SYNBIOTIC THERAPY INCREASES ERADICATION RATE IN HELICOBACTER PYLORI ERADICATION

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[Simbiotici per H. pylori]

ABSTRACT

***Background**: Probiotics are used in combinations of H. pylori eradication regimens with variable results. Many strains tested had shown positive effects on side effect profiles. However, a clear effect on eradication rate is studied thoroughly. We aimed to investigate the beneficial effect of a synbiotic combination in clarithromycin-based triple eradication therapy.*

***Methods**: Ninety-two patients who were infected with H. pylori (confirmed via endoscopic biopsy) were randomized into two groups: those undergoing standard triple treatment (control group (rabeprozol plus amoksisilin plus clarithromycin bid) n=49) and those receiving symbiotic (triple plus symbiotic bid group n=43). The symbiotic product contained lactobacillus, bifidobacterium and enterococcus. The 13C-breath test was performed at least 6 weeks after completing both therapy regimens.*

***Results**: In the synbiotic group, 3 of the patients complained of metallic taste (7.0%), 1 complained of diarrhea (2.3%), 3 had nausea (7.0%), 2 had gas (4.7%), 3 experienced vomiting (7.0%) and 1 had constipation (2.3%). In the control group, 3 of the patients experienced a metallic taste (6.3%), 7 had diarrhea (14.6%), 5 had nausea (10.4%), 3 had intestinal bloating (6.3%), 3 experienced vomiting (6.3%) and 1 had constipation (2.1%). There was no significant difference between the two groups. However, side effect intensity and eradication rates were significant different between the groups ($p<0.05$). The eradication rate in the synbiotic group was 88.4%, while it was 68.8% in the control group ($p<0.05$).*

***Conclusion**: The addition of synbiotic to triple therapy decreases the rate of antibiotic-related side effects. It also increases H. pylori eradication rates in clarithromycin-based triple therapy.*

***Key words:** Helicobacter pylori, eradication, probiotics, synbiotics, lactobacillus, bifidobacteria.*

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Introduction

Helicobacter pylori (H. pylori) is a gram negative bacterium that has a well-known role in the pathogenesis of gastric and duodenal ulcers, gastric cancer, and gastric lymphomas[(1)]. The International Agency for Research on Cancer declared H. pylori a class I carcinogen in 1994[(2)].

Although several different treatment regimens have been evaluated for its successful eradication, the use of proton pump inhibitors with amoxicillin and clarithromycin remains the recommended treatment for H. pylori infection[(3)].

However, increased antibiotic resistance, especially to clarithromycin has significantly lowered the effectiveness of this treatment[(4)]. To solve this problem, alternative regimens including new antimicrobials such as levofloxacin[(5)] and moxifloksasin[(6)] have been used. In addition, antibiotic-associated side effects such as metallic taste, bloating, nausea, vomiting, and diarrhea are major factors of patient noncompliance and treatment failures[(7)].

Probiotics are living microbial species that can have favorable effects on the bowel micro-ecology and can improve health conditions if given in adequate doses[(8)].

Recent studies have hypothesized that probiotics can inhibit H. pylori infection using three main mechanisms. First, lactic acid, which is produced by some strains of probiotics, can inhibit H. pylori urease by lowering gastric pH. Second, the bacteriocin, which is produced by the probiotics, can kill H. pylori, and third, probiotics can inhibit the adherence of H. pylori to the gastric epithelium[9-11]. Although several studies have shown that the use of probiotics during first-line therapy can improve H. pylori eradication rates via these mechanisms, it is still controversial. Opposing studies discuss that the beneficial effects of probiotics are strain specific, and that different strains can cause misleading results[12,13].

A prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confers benefits upon its hosts well-being and health. Synergistic combinations of pro- and prebiotics are called synbiotics[14].

In this study, for the first time, we use synbiotics with clarithromycin-based triple therapy to show beneficial effects on H. pylori eradication rates and side effects.

Materials and Methods

Ninety-two patients diagnosed with an H. pylori infection participated in this study between June and September 2012.Those patients aged below 18 or above 85 years, who previously underwent treatment for H. pylori, who had a suspected or confirmed malignancy, acute infection, a history of gastric operation, and/or pregnancy were excluded from the study.

This randomized, prospective, open-labeled study was performed at Haydarpasa Numune Research and Education Hospital located in İstanbul.

Ninety-two patients who were infected with H. pylori (confirmed via endoscopic biopsy) were randomized into two groups: those undergoing standard triple treatment (control group (rabeprozol plus amoksisilin plus clarithromycin bid) n=49) and those receiving synbiotic (triple therapy plus synbiotic bid group n=43). The synbiotic product was used 2 times a day. Those patients receiving synbiotic began treatment with the synbiotic product 3 days before beginning eradication therapy. After these 3 days, they received triple plus synbiotic therapy for 14 days.

The synbiotic product contained lactobacillus, bifidobacterium and enterococcus. The 13C-breath test was performed at least 6 weeks after completing both therapy regimens.

At the time of therapy, all patients were informed of the side effects, were motivated to complete therapy, and a questionnaire form was given to all patients, which included the probable side effects of eradication treatment. After two weeks of the eradication treatment, compliance and side effects for both groups were evaluated by the same gastroenterologist. Patients were asked to explain all possible side effects and all forms were carefully filled out. As a result, the side effects and compliance were compared, and 6 weeks after the eradication therapy, eradication rates were compared between both groups.

Statistical analysis

In the study, Chi-Square and Mann Whitney-U tests were used for difference analysis of the non-parametric parameters of the participants. Results were considered statistically significant for P values less than 0.05.

Results

Demographic parameters and differences between the group using synbiotics and those in the conventional therapy group (not using synbiotics) are presented in (Table 1).

As seen in Table 1, 51.2% of those in the probiotic group were female and 48.8% were male. There were 47.9% females and 52.1% males in the control group. There were no significant differences between patient groups based on their gender (p=0.757), history of smoking (p=0.450), alcohol use (p=0.932) and ulcer type (p=0.439). Clinical properties and differences between the two groups are given in Table 2.

Table 2 shows that although two of the patients in the synbiotic group (4.6%) were not under follow-up, there were 14 patients in the control group (29.2%) that were not followed-up. However, there was no significant difference between the groups (p>0.05), indicating that follow-up of patients in both groups was similar.

In the synbiotic group, 3 of the patients complained of metallic taste (7.0%), 1 complained of diarrhea (2.3%), 3 had nausea (7.0%), 2 had intestinal bloating (4.7%), 3 experienced vomiting (7.0%)

Parameters	Group				p
	Probiotic		Control		
	n	%	n	%	
Gender					
Female	22	51.2	23	47.9	0.757*
Male	21	48.8	25	52.1	
Smoking					
Yes	7	16.3	5	10.4	0.450**
No	36	83.7	38	79.2	
Ex-smoker	0	0	5	10.4	
Alcohol					
Yes	6	14.0	7	14.6	0.932*
No	37	86.0	41	85.4	
Ulcer Type					
Gastric	3	7.0	4	8.3	0.439**
Duodenal	8	18.6	12	25.0	
Nonulcer	32	74.4	32	66.7	

Table 1: Demographic Properties of the Patient Groups.
**Chi-Square statistics at 0.05 significance level*
***Mann Whitney-U Test at 0.05 significance level*

and 1 had constipation (2.3%). In the control group, 3 of the patients experienced a metallic taste (6.3%), 7 had diarrhea (14.6%), 5 had nausea (10.4%), 3 had intestinal bloating (6.3%), 3 experienced vomiting (6.3%) and 1 had constipation (2.1%). There was no significant difference between these groups.

However, side effect intensity and eradication rates were significant between the groups ($p<0.05$). The patients in the synbiotic group expressed that the side effects they experienced were not significant and none of the patients in that group ranked their side effect range. The eradication rate in the synbiotic group was 88.4%, while it was 68.8% in the control group ($p<0.05$).

Discussion

After the World Health Organization classified H. pylori as a class I carcinogen in 1994 for gastric cancer, many studies have focused on the eradication of H. pylori infection[2]. Although antibiotic resistance, primarily to clarithromycin is increasing, PPI treatment combined with amoxicillin and clarithromycin remains the recommended first line treatment for H. pylori infection (according to the Maastricht IV. guideline)[3]. This guideline also suggests that 14 days of therapy is superior to 7 days of therapy[3]. In Turkey, the most popular prescribed regimen is the same[15]. However, in other developing countries, H. pylori eradiation rates are being reduced due to increasing clarithromycin resistance and noncompliance to therapy because of side effects[16].

Parameters	Group				p
	Probiotic		Control		
	n	%	n	%	
Follow-up					
Followed	41	95.3	34	70.8	0.267**
Not adapted	1	2.3	3	6.3	
Lost to follow up	1	2.3	4	8.3	
Discontinued treatment due to side effects			7	14.6	
Side Effects					
None	30	69.8	26	54.2	0.533**
Metallic taste	3	7.0	3	6.3	
Diarrhea	1	2.3	7	14.6	
Nausea	3	7.0	5	10.4	
Gas	2	4.7	3	6.3	
Vomiting	3	7.0	3	6.3	
Constipation	1	2.3	1	2.1	
Degree of side effects					
None	43	100.	25	52.1	<0.05
Mild			11	22.9	
Moderate			3	6.3	
Severe					
Discontinued treatment			9	18.8	
Eradication ITT analysis					
Yes	38	88.4	33	68.8	0.024*
No	5	11.6	15	31.3	
PP analysisr					
Yes	38	92.7	32	94.1	0.804*
No	5	7.3	2	5.9	

Table 2: Clinical and Demographic Properties of the Study and Control groups.
**Chi-Square statistics at 0.05 significance level*
***Mann Whitney-U Test at 0.05 significance level*

In the present randomized, open labeled study we used a synbiotic product that and which included lactobacillus, enterococcus, biifidobacterim, and prebiotics. We evaluated whether a PPI-based triple therapy with adjunctive synbiotic administration for

2 weeks increased eradication rates. We determined that the eradication rate in the probiotic group was higher than that of the control group. Prebiotics such as oligofructose may function in a primary antibacterial role by augmenting the growth of beneficial probiotic strains, which has been documented in competition experiments between strains of E. coli, Clostridium perfringens, and Bifidobacterium infantis. A combination of prebiotics and probiotics might have a positive effect on H. pylori eradication rates. The majority of previous studies used probiotics in fermented dairy products or food supplements. However, these studies did not achieve desired eradication rates[9,12,17]. S. boulardii was the other choice of probiotics in several studies. In 2006, Cindoruk et al. reported that probiotics had no significant effect on H. pylori eradication rates[18]. Previous studies determined that patients with non-ulcer dyspepsia had significantly lower eradication rates than did patients with non-ulcer dyspepsia. Kadayifci et al. showed a major decrease in eradication rates from 80% to 60% with standard PPI-based triple therapy in an epidemiologic study that included long term analysis[19]. In 2004 Aydın et al. reported that H. pylori eradication rates with PPI based triple therapy had decreased to 47.1% from 93.3% since 1996[20]. These two controlled, randomized trials explain that these unsatisfactory eradication rates are a result of the rising prevalence of clarithromycin resistance. Several studies explain that the NUD group has lower eradication rates with a different hypothesis, one being that different levels of inflammation are caused by different strains of H. pylori. High inflammation increases vascular and epithelial permeability and might allow antibiotics to better penetrate the gastric lumen. In addition, antibiotic-associated side effects such as diarrhea, nausea, vomiting, bloating and metallic taste may contribute to unsatisfactory eradication rates. Alternative treatment regimens, including probiotics, are being assessed to overcome these problems, and so far conflicting results have been reported[12,13,21-23].

Probiotics are living, and when administered in adequate amounts confer a health benefit on the host[23]. In studies that focus on improving H. pylori eradication rates, a mainly used probiotics are Bifidobacterium and Lactobacillus. Probiotics may act by killing H. pylori in vitro or by improving patient compliance to treatment by reducing the incidence of therapy-related adverse effects. Prebiotics, described as "non digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of beneficial bacteria in the colon, thereby improving the host's health" provide an additional mechanism for influencing the population dynamics of the intestinal microflora. Prebiotics are present in significant amounts in a wide variety of fruits and vegetables and are fermented by colonic bacteria to lactic acid and short-chain carboxylic acids. Other oligomers with prebiotic potential are lactulose and sugar alcohols such as mannitol and xylitol[24].

Duman et al. aimed to evaluate the efficacy and safety of Saccharomyces boulardii (S. boulardii) in preventing antibiotic-associated diarrhea in patients receiving antibiotics for H. pylori eradication. Patients with peptic ulcer disease or non-ulcer dyspepsia were enrolled to receive clarithromycin, amoxicillin and omeprazole for H. pylori eradication for 14 days. These patients were then randomized to receive either 500 mg S. boulardii twice daily (treatment group) or no treatment (control group). Overall, diarrhea rates throughout the whole study period were 6.9% in the treatment group and 15.6% in the control group (p=0.007) (25). In 2006 Cindoruk et al. reported that S. boulardii is an effective and safe treatment for the prevention of antibiotic-associated diarrhea(18).

The recent World Gastroenterology Organization (WGO) guideline on probiotics also stated that probiotics might add positive effects on H. Pylori eradication in several aspects, such as decreasing side effects and increasing patient tolerability, increasing immune response[26].

In conclusion, the addition of a synbiotic to triple therapy decreases the rate of antibiotic-related side effects. It also increases H. pylori eradication rates in clarithromycin-based triple therapy. We suggest that addition of a prebiotic and probiotic combination to triple therapy might be on option to improve H. pylori eradication rates. This is a new area of research that needs to be studied with large, randomized, controlled trials.

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