Gastroesophageal reflux disease after *Helicobacter pylori* eradication in gastric ulcer patients: a one-year follow-up study

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Key words: *gastroesophageal reflux disease; Helicobacter pylori eradication; gastric ulcer.*

Summary. *The aim of this study was to evaluate the course of gastroesophageal reflux disease in gastric ulcer patients after successful Helicobacter pylori eradication (group A), in patients with persistent infection after attempt to eradicate Helicobacter pylori (group B), and in control group without Helicobacter pylori eradication treatment (group C).*

Materials and methods. Gastric ulcer patients (n=88) were assigned either to the group receiving Helicobacter pylori eradication treatment (54 patients) or to the control group (34 patients; omeprazole treatment for 4 weeks) and were followed up for 1-year or until gastric ulcer relapsed. Gastroesophageal reflux disease was diagnosed in patients who had erosive esophagitis and/or without esophagitis if they experienced heartburn and/or regurgitation at least 2 times a week and it was associated with impairment of daily activities (Genval consensus).

Results. The study was completed by 69 patients: 25 in group A, 19 in group B, and 25 in group C. At the beginning and at the end of the follow-up, gastroesophageal reflux disease was diagnosed in 10 (40%) and 9 (36%) group A patients, respectively (P>0.05); in 12 (63%) and 8 (42%) group B patients, respectively (P>0.05); and in 9 (36%) and 5 (20%) group C patients, respectively (P>0.05). At the beginning and at the end of the follow-up, reflux esophagitis was found in 3 (12%) and 5 (20%) group A patients, respectively (P>0.05); in 5 (26%) and 5 (26%) group B patients (P>0.05); in 4 (16%) and 3 (12%) group C patients (P>0.05).

Conclusion. There was no statistically significant difference regarding the development of gastroesophageal reflux disease in gastric ulcer patients after Helicobacter pylori eradication, in the patients with persistent infection after attempt to eradicate, and in the control group without Helicobacter pylori eradication treatment.

Introduction

During last decade, many controversies have emerged regarding the course of gastroesophageal reflux disease (GERD) after *H. pylori* eradication (1–3). The study by Labenz *et al.* and some other recent studies have shown that *H. pylori* eradication could provoke or worsen gastroesophageal reflux disease (4–8). Other studies, however, have not confirmed these findings or revealed a relief of reflux symptoms after cure of *H. pylori* infection (9–11). Majority of studies addressing this topic were carried out on dyspeptic patients, duodenal ulcer (DU) patients, or GERD patients. There are very few data on gastric ulcer (GU) patients concerning this issue (12, 13).

Therefore, we conducted a one-year follow-up study of GU patients and evaluated the course of coexisting GERD in patients after *H. pylori* eradication, in patients with persistent *H. pylori* infection after attempt to eradicate the pathogen, and in patients of the control group without *H. pylori* eradication treatment.

Methods

Eighty-eight consecutive *H. pylori*-positive GU patients were enrolled in the study. Patients were excluded if they used nonsteroidal anti-inflammatory drugs or recently (during the last 2 months) used proton pump inhibitors, antibiotics, or bismuth compounds. Patients with any severe comorbid diseases were not included. Upper endoscopy was performed at the beginning of the study, 6–8 weeks and 12 months later or earlier if DU relapses was suspected. In the case of symptomatic relapse, patients were obliged to consult the study physician.

Before each endoscopy, patients were asked to indicate the frequency of heartburn and regurgitation and the impact of these symptoms on everyday activities. Patients experiencing typical reflux symptoms

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(heartburn and/or regurgitation) at least twice a week and/or patients with endoscopic esophagitis were considered patients with concomitant GERD (Genval consensus) (14). Endoscopic reflux esophagitis was defined and graded according to the Savary-Miller classification: grade 1, erythematous or erythemato-exudative erosion (alone or multiple) which can cover several folds (as long as they are not confluent); grade 2, confluent but not circumferential erosion; grade 3, circumferential erosive and exudative lesions; grade 4(a) chronic lesions (ulcer, stenosis, enbrachyesophagus cylindric cell epithelialization) with active inflammation and (b) cicatricial stage (stenosis, brachyesophagus, cylindrical cell epithelialization without active inflammation) (15, 16). During endoscopy, three biopsy specimens from the antrum and three from the corpus were taken for urease testing and histological examination. *H. pylori* infection was diagnosed by the rapid urease test and histological examination. Histological evaluation of biopsies from the antrum and corpus of the stomach were performed according to the Sydney system (17) by a single pathologist who was blinded to any clinical data. *H. pylori* positivity was established if the results of at least one of the tests were positive. Final *H. pylori* status was established during examination 12 months later or during the ulcer relapse. The latter was considered when the peptic ulcer was confirmed on endoscopy 12 months later or earlier if symptoms reoccurred.

Fifty-four (61%) patients were included in the treatment group and assigned to one of the following regimens for eradication:

i) RAM (ranitidine 300 mg b.i.d., amoxicillin 1000 mg b.i.d., metronidazole 400 mg b.i.d.) for 14 days;
ii) OAM (omeprazole 20 mg b.i.d., amoxicillin 1000 mg b.i.d., metronidazole 400 mg b.i.d.) for 7 days;
iii) OAC (omeprazole 20 mg b.i.d., amoxicillin 1000 mg b.i.d., clarithromycin 500 mg b.i.d.) for 7 days.

Thirty-four (39%) volunteers were included in the control group and were treated with omeprazole at a dose of 20 mg b.i.d. for 6 weeks. No maintenance therapy was prescribed for them later on.

Data were analyzed and compared using χ^2 or Student's *t* tests. Values of $P<0.05$ were considered significant. The study was approved by Kaunas University of Medicine Ethics Committee. All patients have signed informed consent.

Results

Sixty-nine patients completed the follow-up study: 44 patients in the eradication group (mean age, 51.3± 13.7 years) and 25 in the control group (mean age, 53.4±±13.0 years).

Demographic and clinical characteristics of the patients are presented in Table. The patients in both eradication and control groups were homogenous with respect of gender, history of peptic ulcer, smoking, and coexisting GERD at the beginning of the study.

The mean follow-up period for all patients was 11.0±2.6 months; for those who did not relapse, 11.9±1.4 months; for those who relapsed, 8.0±3.1 months. Final evaluation of *H. pylori* infection after 12 months or at GU relapse endoscopy revealed that in the eradication group 25 (56.8%) patients were successfully cured from *H. pylori*, and 19 (43.2%) patients remained *H. pylori*-positive. All 25 patients in the control group remained *H. pylori*-positive. GU relapsed in 1 (4%) of the 25 HP-negative patients, in 6 (32%) of the 19 unsuccessfully eradicated patients, and in 11 (44%) of the 25 HP-positive controls ($P<0.05$ comparing HP-negative with HP-positive patients; $P>0.05$ comparing HP-positive unsuccessfully treated patients and HP-positive controls).

Coexisting GERD (according to Genval consensus) (14) was diagnosed in 31 (45%) patients. Erosive esophagitis was found in 12 (17%) patients: I° esophagitis in 11 (92%) patients and II° esophagitis in 1 (8%) patient.

At the beginning of the study and at the end of the follow-up, GERD (according to Genval consensus) was diagnosed in 10 (40%) and 9 (36%) of the 25 patients who were successfully treated for HP, respec-

Table. **Demographic and clinical characteristics of the patients who completed the follow-up**

Characteristic	Eradication group n=44	Control group n=25
Males, n (%)	27 (63)	13 (52)
Females, n (%)	17 (37)	12 (48)
Smokers, n (%)	14 (32)	9 (36)
Coexisting GERD at inclusion, n (%)	22 (45)	9 (36)
Coexisting esophagitis at inclusion, n (%)	8 (18)	4 (16)

GERD – gastroesophageal reflux disease.

tively (P>0.05); in 12 (63%) and 8 (42%) of the 19 HP-positive, unsuccessfully treated patients (P>0.05); and in 9 (36%) and 5 (20%) of 25 control group patients (P>0.05).

At the beginning of the study and at the end of the follow-up, erosive esophagitis was found in 3 (12%) and 5 (20%) patients, respectively, who were successfully treated for HP (P>0.05); in 5 (26%) and 5 (26%) HP-positive non-eradicated patients (P>0.05); and in 4 (16%) and 3 (12%) control patients (P>0.05).

At the beginning of the study and at the end of the follow-up, nonerosive GERD was seen in 7 (28%) and 4 (16%) successfully treated from HP patients, respectively (P>0.05); in 7 (37%) and 3 (16%) of the 19 unsuccessfully treated patients (P>0.05); in 5 (20%) and 2 (8%) control patients (P>0.05).

Trends in the prevalence of erosive esophagitis and nonerosive GERD are represented in Fig. Though differences in the prevalences do not reach the significance level (probably due to insufficient number of cases), there are obvious trends in the increase of erosive esophagitis and decrease of nonerosive GERD after successful *H. pylori* eradication.

Discussion

The noticeably low rate of *H. pylori* eradication (56.8%) in our study could be explained by the use of less effective H_2-receptor antagonist-based eradication regimen and omeprazole, amoxicillin, and metronidazole combination, which were widely used in Lithuania until 2000.

Although Labenz *et al.* established the increase in development of new cases of esophagitis in DU patients during 3 years after successful *H. pylori* eradication (4), further studies did not support these findings (18–21). McColl *et al*. and Murrai *et al.* concluded that *H. pylori* eradication did not provoke the development of GERD in DU patients (10, 19) as well as our previous study in DU patients (22).

The data on patients with functional dyspepsia (23) and patients with GERD are conflicting (9, 11, 20, 21, 24), but it seems that there are more data that *H. pylori* eradication does not increase the prevalence of esophagitis during follow-up.

We investigated gastric ulcer patients. Although the study was not randomized and the number of patients was not very high, we have to stress that there are very few data about the natural course of GERD in the group of GU patients. Therefore, we suppose that our data may contribute to further understanding of this issue. Recent study on both DU and GU patients revealed that the presence of hiatal hernia, duodenal ulcer and HP-eradication failure were independently associated with the incidence of reflux esophagitis in patients followed up for more than 18 months (25). South Korean researchers reported no statistical difference in reflux esophagitis incidence between the eradicated (6.8%) and the noneradicated (8.7%) GU patients. No further development of reflux esophagitis was found in patients with a follow-up period longer than 24 months in either eradicated or noneradicated GU patients (26). In other studies, the number of GU patients was not representative to draw any conclusions (7). We revealed that the frequency of overall GERD and erosive GERD was not influenced by the HP eradication during a one-year follow-up. Although the number of patients is not large, but we observed some trends – after eradication of HP, the prevalence

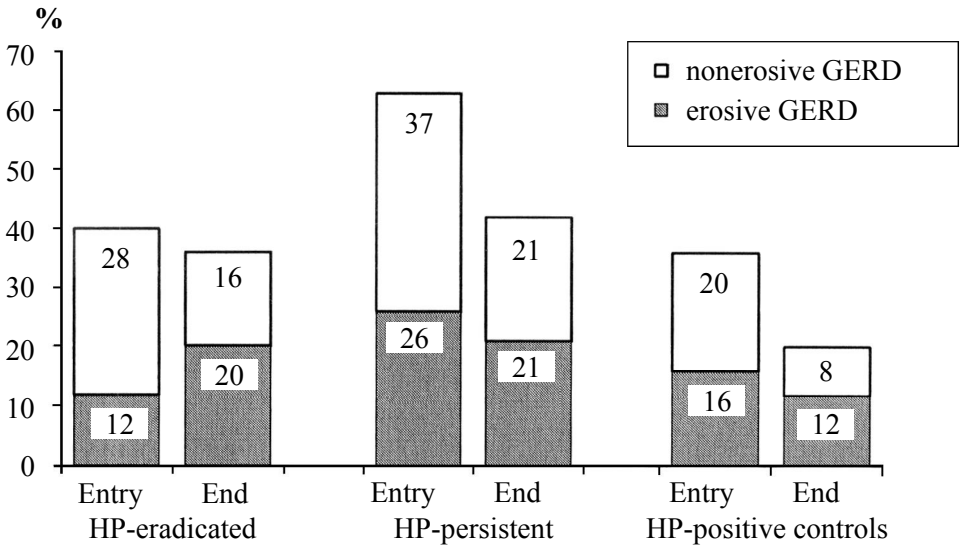

Fig. **Prevalence of erosive and nonerosive gastroesophageal reflux disease (GERD) at the entry and at the end of the study according to *Helicobacter pylori* (HP) status**

of erosive GERD tended to increase and the prevalence of nonerosive GERD to decrease. In our recently published similar study on duodenal ulcer patients, we observed different findings – the nonerosive GERD cases were cured, and the erosive cases were unchanged during the one-year follow-up (22).

Significant corpus gastritis can be associated with decreased acid secretion. The regression of atrophy after eradication of *H. pylori* and enhancement of acid secretion may be achieved (27, 28). Several investigators have observed that GERD was less common in patients with severe corpus gastritis (29, 30), while others have demonstrated that improvement of gastritis in these patients has been associated with an increased risk for the development of GERD (31). Gastric ulcer patients are likely to have the atrophy in the stomach, especially atrophy of the corpus. Therefore, the increase of gastric acidity is quite probable after the HP eradication, especially in patients with incompetent lower esophageal sphincter. In the recent pH-metry-based study, Fukuchi *et al.* indicated that gastric acidity 6 months after *H. pylori* eradication in GU patients was increased at night, while no significant changes in gastric acidity after *H. pylori* eradication were observed in DU patients (32). It might mean that the changes of gastric acidity in gastric ulcer patients might be different from those of duodenal ulcer patients after the healing of gastritis.

There are data that by fluctuating natural course less severe NERD may progress to erosive esophagitis (33). This may explain why the prevalence of NERD tends to decrease and the prevalence of erosive esophagitis increases in the eradicated patient group in our series.

Conclusions

Our study revealed that the prevalence of either nonerosive or erosive gastroesophageal reflux disease is not influenced by the *Heliobacter pylori* eradication during a one-year follow-up. Larger long-term follow-up studies on gastric ulcer patients are necessary to clarify this issue.

Helicobacter pylori išnaikinimo įtaka gastroezofaginio refliukso ligos eigai sergantiesiems skrandžio opalige (vienerių metų stebėjimo studija)

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Raktažodžiai: *Helicobacter pylori*, opaligė, gastroezofaginio refliukso liga.

Santrauka. *Tyrimo tikslas.* Nustatyti gastroezofaginio refliukso ligos eigą skrandžio opalige sergantiems ligoniams po sėkmingo *Helicobacter pylori* išnaikinimo – A grupė, po nesėkmingo *Heliobacter pylori* gydymo – B grupė, ir kontrolinės grupės asmenims, kuriems gydymas *Heliobacter pylori* išnaikinti neskirtas – C grupė.

Tyrimo medžiaga ir metodai. 54 skrandžio opalige sergantiems ligoniams skirtas gydymas *Heliobacter pylori* išnaikinti, 34 kontrolinės grupės asmenims skirtas tik gydymas omeprazoliu keturias savaites. Ligoniai stebėti vienerius metus arba iki opaligės paūmėjimo. Gastroezofaginio refliukso liga diagnozuota ligoniams, kuriems endoskopiškai nustatytas erozinis ezofagitas ir (arba) ligoniams be ezofagito, kuriuos vargina rėmuo arba atpylimai rūgštimi mažiausiai du kartus per savaitę ir tai trikdo jų kasdienę veiklą.

Rezultatai. Studiją baigė 69 pacientai: A grupėje – 25, B grupėje – 19, C grupėje – 25. Gastroezofaginio refliukso liga studijos pradžioje ir pabaigoje atitinkamai diagnozuota: A grupėje – 10 (40 proc.) ir 9 (36 proc.) ligoniams, p>0,05; B grupėje – 12 (63 proc.) – 8 (42 proc.) ligoniams, p>0,05; C grupėje – 9 (36 proc.) ir 5 (20 proc.) ligoniams, p>0,05. Erozinis ezofagitas studijos pradžioje ir pabaigoje atitinkamai nustatytas: A grupėje – 3 (12 proc.) ir 5 (20 proc.) ligoniams, p>0,05, B grupėje – 5 (26 proc.) ir 5 (26 proc.) ligoniams, p>0,05; C grupėje – 4 (16 proc.) ir 3 (12 proc.) ligoniams, p>0,05.

Išvados. Helicobacter pylori išnaikinimas neturėjo įtakos sergamumui gastroezofaginio refliukso liga lyginant su *Helicobacter pylori* infekuotais skrandžio opalige sergančiais ligoniais vienerių metų stebėjimo laikotarpiu.

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Received 3 January 2008, accepted 13 March 2008
Straipsnis gautas 2008 01 03, priimtas 2008 03 13