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ORIGINAL ARTICLE

Role of Racecadotril in Children with Acute Diarrhea

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Abstract

Background: *Diarrhea is a leading cause of illness and death among children in developing countries. Racecadotril (acetorphan), an enkephalinase inhibitor with antisecretory and anti-diarrheal actions, is an effective and safe treatment for acute diarrhea in adults and children.*

Objectives: *The objective of this study is to evaluate the efficacy and tolerability of racecadotril as a treatment of acute diarrhea in children.*

Methods: *This double-blind, randomized controlled clinical trial was conducted in Dr. MR Khan Children Hospital & Institute of Child Health over 1 year (June 2017-May 2018). The study was approved by the ethical committee of the institute. The efficacy and tolerability of racecadotril (1.5 mg/kg) administered orally 3 times daily) as adjuvant therapy to oral rehydration or intravenous fluid were compared with those of placebo in 40 children aged 3 months to 60 months of children who had acute diarrhea.*

Results: *During the first 72 hours of treatment, patients receiving racecadotril had a significantly lower stool output (grams per hour) than those receiving placebo. The mean (±SE) 72-hours stool output was 54.75± 12.92 g per kilogram in the racecadotril group and 152.50±37.64 g per kilogram in the placebo group (p<0.001). The number of purging is significantly reduced in the racecadotril group than the placebo group (11.95±2.41 Vs 14.85±1.95, p= 0.000) on third day of admission. The duration of hospital stay is significantly lower in the racecadotril group than the placebo group (73.30±23.44 vs. 177.30±25.8. p= 0.000) group. Racecadotril was well tolerated; only 3 patients taking racecadotril had adverse effects like vomiting and 2 patients had hypokalaemia and 3 patients in the placebo group developed vomiting and 1patient developed hypokalaemia which all are mild and transient.*

Conclusion: *In young children with acute watery diarrhea, racecadotril is an effective and safe treatment along with rehydration therapy.*

Keywords: *Acute diarrhea, racecadotril.*

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Introduction

Acute diarrhea in children is a global health problem with an estimated 2 billion episodes each year, mostly in developing countries; make a contribution to 18% of under-five childhood mortality. Diarrheal disease is a leading cause of illness and death in children worldwide.[1-2] Many of the deaths are caused by dehydration resulting from loss of water and electrolytes due to intestinal malabsorption or increased secretion. Replacement of these losses by oral rehydration solution is the mainstay of therapy for children with watery diarrhea.[3] Oral rehydration therapy is well accepted as the most effective treatment for rehydration of children with acute diarrhea and is recommended by the World Health Organization for prevention and management of dehydration.[4] Although the use of oral rehydration therapy has achieved a dramatic reduction in both morbidity and mortality in diarrhea,[3-4] rehydration has little effect on stool volume or frequency. Therefore, the World Health Organization has recommended that drug treatment be added to rehydration therapy, as long as the drug used has proven safety and efficacy in the paediatric population.[4-5]

Racecadotril decreases intestinal hypersecretion but not motility.[6-7] It has proven efficacy and safety use in children and adults with acute watery diarrhea when taken orally.[8-9] A previous study of racecadotril was carried out in children three months to four years old in France.[8]

Racecadotril (acetorphan) is an enkephalinase inhibitor (neprilysin, EC 3.4.24.11), a cell membrane peptidase enzyme located in various tissues, notably the epithelium of the small intestine. It exerts its antidiarrheal effects by preventing the breakdown of endogenous peptides such as enkephalins, neurokinin, and substance P in the gastrointestinal tract.[9-12] Moreover, racecadotril does not increase intestinal transit time,[13] implying that the drug has a selective antisecretory mode of action. In adults, racecadotril has been shown to have better efficacy than placebo in randomized, double-blind clinical trials of patients with acute diarrhea. This efficacy has been combined with a side effects profile similar to that of placebo.[14-16]

The present study was performed to compare the efficacy and tolerability of racecadotril with placebo in hospitalized infants and children (aged 3 months to 5years) and also assess the effect of racecadotril as an adjunct to rehydration therapy in infants and children in Bangladesh

Materials and Methods

This double-blind, randomized controlled clinical trial was conducted in Dr. MR Khan Children Hospital & Institute of Child Health over 1 year (June 2017-May 2018). The study was approved by the ethical committee of the institute. A total of 100 patients were included initially in this study who met the inclusion criteria i.e. children aged 3 months to 60 months of either sex who had watery diarrhea (passed three or more diarrheic stools in the 24 hours before admission to the hospital) and who gave consent. Children with bloody stool, chronic diarrhea, severe dehydration (inability to drink because of drowsiness), or any serious concomitant illness and who didn't give consent were excluded from the study.

Of the 100 patients who enrolled in this study (50 in racecadotril group and 50 in the placebo group), 5 were excluded because their stool weights were not recorded (3 in the racecadotril group and 2 placebo group). Stool weights could not be estimated in 7 other patients receiving racecadotril (4 from 12 to 24 hours and 3 from 24 to 36 hours). These data were therefore recorded as missing. Another 8 patients were discarded from the placebo group due to insufficient data.

The full data set consisted of 40 patients who received racecadotril (Racitril sachet 10 and 30 mg) and 40 who received a placebo, orally every eight hours, in addition to oral or intravenous rehydration solution. Both treatments were administered as saccharose-containing powders of identical appearance and taste, with two spoons water to facilitate swallowing. Treatment with antibiotics, other anti-diarrheal drugs, or any other drugs were not permitted during the study. The efficacy and tolerability of racecadotril (1.5 mg/kg) administered orally 3 times daily) as adjuvant therapy to oral rehydration or intravenous fluid were compared with those of placebo in 40 children. Both groups were comparable in terms of age, duration of diarrhea, the number of stools, hospital stay, and complications.

Diarrhea was considered to have stopped after any patient had passed two consecutive formed stools or had not passed a stool for 12 hours. In addition to oral rehydration solution, the patient was given

milk or soft foods, as appropriate to their age, to provide a daily calorie intake of 100 to 120 kcal per kilogram (excluding the calories from glucose in the rehydration solution), accordance to World Health Organization recommendations that diet was maintained during treatment of diarrhea to prevent malnutrition.[3] Fresh stool collected at admission for a routine microscopic test, stool culture, and presence of rotavirus by ELISA.[12] If stool culture showed any growth of bacteria which need antibiotic then this case was excluded from the study. Serum electrolyte and serum creatinine were measured on day 3 after giving racecadotril and placebo to compare any changes or side effects by racecadotril. We didn't do electrolyte and creatinine at admission as severe dehydration was not enrolled or we enrolled it after correction of severe dehydration by intravenous fluid.

A physical examination was performed each day during the study, and stool weight, intake of oral rehydration solution, and output of vomit were measured every four hours. The primary endpoint was stool output in the first 72 hours because both the fluid loss and the risk of dehydration are maximal during this period. During this period, care was taken to ensure that stools were collected separately from urine. Thereafter, stools were collected in preweighed diapers. Stool output was calculated as the sum of the weights of the watery and loose stools (diarrheic stools) divided by the bodyweight at baseline. The total stool output, duration of diarrhea, and total intake of oral rehydration solution were also measured. These assessments were made at the time of recovery or the end of five. Data were collected in a structured questionnaire form and were analyzed by using SPSS version 20.0.

Results

No significant variation was found in demographic profile between racecadotril and placebo group. Both racecadotril and placebo groups are comparable to the socio-demographic variable (Table I).

The duration of diarrhea at admission in both the racecadotril group and placebo group is almost the same (43.65 ± 17.8 Vs 45.9 ± 13.35, p= 0.65). No significant difference was found (Table II).

Table I
Demographic characteristics of the study population

Variable	Racecadotril Group (n=40)	Placebo Group (n=40)	p value*
Mothers Education			
Uneducated	6	12	
Primary	10	20	
Secondary	16	8	0.46
Graduate	8	0	
Source of water			
Supply water	0	2	
Boiled water	18	22	
Filter water	16	14	
Tube well	6	2	0.41
Family income			
<10,000	4	4	0.60
10,000-25,000	26	22	
>25,000	10	14	
Area of living			
Urban	36	34	0.36
Rural	4	6	

*data were analyzed by independent t-test

Table II
Duration of diarrhea at admission

Variable	Racecadotril Group (n=40)	Placebo Group (n=40)	p value*
Duration of diarrhea in hours at admission Mean ± SD	43.65±17.8	45.9±13.35	0.65

*data were analyzed by independent t-test

There is no significant electrolyte and serum creatinine changes between the racecadotril and the placebo group (Table III).

Table III
S. electrolyte and S. creatinine changes between the two groups

Variable	Racecadotril Group (n=40)	Placebo Group (n=40)	p value*
Serum Na^+ mmol/L (Mean±SD)	138.62±3.63	138.92±4.80	0.825
Serum K^+mmol/L (Mean±SD)	4.08±0.59	4.03 ± 0.51	0.775
Serum Cl^-mmol/L (Mean±SD)	99.77±4.14	101.30±5.06	0.302
Serum creatinine in mg/dl (Mean±SD)	0.23±0.18	0.21±0.06	0.734

*data were analyzed by independent t-test

Table IV
Comparison of stool volume and purging in case and control group

Variable	Racecadotril Group (n=40)	Placebo Group (n=40)	p value*
Stool volume at Day 1 (Mean±SD)	170±40.58	172.5±37.8	0.841
Stool volume at Day 3 (Mean±SD)	54.75± 12.92	152.50±37.64	0.000
Stool volume at discharge (Mean±SD)	34.60±13.39	40.15±5.70	0.096
Number of purging at Day 1 (Mean±SD)	21.40±4.20	19.95±3.22	0.231
Number of purging at Day 3 (Mean±SD	11.95±2.41	14.85±1.95	0.000
Number of purging at Day of discharge (Mean±SD)	4.05±1.35	4.45±0.68	0.236
Duration of hospital stayIn hours (Mean±SD)	73.30±23.44	177.30±25.8	0.000

*data were analyzed by independent t-test

Mean stool volume at day one (D1) in two groups is not significant (170±40.58 Vs 172.5±37.8, p-value 0.84) whereas mean stool volume at day 3 (D3) between the case and placebo group is significant (54.75± 12.92 vs. 152.50±37.64, *p*-value 0.000). The number of purging at day 1 in two groups is not significant but at day 3 number of purging is significantly reduced in the racecadotril group than the placebo group (11.95±2.41 Vs 14.85±1.95, *P*-value 0.000). The number of purging at Day of discharge (Mean±SD) was not significant in two groups (4.05±1.35 Vs 4.45±0.68, p=0.236). The duration of hospital stay is significantly lower in the racecadotril group than the placebo group (73.30±23.44 vs. 177.30±25.8 p= 0.000) (Table IV).

Discussion

Racecadotril when used as an adjunct to oral rehydration therapy, may reduce both the severity and duration of diarrhea and the duration of hospitalization.[17]

Our study showed mean stool volume at day 3 between racecadotril and placebo group is significant (54.75± 12.92 vs. 152.50±37.64; p=0.000) and the number of purging at day 3 (48 hours after starting racecadotril) is significantly reduced in the racecadotril group than the placebo group (11.95±2.41 vs. 14.85±1.95; p=0.000). Jean et al[18] showed during the first 48 hours of treatment, patients receiving racecadotril had a significantly lower stool output (grams per hour) than those receiving placebo. The 95% confidence interval was 43% - 88% for the full data set (n=166; p=0.009) and 33%-75% for the per-protocol population (n=116; p=0.001), which is similar to our study.

Another systematic review and Meta-analysis was conducted for the five most frequently used efficacy parameters showed racecadotril was superior to comparator treatments in outpatients and hospitalized patients with a high degree of consistency as confirmed by meta-analysis. For instance, it reduced time to cure of 106.2 h to 78.2 h (mean reduction 28.0 h; p<0.0001 in 24 studies reporting on this parameter).[19] This meta-analysis supports our findings of the efficacy of racecadotril. In another

recent study in India showed racecadotril had less effect on reducing stool volume and purging in rotaviral diarrhea which is opposite to our findings, it may be due to geographical variation or organism causing diarrhea.[20]

In the present study duration of hospital stay is significantly lower in the racecadotril group than the placebo group (73.30±23.44 vs. 177.30±25.8 p-value 0.000). Our findings support other studies median duration of diarrhea in the racecadotril group was 28 hours and the corresponding values in the placebo group were 72 hours, ($p<0.001$).[17,21,22]

Racecadotril seems to be well tolerated in our study, only 3 patients taking racecadotril had adverse effects like vomiting, and 2 patients had hypokalaemia and 3 patients in the placebo group developed vomiting and 1patient developed hypokalaemia which all are mild and transient.

The incidence of adverse effects did not differ between the racecadotril and the placebo group. And acute diarrhea itself can cause vomiting and hypokalaemia. Moreover, no serious adverse effect was observed in our study. These findings correspond with another study conducted in ICDDR'B Bangladesh.[23]

Conclusion

Racecadotril is an effective, well-tolerated adjunct to oral rehydration therapy in infants and children with acute diarrhea.

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