

Simvastatin improves the eradication rate of *Helicobacter pylori*: upper Egypt experience

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Background: *Helicobacter pylori* infection is one of the most prevalent chronic bacterial human infections worldwide. *Helicobacter pylori* colonizes the gastric mucosa and causes persistent gastritis that may progress to gastric cancer. Increased resistance of *H. pylori* presents a major problem in most countries. Statins, including simvastatin, which are currently used to treat hypercholesterolemia, appear to have potential synergistic role to antibiotics. This study aimed to assess the value of adding simvastatin as adjuvant to standard triple therapy in patients infected with *H. pylori*.

Methods: This study was conducted on 100 patients diagnosed with *H. pylori* by the presence of antigen in stools. All patients were randomly subjected either to the standard triple regimen (clarithromycin 500 mg bid + amoxicillin 1 g bid + omeprazole 20 mg bid) (group 1, N=50) or to the standard triple regimen plus simvastatin (clarithromycin 500 mg bid + amoxicillin 1 g bid + omeprazole 20 mg bid + simvastatin 20 mg bid) (group 2, N=50). Both groups were treated for 14 days and eradication of *H. pylori* was assessed by a stool antigen test 4 weeks after therapy.

Results: Eradication of *H. pylori* infection was significantly higher in patients treated with the standard triple therapy plus simvastatin (n=41, 82%) than in patients treated with the standard triple therapy (n=31, 62%) ($P<0.022$).

Conclusion: Simvastatin significantly improves the *H. pylori* eradication rate.

Keywords: eradication of *H. Pylori*, simvastatin, standard triple therapy, clarithromycin resistance

Introduction

Helicobacter pylori is a Gram-negative microaerophilic spiral bacillus and one of the most prevalent chronic bacterial human infections worldwide. About 4.4 billion individuals worldwide are estimated to have *H. pylori* infection.¹

Helicobacter pylori colonizes the gastric mucosa, leading to gastritis, peptic ulcer disease,^{2,3} gastric adenocarcinoma,^{4,5} and type B low-grade mucosal-associated lymphoma.⁶ Also, many extra-digestive diseases are associated with *H. pylori* infection, such as demyelinating neuropathies, ischemic heart disease, and chronic urticaria.⁷⁻⁹ Treating *H. Pylori* markedly decreases the risk of non-cardia gastric adenocarcinoma so there is a will all over the world to eradicate *H. Pylori* to decrease the risk of gastric adenocarcinoma and other several gastrointestinal complications.^{4,5}

The standard triple therapy which is used for eradication of *H. pylori* combines a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole.¹⁰

Antimicrobial resistance has increased in many countries as a consequence; the standard triple therapy eradication rate is less than 80%.^{11,12}

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In Egypt, the standard triple therapy eradication rates show regional variation, ranging between 56.25% and 88.2%; therefore, because of the decreasing eradication rates of this regimen, an alternative regimen, or adding other drugs to this regimen, has been used to augment its efficacy.^{13,14}

Statins are antihyperlipidemic agents that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thus diminishing cholesterol biosynthesis.¹⁵ Statins also have potential direct antibacterial activity, synergistic activity with antibiotics, and ability to stimulate human immune system.¹⁶

Helicobacter pylori has lipid rafts which are composed of cholesterol, phospholipids, and sphingolipids for internalization of cells. Treating cells with cholesterol-lowering agents can dissociate the raft-associated proteins and lipids and render the structure non-functional.^{17–19}

In an in vitro study, Liao et al²⁰ showed that statins reduce the risk of *H. pylori* infection by decreasing the *H. pylori* burden in macrophages. Also, Lai et al²¹ showed that depletion of cholesterol has been demonstrated to attenuate CagA-induced pathogenesis.

Aim

The aim of this study was to assess value of adding simvastatin as an adjuvant to standard triple therapy in patients infected with *H. pylori*.

Patients and methods

Study design and participants

This study was a randomized controlled trial conducted on 100 patients infected with *H. pylori* attending the outpatient clinics of Hepatology, Gastroenterology and Infectious diseases Department, Al-Azhar-Assiut University Hospital, Egypt, from December 2017 to June 2018.

Approval was obtained from the Al-Azhar Assiut Faculty of Medicine ethical committee before the start of the study, and informed written consent was signed by every patient before enrollment in the study, in accordance with the World Medical Association Declaration of Helsinki, as revised in 2000, Edinburgh, UK.

Inclusion criteria

Patients above the age of 18 years with upper gastrointestinal symptoms related to *H. pylori* infection were included in the study. Patients infected with *H. pylori* were diagnosed by a stool antigen test (SAT) (One Step[®] *H. pylori* Antigen Test Device; Abon Biopharm, Hangzhou, China).

Exclusion criteria

Patients aged less than 18 years, who had undergone prior gastric surgery or *H. pylori* eradication therapy, who had a recent intake of antibiotics, PPI, histamine (H₂) receptor blockers, non-steroidal anti-inflammatory drugs within the past month, known allergy to any of the antibiotics used in the study, gastrointestinal malignancy, or active upper gastrointestinal bleeding, and pregnant and lactating women were excluded from study.

Investigatory work-up

Eligible patients were randomized and divided into two groups. Group 1 comprised 50 patients who were treated with the standard triple therapy clarithromycin (Klacid[®]; Abbott Laboratories, Cairo, Egypt) 500 mg bid, amoxicillin (Amoxil[®]; GlaxoSmithKline, Cairo, Egypt) 1,000 mg bid, and omeprazole (Pepzol[®]; Hikma Pharmaceuticals, Giza, Egypt) 20 mg for 14 days. Group 2 comprised 50 patients treated with the standard triple therapy plus simvastatin (Zocor[®]; Global Napi, Giza, Egypt) 20 mg bid, prescribed for 14 days.

All patients were assessed by taking a full history and conducting a clinical examination, with special stress on upper gastrointestinal symptoms, including epigastric pain, heartburn, and vomiting. Body mass index (BMI) was calculated for each patient. All patients were assessed by the following laboratory and imaging tests after fasting since midnight: complete blood count, renal function, liver function (aspartate transferase [AST], alanine transferase [ALT], serum bilirubin, international normalized ratio [INR], total protein, and albumin), fasting blood sugar (FBS), lipid profile including cholesterol and triglycerides, erythrocyte sedimentation rate (ESR), and pelvi-abdominal ultrasonography.

The eradication of *H. pylori* was assessed 4 weeks after end of treatment by the SAT (One Step *H. pylori* Antigen Test Device). During this period, patients were instructed not to use PPIs, H₂ blockers, or antibiotics.

Statistical analysis

Statistical analysis was carried out using SPSS version 22 for Windows 10 (IBM Corp., Armonk, NY, USA). Data are expressed as mean \pm SD, frequency and percentage. The Student's *t*-test was used to compare the results of continuous variables between groups and the chi-squared test for categorical variables. *P*-values were considered significant if <0.05 .

Results

The mean age of patients enrolled in the study was 35.5 ±12.9 years, 29% of patients were male and 71% were female, and no significant differences were found between the two studied groups.

No significant differences were found between the two groups for mean BMI, gender or symptoms ($P>0.05$ for each). Patients infected with *H. pylori* presented with epigastric pain in 53%, bloating in 34%, heartburn in 22%, vomiting in 22%, early satiety in 20%, and urticaria in 5%.

Table 1 shows that there were no significant differences between the two groups concerning laboratory parameters, including complete blood count, renal function, liver function tests (AST, ALT, serum bilirubin, INR, total protein, and albumin), fasting blood sugar, or lipid profile ($P>0.05$ for each).

With regard to ultrasonography, about 52% of patients had normal ultrasonographic findings and 48% of patients had fatty liver. No significant differences were found between the two groups ($P>0.05$ for each) (Table 2).

After 4 weeks of treatment, patients' response was assessed by SAT. The results showed that the eradication rate of *H. pylori* infection was significantly higher in patients treated with the standard triple therapy plus simvastatin ($n=41$, 82%) than in patients treated with the standard triple therapy ($n=31$, 62%) ($p<0.022$) (Table 3).

Table 2 Ultrasonographic findings of the studied patients

Ultrasound finding	Total patients (N=100)	Group 1 (N=50)	Group 2 (N=50)	P-value
Normal	52 (52)	31 (62)	21 (42)	0.66
Fatty liver	48 (48)	19 (38)	29 (58)	

Note: Data are shown as n (%).

Table 3 *Helicobacter pylori* stool antigen test 4 weeks after treatment in the study groups

Stool antigen test	Group 1 (N=50)	Group 2 (N=50)	P-value
Positive, n (%)	19 (38)	9 (18)	0.022
Negative, n (%)	31 (62)	41 (82)	
Eradication rate, %	62.0	82.0	

In this study, all patients were compliant with treatment (100%) and adherent to treatment, and the number needed to treat/benefit ratio was 5 (95% CI 2.7–35.2) ($P<0.05$).

Minor adverse effects were reported in the form of headache, epigastric pain, nausea, and diarrhea, with no significant difference between the two groups (Table 4).

Table 1 Baseline laboratory data for patients in both groups

Parameter	All cases (N=100)	Group 1 (N=50)	Group 2 (N=50)	P-value
Red blood cells ($10^6/\text{mm}^3$)	4.6±0.45	4.56±0.38	4.643±0.51	0.41
Hemoglobin concentration (g/dl)	12.6±1.73	12.5±1.88	12.82±1.58	0.37
Mean corpuscular hemoglobin (pg)	27.4±3.14	27.36±3.39	27.4±2.89	0.9
Mean corpuscular volume (fl)	84.2±7.49	83.98±8.09	84.4±6.91	0.76
White blood cells ($10^3/\text{mm}^3$)	6.6±1.704	6.41±1.75	6.9±1.63	0.15
Platelets ($10^3/\text{mm}^3$)	254.83±61.95	265.9±53.2	243.6±68.34	0.072
INR	1.026±0.046	1.033±0.038	1.019±0.052	0.13
Triglycerides (mg/dl)	107.8±44.62	112.92±48.28	102.5±40.3	0.25
Total cholesterol (mg/dl)	187.1±21.6	185.7±24.3	188.6±22.8	0.78
ESR (mm/h)	20.81±16.51	20.02±14.34	21.6±18.62	0.63
AST (u/l)	21.56±7.5976	21.32±7.77	21.8±7.48	0.75
ALT (u/l)	20.45±9.6759	17.9±5.44	23±15.6	0.32
Albumin (g/dl)	4.212±0.32	4.426±0.22	3.9±0.271	0.75
Total protein (g/dl)	6.972±0.53	7.043±0.50	6.9±0.554	0.18
FBS (mg/dl)	88.35±10.77	85.82±8.05	90.88±12.50	0.18
Urea (mg/dl)	22.1±7.43	21.4±7.103	22.86±7.75	0.36
Creatinine (mg/dl)	0.79±0.21	0.77±0.24	0.78±0.23	0.81

Note: Data are shown as mean ± SD.

Abbreviations: INR, international normalized ratio; ESR, erythrocyte sedimentation rate; AST, aspartate transferase; ALT, alanine transferase; FBS, fasting blood sugar.

Table 4 Side effects of treatment in both groups

Side effects	Total patients	Triple therapy	Triple therapy + simvastatin	P-value
Headache	7	4 (8)	3 (6)	0.76
Diarrhea	11	6 (12)	5 (10)	0.83
Nausea	9	5 (10)	4 (8)	0.69
Epigastric pain	14	6 (12)	8 (14)	0.75

Note: Data are shown as n or n (%).

Discussion

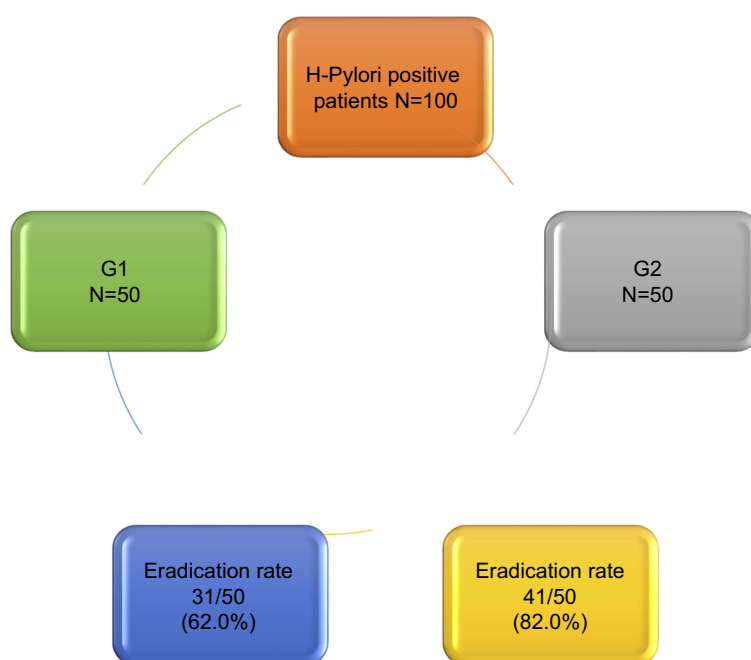
As infection with *H. pylori* may be associated with severe gastric or duodenal ulcers, gastric lymphoma or adenocarcinoma, and many other extra-gastrointestinal diseases, eradication of this microorganism from the human body is a goal with worldwide agreement.^{4,5}

Although many regimens have been used to treat *H. pylori*, triple therapy is still being used as a first line therapy in many parts of the world,²² but unfortunately the standard triple therapy eradication rate is less than 80%¹⁰ owing to antimicrobial resistance.¹¹ In areas with high clarithromycin resistance, the triple therapy is no longer preferred as the standard first line therapy,²³ as any regimen with an eradication rate lower than 80% is not acceptable as a first line eradication therapy.²⁴

In Egypt, the standard triple therapy eradication rates show regional variation, ranging between 56.25% and 88.2%.^{13,14} Thus, because of the decreasing efficacy of this standard triple therapy regimen, an alternative regimen or adding another drug to this regimen may be used to augment its efficacy.

Simvastatin has potential direct antibacterial activity, synergistic activity with antibiotics, and the ability to stimulate the human immune system.¹⁴ Simvastatin also promotes lysosomal fusion, resulting in degradation of sequestered bacteria, and in turn attenuates interleukin-1 β production.²⁰ In addition, Lai et al²¹ showed that depletion of cholesterol can attenuate CagA-induced pathogenesis. On this basis, the present study was conducted to investigate the value of adding simvastatin as an adjuvant to standard triple therapy in patients infected with *H. pylori*.

Eradication of *H. pylori* infection was significantly higher in patients treated with the standard triple therapy plus simvastatin (n=41, 82%) than in patients treated with the standard triple therapy (n=31, 62%) ($P<0.022$), proving that simvastatin has an additive adjuvant effect on eradication of *H. pylori* (Figure 1). This result agrees with the study by Nseir et al,²⁵ in which the addition of statin to the standard triple therapy increased the eradication rate of *H. pylori* infection from 72% to 91%.

**Figure 1** Flow chart of the studied patients.

Minor adverse effects were reported in the simvastatin-based regimen, in the form of headache in 3%, epigastric pain in 14%, nausea in 8%, and diarrhea in 10%, with no significant differences between the two study groups. This makes simvastatin a good adjuvant drug when added to the standard triple therapy.

Our study is a single-center study and has some limitations, such as the small number of patients. Further multi-center randomized clinical trials on larger numbers of patients in different locations are needed to show the efficacy and safety of simvastatin as an adjuvant treatment in the eradication of *H. pylori*.

Conclusion

Adding simvastatin 20 mg twice daily to the standard triple therapy improved the eradication rate of *H. pylori* from 62% to 82%.

Disclosure

The authors report no conflicts of interest in this work.

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