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Efficacy of the Probiotic Probiotical Confirmed in Acute Gastroenteritis

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Conflict of Interest
SK and TVT report no conflicts of interest. YV has participated as a clinical investigator, advisory board member, consultant, and/or speaker for Abbott Nutrition, Biocodex, Danone, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson, Phacobel, and United Pharmaceuticals.

ABSTRACT

Purpose: Some probiotic strains reduce the duration of acute diarrhea. Because of strain and product specificity, each product needs to be supported by clinical data. This study aimed to test the efficacy of the synbiotic food supplement Probiotical (*Streptococcus thermophilus*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Bifidobacterium infantis*, fructo-oligosaccharides) in children with acute gastroenteritis of likely infectious origin. The primary endpoint was the number of children with normal stool consistency during the treatment duration.
Methods: A total of 46 children (aged 3.6 months to 12 years) with acute gastroenteritis that started less than 48 hours prior to their visit at a hospital-based emergency department were included in this prospective, randomized, placebo-controlled trial. All children were treated with oral rehydration solution and placebo (n=20) or the test product (n=26).
Results: Significantly more children had a normal stool consistency on days 1 and 2 in the probiotic group: 5 children (20%) on day 1 in the probiotic group compared with none in the placebo group (p=0.046). On day 2, 11 children in the probiotic group (46%) and 3 (16%) in the placebo group (p=0.024) had a normal stool consistency. The mean duration of diarrhea was shorter in the probiotic group compared with that in the placebo group (3.04±1.36 vs. 4.20±1.34 days) (p=0.018).
Conclusion: The test product was shown to normalize stool consistency significantly more rapidly than the placebo. These data confirm the findings from a previous study in a larger group of children performed in a primary healthcare setting.

Keywords: Acute gastroenteritis; Diarrhea; Probiotics; Synbiotic

INTRODUCTION

Despite improvement in healthcare over the last few decades, infectious acute gastroenteritis or diarrheal disease is still one of the leading causes of death in developing countries [1]. Acute diarrhea is the passage of liquid or loose stools at least three times per day lasting for less than or equal to 7 days, as defined by the Bristol stool criteria ≥type 6 [2]. Treatment with oral rehydration solution (ORS) is recommended to correct dehydration. ORS has reduced the incidence of mortality and morbidity caused by diarrhea but does not shorten the duration of diarrhea, change the stool consistency, or normalize the gastrointestinal microbiota [3].

Table 1. Composition of Probiotical

Content	Amount	Strain	Dose
Streptococci	6.5×10^9 CFU	*Streptococcus thermophilus*	60 mg
Lactobacilli	6.5×10^9 CFU	*Lactobacillus rhamnosus*	28 mg
		Lactobacillus acidophilus	28 mg
Bifidobacteria	6.5×10^9 CFU	*Bifidobacterium infantis*	20 mg
		Bifidobacterium lactis	20 mg
Fructo-oligosaccharides			20 mg
Ascorbic acid			1.2 mg

CFU: colony-forming units.

Probiotics are living microorganisms that survive in the gastrointestinal tract and, when ingested in a sufficiently large amount, confer a health benefit on the host [4]. There is evidence that selected strains of probiotics decrease the duration of acute diarrhea [5,6]. This prospective study was designed to evaluate the additional benefit of Probiotical (Bactecal from 2021 onwards; Astel Medica, Belgium/Luxembourg **Table 1**, composition), a food supplement containing five probiotic strains (*Streptococcus thermophilus*, *Lactobacillus rhamnosus*, *L. acidophilus*, *Bifidobacterium lactis*, *B. infantis*), prebiotic fructo-oligosaccharides (FOS), and 1.2 mg of ascorbic acid, with the standard ORS treatment on a number of children with normal stool consistency during an episode of acute gastroenteritis of likely infectious origin.

MATERIALS AND METHODS

This randomized, prospective, double-blind placebo-controlled trial was conducted in children (ages between 3 and 186 months) visited a hospital-based emergency department in Luxembourg (**Table 2**, patient characteristics; **Fig. 1**, study flowchart).

The inclusion criteria were as follows: an episode of mild to moderate acute diarrhea (>4 [semi] watery stools/day) according to the Bristol criteria (Bristol criteria ≥6) of likely infectious origin in infants and children aged 3 months to 15 years since at least 1 day and lasting within 7 days. Dehydration was evaluated on clinical grounds and estimated weight loss. Furthermore, patients were mildly (<5% weight loss) and moderately (5–10% weight loss) dehydrated based on weight loss [7].

The exclusion criteria were as follows: children under 3 months of age or older than 15 years, exclusively breastfed children, and children with contraindications for ORS or probiotics. Other exclusion criteria were the presence of macroscopic blood in the feces and use of probiotic products except for the probiotics present in infant formula, if the patient developed diarrhea while being fed with this kind of formula.

Table 2. Clinical and demographical findings of the study groups

Patient characteristics	Probiotical	Placebo	*p*-value
Number of children	26	20	
Sex (boy/girl)	14/12	12/8	NS
Age (mo)	32.4 (3.6–149.3)	15.7 (3.9–129.4)	<0.05
Weight (kg)	13.5 (6.1–57.8)	10.7 (5.3–53.4)	NS
Duration of diarrhea at inclusion (d)	1 (0–5)	1 (0–2)	NS
Dehydration >5%	0	0	NS

Values are presented as number only or median (range).
NS: not significant.
Statistics: sex and duration of diarrhea.
Fisher's exact test, and others, Mann–Whitney U-test.

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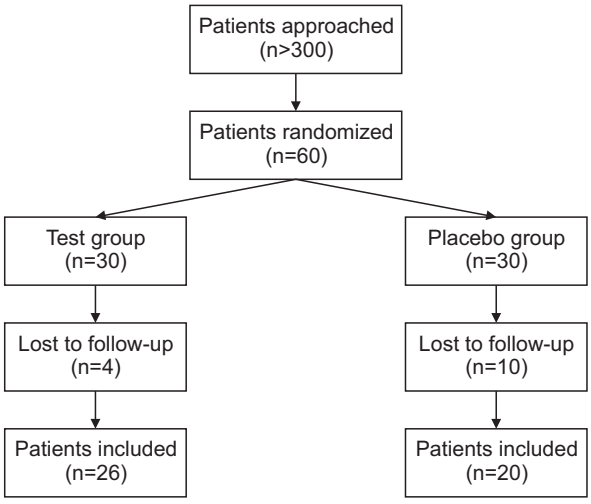

Fig. 1. Study flowchart of patients.

All patients were treated according to the recommendations with the same hypo-osmolar ORS ad libitum (Humana Elektrolyt ORS composed of glucose, maltodextrin, sodium chloride, potassium citrate, sodium citrate, and natural banana flavoring, with an osmolarity of 229 mOsm/L). Re-alimentation with normal food was started after 6 hours.

The product tested was a capsule that could be opened and mixed in ORS or water and administered from the start of ORS (1 capsule/day during 7 days). The placebo was also a capsule but without FOS and probiotics. Both products were supplied by Astel Medica (Belgium/Luxembourg), which had no role in the concept, design, or conduct of the study or the analysis or interpretation of the data. The active product and placebo were packed in identical boxes; they were of the same color, weight, smell, and taste. All physicians and patients were unaware of the real nature of the product. The unblinding procedure was performed after the study was completed and the statistical analyses were finalized. Randomization for every participating physician was performed by a computer. Patients were enrolled according to the computer-determined allocation to product A or B. The sequence was concealed until treatments were assigned. The probiotic group received the active product (Probiotical; **Table 2**), and the placebo group received the placebo. Physicians were allowed to prescribe additional medication according to what they would consider "good clinical practice" if the response of the patient to the study treatment was not satisfactory.

All patients were examined by the treating physician at inclusion and optional at day 7. The physicians registered the demographical data, degree of dehydration, and duration of diarrhea before inclusion and if hospitalization was necessary. Before the inclusion of the patient, all inclusion and exclusion criteria had to be registered. If a patient did not fulfill the inclusion criteria, participation in the study trial was not possible. Parents recorded the number of passages and aspect of the stools according to the Bristol criteria (illustrations were provided) and the use of any other medication in a specific diary. Day 1 was defined as "the first 24 hours of treatment." Parents sent this diary after the end of the study. The primary endpoint was the number of children with normal stool consistency according to the Bristol criteria (stool score ≤5) during the study. The secondary endpoint was the duration of diarrhea.

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This trial was not registered in a publicly accessible registry. The study was approved by the National Ethical Committee of Luxembourg (No. 201509/14), and parents gave their written consent. The sample size had been calculated at 120 to obtain the required power (95%, type 1 error 0.05, two-tailed test), and 60 patients per group were calculated, accepting a dropout rate of 20%. Statistical analysis was performed using an online calculation tool, the statistical software R. Continuous variables were compared using the Mann–Whitney U-test. Categorical variables were presented as percentage (%) and analyzed using Fisher's exact test to compare the differences between two groups. The level of statistical significance was set at $p<0.05$. The factors sex, age, weight, duration of diarrhea before treatment, and group assignment were entered in a backward stepwise regression analysis to test for independent contributions of the different risk factors to the duration of diarrhea.

RESULTS

A total of 60 children were included in the trial, of which 14 were lost to follow-up (4 in the product arm, 10 in the placebo arm). Data from 46 children regarding the primary and secondary endpoints were analyzed. Patients presented with acute diarrhea (median duration, 1 day; range, 0–7 days). There were 26 patients in the Probiotical group and 20 in the placebo group. No patient had a dehydration of >5%.

A significantly higher number of children had a normal stool consistency within the first 24 hours of treatment in the probiotic group than in the placebo group: on day 1, 5 children (20%) in the probiotic group and 0 (0%) in the placebo group ($p<0.05$) had a normal stool consistency. On day 2, 11 children (46%) in the probiotic group and 3 (16%) in the placebo group ($p<0.05$) had a normal stool consistency (**Table 3**).

The mean duration of diarrhea (time between the inclusion and the first defecation with a Bristol score of ≤5) was 1.16 days shorter with Probiotical than with the placebo ($p=0.019$). The duration of diarrhea was 3.04±1.36 days in the Probiotical group and 4.20±1.34 days in the placebo group ($p=0.018$) (**Fig. 2**).

No patients were hospitalized. Adverse effects were not reported.

In the placebo group, 7 out of 20 patients (30%) patients received additional medications (antisecretory drug [racecadotril], 4 patients; antibiotics, 1 patient; and paracetamol, 2 patients). In the Probiotical group, 9 out of 26 (32%) patients received additional medications (antisecretory drug [racecadotril], 4 patients; antibiotics, 1 patient; paracetamol, 3 patients; and montelukast, 1 patient). There was no statistical difference in additional medication use between the two groups.

Table 3. Percentage of children with normal stool consistency

Days	Treatment	Placebo	*p*-value
0	0%	0%	NS
1	20%	0%	<0.05
2	46%	16%	<0.05
3	64%	36%	NS
4	81%	65%	NS

NS: not significant.
Day 0, day when the patients visited the emergency department; Statistics.
Fisher's exact test.

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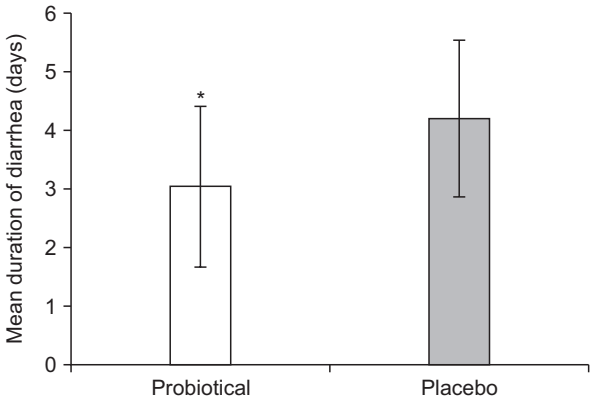

Fig. 2. Mean duration of diarrhea. *p=0.018 (Fisher's exact test).

DISCUSSION

This study showed that the addition of the synbiotic product tested, Probiotical, to ORS decreased the duration of acute gastroenteritis in children. The cornerstone of the management of acute gastroenteritis is oral rehydration [5]. The active treatment of diarrhea with the administration of probiotics and/or drugs may be considered where there is solid proof of efficacy in reducing the intensity and duration of symptoms [5]. Some probiotic strains have been shown to offer a safe intervention for acute infectious diarrhea and reduce the duration and severity of the disorder [8].

The use of probiotics in acute gastroenteritis has become increasingly popular in some countries. Probiotics have been shown to have a luminal action: antitoxic effect against specific pathogens, antimicrobial and metabolic activities, tight junction preservation, and modulation of the intestinal fiora. Some probiotic strains also have a trophic and anti-inflammatory effect on the mucosa [9]. The best studied probiotics include some Lactobacilli species (*L. rhamnosus GG*, *L. reuteri* DSM 17938) and *Saccharomyces boulardii* [5,6]. Several published data focus on hospitalized patients. However, for some probiotics, such as *S. boulardii*, the vast majority of data are obtained in ambulatory care and in the developing world [10]. As a result of strain and product specificities (especially for products containing mixtures of probiotic strains) and to be in agreement with the recommendations of official and scientific organizations, it is recommended to perform randomized controlled trials with each commercialized product [8]. A Cochrane review concluded that the probiotics tested reduced the duration of diarrhea within 24.76 hours (95% confidence interval [CI], 15.9–33.6 hours; n=4,555, trials=35) [6]. According to the same Cochrane review, the frequency of stools decreased on day 2 (mean difference, 0.80; 0.45–1.14; n=2,751, trials=20) [6]. Probiotics were reported to reduce the duration of community-acquired acute diarrhea by 14.0% (95% CI, 3.8–24.2%) and stool frequency on the second day of treatment by 13.1% (95% CI, 0.8–25.3%) [11]. There was no effect on the risk of hospitalization because of diarrhea [11].

Whether the greater efficacy of multi-strain products compared with single-strain products is due to synergistic interactions between strains or a consequence of the higher probiotic dose used remains unclear [12]. Synergism between different strains has been demonstrated. Juntunen et al. [13] showed a better adherence of *B. Bb12* in the presence of *Lactobacillus GG*. The better the adhesion occurs, the more IgA secretion. Mixtures of probiotics have been shown to have possible additional benefits over single-strain products [12]. A total of 16

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studies compared the effect of a mixture with that of its component strains separately, and in 12 cases (75%), the mixture was more effective [12]. One study reported a better efficacy of a single strain (*S. boulardii*) compared with a mixture (*S. boulardii*, *L. acidophilus*, *L. rhamnosus*, *B. longum*) [14]. The efficacy of probiotics may also be dose and age dependent [15,16].

Only 60 children were included despite the calculated sample size of 120. The study did run from 2016 to June 2019. Since the test product was available on the market and parents were informed about the latter, several parents preferred not to participate in the trial but to purchase the test product. The children in the test-product group were older than in the placebo group. Therefore, it cannot be excluded that the more rapid recovery could be partially due to the difference in their age and body size, gastrointestinal function, and immunity although the older the child, the lower the dose of the test product since the same dose was administered, independent of weight. A previous study with a comparable setup with the synbiotic Probiotical showed that both on days 2 and 3, the stool consistency had normalized in significantly more patients using the active product compared with those using the placebo [17]. The synbiotic product tested (Probiotical) contained a mixture of probiotic microorganisms for which there is evidence of efficacy, such as *LGG* [5,9]. According to the results of the study by Canani et al. [18], the duration of diarrhea in the ORS and placebo groups was 115 hours and reduced to 78.5 hours in the *LGG* group and 70 hours in the group treated with a mixture of four bacterial strains (*L. delbrueckii subsp. bulgaricus*, *S. thermophilus*, *L. acidophilus*, and *B. bifidum*). Among preschool children with acute gastroenteritis, those who received a 5-day course of *LGG* did not have better outcomes than those who received the placebo [19]. The administration of a product containing *L. rhamnosus* R0011 and *L. helveticus* R0052 twice daily did not result in the median duration of diarrhea [20]. A formula with *S. thermophilus* and *B. bifidum*, two of the four bacterial species in the preparation studied, prevented nosocomial diarrhea in chronically hospitalized children aged below 24 months [21].

García-Menor et al. [22] tested Prodefen (Italfarmaco, Milan, Italy) composed of 1×10^9 colony-forming units of the probiotic strains (*L. casei PXN 37*, *L. rhamnosus PXN 54*, *S. thermophilus PXN 66*, *B. breve PXN 25*, *L. acidophilus PXN 35*, *B. infantis PXN 27*, and *B. bulgaricus PXN 39*) [19,20]. This randomized trial shows that the addition of Prodefen to the standard ORS treatment shortens the duration of diarrhea and is very well tolerated in children with acute diarrhea.

To date, few studies evaluated the efficacy of synbiotics, a mixture of probiotics and prebiotics, in the treatment of infectious diarrhea. The product tested, Probiotical, is a synbiotic since it contains a small amount of prebiotic oligosaccharides, 20 mg of oligofructose. For comparison, the amount of oligosaccharides in starter infant formula is approximately 800 mg/100 mL or 8 g/L. Prebiotic oligosaccharides did not reduce the duration of diarrhea [23]. However, a synbiotic may confer additional benefits over probiotics because the fermentation of the prebiotic may increase the bifidobacterial levels [24]. The addition of a prebiotic may induce a theoretical benefit to normalize the gastrointestinal microbiota composition of the host more rapidly although the amount of FOS in the product is very small [17]. The presence of vitamin C is related to the manufacturing process of the product, but the very low dosage (1.2 mg/capsule) is unlikely to have a clinical effect since the recommended daily intake varies between 15 and 50 mg/day for the age groups studied. Adverse effects of very high dosages of vitamin C (over 2,000 mg/day) may induce diarrhea.

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Stool cultures were not performed, as is the case in several studies testing the efficacy of probiotics in acute gastroenteritis [23,25]. Moreover, according to the evidence-based guidelines of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and European Society for Paediatric Infectious Disease, it is not recommended to perform stool cultures for acute gastroenteritis [5].

In conclusion, the synbiotic Probiotical was shown to enhance the normalization of stool consistency and reduce the duration of diarrhea. Two independently performed trials with the same product and a comparable protocol suggest that the tested product reduces the duration of infectious diarrhea in children.

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