Bifidobacterium lactis B94 plus inulin for Treatment of *Helicobacter pylori* infection in children : does it increase eradication rate and patient compliance ?

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Abstract

The aim of this study is to investigate the effects of *Bifidobacterium lactis* B94 and inulin (synbiotic) treatment on eradication rate and patient compliance in subjects treated for symptomatic *H. pylori* infection. Patients with symptomatic *H. pylori* infection were divided into two groups. One group was treated with standard triple therapy (lansoprazole, amoxicillin, and clarithromycin) and *B. lactis* B94 (5×10^9 CFU/dose) plus inulin (900 mg) twice daily for seven days. The control group was treated with standard triple therapy and placebo. The side effects and eradication rates were evaluated at the end of the study. Ninety-three patients with *H. pylori* infection were treated with either synbiotic plus triple therapy (n = 47) or placebo plus triple therapy (n = 46). The infection eradication rates were not significantly different between the synbiotic and placebo groups [intent-to-treat (ITT), 80.8% and 67.3%, p = 0.13, respectively ; per-protocol (PP), 86.3% and 81.5%, p = 0.55, respectively]. The drug side effects were significantly higher in the placebo group than in the synbiotic group (63% and 17%, respectively, p < 0.01). Although no intolerable adverse side effects were observed in the synbiotic group, intolerable adverse side effects were observed in 13% of the placebo group (p = 0.01). Our results suggest that twice daily 5×10^9 CFU/dose *B. lactis B94* plus 900 mg inulin treatment did not have a direct positive effect on the *H. pylori* eradication rate. However, this treatment had significantly reduced side effects and indirectly increased eradication rates by increasing patient compliance. (Acta gastroenterol. belg., **2015**, 78, **282-286**).

Key words : *H. pylori* eradication, children, *B. lactis*, inulin.

Introduction

Helicobacter pylori is a common pathogen that often affects children (1). The bacteria typically remain in the patient for life unless properly treated during childhood. The prevalence of infection varies across communities and age groups and has been reported to be as high as 80% in developing countries (2). *H. pylori* infection is a major cause of chronic gastritis and causes peptic ulcers in 15% of infected patients and gastric cancer in 1-5% of infected patients. Colonization of the gastric mucosa by *H. pylori* in children is always associated with chronic gastritis (3). As a result, eradicating *H. pylori* infection is complex and treatment success requires the concomitant use of two or more antibiotics (1).

It was reported that antibiotic resistance reduced treatment success rate to 60-70% in both children and adults (4,5). Therefore, different adjuvant treatment methods are needed to increase the success rate. Probiotics represent one type of alternative treatment. Probiotics are defined as "live microorganisms that when administered in adequate amounts, confer a health benefit on the host'' (6). Probiotics are believed to treat *H. pylori* infection because they produce lactate, autolysin, and bacteriocins that have inhibitory/bactericidal effects. Probiotics also secrete mucin, which has a gastroprotective effect. Mucin also stabilizes the gastric mucosal barrier and reduces mucosal inflammation through eubiotic and immunomodulatory effects (7-9). Moreover, probiotics are believed to increase patient compliance to *H. pylori* treatment. However, there are limited and conflicting results regarding the use of probiotics in *H. pylori* treatment in adults and children. Prebiotics are non-digestible food ingredients that positively affect the health of the host by selectively activating the growth and/or activity of a limited number of microorganism species in the intestinal flora. Synbiotics are a combination of probiotics and prebiotics that synergistically promote the growth of beneficial bacteria or newly added species in the colon (10). There are currently no studies assessing the effects of prebiotics and synbiotics on *H. pylori* treatment. The combined results of previous studies indicate that randomized controlled trials (RCTs) using different probiotics are required. Thus, the aim of this study is to investigate the effects of the probiotic *Bifidobacterium lactis* plus inulin on eradication rate and patient compliance in subjects treated for symptomatic *H. pylori* infection.

Patient Selection and Methods

This study was conducted between July 2012 and April 2013 in the Akdeniz University Faculty of Medicine. Patients were included in this study if they were referred to the pediatric gastroenterology department presenting with dyspeptic complaints (epigastric or abdominal pain, epigastric burning, bloating, quick satiety, epigastric distress, nausea, and vomiting) for at least two months and were diagnosed with *H. pylori* infection. Written and verbal consent were obtained from the patients who agreed to participate in the study and/or their parents. This study was approved by the Clinical Research Ethics Committee of the Akdeniz University (decision number, 2012.343). Patients were excluded

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from the study if they were immunocompromised, had a history of allergic reactions to standard drugs used for the treatment of *H. pylori*, had previously received *H. pylori* treatment, or had a history of malabsorption.

The existence of *H. pylori* was proven by a rapid urease test during gastroscopic and/or histological examination or by monoclonal *H. pylori* antigen test positivity in the feces (Toyo Diagnostics, *H. pylori* antigen, Turklab medical instruments, Turkey). The patients were randomized and assigned to the synbiotic and placebo groups in a double-blind manner by an independent physician using a prepared randomization list. Each patient was given a code. One group was treated with synbiotic and standard triple *H. pylori* therapy (synbiotic group). The other group (placebo group) was treated with placebo and standard triple *H. pylori* therapy. The standard triple therapy consisted of lansoprazole (1 mg/kg/day), amoxicillin (50 mg/kg/day), and clarithromycin (15 mg/kg/day). The patients in the synbiotic group received *B. lactis* B94 (5×10^9 CFU/dose) plus 900 mg inulin (Maflor sachet, Mamsel, Turkey) twice daily. The patients in the placebo group received twice-daily preparations that appeared similar to synbiotic treatment but contained maltodextrin. Patients took the placebo or synbiotic treatments with 50 ml water before breakfast and dinner. The triple therapy and the synbiotic/placebo treatment were administered for seven days. Only the lansoprazole therapy was continued for one month. Diaries were given to the patients to record changes in their symptoms and in their drug-use status as well as any side effects, such as eructation, nausea, vomiting, abdominal or epigastric pain, taste disturbance, and diarrhea (mild, moderate, or severe). The statistical analyses were performed according to the patient codes by a gastroenterologist who was unaware of each patients treatment. A monoclonal *H. pylori* antigen test of the feces was performed 6-8 weeks after the end of the lansoprazole treatment.

Statistical Analysis

Descriptive statistics are presented as frequencies, percentages, means, standard deviations, medians, and minimum and maximum values. Fisher's exact test and Pearson's chi-square test were used to analyze categorical data, and the differences between measurements of the two groups were analyzed using the Mann-Whitney U-test. In this study, P-values < 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS 18.0 software package. The eradication rates were determined using both the intent-to-treat (ITT) and per-protocol (PP) analyses. All enrolled patients were analyzed in the ITT analysis. The patients were analyzed using the PP analysis, with the exception of patients who were excluded from the study (i.e., those who failed to complete the study because of drug side effects or those who could not undergo eradication assessment).

Results

Of 242 consecutive patients presenting with dyspeptic complaints, 108 had *H. pylori* infections. Fifteen patients declined to participate in the study. Of the 93 remaining patients, 47 were assigned to the synbiotic group and 46 were assigned to the placebo groups. All patients in the synbiotic group completed the study (i.e., received all their treatments), whereas six patients in the placebo group (13%) could not complete the study due to intolerable side effects of the antibiotics (Fig. 1). The most frequent complaints in both groups were epigastric or abdominal pain and epigastric burning before endoscopic examination [39.2% and 28.8% for epigastric pain in the probiotic and placebo groups, respectively ($p = 0.43$). and the rates of epigastric burning in the probiotic and placebo groups were 36.4% and 30.6%, respectively ($p = 0.52$)]. The demographic characteristics of the patients in both groups were similar (Table 1). An upper endoscopic examination was performed in 45 of 47 patients of the synbiotic group and in 43 of 46 patients of the placebo group. *H. pylori* infections were detected in these patients using the rapid urease test and/or histological examination. In patients who refused upper endoscopic examination, *H. pylori* was detected by monoclonal antigen testing of the feces. Two patients in the probiotic group and three in the placebo group were tested using the antigen test. The most frequent result of the endoscopic examination was antral hyperemia, whereas the most frequent result of the histological examination was chronic active gastritis (Table 1).

H. pylori was eradicated in 38 of the 47 patients in the synbiotic group. Eradication failed in six patients, and the antigen test could not be performed in three patients. None of the patients in the synbiotic group had side effects preventing them from completing the study. Eradication was successful in 31 of the 46 patients in the placebo group. Eradication failed in seven patients and the antigen test could not be performed in two patients. There were six patients who did not receive their medications (Table 2). Six patients who could not tolerate the drugs stopped their treatments on the second or third day of the study. The eradication rates in both the synbiotic and placebo groups were evaluated using the ITT and PP analyses (Table 3). Eradication rates did not differ significantly between the groups ($p = 0.13$ and $p = 0.55$ by the ITT and PP analyses, respectively). The most frequent side effects experienced during treatment in descending order were the following : abnormal taste, eructation, nausea and vomiting, abdominal or epigastric pain, and diarrhea. The placebo group experienced all side effects at higher rates than the synbiotic group (Table 4). Moderate or severe side effect rates were higher in placebo group than in synbiotic group [78% and 21%, respectively ($p < 0.01$)]. Changes in patient symptoms were evaluated again after the completion of treatment (during eradication control, 6-8 weeks after treatment).

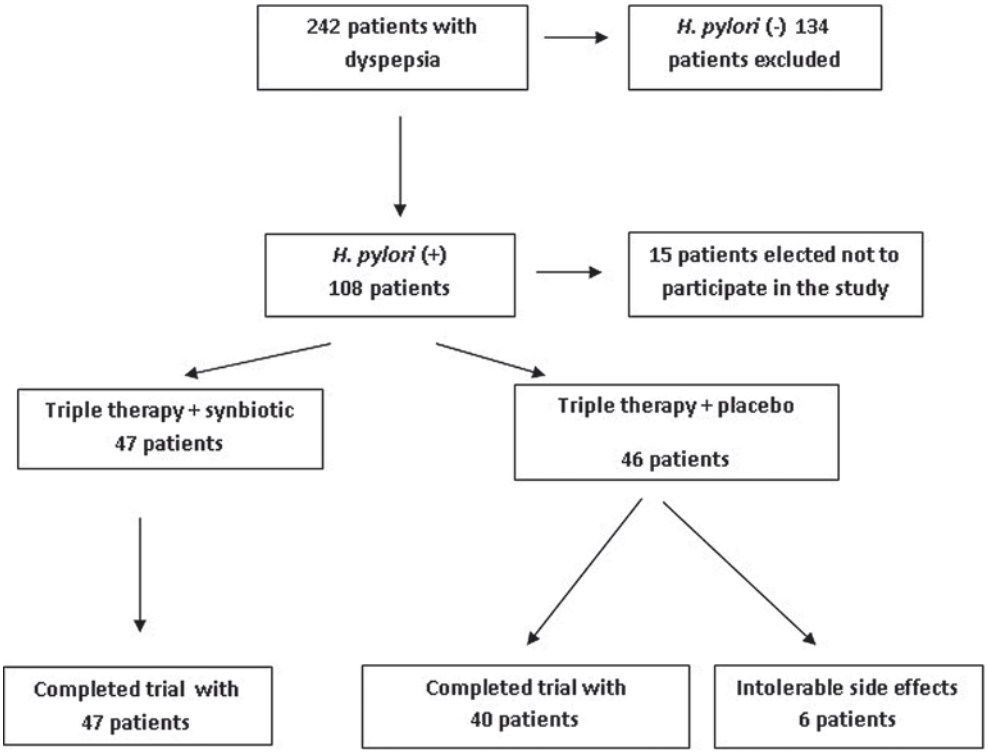

Fig. 1. — Patient recruitment flowchart

Table 1. — **Demographic characteristics of patients**

Patients characteristics	+Synbiotic	+Placebo	p
Age (mean)	11.9 (6–18)	12.0 (6–18)	0.94
Sex (female/male)	27/20	28/18	0.84
Endoscopic findings	*45*	*43*	
Antral hyperemia	33	34	0.99
Antral nodularity	9	10	0.71
Pangastritis	12	9	0.52
Antral ulcer	4	3	0.99
Duodenitis/duodenal ulcer	9	8	0.78
Histological findings			
Chronic active gastritis	34	34	0.99
Atrophic gastritis/metaplasia	11	9	0.69
Duodenitis	25	28	0.36

The data showed that 84.4% of the patients in the synbiotic and 76.3% of patients in the placebo groups had a full recovery ($p = 0.43$).

Discussion

The success of *H. pylori* eradication depends on patient compliance, drug side effects, bacterial resistance, geographic differences, and socioeconomic issues (11). These reasons indicate that there is a need for alternative treatment options, one being the use of probiotics (12).

There are limited and conflicting results regarding the use of probiotics in *H. pylori* treatment in adults and children. In general, most of the studies using probiotics in the treatment of *H. pylori* have not produced promising results. A RCT in children conducted by Goldman *et al.* (13) revealed that eradication rates were similar in placebo and probiotic groups (45.4% and 37.5%, respectively, $p = 0.345$) when *Bifidobacterium animalis* and *Lactobacillus casei* were used at a dose of 10^7 CFU/ml (200 ml) in combination with standard triple therapy for three months. Lionetti *et al.* (14) did not observe any

Table 2. — **Number of patients with and without eradication success in both groups**

Status	Groups	
	Synbiotic (n)	Placebo (n)
Eradication	38	31
No eradication	6	7
Data not completed	3	2
Intolerable	–	6
Total	47	46

Table 3. — **Eradication rates in both groups**

Analysis	Synbiotic group	Placebo group	p
ITT	80.8% (38/47)	67.3% (31/46)	0.13
PP	86.3% (38/44)	81.5% (31/38)	0.55

ITT : Intent-to-treat.
PP : Per protocol.

Table 4. — **Antibiotic associated side effect rates during the study in both groups**

Side effects	Groups		
	Synbiotic	Placebo	p
Eructation	3	14	< 0.01
Abnormal taste	4	18	< 0.01
Nausea/vomiting	2	15	< 0.01
Abdominal/epigastric pain	2	9	0.02
Diarrhea	0	5	0.02

difference between probiotic and placebo groups in their RCT when *Lactobacillus reuteri* (10^{10} CFU, 20 days) was added to 10 consecutive days of amoxicillin, clarithromycin, and tinidazole eradication therapy. Similarly, two other RCTs conducted with *Saccharomyces boulardii* and *Lactobacillus rhamnosus* did not demonstrate any clear benefits for the eradication of *H. pylori* in children (15, 16). In contrast, a study in children conducted by Sykora *et al*. (17) with *L. casei* indicated that eradication rates were higher in the probiotic group than the placebo group. The study administered *L. casei* at a dose of 10^{10} CFU for 14 days in addiction to standard triple therapy (omeprazole, amoxicillin, and clarithromycin for 7 days). The eradication rate was 84.6% in the probiotic group and 57.4% in the placebo group ($p = 0.0045$). There are currently no studies regarding the use of *B. lactis* species in *H. pylori* eradication. However, there have been studies showing that *B. lactis* decreases *H. pylori* load using the C13 urea breath test (18,19). In one of these studies, the patients were asymptomatic carriers of *H. pylori,* and in the other study the target population consisted of patients with antibiotic-associated diarrhea (19). Our study is the first to evaluate the role of *B. lactis* B94 in *H. pylori* eradication. Furthermore, our study included children who were symptomatic carriers of *H. pylori*. We found that the eradication rates did not differ significantly between groups. However, when patients who could not complete their treatments due to side effects were taken into consideration, the eradication rate in the placebo group was notably lower than that of the probiotic group (67.3% and 80.8%, respectively). Thus, we conclude that the addition of probiotics to *H. pylori* eradication treatment has an indirect positive effect. The limitations of this study were that we did not test for antibiotic resistance and we did not evaluate *B. lactis* B94 colonization in the feces.

Patient noncompliance may be another reason for eradication failure (19,20). The side effects of the antibiotics may cause patients to interrupt treatment. The most frequent side effects include taste disturbance, epigastric or abdominal pain, nausea, vomiting, and diarrhea (20). Probiotics have been proposed to increase patient compliance during *H. pylori* treatment. A limited number of studies regarding this issue in children have been published. These studies were conducted using the probiotics *L. reuteri*, *S. boulardii*, and *L. rhamnosus*. The results show that *L. reuteri* and *S. boulardii* treatment increased patient compliance (14-16). Our study is the first to evaluate patient compliance in children treated with *B. lactis* B94 to eradicate *H. pylori* infection. The results of our study showed that *B. lactis* treatment decreased all side effects. However, we found it difficult to explain the positive effects of *B. lactis* B94 treatment on symptoms such as eructation, epigastric pain, vomiting, and taste disturbance. Previous studies have also failed to provide explanations. It is important to note that these symptoms were milder in the probiotic group.

There have been no studies conducted to assess the effects of prebiotics and synbiotics on *H. pylori* treatment. The effects of prebiotics including inulin have been extensively studied in infant nutrition (21). However, their effects on *H. pylori* remain unknown. Although, in the present study, we could not show direct positive effects of treatment with *B. lactis* plus inulin on

H. pylori eradication rate, there was a significant decrease in side effects, which may be a result of the synbiotic relationship between *B. lactis* and inulin. However, further studies are necessary because of the limited knowledge of the positive effects and effective doses of *B. lactis* and inulin.

Conclusion

The results of this study reveal that the administration of *B. lactis* (5×10^9 CFU/dose) plus inulin twice daily did not have a direct positive effect on the *H. pylori* eradication rate in children. However, it had the indirect positive effect of increased patient compliance. Further RCTs conducted with different species and doses of probiotics are required to support these findings.

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