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The Role of Probiotics in the Treatment of Dysentery: a Randomized Double-Blind Clinical Trial

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Abstract Diarrhea is considered as an important cause of morbidity and mortality, even though one of the main reasons of death following diarrhea is initiated by dysentery. In recent years, the consumption of probiotics has been proposed for the treatment of infectious diarrhea. Despite most of the studies on probiotics have focused on acute watery diarrhea, few studies in the field of dysentery have found beneficial effects of probiotics. This study is a randomized double-blind clinical trial. The patients were randomly placed into control and case groups. In the intervention group, the patients received probiotics in the form of Kidilact® sachet, which contained high amounts of 7-strain friendly bacteria strains of *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium infantis*, *Bifidobacterium breve*, and *Streptococcus thermophiles*. On the other hand, the patients in the control group received placebo sachets on a daily basis for 5 days. It is notable that the treatment protocol of acute dysentery was done on both groups. The results of this study showed significant differences in the duration of blood in diarrhea between probiotic consumers (2.62 days) and the control group (3.16 days) (P value = 0.05). Additionally, significant differences in the average length of hospitalization in probiotic consumers (3.16 days) and control (3.66 days), (P value = 0.02) could be claimed that the consumption of probiotics is effective in reducing the duration of dysentery and diarrhea. The results of this study suggest that the use of probiotics can be effective in reducing the duration of blood in diarrhea. This study was also recorded in the Iran center of clinical trials registration database (IRCT2014060617985N1).

Keywords Probiotics · Dysentery · Bacteria · Diarrhea · *Bifidobacterium* · *Lactobacillus* · *Streptococcus* · Fever · Patient

Introduction

Diarrheal diseases are among the major causes of child mortality in developing countries [1]. The World Health Organization (WHO) has defined diarrhea as an unusual movement of bowel that liquid stools occur at least three times a day [2]. However, change in the bowel consistency compared to its previous form has been considered to be a more important factor than the number of bowel movements, especially in the first months of life [3]. Diarrhea falls within three categories, namely acute watery diarrhea, chronic diarrhea, and bloody diarrhea (also named dysentery). From among these types of diarrhea, dysentery is responsible for 20% of the deaths resulting from diarrhea [4, 5]. The essential factors recommended by the World Health Organization for the control of acute gastroenteritis include the use of oral rehydration solution (ORS) with reduced osmolality and, if needed, intravenous fluids and zinc supplements. These have been proved to reduce the severity of diarrhea during treatment. ORS consumption declines the mortality and disability caused by diarrhea but does not influence the treatment length and severity of the disease [6–8]. Many studies have suggested the consumption of probiotics as an adjunct method for the treatment of acute diarrhea. The term probiotic is originally a Greek

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word meaning "for life." This term was first used by Lilly and Stillwell in 1965 to describe the reinforcing effect of a microorganism on the growth of other microorganisms. From that time on, multiple definitions were proposed until in 1985 when Fuller gave a new definition for probiotics as "a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance." The World Health Organization has referred to probiotics as the live microorganisms that will have benefits to the host's health when consumed in adequate amounts [9, 10]. Probiotics are now used in various fields of prevention and treatment, especially in acute infectious diarrhea [11]. The results of a systematic review of 56 studies on infants and children showed that the consumption of probiotics is safe and significantly effective in reducing the duration and the frequency of acute infectious diarrhea [12]. To date, a variety of probiotics, including lactobacilli, which are the bacteria and saccharomyces of a fungus have been identified and their effects on different diseases, such as acute gastroenteritis, have been investigated. The use of yogurt, as a probiotic, has been recognized effective in the treatment of diarrhea since ancient times, and, today, its beneficial effects in the treatment of diarrhea have been reported in many studies [13]. In the case of bloody diarrhea and dysentery, the main treatment includes the use of antibiotics and rehydration where the prescribed antibiotics are considered based on the desired pathogens [14]. In recent years, the use of probiotics has been proposed to reduce the duration and severity of infectious diarrhea treatment in the clinical field. Although most of the studies on probiotics have put their main focus on acute watery diarrhea, the effectiveness of *Lactobacillus* and *Saccharomyces* in the treatment of acute diarrhea and dysentery has been supported by the few studies conducted on dysentery [15, 16]. However, some others assert that there are not enough research findings yet to recommend the clinical use of probiotics in the treatment of diarrhea routinely [17]. The mechanism and effectiveness of probiotics usually depend on the interaction of probiotic microorganisms with one's specific normal flora and immune cells of the intestinal mucosa. From among the effects of probiotics, one can refer to such items as the stimulation of the immune system, reduced competition for the use of nutrients available in the intestine, connection to the intestinal membrane wall and mucus, and prevention of the connection of harmful factors, as well as the production of antimicrobial substances (H2S, bacitracin, and fatty acids). In addition, probiotics lead to the elimination of harmful microorganisms in the digestive system due to the deconjugation of bile salts and pH reduction [17–19]. From the intestinal flora, *Bifidobacteria* and *Lactobacillus* have an important role in health. The prescription of probiotics leads to some changes in microbial profile and metabolic activities of stool in both infants and adults. Although these changes are slight, they are sufficient to modify the disease process in most of the times if prescribed in pathological conditions. In most cases, the prescription of probiotics leads to an increase in the number of *Bifidobacteria* and *Lactobacillus*, to the decrease of stool PH, and to the decline in bacterial enzyme activity [20]. The effect of probiotics on diarrhea and other gastrointestinal disorders can come into play very quickly because the substances secreted by probiotics quickly affect the intestinal wall. However, it takes more time for the reinforcing effects of the immune system on other diseases to come into play [21]. Although the majority of the studies in the field of probiotics' prescription have been done on pediatric acute diarrheal diseases, probiotics are used in the treatment of adult and pediatric diarrhea, diarrhea caused by antibiotics, allergies, and colitis. Although many studies refer to the effect of probiotics in the prevention of diarrhea, the American Academy of Pediatrics does not recommend it except in special circumstances, such as child care centers [21–23]. The present study was conducted to evaluate the effect of available probiotics (Kidilact®), on the length and severity of dysentery in infectious control and children's wards. Similar to other countries and other regions of Iran, dysentery in Kashan occupies a large number of hospital beds each year and is the main concern of a large number of outpatient visitors to pediatric and infectious clinics. It is noteworthy that no similar studies have been undertaken in this region and that few studies in this domain have been done in other countries, which have resulted in controversial findings [24, 25]. Hence, this study is carried out to investigate the effectiveness of probiotics in the improvement of dysentery. In case of the proof of their effectiveness, it is hoped that the use of probiotics can reduce the severity and complication of this disease as well as the economic burden imposed by this disease to some extent. In fact, the control of this disease will be more feasible in the case of reduced duration of the treatment.

Materials and Methods

This study is a randomized double-blind clinical trial. The patients referring to Shahid Beheshti Hospital of Kashan in 2014 were admitted in the infectious control and children's wards (above 12 years) because of fever and bloody diarrhea. The criteria for inclusion in this study were hospitalization in the infectious control and children's wards with complaints of fever and dysentery, and active stool test. However, the exclusion criteria were severe malnutrition, immunodeficiency, and the consumption of antidiarrheal drugs or antibiotics. Regarding the results of previous studies [26], a sample size of 50 patients was considered (totally 100 patients) suitable for each group. Dysentery diagnosis was proved by the stool test containing RBC or WBC, and the patients with severe malnutrition, immunodeficiency or users of antidiarrheal drugs or antibiotics were excluded from the study. For data collection, the patients were

randomly assigned to case and control groups after obtaining the authorization of hospital officials and explaining the research objectives to the hospital as well as receiving prior written consent from the patients. In the intervention group, the patients consumed the probiotics produced by Zisttakhmir Company in the form of Kidilact® sachet. This is a particular probiotic-probiotic combination (synbiotics) for children over 2 years that contains high amounts of 7-strain friendly bacteria strains, such as a child-specific strain "*Bifidobacterium infantis*" along with prebiotic fructo-oligosaccharide (contributing to the growth and activity of probiotics). Its formula has been prepared specifically for children so that they can consume it easily. The strains used in the production of probiotics include *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *B. infantis*, *Bifidobacterium breve*, and *Streptococcus thermophiles*. In the control group, the patients received two placebo sachets every day and were prescribed for 5 days. In addition, the treatment protocol of acute dysentery was done on both groups where 50 mg/kg ceftriaxone was taken each day in the children's ward and 1 g of it was taken every 12 h in the infectious control ward for 3 to 5 days. The essential data including demographic data (age, gender), stool smear results, body temperature, type of antibiotics, dysentery, and fever were collected through looking into the patients' medical records and interrogative of the patients or their companions [27–29]. The improvement criteria were including the number of diarrhea less than three times a day, removal of blood in the stool, and the fever recovery.

Randomization and Blinding

To this end, both groups, in addition to receiving the routine treatment of dysentery, received the probiotic and placebo drug in the form of medicinal sachet, designing in the same size and color. It should be mentioned that a numerical code from 1 to 100 had been recorded on each sachet and numbers of each group were determined by block randomization.

Ethical Consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. This trial was registered at www.irct.ir as IRCT2014060617985N1.

Statistical Method

The Kolmogorov-Smirnov test was applied to determine the normal distribution of variables. The analyses were carried out based on the intention-to-treat principle. To detect differences in anthropometric measures and the dietary intakes between the two groups, we applied one-way, but two-tailed independent sample Student's *t* tests. These analyses were done using analysis of variance (ANOVA) [30–34]. *P* values <0.05 were considered statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 19 (SPSS Inc., Chicago, IL, USA).

Results

The mean value of age was 42.12 years for the probiotic-treated group, which consisted of 27 male and 23 female participants. On the other hand, the mean value of age for the control group was equal to 39.56 years and this group consisted of 25 male and 25 female participants. In addition, both groups were in similar situations in terms of temperature at the time of hospitalization in such a way that the average temperature at that time was 38.92 and 38.75 °C in the probiotic-treated group and in the control group, respectively (Table 1). There was not a statistically significant difference between the groups in terms of the duration of fever (P 0.05) and, thereby, probiotics did not stop fever (Table 2).

The presented data indicated a significant difference in the duration of blood in diarrhea between probiotic consumers (2.62) and the control group (3.16) at the significance level of 0.01 ($P < 0.05$), and it can be claimed that the consumption of probiotics is effective in reducing the duration of diarrhea blood (Table 3). The clinical trial results presented significant improvement of diarrhea in probiotic consumers compared to the control group (P value = 0.03) (Tables 4 and 5). Furthermore, consumption of probiotics significantly showed direct relationship with reducing the duration of hospitalization ($P = 0.02$).

Discussion

The patients had average age of 42.12 years for the probiotic-treated group consisting of 27 male and 23 female participants. On the other hand, the mean value of age for the control group was equal to 39.56 years and this group consisted of 25

Table 1 Comparison of temperature between the groups at the time of hospitalization

Group	Mean (°C)	SD	*P* value*
Probiotics	38.92	0.81	0.28
Control	38.75	0.78	

*Statistical significance was attained when *P* value <0.05

Table 2 Comparison of temperature between the groups in the duration of hospitalization

Group	Mean	SD	*P* value
Probiotics	2.54	1.23	0.11
Control	2.92	1.15	

Table 4 Comparison of the duration of diarrhea between the groups during the hospitalization period

Group	Mean	SD	*P* value
Probiotics	3.04	1.16	0.03
Control	3.52	1.01	

male and 25 female participants. There was no statistically significant difference between the two groups in terms of age and gender, and, thereby, the potential confounding effect of these two factors was deleted. Additionally, both groups were in similar situations in terms of fever at the time of hospitalization such that the average temperature at that time was 38.92 and 38.75 °C in the probiotic-treated group and in the control group, respectively. Duration of diarrhea prior to admission was 2.48 and 2.64 in the probiotic-treated group and in the control group, respectively. There was no significant difference between the groups in terms of the duration of fever, and, thereby, probiotics did not stop fever. Considering the presence of the significant difference in the duration of blood in diarrhea between probiotic consumers (2.62 days) and the control group (3.16 days) at the significance level of 0.01 ($P < 0.05$), and the consumption of probiotics can be considered effective in reducing the duration of dysentery. In a study, the effect of probiotic *Bifidobacterium* was examined on the treatment of patients with acute dysentery. In this research, patients in the intervention group received probiotics in addition to standard treatment during the first 2 days of disease resulting in the reduction of toxicity, pain, and dysentery in comparison with the control group [35]. This issue is directly related to reducing the duration of diarrhea in the present study.

In another study, 245 children with intestinal infection were studied and the effect of *Bifidobacterium*, probiotics, was investigated on *Escherichia coli*. In this study, hemolytic *E. coli* was isolated from 47.3%, enteropathogenic *E. coli* from 12.2%, *Shigella* from 18.3%, and *Salmonella* from 1.8% of the patients. *Bifidobacterium* had a good therapeutic effect on enteropathogenic *E.coli*, including hemolytic forms [36]. Moreover, Vandenplas and colleagues by using of probiotics significantly reduced the duration of diarrhea in acute infectious gastroenteritis [37]. In the current study, the consumption of probiotics was also effective in shortening the duration of dysentery.

During a study on children with acute diarrhea, the intervention group received probiotic plus ORS and control group only ORS, but the use of probiotic (*Lactobacillus*) had no significant effect in reducing the frequency and duration of diarrhea and vomiting as well as shortening duration of hospitalization [25]. Even so, the consumption of probiotic in the current study reduced the duration of hospitalization due to dysentery.

In another research, 75 children aged 5–50 months with rotavirus gastroenteritis were tested in three equal groups. In the first group, the patients were treated with fungal probiotic (*Saccharomyces boulardii*), the second group was administered with bacterial probiotic (*Bifidobacterium lactis*), and the third group received regimen with no probiotic. The duration of diarrhea was 6.6 days in the first group, 4.1 days in the second group, and 7 days in the third group. The use of probiotics has been significantly effective in decreasing diarrhea duration. The effect of *B. lactis* as a bacterial probiotic was higher than the fungal probiotic [38].

In a study of Francavilla to evaluate the effect of *Lactobacillus reuteri* versus placebo in children aged 6–36 months with acute diarrhea, 35 children received probiotic (*L. reuteri*) and 34 patients placebo.The diarrhea duration was 2.1 days in the probiotic group while in the control group was 3.3 days. In probiotic group, on the second and third days of treatment, 55 and 45% of patients had still diarrhea, respectively, while this statistic was respectively 82 and 74% in the control group; these differences were statistically significant. But duration of hospitalization was not significantly different [26]. Conversely, in the present study, duration of hospitalization was significantly different between the two groups.

According to updated guidelines on the treatment of children with acute gastroenteritis in Europe, administration of certain probiotics such as *Lactobacillus* or *S. boulardii* can reduce the duration and severity of diarrhea [39]. The results of an in vitro investigation of *L. casei* on antibiotic-resistant *Shigella* showed that the probiotic strongly inhibited the growth of *Shigella* [40].

Table 3 Comparison of the bleeding duration of dysentery between the groups during the hospitalization period

Group	Mean	SD	*P* value*
Probiotics	2.62	1.17	0.01
Control	3.16	1.05	

*Statistical significance was attained when *P* value <0.05

Table 5 Comparison of the duration of hospitalization between the groups

Group	Mean	SD	*P* value
Probiotics	3.16	1.18	0.02
Control	3.66	0.91	

Due to the significant differences ($P = 0.0$) observed in the diarrhea duration in probiotic consumers (3.04) compared to the control group (3.52), probiotic taking can be effective in reducing the duration of diarrhea. In addition, considering the significant differences ($P = 0.02$) found in the duration of hospitalization in probiotic consumers (3.16) compared to the control group (3.66), and probiotic taking can be effective in reducing the duration of hospitalization.

Conclusion

Although the significant difference observed in the duration of dysentery between the probiotic consumers (2.62 days) and the control group (3.16 days) at the significance level of 0.01 ($P < 0.05$), however, more research clinical trial studies with large sample sizes in other regions are recommended, and if the results of the present research was confirmed, probiotics could be proposed for including in the treatment protocol of dysentery.

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Compliance with Ethical Standards

Ethical Responsibilities of Authors This paper is our original unpublished work and it has not been submitted to any other journal for reviews.

Conflict of Interest The authors declare that they have no competing interests.

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