Original Article

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Probiotics for the Treatment of Pediatric *Helicobacter Pylori* Infection: A Randomized Double Blind Clinical Trial

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Abstract

Objective: *Helicobacter pylori* is recognized as a major etiological factor in the pathogenesis of gastritis and peptic ulcer disease. *H. Pylori* eradication has a failure rate of more than 30% in pediatric patients, particularly because of poor compliance, antibiotic resistance and occurrence of side-effects. This study was aimed to determine whether adding the probiotics to a standard anti-*H. pylori* regimen could minimize the gastrointestinal side-effect prevalence and improve the eradication rate.

Methods: Double-blind randomized placebo controlled study conducted at Children's Medical Center in Tehran, Iran. Sixty six *H. pylori* positive children were treated with a triple drug treatment protocol (omeprazole+amoxycillin+furazolidon) and randomly allocated to receive either probiotic or placebo. All patients underwent esophagogastroduodendoscopy. *H. pylori* infection was diagnosed by either rapid urease test (RUT) or histology. *H. pylori* status was assessed after 4-8 weeks of the completion of treatment with stool *H. pylori* antigen test. The side effects of the treatment were determined in each group.

Findings: Mean age of patients was 9.09 (range 3-14) years, 44 (65.7%) patients were boys (sex ratio 2:1). All 66 patients completed the course of treatment and follow-up. The rate of *H. pylori* eradication was significantly higher in probiotic group (P=0.04). In probiotic supplemented children there was a lower rate of nausea/vomiting (P=0.02) and diarrhea (P=0.039) during treatment.

Conclusion: This study showed that probiotics have positive effect on the eradication of *H. pylori* infection. Adjuvant therapy with probiotic is recommended in order to reduce the frequency of antibiotic induced side-effects during treatment with antibiotics.

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Key Words: Children; Probiotic; Endoscopy; *Helicobacter Pylori*; Eradication

Introduction

H. pylori is a pathogenic Gram-negative spiral bacillus that survives in the acid environment of the stomach. It is a leading cause of chronic gastritis, peptic ulcers, non-ulcer dyspepsia, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. It is estimated that up to 50% of the total world population are infected with *H. pylori*. The prevalence of *H. Pylori* infection is currently rising in the developing world[1-4]. One-week triple therapy (two antibiotics for a week and a Proton Pomp Inhibitors (PPI) for 4-8 weeks) represents the current most widely prescribed first-line regimen for *H. pylori* infection. With current therapeutic regimens, there is a significant failure rate for the eradication of microorganism. The treatment

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failure rate is known to be much more common in children than in adult patients (more than 30%)[5-11]. Numerous factors are associated with the high prevalence of treatment failure; the most common are poor compliance and antimicrobial resistance due to overuse or misuse of common antibiotics. Frequent occurrence of side effects of antibiotic drugs can lead to the reduced compliance of patients with therapeutic regimens[12,13].

Adjuvant therapy with probiotics has been studied in recent years. Probiotics are living or attenuated nonpathogenic microorganisms that have a large variety of potential beneficial effects on the health condition. They have the ability to bind to epithelial cells, survive for a long time in the digestive tract, regulate the immune system and influence metabolic reactions.

The most commonly used probiotics that may increase the resistance of gastric barrier and as a result inhibit the growth of *H. pylori* and its adherence to gastric epithelium are lactobacilli and bifidobacteria species[3,14-17].

Considering the rarity of a comprehensive survey on the potential role of adjunctive therapy with probiotics for the treatment of childhood *H. pylori* infection in our country, we aimed, in this study, to assess the effect of probiotic supplementation as a combination of seven species on the childhood *H. Pylori* infection. In most previous trials only a few species of probiotics are used.

Subjects and Methods

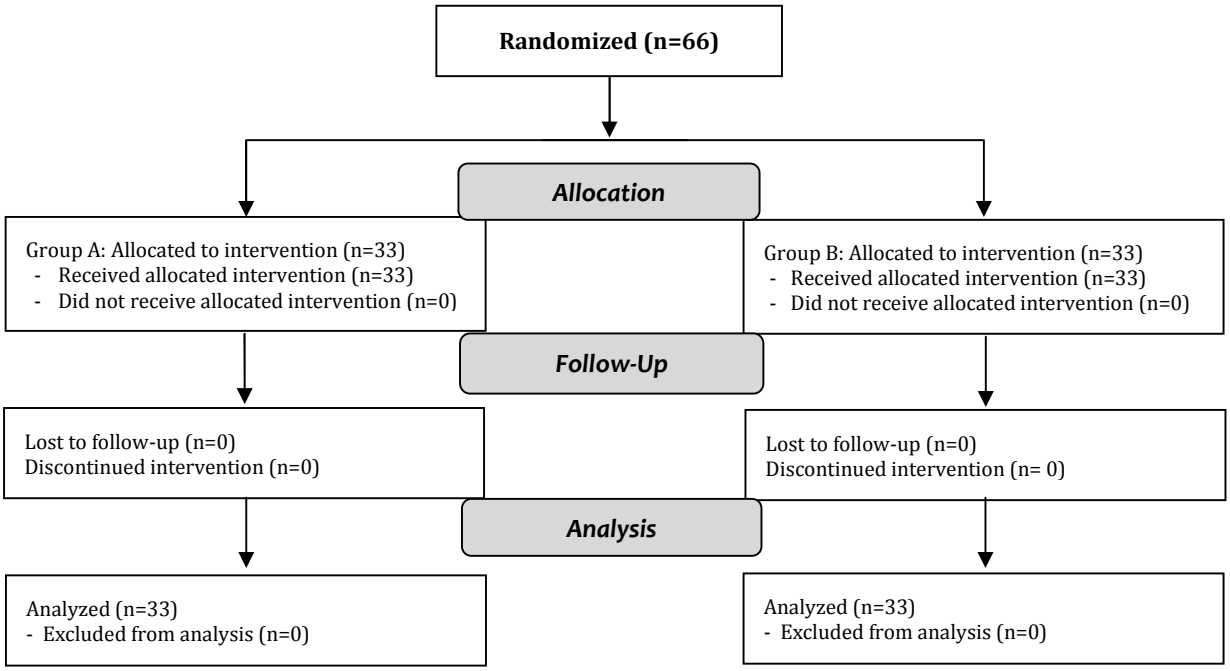
The study was performed at Children's Medical Center in Tehran, Iran, from November 2011 to April 2012. In a randomized double blind clinical trial, sixty six children aged 3-14 years with *H. Pylori* infection enrolled in this study. The patients were referred to gastroenterology clinic for the evaluation of symptoms and signs including chronic abdominal pain, gastrointestinal bleeding, unexplained frequent vomiting and unexplained iron deficiency anemia.

Inclusion criterion was the presence of *H. pylori* infection. Exclusion criteria were as follows: 1) consumption of PPIs, H2 receptor antagonists, bismuth compounds and antibiotics in the previous 2 weeks, 2) previous gastric surgery, 3) known allergy to certain antibiotics, 4)glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency (furazolidone may cause hemolysis and anemia in these deficient patients), and 5) known previous history of renal failure and endocrine, cardiac, or hepatic disease.

Ethics: The research protocol was approved by the medical ethic committee of Tehran University of Medical Sciences and allocated an ethical code. Registration ID of this study in Iranian Registry of Clinical Trials was IRCT201201218793N1. Informed consent was obtained from parents of all patients.

All patients were included for esophagogastro-duodenoscopy. *H. pylori* infection was established by at least one of these criteria: A positive rapid urease test (RUT) or histopathological examination. Upper gastrointestinal endoscopy was carried out after midazolam sedation (0.1 mg/kg). Two pieces of gastric antral biopsy specimens were taken for histology and RUT. Patients were randomly assigned following simple randomization procedures to one of two treatment groups (A: antibiotic+PPI+placebo, B: antibiotic+PPI+probiotic). Label of drugs was replaced by a new one indicating drug A or B. Contents of sachets were not known to the physician, research fellow, and nurses involved in recording data. All *H. pylori* positive children in group A were treated with a one-week course of amoxicillin (50 mg/kg/day bid as syrup or capsule) and furazolidone (6 mg/kg/day bid as syrup or tablet), four weeks of omeprazole (1mg/kg/day) plus placebo. Group B received the same antibiotics and PPI plus probiotic preparation 1 sachet/day (restore, 1×10^9 CFU/1 sachet, Protexin Co, UK). Probiotic combination consisted of strains of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Lactobacillus casei, Streptococcus thermophilus, Bifidobacterium infantis* and *Bifidobacterium breve* (Fig.1).

Study design: After endoscopic evaluation and randomization the treatment was started. During the course of treatment and at follow-up, patients were contacted by phone and were asked about the side effects of therapy on a weekly basis. The side effects included diarrhea, nausea/vomiting and abdominal bloating. They had a visit as an



Flow diagram of randomization, allocation, follow-up and analysis

outpatient at the middle of therapeutic course. All patients were reinvestigated four to eight weeks after accomplished treatment by stool antigen test for *H. pylori*. Successful treatment was defined as a negative stool antigen test for *H. pylori*.

Outcome parameters: Primary outcome measure was the rate of eradication of *H. pylori* defined as a negative stool antigen test. Secondary outcomes were the rate of side effects during the treatment reported by the patients or parents.

Statistical analysis: The SPSS software version 18 (SPSS Inc., Chicago, IL, USA) was used to appraise the statistical analysis; statistical analytical tests Chi-square or Fisher's exact test and Logistic Regression were used for analyzing data. A *P*-value of less than 0.05 was considered significant.

Findings

A total of 66 children with *H. pylori* infection were recruited in the study and randomized into two groups. All 66 patients completed the treatment protocol combined of amoxicillin, furazolidone and omeprazole plus placebo in group A and probiotic in group B. No patient discontinued the treatment and there were no losses to follow-up.

The patient group consisted of 44 (65.7%) males, the male to female ratio was 2:1. Their mean age was 9.09±3.12 years (range 3 to 14 years). Both groups demonstrated improvement in clinical symptoms after treatment. The group treated with the combination of probiotic and standard therapeutic regimen showed more significant eradication rate (Odds Ratio 4.37, Confidence interval: 1.07–17.62, *P*=0.04)(Table 1).

We found that children receiving probiotic suffered less frequently diarrhea and nausea/ vomiting during eradicating treatment; these discrepancies were statistically significant. The difference in the prevalence of abdominal bloating was not significant between the two groups (Table 2). In a subgroup of patients who developed side effects, the symptoms were not severe enough to

Table 1: Comparison of the proportion of patients in two groups with successful eradication

Stool Antigen	Probiotic+Antibiotic	Placebo+Antibiotic	*P.* Value
Negative (eradicated)	30 (90.09%)	23 (69.69%)	0.04
Positive (not eradicated)	3 (9.09%)	10 (30.30%)	

Table 2: Comparison of the adverse effects during treatment in two enrolled groups

Side effect	Probiotic+Antibiotic	Placebo+Antibiotic	*P.* value
Nausea/vomitting (%)	2 (6.06%)	9 (27.27%)	0.02
Diarrhea (%)	2 (6.06%)	8 (24.24%)	0.04
Abdominal bloating (%)	3 (9.09%)	4 (12.12%)	1

stop the treatment.

Table 3 represents the clinical characteristics and endoscopic findings of the studied patients. These percentages are calculated for all enrolled children before randomization and allocation.

Discussion

In this randomized, placebo-controlled double blind study, children on *H. pylori* eradication therapy receiving seven strains of probiotic in addition to the standard triple regimen where compared with patients on the same triple regimen receiving placebo. The findings reported a significant reduction of the treatment complication and improved therapeutic outcome.

New investigations have provided evidence suggesting that probiotics modulate *H. pylori* colonization of the gastric epithelial cells. It is increasingly known that alterations in the intestinal microflora have an important role for the development of complication and patient's intolerance during anti-*H. pylori* treatment. Probiotic supplementation could reduce the nondesirable complications of antibiotics and as a result, maximize the success of therapy[18,19].

Many studies have documented the effectiveness of prophylactic probiotics in association with antibiotics in the modification of *H. pylori* eradication rate and the antibiotic-associated gastrointestinal side-effects during eradication therapy[5,20-24]. Certain probiotics such as Lactobacillus strains are known to interfere with the activity of *H. pylori* by inhibiting its adherence to gastric epithelium and inactivating its main virulence factor, urease enzyme[25,26].

Park SK et al concluded that combining first line anti *H. pylori* therapy with probiotic species, composed of *Bacillus subtilis* and *Streptococcus faecium* reduced side effects, improved patient's tolerance and enhanced the eradication rate of *H. pylori*[27]. Similar results were reported by Bekar O et al from Turkey, who investigated the effect of combining standard triple anti *H. pylori* therapy with kefir, a fermented milk derived product containing probiotics[28]. The results of these two studies confirm our findings. In another study, supplementation of Lactobacillus and Bifidobacterium strains resulted in the modification of stool microflora and enhanced *H. pylori* clearance[29].

In a randomized trial by Hurduc et al, it was concluded that supplementation of *Saccharomyces boulardi* to the standard triple drug regimen resulted in a 12% nonsignificant increased therapeutic effect on *H. pylori* but reduction in the incidence of side effects was significant[30]. The significance of difference in the rate of adverse effects between two groups and higher eradication rate in our survey was in accordance with this study although the latter was statistically significant in our patients.

It is reported that *Bifidobacterium bifidum* could significantly reduce the rate of gastrointestinal complaints in *H. pylori* positive patients and modify the activity of organism in the gastric mucusa[31].

To our knowledge, there is only one relevant study in Iranian children with a small sample size

Table 3: Clinical characteristics and endoscopic findings of patients enrolled in the study

Complaints	Number/percent	Endoscopic Finding	Number/percent
Abdominal pain (%)	43 (65.15%)	Antral nodularity	57 (86.36%)
Gastrointestinal bleeding (%)	14 (21.21%)	Gastric erythema	16 (24.24%)
Vomiting (%)	15 (22.72%)	Duodenal ulcer	14 (21.21%)
Iron deficiency anemia (%)	4 (6.06%)	Gastric ulcer	1 (1.51%)

reporting that supplementation with probiotics, could improve drug compliance and reduce side effects without a change in the eradication rate of *H. pylori*[32]. The profile of adverse effects were similar to our results but this was not true for the eradication rate.

A number of studies have shown no significant discrepancies in the success of *H. pylori* eradication treatment between the groups receiving probiotics and the peers on placebo[5,33]. The wide variety and controversial results in previous studies may be attributed to the differences in study design, patient groups, different therapeutic regimens, probiotic dose, and probiotic species.

In our study the rate of H. pylori eradication was significantly higher in patients who received probiotics. In probiotic supplemented children there was a meaningfully lower rate of nausea/vomiting and diarrhea during treatment.

Conclusion

According to the findings of this clinical trial, probiotic supplementation during the treatment for *H. pylori* eradication, may positively affect antibiotic-related symptoms and treatment success. Further large, randomized, double-blind, placebo-controlled clinical trials must be conducted with minimal variability in study designs, to appropriately evaluate the efficacy of specific probiotic strains in comparison to placebo.

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This study was approved by Research Committee of Tehran University of Medical Sciences. Registration ID of this study in Iranian Registry of Clinical Trials was IRCT201201218793N1.

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Conflict of Interest: None

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