

# Evaluation of the effectiveness of using two different probiotics in helicobacter eradication treatment

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## ABSTRACT

**Introduction:** We aimed to evaluate the effects of the addition of probiotics containing *Lactobacillus acidophilus* + *Bifidobacterium animalis* Subsp *lactis* to the classic triple treatment protocol (lansoprazole + amoxycillin + clarithromycin) on the success of *Helicobacter pylori* eradication and antibiotic side effects.

**Materials and Methods:** Standard therapy (lansoprazole + amoxycillin + clarithromycin), and probiotics containing in addition to standard therapy were determined. Patients in both groups were treated for 14 days. The prebiotic, containing two different strains, was in capsule form and used twice a day. We demonstrated the helicobacter eradication status by looking at the helicobacter antigen from the stool. Statistical analyzes between the two groups were made using the pearson Chi-square test. P<0.05 was accepted as the significance level.

**Results:** The rate of discontinuing treatment due to side effects was 15.3% in group 1, this rate was 4.5% in group 2. When double probiotics were added to the treatment, it was observed that there was a decrease of 11.2% in serious side effects (p<0.001). After the completion of the treatments. It was observed that helicobacter eradication was achieved in 152 out of 222 patients (68%) in group 1 and in 214 (89%) of 240 patients in group 2. When double probiotics were added to the treatment, it was observed that the success of eradication increased by 21% (p<0.001).

**Conclusion:** Combined use of probiotic increases helicobacter eradication in addition to reducing the side effects of antibiotics due to *H. pylori*.

**Keywords:** *Helicobacter pylori*, probiotics, treatment

## Introduction

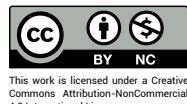
*Helicobacter pylori* is known as a microaerophilic and gram-negative spiral cocoid flagellated bacteria. It is the main cause of duodenal ulcer, peptic ulcer disease, gastric adenocarcinoma, B-type gastritis, and stomach

B-cell lymphoma.<sup>[1-3]</sup> Epidemiological studies reveal that more than 50% of the population is affected by *H. pylori* strains.<sup>[4,5]</sup> The European Maastricht V/Florence consensus statement accordingly stipulates that any person with *H. pylori* infection should undergo treatment to eradicate



Received: 06.09.2021 Accepted: 18.10.2021

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the pathogen.<sup>[6]</sup> Standard therapy with a proton pump inhibitor (PPI) and antibiotics such as clarithromycin and amoxicillin or metronidazol cures only about 70% of patients. At present, triple or quadruple therapy based on PPIs combined with amoxicillin and clarithromycin is recognized as a first-line treatment of *H. pylori*.<sup>[6]</sup> In addition to the side effects of antibiotics used in *H. pylori* treatment, resistance develops, and *H. pylori* eradication rate decreases.<sup>[7]</sup> Probiotics reduce inflammation and damage in the gastrointestinal system mucosa.<sup>[8,9]</sup> In the treatment of *H. pylori* infections, antibiotics are the best treatment method, but the development of resistance to some strains of the bacteria limits the treatment.<sup>[10]</sup> Clinically isolated *H. pylori* has been shown to develop resistance against fluoroquinolone, tetracyclines, penicillins, aminoglycosides, sulfonamides, and macrolides.<sup>[11]</sup> Diarrhea due to antibiotics, abdominal pain, and taste and smell disorders are encountered as side effects.<sup>[12]</sup> Due to these side effects, patients may discontinued their treatment. In our study, the effects of adding two different probiotic strains containing *Lactobacillus acidophilus* + *Bifidobacterium animalis* Subsp Lactis to the triple therapy protocol (lansoprazole + amoxycillin + clarithromycin) on the success of *H. pylori* eradication and antibiotic side effects were evaluated.

## Materials and Methods

Helicobacter (*H. pylori*) + patients were analyzed retrospectively as a result of endoscopic biopsy between 01.09.2019 and 01.09.2020. The patients diagnosed until 01.07.2019 were given standard treatment consisting only of lansoprazole + amoxycillin + clarithromycin. The probiotic agent containing *L. acidophilus* + *B. animalis* Subsp Lactis was added to the patient group after the specified date, in addition to the standard treatment, due to the low success of the treatment and the high rates of discontinuation due to side effects. Considering that a synergistic effect can occur by combining the different effects of the two probiotic strains on *H. pylori*, an agent containing two different probiotic strains was used. The records of the patients enrolled in this study were recorded on real-time follow-up forms by a single clinician who performed the endoscopy and also treated the patients. Standard therapy (lansoprazole + amoxycillin + clarithromycin) (Group 1), and probiotics containing *L. acidophilus* + *B. animalis* Subsp Lactis in addition to standard therapy (Group II) were determined. Age, gender, clinical findings, imaging and histopathological findings of both groups, and HpAg

+/– status in stool, side effects such as abdominal pain, diarrhea, taste disturbance, and allergy developed during medical treatment were compared. The data of all patients were recorded in the SPSS program. Patients in both groups were treated for 14 days. The prebiotic, containing two different strains, was in capsule form and used twice a day. Capsule content is *L. acidophilus* 1 × 109 cfu, *B. animalis* subsp. lactis 1 × 109 cfu for 1 capsule.

In the meta-analysis performed by Gisbert in 2006, the reliability of rapid tests that scan *H. pylori* antigen in stool, especially containing monoclonal antibodies, were examined and the sensitivity was 94% and the specificity was 97%.<sup>[13]</sup> Nguyen showed that this ratio was 96.6%, and 94.9%, respectively.<sup>[14]</sup> Therefore, stool HB test was used to evaluate the post-treatment *H. pylori* eradication status because it was reliable, cheap, practical, and non-invasive. For false negativity, a stool test is recommended 15 days after antibiotic treatment. Therefore, 15 days after the end of medical treatment, we demonstrated the HB eradication status by looking at the helicobacter antigen from the stool.

After collecting all the data, it was planned to investigate the effects of double probiotic addition to triple therapy on serious side effects leading to HB eradication success and discontinuation of triple therapy. Statistical analyzes between the two groups were made using the student test for age. Statistical analyzes between the two groups were made using the Pearson Chi-square test. P<0.05 was accepted as the significance level.

## Results

Four hundred sixty-two patients diagnosed with *H. pylori* as a result of biopsy from 603 patients who underwent endoscopy between 01.09.2019 and 01.09.2020 were included in our study (Table 1). *H. pylori* positivity rate was 76.6% in our patient series. The mean age of the patients was 53 (16–90). Two hundred twenty-two patients were treated with lansoprazole + amoxycillin + clarithromycin (Group 1) and 240 patients with lansoprazole + amoxycillin + clarithromycin + *L. acidophilus* + *B. animalis* Subsp Lactis (Group 2). There was no significant difference between the groups in terms of age, gender, and diagnoses. Thirty-four of 222 patients in group 1 and 11 of 240 patients in group 2 had discontinued treatment due to side effects (Table 2). While the rate of discontinuing treatment due to side effects was 15.3% in group 1, this rate was 4.5% in group 2. When double probiotics were added to the treatment, it

**Table 1. Clinical Characteristics of the Patients**

	<b>Group I</b>	<b>Group II</b>	<b>P</b>
Number of patients	222	240	
Primary diagnosis			
Gastritis	171	187	
Peptic ulcer	51	53	0.872
Number of patients discontinuing treatment due to side effects	34 (%15.3)	11 (%4.5)	0.000
Helicobacter eradication	152 (%68)	214 (%89)	0.000

**Table 2. Side effects seen in patients**

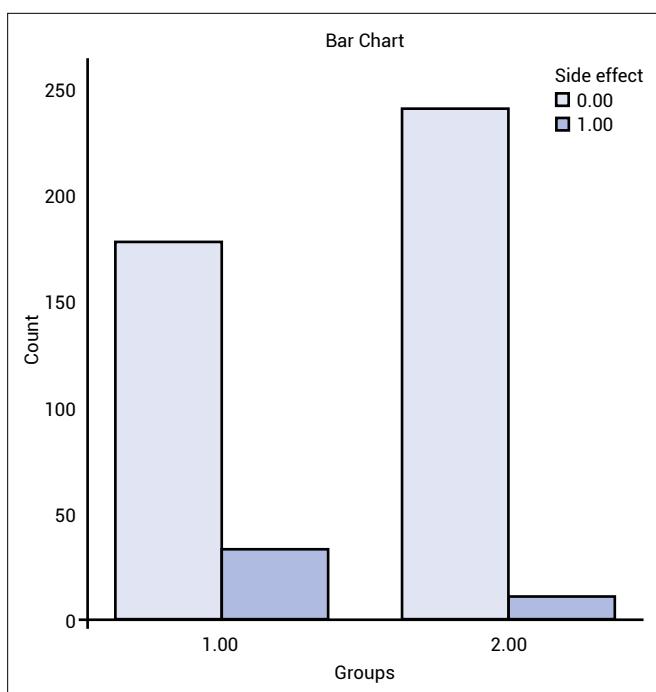
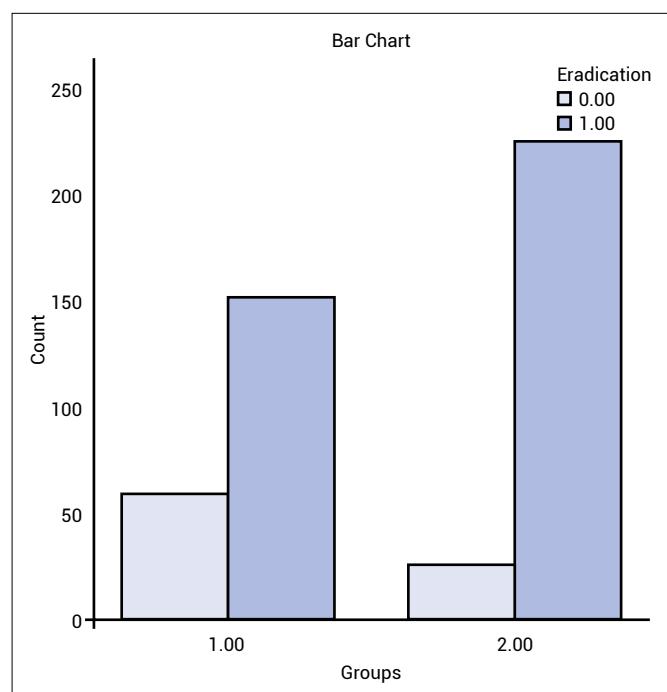
<b>Side Effects</b>	<b>Group 1</b>	<b>Group 2</b>
	34	11
Diarrhea	16	5
Abdominal pain	10	4
Taste disturbance	6	1
Allergy	2	1

was observed that there was a decrease of 11.2% in serious side effects. There was a significant difference between the two groups in terms of serious adverse effects in favor of the group in which double probiotics were added to the treatment ( $p<0.001$ ) (Fig. 1). After the completion of the treatments, it was observed that *H. pylori* eradication was achieved in 152 out of 222 patients (68%) in group 1 and in 214 (89%) of 240 patients in group 2 (Table 2). When

double probiotics were added to the treatment, it was observed that the success of eradication increased by 21%. There was a significant difference between the two groups in terms of *H. pylori* eradication in favor of the group in which double probiotics were added to the treatment ( $p<0.001$ ) (Fig. 2).

## Discussion

*H. pylori* infection is seen in the community with a frequency of 50%.<sup>[4,5]</sup> It is known that this rate is 80–90% in developing countries.<sup>[15]</sup> *H. pylori* is an opportunistic and infectious bacterium in both humans and can cause gastritis, peptic ulcer, gastric cancer, MALTOMA, iron deficiency anemia in humans.<sup>[16,17]</sup> In *H. pylori* eradication, PPIs are often used together with dual antibiotics. Depending on the antibiotics used in the treatment of *H. pylori*, side effects such as abdominal pain, diarrhea, and taste dis-

**Figure 1. Chart of side effect.****Figure 2. Chart of eradication.**

turbance develop due to especially clarithromycin, and results such as discontinuation of treatment occur.<sup>[18]</sup> *H. pylori* develops resistance against antibiotics as well as escape from the immune system thanks to virulence factors.<sup>[12]</sup> The prevalence of *H. pylori* resistance to clarithromycin varies among different countries, such as 10.6 to 25% in North America, 16% in Japan, and 1.7–23.4% in Europe.<sup>[19-21]</sup> In a study conducted in Turkey to 18.7% for clarithromycin and amoxicillin used for *H. pylori* treatment resistance it has been reported that 9.4%.<sup>[22]</sup>

Since the use of antibiotics in the treatment of *H. pylori*, increasing antibiotic resistance and discontinuation of the treatments due to the side effects of these antibiotics have led to a gradual decrease in *H. pylori* eradication rates. It has been reported that adding probiotics to treatment to increase the success rate in *H. pylori* eradication has positive results.<sup>[23,24]</sup> While *H. pylori* disrupts the normal flora in the stomach microbiota, antibiotics used in the treatment cause a decrease in normal strains in the intestinal flora that persist for a long time.<sup>[25]</sup> Probiotics have positive effects in the protection of the intra-stomach microbiota against the negative effects of *H. pylori* and in the renewal of the deteriorated intestinal flora.<sup>[26]</sup> In an experiment with mice with *H. pylori* infection, Lactobacillus was shown to be effective in regulating the microflora in the stomach and intestines.<sup>[27]</sup>

The virulence factors of *H. pylori* are urease, flagella, adhesin, cag A gene, and cytoplasmic cytotoxin.<sup>[28]</sup> Urease hydrolyzes urea and produces ammonia, which buffers cytosol and periplasm and helps create a neutral environment. It maintains intracellular and extracellular ph by forming a layer around the bacterial surface. In this way, *H. pylori* can live in a highly acidic environment such as the stomach and duodenum. Urease is the most important colonization factor of *H. pylori*. Ammonia resulting from urease activity exerts pro-inflammatory effects and increases cytokine release by activating monocytes. This leads to inflammation in the stomach and duodenum and thus direct mucosal damage.<sup>[28]</sup> Under favor of *H. pylori* flagella, it uses ammonia as a chemotactic mediator and enables colonization by moving away from the acidic area.<sup>[29]</sup> Under favor of the adhesin on the bacterial surface, it can be attached to the gastric mucosa.

Binding adhesin, an outer membrane protein of *H. pylori*, contributes to virulence by binding to the Lewis B type antigen of human cells. The CagA gene induces abnormal proliferation and movement of gastric epithelial cells,

promoting the acquisition of a cellularly transformed phenotype.<sup>[30]</sup> VacA induces host cells while releasing proinflammatory chemokines and plays a role in intracellular signaling. VacA is the major virulence factor of *H. pylori*. VacA attaches to stozole and releases bicarbonate and organic anions. At the same time, it provides the entry of iron and nickel, which are needed by *H. pylori*.<sup>[31]</sup>

Lactobacillus secretes metabolites that reduce *H. pylori*'s urease activity.<sup>[32]</sup> Lactobacillus attenuates CagA translocation and phosphorylation, leading to a reduction in *H. pylori*-induced inflammation of gastric epithelial cells.<sup>[33]</sup> Lactobacillus strains reduce *H. pylori* colonization.<sup>[34]</sup>

Bifidobacterium inhibits *H. pylori* adhesion to intestinal mucus by site competition and has been shown to reduce IL 8 levels in in vivo studies and reduce in vivo-in vitro *H. pylori* activity.<sup>[35]</sup> In Maastricht V Consensus Report, it has been accepted that some probiotic strains may have positive effects on *H. pylori* eradication.<sup>[36]</sup> In the light of these data, it is reasonable to assume that using a combination of probiotics that act on *H. pylori* by different mechanisms can create a synergistic effect. This is why we decided to use combined probiotic strains when designing our study.

According to a meta-analysis of 13 studies, with the addition of only Lactobacillus as a probiotic to *H. pylori* treatment, eradication increased by 11% and all side effects decreased by 8%.<sup>[37]</sup> In a meta-analysis including 10 studies investigating the use of probiotic strains containing Lactobacillus and bifidobacter in beer, it was reported that this combination had positive effects on eradication and antibiotic side effects.<sup>[38]</sup> In another meta-analysis including 19 studies, it was reported that all side effects were reduced by 14% in treatment with different types of probiotics, and treatment success was better in treatment groups containing multiple probiotic strains.<sup>[24]</sup>

In our study, the use of combined probiotics containing *L. acidophilus* + *B. animalis* Subsp Lactis increased the *H. pylori* eradication rate by 21%, and the rate of serious side effects that would discontinue treatment decreased by 11%. Only the side effects that were serious enough to cause discontinuation were added to the side effect research conducted in our study. Eradication success rate and reduction in side effects are higher than studies conducted with a single probiotic strain reported in the literature.

## Conclusion

The results we obtained in our study showed that the

addition of two different probiotics to the classical treatment contributed to the continuity and completion of the treatment by preventing the development of side effects. Combined use of *L. acidophilus* + *B. animalis* Subsp *lactis* increases *H. pylori* eradication in addition to reducing the side effects of antibiotics such as abdominal pain, diarrhea, and taste disturbance, and also reduces mucosal damage such as gastritis due to *H. pylori*.

## Disclosures

**Ethichs Committee Approval:** Tokat Gaziosmanpasa University Medical Faculty 21-KAEK-182 29/08/2021.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – B.K.; Desing – B.K., E.K., S.Y.; Supervision – B.K., M.Y., N.Ö.; Materials – C.U., M.S.B.; Data collection and/or processing – B.K.; Analysis and/or interpretation – B.K., M.Y.; Literature search – B.K., S.Y.; Writing – B.K.; Critical review – N.Ö.

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