



Impact of *Lactobacillus Reuteri* and Three Other Probiotics in *Helicobacter Pylori* Eradication

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Abstract

AIM: The aim of the study was to assess the effectiveness and safeness of *Lactobacillus reuteri* and additionally three other probiotics to conventional triple therapy against *Helicobacter pylori*.

MATERIALS AND METHODS: We randomly selected 115 *H. pylori* positive dyspeptic patients, to be treated for 14 days with conventional triple therapy, without and with probiotics. Our first group of 62 patients received conventional triple therapy, while the second group of 53 patients was treated with *L. reuteri* and *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium lactis*, all encapsulated in PharmaS Helicobalans capsules alongside the conventional triple therapy. One month after completion of treatment, *Helicobacter pylori* presence was evaluated. If the *H. pylori* test would turn out negative, it would prove the success of the eradication.

RESULTS: Thirty eight patients in the first group (61.3%) were successfully treated. In the second group, where probiotics were added, the success of eradication was observed in 37 of them (69.8%). Even though eradication was higher in the second group, the difference between the two sides in terms of statistics was not significant ($p = 0.199$). Regarding the side effects of ordered treatment, 27 patients in the first group (43.5%) had complaints, while the second group had 17(32%). Again, there was seen no difference statistically important between the two sides.

CONCLUSION: Including probiotics additionally to conventional *H. pylori* treatment may decrease the side effects of the therapy and increase the *H. pylori* eradication success. Randomized and prospective work is needed on a larger scale.

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Introduction

Helicobacter pylori is the primary cause of chronic gastritis, peptic ulcer disease, adenocarcinoma of the stomach, and MALT lymphoma and is related to some extragastrointestinal diseases [1]. In 1994, *H. pylori* was identified as a carcinogen of class one by the World Health Organization. However, studies have found that the eradication of *H. pylori* can decrease the occurrence of stomach cancer [2].

The Maastricht V/Florence Consensus Report advises eradication therapy for individuals with *H. pylori* infection [2]. However, there are still no options for those who went through the conventional treatment unsuccessfully as a consequence of antibiotic resistance and the considerable amount of side effects of the antibiotics. Alternative treatments against *H. pylori* are being sought. The use of probiotics alone or in combination with antibiotics is being explored as another possible way to control the *H. pylori* infection and reduce the side effects of antibiotic therapy [3], [4], [5].

H. pylori treatment continues to decline. The percentage of successful treatment of *H. pylori* with conventional triple treatment in Kosovo ranges from

68% up to 71% [6]. Perhaps, we should also mention a recent study on levofloxacin with an *H. pylori* eradication rate of about 96% [7].

Supplementary therapy with pro- and pre- as well as synbiotics can be an encouraging option.

Probiotics are described as "living microorganisms that are beneficial to host health when consumed in sufficient amounts." Pre-biotics are non-digestible nutrients that promote the activity and development of favorable probiotics in the colon. Synbiotics are both probiotics and prebiotics in combination that can act cooperatively [8]. *In vitro* examinations have shown suppressive effects of some probiotics on *H. pylori* [9], [10].

There are randomized and controlled trials that show favorable results for the inclusion of probiotics in *H. pylori* eradication treatment. It is thought that probiotics reduce the side effects such as diarrhea related to antibiotics [11], [12].

Lactobacillus reuteri, a probiotic bacterium that can colonize a wide range of mammals, is found in various parts of the human body. Several salutary impacts of *L. reuteri* have been observed.

L. reuteri can produce antimicrobial molecules such as ethanol, reuterin, and organic acids.

It can suppress the colonization of pathogenic microbes and reshape the structure of commensal microbiota. In addition, *L. reuteri* can support the immune system of the host. For instance, some of its strains can decrease the creation of pro-inflammatory cytokines while helping the regulatory T cells develop and function. Finally, colonization with *L. reuteri* may reduce microbe displacement from the gut cavity into tissues due to its effects on strengthening the gut barrier [13].

Pylopass™ is a specific strain of the bacterium *L. reuteri* (DSMZ 17648) that specifically coagulates with *H. pylori* in the stomach. *L. reuteri* has been recognized as a particular binding opponent of *H. pylori* compared to other Lactobacillus strains.

L. reuteri exhibits coaggregation with different strains and *H. pylori* serotypes without affecting other colonizing bacteria in the digestive tract. *L. reuteri* (Pylopass™) contains specific structures that recognize and exhibit coaggregation with *H. pylori* through surface structures. After coagulation in the stomach, they are excreted from the body through the digestive tract.

PharmaS Helicobalans is a unique combination of inactivated bacteria *L. reuteri* DSMZ 17648 (Pylopass™) and lyophilized bacterial probiotics (*Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium lactis*). A PharmaS Helicobalans capsule contains 100 mg of Pylopass™, as well as at least 1×10^9 CFU with *L. acidophilus* strain LA1, *B. lactis* BL3, and *L. casei* LC5.

The additional effect of probiotics in PharmaS Helicobalans is to restore intestinal microflora, which is significantly damaged during intensive antibiotic therapy (triple therapy) [14].

Our study aimed to evaluate whether the addition of probiotics in the capsule form of PharmaS Helicobalans in triple therapy could alter the percentage of *H. pylori* eradication or antibiotic side effects.

Materials and Methods

In this study, 115 patients from the Hospital Gastroenterology Clinic and Kosova Clinical University Service who are positive for *H. pylori* and have dyspeptic symptoms were included in the study. They were split into two groups. The first group of 62 patients received conventional triple therapy; 40 mg pantoprazole twice a day, 30 min before meals; 1 g of amoxicillin, and 500 mg of clarithromycin twice a day after meals for 2 weeks. The second group of 53 patients, in addition to conventional triple therapy, was treated with a combination of *L. reuteri* and three other probiotics (*L. acidophilus*, *L. casei*, and *B. lactis*) in capsule form of PharmaS Helicobalans, 3 h after

antibiotics, for 2 weeks. The first diagnosis was made by the results of several tests, including gastroscopy with rapid urease test or stool antigen test. One month after discontinuation of therapy, *H. pylori* status was assessed with urea breath or stool antigen test. If the *H. pylori* test would turn out negative, it would prove the success of the eradication.

Results

The elimination of *H. pylori* showed success in 38 of the first group of 62 patients, of whom 25 (40.3%) are women and 37 (59.7%) are men, with a median age of 39.82 ± 14.42 years. *H. pylori* was eradicated with standard triple therapy in 38 of them (61.3%). In the second group of 53 patients, 30 women (56.6%) and 23 men (43.4%) with a median age of 42.86 ± 14.23 years in whom probiotics were also included in conventional therapy, eradication occurred in 37 (69.8%) of them. Even though the success of eradication was higher in the second group, the difference between the two groups in terms of statistics was not significant ($p = 0.199$). Regarding the side effects of ordered therapy, 27 patients in the first group (43.5%) had complaints, while the second group had 17(32%). Again, there was seen no difference statistically important between the two sides.

Discussion

Due to the appearance of resistance of *H. pylori* to antibiotics, as well as their side effects, the percentage of *H. pylori* eradication in the past few years has been declining. In developing countries, the eradication success rate is about 50%, while in Kosovo, the success rate with triple therapy is 68–71% [6]. If we compare this with the results of the current work, we see that for 16 years, we have had a decrease in *H. pylori* eradication of about 10%. Clinical studies have concentrated on combining known drugs with supplemental therapies. This has led to studies in which probiotics have been added to standard treatment protocols. As each study used different strains and methods, the conclusions of these trials are incomparable.

In our work, we used the product PharmaS Helicobalans capsules, a new product on the Kosovar market. PharmaS Helicobalans contains Pylopass™ (inactivated culture *L. reuteri* DSM 17648) 100 mg, lyophilized coated culture *L. acidophilus*, lyophilized coated culture *B. lactis*, and lyophilized coated culture *L. casei*. To the best of our knowledge, this is the only study conducted with this product.

Probiotics are known to be used as a single therapy in treatment protocols or as a supplement accompanied by conventional therapy. The first study on the use of only probiotics in the treatment of *H. pylori* is the 1989 study by Bhatia *et al.* In this study, it was found that the *in vitro* development of *H. pylori* is suppressed with the presence of *L. acidophilus* in that culture [9].

Some studies have been conducted with probiotics as monotherapy against *H. pylori*. These studies show that some specific probiotics such as *S. boulardii* or *L. Johnsonii* La1 may decrease the bacterial amount, but cannot eradicate *H. pylori* [15].

Our study showed higher success in infection eradication in the second group that was treated with standard triple therapy combined with probiotics for 8.5% (61.3% vs. 69.8%) although this increase is statistically non-significant ($p = 0.199$). Furthermore, in the appearance of side effects, we found that in the group that received probiotics, side effects were lower by 11.5%, although not statistically significant. In this study, we have observed that *L. reuteri* and three other probiotics not only improved the rate of eradication, but also reduced some of the side effects during therapy, particularly vomiting, nausea, bitter taste, and abdominal discomfort. This reduction of side effects with the help of probiotics could improve the compliance of the patients in the procedure of the complete treatment of *H. pylori*.

Our conclusions are by other results found in published work on the use of probiotics in the treatment of *H. pylori*.

When talking about probiotic monotherapy and *H. pylori* eradication, we should mention the meta-analysis by Losurdo *et al.* (2018), in which they recruited 11 studies with 517 patients, of whom 115 have been treated with placebo and selected as a control group, while the other 403 patients have received probiotic supplements. The probiotics showed success in 50 out of 403 subjects. The weighted average rate of eradication was 14%. Probiotic treatment was unsuccessful in six studies, while an Italian study resulted in the highest rate of success in eradication (32.5%). Lactobacilli eradicated *H. pylori* in 30 of 235 patients or 16%. *S. boulardii* had eradicated *H. pylori* in six individuals out of 63, with a combined eradication rate of 12%. The combination of multiple strains was successful in 14 out of 105 individuals, with a combined eradication rate of 14%. Only three studies have shown side effects throughout probiotic intake. No differences in adverse reactions were observed between probiotics and placebo. They concluded that probiotics alone have a weak effect on *H. pylori* eradication, proposing a direct role [16].

Tang (2007) and Zhu (2014) stated that probiotic supplements are likely to increase the success rate of eradication and decrease side effects. However, the

benefits of probiotics appear to be specific to different strains, so evaluating different strains in a meta-analysis can conduct inaccurate results. Therefore, pooling the data on a single strain and executing a meta-analysis is a better point of view [17], [18].

Furthermore, some other studies have concluded that probiotics can decrease adverse reactions to antibiotics and enhance compliance with the treatment.

A study by Scaccianoce *et al.* (2008) of 65 patients evaluated the effect of *L. reuteri* and high concentrations of probiotics in addition to conventional triple therapy. Although 2 weeks of therapy and a probiotic mixture are likely to achieve a higher rate of eradication (71%), there was no significant difference between the varying therapeutic protocols tested. (range: 53–71%).

The lowest occurrence of the adverse reactions was seen following the 1-week therapy and *L. reuteri* (6%) and the highest with the 2 weeks of triple treatment and probiotic mixture (33%), anyway, there was no statistically significant difference. This study concluded that acceptable eradication rates could not be reached with 1–2 weeks of triple treatment with or without probiotics [19].

In the study by Emara *et al.* (2014), 70 patients who were not treated with eradication therapy were randomly split into two groups. The first group was treated with *L. reuteri* while the other group received a placebo only. Subjects underwent the conventional triple therapy for 14 days and either *L. reuteri* (a combination of *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475) or placebo for 4 weeks. In addition to triple treatment, *L. reuteri* has increased eradication rates by 8.6%, improved outcome of the gastrointestinal symptoms rating scale, decreased adverse reactions, and improved histological characteristics of *H. pylori* infection compared to triple treatment supported with placebo [20].

The objective of Francavilla's (2014) work was to evaluate the role of new probiotics such as *L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475 in *H. pylori* contamination. In conclusion, it is stated that only the *L. reuteri* combination can express the inhibitory effect on the growth of *H. pylori*, and when combined with antibiotic therapy, it causes a notable decrease in adverse reactions caused by antibiotics [21].

According to research, probiotic supplements can increase the rate of eradication during the first and second line regimen [22]. However, some other studies conclude that probiotic supplements do not affect the rate of eradication by a significant amount.

Wang *et al.* (2017) concluded that triple therapy supplemented with probiotics did not increase the rate of eradication [23]. Furthermore, many works have observed that side effects were significantly lower in the group treated with probiotics and antibiotics than

in the control group, but the results differed in some other studies [21], [24], [25]. It is worth emphasizing that probiotic monotherapy is not satisfactory, but can be recommended as a supportive therapy [26].

There are some systematic innovations and meta-analyses on the impact of probiotics as an additional treatment in conventional therapy against *H. pylori*.

We must mention a meta-analysis by Lau *et al.* (2016) that has evaluated the effect of most probiotic supplements on the efficiency of triple treatment. The study includes 30 randomized studies done with several subjects >4000, both adults as well as children.

Including probiotics in the treatment increased the rate of eradication by 12.2%.

Probiotics were seen to be useful for adults, children, or both Asian and non-Asian populations. The difference between the effectiveness of probiotics was non-significant.

The possibility of adverse reactions was observed to be low [27].

Another meta-analysis that should be mentioned in the study by Shi *et al.* (2019) aimed to test the effects and safety of probiotics in the eradication of *H. pylori* and estimate the adequate duration and timing of supplements. Forty types of research with 8924 patients were included in the analysis. The eradication rate was observed to be higher in the probiotic group. They stated that probiotic supplements increased the eradication rate and decreased the adverse reactions when used additionally with antibiotics [28].

To evaluate the effect of Lactobacillus supplementation on the eradication of *H. pylori* and the side effects of triple therapy, Yu *et al.* (2019) performed a meta-analysis with 11 randomized studies and 724 patients. The elimination rate of *H. pylori* was significantly higher in the Lactobacillus-supplied group than in the control group. As for the adverse reactions, supplementation reduced the taste disturbance in notable amounts. It is stated that probiotic supplements throughout *H. pylori* therapy may significantly improve the rate of eradication and decrease the occurrence of effects related to taste [29].

The Yang *et al.* (2021) meta-analysis also studied the effects of adding *L. reuteri* to *H. pylori* treatment and related adverse reactions to the therapy. Six RCTs conducted with 378 subjects were involved in the study. An intention-to-treat analysis using observed that the relative combined risk of eradication rate was greater in the *L. reuteri* supplement group, but there was no significant difference. The occurrence of adverse reactions was reduced in the supplemented group [30].

Our data are consistent with other evidence from reviews suggesting that probiotics may be advised as a substitute therapy for *H. pylori*.

Limitations

The limitations of our study may be:

- *H. pylori* cultures, drug resistance, and antibiotic sensitivity tests were not conducted.
- We assessed only the presence or absence of adverse reactions without measuring the intensity.

Conclusion

In our study, *L. reuteri* and three other probiotics not only increased the rate of eradication but also reduced some of the adverse reactions throughout therapy, particularly nausea, vomiting, abdominal pain, and taste issues. By reducing these side effects with probiotic supplementation, patients' compliance with therapy could improve toward complete eradication.

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