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Effects of probiotic addition to standard treatment of *Helicobacter pylori* on eradication success and side effect profile

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ABSTRACT

Aims: To reveal the effect of probiotics added to standard *Helicobacter pylori* eradication treatment on the eradication success and side effect profile.

Methods: This is a prospective cross-sectional study that included male and female patients between the ages of 18-65 who presented to internal medicine and general surgery outpatient clinics with dyspeptic complaints and had a positive stool *Helicobacter pylori* antigen test. The patients were divided into two groups with the first receiving standard treatment consisting of amoxicillin 1000 mg 2x1, clarithromycin 500 mg 2x1, and lansoprazole 30 mg 2x1. In addition to standard treatment, the second group also received a probiotic supplement containing 1.5 billion colony-forming units (CFU) per tablet twice a day. Both groups were treated for 14 days and were called 1 month later for a stool *Helicobacter pylori* antigen check. In addition, a questionnaire was administered to the patients aiming to determine the presence and severity of common side effects due to antibiotic use. These side effects were determined as epigastric burning, flatulence, diarrhea, nausea and vomiting, bitter taste and retrosternal burning. 0 means none, 1 means mild, 2 means moderate, and 3 means severe. Patients were asked to score the symptoms they felt while using antibiotics according to this scale. The aim was to investigate whether there was a difference between the two groups in terms of eradication success and side effect profile.

Results: The study included 150 patients (87 males and 63 females) with a mean age of 43.37±12.13 (range 23-65). Group 1 consisted of seventy-five patients who received only antibiotic treatment and group 2 consisted of 75 patients who received antibiotic and probiotic treatment. Eradication percentage was 77.33% in the antibiotic group and 85.33% in the antibiotic+probiotic group. On the other hand, the difference between groups was found to be non-significant (p=0.295). The odds ratio for association between treatment and eradication was 1.705 (95% CI: 0.738-3.940, p=0.212). The percentages of epigastric burning, flatulence, diarrhea, and nausea/vomiting were significantly higher in the antibiotic group than in the antibiotic+probiotic group (p<0.001, p<0.001, p<0.001, p=0.002, respectively). No significant differences between treatment groups in terms of bitter taste and retrosternal burning were found (p=0.323, p=0.579, respectively).

Conclusion: Probiotics cannot be an alternative option to antibiotics in the treatment of *Helicobacter pylori*; however, when used in combination with antibiotics, they can have a synergistic effect by increasing the eradication success and reducing side effects.

Keywords: *Helicobacter pylori*, gastritis, probiotics, antibiotics

INTRODUCTION

Helicobacter pylori (HP), a gram-negative, micro-aerophilic, spiral-shaped, flagellated bacterium, was first detected in the human stomach by Warren and Marshall in 1982. In 1989, Goodwin named the bacterium HP due to its helical structure and the fact that it lives in the pyloric region of the stomach. Approximately half of the world's population is infected with HP. According to a TURHEP study, the average prevalence of HP is 82.5% across Turkiye, which prevalence levels varying from region to region. The highest positivity rate is in the Southeastern Anatolia Region with a rate of 88.7%, while prevalence drops to 71.8% in the Marmara Region.[1] HP causes atrophy and metaplasia in the gastric mucosa. The relationship between HP and gastritis, gastroduodenal ulcer, gastric mucosa-associated lymphoma (MALTOMA), and gastric adenocarcinoma has been definitively proven and it is considered a class 1 carcinogen by the World Health Organization.[2] For this reason, all national and international guidelines recommend investigating the presence of HP in patients presenting with dyspeptic complaints and eradicating it if positive.[3] Since HP shows high antibiotic resistance, various eradication regimens have been defined and updated over the years.[4] In recent years, the use of probiotics, which increase the success of treatment through different mechanisms, has come to the fore in addition to antibiotics. Probiotics are defined by the World Health Organization as bacteria that are beneficial to human health when consumed in sufficient

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amounts.[5] In order to ensure eradication of HP, some current guidelines recommend the use of probiotics as they increase treatment compliance and eradication success.[6] There are publications showing that probiotics prevent HP colonization through various mechanisms and increase the success of eradication, and also increase compliance with treatment by reducing the side effects of antibiotic therapy.[7,8] However, there are conflicting results in the literature which conclude that probiotics do not provide additional benefit to HP treatment.[9] Taking these opposing views into consideration, the present study was planned to evaluate the effectiveness of probiotics on both eradication success and treatment-related side effects.

METHODS

Ethical approval was received from the Ethics Committee of İstanbul Medipol University Faculty of Medicine (Date: 07.12.2023, Decision No: 1017). All stages of the study were carried out in accordance with the Declaration of Helsinki. Patients were informed of the purpose and method of the study and their written consent was obtained. The sample size was calculated using the descriptive statistics (effect size=0.229) in the article titled "The effect of probiotics on gut microbiota during the *Helicobacter pylori* eradication: randomized controlled trial". The minimum number of patients required to complete the present study with a 95% confidence level (α=0.05) and 80% power was determined as 150 (Hintze, J. (2011), PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).[10] The study was conducted at İstanbul Medipol University's Faculty of Medicine Hospital between December 2023 and March 2024. Male and female patients between the ages of 18 and 65, who applied to internal medicine and general surgery outpatient clinics with dyspeptic complaints and had a positive stool HP antigen test, were included in the study. Patients were numbered according to the order of arrival. Those with odd numbers were placed in group 1 and received standard treatment, while those with even numbers were placed in group 2 and received standard treatment+probiotics. The treatment applied to the first group consisted of amoxicillin 1000 mg 2x1, clarithromycin 500 mg 2x1, and Lansoprazole 30 mg 2x1. In addition to standard treatment, group 2 received probiotic supplementation containing 1.5 billion colony-forming units (CFU) per tablet in a 2x1 dosage. Probiotics included *Enterococcus faecium* (CBT EF4), *Lactobacillus plantarum* (CBT LP3), *Streptococcus thermophilus* (CBT ST3), *Bifidobacterium lactis* (CBT BL3), *Lactobacillus acidophilus* (CBT LA1), and *Bifidobacterium longum* (CBT BG7) strains. Both groups were treated for 14 days and were called 1 month later for a stool HP antigen check. The antigen checks were compared to determine whether there was a significant difference in terms of eradication success between the two groups. In addition, a questionnaire was administered to each patient aiming to determine the presence and severity of common side effects due to antibiotic use. These side effects were determined to be epigastric burning, flatulence, diarrhea, nausea and vomiting, bitter taste, and retrosternal burning. Patients were asked to score their symptoms according to the following scale: 0 for no side effects, 1 for mild, 2 for moderate, and 3 for severe side effects. Exclusion criteria included: pregnant and breastfeeding women; patients <18 years of age and >65 years of age; patients previously treated for HP eradication; patients using antibiotics and/or probiotics, proton pump inhibitors, H2 receptor antagonists, or antiacids within the last 3 months; the presence of any acute or chronic infection other than HP; the presence of malignancy, liver, or kidney dysfunction; and patients using immunosuppressive agents.

Statistical Analysis

All analyses were performed on IBM SPSS statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). For the normality check, histogram and Q-Q plots were used. Descriptive statistics were presented by using mean±standard deviation for continuous variables due to normality of distribution and frequency (percentage) for categorical variables. Continuous variables were analyzed with the student t test. Categorical variables were analyzed with the chi-square test or Fisher-Freeman-Halton test. Odds ratios for eradication were calculated via univariable logistic regression analysis. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

The study included 150 patients (87 males and 63 females) with a mean age of 43.37±12.13 (range 23-65). Group 1 consisted of seventy-five patients who received only antibiotic treatment and group 2 consisted of 75 patients who received antibiotic and probiotic treatment. No significant differences between treatment groups were found in terms of age (p=0.511), sex (p=0.620), alcohol use (p=0.650), and smoking (p=0.741). Eradication percentage was 77.33% in the antibiotic group and 85.33% in the antibiotic+probiotic group (Figure). The differences between groups was found to be non-significant (p=0.295) (Table 1). The odds ratio for association between treatment and eradication was 1.705 (95% CI: 0.738 - 3.940, p=0.212). In addition, no association was found between eradication and age (p=0.816), sex (p=0.244), alcohol use (p=0.682), or smoking (p=0.656) (Table 2). The percentage of no epigastric burning was significantly higher in the antibiotic+probiotic group than in the antibiotic group. The percentages of moderate and severe epigastric burning were significantly higher in the antibiotic group than in the antibiotic+probiotic group (p<0.001). The percentage of mild flatulence was significantly higher in the antibiotic+probiotic group than in the antibiotic group. The percentages of moderate and severe flatulence were significantly higher in the antibiotic group than in the antibiotic+probiotic group (p<0.001). The percentage of no diarrhea was significantly higher in the antibiotic+probiotic group than in the antibiotic group. The percentages of moderate and severe diarrhea were significantly higher in the antibiotic group than in the antibiotic+probiotic group (p<0.001). The percentage of no nausea/vomiting was significantly higher in the antibiotic+probiotic group than in the antibiotic group. And the percentage of moderate nausea/vomiting was significantly higher in the antibiotic group than in the antibiotic+probiotic group (p=0.002). No significant differences between treatment groups was found in terms of bitter taste (p=0.323) and retrosternal burning (p=0.579) (Table 3).

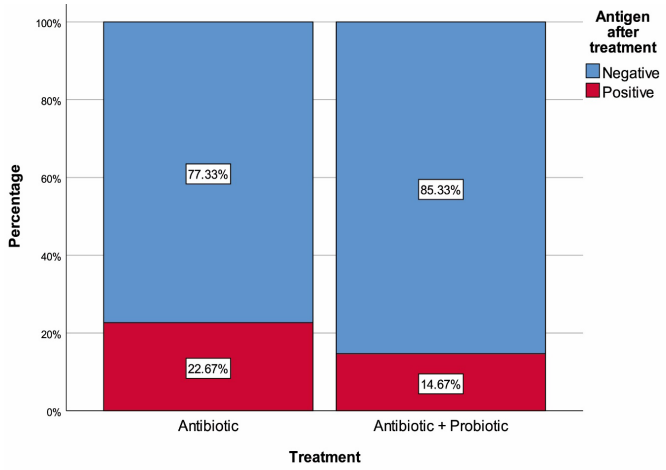

Figure. *Helicobacter pylori* antigen results after treatment

Table 1. Summary of demographics and antigen results with regard to treatment groups

	Treatment		
	Antibiotic (n=75)	Antibiotic+Probiotic (n=75)	p
Age	42.72±12.43	44.03±11.87	0.511§
Sex			
Male	45 (60.00%)	42 (56.00%)	0.620†
Female	30 (40.00%)	33 (44.00%)	
Alcohol use	10 (13.33%)	13 (17.33%)	0.650†
Smoking	33 (44.00%)	31 (41.33%)	0.741†
Helicobacter pylori antigen after treatment			
Negative	58 (77.33%)	64 (85.33%)	0.295†
Positive	17 (22.67%)	11 (14.67%)	

Descriptive statistics were presented by using mean±standard deviation for continuous variable due to normality of distribution and frequency (percentage) for categorical variables. §: Student t test, †: Chi-square test

Table 2. Odds ratios for *Helicobacter pylori* eradication, univariable logistic regression analysis results

	OR (95% CI)	p
Age	1.004 (0.970-1.039)	0.816
Sex, female	1.676 (0.702-4.001)	0.244
Alcohol use	0.796 (0.268-2.365)	0.682
Smoking	0.829 (0.363-1.892)	0.656
Treatment, antibiotic+probiotic	1.705 (0.738-3.940)	0.212

OR: Odds ratio, CI: Confidence interval

Table 3. Summary of symptoms with regard to treatment groups

	Treatment		
	Antibiotic (n=75)	Antibiotic+Probiotic (n=75)	p
Epigastric burning			
No	4 (5.33%)	24 (32.00%)*	<0.001†
Mild	22 (29.33%)	31 (41.33%)	
Moderate	32 (42.67%)	13 (17.33%)*	
Severe	17 (22.67%)	7 (9.33%)*	
Flatulence			
No	13 (17.33%)	23 (30.67%)	<0.001†
Mild	19 (25.33%)	33 (44.00%)*	
Moderate	29 (38.67%)	17 (22.67%)*	
Severe	14 (18.67%)	2 (2.67%)*	
Diarrhea			
No	14 (18.67%)	35 (46.67%)*	<0.001†
Mild	20 (26.67%)	23 (30.67%)	
Moderate	27 (36.00%)	12 (16.00%)*	
Severe	14 (18.67%)	5 (6.67%)*	
Nausea/vomiting			
No	18 (24.00%)	32 (42.67%)*	0.002‡
Mild	33 (44.00%)	36 (48.00%)	
Moderate	21 (28.00%)	6 (8.00%)*	
Severe	3 (4.00%)	1 (1.33%)	
Bitter taste			
No	25 (33.33%)	19 (25.33%)	0.323†
Mild	23 (30.67%)	34 (45.33%)	
Moderate	19 (25.33%)	16 (21.33%)	
Severe	8 (10.67%)	6 (8.00%)	
Retrosternal burning			
No	1 (1.33%)	1 (1.33%)	0.579‡
Mild	48 (64.00%)	53 (70.67%)	
Moderate	21 (28.00%)	14 (18.67%)	
Severe	5 (6.67%)	7 (9.33%)	

Descriptive statistics were presented by using frequency (percentage) for categorical variables. †: Chi-square test, ‡: Fisher-Freeman-Halton test, *: Significantly different category

DISCUSSION

In this study, the HP eradication success rate of standard treatment was found to be 77.33%, while this rate was found to be 85.33% in the group using standard treatment+probiotics. It was observed that the use of probiotics increased the success of eradication. In addition, epigastric burning, flatulence, diarrhea, nausea and vomiting were detected significantly less in the group using probiotics, while no significant difference was detected between the two groups in terms of bitter taste and retrosternal burning.

There are studies in the literature showing the various effects of probiotics on human health. In order for a strain to be defined as a probiotic, it must meet certain criteria such as not having pathogenic properties, being resistant to gastric acid and bile salt, being able to adhere to the intestinal epithelium, being able to produce antimicrobial compounds, and being able to stimulate the immune response.[11] These criteria were determined by The Lactic Acid Bacteria Industrial Platform (LABIP). The most commonly used and most effective probiotic species are *Lactobacillus* and *Bifidobacterium* species, which were used in the present study.

Treating HP is much more than treating an infection. Eradicating HP not only treats gastritis and gastroduodenal ulcers, but it may also prevent gastric adenocarcinoma and MALTOMA caused by HP. Unfortunately, it is not easy to destroy HP due to its resistance to antibiotics and difficulty in patient compliance with treatment.[12]

The prevalence of HP is increasing year by year all over the world as well as in Turkiye.[13] To create consensus on HP treatment, the American College of Gastroenterology (ACG) guidelines and the Maastricht V consensus report were last announced in 2017. Both recommended that all HP positive patients should be treated and that the treatment protocol should be decided according to clarithromycin and metronidazole resistance.[14] Today, the most commonly used global first-line treatment regimen is triple therapy which includes amoxicillin, clarithromycin, and a proton pump inhibitor.[15] The present study used this treatment regimen.

Studies on clarithromycin resistance in Turkiye have found results varying between 15% and 55%. The reason for this variation of results may be due to the difference in the method and region where resistance was studied.[16] Again, in various studies conducted in Turkiye the success rates of the classic triple therapy were found to be between 43.5% and 86.2%.[17] In the present study, the eradication rate was found to be 77.33%, consistent with these data. Due to the bacteria's ability to develop high antibiotic resistance, many different treatment protocols have been created over the years. After antibiotic resistance, the most important factor affecting eradication success is patient non-compliance. Studies have shown that the incidence of side effects varies between 5-30% and that these side effects cause patients to fail to comply with the treatment.[18] There are studies in the literature showing that probiotics increase compliance with treatment by reducing side effects, as in this study.[19] Probiotics prevent HP adhesion by colonizing the gastric mucosa, inhibiting the urease activity of HP by producing short-chain fatty acids, and thus blocking the adhesion of HP to the gastric mucosa.[20] Probiotics compete with HP for nutrients and cause immune modulation via IL-8.[21]

There are many studies in the literature aiming to reveal the effect of probiotics on HP. In a multicenter study conducted on 664 patients in Greece, the success rate with standard treatment was found to be 86.8%, while the success rate increased to 92.0% in the group which probiotics were added to the same treatment. In addition, the frequency of side effects was much less in the group using probiotics.[19] A meta-analysis examining 40 studies covering data from 894 patients published in 2019 concluded that a higher eradication rate ($p<0.001$) and a lower incidence of total side effects ($p<0.001$) were observed in the group using probiotics compared to the control group.[22] The 2017 ACG clinical guidelines recommended the use of probiotics, stating that they increase HP elimination rates and reduce the occurrence of side effects. However, no conclusion has been reached about the best probiotic choice, as well as its dosage and treatment process.[14]

Despite these positive results in the literature, there are also studies that conclude that the use of probiotics is useless. In a small-scale Turkish study conducted on 61 children, it was concluded that probiotics did not contribute to eradication success or to reducing the rate of side effects.[23] The reason for the negative results in this study may be the small number of patients and the content of the probiotic used. While a powerful probiotic containing *Enterococcus faecium*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium lactis, Lactobacillus acidophilus,* and *Bifidobacterium longum* was used in the present study, the probiotic used in the small-scale study contained only *Lactobacillus casei, Lactobacillus acidophilus,* and *Bifidobacterium lactis*. Another study conducted on 209 patients in Spain concluded that probiotic treatment added to standard treatment did not contribute to eradication success or reducing side effects. The reason for this result may be that the probiotic used contained only *Lactobacillus plantarum* and *Pediococcus acidilactici* and was used once a day. The present study applied the probiotics in a 2x1 posology.[24]

When the results of 4 studies conducted between 2016 and 2017 are examined, the general opinion is that probiotics cannot be an alternative option to antibiotics in the treatment of HP; however, their combined use can have a synergistic effect by increasing the eradication success and reducing side effects.[25]

Limitations

This study was a relatively small-scale study conducted with 150 patients. Definitive results can be reached with studies on more patients. Since it was a single-center study, it covered a certain segment of the society. The results cannot be generalized to the entire population. The presence of HP was detected by examining the stool antigen test. Culture, antibiotic susceptibility, and drug resistance tests were not performed. As the symptoms questioned within the study to evaluate post-treatment antibiotic side effects may also occur due to HP infection, it would have been more accurate to apply the same questionnaire both before and after treatment.

CONCLUSION

Considering the increase in the prevalence of HP infection as well as the increase in antibiotic resistance both globally and in Turkiye, supporting antibiotic therapy with probiotics can contribute to the success of treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ethics Committee of İstanbul Medipol University Faculty of Medicine, (Date: 07.12.2023, Decision No: 1017).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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