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Original Article

Tolerability and Efficacy of Racecadotril in Acute Diarrhoea, A Prospective, Randomised, Parallel Study in an Indian Tertiary Care Teaching Hospital

R ***Sarangi***, B ***Biswal***, B ***Dash***, A ***Dhanawat***

Abstract ***Objective:*** To study the tolerability and efficacy of racecadotril versus placebo in hospitalised children with acute diarrhoea. ***Methods:*** This prospective randomised placebo-controlled double blind trial was carried among 3-36 months age hospitalised children with acute diarrhoea. Out of 140 children, 67 children received placebo and 73 received racecadotril at 1.5 mg/kg, three times a day till recovery or five days whichever was earlier. Stool volume in 48 hours, duration of hospitalisation and tolerability of the drug were the outcome measures. ***Result:*** The mean stool volume in 48 hours (179.5±17.31 g/kg body weight versus 191.04±33.4 g/kg body weight, p=0.0001) and mean duration of hospital stay (62.4±11.4 hours versus 95.6±19.5 hours, p=0.0001) were significantly lower in racecadotril arm compared to placebo arm respectively. No serious adverse event was documented in either group. ***Conclusion:*** Racecadotril is both safe and effective in children with acute diarrhoea in decreasing the stool volume and duration of hospitalisation.

Key words *Acute diarrhoea; Teaching hospital; Tolerability*

Introduction

Acute diarrhoea in children accounts a major health burden in different parts of world with an estimated 2 billion episodes each year and 1.9 million deaths mostly in developing countries, amounting to 18% of under-five mortality.[1] Diarrhoea is the third leading cause of childhood mortality in India and it accounts for 13% of all deaths per year in under-five children.[2] The mainstay of therapy in acute diarrhoea, is the Oral Rehydration Therapy and its global adoption has reduced the mortality and morbidity due to diarrhoea, over the last 25 years.

Racecadotril (acetorphan) is an anti-secretary agent; inhibits enkephalinase, which is a cell membrane peptidase enzyme, located in various tissues, predominantly in the epithelium of the small intestine.[3] This peptidase is responsible for both the digestion of exogenous peptides and endogenous peptides such as enkephalins and neurokinin.[4] So the drug enhances the activity of endogenous enkephalins, leading to decrease in intracellular cAMP level thereby reducing secretion of water and electrolytes,[5,6] without altering the motility, intestinal transit time or bacterial overgrowth.[7]

Though there are several studies available from developed world with mixed outcome, there are limited studies regarding efficacy and tolerability of racecadotril in the developing country. So this study was planned in Indian children and the aim of this double blind, prospective randomised placebo-controlled trial was to compare the tolerability and efficacy of racecadotril versus placebo among hospitalised children with acute diarrhoea.

Department of Pediatrics, IMS and SUM Hospital, SOA Deemed to be University, Bhubaneswar-751003, Orissa, India

R **Sarangi** *MD*
B **Biswal** *MD*
B **Dash** *MD*
A **Dhanawat** *MD*

Correspondence to: Dr B **Biswal**
Email: biswalbasu@gmail.com

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Materials and Methods

Patient Population: This study was carried out in the department of Pediatrics, IMS & SUM Hospital, Bhubaneswar, Odisha, India. Children with acute diarrhoea aged between 3 to 36 months with or without dehydration were included in this study. Diarrhoea was defined as passage of at least three loose stools in previous 24 hours.[8] Patients with dysentery, severe malnutrition(weight/height less than 3SD of WHO growth chart), who were on any anti-diarrhoeal drugs or antibiotics before admission or started on new drug for any reason during the hospitalisation period or with chronic diseases were excluded from the study. In our study sample size was calculated as per prevalence of acute diarrhoea in our locality and variables from previous study.[9] In their study the Mean (±SE) stool output was 92±12 gms with SD± 98.95 gms in Racecadotril group and 170±15 gms with SD±122.87 gms in Placebo group. Taking Alpha Value of 5% and Power to be 80%, sample size calculated to be 66 with 33 in each group. However in view of high prevalence of acute diarrhoea in our locality we have increased the sample size of our study to 74 in each group and retrospectively calculated Power of our study to 99% approximately.

Study Design: This was a prospective randomised placebo-controlled double blind trial carried out in this tertiary care set up from April 2017 to March 2018. Institutional Ethics Committee approval for the study protocol was done and written informed consent was obtained from the parents or the legal guardian of all children. The sample size calculated to be 148 and 74 patients were randomised to racecadotril group and 74 patients to placebo group by computer generated random sequence. The person who is responsible for generation of Sequence was not directly involved in execution of the study. Allocation concealment was done using proper opaque sealed envelope with randomisation code. Patients in both groups were treated as per the WHO recommendation as the standard of care.[8] Additionally, they received racecadotril or placebo, packed in two weight bands (10 mg for less than 10 kg, 20 mg for more than 10 kg) which are identical in appearance, smell, and taste and dispersion activity. The drugs were given orally at every eight-hour interval, 30 minutes before food. The treatment was discontinued when the patients have two stools of normal consistency or absence of stool in last 12 hours or maximum up to five days. Per-protocol Analysis were carried out, comprising of only fully evaluable patients like availability of stool weight data (recorded up to 48 hours), recovery or end of treatment (whichever occurred earlier), time of discharge and any adverse effect. Total of 140 children were analysed for this study as per per-protocol analysis, placebo group comprising of 67 patients and racecadotril group 73 patients (Figure 1).

Patient Evaluation: At initial visit the detailed demographic variables, family history of diarrhoea, medical history, treatment history, characteristics of current diarrhoea, vitals, physical examination including anthropometry and hydration status were properly documented. Clinical manifestation such as fever, vomiting and abdominal circumference were assessed every 4 hours or as required. Strict vigilance was adhered on intake of oral rehydration solution and diet of the children. The number of stools and their characteristics were documented every 4 hours. The baseline body weight and hydration status were assessed and re-assessed at 3, 6, 12, 24, 36 and 48 hours. Stool weight was calculated by weighing the used diapers and subtracting them from the weight of pre-weighed fresh diapers every 6 hours for the first 48 hours. Urine was collected separately in urine bags/ bottles. In female children attempts were made to avoid mixing of urine, however in unavoidable situation both urine and stool volumes were calculated together. Rotavirus antigen as identified by using the enzyme immunoassay kit, [Ridascreen_ Rotavirus (C0901, R-Biopharm AG, Germany)]. During each clinical evaluation adverse events and tolerability of the drug or Placebo were assessed.

Outcome Measures

Primary Outcome:

(1) Stool Output in 48 hours in g/kg of body weight
(2) Stool Output in 48 hours in g/hour

Secondary Outcome:

(1) Duration of hospitalisation in hours
(2) Outcome in Rota viral diarrhoea
(3) Adverse events if any

Statistical Analysis

The main criteria were stool output during the first 48 hours, duration of discharge after the initiation of therapy with racecadotril versus placebo. Continuous variables are described by mean and standard deviation and the difference was analysed by independent t-test, percentages and chi-squared test were used to describe categorical variables.

The analysis was done by SPSS software version 20 licensed to institution.

Results

The study population comprised of 140 children with a mean age of 15.33 months and male to female ratio 74: 66. The male to female ratio in the racecadotril group was 40:33, whereas it was 34:33 in the control group. Similarly, the average age for the experimental group was recorded to be 14.47±5.82 months and for the control group the value was 16.20±5.84 months. Further, in the racecadotril group of 73 patients, 35 had watery stools whereas in the control group, 21 had watery stools (p=0. 057). The average ORS intake in racecadotril group was 342.15±141.73 ml whereas in placebo group it was 318.65±108.30 ml (p=0.255). The intravenous fluid was required equally in both groups (14 patients in racecadotril and 13 patients in placebo, p=1.00). In racecadotril group, 20 patients had rotavirus infection whereas 17 patients had rotavirus infection in placebo group. Demographic variables, stool characteristics, amount of ORS and IV fluid requirement, duration and frequency of diarrhoea before hospitalisation between two groups were comparable (Table 1).

The average stool output in 48 hours in the racecadotril group was 79.52±17.34 g/kg body weight whereas in the placebo group the value recorded was 191.04±33.44 g/kg body weight (p=0.001), also the stool output in 48 hours expressed as g/hour was significantly lower in children treated with racecadotril (p=0.0001). In Rota viral positive cases the Stool output in 48 hours expressed as g/kg is significantly lower in racecadotril group than the placebo group (p=0.0001) but the stool output in 48 hours in g/hour is not statistically significant. Both in total patients analysis and also in Rota viral diarrhoea cases, the average duration of discharge in hours among the patients received racecadotril is shorter than the placebo group which is statistically significant (p=0.0001) (Tables 2 and 3).

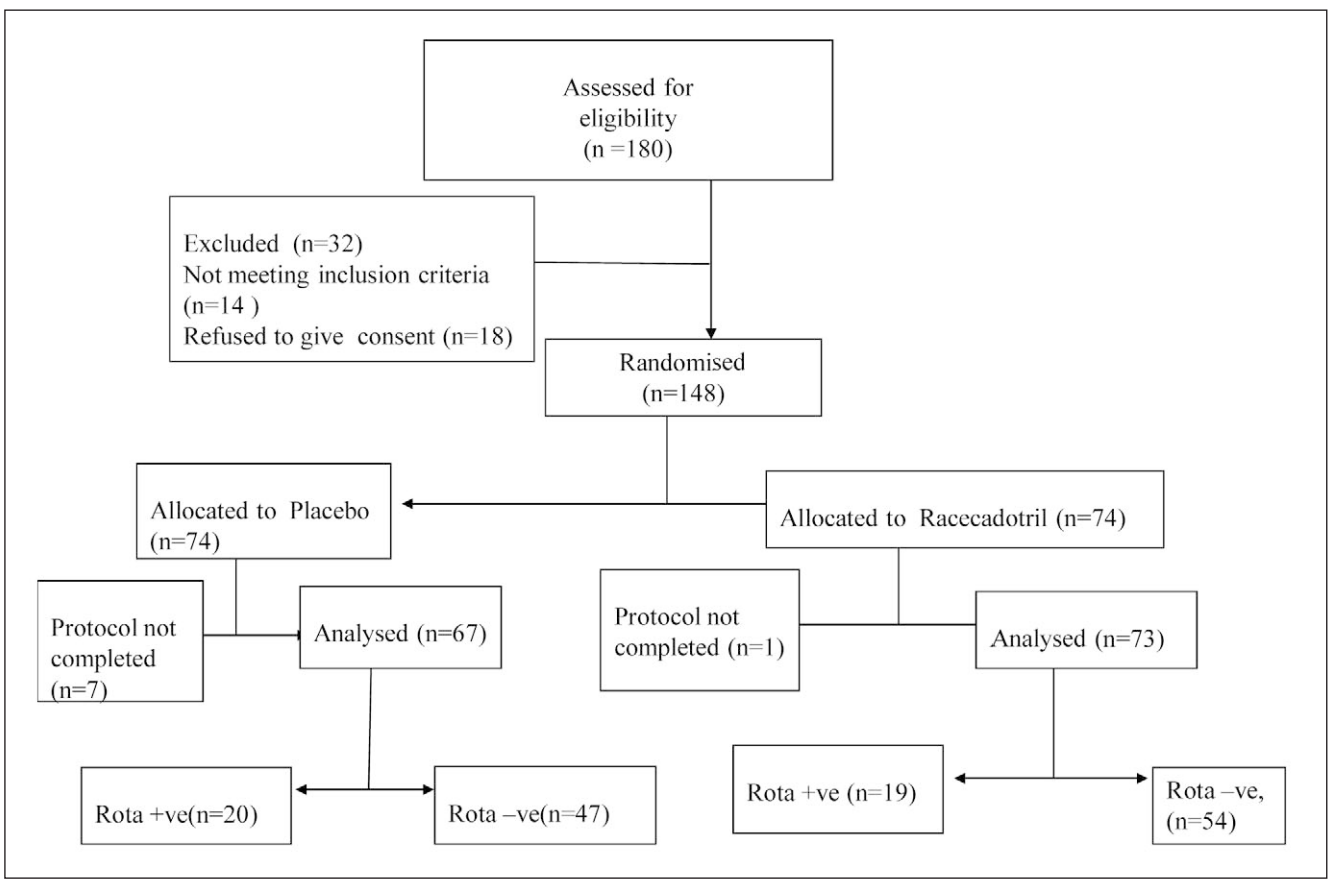

Figure 1 Flowchart of participants in the study

Adverse events like abdominal distension, vomiting, rebound constipation were observed in 6.9%, 2.8%, 1.4% of cases in racecadotril group and 7.8%, 3.5%, 1.6% of cases in placebo group respectively, which were not statistically significant. However, no serious adverse events were noted in both placebo and racecadotril group.

Discussion

In this randomised controlled trial, racecadotril given (1.5 mg/kg) three times a day maximum for 5 days to children aged 3-36 months admitted with acute diarrhoea resulted in significant reduction in stool output in 48 hours and duration of hospitalisation. There is also significant therapeutic response amongst the children receiving racecadotril in Rota viral diarrhoea cases.

Previous studies comprising of children found that racecadotril use in moderate to severe diarrhoea decreased the stool volume by 56% to 60% after 48 hours of treatment in comparison with placebo.[5,9,10] In a recently published systematic review of RCTs concluded that racecadotril is more effective than placebo in terms of decreasing the duration of diarrhoea and stool volume in children.[11]

Liang et al in their systemic review found, Racecadotril may reduce the risk of rehydration failure (RR 0.41, 95%CI 0.13 to 1.23). However there were insufficient data to show effect on duration of diarrhoea, number of stools in the first 48 hours.[12]

Multiple efficacy parameters were taken in different studies in a Meta-analysis by Eberlin et al, about the use of racecadotril in the treatment of acute diarrhoea in children. Stool output in 48 hours in gm/kg and stool output in gms/hr and duration of hospital stay in hours are

Table 1 Baseline characteristics of children with acute diarrhoea

Baseline characters	Racecadotril (n=73)	Placebo (n=67)	P value
Age in months, (Mean±SD)	16.2±5.84	14.47±5.82	0.081
Sex (M:F)	40:33	34:33	0.734
Stool consistency (Watery)	35/73	21/76	0.057
Amount of ORS (ml) before hospitalisation in 24 hour; (Mean±SD)	343.15±141.73	318.65±108.30	0.255
Number of patients required IVF before hospitalisation	14/73	13/67	1.00
Number of stool before hospitalisation in 24 hours; (Mean±SD)	9.712±0.297	9.328±0.309	0.373
Duration of diarrhoea before hospitalisation in hours; (Mean±SD)	30.85±0.971	36.55±1.207	0.0666
Rotavirus positive cases	19/73	20/67	0.849

Table 2 Comparisons of efficacy of racecadotril and placebo in acute diarrhoea

Outcome (Mean±SD)	Racecadotril (n=73)	Placebo (n=67)	P value
Stool output in 48 hours in grams/kg body weight	79.5±17.3	191.04±33.4	0.0001
Stool output in 48 hours in grams/hour	28.5±7.4	35.9±5.9	0.0001
Duration of hospital stay in hours	62.4±11.4	95.6±9.5	0.0001

Table 3 Comparisons of efficacy of racecadotril and placebo in Rota virus positive cases (n=39)

Outcome (Mean±SD)	Racecadotril (n=19)	Placebo (n=20)	P value
Stool output in 48 hours in grams/kg body weight	89.47±3.705	208.0±5.410	0.0001
Stool output in 48 hours in grams/hour	34.84±1.388	38.55±1.268	0.0557
Duration of hospital stay (hours)	60.32±2.597	104.4±2.014	0.0001

considered important primary end point in multiple studies, and hence, taken for comparison for assessing efficacy of racecadotril in acute diarrhoea in our study.[13]

In the present study, there is significant reduction in stool output in 48 hours (79.5±17.3 g/kg body weight) in racecadotril group in comparison to placebo group (191.04±33.4 g/kg body weight). Liang et al in their systemic review found lower stool output in the first 48 hours in two trials.[12] Another double blind randomised study comprising of 135 boys of similar age group, also suggestive of significant reduction in 48 hr stool output (92±12 g/kg) in racecadotril as compared to placebo (170±15 g/kg) group ($p<0.001$).[9] Study done in south-India by Kang et al concluded, racecadotril did not reduce duration of diarrhoea, volume of stool or fluid requirement in under five children with acute gastroenteritis with or without rotavirus infection.[14] The reason for the lack of impact may be possible co-infection in developing country. However, Santos et al in their study among 189 children in 3-36 month age group revealed no difference in terms of frequency of stool or duration of diarrhoea among racecadotril and placebo group.[15] This may be explained as the later study was in outpatient children and stool volume assessment was by parents, so presence of observation bias could not be excluded. The present study also demonstrates significant reduction in duration of hospitalisation/duration of diarrhoea after treatment with racecadotril in comparison to placebo. Similar type of observation was documented in recently published meta-analysis.[13]

There is significant reduction of 48 hr stool volume and discharge duration in hours in rota viral diarrhoea treated with racecadotril in comparison to placebo in current study. Cèzard et al in their study demonstrated up to 50% reduction in stool volume with racecadotril as adjuvant therapy to ORS in the treatment of severe diarrhoea both in rota and non-rota viral diarrhoea among infants and children.[10] Similar observation was made by Alvarez et al that racecadotril found to be effective in terms of reducing the stool frequency within the first 48 hours and is associated with a shorter disease course and fewer visits to emergency services, as well as hospital admissions.[16] However few studies using different efficacy parameters also found racecadotril is equally effective in both rota positive and rota-negative diarrhea.[17,18]

Racecadotril is found to be safe and well tolerable drug as no serious adverse event was documented in this study and side effects documented are abdominal distension, vomiting, rebound constipation which are statistically insignificant in both the groups. Similar observation was also done in different studies and racecadotril found to be safe for use in children with acute diarrhoea.[9-11,13,15]

As there is paucity of data from a developing country like India where the disease burden is very high with significant morbidity and mortality, this study was done to find out the effect of racecadotril in acute diarrhoea. This is the only double blinded randomised study from eastern part of India comparing racecadotril versus placebo in acute diarrhoea in hospitalised children, thus minimising possibility of observation bias; more so over the intervention was started early (median duration of diarrhoea before hospitalisation of 30.85 hours) comparing to other Indian study, where the median duration of presentation is around 2 days.[14] Potential limitations of our study include small sample size, inability to have different subgroup analysis and cost-effective analysis. Further among female children the exact stool volume calculation was cumbersome.

Conclusion

Racecadotril is both safe and effective in reducing the stool volume and duration of hospitalisation in children with acute diarrhoea. It is also found to be effective in Rota viral positive cases. Though some more trials with rigorous methodologies in larger population involving multiple centers with high disease burden and similar etiological spectrum may be needed to support the evidence.

Declaration of Interest

The authors declare that there is no conflict of interest.

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