

# No Significant Impact of *Lactobacillus reuteri* on Eradication of *Helicobacter pylori* in Children (Double-Blind Randomized Clinical Trial)

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## Abstract

**Background:** *Lactobacillus reuteri* is a probiotic that originated from humans and have been used for eradication of the *Helicobacter pylori* (HP) infection.

**Objectives:** This study was aimed to determine whether adding probiotics to a triple regimen against HP could improve the eradication rate.

**Methods:** In a double-blind randomized clinical trial in Iran between October 2012 and January 2014, all eligible patients (Fifty HP positive children, 5 - 14 years old, mean age: 8.5 + 2.5 years, Male/female: 17/33) were entered into the study based on the convenience sampling method and random selection. An endoscopy was performed on all patients and the subjects received antibiotics as well as proton pump inhibitors with or without the probiotic (*Lactobacillus reuteri*) in two separate groups. Four weeks after the end of treatment (discontinuation of all medicine) a urea breath test was performed in both groups in order to evaluate eradication of the HP infection.

**Results:** Eradication rate in the group that received *Lactobacillus reuteri* was 88% compared to the group that was treated with standard *Helicobacter pylori* regimen (76%). This study showed the eradication rate of the probiotics group was 12% higher than the control group, although it was not significant ( $P = 0.46$ ). Furthermore, results of this study showed a reduction of symptoms before and after treatment in both groups, although the difference between two groups was not significant.

**Conclusions:** There was no significant effect of *Lactobacillus reuteri* on the eradication of *Helicobacter pylori* compared to the standard group. More research in this regard is recommended.

**Keywords:** Children, *Lactobacillus reuteri*, *Helicobacter pylori*

## 1. Introduction

*Helicobacter pylori* (HP) is recognized as a cause of gastritis and usually develops during early childhood. In spite of the decreasing prevalence of *H. pylori* in some European countries, the infection is still a challengeable issue in some parts of the world, especially in Asia (1). Prevalence of *H. pylori* is different amongst developing and developed countries (80% - 90% vs. 30% - 50%), respectively (2). Numerous strategies for HP treatment have been recommended. Triple therapy, consisting use of a PPI in combination with clarithromycin, and amoxicillin or metronidazole for two weeks is one of the well-tolerated and acceptable regimen in children (3). Unsatisfactory reports of eradication rates of *H. pylori* (failure as much as 30%) as well as therapy-associated adverse events are some of limitations, which provoke enthusiasm for alternative thera-

pies such as probiotics (4, 5).

Probiotics are live microbial ingredients that can inhibit the growth of *H. pylori*. Researches done in children have shown that probiotic could be effective in prevention of side effects of antibiotics as well as lowering their complications. This effect is related to the decreasing density of HP that inhibits adhesion of microorganism to gastric epithelial cells (6). Previous studies have shown that persistent *H. pylori* infection affects the distribution and density of flora in the gastrointestinal tract and decreases the density of *Lactobacillus* in the stomach (5). Moreover, administration of *Lactobacillus reuteri* could help prevent infection at early stages of colonization and is associated with significant alterations of the immune response in the gastrointestinal mucosa (7, 8). Furthermore, an inhibitory effect on *H. pylori* was demonstrated in several studies (9).

Other studies have used different probiotic strains as adjuvant therapy or alone in order to achieve better outcomes in *H. pylori* infected patients (10, 11). There are also some evidences that show that using probiotics may minimize side effects during treatment of *H. pylori* (12). Additionally, some researchers have shown supplementation with probiotic during treatment of *Helicobacter pylori* may be effective for improving eradication rates as well as lowering the incidence of therapy-related adverse events and clinical symptoms of patients (5).

There have been limited studies performed on Iranian children regarding supplementation with probiotics for eradication of the *H. pylori* infection. A study on 66 *H. pylori* positive children with triple therapy treatment alone or with different probiotics, showed probiotics were associated with a reduction of nausea, vomiting, and diarrhea in the treated groups (13). Another study on asymptomatic Iranian children with a positive *H. pylori* stool antigen showed that using probiotics has a positive effect on reducing the colonization of *H. pylori* although it was not capable of eradication of infection (14).

Regarding the lack of studies in Iranian children, the aim of the present study was to evaluate the effect of adding *Lactobacillus reuteri* to triple therapy for eradication of *H. pylori*. Additionally, the other purpose of the study was to compare the symptoms before and after the treatment in subjects with the *H. pylori* infection.

## 2. Methods

In a double blind clinical trial (2013 - 2015), 50 children (ages 5 or more) with positive *H. pylori* were referred to the Ali-ibn-Abitalib hospital at Zahedan, Iran and were enrolled in the study (male/female: 17/33, mean age  $8.5 \pm 2.5$  years, range 5 - 14 years). The hospital is a tertiary referral center with resources such as upper endoscopy and pediatric gastroenterology clinics, which accept many patients from the entire Sistan and Baluchistan province (the province is the largest in Iran, located in the south-east of Iran). They were candidates for esophago-gastro-duodenoscopy (EGD) for different reasons including uninvestigated dyspepsia, epigastric burning pain or fullness, nocturnal pain waking the child, heartburn, nausea, vomiting, bloating, halitosis, and decreased weight gain. The main investigator works as a pediatric gastroenterologist in this referral center in the province. All referred patients during 2013 - 2015 were examined. Due to time limitation (shortage of time), it was not possible to enroll more patients and continue the research for more than 2 years. Furthermore, children with the following conditions were excluded from the study: prior history of using *H. pylori* eradication regimen and probiotic in the previous month, his-

tory of gastrointestinal bleeding, and presence of chronic diseases.

From the 95 eligible patients, 21 subjects were excluded (Figure 1). From the 74 remaining cases, 55 subjects had proven *H. pylori* in pathology samples (5 subjects were excluded due to celiac disease, Figure 1).

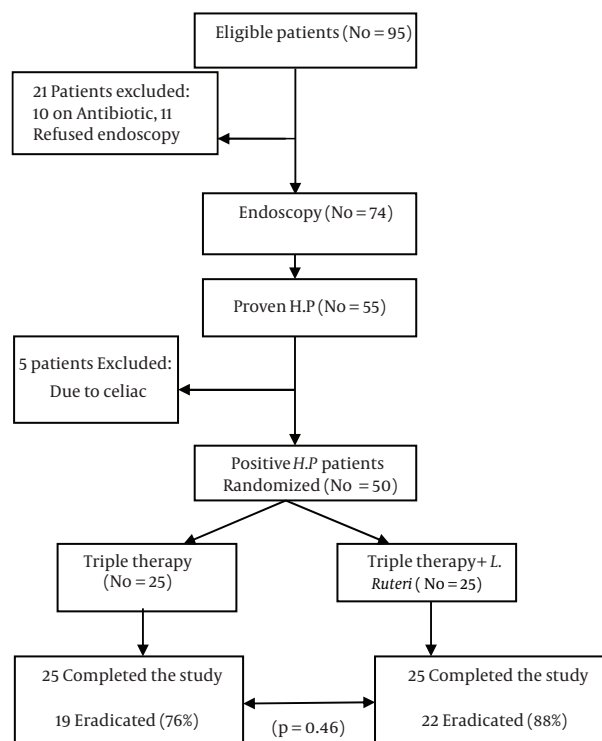


Figure 1. Collection and Follow Up of Patients in the Study

50 remaining *H. pylori*-positive subjects were randomized into two groups using the block permutation method. Patients in group 1 received triple therapy including omeprazole 1 mg/kg/day bid for 1 month + two antibiotics (amoxicillin 50 mg/kg/day, and clarithromycin 15 mg/kg/day bid) for 2 weeks+ one tablet of *Lactobacillus reuteri* for 4 weeks (tablet, BioGaia®, Farmasierra manufacturing, Spain, the active ingredient was 100 million live *Lactobacillus reuteri* protectis per tablet). Patients in group 2 were given triple therapy including (omeprazole 1 mg/kg/day bid for 1 month + two antibiotics (amoxicillin 50 mg/kg/day, and clarithromycin 15 mg/kg/day bid) for 2 weeks. Other investigators were blind to the treatment and a pharmacist gave the medication to patients without the investigators knowledge of who received the additional probiotic tablet. At baseline, for all patients, the same gastroenterologist using a pediatric fiberoptic endoscope (Pentax EG-2730, Japan) performed fecal antigen

of *H. pylori* (Acon, England manufactured) and EGD. After written informed consent, multiple biopsy samples from antrum and corpus were taken. Then, hematoxylin and eosin staining as well as Giemsa stain for detection of *H. pylori* was done. To access the *H. pylori* status, Urea breath test (UBT) was performed four weeks after the end of treatment (discontinuation of all medicine) and after an overnight fasting.

A questionnaire for evaluating the symptoms was completed before starting the treatment and 4 weeks after completion of the treatment; (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe) regarding abdominal pain, flatulence, halitosis, and vomiting. Patients and their parents were asked to grade each symptom before and after treatment according to severity: mild (little effect that can be ignored), moderate (effect sometimes interfered with daily activities), and severe (effect continuously interfered with daily activities).

The study protocol was approved by the ethics committee of children and adolescent health research center, Zahedan University of Medical Sciences, Zahedan, Iran. Registration ID of this clinical trial was IRCT2013071814048N1.

### 2.1. Statistical Analysis

All statistical analyses were performed using the SPSS (version 17). The results are presented as mean  $\pm$  standard deviation and proportion. The chi-square test, Mann-Whitney Test, and Wilcoxon signed Ranks Test were used for comparison in the groups. Two independent sample T tests were used for comparison of age, weight, and height between the two groups. Chi square test was performed for comparing family BP, smoking and UBT between the two groups. To compare the severity of symptoms before and after intervention in each group, Wilcoxon signed rank test was used. Mann-Whitney test compared the severity of symptoms between the two groups. P values  $<$  0.05 are considered statistically significant.

### 3. Results

Figure 1 shows the flow chart of the study, with the eligible and enrolled patients. Demographic and clinical characteristics of the study group have been shown in Table 1. All 50 patients completed the prescribed regimen with and without probiotic (group 1 and 2, respectively). There was no difference in both groups for age, sex, baseline characteristic such as clinical symptoms, physical examination, familial history of peptic ulcer disease, smoking habits in family, and fecal antigen of *H. pylori*. Furthermore, no difference was found in the endoscopy and histology results. *H. pylori* were observed in the antral specimen

of all patients with antral nodularity in most cases (54% of patients). Eradication rate in the group that received *Lactobacillus reuteri* was 88% compared to group that was treated with the standard *Helicobacter pylori* regimen (76%). In the other words, the eradication rate of the probiotics group was 12% higher than the control group, although it was not significant (P = 0.46).

**Table 1.** Baseline Demographic and Clinical Characteristics in Two Groups<sup>a</sup>

	Group 1 (No = 25)	Group 2 (No = 25)	P Value
<b>Gender</b>			0.27 <sup>b</sup>
Male	10 (40)	7 (28)	
Female	15 (60)	18 (72)	
<b>Age, y</b>	2.5 $\pm$ 8.5	2.5 $\pm$ 7.8	0.34 <sup>c</sup>
<b>Weight, kg</b>	6.42 $\pm$ 23.16	22.16 $\pm$ 8.47	0.64 <sup>c</sup>
<b>Height, cm</b>	125.6 $\pm$ 15.59	123.32 $\pm$ 20.9	0.66 <sup>c</sup>
<b>Family history BP</b>	8 (32)	14 (56)	0.07 <sup>b</sup>
<b>Family history smoking</b>	3 (12)	2 (8)	0.5 <sup>b</sup>

<sup>a</sup> Values are expressed as mean  $\pm$  SD or No. (%).

<sup>b</sup> Chi-square.

<sup>c</sup> Independent samples T-test.

A significant difference was observed between the two groups concerning the symptoms that they experienced. Patients in both groups showed improvements in each symptom compared to the entrance of the study, exception for flatulence in Group 2. However, comparison between two groups did not show any statistically reduction in symptoms. The results have been shown in Table 2.

### 4. Discussion

In spite of different therapeutic regimens currently available for the *H. pylori* treatment, failure in the eradication rate of the infection remains a big challenge for physicians in practice. Several factors might be responsible for less success in such trials including antibiotic resistance and poor patient's compliance as the most common causes (15). The results of our study showed the eradication rate of 88% and 76% in probiotic and standard group, respectively, which was not significant.

Probiotics are microorganisms that have been found to have multiple potential effects in both vitro and in vivo studies in management of *H. pylori* infection (4). Previous studies have suggested that the supplementation of standard anti-*H. pylori* regimens with probiotics may improve the eradication rate of the organism as well as a reduction of side effects (15, 16)). *Lactobacillus reuteri*, through

**Table 2.** Comparison of Symptoms in the Two Groups Before and After Treatment

Symptoms		None		Mild		Moderate		Severe		Median	IR
		Group 1 No.	Group 2 No.	Group 1 No.	Group 2 No.	Group 1 No.	Group 2 No.	Group 1 No.	Group 2 No.		
Vomiting	Before	5	12	0	0	4	2	16	11	1	1
	After	20	20	3	2	1	2	1	1	2	0
Abdominal Pain	Before	2	6	0	0	4	5	19	14	1	0
	After	19	21	3	2	2	1	1	1	2	0
Flatulence	Before	20	23	0	0	2	2	3	0	2	1
	After	23	24	1	1	1	0	0	0	2	0
Halitosis	Before	19	17	0	0	1	1	5	7	1	1
	After	21	23	2	1	1	1	1	0	2	0

different mechanisms, including production of reuterin, has anti-*H. pylori* activity and has been evaluated for the improvement in the eradication of infection (17) with conflicting results (15, 18, 19). In our randomized study, four weeks of treatment with *Lactobacillus reuteri* was associated with a more eradication rate (12%) compared to other group. There are different published data regarding usage of single or mixtures of probiotic strains for treatment of *H. pylori*. In some reports, significant benefits in the eradication rate have been reported. In a study performed by Khodadad et al. children who were treated with the combination of probiotic and standard therapy demonstrated a higher eradication rate and the authors recommended adjuvant therapy with probiotic strains (13). These results are in line with a study done on 70 *H. pylori* positive patients with an improvement rate of 74% (19). In addition, a recent meta-analysis found that an adjunctive use of multi-strain probiotics might improve *H. pylori* eradication rates and prevent the development of adverse events (20).

Other studies in adults have shown no benefits of adding probiotics to *H. pylori* regimens questioning their benefit due to the higher cost and need for an extra medication (21). Additionally, a research done on 21 randomized controlled trials have shown adding probiotics with triple therapy did not have any improvement on the eradication of *H. pylori* infection (22). Furthermore, some researches did not show any evidence of a more eradication rate in the probiotic group (23). Another concern is optimal time and duration of probiotic administration. Some studies have shown that probiotic administration prior or subsequent to therapy and for a duration of more than two weeks may increase the eradication efficacy (24). Controversial results in different studies may be attributed to the differences in dosage or kind of probiotic, sample size, and different geographical area with varies races and lack of standardization of diagnostic tests for detecting the *H. pylori* infection.

One of the strengths of our study was confirmation of results by the upper endoscopy and biopsy. The high percentage of *H. pylori* infection in our population amongst

symptomatic children (72%) shows that this infection can be a major concern in developing countries, in contrast to the low rate of that in developed countries. In the present study, UBT was performed four weeks after the end of therapy, which was positive in 12% and 24% of subjects in Group 1 and 2, respectively. It is not clear that UBT-positivity in our sample is related to persistent infection or reinfection. All *H. pylori* positive patients in the present study had chronic gastritis in histology, with nodularity of antrum in most cases. Similar to other studies (25), antral nodularity was correlated with *H. pylori* colonization and severity of gastritis.

Additionally, the results of this study showed a reduction of symptoms before and after treatment in both groups although the difference between the two groups was not significant. In a randomized trial done by Hurdud et al. addition of *Saccharomyces boulardi* to the standard triple therapy resulted in reduction of side effects (26). The results of the study of Khodadad et al. done in Iran, revealed a lower rate of nausea/vomiting in probiotic-supplemented children. This research also showed that mixtures of probiotics have positive effects on eradication of *H. pylori* infection and a lowering rate of side effects during treatment with antibiotics (13). Some other researches demonstrated the same findings (20, 27). However, there was no impact of reducing adverse complication after the addition of probiotics to standard treatment in some studies (22, 23). Finally, our study had some limitations. A small sample size of patients, short follow-up period and lack of using combination of probiotic strains could be some of them.

In conclusion, probiotic supplementation during the eradication of *H. pylori* might have a positive effect on antibiotic-related symptoms and success of treatment. However the rate of eradication in our study did not reach statistical significance. Further trials in different geographical areas and with a large number of patients may be needed in order to confirm these results.

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## Footnote

**Conflict of Interests:** Authors have no conflict of interests.

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