

Original Article



Comparing the Efficacy of Anti-Secretory and Oral Immunoglobulins in Reducing the Duration of Diarrhea Episodes in Children; A Randomized Controlled Trial

Zunash Fateh¹, Nighat Haider², Saida Riaz³, Muqadar Shah⁴, Hafsa Khalid⁵, Saad Abdullah Fateh⁶

Jai Krishin⁷

¹Postgraduate Resident, ^{2,4}Assistant Professor, Peeds, ³Associate Professor, ^{5,6}Peeds Dept, ⁷Professor (The Children Hospital Islamabad)

Author's Contribution

¹Conception and design,
^{5,6}Collection and assembly of data,
⁷Final approval and guarantor of the article,
²Analysis and interpretation of the data,
^{3,4}Drafting of the article, Critical revision of the article for important intellectual content,

Funding Source: None

Conflict of Interest: None

Received: Jan 12, 2024

Accepted: June 02, 2024

Address of Correspondent

Dr. Zunash Fateh
 Postgraduate resident
 Children Hospital, PIMS,
 Islamabad
 zunash.ammar@gmail.com

ABSTRACT

Objective: To compare the efficacy of anti-secretory and oral immunoglobulins in reducing the episodes of diarrhea in children.

Methodology: This randomized controlled trial, carried out at The children Hospital, Islamabad. Eighty-four children aged 6 to 36 months with acute diarrhea were included. Patients were divided into two groups: Group A patients received anti-secretory (racecadotril) and oral rehydration and zinc, while Group B was given egg solids and bovine colostrum in powdered form, ingested with water, alongside oral rehydration and zinc. Treatment efficacy was measured by time to fewer than 3 semi-solid stools within 24 hours. Outcomes were observed over 72 hours. Data was entered and analysed using SPSS version 26.0.

Results: The study involved 84 children (39 males, 45 females) aged 6 to 36 months, treated for acute diarrhea with Group A (anti-secretory, racecadotril) or Group B (Bovine colostrum). Baseline characteristics including age, gender, and duration of symptoms showed no significant differences between the groups ($P=0.331$ for gender, $P=0.194$ for age, $P=0.187$ for symptom duration). Treatment response varied significantly between the groups ($P=0.000$): In Group B, 18, 12, and 6 patients responded on days 1, 2, and 3, respectively, while in Group A, 5 patients responded on day 1 and 20 on day 2, with no 3-day responses. Out of 84 patients, 36 in Group B and 25 in Group A responded positively, and treatment was overall effective for 61 patients (p -value 0.001).

Conclusion: Both treatments were effective, with 85.7% efficacy in the Bovine colostrum group and 60% in the Racecadotril group after 3 days. The Bovine colostrum group demonstrated a significantly quicker treatment response compared to Racecadotril.

Keywords: Acute diarrhea, anti-secretory, bovine colostrum, immunoglobulins, oral rehydration, racecadotril.

Cite this article as: Comparing the Efficacy of Anti-Secretory and Oral Immunoglobulins in Reducing the Duration of Diarrhea Episodes in Children; A Randomized Controlled Trial. *Ann Pak Inst Med Sci.* 2024; 20(3):232-236. doi: 10.48036/apims.v20i3.961.

Introduction

Acute diarrhea starts within 24 hours or less and lasts for less than 14 days.¹ Even though treatments for acute diarrhea in children have come a long way in the last few decades, it is still a major cause of illness and death in children.² There is 19% prevalence of diarrhea among children of under the age of five between the periods of 2017-18 in Pakistan, half (52%) of these episodes are in children less than 12 months.³

Acute diarrhea is characterised by loose or watery stools that may be followed by vomiting, and abdominal colic.⁴ The severe diarrhea may lead to dehydration, electrolyte imbalance, poor intestinal healing and weight loss.⁵ The most common organisms responsible for diarrhea in younger children is rotavirus 70–90% followed by Bacteria as Shigella, Salmonella, Campylobacter and, enterotoxigenic E. coli (ETEC), and less frequently enter invasive E. coli (EIEC), are causative agents in 10–20% of cases.^{6,7}

The World Health Organization's findings indicate that 65% of children are not receiving appropriate treatment for diarrhea, whereas 35% are benefiting from dehydration treatment. It is important to note that timely treatment significantly contributes to reducing both mortality and morbidity rates. Despite their widespread use, oral rehydration salts (ORS) have been shown to have little effect in reducing the length of severe diarrheal episodes, healing the irritated intestinal mucosa, or restoring nutritional status. The mainstay of treatment for acute diarrhea in children is the administration of oral rehydration solution (ORS). Other co-adjuvant therapeutic options include racecadotril, smectite, probiotics, oral immunoglobulins and zinc.^{4,8}

Breast milk contains immunoglobulins (primarily IgA) that chelate with bacterial and viral antigens and hinders their colonization.⁹ Other gut-active compounds in colostrum, including cytokines, defensins and lactoferrin promote intestinal healing. The use of bovine colostrum secure children from diarrhea as mother feed is not acquired by every child. The egg of hen is considered to be a source of diarrheal treatment based on nutrition, which contains IgY. It changes the surface configuration of the virus and prevent the virus from adsorbing to cells and bind to viruses. Better clinical outcome has been observed with decrease in frequency and improvement in consistency of stool.^{10,11}

Racecadotril inhibits enkephalinase, which is an endorphin-metabolizing enzyme, neutral endopeptidase (NEP), resulting in a rise in levels of enkephalin, which slows intestinal secretions without affecting its motility, allowing the infectious pathogen to be expelled. This would progressively reduce the frequency of diarrhea and loose stools.^{12,13}

There is a considerable amount of information across the globe about the efficacy and safety of several anti-diarrheal agent in children. No data regarding the use of these therapeutic agents and their effectiveness is available from Pakistan and no data regarding the comparison of these medicines is available in literature from anywhere. So, this study will help to assemble evidence regarding the better agent to reach a systematic approach towards treatment of this common but dangerous disease.

Methodology

It was a parallel randomized controlled trial study conducted at the department of Pediatrics over the period of six months after taking ethical approval from the

institutional review board. This trial was registered at Clinical Trial.gov (Identifier: NCT04885049). We enrolled 84 Children of 6 to 36 months who were diagnosed with acute non-bacterial diarrhea. We excluded children requiring emergency resuscitation, having diarrhea of more than 15 days duration, children with other comorbidities including cardiac, renal and hepatic failure, having fructose intolerance, glucose malabsorption syndrome and saccharase isomaltase deficiency and children allergic to egg or any of the contents. Children who had already taken treatment (antibiotics, prebiotics, probiotics etc.) for acute diarrhea were also excluded. Written consent was taken from parents before enrollment.

Patients were divided into two groups after taking demographic details included name, age and gender of patient. Group A (GA) received anti secretory (racecadotril) 1.5mg/kg/dose, orally and three doses were given in 24 hours, while Group B (GB) received bovine colostrum and egg solids as a single dose where 7g of dry powder was reconstituted in 30ml of water. Both drugs were taken for 3 days along with oral rehydration and zinc as standard protocol. Efficacy of treatment involved the period of drug administration to the appearance of less than 3 semi-solid/solid stools in 24 hours. Patients were monitored for 3 days and those who failed to pass less than 3 formed stools/ 24 hours during the time of 72 hours of monitoring were labelled as treatment failure.

Proforma was designed to collect data while the analysis of data was done through SPSS version 20.0. The variables like age and time considered as quantitative variables were calculated as mean and standard deviation while sex and age group which are considered as qualitative variables were calculated as frequencies and percentages. Chi-square and t-test were applied to compare qualitative variables and quantitative variables. A p-value ≤ 0.05 was considered statistically significant.

Results

Out of a total of 84 patients, 39 (46.4%) were male and 45 (53.6%) were female children. The majority of the children were in the 6-12 months age group, comprising 27 (32.1%), followed by 23 (27.4%) in the 12-18 months age group. The overall mean age of the children in the study was 17.86 ± 8.21 months.

The baseline characteristics between the Bovine colostrum and Racecadotril treatment groups were comparable, with no statistically significant differences in gender

distribution ($P=0.331$), age groups ($P=0.194$), or duration of diarrheal symptoms ($P=0.187$) (Table I).

Table I: Baseline Demographic and Symptomatic Distribution between Bovine Colostrum and Racecadotril Treatment Groups. (n=84)

Baseline characteristics	Treatment group		p-value
	Bovine colostrum	Racecadotril	
Gender			
Male	21	18	0.331
Female	21	24	
Age group (in months)			
6-12	14	13	
12-18	11	12	0.194
18-24	3	9	
24-36	14	8	
Duration of symptoms (in days)			
1-4	19	20	
5-9	20	14	0.187
10-14	3	8	

The average age of patients in the Bovine colostrum group was 18.43 ± 8.82 months compared to 17.29 ± 7.52 months in the Racecadotril group, with no statistically significant difference ($P=0.52$). The duration of the disease at the time of presentation was 4.79 ± 2.055 days for Bovine colostrum and 5.69 ± 3.368 days for Racecadotril, also with no significant difference ($P=0.142$). The mean episodes of diarrhea per day at the time of presentation were 4.12 ± 1.064 for Bovine colostrum and 4.55 ± 1.273 for Racecadotril, with a P-value of 0.098, indicating no statistically significant difference between the two groups.

The treatment response duration varied significantly between the Bovine colostrum and Racecadotril groups ($P=0.000$). In the Bovine colostrum group, 18, 12, and 6 patients responded on day 1, 2, and 3 of treatment respectively. In the Racecadotril group, 5 patients responded to treatment on day 1, and 20 on day 2, with no on day 3. (Table II)

Table II: Comparison of treatment response duration in days between bovine colostrum and racecadotril groups.

Treatment response duration (in days)	Treatment group		p-value
	Bovine colostrum	Racecadotril	
1 day	18	5	0.000
2 days	12	20	
3 days	6	0	

Table III: Comparison of Efficacy of Treatment among treatment groups.

Treatment group	Efficacy		p-value
	Yes	No	
Bovine colostrum	36 (85.7%)	6 (14.3%)	0.001
Racecadotril	25 (59.5%)	17 (40.5%)	

Out of 84 patients, 36 in the Bovine colostrum group and 25 in the Racecadotril group responded positively to treatment, while 6 and 17 patients respectively did not. Overall, treatment was effective for 61 patients and ineffective for 23 across both groups (p-value). (Table III)

Discussion

Even though the majority of children hospitalized for acute diarrhea have illnesses that are mild to self-limiting, it is nevertheless one of the most prevalent reasons for hospitalization in children.¹⁴ During this study, we examined the racecadotril efficacy, an anti-secretory medication and oral immunoglobulins IgA and IgY (IgA is derived from bovine colostrum, and IgY is derived from hen's yolk). The participants ranged in age from 6 to 36 months and had acute diarrhea. Hydration status was not different between the two groups at the time of enrollment. Most previous studies, have primarily focused on comparing these treatments against a placebo. The absence of direct comparative studies highlights the unique and meaningful contribution of this research within the wider scope of therapeutic approaches for addressing diarrhea.

In our investigation, each group had 42 patients. Twenty five out of 42 patients who received racecadotril in addition to normal rehydration therapy recovered within 72 hours of treatment beginning. Five patients recovered within 24 hours of the initiation of treatment and 20 patients within 48 hours. The effects of racecadotril on acute diarrhea in children have been studied extensively; however, the results have been inconclusive. A study by Mirza Muhammad Ahsan Baig et al. found that stool frequency was reduced significantly in the racecadotril group compared with the placebo group at day-3 ($p<0.001$).²

In a comprehensive review of 58 trials spanning nine countries included six trials of racecadotril in comparison to placebo, 15 in comparison to various active treatments, and 41 as add-on to standard treatments. Racecadotril reduced the time to cure from 106.2 hours to 78.2 hours (mean reduction 28.0 hours; $P < 0.0001$ in 24 studies) and displayed tolerability comparable to placebo or other active comparator treatments (2.4% adverse events).¹³

This study found that out of 42 patients in Racecadotril group, 5 patients responded to treatment in 24 hours, and 20 in 48 hours, with no day 3 responses, overall response rate after 3 days was 60%. Similarly, Seyed Motahari et al. reported that the Racecadotril group had an average diarrhea duration of $3.0 \text{ days} \pm 1.4 \text{ SD}$ compared to $3.9 \pm$

1.6 SD days in the control group ($P = 0.005$). However, the total duration of diarrhea between these groups was not statistically significant ($P = 0.78$).¹⁵ Contrarily, Salazar-Lindo et al. documented that the production of stool of two days, total stool, and mean duration of diarrhea were significantly less pronounced in the racecadotril group compared to the placebo group after 48 hours. In their study the median duration of diarrhea significantly less in the Racecadotril group (28 hours) than in the placebo group (52 hours, $P<0.001$).¹⁶ Similarly, Kang et al. had not depicted benefit in the treatment of racecadotril in terms of diarrhea duration, amount of stool, or defecation frequency.¹⁷ A local study found that there was a reduction in stool frequency at 48 hours in the Racecadotril group with a mean of 5.10 ± 2.589 as compared to Placebo 7.22 ± 2.835 (P -value 0.012). Although the stool frequency was more in that study but Racecadotril still demonstrated better outcomes compared to the placebo. Moreover, the length of hospital stay was lower in the Racecadotril category (76.40 ± 31.08 hours) as compared to placebo (92.400 ± 38.98 hours) (P -value: 0.029). These findings align with the prompt response observed in our Racecadotril group, further supporting its potential benefits.¹⁸

Bovine colostrum is the name used for the treatment and prevention of gastrointestinal infections from several decades. A commercial nutraceutical product made from Bovine colostrum has recently been introduced with manufacturers emphasizing its advantages for addressing gastrointestinal disorders.⁹

In our current study, 36 out of 42 patients (85.7%) exhibited a positive response to oral immunoglobulins. Within the bovine colostrum group, treatment response was staggered across three days, with 18, 12, and 6 patients responding on days 1, 2, and 3, respectively. These findings align with those of Barakat et al., who discovered that, regardless of the causative pathogen (Rotavirus or *E. coli*), the bovine colostrum group had significantly reduced vomiting and diarrhea after 48 hours compared to a placebo group ($p = 0.000$).¹⁹ A similar outcome was observed by Suwarba et al., who noted that in comparison to a control group, the bovine colostrum group's time to achieve defecation frequency of three times per day 2.31 ± 0.76 vs. 3.34 ± 1.45 ($P=0.001$) and normal stool consistency 2.40 vs. 3.43 days was shorter.²⁰ Contrarily, Casswell et al. reported no significant differences between two groups of 86 children suffering from *E. coli* diarrhea, one receiving oral bovine milk concentrate and the other a placebo, in terms of ORS intake, stool output, frequency

of diarrhea, *E. coli* clearance, or duration of diarrhea.²¹ This discrepancy across various studies might be attributed to different causative microbes, variations in sample size, distinct population characteristics, and the diverse composition of immunoglobulin utilized.

Clinical trials in Myanmar involved 54 infected children of retrovirus that depicted hen's egg yolk is effective against diarrhea. The group of IgY had showed significantly decreased mean of intake of ORF ($p=0.004$), while the mean of the period of intravenous fluid was ($p=0.03$), the mean of duration of diarrhea and clearance of retrovirus from the time of admission was ($p=0.01$) and ($p=0.05$) compared to placebo IgY group.²²

The present study fills a gap in the literature by directly comparing the efficacy of racecadotril and oral immunoglobulins, rather than comparing them solely to placebos, as seen in much of the previous literature. There were some limitations to our study. It was single centered study having small sample size. Secondly, using parental/guardian observations to evaluate stool-related information in this study may have its own repercussions. Specific outcome variables such as etiology, stool volume, length of hospitalization, adverse effects and cost estimation were not considered while comparing both treatments, potentially restricting the comprehensiveness of our findings. Future research should focus on standardized treatments and methodologies to reduce discrepancies across studies. The potential roles of causative microbes, the composition of treatments, and other influencing factors must be explored in depth. Also, further investigations into the efficacy of oral immunoglobulins against diarrhea, could open new therapeutic avenues. Lastly, broader multicenter studies with larger sample sizes are essential to derive more conclusive and universally applicable findings.

Conclusion

Both treatments exhibited promising results. The Bovine colostrum group had an 85.7% efficacy, while the Racecadotril group showed a 60% efficacy after 3 days. The treatment response duration showed a significant difference, with more rapid responses observed in the Bovine colostrum group ($P=0.000$). The importance of further research into these therapeutic interventions is highlighted by these findings, which offer insightful information about the management of pediatric acute diarrhea.

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