

Effect of *Helicobacter pylori* Eradication on Reflux Esophagitis Therapy: A Multi-center Randomized Control Study

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) frequently colonizes the stomach. Gastroesophageal reflux disease (GERD) is a common and costly disease. But the relationship of *H. pylori* and GERD is still unclear. This study aimed to explore the effect of *H. pylori* and its eradication on reflux esophagitis therapy.

Methods: Patients diagnosed with reflux esophagitis by endoscopy were enrolled; based on rapid urease test and Warth–Starry stain, they were divided into *H. pylori* positive and negative groups. *H. pylori* positive patients were randomly given *H. pylori* eradication treatment for 10 days, then esomeprazole 20 mg bid for 46 days. The other patients received esomeprazole 20 mg bid therapy for 8 weeks. After treatment, three patient groups were obtained: *H. pylori* positive eradicated, *H. pylori* positive uneradicated, and *H. pylori* negative. Before and after therapy, reflux symptoms were scored and compared. Healing rates were compared among groups. The χ^2 test and *t*-test were used, respectively, for enumeration and measurement data.

Results: There were 176 *H. pylori* positive (with 92 eradication cases) and 180 negative cases. Healing rates in the *H. pylori* positive eradicated and *H. pylori* positive uneradicated groups reached 80.4% and 79.8% ($P = 0.911$), with reflux symptom scores of 0.22 and 0.14 ($P = 0.588$). Healing rates of esophagitis in the *H. pylori* positive uneradicated and *H. pylori* negative groups were, respectively, 79.8% and 82.2% ($P = 0.848$); reflux symptom scores were 0.14 and 0.21 ($P = 0.546$).

Conclusions: Based on esomeprazole therapy, *H. pylori* infection and eradication have no significant effect on reflux esophagitis therapy.

Key words: Gastroesophageal Reflux Disease; *Helicobacter pylori*; Reflux Esophagitis; Therapy

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a type of bacterium that frequently colonizes the lining of the stomach. *H. pylori* infection is recognized to be the most important acquired factor in the etiology of ulcers of the stomach and duodenum. *H. pylori* infection was also shown to be associated with active gastritis, gastric carcinoma and gastric mucosal associated lymphatic tissue (MALT) lymphoma. It is believed that eradication therapy is a powerful way to cure *H. pylori*-related diseases.^[1] But the relationship between *H. pylori* and gastroesophageal reflux disease (GERD) is still unclear, and the effect of *H. pylori* eradication on GERD treatment is unknown. In

this study, we selected patients with reflux esophagitis to explore the effect of *H. pylori* and its eradication on reflux esophagitis treatment.

METHODS

Patients

Patients from Digestive Disease Center of Peking University Third Hospital, Wu Han Union Hospital, Shanghai Changhai Hospital, and The First Affiliated Hospital, Sun Yat-Sen University were enrolled between January 2007 and October 2010.

Included criteria were: Almost 18–70 years of age, typical reflux symptoms (heartburn, acid regurgitation and chest pain), and diagnosis of reflux esophagitis (Los Angeles [LA] A–D degree). The LA classification was used for the patients

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with reflux esophagitis, and those with reflux esophagitis LA-A to LA-D were all enrolled.

Patients were excluded with: Peptic ulcer, carcinoma of upper gastrointestinal tract, esophageal varices, Zollinger–Ellison syndrome, esophageal stricture, Barrett’s esophagus, other severe gastrointestinal disease (for example ulcerative colitis), and accompanying severe diseases of other systems. Pregnant or lactating females, and patients who had undergone proton pump inhibitor (PPI) or bismuth therapy during the preceding 2 weeks were also excluded. All patients signed the informed consent forms. The Ethics Committee of Health Center of Peking University approved this study.

Criteria for *Helicobacter pylori* presence

Biopsy specimens for rapid urease test (RUT) were obtained from biopsy forceps with a sterile needle and assessed immediately; the results were examined by an experienced observer blinded to the clinical details. The biopsy specimens for pathology were examined by an experienced pathologist after Warthin–Starry (WS) staining. A sample was considered *H. pylori* positive with both RUT and WS staining results positive. *H. pylori* negative samples showed negative results in both tests. When discordant results were obtained for RUT and WS, the patients were excluded from the study. After eradication treatment, the patients underwent gastroscopy again. Biopsy specimens were examined by WS staining, and samples were considered *H. pylori* positive with positive WS staining.

Definition of reflux esophagitis

Before and after treatment, patients underwent gastroscopy and were examined by experienced doctors. Reflux esophagitis was defined as mucosal breaks extending proximally from the Z-line. Patients from LA-A to LA-D were all enrolled. The severity of reflux symptoms was scored by the frequency and severity of the symptoms [Table 1].

Treatment

H. pylori positive patients were first randomly divided into eradicated and uneradicated groups by random envelope. In the eradication group, patients underwent *H. pylori* eradication for 10 days, then received esomeprazole 20 mg

bid for the following 46 days. Two eradication regimens were randomly selected in this study: The EAC regimen consisted of esomeprazole 20 mg bid, amoxicillin 1.0 bid and clarimothin 0.5 bid; in the sequential regimen, esomeprazole 20 mg bid and amoxicillin 1.0 bid were administered for the first 5 days, while esomeprazole 20 mg bid, clarimothin 0.5 bid and tinidazole 0.5 bid were given for the following 5 days. In *H. pylori* positive uneradicated and *H. pylori* negative groups, patients were treated with esomeprazole 20 mg bid for 8 weeks. Afterward, all patients underwent gastroscopy again, and the WS staining test was repeated. Therefore, three groups were obtained: *H. pylori* positive eradicated, *H. pylori* positive uneradicated (patients without *H. pylori* eradicated or unsuccessful eradication) and *H. pylori* negative groups.

Endpoint and indicator evaluation

For all patients, the course of treatment was 8 weeks. Then, the healing rate of reflux esophagitis and remission of reflux symptoms were evaluated.

- “Healed” was considered if there was no esophageal mucosal break after treatment; “unhealed” indicated the presence of mucosal breaks. The healing rates among groups were compared
- Remission of reflux symptoms. The main reflux symptoms, including acid regurgitation, heartburn, and chest pain were scored before and after treatment. The remission of reflux symptoms was compared among groups.

Statistical analysis

The χ^2 test and *t*-test were used, respectively, for enumeration and measurement data. All statistical analyses were carried out with SPSS 15.0 (SPSS Inc., USA). All statistical tests were two-sided, and a $P < 0.05$ was considered statistically significant.

RESULTS

General status

A total of 356 patients were enrolled, including 259 males and 97 females. There were 176 patients infected with *H. pylori* and 180 patients without *H. pylori*. For *H. pylori* positive patients,

Table 1: Scores of frequency and severity of reflux symptoms

Clinical symptoms	Scores			
	0	1	2	3
Heartburn	No heartburn	Appears in 1 period	Appears in 2 periods	Appears in 3 periods
Acid reflux	No acid reflux	Appears in 1 period	Appears in 2 periods	Appears in 3 periods
Chest pain	No pain	Appears in 1 period	Appears in 2 periods	Appears in 3 periods
Heartburn	No heartburn	Has heartburn, but easy to endure	Discomfort of heartburn, which affects daily activities (including sleep)	Cannot carry out normal activities (including sleep)
Acid reflux	No acid reflux	Has acid reflux, but easy to endure	Discomfort of acid reflux, which affects daily activities (including sleep)	Cannot carry out normal activities (including sleep)
Chest pain	No pain	Has pain, but easy to endure	Discomfort of pain, which affects daily activities (including sleep)	Cannot carry out normal activities (including sleep)

We divided a day into three periods: From breakfast to lunch, lunch to supper and supper to breakfast. If a reflux symptom appears in one, two or three periods, a score of one, two or three, was attributed, respectively.

122 were given *H. pylori* eradication treatment. Ninety-two patients showed successful eradication, while the remaining 30 still had the bacteria, indicating an eradication rate of 75.4%. Therefore, there were 92 and 84 patients in the *H. pylori* positive eradicated and *H. pylori* positive uneradicated groups, respectively. No significant difference in age, gender, height, and weight was obtained among groups [Table 2].

Comparison between *Helicobacter pylori* positive groups

Before treatment, reflux symptom scores in the *H. pylori* positive eradicated and *H. pylori* positive uneradicated groups were 8.04 and 7.13, respectively ($P = 0.062$). There was no statistically significant difference in the LA degree between the two groups ($P = 0.307$) [Table 3].

After treatment, reflux symptom scores of 0.22 and 0.14 were obtained for the *H. pylori* positive eradicated and *H. pylori* positive uneradicated groups, respectively ($P = 0.588$). The healing rate of reflux esophagitis were 80.4% and 79.8%, respectively, in the *H. pylori* positive eradicated and *H. pylori* positive uneradicated groups ($P = 0.911$) [Table 4]. There was no significant difference between the two groups.

Comparison between *Helicobacter pylori* positive uneradicated group and *Helicobacter pylori* negative group

Before treatment, reflux symptom scores in the *H. pylori* positive uneradicated and *H. pylori* negative groups were 7.13 and 7.18, respectively ($P = 0.910$), and no statistically significant difference in LA degree between the two groups was obtained ($P = 0.848$) [Table 5].

After treatment, reflux symptom scores in the *H. pylori* positive uneradicated and *H. pylori* negative groups were

0.14 and 0.21, respectively ($P = 0.546$). The healing rates of reflux esophagitis were 79.8% and 82.2%, respectively, in *H. pylori* positive uneradicated and *H. pylori* negative groups, respectively ($P = 0.632$) [Table 6]. There was no significant difference between the two groups.

DISCUSSION

H. pylori is one of the most common bacteria around the world. *H. pylori* infection leads to chronic active gastritis with the potential for the subsequent development of peptic ulcer, MALT lymphoma, and distal gastric cancer in some patients. *H. pylori* should be eradicated in these patients.^[1] GERD is a common and costly disease in the community, with a negative impact on patients' quality of life. Unfortunately, GERD incidence is increasing worldwide.^[2] The major mechanisms associated with GERD include decreased pressure and increased frequency of spontaneous relaxation of the lower esophageal sphincter, with normal or increased secretion of gastric acid. The relationship between *H. pylori* infection and GERD remains unclear, and the treatment of *H. pylori* in patients with GERD is highly controversial.

Indeed, some epidemiological studies suggested *H. pylori* as a protective factor in GERD. The prevalence of *H. pylori* infection has been steadily decreasing while GERD incidence is increasing in developed countries, suggesting a possible protective role of *H. pylori* infection in the development of GERD. Other evidences include the following: The infection rate of *H. pylori* in GERD patients is much lower than in the general population; *H. pylori* is associated with the severity of GERD; the infection rate of *H. pylori* in severe GERD patients is much lower than those with mild GERD.^[3] In addition, GERD incidence is

Table 2: General status of patients in different groups before treatment

Items	<i>H. pylori</i> positive eradicated (n = 92)	<i>H. pylori</i> positive uneradicated (n = 84)	<i>H. pylori</i> negative (n = 180)	Statistics	P
Gender (n)					
Male	69	56	131	$\chi^2 = 1.645$	0.439
Female	23	28	49		
Age (years)					
Mean	48.26	48.70	49.49	$F = 0.268$	0.765
SD	13.03	13.62	14.19		
Height (cm)					
Mean	167.79	168.07	168.36	$F = 0.207$	0.813
SD	6.82	7.60	6.78		
Weight (kg)					
Mean	66.71	68.76	68.46	$F = 1.236$	0.292
SD	8.37	11.08	9.85		
Smoking (n)					
Yes	23	19	44	$\chi^2 = 0.152$	0.927
No	69	65	136		
Drinking (alcohol) (n)					
Yes	16	24	45	$\chi^2 = 3.273$	0.195
No	76	60	135		

H. pylori: *Helicobacter pylori*; SD: Standard deviation.

Table 3: Esophagitis grade and symptom scores in the *H. pylori* positive groups before treatment

Variables	<i>H. pylori</i> positive eradicated (n = 92)	<i>H. pylori</i> positive uneradicated (n = 84)	Statistics	P
RE grade (n)				
A	41	33	$\chi^2 = 3.604$	0.307
B	40	44		
C	6	6		
D	5	1		
Symptoms scores				
Mean	8.04	7.13	$t = 1.88$	0.062
SD	3.35	3.06		

H. pylori: *Helicobacter pylori*; SD: Standard deviation.

Table 4: Healing rate and symptoms scores in the *H. pylori* positive groups after treatment

Variables	<i>H. pylori</i> positive eradicated (n = 92)	<i>H. pylori</i> positive uneradicated (n = 84)	Statistics	P
Number of healed or unhealed cases				
Healed	74	67	$\chi^2 = 0.012$	0.911
Unhealed	18	17		
Symptom scores				
Mean	0.22	0.14	$t = 0.543$	0.588
SD	0.99	0.81		

H. pylori: *Helicobacter pylori*; SD: Standard deviation.

increased after *H. pylori* eradication.^[4] There were also studies suggesting no relationship between *H. pylori* and GERD. Indeed, the prevalence of *H. pylori* was shown to be similar between GERD and other patients, and *H. pylori* was not related to the severity of GERD.^[5,6] Recently, Japanese studies suggested that after *H. pylori* eradication, GERD symptoms are relieved, and life quality improved.^[7,8] The *Management of Helicobacter pylori Infection the Maastricht IV/Florence Consensus Report* declares that *H. pylori* status has no effect on symptom severity, symptom recurrence and treatment efficacy in GERD. *H. pylori* eradication does not exacerbate preexisting GERD or affect treatment efficacy.^[9] In the Chinese guideline for *H. pylori* treatment, it was indicated that GERD incidence may be increased in some eastern countries after *H. pylori* eradication. Therefore, the question remains as whether for GERD patients with *H. pylori* infection, *H. pylori* eradication is necessary or useful.

For the treatment of GERD, an agreement has been reached that PPI is the most important medicine. In the definition of Montreal, the symptoms of GERD could be relieved significantly by PPI.^[10] However, in case of *H. pylori* infection combined with gastroesophageal reflux, *H. pylori* eradication therapy is needed, which is confusing to the clinicians; this problem needs to be clarified as soon as possible.

Table 5: Esophagitis grade and symptom scores in the *H. pylori* positive uneradicated and *H. pylori* negative groups before treatment

Variables	<i>H. pylori</i> positive uneradicated (n = 84)	<i>H. pylori</i> negative (n = 180)	Statistics	P
RE grade (n)				
A	33	76	$\chi^2 = 0.807$	0.848
B	44	87		
C	6	16		
D	1	1		
Symptoms scores				
Mean	7.13	7.18	$t = 0.113$	0.910
SD	3.06	3.18		

H. pylori: *Helicobacter pylori*; SD: Standard deviation.

Table 6: Healing rate and symptom scores in *H. pylori* positive uneradicated and *H. pylori* negative groups after treatment

Variables	<i>H. pylori</i> positive uneradicated (n = 84)	<i>H. pylori</i> negative (n = 180)	Statistics	P
Number of healed or unhealed cases				
Healed	67	148	$\chi^2 = 0.229$	0.632
Unhealed	17	32		
Symptom scores				
Mean	0.14	0.21	$t = 0.604$	0.546
SD	0.81	0.77		

H. pylori: *Helicobacter pylori*; SD: Standard deviation.

For most patients, *H. pylori* infection does not affect acid secretion significantly. But for different infection sites and types of gastritis, acid secretion may be decreased or increased after *H. pylori* infection.^[11] Based on this theory, some scientists have suggested that if acid secretion is increased by *H. pylori* infection, then the bacteria should be eradicated. On the other hand, if acid secretion is decreased by *H. pylori*, its eradication is not necessary. So before *H. pylori* eradication, its effect on acid secretion should be first evaluated.^[12,13] But it is difficult in clinical practice for doctors.

In a study by Calleja *et al.*,^[14] 846 patients with reflux esophagitis underwent treatment with pantoprazole 40 mg qd. After 4 weeks treatment, the healing rate of reflux esophagitis was 86.6% in *H. pylori* positive patients. In *H. pylori* negative patients, the healing rate was 76.1%. After 8 weeks treatment, the healing rates in positive and negative groups were 96.4% and 91.8%, respectively. The healing rates in the positive group were, therefore, higher than in the negative group, with significant differences. Also, the rate of GERD symptom relief was higher in *H. pylori* positive patients compared with negative patients. These findings suggested that based on the same treatment, a better outcome was obtained in *H. pylori* positive patients. In a prospective study by Tefera *et al.*,^[15] GERD patients

with *H. pylori* infection were included. After 15 months of *H. pylori* eradication, there was no significant difference between acid secretion and GERD symptoms. In a study by De Boer *et al.*,^[16] 1548 GERD patients underwent treatment with Rabeprazole; there was no significant difference between *H. pylori* positive and negative patients in rates of GERD symptom relief. From the above studies, a clear misunderstanding can be seen in this field. A large-scale study to compare the treatment outcome between *H. pylori* positive and negative comprehensively is needed.

This was a multi-center, randomized, control, prospective study, with 356 patients enrolled. Based on the treatment of PPI, we explored the effect of *H. pylori* eradication on the treatment of reflux esophagitis. We analyzed the effect of *H. pylori* infection first, and patients in *H. pylori* negative and *H. pylori* positive control groups were compared. After PPI treatment, no significant differences in healing rates of reflux esophagitis and the severity of reflux symptoms were obtained, indicating that *H. pylori* infection has no significant effect on the treatment of reflux esophagitis. Then, we analyzed the effect of *H. pylori* eradication. Patients with *H. pylori* infection were enrolled, and *H. pylori* eradicated and *H. pylori* positive uneradicated groups were compared. After the treatment with PPI, no significant difference was found in healing rates of reflux esophagitis and the severity of reflux symptoms. It was concluded that *H. pylori* eradication has no significant effect on the treatment of reflux esophagitis.

Although we found that *H. pylori* eradication itself has no significant effect on erosive esophagitis treatment, the Asia-Pacific consensus on *H. pylori* infection^[1] mentioned that long-term use of PPI therapy causes increased risk of gastric atrophy, which is a precancerous lesion. For patients with GERD, PPI is used for a long time, therefore, *H. pylori* therapy is recommended. In this study, patients were followed-up for only 8 weeks, and we plan to continue follow-up for years in order to determine the changes by *H. pylori* eradication therapy; reflux esophagitis and relapse of reflux symptoms will be monitored, as well as gastric pathology.

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