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Original Article

Study of probiotic and simvastatin additive effect on *Helicobacter pylori* eradication rate Abazar Parsi^{1,*}, Maryam Biuseh¹, Samira Mohammadi¹, Eskandar Hajiani¹, Seyed Jalal Hashemi¹, Hooman Saeidian², and Mehdi Biuseh³

A B S T R A C T

Background: *Helicobacter pylori* infection is a major cause of chronic gastritis, peptic, mucosa associated lymphoid tissue. Misdiagnosed as lymphoma and gastric cancer. The eradication rate of *H. pylori* with standard treatments are decreasing worldwide. The aim of this study was to determine the efficacy of adding simvastatin or probiotic as adjuvant to quadruple therapy on the eradication of *H. pylori*.

Methods: This randomized clinical trial study was conducted on 160 patients with *H. pylori*. The patients were randomly divided into 4 groups. The group 1: standard quadruple eradication regimen consisting of two antibiotics (clarithromycin 500 mg and amoxicillin 1 g, all twice per day), a proton pump inhibitor (pantoprazole 40 mg twice daily), Bismuth (120 mg twice daily) with placebo (daily), group 2: standard regimen plus probiotic (daily 250 mg), group 3: standard regimen supplemented with simvastatin (10 mg daily) and group 4: standard regimen plus simvastatin (20 mg daily) for 14 days was given. The Eradication was determined by stool antigen test at least 1 month after treatment.

Results: The risk ratio of eradication of the infection in the simvastatin group 10 mg and simvastatin 20 mg was 0.375 and 0.625 times in compare with the placebo group, indicating a negative effect of simvastatin 10 and 20 mg on the treatment of *H. pylori* infection, this relationship is not statistically significant ($P > 0.05$).

Conclusion: Due to the high efficacy of simvastatin in *H. pylori* eradication, further studies are needed to evaluate the use of statins as adjunctive to improve the eradication rate.

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Keywords: Adjuvant therapy; Eradication; *Helicobacter pylori*; Probiotic; Simvastatin

Introduction

Peptic ulcer disease (PUD) refers to the presence of one or more ulcerative lesions in the lining of the stomach (gastric ulcers) or in the first part of the small intestine (duodenal ulcers). Rarely, nevertheless, peptic ulcers can also occur in the esophagus, jejunum or sometimes in a Meckel's diverticulum.¹ The 2 main etiologies of PUD are infection with the bacterium *Helicobacter pylori* (most common) and prolonged use of nonsteroidal anti-inflammatory drugs.² Despite the reduction of this disease due to *H. pylori*, the incidence of PUD is still high in several countries. Without treatment complications of PUD include bleeding, perforation, gastric outlet obstruction, and gastric cancer may lead to increase in hospitalization and mortality.³

H. pylori is a spiral-shaped gram-negative, microaerophilic bacterium that colonizes the stomach of half of the human population in the world.⁴ *H. pylori* able to penetrate the mucus layer attach to gastric epithelial cell and intracellularly evades host immune responses and antimicrobial therapy, in result can cause persistent infection.⁵

H. pylori considered to be the major cause of inflammatory gastroduodenal diseases, including duodenal ulcer, peptic ulcer, iron deficiency or vitamin B₁₂, gastric adenocarcinoma and primary B-cell gastric lymphoma.^{6,7} Therefore, eradication of *H. pylori* can lead to a reduction in the incidence of peptic ulcer and prevent gastric cancer.^{8,9}

Standard triple therapy (TT), which consists of proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole,

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is recommended as first-line therapy for eradication of *H. pylori* in clinical guidelines worldwide.¹⁰ According to studies, the addition of bismuth salts to standard three-drug therapy has been shown a favorable effect on eradication rates. The three-drug therapy, including bismuth, in areas with high resistance to clarithromycin as the first line therapy and in areas with low prevalence of clarithromycin resistance as a standard substitute for triple drug regimen or recommended as a rescue regimen for eradicating *H. pylori*.¹¹

In recent years, despite many efforts to eradicate *H. pylori*, the success of the first-line therapies of *H. pylori* eradication has declined in many countries and the rate of eradication has been reported between 57% to 55% in developing countries and Western European countries.¹² Recently, several studies and meta-analyses have demonstrated a lower eradication rate for treating three-drug, a large part of this reduction is due to a significant increase in antibiotic resistance.¹³

Several factors involved in the therapy failure such as strain type, high bacterial load, low gastric pH and impairment of mucosal immunity. However, the main reason for the failure therapy is poor compliance and antimicrobial resistance.¹⁴ So, *H. pylori* eradication therapy success remains a challenge and more research is needed to increase eradication.

Statins, or 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, are a class of lipid-lowering medications that widely prescribed for patients with hypercholesterolemia,¹⁵ and have a protective role in several bacterial diseases. In addition to cholesterol lowering effect, statins also have anti-inflammatory properties, including modulation of immune response, regulation of major histocompatibility complex class expression, mucosal proliferation and secretion activity.¹⁶ On the other hand, statins have gastroprotective effects and attenuation of peptic ulcer development.¹⁷ Studies have recently been reported that combination therapy includes TT regimen (PPI, clarithromycin and amoxicillin) along with statins accelerate the clearance of *H. pylori* and ameliorate ulcer development,¹⁵ and also treatment with statins reduce *H. pylori*-related inflammation.¹⁸

Nowadays, probiotics are also considered as an adjuvant therapy to increase the rate of eradication and reduce the side effects of therapy regimens. Administration of probiotics to adults and children have improved *H. pylori* eradication rates and reduced PPI- associated with side effects.¹⁹ However, the probiotic administration time along with four-drug regimen is not well determined.

H. pylori can be affected by probiotics through multiple mechanisms.²⁰ For example, probiotic lactic acid bacteria inhibit of *H. pylori* urease activity by the lowering of the pH. Another mechanism is that bacteriocins produced by lactic acid bacteria able to kill *H. pylori*. Probiotics are also effective in preventing *H. pylori* colonization of the gastric mucosa by inhibiting its adhesion to epithelial cells.²¹ In addition, several studies have shown that probiotics can reduce the side effects of antibiotics and improve the tolerability of *H. pylori* eradication therapy.²² The first line therapy of *H. pylori* infection is a three-drug regimen. But given the increasing resistance of these bacteria, alternative therapies and combination therapies are needed more than before. The aim of the present study was the effect of adding probiotic and simvastatin as an adjuvant therapy to a four-drug regimen on the rate of eradication of *H. pylori*.

Methods

Study population

This randomized clinical trial study was performed on 237 patients with *H. pylori* infection confirmed by endoscopy and biopsy who were referred to gastroenterology clinics of the imam Khomeini of the Ahvaz city, the capital city of Khuzestan, in 2017. Inclusion criteria for this study consisted of consent to participate in a research study, age over 18 years old, lack of treatment until now. Also, the exclusion criteria of study were including patient dissatisfaction, history of antibiotic consumption, not taking the drug and any contraindication of taking probiotic or simvastatin, drug-related side effects while taking medications, alcohol consumption, smoking, pregnant women, diabetic patients, history of recent gastrointestinal bleeding and patients with suspected malignant in endoscopy. Finally, 160 patients selected according to exclusion and inclusion criteria. Seventy seven patients excluded of study due to incompatible with inclusion criteria (38 patients), unwilling to participate in the study (27 patients) and other reasons (12 patients). This study was registered with the Ethics Committee of Jundishapur University of Medical Sciences (No. IR.AJUMS.REPC.1396.892) and patient demographic information (age and sex) and clinical information was collected with permission from the Jundishapur University of Medical Sciences' questionnaires. The ethnic consent was obtained from each individual participated in this research work.

Clinical trial performance

The patients were randomly divided in four groups of 40. The group 1 received a standard quadruple eradication regimen consisting of two antibiotics (clarithromycin 500 mg and amoxicillin 1 g, all twice per day), a PPI (pantoprazole 40 mg twice daily), Bismuth (120 mg twice daily) with placebo (daily), group 2: standard regimen plus probiotic (daily east 250 mg), group 3: standard regimen supplemented with simvastatin (10 mg daily) and group 4: standard regimen plus simvastatin (20 mg daily). Patients were treated for 2 weeks and explanation of the amount and how of taking the drug was given to the participants.

Evaluation of response to treatment

The Eradication was determined by Stool antigen tests at least 1 month after treatment. The presence of *H. pylori* antigen in the stool is an indication of the failure of the treatment.

Statistical analysis

Statistical analysis was conducted with the chi-square for qualitative variables, and analysis of variance (ANOVA) for quantitative analysis of 2 or more groups (IBM SPSS Statistics, ver. 22; IBM Corp., Armonk, NY, USA) with 95% confidence interval. The *P*-values of lower than 0.05 were regarded as statistically significant. The results were presented as frequencies or percentage. The modified Poisson regression test was used to evaluate the risk ratio (RR) of *H. pylori* eradication in different groups and to adjust for age and sex. The type of analysis based on intention-to-treat (ITT) is a gold standard for randomized clinical trial, although since the value of the value was zero, and compliance was 100%, there would be no difference between the ITT and the protocol (STATA, ver. 14; Stata Corp., College Station, TX, USA).

Results

Age/sex of patients

In this study, 73 (45.63%) of the subjects were male and 87 (54.38%) were female. There was no significant relationship between patients' sex in the 4 groups ($P = 0.250$; Table 1). The average ages of patients were 2.6 ± 3.0 years. No significant relationship was found between patients' age in the 4 groups ($P = 0.347$; Table 2).

H. pylori eradication

The results of RR of eradication of *H. pylori* infection in probiotic groups, simvastatin 10 mg and simvastatin 20 mg compared to placebo group are shown in Table 3. The highest RR was related to the probiotic group with 1.125, this difference was not statistically significant ($P = 0.785$). The RR of eradication of the infection in the simvastatin group 10 mg and simvastatin 20 mg was 0.375 and 0.625 times in compare with the placebo group, indicating a negative effect of simvastatin 10 and 20 mg on the treatment of *H. pylori* infection, this relationship is not statistically significant ($P > 0.05$).

The results of RR of eradication of *H. pylori* infection in the groups of probiotics, Simvastatin 10 mg and simvastatin 20 mg in compared with Placebo groups adjusted based on sex have been shown in Table 4. Sex is not a confounding variable for the type of treatment and eradication of *H. pylori* infection ($P = 0.196$).

Table 1 The Results of Frequency Distribution of the Sex Patients in the 4 Groups

Group	Male	Female	P-value
Placebo	18 (45.0)	22 (55.0)	0.250
Probiotic	14 (35.0)	26 (65.0)	
Simostatin 10 mg	18 (45.0)	22 (55.0)	
Simostatin 20 mg	23 (57.5)	17 (42.5)	

Values are presented as number (%).

Table 2 The Mean Age of Participants in Different Groups

Group	Age (yr)	P-value
Placebo	38.02 $\pm$ 10.33 (19–53)	0.347
Probiotic	37.85 $\pm$ 9.14 (23–56)	
Simostatin 10 mg	38.17 $\pm$ 9.99 (21–53)	
Simostatin 20 mg	34.85 $\pm$ 8.86 (21–52)	

Values are presented as mean $\pm$ standard deviation (range).

Table 3 The Results of the Comparison of *Helicobacter pylori* Eradication in the 4 Groups

Group	Risk ratio (95% confidence interval)	Standard error	z	P-value
Probiotic	1.13 (0.48–2.62)	0.486	0.27	0.785
Simostatin 10 mg	0.38 (0.11–1.31)	0.24	–1.53	0.126
Simostatin 20 mg	0.63 (0.22–1.75)	0.328	–0.89	0.372

The results of RR of eradication of *H. pylori* infection in the groups of probiotics, simvastatin 10 mg and simvastatin 20 mg in compared with Placebo groups adjusted based on age have been shown in Table 5. Age is not a confounding variable for the type of treatment and eradication of *H. pylori* infection ($P = 0.785$).

Discussion

The results of the current study demonstrated that simvastatin accompanied by the 4 drugs standard or routine treatment for 14 days, was able to increase the *H. pylori* eradication; however, there was no significant difference among those four treatment groups. In addition, no significant difference was revealed in the rate of *H. pylori* infection eradication in both groups considering age and sex.

Mahdavi²³ examined the effect of atorvastatin 40 mg with a three-drug regimen for 14 days aiming at eradication of *H. pylori* in the stomach. Their results demonstrated that the success rate of *H. pylori* treatment and its eradication in patients receiving the three-dose regimen with atorvastatin was 73% and in the non-atorvastatin received group was 69% not being significant. Although individuals who received atorvastatin were more successful in the eradicating of *H. pylori* infection this observation was not statistically significant. The results of this study were consistent with our findings, although in our study, the rate of eradication in all groups was higher. The reason for the difference in the rate of infection eradication is possibly due to the differences in the sample size, dietary conditions, and antibiotic resistance. On the other hand, the results of clinical trials conducted by Nseir et al¹⁵ indicated that addition of simvastatin to the three drugs standard therapy for 7 days significantly improved the rate of *H. pylori* eradication from 72% to 91%. The results of their study did not similar to those from our study. In our study, although the rate of eradication with statins at 10 mg and 20 mg (92.5% and 87.5%, respectively) was high similarly, its rate was not significantly different with the placebo group. Since the pattern of antibiotic re-

Table 4 Comparison of the Probability Risk Ratio (RR) of Eradication of *Helicobacter pylori* Infection Treatment Adjusted Groups Based on Sex

Variable	RR (95% confidence interval)	Standard error	z	P-value
Group				
Probiotic	1.07 (0.46–2.48)	0.46	0.16	0.872
Simostatin 10 mg	0.38 (0.11–1.32)	0.24	–1.52	0.128
Simostatin 20 mg	0.66 (0.24–1.85)	0.34	–0.78	0.437
Sex				
Male	0.59 (0.26–1.3)	0.23	–1.29	0.196

Table 5 Comparison of the Probability Risk Ratio (RR) of Eradication of *Helicobacter pylori* Infection Treatment Adjusted Groups Based on Age

Variable	RR (95% confidence interval)	Standard error	z	P-value
Group				
Probiotic	1.12 (0.48–2.62)	0.48	0.27	0.786
Simostatin 10 mg	0.38 (0.11–1.31)	0.24	–1.53	0.126
Simostatin 20 mg	0.66 (0.21–1.77)	0.33	–0.9	0.367
Age	0.99 (0.95–1.03)	0.019	–0.27	0.785

sistance in different individuals may vary, the effectiveness of the drug regimen also varies according to regional conditions. This could be the reason for the difference in the results. In addition, no statistically significant difference observed between statins group and control group in our study in the *H. pylori* eradication may be associated with the antibiotic resistance. In most consumer patients, negligible side effects have been reported following statins. The most commonly observed side effects of statins in the clinic are muscular problems ranging from myalgia to rhabdomyolysis.²⁴ Other side effects of these drugs include increased serum levels of liver enzymes. Since most of the clinical trials implemented and observed these complications over a long period of time, this effect was not observed in our study for 14 days. The reason for the lack of observation of these complications may be due to the low number of samples in our study. Another finding from our study was that the use of probiotics with four drug treatments did not enhance the *H. pylori* eradication rate. Several studies on the efficacy of prescribing probiotics in addition to standard treatments have been conducted to eradicate *H. pylori* and various and sometimes contradictory results have been obtained. The strain and dosage of probiotics and the duration of their use in previous studies have been mentioned as an important issue. The results of our studies are not comparable with these findings, which may be due to the use of various strains and various treatment strategies. Some studies have reported a lack of positive effects of probiotics on *H. pylori* eradication. For example, according to studies by Goldman et al,²⁵ Hurdut et al,²⁶ and in addition Padilla Ruiz et al,²⁷ administration of probiotics had no effect on the eradication of *H. pylori*.²⁷ Furthermore, in a study performed on children, the use of probiotics did not enhance the eradication rate of the infection nor reduce the side effects.²⁸ Another study by Yaşar et al,²⁹ they found that the addition of probiotic yogurt to three-drug therapy for 14 days did not increase the rate of *H. pylori* eradication. The results of these studies coincide with the findings of our study. Akcam et al,³⁰ also demonstrated that the use of probiotics with standard three-drug therapy had no effect on the eradication of *H. pylori* infection in children nor the reduction of side-effects of treatment. Saneeyan et al³¹ and Mirzaee and Reza Hosseini³² from 2 separate studies demonstrated that the diet of three standard drugs with probiotics have had no significant effect on *H. pylori* eradication rate. The results of this study are also consistent with the results of our study. However, in contrast to our study results, a study by Du et al³³ found that addition of probiotics before or after standard treatment by the three drugs would significantly enhance the *H. pylori* eradication. Eradication rates are in addition higher if probiotics are consumed after standard treatment. In another study, Dinleyici et al³⁴ demonstrated a significant improvement in the eradication of *H. pylori* after use of probiotics. In addition, Kim et al²¹ revealed that prescribing probiotics with three-drug therapy can increase eradication rates; however, they found that this method had no effect on the reduction of the side-effects of standard treatment. A study by Tongtawee et al³⁵ found that pretreatment with probiotics could improve the effectiveness of three drugs treatment success against *H. pylori* eradication, but it had no effect on the reduction of side effects. The results of these studies do not similar to the findings of our study. Lü et al³⁶ observed in their meta-analysis study that the use of probiotic supplements during treatment of three drugs for 7 and 14 days may improve the *H. pylori* eradication, but because of the existence of heterogeneity in these studied regions in the commentary, these results should be taken with care. Tong et al's meta-analyzes study³⁷ resulted that the use of probiotics increase the eradication of *H. pylori* infection. In this study, the

rate of eradication of *H. pylori* by three-drug therapy alone, and compared to three-drug treatment with probiotic was 74.8% and 83.6%, respectively. However, the rate of eradication varies in various surveys. Despite these contradictory results, probiotics are still in daily use, not with the goal of increasing eradication, but to reduce side effects and using their beneficial effects against drug resistance. Therefore, more randomized controlled trial studies are needed to understand and appreciate the effects of probiotics against *H. pylori* infection. Eventually, it should be noted that the present study was conducted for the first time aiming at comparing adjuvant therapy with simvastatin with four bismuth-containing drugs to increase the *H. pylori* eradication, thus there was no possibility to compare definitive findings and conclusions in this regard. In addition, our study contained some limitations, including the fact that the study was conducted only in a health center, with relatively low number of samples. Other limitation of the present study was the lack of evaluation of the adherence to the regimen, the lack of antibiotic susceptibility or drug resistance evaluation, the lack of examination of the side effects and the type of complication and the severity of the symptoms, the failure to check the burden of *H. pylori* by biopsy or bacterial culture and the short-term period follow-up.

Our results demonstrated that the use of probiotic had no significant effect on the rate of *H. pylori* eradication. However, the administration of simvastatin accompanied by the four-drug regimen increased the *H. pylori* eradication rate, although no statistically significant difference was observed among the groups. In addition, because of the high efficacy of simvastatin in *H. pylori* eradication, other controlled randomized trials are necessary for more accurate evaluation of the use of simvastatin or other statins as adjuvant therapy in improving the eradication of this infection. If confirmed, statin administration can be used as an inexpensive and safe drug to enhance the *H. pylori* infection eradication.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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