standard therapy (ORS and zinc Sulphate) for acute watery diarrhea, this study was designed to make a contribution from the Hyderabad region.

METHODOLOGY

From 12 March 2021 to 12 September 2021, this Randomized controlled trial was carried out at the paediatric department of University Hospital. Using an epi sample size calculator with a 95% confidence interval and 80% power of beta, the sample size was calculated by taking the efficacy of the experimental group, which was 88%, and the control group, which was 76% [6]. The result was a

total sample size of 252 and 126 in each group. All children aged three months to five years, of both genders, with acute watery diarrhea lasting less than three days were included.

Children who had taken an antibiotic or any antidiarrheal medication during the previous 48 hours, had blood in their stool, a high-grade fever, a history of chronic diarrhoea (duration > 14 days), continuous vomiting (>3 episodes/hour), were excluded from the trial. Children with severe acute malnutrition (weight for age or weight for length less than -3 Z-score, or weight for height less than -3 Z-score) and children with underlying comorbidities were also eliminated.

After receiving approval from the ethical review committee, this study was launched. Children who meet the requirements for inclusion were registered for the study. Parents' informed consent was obtained after being told of the purpose, process, and advantages. The study's patients were allowed to withdraw at any time, were not to be denied any benefits, and their confidentiality was upheld. All information was gathered using a pre-planned study proforma. A history was obtained for the duration of the diarrhoea, the presence of blood in the stool, fever, or underlying comorbidities. A thorough examination was conducted to look for dehydration signs. Before participants were enrolled in the trial, a gross examination of the stools was performed to establish the existence of watery diarrhoea.

The attending physician admitted all of the children and began the WHO-recommended course of therapy for them. They were given intravenous fluids according to WHO plan C (30 mL/kg followed by 70 mL/kg over 1 and 5 hours, respectively, for newborns and over 30 min and 2.5 hours for individuals over 12 months of age) or low osmolality ORS in accordance with WHO plan B (75 mL/kg over 4 hours). All patients received low osmolar ORS and low doses of oral zinc (10 mg for children under 12 months and 20 mg for those over 12 months), based on their state of hydration. Apart from ORS and zinc, the subjects were given age-appropriate milk, soft food, and breastfeeding to achieve a daily calorie intake of 100–120 Kcal/kg (not including the calories from glucose in ORS). This is in line with the WHO's recommendation that diet be continued while treating diarrhea to avoid nutritional disruption.

Children were placed into two groups at random. Random numbers were produced by a computer Programme in blocks of varied sizes. These were utilized to randomly place patients in either group A or group B. Group B (the treatment group) received Racecadotril in addition to ORS and Zinc Sulphate while Group A (the placebo group) received only ORS and Zinc Sulphate.

Racecadotril was administered to Group B in accordance with the manufacturer's recommendations: 10 mg per dosage for infants under 12 months and 30 mg for infants over 12 months. For a maximum of three days, this was given as granules that were to be dissolved in 10 mL of water and taken three times each day. Children who couldn't take the medication orally were given it through a nasogastric tube until their conditions were stable enough.

At the time of enrollment, the first dosage of the medication or placebo was administered. At that time, the parents were instructed on how to administer the medication, and it was verified by a return demonstration. Daily interviews were used to check in with the participants and inquire about their feces' frequency, consistency, and blood content as well as any new symptoms and whether they had started taking any antidiarrheal drugs or other medications.

Treatment was administered for a total of three days or until the stools became formed, whichever happened first. Before their full recovery, children who were discharged from the hospital before all of their symptoms had disappeared underwent phone interviews and home visits. The duration of the inpatient stay was determined by counting the days from the start of the medicine to the day of discharge, as specified by the attending physician.

The time between the time the medicine was administered and the emergence of three formed faeces within a 24-hour period was used to determine the length of the illness.

The frequency of stools in the first 72 hours following admission served as the main effectiveness criterion. The number of days after the introduction of Racecadotril that the diarrhoea resolved was the major outcome measure. Age, gender, place of residence, length of diarrhoea, weight, height, SD score, MUAC, blood in stool, vomiting, dehydration status, and effectiveness were all recorded on a pre-made proforma.

Version 22.0 of SPSS was used to analyse the study's data. The frequency and percentage of categorical characteristics such as gender, residence status, blood in the stool, vomiting, dehydration condition, and efficacy were measured. Age, diarrheal duration, weight, height, SD score, MUAC, temperature, and the day the diarrhoea stopped were all quantified and expressed as mean and standard deviation.

The chi-square test was used to assess the effectiveness between the two groups, and a p-value of less than or equal to 0.05 was regarded as significant. Through stratification, effect modifiers such as age, gender, height, weight, MUAC score, SD score, temperature, residential status, vomiting, blood in the stool, and dehydration status were managed. Following stratification, the Chi-square test was used, and a p-value of 0.05 or less was deemed significant.

RESULTS

A total of 252 children each were assigned at random. Overall 126 patients in group B (the drug group) received the medication Racecadotril in addition to ORS and Zinc Sulphate, and 126 patients in group A (the placebo group) received only ORS and Zinc Sulphate. The children ranged in age from 23.31±14.05 months. Table 1 also contained information on averages for height, weight, diarrheal duration, MUAC, and temperature. There were 118 (46.8%) girls and
134 (53.2%). Table 1 also displays the children's residential status.

In groups, A and B, respectively, 58.7% and 79.4% of people had a fever. Only one patient had blood in his or her faeces. However, in groups A and B, respectively, 20.6% and 33.3% of children reported vomiting. According to groups A and B, mild dehydration affected about 35% and 40% of each, while severe dehydration affected 3.17 percent of group B, as shown in Table
2. Table 3 compares the effectiveness of racecadotril to a control group for treating acute diarrhoea in children. In comparison to group A, group B performed much better (97.6% vs. 81.7%; p=0.0005). Age, gender, residence status, height, weight, SD score, MUAC, fever, blood stool, vomiting, and dehydration categories were stratified, and the results show that group B is generally more effective than group A as shown in Table 4 to 6, respectively.

Table 1: DEMOGRAPHIC CHARACTERISTICS OF CHILDREN ACCORDING TO GROUPS

Variables	**Group A**	**Group B**
Age (months)	23.38±13.80	23.23±14.35
Weight (kg)	9.06±3.70	7.85±2.27
Height/Length (cm)	73.0±11.88	69.26±9.90
Duration of Diarrhea (days)	1.6±0.49	1.46±.500
MUAC	13.03± 0.25	13.15± 0.43
Gender		
Male	83 (65.87%)	51 (48.48%)
Female	43 (34.13%)	75(59.52%)
Residence		
Rural	57(45.24%)	48(38.10%)
Urban	69(54.76%)	78(61.90%)

TABLE 2 CLINICAL PRESENTATION ACCORDING TO GROUPS

Variable	**Group A**	**Group B**
Fever		
Yes	74 (58.7%)	100 (79.4%)
No	52 (41.3%)	26 (20.6%)
Blood in stool		
Yes	1 (0.8%)	0 (0%)
No	125 (99.2%)	126 (100%)
Vomiting		
Yes	26 (20.6%)	42 (33.3%)

No	100 (79.4%)	84 (66.7%)
Dehydration		
Some dehydration	88 (34.92%)	100 (39.68%)
Severe dehydration	2 (0.79%)	8 (3.17%)
No dehydration	36 (14.29%)	18 (7.14%)

TABLE 3 COMPARISON OF THE EFFICACY OF RACECADOTRIL VERSUS THE CONTROL GROUP FOR THE TREATMENT OF ACUTE DIARRHOEA IN CHILDREN

Effectiveness	**Group A (n=126)**	**Group B (n=126)**	**Total**	**P-value**
Yes	103(81.7%)	123(97.6%)	226(89.7%)	0.0005
No	23(18.3%)	3(2.4%)	26(10.23%)	

Chi-square test

Table 4: COMPARE THE EFFICACY OF RACECADOTRIL VERSUS THE CONTROL GROUP FOR THE TREATMENT OF ACUTE DIARRHOEA IN CHILDREN BY VARIOUS FACTORS

Variable	**Outcome**	**Group A**	**Group B**	**P-value**
Age ≤ 24 months	Effective	60(81.1%)	76(96.2%)	0.004
	Not Effective	14(18.9%)	3(3.8%	
>24 months	Effective	43(82.7%)	47(100%)	0.003
	Not Effective	9(17.3%)	0(0%)	
Male	Effective	60(72.3%)	49(96.1%)	0.001
	Not Effective	23(27.3%)	2(3.9%)	
Females	Effective	43(100%)	74(98.7%)	0.447
	Not Effective	0(0%)	1(1.3%)	
Rural	Effective	48(84.2%)	45(93.8%)	0.126
	Not Effective	9(15.8%)	3(6.3%)	
Urban	Effective	55(79.7%)	78(100%)	0.0005
	Not Effective	14(20.3%)	0(0%)	
Weight ≤10	Effective	85(84.2%)	98(97%)	0.002
	Not Effective	16(15.8%)	3(3%)	
>10	Effective	18(72%)	25(100%)	0.010
	Not Effective	7(28%)	0(0%)	

Chi-square test

Table 5: COMPARE THE EFFICACY OF RACECADOTRIL VERSUS THE CONTROL GROUP FOR THE TREATMENT OF ACUTE DIARRHOEA IN CHILDREN BY VARIOUS FACTORS

Variable	**Outcome**	**Group A**	**Group B**	**P-value**
Height ≤70 cm	Effective	47(78.3%)	72(96%)	0.002
	Not Effective	13(21.7%)	3(4%)	
>70 cm	Effective	56(84.8%)	51(100%)	0.005
	Not Effective	10(15.2%)	0(0%)	
SD Score-1 to -3	Effective	46(85.2%)	61(96.8%)	0.025
	Not Effective	8(14.8%)	2(3.2%)	
Median	Effective	21(67.7%)	16(100%)	0.10
	Not Effective	10(32.3%)	0(0%)	
>Median	Effective	36(87.8%)	46(97.9%)	0.062
	Not Effective	5(12.2%)	1(2.1%)	
MUAC ≤13	Effective	89(80.9%)	114(97.4%)	0.0005
	Not Effective	21(19.1%)	3(2.6%)	
>13	Effective	14(87.5%)	9(100%)	0.520
	Not Effective	2(12.5%)	0(0%)	
Fever	Effective	52(70.3%)	97(97%)	0.0005
	Not Effective	22(29.7%)	3(3%)	

Afebrile	Effective	51(98.1%)	26(100%)	0.477
	Not Effective	1(1.9%)	0(0%)	

Chi-square test

Table 6: COMPARE THE EFFICACY OF RACECADOTRIL VERSUS THE CONTROL GROUP FOR THE TREATMENT OF ACUTE DIARRHOEA IN CHILDREN BY VARIOUS FACTORS

Variable	**Outcome**	**Group A**	**Group B**	**P-value**
Blood in stool	Effective	0	0	NA
	Not Effective	1	0	
No blood in the stool	Effective	103(82.4%)	123(97.6%)	0.0005
	Not Effective	22(17.6%)	3(2.4%)	
Vomiting	Effective	26(100%)	41(97.6%)	0.428
	Not Effective	0(0%)	1(2.4%)	
No vomiting	Effective	77(77%)	82(97.6%)	0.0005
	Not Effective	23(23%)	2(2.4%)	
Some dehydration	Effective	67(76.1%)	98(98%)	0.0005
	Not Effective	21(23.9%)	2(2%)	
Severe dehydration	Effective	0(0%)	7(87.5%)	0.016
	Not Effective	2(100%)	1(12.5%)	
No dehydration	Effective	36(100%)	18(100%)	NA
	Not Effective	0(0%)	0(0%)	

Chi-square test

DISCUSSION

Thiorphan has been diesterified to produce racecadotril. It is metabolized to its parent chemical (Thiorphan) after being ingested, and this process lengthens the half-life of enterocyte methionine-enkephalin, a potent antisecretory drug. [11] Since it has been used in Europe for the past 20 years, racecadotril has continuously been effective in treating diarrhoea while having a manageable side effect profile.[12-14] None of the clinical trials examining the effectiveness of

Racecadotril has included zinc in their protocols, despite the fact that it has been demonstrated to have a significant impact on the length and severity of diarrhoea and is a component of the WHO's basic treatment recommendations.[13, 15]

There have been numerous studies conducted around the world. The majority of the few studies conducted in the poor world have been inpatient studies, many of which have been found to have methodological errors. [13]

In this study average age of the children was 23.31±14.05 months. A similar [9] result was also reported in another study where the average age was 24.35±20.08 (month). In the present study, fever was observed in 58.7% and 79.4% of groups A and group B. Blood in stool was only seen in one patient. However, vomiting was noted in 20.6% and 33.3% of Group A and Group B respectively.

Groups A and B had moderate dehydration rates of around 35% and 40%, respectively, whereas group B reported severe dehydration rates of 3.17%. The difference in dehydration levels between the groups in the Gharial et al research [16] was not statistically significant (p=0.25). Most research participants were found to be mild to moderately dehydrated, with only 15% of the medication group and 27% of the placebo group experiencing severe dehydration.

The majority of research examining Racecadotril's effectiveness in treating acute gastroenteritis in children has been conducted in hospitals [16–19]. Children receiving Racecadotril had shorter bouts of diarrhoea and less stool production, according to systematic reviews based on data from these trials [21–23]. In contrast, no significant changes were discovered in the number of bowel movements or the average length of diarrhoea between children treated with Racecadotril or conventional oral

rehydration therapy in one research carried out in an outpatient environment [23].
Racecadotril was substantially more effective than the control group in this research for treating acute diarrhoea (97.6% vs. 81.7%; p=0.0005). Another systematic review and meta-analysis was conducted for the five most comparable treatments in hospitalized and outpatient patients with a high degree of consistency. For example, it reduced the time to cure from 106.2 hours to 78.2 hours (mean reduction of 28.0 hours; p0.001) in 24 studies that reported on this parameter.[24]
This meta-analysis backs up our conclusions about Racecadotril's effectiveness. It may be because of geographical diversity or the type of organism causing diarrhoea, however, a recent study conducted in India found Racecadotril had less of an impact on rotavirus diarrhoea patients' purging and reduction of stool volume. [25] Racecadotril was tested by Alam et al. [26] for the treatment of cholera in adults, and they discovered that there was no significant difference in ORS consumption between the two groups, but that Racecadotril reduced mean stool frequency in 48 hours by 34.1% (10.47 vs. 15.87 episodes).
Children receiving Racecadotril experienced a 50% decrease in stools produced in 48 hours when compared to placebo, according to Cezard et al. [17]. With Racecadotril [16], Salazar- Lindo et al. saw a 46% decrease in 48-hour stool production (157 vs. 331 g/kg). Racecadotril, according to Cojocaru et al. [18], was likewise associated with much fewer stools and quicker recovery.
According to the children's rotavirus status, Salazar-Lindo et al. compared the median duration of diarrhoea in the Racecadotril group and the placebo group, and they discovered that regardless of the children's rotavirus status, the median duration of diarrhoea in the Racecadotril group was 28 h, while the median duration of diarrhoea in the placebo group was 72 and 52 h, respectively [16]. According to Cezard et al.'s comparison of the length of diarrhoea in rotavirus-positive patients, 50% of those taking Racecadotril recovered in 6.9 hours as opposed to 36 hours for the placebo group [17]. In their trial of 200 patients with acute watery diarrhoea, Baumer et al. discovered that the Racecadotril group's mean duration of diarrhoea was 22.8% shorter than the control group's (3.4 vs. 4.4 days) [27].
Due to the limited sample size, it might not be able to prove the drug's effectiveness in managing acute watery diarrhoea to the level and in the way required for a routine recommendation. Larger studies are also required to discover a significant difference in diarrheal length and its morbidity in various types and severity of diarrhoea because this study lacked the power to examine the mortality or number of complications. Diarrhoea can have a variety of different causes. The scientific information presented in this trial might not be all-inclusive, hence using antisecretory medications like Racecadotril should be postponed until more evidence is obtained from well executed randomized controlled trials.

CONCLUSION

In this study efficacy of Racecadotril versus control group for the treatment of acute diarrhea was significantly effective. It showed that Racecadotril is an effective, well-tolerated adjunct to oral rehydration therapy in infants and children with acute diarrhea

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It was taken

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