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Atorvastatin in combination with conventional antimicrobial treatment of *Helicobacter pylori* eradication: A randomized controlled clinical trial

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Abstract

Background and Aim: *Helicobacter pylori* is one of the main causes of digestive diseases, which is difficult to treat and requires the administration of several antimicrobial agents. Considering the anti-inflammatory and antibacterial effect of atorvastatin, the present study aimed at adding this agent to a four-drug regimen in order to eradicate *H. pylori*.
Methods: A total of 220 patients with *H. pylori* infection were included in the current randomized controlled clinical trial. In the current study, 110 patients in the control group received a 14-day regimen of amoxicillin, clarithromycin, bismuth, and esomeprazole, and 110 patients in the intervention group received 40 mg of atorvastatin daily plus the antibiotic regimen for 14 weeks. The treatment results were evaluated 1 month later using *H. pylori* stool antigen test. Data were collected using checklist and analyzed using chi-squared and Fisher's exact tests with SPSS version 18.
Results: *Helicobacter pylori* eradication rate in the intervention and control groups was 78.18% and 65.45%, respectively ($P = 0.025$), and there was a significant difference in terms of non-ulcer dyspepsia between the groups ($P = 0.049$), but there was no significant difference in age, gender, and body mass index between the two groups ($P < 0.05$).
Conclusion: The present study results showed that adding atorvastatin to the four-drug regimen of omeprazole, clarithromycin, bismuth, and amoxicillin is effective in the eradication of *H. pylori*. Also, the addition of atorvastatin to *H. pylori* eradication therapy is more effective in patients with non-ulcer dyspepsia.

Introduction

Helicobacter pylori is identified as the main cause of gastrointestinal diseases, such as peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma; therefore, its eradication is of great importance, and its treatment is of particular interest to most scientific communities.[1,2] *H. pylori* is difficult to treat, and its successful treatment requires simultaneous administration of several antimicrobial agents, such as metronidazole, amoxicillin, bismuth compounds, tetracycline, and clarithromycin, in order to achieve an initial eradication of about 85–90%.[3]

H. pylori are Gram-negative, microaerophilic, non-spore-forming, motile bacteria commonly located deep in gastric mucosa, close to the epithelium. These bacteria bind to gastric epithelium, without invading cells. At first, the bacteria involve antrum, but they migrate over time to the proximal parts of the stomach.[4,5] The prevalence of *H. pylori* is not the same throughout the world and largely depends on the general standards of living in a region. In the developing countries, 80% of the population < 20 years old, and in the industrialized countries, 20–50% of the total population are infected with these bacteria. Low socioeconomic status and lower educational levels are the two predisposing factors for the increase of *H. pylori* colonization.[2] Other risk factors include born or residence in the developing countries, population growth, unsanitary living conditions or contaminated food, and contact with the stomach contents of the infected patient. *H. pylori* are transmitted by the fecal–oral or oral–oral routes. The final outcome of *H. pylori* infection is chronic gastritis, peptic ulcer, stomach adenocarcinoma, and gastric MALT lymphoma, which is characterized by a complex interaction between bacterial and host factors.[3,6]

Several medications have been evaluated in the treatment of *H. pylori*. The choice of a particular regimen is influenced by various factors such as efficacy, patient tolerance, antibiotic resistance, and drug prices. The most commonly used drugs include amoxicillin, metronidazole, tetracycline, clarithromycin, bismuth compounds, and omeprazole.[3]

The statin drugs, that is, atorvastatin, which inhibit HMG-CoA reductase, are mainly used for treatment of hypercholesterolemia. Some studies demonstrate that statins have an anti-inflammatory effect and can reduce C-reactive protein level, independent from their effect on hypercholesterolemia.[1,7–10] Some recent studies indicated the antimicrobial activity of statins against Gram-positive and Gram-negative bacteria and some viruses.[1] Also, statins

inhibit the accumulation of eosinophils by inhibiting the LFA-I/ICAM-I response and contribute to tissue restoration and regeneration in chronic inflammations. Therefore, statins have anti-inflammatory properties and reduce and inhibit the adhesion of leukocytes.[11–14] Although their side effects are known, including muscle weakness and myalgia, recent studies showed that statins are beneficial in the treatment of cardiovascular disease, asthma, rheumatoid arthritis, stroke, and autoimmune diseases, and it seems that they can contribute to the development of anti-inflammatory activities in immune and inflammation diseases.[14,15] Considering the need to eradicate *H. pylori* and its effective treatment, and because statins are introduced as a new class of antibiotics in recent studies, the present study aimed at investigating the effect of atorvastatin on eradication of *H. pylori*.

Methods

The present randomized controlled clinical trial was conducted on patients with *H. pylori* infection referred to Gastroenterology and Hepatology Research Center of Shahid Beheshti Hospital in Qom, Iran.

The required sample size, based on the results of the study by Nseir *et al.*,[16] on the eradication rate of *H. pylori* in the intervention and control groups that was 86% and 69% respectively, with an α error of 0.05 and the study power of 80%, using the sample size formula, was calculated in 91 subjects in each group. Considering possible dropouts and loss to follow-up, the sample size in each group was set to 110.

The inclusion criteria were age above 45 years old with dyspepsia, age less than 45 years old with dyspepsia, high risk factors (weight loss, repeated vomiting, gastrointestinal bleeding, icterus, palpable mass, adenopathy, odynophagia, and familial history of gastrointestinal malignancy), treatment-refractory dyspepsia, history of gastric cancer in grade I relatives, history of peptic ulcer, and history of gastric MALT lymphoma based on the pathologic studies. The exclusion criteria were negative result for the urease testing of tissue samples, unwillingness to participate in the study, contraindication for upper endoscopy, sensitivity to Fromilid (clarithromycin), amoxicillin, bismuth, esomeprazole, or atorvastatin, and high risk for endoscopy due to cardiovascular disease.

Of the patients referring to the gastroenterology clinic during the 1-year period of the study, 316 subjects had upper endoscopy indication based on their medical history, physical examination, and the aforementioned inclusion criteria, of which 80 cases were excluded because of not allowing for endoscopy. The remaining 236 patients were enrolled in the study after obtaining the informed consent and underwent endoscopy and biopsy for the urease testing of tissue specimens from which 16 were excluded because of the negative result of urease test. Finally, 220 eligible patients with positive results for urease test were enrolled. Figure 1 demonstrates the study flowchart and sampling. Patients were then assigned to intervention (A) and control (B) group by block randomization method. The size of each block was 4. Assignment of the type of treatment (A and B) was performed by simple randomization (using coin).

The control group received a four-drug regimen for the eradication of *H. pylori* including Fromilid 500 mg (clarithromycin; Actors Co., Chamran Highway, Tehran, Iran) twice daily, amoxicillin 1 g (Dr. Abidi Co., Shahid Lashgari Exp, Tehran)

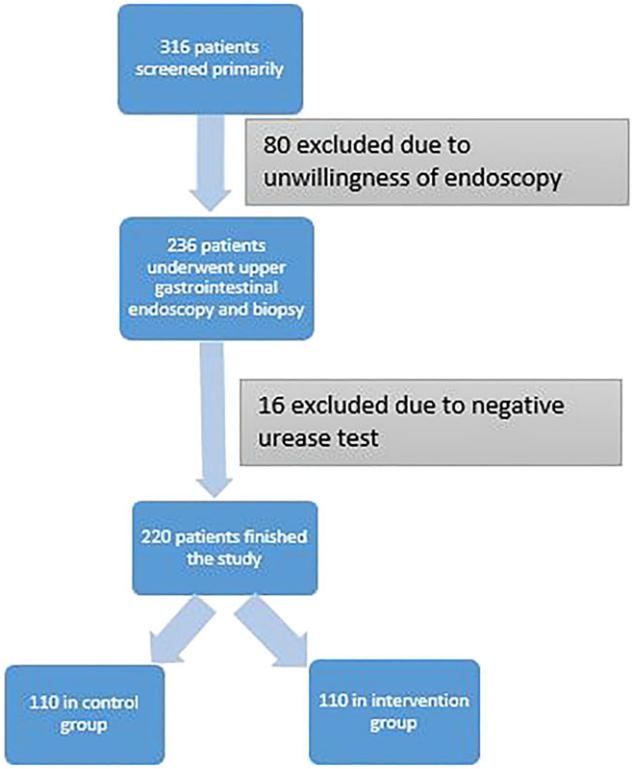

Figure 1 Study flowchart.

twice daily, bismuth 500 mg (Dr. Abidi Co.) four times daily, and esomeprazole 20 mg (Koushan Pharmed Co.,Padidar Alley, Africa) twice daily for 14 days. The intervention group received 40 mg of atorvastatin daily (Dr. Abidi Co.) as a single dose for 14 days. One month after the completion of the treatment, *H. pylori* stool antigen test was performed (Turkey TOYO kits 2015, with sensitivity and specificity of 99.9%), and the eradication rate of *H. pylori* was compared between the two groups.

Data collection was performed using endoscopic instruments, patients' checklist (including age, gender, and underlying diseases), and stool antigen test; for this purpose, eligible patients underwent endoscopy and urease testing of the tissue specimens. If the results of evaluations were positive for *H. pylori*, the patient was assigned to one of the study groups, and 1 month after the treatment completion, the *H. pylori* eradication rate was evaluated by the stool antigen test.

Data were analyzed with SPSS version 18(IBM Crop.,Armonk, N.Y., USA). To determine the effect of intervention on the eradication of *H. pylori* in two study groups, chi-squared test was used. The relationship between response to treatment and endoscopic findings as well as familial history of gastric cancer was determined using chi-squared and Fisher's exact tests. In the current study, the body mass index (BMI) 18.5–24.9 was considered normal, 25–29.9 overweight, and > 30 kg/m^2 obese. The independent *t*-test was used to compare the two groups in terms of age and BMI at baseline. The $P < 0.05$ was the level of significance.

The informed consent was obtained from participants before the study onset; the study protocol was approved by the Ethics Committee of Qom University of Medical Sciences (ethical code: IR.

MUQ.REC.1396.139), and the study was also registered at the Iranian Registry of Clinical Trials (code: IRCT20161205031252N7). The subjects' information was confidential, and all patients were aware of their rights and were also free to withdraw from the study at any stage.

Results

The present study was conducted on 220 patients with the mean age of 43.97 ± 17.47 years, ranged 17 to 88. Most of the patients (40.4%) were in the age group of 20–40 years. Their mean BMI was 25.84 ± 2.55 kg/m^2, and the distribution of the patients according to BMI showed that 33.8% were normal, 62% overweight, and 3.7% obese. The age distribution of patients also showed that 40.83% belonged to the age group of 20–39 years, and only 5.96% of them were in the group < 20 years old. Also, 40.6% of the patients were male. The prevalence of smoking in the studied patients was 28.7%. Table 1 compares the two groups based on demographic variables including age, gender, smoking, and BMI. According to the independent *t*-test results, the two intervention and control groups were similar in terms of age and BMI, and there was no statistically significant difference between them. The results showed a significant difference in the distribution of BMI between the two groups in favor of the overweight group. Also, according to Table 1, chi-squared test showed no statistically significant difference between the intervention and control groups in terms of gender ($P = 0.181$) and smoking ($P = 0.206$).

The results presented in Table 2 showed no significant difference between the intervention and control groups in terms of taking sedatives, smoking, heartburn, epigastric pain, familial history of gastric cancer, erosion, non-ulcer dyspepsia (NUD), GU, GERD, and SHH ($P > 0.05$). However, there were significant differences between the two groups in terms of nausea and vomiting, early satiety, and duodenal ulcer ($P < 0.05$).

The results of Table 3 show that the antigen level in the intervention and control groups was 21.72% and 34.55%, which was significantly different based on chi-squared test. In other words, the intervention could reduce the antigen level in the intervention group compared with the control group. Thus, the eradication rate of *H. pylori* in the intervention group was 78.18% *versus* 65.55% in the control group and the difference between the groups was statistically significant; hence, it is recommended to add statin to *H. pylori* eradication regimen.

Table 4 showed no significant difference between the age, gender, and BMI groups of the study subjects in terms of the eradication of *H. pylori* (response to treatment) ($P < 0.05$). Based on the results, the prevalence of *H. pylori* infection in female patients was different from that of male subjects. *H. pylori* infection was observed in the normal subgroup higher than other subgroups, but the difference between the two groups in terms of the distribution of overweight and obesity was nonsignificant. Figure 1 shows that the *H. pylori* infection was mostly involved patients within the age range of 40 to 59 years than other groups. However, the difference was not obvious in other age groups.

Table 1 Demographics of patients

Variable	Intervention group	Control group	*P*-value
Age (mean ± SD)	45.02 ± 18.86	43.37 ± 16.63	0.248
BMI (mean ± SD)	26.4 ± 2.88	25.3 ± 2.09	0.229
Smoking, *N* (%)	27 (26)	34 (31.8)	0.206
Using of analgesics, *N* (%)	48 (43.6)	43 (39.1)	0.292

BMI, body mass index.

Table 2 Endoscopic and clinical findings between two groups

Variable	Control		Intervention		*P*-value†
	Frequency	%	Frequency	%	
Heartburn	43	39.1	48	43.6	0.292
Epigastric pain	85	77.3	86	78.2	0.50
Nausea and vomiting	76	69.1	33	30	0.000
Fullness	61	55.5	33	30	0.000
Positive family history of gastric cancer	10	9.1	13	11.8	0.330
NUD	28	25.5	32	29.1	0.325
DU	21	19.1	11	10	0.042
GU (distal)	8	7.3	13	11.8	0.364
GU (proximal)	0	0	1	0.9	0.544
Erosion	20	18.2	20	18.2	0.569
GERD	20	18.2	19	17.3	0.50
SHH	14	12.7	17	15.5	0.269

†Based on chi-squared test.
DU, duodenal ulcer; GERD, gastroesophageal reflux disease; GU, gastric ulcer; NUD, non-ulcer dyspepsia; SHH, sliding hiatal hernia.

Table 3 Comparison of *Helicobacter pylori* eradication rate between the groups

Group			Not eradicated		Eradicated		*P*-value†
	N	%	*N*	%	*N*	%	
Control	110	50	38	34.55	72	65.45	0.025
Intervention	110	50	24	21.82	86	78.18	

†Based on chi-squared test.

Table 4 Comparison of *Helicobacter pylori* eradication based on demographics

		Group				*P*-value†
		Control		Intervention		
		N	%	*N*	%	
Age	< 20	5	6.9	5	5.8	0.699
	20–39	34	47.2	35	40.7	
	40–59	22	30.6	27	31.4	
	< 60	11	15.3	19	22.1	
Sex	Male	33	38.4	37	51.4	0.101
	Female	53	61.6	35	48.6	
BMI	< 25	29	40.3	29	32.6	0.179
	25–29.9	42	58.3	52	60.5	
	≤ 30	1	1.4	6	7	

†Based on chi-squared test.
BMI, body mass index.

According to Table 5, the results of chi-squared test showed a significant difference between the two groups in terms of eradication of *H. pylori* ($P = 0.049$), based on the endoscopic findings in the NUD group. Although the addition of statin increased the *H. pylori* eradication rate in terms of all variables, it was statistically significant only in the NUD group. Also, comorbidity of GERD and SHH as well as GERD and duodenal ulcer was observed in some patients.

The frequency of reflux, pain, and nausea in the studied patients was 41.4%, 77.7%, and 49.5%, respectively.

Discussion

Results of the present study demonstrate that combination of atorvastatin with conventional antimicrobial treatment of *H. pylori* significantly increases the rate of bacterial eradication. Atorvastatin is a cholesterol-reducing agent, which may have anti-inflammatory and immunomodulatory effects based on the recent studies.

With respect to the serious complications of *H. pylori* infection and knowing the fact that antimicrobial resistance limits the response to treatment, introducing new ways to improve the rate of *H. pylori* eradication is of a growing interest in recent years. There are limited studies that introduce statins as an effective complement of conventional antimicrobial regimen. In this regard, Nseir *et al*.[16] in a clinical trial on 113 *H. pylori*-infected patients concluded that adding 20 mg of simvastatin to a 7-day triple anti-*H. pylori* regimen significantly increases the rate of bacterial eradication.

The exact mechanism by which statins improve the microbial eradication is not clear, but many previous studies showed the immunomodulatory effect of statins in different infectious diseases. A cohort study by Nassaji *et al*.[3] demonstrated that previous regular use of atorvastatin or simvastatin decreases the rate of acute bacterial infection, including pneumonia, pyelonephritis, and sepsis with unknown origin. This finding is supported by others including van de Garde *et al*.,[17] Hackam *et al*.,[18] and Vinogradova *et al*.[19]

The anti-inflammatory effect of statins is through different pathways, including inhibition of tumor necrosis factor-α and interleukin-6 production by mast cells. A retrospective observational study by Nseir *et al*.[20] concluded that patients on chronic treatment with statins show a reduction in the severity of chronic gastritis. Yamato *et al*.[1] in an animal study on mice reported that simvastatin reduces the inflammatory markers, which is more significant in *H. pylori*-infected mice than noninfected mice.

On the other hand, a clinical trial by Mahdavi and Nikpour[21] on 66 *H. pylori*-infected patients showed that adding atorvastatin to the conventional triple regimen for *H. pylori* eradication did not improve the bacterial eradication compared with the control group. By comparing the results of Mahdavi and Nikpour's[21] studies with the results of Nseir *et al*.[16] study and the present study with larger population, it seems that the reason of the difference is due to the small population of Mahdavi's study. However, available studies are limited, in both number and population. Multicentric clinical trials in different ethnic populations are needed to clarify the efficacy of statins on *H. pylori* eradication rate.

Table 5 Response to treatment based on the endoscopic findings and family history of gastric cancer

Variable	Group	Total		Eradicated		*P*-value†
		N	%	*N*	%	
Erosion	Intervention	20	18.2	15	17.4	0.452
	Control	20	18.2	14	19.4	
NUD	Intervention	32	29.1	25	29.1	0.049
	Control	28	25.5	12	16.7	
DU	Intervention	11	10	9	10.5	0.113
	Control	21	19.1	12	16.7	
GU (distal)	Intervention	13	11.8	11	12.8	0.364
	Control	8	7.3	7	9.7	
GU (proximal)	Intervention	1	0.9	1	1.2	0.544
	Control	0	0	0	0	
SHH	Intervention	17	15.5	16	18.6	0.204
	Control	14	12.7	9	12.5	
GERD	Intervention	19	17.3	13	15.1	0.06
	Control	20	18.2	19	26.4	
Family history of gastric cancer	Intervention	13	11.8	10	11.6	0.07
	Control	10	9.1	3	4.2	

†Based on chi-squared test.

DU, duodenal ulcer; GERD, gastroesophageal reflux disease; GU, gastric ulcer; NUD, non-ulcer dyspepsia; SHH, sliding hiatal hernia.

Conclusion

Available data demonstrate that atorvastatin can be an efficient complement of conventional antimicrobial treatment of *H. pylori* to improve the rate of bacterial eradication. With respect to the limitations of the present study (limited number of cases in one center), and small number of available studies in this regard, further studies will be helpful in clarifying the effectiveness of this treatment.

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