ORIGINAL ARTICLE

Efficacy and Safety of Racecadotril in Management of Acute Diarrhea in Severely Malnourished Children Under 5 Years

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ABSTRACT

Objective: To evaluate the efficacy and safety of racecadotril in the management of acute diarrhea in severe acute malnourished children (SAM).

Study Design: Single-blinded randomized control trial

Place and Duration of Study: The study was conducted at the Children's Hospital and the Institute of Child Health Multan from January 1, 2019, to December 31, 2019.

Material and Methods: This was a single-blinded, randomized control trial from January to December 2019 at the Children's Hospital, Multan. 174 children were enrolled in this study, aged between 6-60, who were diagnosed with Severe Acute Malnutrition according to the WHO criterion: weight-for-height >-3 SD or mid-upper arm circumference <11.5 cm. The patients were divided into two random groups. The patients in group A administered standard diarrheal management according to IMNCI. IV fluids, zinc supplement, and racecadotril were given, but group B received all the treatments except racecadotril. This was a double blinded trail in which patient was included by random sealed envelope selection. The patients were followed for stool consistency, frequency, and hydration status for 72 hours.

Result: There was no significant difference in both groups in first 24 hours, but in the third dose after 72 hours, group A showed improvement, 85% of them became better hydrated with minimal diarrhea, contrasted with 70% in the group B on the Bristol Stool Scale and Mann-Whitney U test, the racecadotril group showed better recovery where the p-value was less than 0.05 with no side effects.

Conclusion: The study concludes that racecadotril is effective and relatively safe adjunct treatment for SAM children with diarrheal diseases, especially after the first 72 hours of treatment.

Keywords: *Diarrhea, Rehydration therapy, Racecadotril, Severe acute malnutrition*

INTRODUCTION

Diarrhea is one of the top causes of morbidity and mortality among children under five years of age.[1] This holds especially true in Pakistan and other developing countries.[2] Diarrhea accounts for 9%

of all children's deaths; diarrhea, therefore, is the second leading cause of death among children under age five in the world.[3] Diarrhea and its complications take the lives of one in every twenty children in Pakistan annually, according to reports.[2] This condition, therefore, needs such interventions to be vigorously undertaken to control it and avoid its burden.[4] Most episodes of acute diarrhea are self-limiting, but effective early management will improve hydration significantly, reduce morbidity, and avoid complications in such children.[4]

Severe acute malnutrition (SAM) increases the risk of diarrhea in children.[5] So, early intervention is essential where SAM patients and diarrhea are treated simultaneously.[5] Though SAM victims are exposed to a high risk of mortality and long-term developmental complications due to a poor immune system and lack of nutritional reservation during the time of infection, among the causes of mortality for children suffering from SAM is diarrhea itself, according to WHO.[6] The standard care packages, for instance, Integrated Management of Neonatal and Childhood Illness guidelines, give guidelines on treatment protocols, which include ORS-based rehydration therapy, zinc supplementation, among others and supportive care.[7] Nonetheless, the search for additional adjunctive therapies that might reduce the period and severity of diarrheal diseases is an issue of significant interest in pediatric care.[8]

Among such adjunctive therapies is racecadotril.[9] This is an antidiarrheal which act as a prodrug of thiorphan.[9] It is used because of its antisecretory effects through the inhibition of the enzyme enkephalinase in the mucosa of the intestines, which reduces the catabolism of endogenous enkephalins.[10] Enkephalins are peptides that stimulate pro-absorptive and antisecretory intestinal effects. Most other antidiarrheal medications were found to inhibit gut motility, leading to rebound constipation, among other side effects.[11] Racecadotril uniquely inhibits water and electrolyte secretion to address the root cause without having side effects like rebound constipation[10]. This makes it a promising candidate for the treatment of diarrhea in children, especially when given together with conventional therapies.[12]

Racecadotril has proven to be quite effective in reducing the duration of diarrhea, its application in the management of diarrhea in SAM children has not been studied intensely within the framework of standard IMNCI guidelines. Although studies on the use of racecadotril in stool frequency reduction and hydration improvement abound, very few have targeted the comparative effectiveness of racecadotril used with traditional rehydration therapy in resource-limited settings.[13] Adding to this, there remains a huge gap in the availability of local data about the efficacy and safety of racecadotril in children under five suffering from SAM with acute diarrhea, which makes this study more relevant.

This trial proposes to fill this gap by assessing the safety and efficacy of racecadotril in children diagnosed with SAM presenting with acute diarrhea. This study will compare outcomes between children receiving racecadotril together with IMNCI guidelines versus standard care only, with the hope of giving insight into whether racecadotril improves recovery rates, consistency of stools, and hydration outcomes. This leads to the final implication of the results, which is how it can be beneficial in guiding the management of diarrhea in otherwise vulnerable pediatric populations in arriving at updates and recommendations to future guidelines and treatment protocols.

MATERIAL AND METHODS

This randomized, controlled, single blinded trial was conducted at the Nutritional Rehabilitation Centre, Children's Hospital and Institute of Child Health (CH&ICH) Multan, from January 1, 2019, to December 31, 2019. Ethical approval was received from the Institutional Review Board of CH & ICH (2462, 03.11.2018) before starting the study. Children aged 6 to 60 months who were diagnosed with Severe Acute Malnutrition according to the WHO criterion: weight-for-height >-3 SD or mid-upper arm circumference <11.5 cm, who manifested acute diarrhea and dehydration and whose guardians gave informed consent permission were included in the study. Patients with chronic diarrhea, secondary malnutrition, critically ill patients, and those whose guardians refused to provide consent were excluded.

One hundred and seventy-four eligible malnourished participants were enrolled through

simple random sampling techniques. The participant was then assigned randomly through the lottery method to one of the two groups through the envelope technique. Group A and group B were written on a plain piece of paper and the papers were sealed inside an envelope, the envelopes were all alike and were shuffled for further transparency. Upon fulfillment of enrollment criteria each patient was asked to choose an envelope out of the pile. Group A received standard management per guidelines of Integrated Management of Neonatal and Childhood Illness, comprising IV fluids, zinc supplementation and the antidiarrheal drug racecadotril 1.5 g/kg and given three times daily. Group B received the same management except for the racecadotril. Data was collected by the trained and experienced nursing staff by using a predesigned proforma. The parameters monitored were as follows:

- **Hydration status:** Assessed at admission and discharge.
- **Stool consistency and frequency:** Measured by the Bristol Stool Scale.
- **Lab Tests:** CBC, serum electrolytes, and renal function tests were carried out at admission and discharge.

The primary outcome is the efficacy of racecadotril in reducing stool frequency and improving stool consistency. The secondary outcomes are improvement of hydration status and safety and tolerability of racecadotril. Efficacy was examined through a comparison of outcomes from the Bristol Stool Scale between the groups at 24 hours and 72 hours into treatment.

Data was analyzed using SPSS version 20.0. The efficacy of racecadotril was calculated using the Mann-Whitney U test to compare the outcomes of Bristol between both groups and t test for hydration status between two groups A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 174 SAM participants were registered, out of which 100% had diarrhea and were dehydrated. The mean age of participants was 14.5 months ± 8.0 months. Out of the total, 91 (52%) were male, and 83 (48%) were female. The patients were divided into two groups, A and B, through the envelope method. There was no significant difference in the mean weight of both groups at the time of admission, i.e., the mean weight was 5.5 ± 2 kg, and the value was 0.056 %. At the time of admission, all the children had diarrhea, and in group A, 75% were presented with vomiting, and in group B, 72 % were presented with vomiting. After 24 hours of therapy, there was no significant difference in reduction in stool frequency and amount in both groups (85% in group A and 80 % in group B). After 72 hours of therapy, the frequency of stool, volume and hydration status improved in group A, i.e., 85%, as compared to group B, i.e. 70 % reduction in diarrhea. The recovery rate of group A children was significant as compared to group B, skin rash and constipation were anticipated side effects however no side effects were noted, and all children tolerated racecadotril well. Data shows no improvement or difference between the two groups in the first 24 hours, but significant progress was noticed in group A receiving racecadotril after the 72-hour time frame.

TABLE I: Age and gender distribution of patients (n=174)

	Group A (n=87)	Group B (n=87)
Male	47 (54 %)	45 (52%)
Female	40 (46 %)	42 (48%)
Mean age	14.6 ± 8.0 months	13.6 ± 10.0 months

The mean age of patients in both groups was approximately 14 months, and there was no statistical difference in gender between both groups.

TABLE 2: Presentations at the time of admission in patients (n=174)

	Group A (n=87)	Group B (n=87)	p-value
Diarrhea	87 (100.0)	87 (100.0)	0.67
Vomiting	65 (75.0)	62 (72.0)	0.04
Fever>98.9F*	43 (50.0)	39 (45.0)	0.06
Hypoglycemia	24 (28.0)	18 (21.0)	0.12
Hypothermia	7 (8.0)	4 (5.0)	0.2

At the time of admission, all patients presented with diarrhea and were severely dehydrated. Almost 70% of patients were suffering from vomiting, and nearly half of patients had fever as well.

TABLE 3: Improvement in patients after periodic intervals of treatmen

	After 24 hours		After 72 hours	
	Improved	**Not improved**	**Improved**	**Not improved**
Group A (n=87)	74(85.0)	13 (15.0)	74 (85.0)	13 (15.0)
Group B (n=87)	70 (80.0)	17(20.0)	61 (70.0)	26 (30.0)
	p-value= 0.04		p-value=0.02	

After the first 24 hours of treatment, there was no significant difference between the treatment outcome of both groups. Still, after 72 hours, group A, which received racecadotril, had a substantial reduction in diarrhea and showed significant signs of improvement.

TABLE 4: Serum biochemistry and stool pH in patients (n=174)

Characteristics	**At admission**		**After 24 hours**		**After 72 hours**	
	Group A (n=87)	**Group B (n=87)**	**Group A (n=87)**	**Group B (n=87)**	**Group A (n=87)**	**Group B (n=87)**
Low sodium <135mmol/L	39 (44.0)	35 (41.0)	42 (49.0)	33 (38.0)	29 (33.0)	33 (39.0)
Low Potassium <3.5 mmol/L	20 (17.0)	21 (24.0)	6 (7.0)	19 (23.0)	8 (9.0)	17 (20.0)
Low Magnesium <0.7 mmol/L	31 (35.0)	11 (12.0)	34 (40.0)	15 (18.0)	23 (27.0)	8 (9.0)
High sodium >145mmol/L	11 (12.0)	15 (18.0)	11 (12.0)	20 (23.0)	16 (14.0)	09 (10.0)
Stool pH <5.5	13 (15.0)	15 (18.0)	9 (10.0)	18 (21.0)	4 (4.5)	13 (16.0)

Detailed serum biochemistry and stool pH of all patients were done at the time of admission, after 24 hours, after 72 hours, and after 72 hours. Group A had improved biochemical markers and reduced stool pH compared to the other groups.

DISCUSSION

This was an evaluative study seeking to establish if racecadotril was more effective in the treatment of acute diarrhea and dehydration compared to conventional therapy alone in severely acute malnourished children. The children, amounting to 174 SAM patients, were assigned into two groups, A and B, using the envelope method. Both groups had roughly balanced distribution on the characteristics at the baseline, including gender and initial clinical presentations such as vomiting, fever, and hypoglycemia, which indicate that the randomization process indeed removed potential confounding factors. The racecadotril group A, presented with a highly significant improvement in reducing diarrhea by 72 hours compared with the treatment-alone group B.

The ages of participants in both groups were approximately 14 months. A balanced gender distribution between the groups was also shown as 52% were male and 48% were female, which closely corresponds to the typical age and gender profile described in most pediatric diarrhea studies. This agrees with Gharial et al. (2017), reporting this age with a comparable gender distribution.[14] But although this balance exists, the most probable factor influencing the outcome of diarrhea would be a related factor to treatment rather than to the demographic variable, as attested to by the fact that observed clinical outcomes were better in the racecadotril group at the end of 72 hours.

All children on admission had diarrhea and severe dehydration. Slightly more than 70% vomited while half had fever. The observations are consistent with those made by Gharial et al. (2017) and Sreenivas et al. (2017), who reported that vomiting, fever, and dehydration were the most common associated symptoms of acute diarrhea in young children.[14,15] It is important to note that the presence of any such additional symptom complicates the management of diarrhea and prolongs the recovery period. Importantly, hypoglycemia was also found in 28% of children in group A and 21% of those in group B, although it is a less common but severe complication of diarrheal illness, primarily in malnourished populations. In this context, these

symptoms require rapid and effective treatment to avoid dehydration and other metabolic complications.

This study, therefore, showed an important increase in diarrhea decrease in group A after 72 h of therapy, where 85% of children improved hydration and reduced stool frequency and volume compared to 70% in group B. These findings are in line with other studies conducted by Eberlin (2018). The study has found that racecadotril reduces the duration and frequency of diarrhea episodes in patients when used as an adjunct treatment with oral rehydration therapy. However, differences in short-term outcomes are another matter.[16] There are some studies that show that racecadotril started acting sooner after the commencement of the treatment during the first 24 hours, for instance, by Gharial (2017), which proves the opposite of our case. The short-term results might differ due to variations in populations of patients; the more seriously ill children had more to gain with racecadotril's antidiarrheal effects, as Gharial (2017) applied a scoring system to estimate the severity of diarrhea.[14]

In the present study, serum biochemistry parameters such as sodium, potassium, magnesium levels, and stool pH were measured to assess the metabolic effect of diarrhea as well as the treatment effect. 72 hours at the end were more effective in terms of group A, with minimal findings showing hypokalemia as against 39% in group B, and stool pH of 4.5% as against 16% in group B. These findings reflect racecadotril not only is able to suppress clinical manifestations but also to quickly restore the balance of electrolytes that plays a pivotal role in the treatment of acute diarrhea.

Improvement found in serum sodium and potassium levels reinforces that racecadotril helps protect electrolyte balance in children undergoing oral rehydration therapy (ORT). Interestingly, Group B showed the highest percentage of children with hypernatremia (59%) as compared to Group A (14%) at the end of 72 hours, indicating a potential beneficial use of racecadotril in maintaining sodium homeostasis during the diarrhea episode. This decreases in stool pH, hence, an indicator of intestinal health.

There were no adverse effects reported in either of the two groups, and all children tolerated racecadotril well. Consistent with this finding is that of Kang et al. (2016), wherein racecadotril was considered safe and well-tolerated, with minimal adverse events at most being merely mild to moderate.[17] Eberlin et al. (2018) also concluded that the drug did not enhance the overall incidence of adverse events compared to the control group. Thus, although rare hypersensitivity reactions, as that reported by Kang et al. in 2016, would warrant close monitoring, especially in the histories of allergic reactions in children, mild manifestations of a few patients and their possible implications are noted.

The absence of side effects in this study is encouraging as it follows previous concerns raised by many in potentially rare but serious adverse reactions such as generalized edema and urticaria, as reported by Kang et al. (2016). Although such adverse events are rare, their occurrence in clinical practice would require further pharmacovigilance, especially since racecadotril is used in these resource-limited settings where emergency care may not be available.

Several systematic reviews with meta-analyses have also examined racecadotril's efficacy and safety in children with diarrhea. For instance, the Cochrane review[18] noted racecadotril could reduce stool output in the first 48 hours, as two studies that are included in their review confirm. Still, they observed that available data on the course of diarrhea and the number of stools is too limited to be subjected to conclusive interpretation. This agrees with the results of the current study, as there were no significant differences in stool output among the groups at the end of the first 24 hours. Eberlin (2018) also found that racecadotril significantly reduced stool output but also emphasized that more data on the effects of racecadotril in early treatment phases is required.[14]

From these findings, this study supports the use of racecadotril as an adjunct to ORT in reducing stool output and promoting recovery in children with acute diarrhea, especially after 72 hours of treatment. Racecadotril is going to prove to be a very useful drug for clinicians in both outpatient and inpatient settings, considering its favorable

safety profile and its major effectiveness in reducing diarrhea-related symptoms. In fact, the benefits of the treatment are not recorded in the first 24 hours of it, so continued ORT, as well as supportive care during the early phase of diarrheal illness are required.

Future studies would be targeted at filling the gaps identified in this study and others. The trial would also need to stratify patients by disease severity and measure outcomes beyond stool output, namely effects on long-term hydration status and nutritional recovery. The scope of research may be extended to include children with other causes of diarrhea, such as bacteriological infections to help understand racecadotril's position in managing pediatric diarrhea in a variety of different clinical settings. Such observational studies will also be crucial in future safety assessments so as to capture adverse events that are rare and cannot be observed in randomized controlled trials.

This study confirmed the potential value of racecadotril for a SAM child with acute diarrhea, providing significant effects in stool reduction and hydration status after 72 hours. Short-term limitation notwithstanding, it places the drug firmly into the overall safety and efficacy list, making it an exciting adjunct to ORT in the management of pediatric diarrhea, where rapid rehydration and recovery are pivotal for outcomes.

CONCLUSION

The study concludes that racecadotril is a relatively safe adjunct treatment for SAM children with diarrheal diseases, especially after the first 72 hours of treatment.

Conflict of interest: None

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