Original Article

Efficacy and safety of racecadotril as an adjunct to oral rehydration therapy for acute watery diarrhea in children

S K Sreenivas, M Lakshmi, N A Pavitra

From Department of Pediatrics, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

Correspondence to: Dr. S K Sreenivas, Department of Pediatrics, Bangalore Medical College Research Institute, Bengaluru - 560 002, Karnataka India. Phone: +91-9986551735. E-mail: sreenivaraj2007@gmail.com

Received – 21 September 2016 Initial Review – 07 October 2016 Published Online – 15 December 2016

ABSTRACT

Background: Racecadotril, an enkephalinase inhibitor with antisecretory action is a safe and effective treatment for acute diarrhea for children and adults. As an adjunct to oral rehydration therapy (ORT) in Indian children, its efficacy and safety data are scarce. **Methods:** A total of 117 children with acute watery diarrhea for not more than 7 days were randomized into two groups. Group A (control group) received ORT and zinc only while Group B (study group) received a combination of racecadotril (1.5 mg/kg q8 h), zinc and ORT. Primary end point was the number of loose stools during first 48 h of treatment. Time to cure as well as total volume of oral rehydration solution (ORS) consumed was also measured. **Results:** Baseline characteristics were not significantly different between the groups. Mean 48 h stool frequency in the study group was 10.47±3.2 episodes and that in control group was 15.87±4.6 episodes indicating a significant reduction of 34.1% with racecadotril (p=0.00016). The mean time for recovery in the study group was 37.98±6.1 h and 51.02±9.4 h in control group indicating a significant reduction of 25.6% with racecadotril (p=0.002). The mean volume of ORS consumed before recovery in the study group was 162.72 ml as compared to 232.68 ml in control group pointing to a significant reduction of 30.1% in the study group. **Conclusions:** Racecadotril is effective as an adjunct to ORT and early continued feeding in infants and children with acute watery diarrhea.

Key words: *Acute watery diarrhea, Adjunct, Oral rehydration therapy, Racecadotril*

Diarrhea is defined as the passage of three or more loose or watery stools in a 24 h period, a loose stool being one that would take the shape of container [1]. More than 90% of acute diarrhea is due to infectious agents [2]. Most of the deaths from acute infectious diarrhea result from excessive fluid and electrolyte losses that result in dehydration and acidosis; thus, the majority of times, deaths are avoidable as long as fluid and electrolyte losses are replaced properly.

Although the use of oral rehydration therapy (ORT) has achieved a dramatic reduction in both morbidity and mortality in diarrhea, rehydration has little effect on stool volume or frequency. As oral rehydration solution (ORS) *per se* cannot be the ultimate management of diarrhea, the World Health Organization (WHO) has recommended the drug treatment should be added as long as the drug used has proven safety and efficacy in the pediatric population [3]. Racecadotril is a specific enkephalinase inhibitor that exhibits intestinal antisecretory activity not only in animals but also in humans [4]. Various preclinical and clinical trials on racecadotril have established it to be a safe and potent antisecretory agent for use in children with diarrhea [5] and the drug controller general of India has approved it as antidiarrheal on 10-10-2001 [6].

However, the efficacy and safety of racecadotril in Indian children have not been studied extensively. Hence, this study was planned to evaluate the efficacy of the drug in the management of acute diarrhea in children in a tertiary care hospital with a diarrhea treatment and training unit.

METHODS

This was a randomized controlled single center trial. Patients with acute watery diarrhea aged between 3 months to 5 years with the duration of diarrhea of fewer than 7 days were selected for the study. We could not classify the etiology of diarrhea due to limited diagnostic facilities. The presence of watery diarrhea was confirmed by gross examination of stool before inclusion of patients for the study. Subjects were excluded if they had persistent vomiting >3 episodes/h, severe dehydration, or any serious concomitant illness including HIV seropositive status and severe malnutrition, blood in stool, received an antibiotic or any antidiarrheal drug within the preceding 48 h.

The study protocol was approved by the institutional ethical committee. Parents were explained about the study in the language they understand best, and a proper informed consent was taken from them. A detailed history was obtained from the parents of each of the admitted child with acute watery diarrhea and recorded as per the pro forma designed for this study. A standard physical examination including assessment of dehydration and a basal blood and stool examination was performed.

Intervention

Simple random sampling was used to randomize the subjects into two groups (study and control) by computer-generated numbers. All patients from both the groups were given standard WHO-ORS depending on their hydration status and oral zinc. A uniform dose of 20 mg of elemental zinc was given to all children in both the groups during the period of diarrhea and for 7 days after cessation of diarrhea as per the recommendations of the IAP national task force for the use of zinc in diarrhea [7]. Children in study group also received racecadotril at a dose of 1.5 mg/kg/day 8 hourly by mixing it with plain water. In addition to ORS, all the subjects were given breastfeeding, milk and soft food, as appropriate to their age, to provide a daily calorie intake of 100-120 Kcal/kg (excluding the calories from glucose in ORS), in accordance with WHO recommendations that diet be maintained during treatment of diarrhea to prevent nutritional disturbance.

The patients were not given any other medications apart from these, and the treatment was given for 5 days or until the patient recovered (whichever was earlier). The patient was considered to have recovered if he/she had any one of these, (1) <2 stools/day for two consecutive days, (2) two consecutive formed stools, (3) not passed stools for 12 h.

Outcomes

The primary efficacy criteria were stool frequency during first 48 h because the fluid loss and risk of dehydration are maximal during this period. The secondary efficacy criteria were the total volume of ORS consumed until the cure of diarrhea and time taken for a cure.

Tolerability was assessed during each clinical evaluation, and all adverse effects were recorded. Clinical symptoms such as fever, vomiting, and abdominal distension were assessed every 4 h. Abdominal distension was assessed by taking abdominal girth at the level of the umbilicus. Serum potassium levels were measured 24 h after starting racecadotril, and ECG was taken if serum potassium levels were low or if the patient had any clinical signs of hypokalemia such as hypotonia, abdominal distension, weakness, and easy fatigability.

Statistical Analysis

Primary and secondary outcomes (continuous variables) were compared between the groups by unpaired *t*-test. The percentage (ratios) of patients achieving certain outcomes was compared between the groups by Chi-square test/fisher's exact test.

RESULTS

A total of 117 patients recruited in the study and out of these 55 were assigned to receive ORS+racecadotril+zinc and 62 to receive only ORS+zinc. Of these, one patient turned out to be seropositive for HIV so was excluded from the study. One patient in the study group and two from control group withdrew in view of persistent vomiting. Hence, the efficacy criteria were assessed in total 113 patients, out of which 53 (female=28) patients were assigned to study and 60 (female=25) patients to control group. Baseline characteristics are given in Table 1.

A significant difference in stool frequency in 48 h between the two groups was observed (Table 2). The mean 48 h stool frequency in study and control group was 10.47±3.2 and 15.87±4.6 episodes, respectively, indicating a significant reduction of 34.1% with the use of racecadotril (p=0.00016). A significant reduction of 25.6% in the time for recovery was also seen in the study group, and the mean time for recovery was 37.98±6.1 and 51.02±9.4 h in the study and control group, respectively, (p=0.002).

The mean volume of ORS consumed before recovery in the study group was significantly lesser (30.1%) than that in control group (162.72±52.65 ml vs. 232.68±39.86 ml). No significant difference in the number of patients who required IV fluids between two groups was seen and 3 from the study and 7 patients from control group required intravenous fluid therapy due to worsening of diarrhea. No significant difference in response rate was seen between two groups (94.03% vs. 88.03%).

We also observed the difference in the time of recovery between the two groups and more number of patients in the study group responded in first 24 h as depicted in Table 3.

No significant differences between the groups in the adverse events reported. A total of 6 patients from control and 5 from study group had serum K+ values <3.5 mmol/L, but none in both the groups had any ECG changes or symptoms and all recovered without any treatment and had normal serum K+ when repeated after 24 h.

DISCUSSION

The results of this study support the efficacy of racecadotril as an adjunct to ORT and early continued feeding in infants and children with acute watery diarrhea. Patients who received racecadotril had a substantial reduction in stool frequency (34.1%), total amount of ORS consumed (30.1%), and the time taken for recovery (25.6%). The rapidity of effect on stool frequency was shown by the fact that a significant difference was seen within first 24 h of treatment.

Salazar-Lindo et al. had compared the duration of diarrhea in racecadotril and placebo groups according to their rotavirus status, and they found that median duration of diarrhea in racecadotril group was 28 h regardless of rotavirus status and that of placebo was 72 and 52 h, respectively, for rotavirus positive and negative children [5]. Cezard et al. compared the duration of diarrhea in rotavirus-positive patients and found that 50% of patients on racecadotril had recovered in 6.9 h as compared to 36 h in the placebo group [8]. Baumer et al. in their study on 200 patients with acute watery diarrhea had found that mean duration of diarrhea was 22.8% less in racecadotril group (3.4 vs. 4.4 days) than the control group [9].

The total amount of ORS consumed in our study was 162.72 ml in racecadotril group which was 30.1% less than the control group. Salazar-Lindo et al. had documented 35.4%

Table 1: Baseline characteristics of study population

Variables	Control group		Study group		Unpaired t-test	
	N	Mean±SD	N	Mean±SD	*t*	p
Body weight (Kg)	60	9.65±4.58	53	10.72±4.53	−1.250	0.214*
Age (months)	60	24.35±20.08	53	31.13±21.48	−1.734	0.086*
Diarrhea before recruitment						
Duration (days)	60	2.40±1.62	53	1.87±1.19	2.668	0.061*
Frequency (episodes)	60	7.22±3.23	53	7.09±4.12	0.177	0.860*
Vomiting before recruitment						
Duration (days)	40	1.80±1.16	38	1.68±1.21	0.432	0.667*
Frequency (episodes)	40	3.75±2.05	38	4.21±2.98	−0.799	0.427*

SD: Standard deviation, * Not significant

Table 2: Comparison of outcome variables in two groups

Variables	Control group mean±standard deviation	Study group mean±standard deviation	% reduction	Unpaired t test	
	(n=60)	(n=53)		t	p
48 h stool frequency	15.87±4.6	10.47±3.2	34.1	7.152	0.00016*
Time for recovery (hour)	51.02±9.4	37.98±6.1	25.6	8.620	0.00012*
ORS consumed (ml)	232.68±52.65	162.72±39.86	30.1	7.881	0.0001*

ORS: Oral rehydration solution, *p<0.05 - Significant

Table 3: Time of recovery in two groups

Time of recovery (h)	Number (%)		Total
	Control group	Study group	
6 to 12	3 (5.40)	5 (9.40)	8 (7.30)
>12 to 24	1 (1.80)	9 (17.00)	10 (9.20)
>24 to 48	30 (53.60)	28 (52.80)	58 (53.20)
>48	22 (39.30)	11 (20.80)	33 (30.30)
Total	56 (100.00)	53 (100.00)	109 (100.00)

reduction in the consumption of ORS with racecadotril [5]. Alam et al. studied the role of racecadotril in cholera in adults and found no significant difference in ORS consumption between the two groups; however, mean stool frequency in 48 h was reduced by 34.1% with racecadotril (10.47 vs. 15.87 episodes) [10]. Cezard et al. had found 50% reduction in the stool output in 48 h in children receiving racecadotril when compared to placebo [8]. Salazar-Lindo et al. noted 46% reduction in 48 h stool output (157 vs. 331 g/kg) with racecadotril [5] Cojocaru et al. also found significantly lower number of stools and faster recovery with racecadotril [11].

Three of 53 cases and seven of 60 controls required IV fluid therapy. Other authors also had a similar experience in their study [8-10].Salazar-Lindo et al. reported that overall 5-day cure rate was 84% with racecadotril and 66% with placebo. There were no significant adverse effects in both the groups in our study, and none of the 11 children with serum potassium value <3.5 mmol/l had any ECG changes or clinical symptoms. In a study by Salazar-Lindo et al., one from racecadotril and two patients from control group had persistent vomiting without hypokalemia [5]. Cezard et al. reported that 7 from racecadotril and 3 from placebo group had vomiting but none had hypokalemia [8].Alam et al. reported no difference in the incidence of vomiting, reappearance of dehydration, abdominal pain, and headache or anorexia between racecadotril and placebo group [10].

On the contrary to the mentioned studies, Santos et al. found that the use of racecadotril did not improve the symptoms of diarrhea compared with standard ORT in children with gastroenteritis in an outpatient setting [12]. Still, most of the studies support the beneficial effects of racecadrotil in children with acute diarrhea including a recent meta-analysis. Lehert et al. conducted a meta-analysis on 9 randomized controlled trials to assess the efficacy of racecadrotil as an adjunct to ORS in childhood acute gastroenteritis [13]. Authors concluded that as an adjunct to ORS, racecadotril has a clinically relevant effect in reducing diarrhea (duration, stool output, and stool number), irrespective of baseline conditions (dehydration and rotavirus or age), treatment conditions (inpatient or outpatient studies) or cultural environment [13].

Whenever a patient of acute watery diarrhea is admitted to the pediatric ward, the hospital stay and bed occupancy rate is increased. Once the child is admitted, until the frequency of passage of loose stools is diminished, consistency of stool improves, and vomiting is controlled the parents are reluctant to take their child home in spite of good advice on home management of diarrhea. In this study, it was observed that 26.4% of patients on racecadotril had recovered within 24 h as compared to 7.2% of ORS group, so hospitals with pediatric units who have to deal with large number of diarrhea cases can adopt the policy of supplementing racecadotril as an adjunct to ORS to reduce the hospital stay of patients. It can be of some help in current health economics norm of cost versus benefit analysis.

However, as the sample size was small, it may not be possible to document the benefit of this drug to an extent and in a manner for a routine recommendation as a drug of choice

for the management of acute watery diarrhea. This study was not powered for assessing the mortality or number of complications, so, larger trials are also needed to detect a significant difference in diarrheal duration and its morbidity in different types and severity of diarrhea. The scientific evidence shown in this trial may not be the total evidence and use of antisecretory drugs like racecadotril should await more evidence from well-designed randomized controlled studies.

CONCLUSION

Racecadotril is effective as an adjunct to ORT and early continued feeding in infants and children with acute watery diarrhea.

REFERENCES

1. Shankarnaryanan VS. Diseases of gastrointestinal system and liver. IAP Textbook of Pediatrics. 3rd ed. New Delhi: Iaypee Brothers Medical Publishers (P) Ltd; 2006. p. 478-84.
2. Camilleri M, Murray JA. Diarrhoea and constipation. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 19th ed. New York, NY: McGrawHill; 2005. p. 224-33.
3. WHO. The Rational Use of Drugs in Management of Acutediarrhoea. Geneva: WHO; 1990.
4. Wang HH, Shieh MJ, Liao KF. A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. World J Gastroenterol. 2005;11(10):1540-3.
5. Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, Gutierrez M. Racecadotril in the treatment of acute watery diarrhea in children. N Engl J Med. 2000;343(7):463-7.
6. New Drugs Approved for Marketing in India: List of Drugs Approved During 1999 – 2005. Available form: http://www.cdsco.nic.in/forms/list.aspx?lid=2056&Id=11. [Last accessed on 2016 Dec 10].
7. Bhatnagar S, Bhandari N, Mouli UC, Bhan MK; IAP National Task Force. Consensus Statement of IAP National Task Force: Status report on management of acute diarrhea. Indian Pediatr. 2004;41(4):335-48.
8. Cézard JP, Duhamel JF, Meyer M, Pharaon I, Bellaiche M, Maurage C, et al. Efficacy and tolerability of racecadotril in acute diarrhea in children. Gastroenterology. 2001;120(4):799-805.
9. Baumer P, Danquechin Dorval E, Bertrand J, Vetel JM, Schwartz JC, Lecomte JM. Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhoea. Gut. 1992;33(6):753-8.
10. Alam NH, Ashraf H, Khan WA, Karim MM, Fuchs GJ. Efficacy and tolerability of racecadotril in the treatment of cholera in adults: A double blind, randomised, controlled clinical trial. Gut. 2003;52(10):1419-23.
11. Cojocaru B, Bocquet N, Timsit S, Wille C, Boursiquot C, Marcombes F, et al. Effect of racecadotril in the management of acute diarrhea in infants and children. Arch Pediatr. 2002;9(8):774-9.
12. Santos M, Marañón R, Miguez C, Vázquez P, Sánchez C. Use of racecadotril as outpatient treatment for acute gastroenteritis: A prospective, randomized, parallel study. J Pediatr. 2009;155(1):62-7.
13. Lehert P, Chéron G, Calatayud GA, Cézard JP, Castrellón PG, Garcia JM, et al. Racecadotril for childhood gastroenteritis: An individual patient data meta-analysis. Dig Liver Dis. 2011;43(9):707-13.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Sreenivas SK, Lakshmi M, Pavitra NA. Efficacy and safety of racecadotril as an adjunct to oral rehydration therapy for acute watery diarrhea in children. J Child Health. 2017; 4(1):68-71.