ORIGINAL ARTICLE

COMPARISON OF RACECADOTRIL WITH ORAL REHYDRATION SOLUTION AND ORAL REHYDRATION SOLUTION ALONE IN ACUTE WATERY DIARRHEA IN CHILDREN AGED 6 MONTHS - 5 YEARS

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ABSTRACT

Background: A significant share (18%) of pediatric mortality is caused by diarrheal diseases. Children under the age of five are most susceptible to viral diarrhea.

Objective: To compare the number of loose stools within the first 48 hours of admission between the children treated with and without Racecadotril, as well as the mean recovery time in children in both groups, in order to determine the efficacy of Racecadotril in treating acute watery diarrhea in children aged 6 months to 5 years.

Methods: It was a Randomized Controlled Trial conducted from October 2020 to March 2021 at the Department of Pediatrics General Hospital, Lahore. Patients were divided into two equal groups at random using a computer-generated random number table. Racecadotril (1.5 mg/kg body weight, orally three times per day for 5 days or until diarrhoea ceases, whichever happens first) was given to 100 patients in group A coupled with Low Osmolality ORS, while Low Osmolality ORS was given to 100 patients in group B. Blood urea and creatinine, blood sugar, serum electrolytes, and stool C/E, blood samples were sent to a hospital pathology lab. As per operational definition, recovery time was documented.

Results: In our study, the mean recovery time was 37.88 hours in group A (racecadotril plus low osmolality ORS) and 47.40 hours in group B (low osmolality ORS), demonstrating a substantial reduction in recovery time of 20.08 percent (p value = 0.0026). The mean 48-hour stool frequency was 11.34 episodes in the Racecadotril + low osmolality ORS group and 14.98 episodes in the low osmolality ORS group, demonstrating a statistically significant decrease in stool frequency of 24.29 percent with the Racecadotril group (p value = 0.025). Faster recovery (20.08 percent) and a reduction of 20.52 percent in ORS consumption, which is comparable with earlier trials on Racecadotril conducted in children with acute watery diarrhea.

Conclusion: There is a substantial difference in the mean recovery time when Racecadotril and Low Osmolality Oral Rehydration Solution (ORS) are used in combination.

Key words: Children, acute watery diarrhea, racecadotril

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INTRODUCTION

With 1.5 billion episodes and 1.5–2.5 million deaths each year among children under the age of five, acute diarrheal illness is a significant public health issue and a primary cause of pediatric morbidity and mortality [1]. About 2.2 million children died of dehydration brought on by diarrhea in 2002, which equates to 42,000 per

week, 6000 per day, 4 per minute, and one death every 14 seconds [2]. In impoverished nations, children under the age of five experience an average of 3.2 episodes of diarrhea per kid per year, with a mortality rate of 4.9 per 1000 episodes per year, or 21% of all pediatric deaths [3.] In developing nations, acute diarrhea is one of the main causes of child mortality. It mostly affects kids up to the age of five, especially neonates in the second half of the first year and kids up to the age of three. Rotaviruses, noroviruses, and Escherichia coli are the main pathogens. 90 percent of deaths from diarrhea can be attributed to poor sanitation. Acute diarrhea is the second largest cause of paediatric mortality overall and is responsible for 18% of fatalities in children under the age of five [2].

Acute diarrhea in children under five years of age remains a public health issue despite significant advancements in therapy [4]. Since diarrhea in children is one of the leading causes of morbidity and mortality in children, prevention and treatment of this condition are top public health priorities in undeveloped nations. Worldwide, there has been evidence of limited adherence to therapeutic recommendations for the treatment of paediatric diarrhea. The major goal of treatment is to stop acute diarrhea from depleting electrolytes and fluid from the intestine.

The mainstay of treatment for acute diarrhea in kids is oral rehydration solution (ORS)[3]. When used with ORS, racecadotril is an antisecretory medication with a different mode of action from currently available antidiarrheal medications. Racecadotril is an antisecretory drug that, without changing intestinal motility, can stop the loss of fluid/electrolytes from the colon as a result of acute. Racecadotril is an antisecretory drug that, without changing intestinal motility, can stop the loss of fluid/electrolytes from the colon. Racecadotril has emerged as the go-to medication for children with severe diarrhea, however current recommendations and earlier analyses of the subject are based on a scant amount of published data[4]. According to a comprehensive review published in 2018 and supported by meta-analysis for the five most frequently used outcome measures, Racecadotril consistently outperformed comparator treatments in outpatients and hospitalised patients.To give one example, it decreased the time to cure from 106.2 hours to 78.2 hours (a mean reduction of 28.0 hours; P 0.0001 in 24 studies reporting on this parameter).

The goal of the current study is to examine the effectiveness of Racecadotril and oral rehydration solution in treating acute watery diarrhea in children under the age of 5 in the local population.

Racecadotril was advised by studies on other populations, as no local investigations have been conducted to date [4]. In the future, Racecadotril will be used for the effective management of acute diarrhea. By lowering recoverytime, will help to reduce hospital stay and boost early recovery. The current study will create the baseline information for local community as well. Mostly, deaths are preventable as long as fluid and electrolyte losses are effectively restored because the majority of acute infectious diarrhea deaths are caused by excessive fluid and electrolyte losses that lead to dehydration and acidosis. Since it was initially developed nearly 30 years ago, oral rehydration therapy with glucose-electrolyte solution has saved the lives of millions of kids and is still the go-to treatment for acute watery diarrhea. Replace water losses orally in high volume watery diarrhea, such as cholera, remains a significant challenge for medical professionals[5]. Racecadotril is a particular enkephalinase inhibitor that has intestinal antisecretory properties in both humans and animals. Racecadotril has been proven to be a safe and effective antisecretory agent for usage in children with diarrhea by numerous preclinical and clinical trials [6].

There are few reports of Racecadotril use in Pakistani teaching hospitals, and any trials that have been done on the drug have taken place outside of Pakistan. In a tertiary care hospital with a unit dedicated to treating and training patients with diarrhea, this study was designed to assess the medication's effectiveness in the treatment of acute diarrhea in children.

Additionally, because viral aetiology is the most frequent cause of diarrhea in children under the age of five, this trial also evaluates racecadotril's efficacy against rotavirus diarrhea.

METHODS

This randomized controlled was conducted in 14 months in the department of Pediatrics, Lahore General Hospital, Lahore. Total 200 samples were taken (100 in each group) Group A consisted of 100 patients who received Racecadotril and ORS, while Group B consisted of 100 patients who received only O R S. Children with mild, moderate, and severe acute watery diarrhea of either gender, aged 6 months to 5 years, were included. Before participants were enrolled in the trial, a gross examination of the stools was performed to establish the existence of watery diarrhea. Patient had symptoms of sepsis, including impaired mental functions, acute malnutrition, and Children who had received any drug or intervention prior to enrolling in the research and who had third-degree malnutrition according to the WHO Classification were excluded. The institutional ethical review board gave its approval to the study protocol. 100 patients with acute watery diarrhea were admitted to the pediatrics department at Lahore

General Hospital after the Ethical Review Committee at the hospital received their informed consent. Age, sex, the hospital's number, the patient's name, drug history, and allergy history were baseline demographics that were gathered at the time of recruitment. The kids were then divided into one of the two groups at random (in each group). Racecadotril was given to one group (Group A) along with low osmolality ORS for three days or until the diarrhea ceased, whichever came first. The other group (Group B) also received low osmolality ORS. Every bit of data was gathered on a proforma that was especially created (attached). For the treatment of dehydration, both groups followed the WHO and IMCI (Integrated Management of Childhood Illness) standard. The effectiveness of all drugs was evaluated by counting the frequency of loose stools, hospital days, and mean recovery times with and without racecadotril. Following parental approval, 15-20 ml of stool specimen were collected in a sterile, wide-mouthed container, and were immediately sent to the lab. The Lahore General Hospital's Microbiology Lab processed the stool specimen for Ph, microscopic examination, culture, and sensitivity.

Data entry and analysis were done with SPSS version 24. For quantitative information like age and recuperation time, the mean and S.D. were determined. For categorical data, such as gender and baseline diarrhea grades, frequency and percentage were calculated in percentage. The independent sample t-test was used to compare the average recovery time between the two groups. Stratification was used to control effect modifiers like age, gender, baseline grades of diarrhea, duration of diarrhea, and malnourishment. An independent sample t-test using post-stratification was used. A p-value of 0.05 or less was regarded as significant.

RESULTS

200 patients in total were admitted, of which 100 were given ORS+Racecadotril (Group A) and 100 just ORS (Group B) for acute watery diarrhea in children under the age of five. There was no discernible difference in mean weight between the Racecadotril + low osmolality ORS (Group A) and the low osmolality ORS (Group B) groups. (p value=0.584) The patients' ages ranged from 6 months to 5 years, with a mean age of 19.72 months in the Racecadotril + ORS group and 20.68 months in the ORS group. There was no statistically significant difference between the two groups. (P = 0.734). For Group A, the mean and standard deviation were 19.72 12.74 and 20.68 15.31, respectively. Out of 200 patients, the gender breakdown reveals that 126 were men and 74 were women. There is no discernible variation in gender between Group A and Group B. Samples are gender-matched using the Chi-Square test, P=0.836.

Regarding the amount of time that the two groups had experienced loose stools before to hospital admission, there was no discernible difference. (p = 0.895). There was no discernible difference between the two groups in the frequency of loose motions on the day of admission. There was no discernible difference between the two groups in the mean number of days that diarrhea lasted prior to treatment between Racecadotril + low osmolality ORS (Group A) and low osmolality ORS (Group B), which was 2.38 days on average. Racecadotril + ORS group averaged 7.60 episodes of loose stools per day on the day of admission, whereas ORS group averaged 7.26 episodes. There was no statistically significant difference between the two groups (p value = 0.625). Table No. 2. Between the two groups, there was no discernible difference in the degree of dehydration (p value = 0.102). Table No. 3. In comparison to low osmolality R S (Group B), the mean amount of low osmolality ORS eaten prior to recovery in Racecadotril + ORS (Group A) was 161.20 ml as opposed to 202.84 ml, indicating a substantial reduction of 20.52 percent in the treatment group. Significant variation between the two groups' 48-hour stool frequency. The mean 48-hour stool frequency in the Racecadotril + low osmolality ORS group (Group A) was 11.34 episodes, while it was 14.98 episodes in the low osmolality ORS group (Group B), indicating a statistically significant decrease in stool frequency of 24.29 percent with Racecadotril (Group A) (p value = 0.025).

In our study, the mean recovery time was 37.88 hours in group A (racecadotril plus low osmolality ORS) and 47.40 hours in group B (low osmolality ORS), demonstrating a substantial reduction in recovery time of 20.08 percent (p value = 0.0026). Table No.5. Six patients from Racecadotril+ low osmolality ORS (Group A) and eighteen patients from low osmolality ORS (Group B) required intravenous fluid therapy as a result of the diarrhea getting worse. Racecadotril + low osmolality ORS (Group A) had a response rate of 94%, whereas Group B had a response rate of 82%. 14 patients in Group A (Racecadotril + Low osmolality ORS) and 6 patients in Group B (low Osmolality ORS) were found to be underweight throughout the course of the research. However, there was no discernible difference in the two groups' responses. Tables No. 6 and 7 show the data stratified for age, gender, baseline diarrhea grade, duration of diarrhea, and malnourishment, respectively.

Table 1: Age distribution of patients studied in two groups: Group A (Racecadotril + low osmolaity ORS) and Group B (low osmolaity ORS).

Age in months	Group A	Group B	Total
6	10(10%)	14(14%)	24(12%)
7-12	38(38%)	34(34%)	72(36%)
13-18	8(8%)	6(6%)	14(7%)
19-24	24(24%)	24(24%)	48(24%)
>24	20(20%)	22(22%)	42(21%)
Total	100(100%)	100(100%)	200(100%)
Mean ± SD	19.72±12.74	20.68±15.31	20.20±14.02

Samples are age matched with P=0.734, Student t test

Table 2: Comparison of mean of number of days of loose stools beforeadmission and frequency of loose stools on the day of admission in two groups of patients studied

	Group A	Group B	Total	P value
Number of days of loosestools before admission	2.38±1.64	2.52±1.63	2.45±1.63	0.670
Frequency of loose stoolson the day of admission	7.60±4.10	7.26±3.39	7.43±3.75	0.652

Table 3: Grade of dehydration in two groups of patientsStudied: Group A (Racecadotril + low osmolality ORS) Group B (Low Osmolaity ORS)

Grade ofDehydration	Group A	Group B	Total
Mild dehydration	62(62%)	50(50%)	112(56%)
Moderate dehydration	32(32%)	42(42%)	74(37%)
Severe dehydration	6 (%)	8 (8%)	14 (7%)
Total	100(100%)	100(100%)	200(100%)

P=0.102, Not Significant, Chi-Square test

Table 4: Number of episodes of loose stools in 48 hours afterstarting treatment

Number of episodes of loose stools in 48 hours after starting treatment	Group A	Group B	Total
<15	70(70%)	56(56%)	126(63%)
15-30	28(28%)	36(36%)	64(32%)
>30	2(2%)	8(8%)	10(5%)
Total	100(100%)	100(100%)	200(100%)
Mean ± SD	11.34±6.41	14.98±9.28	13.16±8.14

P=0.025*, Significant, Student t test

Table 5: Recovery time in hours in two groups of patients studied

Recovery Time Hours	Group A	Group B	Total
<12	8(8%)	4(4%)	12(6%)
12-24	16(16%)	12(12%)	28(14%)
24-48	54(54%)	54(54%)	108(54%)
>48	22(22%)	30(30%)	52(26%)
Total	100(100%)	100(100%)	100(100%)
Mean ± SD	37.88±19.05	47.40±22.79	42.64±21.44

P=0.026*, Significant, Student t test

Table 6. Stratification For Grade Of Diarrhea & MalnutritionWith Regards To Mean Recovery Time **(n=200)**

Up to 7 stools and No malnutrition

Mean RecoveryTime	Group-A(n=100)		Group-B(n=100)		
	Mean	SD	Mean	SD	P value
Mean change	2.55	0.76	2.14	0.73	0.08

>7 stools and malnutrition

Mean RecoveryTime	Group-A(n=100)		Group-B(n=100)		
	Mean	SD	Mean	SD	P value
Mean change	2.55	0.77	1.63	0.50	0.0001

Table 7. Stratification for duration of diarrhea with regards to mean recovery time (n=200)

Up to 14 days

Mean RecoveryTime	Group-A(n=100)		Group-B(n=100)		
	Mean	SD	Mean	SD	P value
Mean change	2.50	0.76	1.88	0.69	0.001

<7 days

Mean recoveryTime	Group-A(n=100)		Group-B(n=100)		
	Mean	SD	Mean	SD	P value
Mean change	2.75	0.71	2.00	0.63	0.06

DISCUSSION

The findings of this trial confirmed Racecadotril's effectiveness in treating infants and kids with acute watery diarrhea as a supplement to oral rehydration therapy and early continuous feeding. Patients who received Racecadotril saw a significantly lower frequency of stools, ORS consumption overall, and recovery time. The fact that a significant difference between treatments was observed during the first 48 hours of treatment demonstrated the speed of effect on stool frequency. The study group's mean recovery time was 20.08 percent shorter than that of the control group (20.40 hours vs. 47.88 hours). In their study, Lindo et al. compared the mean duration of diarrhea in the Racecadotril group to 25 hours in both rotavirus positive and negative children and found that the placebo group's mean duration was 72 hours and 52 hours for rotavirus positive and negative boys, respectively, and that it was 61.2 percent less in rotavirus positive boys and 52.2 percent less in rotavirus negative boys [7]. According to Cezard et al study from 2001, which evaluated the length of diarrhea in rotavirus-positive individuals, 50% of those taking Racecadotril recovered in 6.9 hours as opposed to 36 hours for the placebo group, or 80.1 percent less in study group [8]. In their investigation of 200 patients with acute watery diarrhea, Baumer et al. (1992) discovered that the mean diarrheal duration was 3.4 days in the Racecadotril group as opposed to 4.4 days in the control group, which was 22.8 percent shorter in the study group[9] In this trial, the Racecadotril group consumed 161.20 ml of ORS in total, 20.52 percent less than the control group. When compared to the placebo group, Lindo et al. found that ORS intake had decreased by 35.4%. In their research on Racecadotril for cholera in adults, Alam, Ashraf, et al. observed that ORS intake was 264 ml in the study group and 240 ml in the control group with no discernible difference between the two [10]. The average number of episodes of constipation in a 48-hour period was 11.34 in the Racecadotril group and 14.98 with ORS alone, indicating a reduction of 24.29 percent. In their study "Racecadotril in acute watery diarrhea in children," Cezard et al. examined stool production in 48 hours and discovered a 50% reduction in the group receiving Racecadotril when compared to the placebo [8]. In their study, Lindo et al. noticed that the stool production was 157 gm/kg in the Racecadotril group as opposed to 331 gm/kg in the placebo group, indicating a reduction in stool output with Racecadotril of 53%[7]. Racecadotril significantly reduced the number of stools in children with acute watery diarrhea, according to Cojocaru. et al. in their study (p0.001)[11]. In castor oil-induced diarrhoea, Baumer et al. observed a stool output of 426 gm with Racecadotril compared to 672 gm with placebo, showing a 37 percent decrease in the stool

output [9]. In this study, the overall clinical outcome was evaluated by categorising the number of patients who required intravenous fluid therapy.

Significantly, only three patients in the experimental group and nine in the control group required intravenous hydration therapy.Alam, et al. did notice that 8 out of 56 patients in the placebo group and 12 out of 54 patients taking Racecadotril needed intravenous fluid treatment, which was not significant [10]. According to Lindo et al., Racecadotril had an overall 5-day cure rate of 84 percent while a placebo had a rate of 66 percent. In terms of tolerance, neither group in this study experienced any noteworthy adverse effects[7]. Seven (14%) individuals in the Racecadotril group and fifteen (30%) patients in the ORS group had serum potassium values below 3.5 mmol/l, however neither group had any clinical symptoms or substantial ECG alterations. Two boys were diagnosed by Lindo et al. with mild hypokalemia, one of them also had ileus. 35 boys from each group in the research had vomiting[7]. There were 7 cases of vomiting in the Racecadotril group and 3 in the placebo group, but no one experienced hypokalemia, according to Cezard et al[8]. According to Alam et al., there was no difference between the Racecadotril and placebo groups in terms of the frequency of vomiting, recurrence of dehydration, stomach pain, headaches, or anorexia[10]. In our study, children under the age of five were sampled, with the age range of 7 to 12 months having the highest number of instances.

CONCLUSION

In managing children under the age of five who have acute watery diarrhea, we came to the conclusion that there is a substantial difference in the mean recovery time when Racecadotril and Low Osmolality Oral Rehydration Solution (ORS) are used in combination.

ETHICAL APPROVAL

The study was approved by the Research Evaluation Unit of College of Physicians and Surgeons Pakistan vide Reference No. CPSP/REU/PED-2018-069-4785 dated January 21, 2022.

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AUTHOR'S CONTRIBUTIONS

AR: Manuscript writing, Data collection,
NZ: Data collection
AA: Statistical analysis
MAK: Data collection, Statistical analysis