

Efficacy of Racecadotril in Acute Watery Diarrhea as Compared to Placebo

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Racecadotril in
Acute Watery
Diarrhea

Arshia Munir¹, Kashif Ali², Muhammad Bilal Khattak³, Muhammad Aqeel Khan⁴ and
Faiqa Hashmat¹

ABSTRACT

Objective: To determine the efficacy of racecadotril with placebo in patients presenting with acute diarrhea.

Study Design: Randomized Controlled Trial study

Place and Duration of Study: This study was conducted at the Department of Pediatric Medicine, Hayatabad Medical Complex, Peshawar from December, 2020 to June, 2021.

Materials and Methods: A total of 142 children of age 6 months to five years with acute watery diarrhea fulfilling the inclusion criteria were included in the study and randomly allocated in to two groups. Racecadotril was given to Group A patients while group B patients were subjected to placebo. The patients were followed to determine the efficacy in term of reduction of stool frequency and duration of diarrhea.

Results: The mean age was 3 ± 1.5 years. The mean age of children in group A was 3 ± 1.5 years while in group B 2.9 ± 1.5 years (p 0.646). The percentage of male patients was 60.6% in group A and 49.3% in group B (p .177). The mean weight of the child in group A was 11 ± 4.7 kg compared to 10.8 ± 4.9 kg (p 0.861). The mean duration of diarrhea in group A was 36.2 ± 7.92 hours compared to 36.1 ± 7.7 hours (0.0983). The mean baseline stool frequency was 4.9 ± 1.4 compared to 4.7 ± 1.5 (0.536). Racecadotril was found more effective (80.3 %) than placebo (63.4%) group (0.025).

Conclusion: Racecadotril is has more encouraging results in the management of acute watery pediatric diarrheas under five years of age compared to placebo.

Key Words: Pediatric diarrhea, racecadotril, stool frequency, placebo

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INTRODUCTION

Diarrhea is passing of one big watery stool or three or more than three stool of loose consistency. Diarrhea is broadly classified as acute watery diarrhea, acute dysentery persistent diarrhea and chronic diarrhea¹. Acute watery diarrhea is one which confirms the criteria of acute diarrhea i.e. stays for less than two weeks and is watery in consistency². It may or may not be associated with fever and vomiting.

¹. Department of Pediatric Medicine, Khyber Medical College, Khyber Teaching Hospital, Peshawar.

². Department of Pediatric Medicine, MTI Hayatabad Medical Complex, Peshawar.

³. Department of Medicine / Pediatric Medicine⁴, Khyber Girls Medical College, Hayatabad Medical Complex, Peshawar.

Correspondence: Muhammad Bilal Khattak, Associate Professor of Medicine, Khyber Girls Medical College, Hayatabad Medical Complex, Peshawar.

Contact No: 0333-9346838

Email: bilalkhattak120@gmail.com

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Diarrhea is one of the leading causes of death in children less than one year of age. Almost 9 million children are dying each year due to various causes, out of these 4 million deaths are caused by diarrhea. The major burden of these deaths is shared by five developing countries including Pakistan¹⁻⁴.

The major cause of death in acute watery diarrhea is dehydration. Though rehydration therapies including both oral and intravenous play a vital role in the treatment of dehydration yet it has no effect on decreasing the frequency and consistency of the watery stools. Racecadotril and antisecretory drug has a definite role both in decreasing the frequency and consistency of the watery stool⁵. Racecadotril selectively inhibits endopeptidase (enkephalinase) which is lying in human gut epithelium. Enkephalin (an endogenous opioid) has finally antisecretory effects⁶. The end result is decrease in water and electrolytes loss without affecting intestinal motility. Therefore, racecadotril prevents fluid and electrolytes loss and treats acute watery diarrhea effectively. So it can be used in combination with oral rehydration therapy as recommended by National Institute of Health and Excellence in infant age more than 3 months of age^{7,8}.

Racecadotril should be given for a short period and should not be administered to patients for more than week duration. A few side effects like abdominal pain

and bloating may be experienced with racecadotril. Studies have shown efficacy with racecadotril as compared to placebo in reducing days of diarrhea and stool frequency of stools with no significant adverse effects⁹⁻¹².

The purpose of our study was to look for efficacy of racecadotril in acute diarrhea in terms of decreasing duration of the diarrhea and preventing dehydration as well in children age less than five years of age and updating our medical population by its efficacy in the management of acute watery diarrhea and thus reducing the under-five mortality.

MATERIALS AND METHODS

This randomized control trial was conducted from December 2020 to June 2021 at the department of pediatrics Hayatabad Medical Complex, Peshawar. A total of 142 children (6 months to five years) with diarrhea were included in the study and randomly allocated into two groups. Patients in one group were subjected to racecadotril (group A) while other group was subjected to placebo (group B) along with fluid replacement. Follow up was done to determine the efficacy in terms of reduction in stool frequency and duration of diarrhea.

All children age 6 months to 5 years, of both gender and having loose stool of less than 14 days duration were included in the study. Patients having blood in stool, with history of anti-diarrheal use and duration of more than 14 days were excluded from the study.

The study was conducted after approval from Institutional Ethical Research Board. Patients fulfilling the inclusion criteria were included in the study both from outdoor and admitted patients in the pediatric department. The purpose, benefits and all relevant information were shared with the parents and attendants of the patients. They were also explained the benefits, risks and also explained that the study is purely conducted for research purpose. On being agreed written informed consent was also taken from the parents and attendants.

All the patients fulfilling the operational definition, inclusion and exclusion criteria were subjected to detailed history and clinical examinations. Stool routine examination was carried out at hospital laboratory. All the patients were assigned two groups A and B by randomly allocating the patients to the groups to avoid any bias to the randomized control trial.

Group A were given racecadotril 1.5 mg/kg body weight orally three times a day along with Low ORS and Group B received Low osmolar ORS and placebo. Patients of both groups were followed for 48 hours. All information including gender, duration of loose motion and weight was recorded on predesigned proforma. To control confounders and bias in the results of our study exclusion criteria was strictly followed.

The data was analyzed in SPSS version 22.0 and mean and standard deviation was calculated for numerical variables like age, weight and duration of diarrhea. Frequencies and percentages were computed for categorical variables like gender and efficacy. Efficacy was stratified by age, gender, weight, and duration of diarrhea. Groups were compared with respect to efficacy by using chi square tests. Post stratification chi square test was applied and p value of < 0.05 was considered as significant. Data was interpreted in the form of tables.

RESULTS

A total of 142 patients age 6 months to 5 years were included in the study. The mean age of the study population was 3 ± 1.5 years. Mean age in group A was 3 ± 1.5 years while 2.9 ± 1.5 years (p 0.646) table1. Male patients constituted 43 (60.6 %) of group A while group B comprised of 35 (49.3%) male patients.

Table No. 1: Comparison of Duration of Diarrhea in Both Groups (n =71 in each group)

Duration of diarrhea	Treatment group		P-value
	Racecadotril	Control	
24-36hours	40	41	0.865
	56.3%	57.7%	
>36-48hours	31	30	
	43.7%	42.3%	
Total	71	71	
	100.0%	100.0%	

Table No. 2: Comparison of Baseline Stool Frequency of Both Groups (N=71each)

Base line stool frequency	Treatment group		P value
	Racecadotril	Control	
3-5/day	44	45	0.862
	62.0%	63.4%	
>5-7/day	27	26	
	38.0%	36.6%	
Total	71	71	
	100.0%	100.0%	

Table No. 3: Comparison of Efficacy between Both Groups (N=71each)

Efficacy of both groups	Treatment group		P value
	Racecadotril	Control	
Yes	57	45	0.025
Efficacy	80.3%	63.4%	
No	14	26	
	19.7%	36.6%	
Total	71	71	
	100.0%	100.0%	

The mean weight of child in both A and B group were 11 ± 4.7 kg and 10.8 ± 4.9 kg respectively (p 0.861). The comparison of duration of diarrhea, frequency of stools and comparison of efficacy in both groups has been given in table 1, 2 and 3 respectively. The stratification of duration of diarrhea and frequency of stool for both groups has been demonstrated in table 4 and 5 respectively.

Table No. 4: Duration of Diarrhea Wise Stratification of Efficacy (n=71 in each group)

Duration of diarrhea		Treatment group		P value
		Racecadotril	Control	
	Yes	30	25	
24-36hours	Efficacy	54.5%	45.5%	0.176
	No	10	16	
		38.5%	61.5%	
	Yes	27	20	
>36-48hours	Efficacy	57.4%	42.6%	0.058
	No	4	10	
		28.6%	71.4%	

Table No. 5: Baseline Stool Frequency Wise Stratification of Efficacy (n=71 in each group)

Base line stool frequency		Treatment group		P value
		Racecadotril	Control	
	Yes	37	28	
3-5/day	Efficacy	56.9%	43.1%	0.020
	No	7	17	
		29.2%	70.8%	
	Yes	20	17	
>5-7/day	Efficacy	54.1%	45.9%	.491
	No	7	9	
		43.8%	56.2%	

DISCUSSION

Diarrhea is one of the leading health problems in pediatric age group around the globe and is one of the leading causes of under-five mortality in developing countries and one of the major causes of hospital admission in developed countries. No doubt oral rehydration therapy (ORT) in the form of oral rehydration solution (ORS) is the counter stone in acute diarrhea management for the past three decades. Multiple medications especially adsorptive agents, zinc, probiotics, antibiotics and opioid receptor agonist loperamide are used for the treatment of diarrhea, though the latter is no more recommended¹³⁻¹⁴.

Racecadotril is recently used to treat acute watery diarrhea which is an inhibitor of the endorphin

metabolizing enzyme neutral endopeptidase also known as enkephalinase. Thiorphan is the immediate metabolite formed from racecadotril. The ultimate action of thiorphan is its effective role in decreasing the loss of electrolytes and fluid from the gut epithelium. Racecadotril has also antisecretory activity in Rota virus and cholera induced secretion. Racecadotril has no effect on gut motility¹⁵⁻¹⁶. Racecadotril does not increase *E. coli* growth in the gut due to its antisecretory effect which is there in case of loperamide use. Therefore it has a positive effect on decreasing the stool frequency and dehydration without causing increase in bacterial growth and rebound constipation¹⁷. Several reviews and meta-analysis have proved efficacy of racecadotril use in pediatric diarrhea. Therefore international guidelines also recommend its use in children suffering from acute watery diarrhea¹⁸.

Our study results establish efficacy of racecadotril in children with acute diarrhea. The results of our study showed decrease in duration and the frequency of stool which was significant statistically. The same results were found by other studies. The results confirm that racecadotril reduces both water and electrolytes loss from the gut. Though other medications like Loperamide and bismuth subsalicylate reduce the stool output but are not used because of their untoward adverse effects in many countries^{19, 20}. A big chunk of pediatric diarrhea patients are there below two years of age where loperamide is also contraindicated in these children below two years of age²¹. Though other drugs may have beneficial effect on diarrhea duration and stool frequency but in current study we have compared the efficacy of racecadotril with placebo^{21, 22}.

Racecadotril was well tolerated by pediatric population and no adverse event was related to use of the medicine in our study. Our study result well tolerability and safety is confirmed by other international and local. Racecadotril has no effect on intestinal motility and has an exclusive antisecretory effect on the gut²³. Studies have proved that racecadotril has encouraging results in terms of decreasing the duration of diarrhea and positive effect on decreasing stool frequency as well. The overall efficacy of racecadotril in comparison was really encouraging and had statistical significance result²⁴. Our study also confirmed the effective nature of the antisecretory racecadotril with significant statistical response and result as compared to placebo. In randomized placebo controlled trials in adults almost same results have been found confirming efficacy of racecadotril on consistency and decrease in duration of diarrhea along with tolerability and safety²⁵.

CONCLUSION

Racecadotril ineffective in the treatment of acute diarrhea in children less than five years of age compared to placebo. We recommend more randomized controlled trials specially on much larger sample sizes and multicenter to find the best possible local evidence encouraging racecadotril therapy in pediatric acute watery diarrhea.

Author's Contribution:

Concept & Design of Study: Arshia Munir
 Drafting: Kashif Ali, Muhammad Bilal Khattak
 Data Analysis: Muhammad Aqeel Khan, Faiqa Hashmat
 Revisiting Critically: Arshia Munir, Kashif Ali
 Final Approval of version: Arshia Munir

Conflict of Interest: The study has no conflict of interest to declare by any author.

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