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Efficacy and Rationale of Differentiated Racecadotril Doses Combined with Bifidobacterium Triple Viable in Managing Pediatric Persistent Diarrhea: A Comprehensive Analysis

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ABSTRACT

Objective: Pediatric persistent diarrhea poses a severe burden on children's health. This study investigates the efficacy and fundamental mechanisms of varying doses of racecadotril in combination with bifidobacterium triple viable for treating this condition in children.

Methods: Employing a randomized controlled trial design, participants diagnosed with pediatric persistent diarrhea were randomly allocated to a high-dose group (observation) and a low-dose group (control), both treated with racecadotril combined with *bifidobacterium* triple viable. During treatment, clinical parameters were meticulously recorded and analyzed. ELISA techniques were utilized to quantify alterations in immune, inflammatory, and oxidative stress markers in serum. Quantitative culture methods for gut microbiota were employed to assess changes in intestinal flora composition before and after treatment.

Results: Compared to the low-dose group, the high-dose treatment group demonstrated significantly shorter durations for fever resolution, vomiting cessation, diarrhea control, and dehydration correction. Furthermore, the overall treatment efficacy was higher in the high-dose group without notable increases in adverse reactions. The high-dose group showed elevated IgG and IgA levels, reduced inflammatory markers (hs-CRP, IL-6, TNF-α), and increased anti-inflammatory factor IL-10. Additionally, oxidative stress marker MDA decreased while SOD activity enhanced. Gut microbiota analysis revealed substantial improvement in the high-dose group, with an increase in beneficial bacteria and a decrease in harmful bacteria.

Conclusion: The high-dose group of racecadotril combined with *bifidobacterium* triple viable demonstrated superior efficacy in improving clinical and laboratory manifestations in pediatric persistent diarrhea compared to the low-dose group.

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Introduction

Persistent diarrhea in children is defined as a condition in which there is an abnormally increased frequency of defecation and a change in the texture of feces (such as thin or watery) that persists for more than two weeks and does not show significant improvement even after initial treatment.[1],[2] Persistent diarrhea in children not only directly threatens the physical health of children, affecting their regular nutrient intake and growth and development, but may also further aggravate the impact of the disease due to complications such as dehydration, electrolyte imbalance, and malnutrition.[3] In the field of global pediatric healthcare, this condition is widespread, especially in regions with relatively scarce medical resources.[4,5] Therefore, conducting in-depth research and optimizing treatment plans is crucial for reducing the adverse effects of persistent diarrhea in children and promoting their recovery and healthy growth.

During childhood diarrhea, the proliferation of harmful bacteria in the gastrointestinal tract accelerates, disrupting gut microbiota balance and prolonging the diarrhea episode. Research has identified bifidobacterium triple viable as a biotherapeutic agent that effectively modulates intestinal pH, stabilizes microecological equilibrium, and repairs intestinal mucosal barriers.[6,7] Nevertheless, its solitary administration exhibits suboptimal efficacy, necessitating combination with other medications for enhanced therapeutic outcomes. The ideal clinical approach aims to curtail excessive intestinal secretion without compromising gastrointestinal motility and address water-electrolyte imbalances.[8,9] Reports suggest that racecadotril, an enkephalinase inhibitor, safeguards endogenous enkephalins from degradation, prolongs their physiological activity in the gut, and potently inhibits water and electrolyte secretion, demonstrating clinical efficacy in diarrhea management.[10,11] Given these insights, it was hypothesized that the combined therapy of racecadotril and bifidobacterium triple viable might offer superior outcomes in treating pediatric persistent diarrhea. Through an extensive literature search, we found that reports on the combined use of these two agents specifically for pediatric intestinal diseases are limited. This underscores the importance and novelty of exploring the treatment outcomes of their combined administration for pediatric persistent diarrhea. Given the potential synergistic effects and the distinct mechanisms of action these two therapies offer, their combination could address the disease's multifaceted pathophysiological aspects more comprehensively.

This study employed varying doses of racecadotril in combination with bifidobacterium triple viable to treat children with persistent diarrhea. A comprehensive analysis was conducted on clinical efficacy, symptom relief time, inflammatory factor levels, immunoglobulin levels, and oxidative stress-related indicators across different patient groups. This research aims to provide an effective therapeutic regimen for clinical practice while elucidating its underlying rationale and evidence base.

Materials and Methods

This study included 100 cases of children with persistent diarrhea admitted to the pediatric department of our hospital from January 2022 to October 2022. This study was performed in line with the principles of the Declaration of Helsinki. The Ethics Committee of Hebei Chest Hospital granted approval. Inclusion criteria:[1] Consistent with the relevant diagnostic criteria for persistent diarrhea in the Expert Consensus on the Principles of Diagnosis and Treatment of Childhood Diarrhea;[2] age: 1 - 6 years;[3] Children with full-term delivery;[4] Accept the treatment plan and the compliance is good;[5] Obtain the informed consent of the parents of the child, and voluntarily sign an informed agreement. Exclusion criteria:[1] children with severe dehydration, coma, and amebic dysentery;[2] children with mental illness;[3] children with drug allergy or allergic constitution in this study;[4] children with inherited metabolic diseases, pneumonia, and chromosomal diseases;[5] children with serious primary diseases such as cardiovascular and cerebrovascular, liver and kidney, and hematopoietic system.

Using a computer-generated random number sequence, one hundred subjects were randomly assigned to either a control or observation group. Each subject was assigned a unique number, and these numbers were then randomly distributed into two groups of 50, ensuring an equal distribution of subjects between the control and observation groups. Before the study's initiation, clinical data from all participants were collected, encompassing age, gender, duration of illness, and diarrhea frequency. Both groups of children underwent uniform conventional treatment, encompassing standard symptomatic management, a balanced diet tailored to correct water and electrolyte imbalances, antibiotic administration for those with infections, and intravenous nutritional support, among other measures, to ensure consistency across all patients. This study utilized a combination therapy of *bifidobacterium* triple viable tablets (Inner Mongolia *Bifidobacterium* Pharmaceutical Co., Ltd, National Drug License No. S19980004, specification: 0.5 g*12 tablets*2 boards/box) and racecadotril granules (Sichuan Baili Pharmaceutical Co., Ltd, National Drug License No. H20050411, specification: 10 mg*18 bags). In the control group, children received a small-dose combination therapy. The small dose for *bifidobacterium* triple viable was 0.5 g **(2 tablets)** twice daily for children aged 1-3 years and 0.5 g **(3 tablets)** twice daily for children aged 4-6 years. The small dose for racecadotril was 1.5 mg/kg, administered three times daily, with a total daily dose not exceeding 6 mg/kg. These doses were based on common standards in current pediatric clinical practice and were consistent with relevant pediatric medication guidelines[12]. In the observation group, children received a high-dose combination therapy. The high dose for *bifidobacterium* triple viable was 0.5 g **(2 tablets)** three times daily for children aged 1-3 years and 0.5 g **(3 tablets)** three times daily for children aged 4-6 years. The high dose for racecadotril granules was 2 mg/kg, administered three times daily, with a total daily dose not exceeding 6 mg/kg. Both groups of patients were administered the medications with warm water, with a treatment duration of 7 days.

Criteria for Clinical Diagnosis and Efficacy Evaluation: 1) Cure: after 2 days of treatment, the children's clinical symptoms disappeared, and the number and nature of stools returned to normal. 2) Improvement: after 3 days of treatment, the children's clinical symptoms improved significantly, the number of stools decreased to 2 times/day, and the water in the stools decreased or returned to normal. 3) Ineffective: There was no significant improvement in the children's clinical symptoms within seven days of treatment, no substantial reduction in the number of stools, and no change in their consistency.

Total response rate = (cure + improvement)/Total cases ×100%.

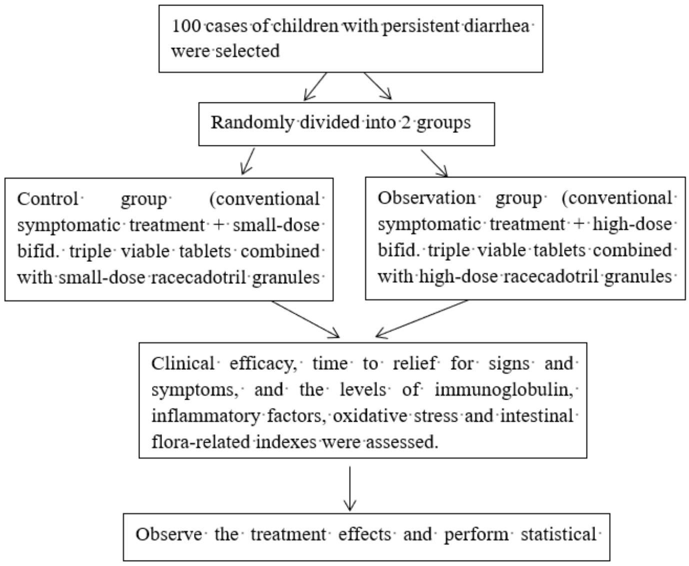

Figure 1. Flowchart of the study design.

Observation index: Compare the time to clinical symptom improvement, clinical efficacy, and occurrence of adverse reactions between the two groups of children. Clinical symptom improvement time includes antipyretic time, vomiting disappearance time, antidiarrheal time, and dehydration correcting time. Blood samples were collected from both groups of patients in the morning, after they had fasted, both before treatment and on the seventh day of treatment, with each sample measuring approximately 5 mL, centrifuged at 3,000 rpm for 10 min. Then the upper serum was taken and stored at -80°C temporarily. It was used to measure the serum levels of immunoglobulin G (IgG) and immunoglobulin A (IgA) before and after treatment in the two groups of patients by immuno-single diffusion method; enzyme-linked immunosorbent (ELISA) method was used to determine the children's serum inflammatory factors: high-sensitivity C-reactive protein (hs-CRP), Interleukin-6 (IL6), IL-10, and tumor necrosis factor-alpha (TNF-α) before and after the treatment, as well as the changes in the levels of oxidative stress superoxide dismutase (SOD), malondialdehyde (MDA) levels. To compare the intestinal microecological flora of the two groups of children before and after treatment: Fresh feces of 0.5-1 g were collected from both groups, added to saline, diluted with a 10-fold dilution method, and dropped into the culture medium for qualitative and quantitative analysis. *Bifidobacterium* and *Lactobacillus* were cultured on *Enterococcus* agar medium; *Enterococcus* and *Enterobacteriaceae* were cultured on anaerobic agar medium;

Table 1. Comparison of the time to relief for signs and symptoms between the two groups of children

Group	Cases	Antipyretic time	Vomiting disappearance time	Antidiarrheal time	Dehydration correction time
Control	50	23.01±3.31	36.43±15.38	27.23±11.23	67.89±4.2
Observation	50	16.94±2.69	26.29±11.66	18.27±8.27	53.81±3.24
t	-	10.07	3.72	4.54	18.7
P	-	<0.0001	0.0003	<0.0001	<0.0001

The time is specified in number of days.

Table 2. Comparison of treatment outcomes between the two groups of children

Group	Cases	Cure	Improved	Ineffective	Overall efficiency rate	Adverse reaction
Control	50	27 (54%)	12 (24%)	11 (22%)	78%	0
Observation	50	39 (74%)	8 (16%)	3 (6%)	94%	0
χ2	-	-	-	-	5.316	-
P	-	-	-	-	0.02	-

Bacteroides were cultured on sugar fermentation medium. Statistical comparisons were made, and the results were expressed as logarithmic values of colony-forming units in 1 g of fecal wet weight (CFU/g). SPSS 19.0 statistical software was deployed for analysis and processing. The measurement information was described by mean ± standard deviation, and independent samples t-test was used for comparison between groups, and a paired t-test was used for comparison within groups. The count data were described by %, and comparisons between groups were made using the $\chi2$ test. It was regarded as statistically considerable if $P < 0.05$. The specific technical route of this study is shown in **Figure 1**.

Results

Comparison of baseline data between the two groups

The baseline characteristics of the two pediatric patient groups are detailed in **Table S1.** The control group encompasses 50 patients, including 24 males and 26 females. Their ages span from 1 to 6 years, with a mean of 2.26 ± 0.40 years. The duration of illness ranges from 4 to 14 days, averaging 7.14 ± 2.57 days, and diarrhea occurs 3 to 8 times per day, with a mean frequency of 6.62 ± 1.60 times per day. The observation group consists of 50 patients as well, with 27 males and 23 females. Their ages also fall within the 1 to 6-year range, averaging 2.48 ± 1.22 years. The illness duration varies from 4 to 13 days, with a mean of 6.88±2.40 days, and diarrhea occurs 2 to 10 times per day, averaging 6.26 ± 1.75 times per day. Statistical comparison of the baseline data between the two groups indicated no statistically significant differences ($P > 0.05$).

For children in the observation group, antipyretic time, vomiting disappearance time, antidiarrheal time, and dehydration correcting time were remarkably shorter than those in the control group **(**$P < 0.0001$, **Table 1).**

The total effective rate of treatment in the observation group was considerably greater compared with the control group, and the difference was statistically significant ($P = 0.02$), as shown in **Table 2.** In addition, children in the observation and control groups experienced no adverse effects during treatment. As is evident from **Table 3,** after 7 days of treatment, serum IgG levels increased dramatically in both groups and were considerably higher in the observation group than in the control group, and the differences were found to be statistically meaningful ($P < 0.05$). The post-treatment IgA concentration in the observation group was significantly higher than the pre-treatment

Table 3. Comparison of indicators related to inflammation and oxidative stress between the two groups of children

	pre-treatment				post-treatment			
	Control	Observation	t	p	Control	Observation	t	p
Immunoglobulin level								
IgG（ng/L）	8.41±0.82	8.50±0.85	0.505	0.614	12.73±3.4**	15.92±4.8**	3.82	0.0002
IgA（ng/L）	0.90±0.13	0.89±0.12	0.687	0.494	1.08±0.44	1.73±0.59**	3.370	0.001
Inflammatory factor level								
hs-CRP（mg/L）	132.34±43.17	137.48±46.34	0.575	0.567	129.35±33.42	77.67±26.25**	4.110	<0.0001
IL-6（ng/L）	91.82±29.32	98.93±23.13	1.346	0.181	79.54±14.52*	48.25±14.51**	3.543	0.0006
IL-10（ng/L）	19.51±2.73	20.10±2.96	0.104	0.301	23.62±3.58*	37.5±6.32**	5.734	<0.0001
TNF-α（ng/L）	32.00±3.73	31.66±4.14	0.431	0.668	30.47±3.90	18.38±2.60**	12.640	<0.0001
Oxidative stress level								
MDA (μmol /L)	2.89±0.63	2.92±0.58	0.289	0.774	2.32±0.54*	1.21±0.55**	5.590	<0.0001
SOD (μ/L)	0.032±0.007	0.03±0.006	0.805	0.423	0.041±0.023	0.083±0.021**	5.941	<0.0001

Immunoglobulin G (IgG); Immunoglobulin A (IgA); Hypersensitive C-reactive protein (hs-CRP); Interleukin-6 (IL-6); Interleukin-1β (IL-1β); Tumor necrosis factor (TNF-α); Malondialdehyde (MDA). superoxide dismutase (SOD)
*P < 0.05, **P < 0.001 compared with the same group pre-treatment.

Table 4. Comparison of intestinal microecological flora before and after treatment in two groups of children

Flora name (lgCFU/g)	**pre-treatment**				**post-treatment**			
	Control	**Observation**	**t**	**p**	**Control**	**Observation**	**t**	**p**
Bifidobacterium	4.16±0.69	4.3±0.64	1.039	0.301	6.31±1.37*	8.54±1.56**	7.604	<0.0001
Lactobacillus	5.79±1.23	5.48±1.36	1.196	0.235	7.7±1.54*	9.52±1.86**	5.311	<0.0001
Enterococcus	8.41±0.82	8.5±0.85	0.505	0.614	6.42±1.33*	5.06±1.7**	4.442	<0.0001
Enterobacteriaceae	9.73±1.06	9.78±1.2	0.223	0.824	8.21±0.95*	6.67±1.41**	6.391	<0.0001
Bacteroides	9.11±1.85	8.91±1.77	0.543	0.589	7.54±1.48*	6.10±1.20**	5.351	<0.0001

*P < 0.05, pre-post control group comparison; **P < 0.001, pre-post observation group comparison.

concentration, whereas the IgA concentration in the control group showed no apparent change from the pre-treatment concentration. After treatment, serum IL-6 levels were markedly reduced, and IL-10 levels were enhanced in both groups, with statistically meaningful differences ($P < 0.05$). Notably, the hs-CRP and TNF-α levels of patients in the observation group were remarkably lower after treatment compared with those before treatment ($P < 0.001$), while the hs-CRP and TNF-α levels of the control group did not change dramatically after treatment ($P > 0.05$). In addition, MDA levels were found to be considerably lower, and SOD levels were markedly raised in the observation group post-treatment compared to pre-treatment ($P < 0.0001$), but the control group only dramatically inhibited the production of MDA ($P < 0.05$), and the effect on the release of SOD was not significant ($P > 0.05$).

It can be noted, as presented in **Table 4**, that before treatment, there was no marked difference in the number of intestinal microecological flora between the two groups ($P > 0.05$); after treatment, the observation group had more Bifidobacteria and Lactobacillus than the control group, and fewer Enterococcus, Enterobacteriaceae, and Bacteroides than the control group ($P < 0.0001$).

Discussion

Pediatric persistent diarrhea poses a persistent challenge for pediatricians in clinical settings, as conventional therapeutic approaches frequently fail to promptly and efficiently alleviate symptoms, thereby prolonging the disease course and adversely impacting patients' quality of life and growth trajectory.[13] The current study underscores a pivotal finding: the integration of high-dose racecadotril with *bifidobacterium* triple viable notably enhances the amelioration of symptoms and clinical signs among pediatric patients, such as diminishing diarrheal frequency, improving stool consistency and alleviating abdominal pain, thus markedly augmenting clinical efficacy. This observation aligns with the prevailing trend in contemporary research,[14-16] which emphasizes the superiority of combination therapy over monotherapy in managing pediatric diarrhea. A double-blind study on 40 children administered with low and high-dose bacterial therapies revealed that high-dose anaerobic fecal Lactobacillus combined with oral bacterial treatment yields superior outcomes in managing chronic nonspecific diarrhea in infants.[17] Similarly, our investigation underscores the pivotal role of dosage adjustment, particularly the advantages of employing high-dose regimens in persistent diarrhea, offering a novel insight for clinical practice. Notably, the high-dose therapeutic strategy adopted in this study has been well-substantiated in efficacy and safety. While previous studies have reported mild and transient adverse reactions in seven cases of children treated with racecadotril,[18] a meta-analysis encompassing five studies with 949 participants revealed no significant difference in adverse events between racecadotril and placebo.[11] Although the potential risk of increased adverse drug reactions with high-dose treatment cannot be overlooked, this study did not discern notable untoward effects, which may be attributed to the selectivity of the medications, individual variability among patients, and rigorous medication monitoring. Consequently, in clinical practice, physicians should meticulously assess each patient's unique circumstances, balance the benefits against potential risks, and select the most appropriate therapeutic strategy.

Persistent diarrhea, often accompanied by chronic intestinal mucosal inflammation, significantly contributes to its protracted course.[19] Our study underscores that high-dose therapy effectively reduces inflammatory cytokines, likely attributed to the potent antidiarrheal effect of high-dose racecadotril, minimizing noxious gut stimuli and the modulation of gut microbiota balance by high-dose *bifidobacterium* triple viable, thereby decreasing inflammatory cytokines from harmful bacteria.[20] It has been reported that TNF-α and IL-6 levels in adipose tissue were significantly decreased in obese mice after *bifidobacterium* triple viable treatment.[21,22] In contrast, low-dose treatment exhibited limited anti-inflammatory efficacy, emphasizing the significance of dose escalation in combined therapy for persistent diarrhea. Additionally, immunity plays a pivotal role in the recovery process of pediatric diarrhea.[23,24] Our study demonstrates that high-dose combined therapy significantly augments patients' immune function, aligning with recent research on the immunomodulatory effects of probiotics and antidiarrheal agents.[25] *Bifidobacterium* triple viable bolsters immune system development and functionality through various mechanisms.[26] It can ferment sugar, restore intestinal motility, promote the synthesis of various vitamins and biological enzymes, improve the absorption of calcium, iron, vitamins, and other trace elements, and enhance immune function.[27] A study noted that *bifidobacterium* triple viable treatment significantly increased IgA levels in the colonic mucosa.[28] While racecadotril primarily targets intestinal secretory function, it may also indirectly positively impact immunity. Our study has pronounced the immune-enhancing effect of high-dose combination therapy, suggesting a synergistic immunomodulatory interaction between these two drugs.

In pediatric persistent diarrhea, gut microbiota dysbiosis emerges as a core issue, characterized by a decline in beneficial bacteria and a surge in harmful species, exacerbating intestinal inflammation and diarrhea symptoms.[29,30] Restoring and maintaining gut microbial balance is thus pivotal for managing this disease. Our study reveals that, compared to low-dose treatment, high-dose therapy significantly improves the gut microbiota composition in pediatric patients. *Bifidobacterium* triple is viable as a probiotic supplement, directly augmenting beneficial bacteria and inhibiting harmful ones, thereby restoring gut microecological balance.[31,32] High-dose therapy likely facilitates quicker colonization of the gut niche with higher concentrations of probiotics, effectively repelling harmful bacteria and accelerating gut microbiota restoration.[33] Previous studies on probiotics in pediatric diarrhea, often focusing on single probiotics or lower-dose combinations, demonstrated moderate and delayed improvements in gut microbiota. In contrast, our high-dose combination therapy exhibits more rapid and pronounced effects on gut microbiota, reinforcing the pivotal role of probiotics and underscoring the significance of dosage adjustment in optimizing therapeutic outcomes.

While highlighting the benefits of high-dose racecadotril and *bifidobacterium* triple viable in managing persistent diarrhea in children, this study has certain limitations.

The sample size and data on the change in symptoms before and after treatment of the child might be too small to ensure broad applicability of the findings, and the single-center design may have introduced selection bias. Furthermore, potential confounding factors might not be fully considered, affecting the interpretation of results. For example, all enrolled pediatric patients received antibiotic treatment for consistency, which may affect the assessment of gut microbiota as antibiotics change its composition and diversity.[34] Not all patients received zinc supplementation, yet it plays an important role in persistent diarrhea in children. As this was a retrospective study, it was challenging to collect comprehensive clinical data on variables such as changes in weight and white blood cell count (WBC) before and after treatment. These variables could significantly influence the assessment of treatment effectiveness. To comprehensively evaluate the efficacy of this treatment regimen in controlling pediatric persistent diarrhea, future studies should include a more diverse patient population, incorporate more complex variables (such as antibiotic treatment and zinc supplementation), and collect more comprehensive clinical data. A placebo or alternative treatment control group should also be established to more thoroughly assess the efficacy of the treatment regimen under different conditions.

Conclusion

In conclusion, the study demonstrates that high-dose racecadotril combined with high-dose *bifidobacterium* triple viable significantly enhances clinical outcomes in pediatric persistent diarrhea by expediting the improvement of symptoms and signs, bolstering immune function, mitigating systemic inflammation, and optimizing gut microbiota composition, compared to low-dose therapy. This discovery validates the efficacy of this combined therapy and underscores the critical role of dosage optimization in enhancing therapeutic outcomes. With its potential to expedite recovery and improve patient well-being, this high-dose approach holds promise for the future management of pediatric persistent diarrhea, inviting further investigation into its long-term effects and mechanisms of action.

Declarations

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Conflict of interest

The authors declare that they have no conflict of interest.

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