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Probiotic or Conventional Yogurt for Treating Antibiotic-associated Diarrhea: A Clinical Trial Study

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Abstract

Background
The popularity of probiotics is on the rise. Despite the beneficial effects of antibiotics, gastrointestinal health is at risk of diarrhea. This study aimed to investigate whether probiotic yogurt is of capability to prevent the incidence of diarrhea versus conventional yogurt.

Materials and Methods
This controlled, randomized, double-blind trial was designed to recruit 48 hospitalized children, whose treatments included different types of antibiotics. They were subsequently assigned into a 1:1 ratio into groups A and B at random. The first group was instructed to consume probiotic yogurt (*Bifidobacterium* strains and *Lactobacillus acidophilus*), while the second were on conventional yogurt (placebo containing *Streptococcus thermophiles* and *Lactobacillus bulgaricus*) at least for 7 days. The incidence of diarrhea, its onset and duration were compared between the two groups.

Results
The findings indicated that there was no statistically significant difference between the experimental and control groups ($p > 0.05$). No significant decrease was observed in the incidence of diarrhea between the groups following adjustment for negative C-reactive protein (CRP) ($p > 0.05$).

Conclusion
According to the results, the consumption of yogurt, either probiotic or conventional, reduced the incidence, duration, and onset of antibiotic-associated diarrhea in pediatric population. This study showed no significantly better performance for probiotic yogurt than conventional yogurt.

Key Words: Diarrhea, Pediatrics, Probiotics, Yogurt consumption.

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1- INTRODUCTION

Diarrhea consequent to the use of antibiotics constitutes one of the main causes of morbidity and mortality across the globe (1, 2). This complication occurs when patients apply broad-spectrum antibiotics, particularly the beta-lactams, clindamycin, and vancomycin, which exert changes in normal bowel flora, growth of some undesirable strains (*Staphylococcus*, *Candida*, *Enterobacteriaceae*, *Klebsiella*, and *Clostridium*), or intestinal mucosa and motility (3, 4). Therefore, these events are more likely to induce poor compliance with antibiotic therapy (5, 6). The occurrence of antibiotic-related diarrhea is contingent not only on the definition of diarrhea, but also on patient's age category. Antibiotic-related diarrhea is reported to affect up to 30% of children on oral antibiotics (7-10).

On the other hand, probiotics refer to live microorganisms that their adequate numbers are beneficial to the host health (11-13). There have been some evidence supporting the safety and effectiveness of probiotics in the management of diarrhea (13-18). The probable mechanisms behind such effects arise from direct antimicrobial actions, enhanced function of mucosal barrier, and immunomodulation of the innate and adaptive immunity system (14, 19, 20). Moreover, probiotics may cause receptor competition, nutrient limitation, prevention of adherence of pathogens to epithelia, or lower colonic pH to increase growth of nonpathogenic strains and reduce gut microbiota disturbance (21, 22).

A range of probiotic species have been utilized, such as *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Enterococci*, *Streptococci*, and *Escherichia coli* (23). These probiotics can be applied in the form of capsules, tablets, and yogurts (24). In the pediatric context, most studies have used probiotic tablets and powders against antibiotic-associated diarrhea. Given that yogurt is attractive to children, recent attempts have employed it as a vehicle to deliver targeted probiotics along with other vitamins, minerals, and proteins (15, 25-27). A recent systematic review and meta-analysis has shown that there is a lack of consistency among the studies involving the consumption of yogurt, thus, further randomized clinical trials are warranted (28). In the light of such evidence, we aimed at comparing the influence of probiotic yogurt on the prevention of diarrhea versus conventional one.

2- MATERIALS AND METHODS

2-1. Study design and population

This controlled, randomized, double-blind, clinical trial was carried out in Department of Pediatrics, Ghaem Hospital, one of the large governmental, educational, clinical hospitals in Mashhad, Iran. It contained a sample of convenience involving 48 children who were hospitalized in this department. For a two-tailed analysis, this study had $\alpha = 0.05$ and $\beta = 80.0\%$ to detect an effect size of 0.165 (29, 30).

2-2. Laboratory measurements

Data, including demographic characteristics and biochemical analyses, were collected in two phases. Initially, demographic variables were collected at baseline: age, gender, disease type, antibiotic therapy, hospital stay, type of feed, and other medicinal treatments. With respect to antibiotics, its type before and after discharge, as well as treatment duration were taken into account. Type of feed refers to common diet, breast feeding along with supplementary foods, and nasogastric tube feeding. Blood parameters, such as white blood cell (WBC), hemoglobin, and mean cell volume (MCV) were measured applying an automated hematology analyzer K-21 (Sysmex Corporation, Japan). Serum levels of C-reactive protein (CRP) were analyzed with Pars Azmoon kit (Pars Azmoon Co., Iran). Serum potassium was evaluated by flame photometry.

2-3. Intervention

Eligible patients were randomly assigned into groups A and B. The former was instructed to use probiotic yogurt while group B as the control received conventional yogurt. They were asked to adhere to the specified amount (100 ml) of yogurt consumption, and inform the observer in charge in case of diarrhea. Probiotic yogurt was purchased from local suppliers, namely Razavi, Pegah, and Kaleh (Made in Mashhad, Iran). These commercial products consisted of *Streptococcus thermophiles*, *Lactobacillus bulgaricus* (as starter bacteria in conventional yogurt), *Bifidobacterium* strains, and *Lactobacillus acidophilus* (as probiotic bacteria in probiotic yogurt). Each gram of yogurt contained 10^6 colony forming units (CFUs) of probiotics.

Despite the intervention of yogurt intake, all patients maintained their common diet. The intervention commenced up to 24 hours following the administration of antibiotics. Each child was initially monitored in terms of yogurt intake, compliance with the yogurt, bowel movement frequency, and stool consistency in daily visits. Upon the incidence of diarrhea, screening tests were conducted to detect infectious diarrhea based on fecal mucus and fecal leukocytes, as well as *Clostridium difficile* infection by means of its toxins. Having confidence in non-infectious causes, the treatment (i.e., oral rehydration solution [ORS], the water, electrolytes), and the intervention (i.e., probiotic, conventional yogurt) were continued as prescribed.

The participants were on their treatments up until the time that antibiotics were administered for at least seven days. Early discharge patients followed the intervention at home. The study also included telephone calls for two weeks to all patients after discharge from the hospital.

2-4. Ethical consideration

This study was approved by the Human Research Ethics Committee affiliated to Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.fm.REC.1395.232).

The intervention constituted the only change in the consumption of yogurt or probiotic yogurt that would not interfere with the patient's treatment. Additionally, data analysis was performed in a non-identifiable patient fashion, and accessed by authorized persons only at the department. The patient's parents were asked to sign a written informed consent form. This trial is registered with the Iranian Registry for Clinical Trials (www.irct.ir, registration number: IRCT201011070051 23NZ).

2-5. Inclusion and exclusion criteria

Hospitalized pediatric patients aged 1-13 years prescribed oral antibiotics were included in 2015. The following factors would exclude the participants: severe respiratory infections (pneumonia), frequent seizures, nil per os (npo or NPO) status, gastroenteritis, evidence of infectious diarrhea associated with fever, vomiting, bloody diarrhea, and positive stool culture for a bacterial pathogen.

2-6. Data analysis

Main outcome measures were diarrhea incidence, duration and onset. Data related to demographics (gender, age), blood parameters, antibiotic type, and its duration were also documented. Data collection, statistical analysis, and clinical visits were performed by the researchers and physicians blinded to group allocation. All data were fed into SPSS version 13.0 (BMI, USA) and analyzed at significant level less than 0.05. Test of normality was carried out applying the Kolmogorov–Smirnov test. Categorical variables were compared by means of chi-square test. Independent sample t-test or its non-parametric equivalent (Mann-Whitney U test) was utilized to compare continuous variables. Logistic regression was performed to explore the potential interaction of negative CRP with effective therapy.

3- RESULTS

This study recruited a total of 48 patients admitted to Ghaem Hospital in 2014. These participants were equally allocated into groups A (n = 24; 58% males, 42% females) and B (n = 24; 54% males, 46% females). The mean ages of the study population were 4.3 ± 3.5 (group A) and 5.9 ± 4.4 (group B) years. Both groups were comparable for different characteristics showed in Table 1 except for C-reactive protein (CRP) ($p > 0.05$). Notably, negative CRP occurred lesser in the experimental group (A) than in the controls (B) ($p = 0.010$).

It was found that only five cases of diarrhea was reported during the study (**Table.2**). The mean time to onset diarrhea was 3.5 ± 2.1 days in group A and 4.0 ± 2.6 days in group B, which demonstrated no significant difference between the two ($p = 0.767$). Diarrhea took place in two cases from group A on days 2 and 5. When it comes to group B, three cases developed diarrhea on days 2, 3, and 7. As can be seen in Table 2, the mean diarrhea duration was 2.0 ± 0.0 and 3.3 ± 0.57 days in groups A and B, respectively. In this regard, no remarked disparity was observed between the two ($p = 0.068$). Considering negative CRP as the only baseline variable that was significantly different between the two groups, it was indicated that of 43 patients who did not experience diarrhea, 81.7% (n = 27) showed negative CRP, while four (12.9%) of the patients with diarrhea (n = 5) had negative CRP.

The results of logistic regression indicated that no statistically significant difference was determined in the incidence of diarrhea ($\beta = -0.128$, $p = 0.877$) between the groups after adjusting for the baseline frequency of negative CRP. Therefore, the baseline measures of negative CRP had no remarkable effect on the patients' response to the intervention. Moreover, the odds of developing diarrhea was 88% in group A versus the controls, suggesting that negative CRP presented a protective role for the incidence of diarrhea. Also, it was observed that the incidence of diarrhea in this study was not associated with reasons for antibiotic use ($p = 0.579$).

Table-1: The characteristics of the study patients in groups A and B

Variables	Study groups		P-value
	Group A (n = 24)	Group B (n = 24)	
Mean age (SD), year	4.3 (3.5)	5.9 (4.4)	0.149
Males, number (%)	14 (58)	13 (54)	0.149
Disease types, number (%)			0.341
Pneumonia	4 (16.7)	7 (29.2)	
Meningitis	5 (20.8)	7 (29.2)	
Others	15 (62.5)	10 (41.7)	
Antibiotic type before discharge, number (%)			0.732
Ceftriaxone	11 (45.8)	7 (29.2)	
Ceftriaxone-Vancomycin	8 (33.3)	10 (41.7)	
Ceftriaxone-Azithromycin	2 (8.3)	4 (16.7)	
Others	3 (12.5)	3 (12.5)	
Antibiotic type after discharge, number (%)			0.553

Cephalexin	1 (4.2)	0 (0)	
Coamoxyclav	2 (8.3)	2 (8.3)	
Cefixime	1 (4.2)	0 (0)	
None	20 (83.3)	22 (91.7)	
Mean hospital stay (SD), day	8.5 (3.9)	8.9 (4.1)	0.748
Mean duration of antibiotic therapy (SD), day	6.3 (2.9)	6.5 (3.1)	0.814
Mean number of WBCs (SD), /mL	12.6 (5.9)	13.8 (6.0)	0.514
Mean serum hemoglobin (SD), g/dL	11.1 (1.6)	11.8 (1.2)	0.128
Mean serum potassium (SD), mEq/L	4.4 (0.6)	4.2 (0.6)	0.276
MCV (SD), fL	78.6 (6.8)	80.6 (5.1)	0.277
Negative CRP, number (%)	10 (41.7)	21 (87.5)	0.010
Types of feed, number (%)			0.760
Common diet	15 (62.5)	16 (66.7)	
Breast feeding + Supplementary foods	9 (37.5)	7 (29.1)	
Nasogastric tube feeding	0 (0)	1 (4.2)	
Other medicinal treatments, number (%)			0.622
Corticosteroids	10 (41.7)	13 (54.2)	
Albendazole, acyclovir, omeprazole, fenitoin	4 (16.7)	2 (8.3)	
None	10 (41.7)	9 (37.5)	

SD: Standard deviation, CRP: C-reactive protein; WBC: white blood cell; MCV: Mean corpuscular volume.

Table-2: The comparisons of diarrhea-related variables

Variables	Study groups		P-value
	Group A (n = 24)	Group B (n = 24)	
Incidence of antibiotic-associated diarrhea, n (%)	2 (8.3)	3 (12.5)	0.990
Mean time to onset diarrhea (SD), day	3.5 (2.1)	4 (2.6)	0.767
Mean diarrhea duration (SD), day	2.0 (0)	3.3 (0.57)	0.068

SD: Standard deviation.

4- DISCUSSION

This randomized clinical trial was intended to compare the incidence of diarrhea, its duration, and onset in the pediatric patients undergoing antibiotics after the consumption of probiotic yogurt as opposed to conventional yogurt. The results of the present trial demonstrated that the consumption of probiotic yogurt and conventional yogurt decreased the incidence of diarrhea to the same extent. Also, they were found to reduce the mean onset and duration of diarrhea. The protective effect of probiotics and yogurt against diarrhea was confirmed by previous randomized controlled trials (5, 26, 31-34). Intriguingly, Patro-Golab et al. by a systematic review confirmed that yogurt by itself can prevent diarrhea (28). This to some extent can justify the insignificant improvement in the experimental group as compared to the controls since both groups consumed yogurt (probiotic versus conventional). Of note, the conventional yogurt used in this study contained live bacteria (S. thermophiles, L. bulgaricus) which may appear beneficial, as well (35, 36). In contrast with our findings, Fox et al. showed that probiotic yogurt with L. rhamnosus GG (mean dose 5.2×109 CFU/day), L. acidophilus (mean dose 5.9×109 CFU/day), and B. lactis (mean dose 8.3×109 CFU/day) was significantly effective than conventional yogurt containing S. thermophiles (mean dose 4.4×104 CFU/day), and L. bulgaricus (mean dose 1.2×103 CFU/day) (18). There was another report showing a significantly marked amelioration of diarrhea in patients consuming probiotic yogurt (*S. thermophiles*, *L. bulgaricus*, *Bifid bacterium*, *Lactobacillus* with 10^9 CFU/dose) versus traditional yogurt (37). It was reported that the decrease in the duration of diarrhea relied on the dose of probiotics (38). *Lactobacillus* GG at the concentration of 3×10^9 CFU/g diminished the diarrhea (39). In our study, *Bifidobacterium* strains and *L. acidophilus* in probiotic yogurt and starters in conventional yogurt were used at 10^6 CFU/g. The probiotic concentrations were considerably lower, while on the contrary starters were used at higher concentrations than those reported by Fox et al. (18) and Heydarian et al. (37).

This can explain the insignificant results in our clinical trial. Concerning the comparisons between probiotic and conventional yogurt, there have been some evidence presenting that the presence of probiotics in yogurt does not lead to greater benefits. For example, Meyer et al. documented similar effects of probiotic and conventional yogurt on the stimulation of cellular immune functions (40). Likewise, Fabian et al. showed that both probiotic and conventional yogurt can result in the improved uptake of vitamin B_1 and B_2 (41). Of all baseline parameters evaluated in this study, only negative CRP contributed to diarrhea; put differently, negative CRP may affect the results of comparisons between the study groups. Therefore, logistic regression was used that no significant decrease occurred in the incidence of diarrhea between the groups following adjustment for negative CRP.

As for the limitation, this study cannot apply a strict diet due to the age range of the target population; that is, the only intervention occurred in the intake of yogurt, either probiotic or conventional. Thus, they were allowed to take their common diet as per usual. Besides, the small sample size of this study limit generalizability of these findings.

5- CONCLUSION

In conclusion, this controlled, randomized trial unraveled that there was an interventional association between the consumption of yogurt and the decreased incidence of diarrhea in hospitalized children under treatment with antibiotics. These positive effects were also found for diarrhea duration and onset. However, such associations depend on the presence of live bacteria in placebo, and concentration of probiotics and starters in yogurt.

6- CONFLICT OF INTEREST: None.

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