

# Evaluate the Racecadotril Efficacy in Contrast the Reatment of Acute Diarrhea with Tril Compared to Probiotics and Loperamide in Adults

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## ABSTRACT

**Objective:** The study's objective is to compare the efficacy, safety, and acceptability of racecadotril to that of probiotics and loperamide in the treatment of patients with severe diarrhea.

**Study Design:** A cross-sectional study

**Place and Duration:** Conducted at Department of Gastroenterology Mayo Hospital Lahore, during from the period Sep 2021 to Feb 2022.

**Methods:** There were 150 patients of both genders had age 18-60 years with acute diarrhea included in this study. After obtaining informed written consent detailed demographics of enrolled cases were recorded. Patients were equally divided in three groups. Group I received 2mg probiotics among 50 patients, group II received 2mg loperamide in 50 patients and 50 patients of group III received 100 mg acetorphan (racecadotril) three times a day. Patients were continuously received oral rehydration therapy for 3-days. Outcomes were assessed in terms of efficacy and complications among three groups.SPSS 22.0 was used to analyze complete data.

**Results:** Among 150 presented case, majority of the patients were males 88 (58.7%) and the rest of the patients 62 (41.3%) were females. 60 (40%) patients had age 18-28 years, 40 (26.7%) had age 29-38 years, 30 (20%) had age 39-50 years and 20 (13.3%) had age >50 years. Majority of the cases had poor socio-economic status 90 (60%). We found that effectiveness of racecadotril 47 (94%) and loperamide 42 (84%) is significantly higher as compared to probiotics 15 (30%) with p value <0.005. Complications in group II was higher found in 18 (36%) cases as compared to group I 4 (8%) and 1 (2%) in group I.

**Conclusion:** We concluded that loperamide and racecadotril are fast, effective treatments for acute diarrhoea. Probiotics are less effective than other medications yet have fewer adverse effects. Loperamide group had higher treatment-related constipation complications than others.

## INTRODUCTION

Mild to severe cases of diarrhoea kill millions of people every year. Baby children in underdeveloped countries are disproportionately affected. Diarrhea is a major health concern not just for children but also for adults in developed nations [1], where it remains a major contributor to hospitalizations, doctor visits, and missed work days [2]. For instance, each year in the United States there are around 375 million cases of acute diarrhoea, which results in 900,000 hospitalizations and 6,000 fatalities [3,4]. There is still a significant problem with infectious enteritis in several developed nations, including Germany [5]. Acute diarrhoea typically results from an infection with bacteria, viruses, or parasites [2]. However, whereas bacteria are the most common cause of acute diarrhoea in impoverished nations, viruses are the most common cause in developed countries. The majority of incidents of transmission involve either water or foodborne contamination [6]. The prevalence of broad-spectrum antibiotic use and tourism abroad may contribute to an already alarming rise in cases of severe diarrhoea among adults in developed nations.

Oral rehydration therapy is crucial in treating acute diarrhoea since dehydration is the leading cause of death from the condition. Increases in its use have been linked to a precipitous drop in mortality caused by severe diarrhoea [2]. In otherwise healthy persons, infectious acute diarrhoea usually resolves on its own, although it still causes discomfort and has social consequences including missed workdays [3]. However, dehydration owing to diarrhoea can be fatal, especially in the elderly, even in affluent countries[4]. This is due to visceral failure.

The antisecretory effects of endogenous enkephalins are maintained for a longer period of time in the intestines when enkephalinase, an enzyme found in membranes, is inhibited. Orally active, potent enkephalinase inhibitor racecadotril [racecadotril is the official international nonproprietary name (INN); the drug was known as acetorphan in early studies] has been shown to exert naloxone-reversible antidiarrheal effects in rodents, effects that result from the protection of endogenous enkephalins. [7,8] In addition, racecadotril did not speed up intestinal transit time in these mice. Tests on healthy adults demonstrated that

racecadotril had no effect on either oro-caecal or colonic transit times. [9]

Several reviews and meta-analyses [10-12] have examined the efficacy and safety of racecadotril in the treatment of acute diarrhoea in children. According to these findings, racecadotril is a viable therapeutic choice for acute diarrhoea in children, as recommended by worldwide recommendations [13,14]. Previous literature surveys, however, were limited in scope due to language and/or cultural barriers and so only covered a subset of the total literature (2–9 studies largely excluding those from China or 19 studies only from China). Racecadotril has been shown to be effective in the treatment of acute diarrhoea in children, and a recent systematic search in which the language of the report was not a restriction yielded 57 randomised trials, which is more than three times as many as the most comprehensive review of the topic that had previously been published. [15]

The mechanism of action of racecadotril involves the selective inhibition of enkephalinase, which prevents the overproduction of gastrointestinal fluids and electrolytes without disturbing the digestive process. Adults who are experiencing acute diarrhoea often take antibiotics alongside probiotics (such as *Saccharomyces boulardii* and *Lactobacillus rhamnosus*). Enteromorbific bacteria (such as shigella, salmonella, and *E. coli*) are inhibited in their metabolic activity, growth, and ability to adhere to the gut wall by the use of probiotics. [13-15]

Comparing racecadotril to probiotics and loperamide for the treatment of patients with severe diarrhoea was the goal of this study.

## MATERIAL AND METHODS

This cross-sectional study was conducted at Department of Gastroenterology Mayo Hospital Lahore, during from the period Sep 2021 to Feb 2022 and comprised of 150 patients with acute diarrhea. After obtaining informed written consent detailed demographics of enrolled cases were recorded. Patients <18 years of age, had other severe medical illness, allergic to medicines, renal or hepatic failure, lactation or gestation and those who did not provide any written consent were not included in our study.

Acute diarrhoea was defined as three or more loose, watery stools in 24 hours, with no history of previous antibiotic use. Patients were randomly assigned to one of three groups. Group I received 2mg probiotics among 50 patients, group II received 2mg loperamide in 50 patients and 50 patients of group III received 100 mg acetorphan (racecadotril) three times a day. Patients received care for 3 days, or until they felt better if that time came sooner. Most importantly, effectiveness was evaluated by patients' responses to therapy for severe diarrhoea. Acute diarrhoea patients were treated in the hopes that they would recover, where recovery was defined as having two normal bowel movements within 24 hours. When patients taking anti-diarrheals didn't start to feel better after the allotted time, doctors gave them something else to try. During the first appointment, patients were instructed to report any symptom improvements, such as the resolution of diarrhoea, constipation, or others. Patients were not informed that achieving a normal frequency of bowel movements was the primary goal of the research.

**RESULTS**

Among 150 presented case, majority of the patients were males 88 (58.7%) and the rest of the patients 62 (41.3%) were females.(figure 1)

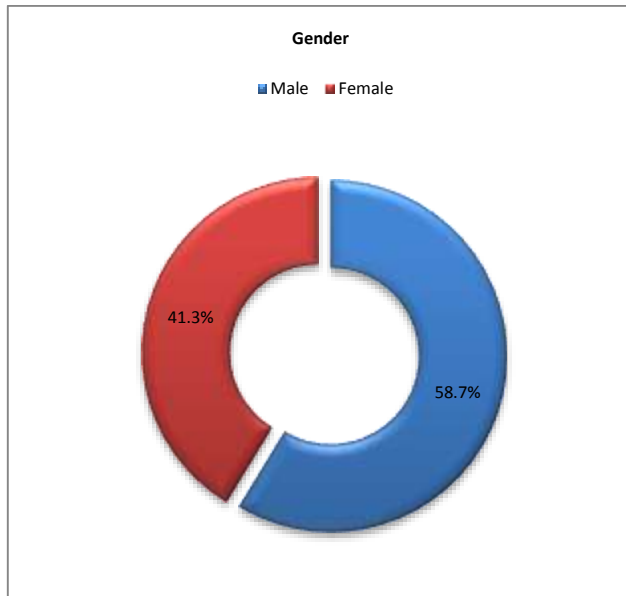


Figure-1: Gender distribution among all cases

In all cases, 60 (40%) patients had age 18-28 years, 40 (26.7%) had age 29-38 years, 30 (20%) had age 39-50 years and 20 (13.3%) had age >50 years. Majority of the cases had poor socio-economic status 90 (60%). There were 102 (68%) cases from rural areas and 48 (32%) had urban residency.(table 1)

Table-1: Included patients with detailed demographics

Variables	Frequency	Percentage
<b>Age (years)</b>		
18-28	60	40
29-38	40	26.7
39-50	30	20
>50	20	13.3
<b>Socio-Economic status</b>		
Poor	90	60
Middle	40	26.7
Upper	20	13.3
<b>Residency</b>		
Urban	48	32
Rural	102	68

We found that effectiveness of racecadotril 47 (94%) and loperamide 42 (84%) is significantly higher as compared to probiotics 15 (30%) with p value <0.005.(fig 2)

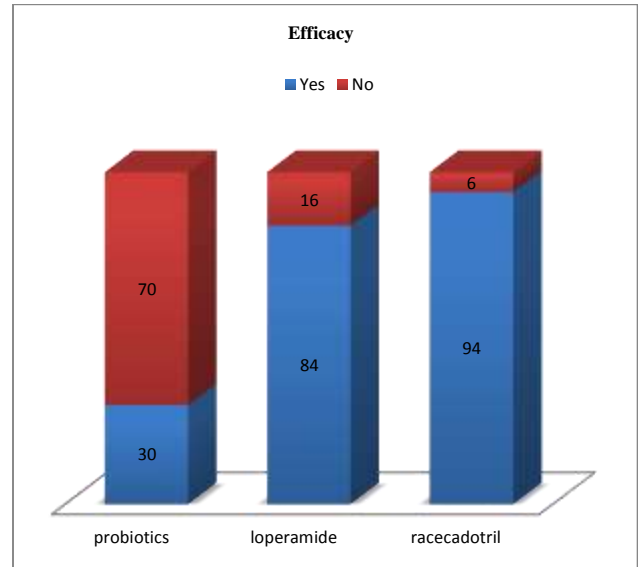


Figure-2: Comparison of efficacy among three groups

Complications in group II was higher found in 18 (36%) cases as compared to group I 4 (8%) and 1 (2%) in group I.(table 2)

Table-2: Association of complications among all cases

Variables	Group I	Group II	Group III
<b>Complications</b>			
Yes	4 (8%)	18 (36%)	1 (2%)
No	46 (92%)	32 (64%)	49 (98%)
<b>Types of Complications</b>			
Constipation	2 (4%)	15 (30%)	0
Dizziness	1 (2%)	2 (4%)	1 (2%)
Fatigue	1 (2%)	1 (2%)	0

**DISCUSSION**

Acute diarrhoea in adults often results from an intestinal virus infection. Mild cases of diarrhoea can usually be treated with oral rehydration therapy, probiotic-rich foods, a gentle diet, and plenty of liquids. [16] The severe consequences of acute diarrhoea in adults necessitate a clear treatment plan for mild to severe cases. [17] Racecadotril delays the anti-scripural action of endogenous enkephalinase by inhibiting the enzyme. [18]

In our study 150 patients of both genders with acute diarrhea were presented. Among 150 presented case, majority of the patients were males 88 (58.7%) and the rest of the patients 62 (41.3%) were females. Results of our study was comparable to the study conducted in past.[19] In all cases, 60 (40%) patients had age 18-28 years, 40 (26.7%) had age 29-38 years, 30 (20%) had age 39-50 years and 20 (13.3%) had age >50 years. Majority of the cases had poor socio-economic status 90 (60%). There were 102 (68%) cases from rural areas and 48 (32%) had urban residency. Previous studies presented same results to current research.[20,21] There is evidence that racecadotril is more effective than a placebo. Even while racecadotril consistently performed better in the experiments, the sample sizes were too small for the results to be statistically significant in the first dose-ranging study[22]. Two meta-analyses supported the overall efficacy of racecadotril compared to placebo for the endpoint of time to cure, one using pooled data from five studies [23] and the other using individual patient data from four of these studies [24].

As compared to above mentioned results, our study also presented comparable results. We found that effectiveness of racecadotril 47 (94%) and loperamide 42 (84%) is significantly higher as compared to probiotics 15 (30%) with p value <0.005. Three studies found a benefit for racecadotril [25], one found a numerical but non-significant benefit for racecadotril [26], and one found no difference between the two treatments [25, 26]. Four studies comparing racecadotril to placebo or other therapies found slight but consistent improvements in cure rates after 7 days of therapy [27]. Two double-blind studies recorded Kaplan-Meier analysis for 4-5 days following the commencement of treatment [28] to better understand the temporal course of remission of diarrhoea upon treatment with racecadotril in comparison to placebo.

Compared to this investigation, the results of a double-blind, randomised trial conducted by J.M. Vetel and H. Berard showed that racecadotril was only moderately effective. Possible causes include individuals who don't take their medications as prescribed, a large sample size, racial diversity, and a lengthy study duration. [29] Our results are comparable to those of Cologne et al., who found that probiotics helped 29% of patients with acute diarrhoea. [30].

Even though our trial included a similar number of patients as others that employed loperamide and probiotics, racecadotril showed significantly greater improvement in reducing diarrhoea's persistence and symptoms. Time to recovery is short. Loperamide users were more likely to have constipation than those taking the other two drug categories. Rapid relief from motion sickness, nausea, and abdominal pain was observed in the racecadotril and loperamide groups.

## CONCLUSION

We concluded that loperamide and racecadotril are fast, effective treatments for acute diarrhoea. Probiotics are less effective than other medications yet have fewer adverse effects. Loperamide group had higher treatment-related constipation complications than others.

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