RESEARCH PAPER

Racecadotril in the Management of Rotavirus and Non-rotavirus Diarrhea in Under-five Children: Two Randomized, Double-blind, Placebo-controlled Trials

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Objective: To study the effect of racecadotril on reduction in the duration of acute rotavirus and non-rotavirus diarrhea.

Design: Two randomized double-blind placebo-controlled trials

Setting: Community-based trial in an urban area in Vellore, hospital-based trial at a secondary hospital in Vellore

Participants: 199 and 130 3-59 month old children in the community- and hospital-based trials, respectively.

Methods: Racecadotril (1.5 mg/kg/dose, thrice a day for three days) or placebo were given to manage acute diarrhea in both trials.

Main outcome measure: Median duration of diarrhea.

Results: Among 124 children completing the hospital trial, the median duration of diarrhea was 25 h in both arms (*P*=0.5); median total stool weight was 74 g/kg and 53.5 g/kg in racecadotril group and placebo group, respectively (*P*=0.4); and average fluid intake per day was 3.6 mL/kg/h and 3mL/kg/h in racecadotril and placebo arms, respectively (*P*=0.3). Among rotavirus-positive children, median duration of diarrhea was 26.9 h and 30.2 h in racecadotril and placebo arms, respectively (*P*=0.7). In the community, 196 completed the trial, the median duration of diarrhea was 2 days for both arms (*P*=0.8) and rotavirus positive children had similar outcomes with median diarrheal duration of 3 d in both arms (*P*=0.4).

Conclusion: Treatment with racecadotril did not reduce diarrheal duration, stool volume or the requirement for fluid replacement in children with acute gastroenteritis, both with and without rotavirus infection.

Keywords: *Antidiarrheal, Anti-secretory, Outcome, Treatment.*

Infectious diarrhea is a leading cause of death among children under 5 years of age, particularly in developing countries [1]. Oral rehydration therapy (ORT) has been shown to reduce mortality due to dehydration [2], but does not reduce the duration of illness or stool frequency. Racecadotril, (acetorphan: N-((R, S)-3-acetylmercapto-2benzylpropanoyl)-glycine, benzyl ester) is an enkaphalinase inhibitor augmenting the anti-secretary action of enkaphalin in the submucous myentric neurons [3,4], which has been shown to be safe and effective in decreasing the duration of diarrhea in children [5].

Clinical trials comparing the efficacy of racecadotril with acute gastroenteritis have shown varying results. While some trials have reported a significant reduction in stool output, frequency of bowel movement and diarrheal duration [5-8], others did not find any such association [9-10]. We evaluated the efficacy of racecadotril in children less than 5 years of age with acute diarrhea in two randomized control trials in hospital and community settings in India.

METHODS

Study design and participants: Two randomized, double-blind, placebo-controlled trials were conducted one at the Community Health and Development (CHAD) hospital and the other at an urban area of approximately 150000 population served by a study clinic run by the Christian Medical College (CMC), Vellore, India between April 2008 and September 2010.

All children between 3 and 59 months of age with acute diarrhea (defined as ≥3 episodes of loose, watery stools in last 24 hours [6] for less than 3 days of duration were enrolled. In the hospital study, children were

enrolled only if the study physician recommended hospitalization for management of diarrhea. In the community study, children were enrolled only if the study physician recommended management of the diarrheal episode at home. Children with weight less than 5 kg, with severe co-existing disease, including pneumonia, meningitis, or severe malnutrition (defined as Grade III or Grade IV malnutrition IAP Grading based on weight for age), chronic diarrhea (duration>14 d), or with blood and mucus in stool were excluded from both trials. Those with history of having received antibiotics, probiotics, steroids, herbal medicines, antiemetics or antimotilty drugs or other treatment of unknown nature were also excluded. Children who fulfilled the eligibility criteria and whose parents or legal guardians provided written informed consent were randomized to receive either racecadotril or an identical placebo. The studies were approved by the Institutional Review Board, Ethics committee and registered with the Clinical Trials Registry of India (CTRI/2010/091/003067 and CTRI/2007/091/000001).

Sample size: The sample size for these studies were calculated based on the primary outcome of a reduction in diarrheal duration of 24 hours. With an alpha error of 5% and a power of 80%, in order to show at least a one-day reduction in duration of diarrhea following intervention, 65 children needed to be enrolled in each arm of each trial. In the community trial, to account for disease progression and increased loss to follow up, the sample size was increased to 100 in each arm.

Randomization and blinding: For both settings, individual randomization codes were generated by a statistician not associated with the study. The randomization was performed in multiple permuted blocks with 1:1 allocation ratio. Sealed envelopes with the randomization codes were given directly to the hospital pharmacy which provided identically packed study drug or placebo. The placebo contained a mixture of lactose, calcium stearate and sterile starch powder.

Intervention: Racecadotril (Zedott, Torrent Pharmaceuticals Ltd, Gujarat, India) or placebo were administered at a dose of 1.5 mg/kg, three times a day for three days if the child's diarrheal episode ended by the third day or up to five days if the diarrheal episode had not ended by the third day. Apart from interventional products, all children received treatment as per the World Health Organisation (WHO) recommendations as the standard of care [7]. In the hospital, the study intervention was administered by a study nurse. In the community-based study, racecadotril and placebo were packed as powder with 9 packets for every child, given to mothers with instructions for storage at room temperature and daily administration of three doses. All children were followed-up at home by a field worker daily and if the child required hospitalization, the child was referred to CHAD hospital.

Data Collection: Both studies collected baseline demographic details of age (months), gender and weight (kg). The community trial also assessed the socio-economic status using the modified Kuppuswamy scale [8]. At the time of enrolment, a detailed clinical history was elicited by the study physician containing information on the duration of diarrhea, maximum number of stool passed in a 24-hour time-frame, presence of vomiting and/or fever, history of previous illnesses, and a detailed drug and vaccination history (including history of rotavirus vaccination). Severity of diarrhea was assessed at admission for all hospitalized children using the 20-point Vesikari scoring system [9]. An episode was considered mild for scores 0-5, moderate for 6-10 and severe for score ≥11. Level of dehydration was assessed using the WHO Integrated Management of Neonatal and Childhood Illness classification [10].

Study outcomes: The primary outcome was median duration of diarrhea in hours, defined as the time from onset of diarrhea to the time of resolution, identified as the time of the last abnormal stool or the start of a 12-hour period with no stool. This was recorded by a study nurse in the hospital and by mother's recall during the field worker's visit in the community-based study. Secondary outcomes for the hospital study included diarrheal stool volume (total and average), rehydration requirement (oral and intravenous) and presence of vomiting after administering the drug or placebo. In the hospital study, for male children urine collection bags (Minicom, Techplast, Mumbai, India) were used to collect urine and stool separately for measuring stool weight using pre-weighed diapers, while this was not done for the female children or in the community-based study. In the hospital study, for female children, while attempts were made to avoid urine, where unavoidable both urine and stool were collected together. Stool volume was calculated and compared separately for male and female children. In hospital, the requirement of rehydration fluid was calculated based on the intravenous fluid and oral rehydration solution requirement per kg of baseline body weight per day. A secondary outcome for the community study was presence of vomiting, fever and history of day care and/or hospital visit during the period of observation.

Screening for rotavirus was performed from the first stool sample collected immediately post-enrolment. A 10% fecal suspension was screened for rotavirus using a commercial enzyme immunoassay (EIA) for detection of

VP6 antigen (Rota IDEIA, Dako Ltd, Ely, United Kingdom) according to the manufacturer's instructions.

Statistical analysis: Data were collected using case records for each child and entered into an EpiInfo database. All variables were examined using descriptive statistics, dispersion for continuous variables, frequency counts and marginal percentages with 95% confidence intervals (CI) for categorical variables. Comparisons between the two groups were done using t-tests for normally distributed variables (or non-parametric tests for non-normally distributed variables) and chi-square tests for categorical variables. All differences were considered statistically significant if the two-tailed *P*-value was <0.05. Data analysis was performed using STATA 10 for Windows (Stata Corp, College Station, TX USA). Subgroup analysis was done for children who had rotavirus diarrhea compared those who had other cause diarrhea.

RESULTS

Hospital-based study: Of the 130 children enrolled, per-protocol analysis could be conducted for 124 children, (61/65 in the children assigned to the racecadotril group, 63/65 children in the placebo group), with 6 children not available for follow-up (***Fig.* 1**). At baseline, the median (IQR) duration of diarrhea prior to enrollment was 2 (1,3) days in both groups; 31 (47.7%) children in the racecadotril group and 28 (43.1%) in the placebo group tested positive for rotavirus (*P*=0.60). Severe dehydration (>10%) was seen in 4 (6.2%) children in the racecadotril group and 6 (9.2%) in the placebo group (***Table* I**). A total of 14 (10.8%) children required >3 days of treatment. The proportion of children receiving >3 days of treatment was comparable between racecadotril and placebo groups (6/61, 9.8% *vs*. 8/63, 12.7%; *P*=0.62). The duration of hospitalization was also similar in children receiving racecadotril and placebo (median [IQR] = 3 [2,4] in both groups, *P*=0.96).

The primary outcome of diarrheal duration in hours did not change with racecadotril treatment with the median (IQR) being 25.5 (14.8, 44.3) and 25.0 (17,44.5) hours in rececadotril and placebo groups, respectively. The total and average stool weight among the two groups were also similar. The findings were similar when the total and the average stool weights were compared separately for males and females (data not presented). Other outcomes were also similar (***Table* II**).

A total of 58 (46.7%) children tested positive for rotavirus of whom 31 (53.4%) were assigned to the racecadotril group and the remaining to the placebo group. The median (IQR) diarrheal duration was 26.9 (17.1,54.9) hours in the rotavirus positive racecadotril group and 30.2 (19, 47.1) hours in the placebo group (*P*=0.79). The total stool volume passed had a median (IQR) of 75.8 (24.6,200.8) g/kg with racecadotril and 91.6 (9.5,194.7) g/kg in the placebo group (*P*=0.67). Other clinical outcomes including stool volumes (total, and average) were also similar among those positive for rotavirus (***Web Table* I**).

Community-based trial: Of the 199 (102 in racecadotril, 97 in placebo) children randomized, 196 (98%) were available for per-protocol analysis. Both arms were comparable, in terms of socioeconomic status, education of head of household, family size, number of siblings and breast feeding practices (data not presented). None of the children reported receiving rotavirus vaccine.

Median duration of diarrhea at presentation and other baseline characteristics were similar between both arms **(*Table* I)**. The proportion of children requiring treatment for >3 days was comparable between children in the

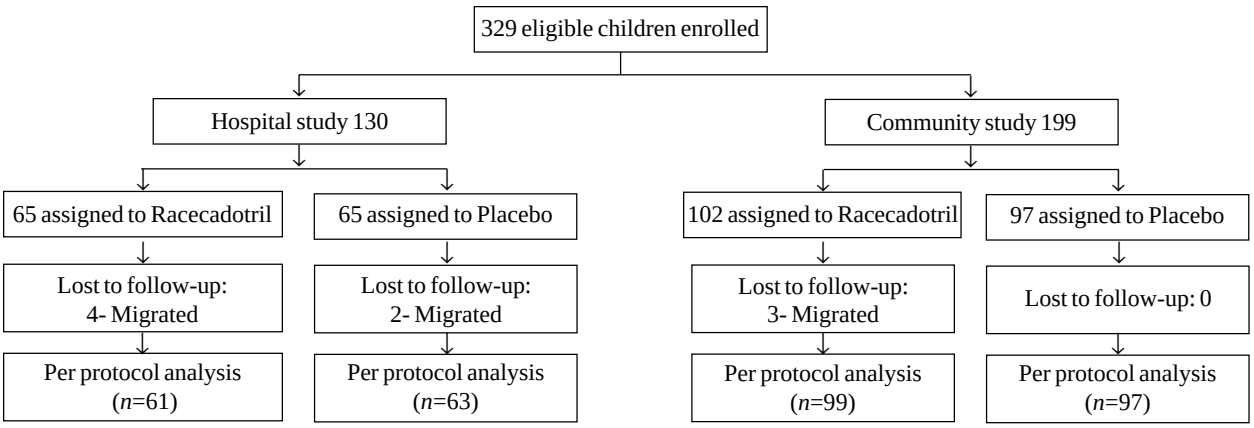

FIG. 1 T*rial profile.*

TABLE I BASELINE CHARACTERISTICS OF CHILDREN WITH ACUTE DIARRHEA IN THE HOSPITAL AND THE COMMUNITY TRIALS

	Hospital trial (n=130)		*Community trial (n=199)*	
	Racecadotril (n=65)	*Placebo (n=65)*	*Racecadotril (n=102)*	*Placebo (n=97)*
Age (mo); mean (SD)	12.9 (9.9)	13.5 (8)	15.9 (10.9)	17.5 (12.9)
Male gender; No. (%)	36 (55.4)	43 (66.2)	50 (49)	42 (43)
Duration of diarrhea (d); median (IQR)	2 (1,3)	2 (1,3)	2 (1,2)	2 (1,2)
No. of diarrheal episodes 24 h prior to admission; madian (IQR)	10 (7,15)	8 (6,12)	5 (4,6)	5 (4,6)
Vomiting; No (%)	45 (69.2)	50 (76.9)	30 (29.4)	33 (34)
Weight (Kg); mean (SD)	7.6 (2.2)	7.7 (1.8)	8.0 (1.9)	8.8 (2.3)
Rotavirus positive; No. (%)	31 (47.7)	28 (43.1)	18 (17.6)	11 (11.3)
Dehydration; No. (%)				
Mild-to-moderate	59 (90.8)	58 (89.2)	20 (19.6)	18 (18.6)
Severe	4 (6.2)	6 (9.2)	0 (0)	0 (0)
Severe Vesikari Category (*n*=101)	52 (80)	49 (75.4)	4 (3.9)	5 (5.2)

TABLE II EFFECT OF RACECADOTRIL ON DIARRHEAL OUTCOMESIN THE HOSPITAL TRIAL

	Racecadotril (*n*=61)	Placebo (*n*=63)	*P* value
Duration of diarrhea (h); median (IQR)	25.5 (14.8,44.3)	25 (17,44.5)	0.57
Volume of stool (g/kg body Wt); median (IQR)	74 (20.6,159.4)	53.5 (12.7,153.6)	0.47
Vol. of stool (g/Kg/h); Median (IQR)	2.9 (1.3,4.4)	2.2 (0.6,3.8)	0.09
Fluid intake (mL/Kg/h); Median (IQR)	3.6 (1.9,5.2)	3 (1.8,4.9)	0.36
Presence of vomiting (overall); No. (%)	27 (44.3)	25 (39.7)	0.72
Presence of vomiting beyond 12 h; No. (%)	14 (22.9)	9 (14.3)	0.25

racecadotril and placebo groups (8/99, 8.1% *vs*. 9/97, 9.3%; *P*=0.77). The primary outcome of the median duration (IQR) of diarrhea at the end of trial was unaffected at 2 (2,4) days for both groups (*P*=0.88). There were no differences among other parameters (***Table* III**).

A total of 29 (14.7%) children tested positive for rotavirus in the community trial, of which 18 (62%) received racecadotril and the remaining 11 (37.9%) received placebo. The outcomes among those who were positive for rotavirus as compared to that of the rotavirus negative group were similar in terms of diarrheal duration, presence of vomiting and fever. There was a statistically significant reduction of vomiting among rotavirus positive children receiving racecadotril (5.6% vs. 63.6%; *P*=0.001). No such differences were noted in the rotavirus negative children (***Web Table* II**).

TABLE III EFFECT OF RACECADOTRIL ON DIARRHEAL OUTCOMES IN THE COMMUNITY TRIAL

Diarrhea Outcome, No. (%)	*Racecadotril (n=99)*	*Placebo (n=97)*
Diarrhea duration (d)	2 (2,4)	2 (2,4)
Vomiting (overall)	22 (22.2)	31 (320)
Fever (overall)	23 (23.2)	18 (18.6)
[#]Day care visit	66 (66.7)	58 (59.8)

**Median(IQR); All P>0.05; [#]for oral rehydration*

DISCUSSION

This paper reports findings from two clinical trials in Southern India that recruited children from the hospital and the community to study the effect of racecadotril on acute childhood gastroenteritis, thereby capturing both mild and moderate-to-severe form of the disease. The hospital trial had significantly more children with rotavirus (45%) than the community trial (14.5%). We did not observe any benefit of treatment with racecadotril in terms of duration of diarhea, stool volume or rehydration fluid requirement.

Most studies evaluating the efficacy of racecadotril on acute childhood gastroenteritis have been carried out

WHAT IS ALREADY KNOWN?

- Racecadotril has been shown to reduce diarrheal duration especially in rotavirus diarrhea.

WHAT THIS STUDY ADDS?

- There is no significant effect of racecadotril on diarrheal duration in community or hospital settings with both rotavirus and non-rotavirus diarrhea.

in the hospital setting [5-8]. Systematic reviews carried out using data from such studies have reported a reduction in stool output and diarrheal duration in children receiving racecadotril [16-18]. In contrast, the only study conducted in an outpatient setting found no significant differences in the number of bowel movements or the average duration of diarrhea between children treated with racecadotril or standard oral rehydration therapy [9]. A possible reason for this lack of impact of racecadotril on the treatment of diarrhea may be because children were brought to hospital a median of two days after onset of diarrhea; earlier intervention could have had a different outcome. It is also possible that some of the children were infected or co-infected with pathogens causing osmotic diarrhea such as *Cryptosporidium*, *Salmonella* and *Vibrio* spp., all of which are important causes of childhood diarrhea in developing countries [19]. In such a scenario, racecadotril, which acts only on secretory diarrhea, would not have had a significant impact, irrespective of rotavirus etiology. In a study involving Bangladeshi adults, the use of racecadotril did not provide any additional benefit in the treatment of severe cholera [20].

Drugs from different manufacturers are not necessarily equivalent and this may have been a limitation of this study. There are few independent comparisons in most countries, of efficacy of licensed drugs and it may be important for clinical researchers to consider future studies in this area to ensure optimum benefit to patient populations. Another limitation of this study was the small sample size. This also restricted our ability to perform multiple subgroup analyses (age-wise and severity-wise comparisons).

Trials conducted with rigorous methodologies in multiple settings are required to inform evidence. This study indicates the need for more evidence to advocate or refute use of racecadotril in settings with high disease burden, where diarrheal episodes with multiple etiologies cannot be ruled out.

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WEB TABLE I OUTCOMES AMONG CHILDREN WITH ACUTE DIARRHEA AFTER TREATMENT WITH RACECADOTRIL IN THE HOSPITAL TRIAL (*N*=124)

Variable	*Rotavirus positive(n=58, 46.7%)*			*Rotavirus negative(n=66, 53.2%)*		
	Racecadotril (n=31)	*Placebo (n=27)*	*P value*	*Racecadotril (n=30)*	*Placebo (n=36)*	*P value*
Median (IQR) duration of diarrhea (h)	26.9 (17.1,54.9)	30.2 (19, 47.1)	0.79	19.6 (14, 43.7)	23.2 (16.5,40.5)	0.45
Total volume of stool g/kg body weight: Median (IQR)	75.8 (24.6,200.8)	91.6 (9.5,194.7)	0.67	40.5 (14,118.8)	49.4 (14.6,118.8)	0.81
Average vol. of stool g/kg body weight (h): Median (IQR)	2.9 (1.7,4.7)	2.4 (0.7,4.2)	0.26	3 (1.,-4.4)	2 (0.5,3.5)	0.26
Average total fluid intake (ORS+IV) in mL g/kg body weight-h: Median (IQR)	3.6 (1.7,5.3)	3.4 (2.2,4.7)	0.84	3.6 (2.4,5.2)	2.4 (1.5,5.4)	0.30
Presence of vomiting (overall)	17 (54.8)	14 (51.9)	0.82	10 (33.3)	10 (37)	0.62
Presence of vomiting beyond 12 h; No. (%)	9 (29)	4 (14.8)	0.19	5 (16.7)	4 (11.1)	0.51
Presence of vomiting beyond 24 h; No. (%)	3 (9.7)	1 (3.7)	0.61	1 (3.3)	4 (11.1)	0.36

WEB TABLE II OUTCOMES AMONG CHILDREN WITH ACUTE DIARRHEA AFTER TREATMENT WITH RACECADOTRIL IN THE COMMUNITY TRIAL (N=196)

Variable	*Rotavirus positive (n=29)*			*Rotavirus negative (n=167)*		
	Racecadotril(n=18)	*Placebo(n=11)*	*P value*	*Racecadotril (n=81)*	*Placebo (n= 86)*	*P value*
Median (IQR) duration of diarrhea, d	3 (2,3)	3 (2,5)	0.48	2 (2,4)	2 (2,4)	0.83
Presence of vomiting (overall)	1 (5.6)	7 (63.6)	0.001	21 (26)	24 (28)	0.77
Presence of fever (overall)	6 (33.3)	2 (18.2)	0.67	17 (21)	16 (18.6)	0.69
Day care visit for oral rehydration; No. (%)	12 (66.7)	9 (81.8)	1.00	54 (66.7)	49 (57)	0.14