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BRIEF ARTICLE

Reinfection rate and endoscopic changes after successful eradication of *Helicobacter pylori*

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Abstract

AIM: To determine the long-term outcomes regarding reinfection with *Helicobacter pylori* (*H. pylori*) and endoscopic changes after successful *H. pylori* eradication.

METHODS: From June 1994 to January 2007, 186 patients (M:F = 98:88; mean age 50.0 ± 11.4 years), in whom *H. pylori* had been successfully eradicated, were enrolled. The mean duration of follow up was 41.2 ± 24.0 mo.

RESULTS: *H. pylori* reinfection occurred in 58 patients (31.2%). The average annual reinfection rate was 9.1% per patient year. No recurrence of peptic ulcer was detected at the follow up endoscopy. There were no significant differences between the *H. pylori* eradication regimens for the reinfection rate and no significant differences in endoscopic findings between the *H. pylori*-recurred group and the *H. pylori*-cured group.

CONCLUSION: The reinfection rate in Korea is 9.1% which represents a decreasing trend. There was no relationship between *H. pylori* infection status and changes in endoscopic findings. There was also no recurrence or aggravation of ulcers.

Key words: *Helicobacter pylori*; Eradication; Reinfection; Endoscopy

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is known to cause many gastrointestinal diseases including peptic ulcers, gastric carcinoma and mucosa-associated lymphoid tissue lymphoma[1]. Successful eradication of *H. pylori* infection is important in the prevention of recurrent peptic ulcer disease and gastric cancer[2-4]. Reinfection rate of *H. pylori* infection after successful eradication is an important problem in the management of peptic ulcer disease. The reinfection rate of *H. pylori* varies considerably among different studies. Reported rates of *H. pylori* recurrence in western countries range from 0.5% to 2.5%[3,5,6]. The high prevalence of *H. pylori* infection in Korea suggests the possibility that the reinfection rate might be higher than in western countries. The high prevalence of *H. pylori* infection may possibly be associated with high

rates of reinfection after eradication because of the high risk of re-exposure to infection[7]. The aims of this study were firstly to determine the rate of *H. pylori* reinfection and secondly to determine endoscopic changes after successful eradication of *H. pylori* and after subsequent reinfection in an endemic area such as Korea.

MATERIALS AND METHODS

Patients, who were treated for *H. pylori* infection between June 1994 and January 2007 at Ewha Womans University Mokdong Hospital, Seoul, Korea and who had a negative ^{14}C urea breath test (UBIT®, Otsuka, Japan) 1 mo after eradication, were enrolled. Informed consent was obtained from the patients and ethical approval was given by Ewha Womans University Mokdong Hospital ethical committee (approval No. 187-16). After successful eradication of *H. pylori* infection and cessation of acid-suppression therapy, patients were offered endoscopic examination routinely every year. Follow up endoscopic examination and rapid urease testing (ASAN Helicobacter Test®, Asan Pharmaceutical, Korea) were performed. The initial and follow up endoscopies were performed by one endoscopist. The presence and grading of reflux esophagitis, atrophic gastritis, and gastric intestinal metaplasia were determined according to LA classification and Kimura-Takemoto classification of atrophic pattern[8]. Atrophic gastritis and gastric intestinal metaplasia were also evaluated histologically. Three endoscopic specialists reviewed the images of the endoscopic findings to reduce the inter-observer variation. Improvements and aggravation were determined by endoscopic and histologic findings. Rapid urease test was performed on biopsy specimens from the body of the stomach at the greater curvature.

Follow up duration was defined as being the length of time from successful eradication until the final test in each patient. Reinfection was defined as being when *H. pylori* recurrence took place at least 1 year after eradication therapy. The cumulative and average annual reinfection rates were calculated. Demographics and mucosal changes were compared between recurred patients (*H. pylori*-recurred group) and those remaining successfully eradicated (*H. pylori*-cured group) using Student's *t*-test and χ^2 with significance set at $P < 0.05$.

RESULTS

Subjects

One hundred and eighty six patients (98 men and 88 women) were enrolled. Sixteen patients showed recurrence of *H. pylori* within 1 year post eradication, and these were excluded from the study. Mean age was 50.0 ± 11.4 years. The reasons for the initial endoscopy were; epigastric pain (40.9%), indigestion (25.3%), bleeding (5.9%) and routine check (28.0%). At the initial endoscopy, 19 patients had gastric ulcers, 79 patients had duodenal ulcers and 8 patients had gastroduodenal ulcers. The other mucosal findings at initial examination were; 23 had reflux esophagitis (12.4%), 91 had chronic superficial gastritis (48.9%), 60 had erosive gastritis (32.3%), 21 had atrophic gastritis (11.3%) and 14 patients had gastric intestinal metaplasia (7.5%).

Post eradication follow up varied from 13 to 112 mo and mean follow up duration was 41.2 ± 24.0 mo.

Table 1 Recurrence of *Helicobacter pylori* (*H. pylori*) after successful eradication therapy *n* (%)

Follow up period	*n*	Recurrence
1 ≤ yr < 2	186	14 (7.5)
2 ≤ yr < 3	133	15 (11.3)
3 ≤ yr < 4	90	8 (8.9)
4 ≤ yr < 5	62	8 (12.9)
5 ≤ yr < 6	40	3 (7.5)
6 ≤ yr < 7	27	6 (22.2)
7 ≤ yr < 8	13	2 (15.4)
8 ≤ yr < 9	7	2 (28.5)
9 ≤ yr < 10	1	0 (0.0)
Total		58 (31.2)

Table 2 Recurrence rate according to the *H. pylori* eradication regimen *n* (%)

Therapeutic regimens	*n*	Recurrence
Omeprazole + clarithromycin + amoxicillin	137	41 (30.0)
Bismuth subcitrate + ranitidine + metronidazole + amoxicillin	39	14 (35.9)
Omeprazole + bismuth subcitrate + metronidazole + tetracycline	10	3 (30.0)

Reinfection of H. pylori after successful eradication

Reinfection of *H. pylori* after successful eradication occurred in 58 of 186 patients (31.2%). The follow up period and the time when recurrences were found are summarized in Table 1. The annual reinfection rate was 9.1% per patient year (58/638.8 patient years).

One hundred and thirty seven patients were treated with proton pump inhibitor-based triple regimens, 41 of these patients (30.0%) had recurrence. Thirty nine patients were treated with bismuth-based quadruple regimens, 14 of these (35.9%) had recurrence. Among 10 patients who were treated with proton pump inhibitor-based quadruple regimens, 3 (30.0%) patients had recurrence. There was no significant difference among the regimens for reinfection rate (Table 2).

Endoscopic mucosal changes and comparison between H. pylori-recurred group and H. pylori-cured group

A comparison between the *H. pylori*-cured group and recurred group is summarized in Table 3. In the recurred group, mean follow up period was 42.5 mo (range 13-104 mo) and in the cured group, mean follow up was 40.6 mo (range 13-112 mo).

At the initial endoscopy, 23 cases of reflux esophagitis, 21 cases of atrophic gastritis and 14 cases of gastric intestinal metaplasia were noted. Peptic ulcers including

Table 3 Comparisons between the *H. pylori*-cured and -recurred group (mean ± SD) *n* (%)

	Cured group (*n* = 128)	Recurred group (*n* = 58)	*P*
Age (yr)	49.4 ± 11.2	51.5 ± 11.9	NS
Male:Female	65:63	33:23	NS
Follow up (mo)	40.6 ± 24.3	42.5 ± 23.7	NS
Endoscopic findings			
Reflux esophagitis			
Presence at initial investigation	19 (15.0)	3 (5.2)	NS
Newly developed or aggravated at follow up	25 (19.7)	8 (13.8)	NS
Improved at follow up	9 (7.1)	3 (5.2)	NS
Atrophic gastritis			
Presence at initial investigation	11 (8.7)	8 (13.8)	NS
Newly developed or aggravated at follow up	7 (5.5)	2 (3.4)	NS
Improved at follow up	3 (2.4)	1 (1.7)	NS
Metaplastic gastritis			
Presence at initial investigation	12 (9.4)	4 (6.9)	NS
Newly developed or aggravated at follow up	5 (3.9)	2 (3.4)	NS
Improved at follow up	7 (5.5)	2 (3.4)	NS

NS: Not significant.

scar stage were observed in 106 cases. Six cases of ulcer were in the acute or healing stage and 100 cases were in the scar stage. At the follow up endoscopy, there were no cases of recurrence or aggravation of ulcers. Newly developed or aggravated cases of reflux esophagitis at the follow up endoscopy were seen in 33 subjects and improved cases were seen 12 subjects. Nine subjects were newly developed or aggravated and 4 subjects were improved in the atrophic gastritis group and for the gastric intestinal metaplasia group, 7 were newly developed or aggravated and 9 were improved at the follow up endoscopy. There were no significant differences in mucosal changes at the initial and follow up endoscopies between *H. pylori*-recurred group and *H. pylori*-cured group.

DISCUSSION

Infection with *H. pylori* occurs worldwide, but the prevalence varies greatly between countries and among population groups within the same country. The overall prevalence of *H. pylori* infection is strongly correlated with socioeconomic conditions[2]. The prevalence is over 80% in many developing countries, and in Korea the prevalence of *H. pylori* infection is also high at 69.4%, as compared with 20% to 50% in industrial countries[2,5,6,9].

The reinfection rate after eradication therapy for *H. pylori* is extremely low in developed countries such as Europe and the USA. Here, the annual reinfection rates are reported to be around 1%. In contrast to the low rates of *H. pylori* reinfection reported in western populations, high recurrence rates have been reported in such developing countries as Peru, Brazil, Chile, Vietnam and Bangladesh, all of which are countries with a high prevalence of *H. pylori* infection[1,5-7,10-12]. The high prevalence of *H. pylori* infection may possibly be associated with high recurrence of infection after eradication because of the high risk of re-exposure to infection[7].

In 1998, Kim *et al*[13] reported that *H. pylori* reinfection rate in patients followed for up to 5 years was 12.8%. In our study, the patients were followed for up to 9 years and the average annual reinfection rate was 9.1% per patient year. The *H. pylori* reinfection rate was lower than the rate of the previous report but still higher than that of developed countries[14]. This high rate of reinfection could be explained by the high prevalence of *H. pylori* infection among asymptomatic Korean adults which may facilitate the transmission of *H. pylori* within families and may affect the high reinfection rates. Since the Korean economy has developed and sanitary conditions have been improved, recent reports have shown that rates of reinfection are lower than in previous reports[3,15].

Recurrence of *H. pylori* is thought to occur *via* two distinct mechanisms, recrudescence and reinfection. Recrudescence reflects reappearance of the original strain of *H. pylori* following its temporary suppression rather than successful eradication. True reinfection occurs when, after successful eradication, a patient becomes infected with either the original strain or a new strain of *H. pylori*[16]. Many investigators have found that recurrence rates during the first 3-12 mo after cure are due to late recrudescence. Demonstrated *H. pylori* negativity for 1 year post-treatment is a reliable indicator of successful eradication without recrudescence[3,7,15,17]. Recrudescence is related to the efficacy of the regimen used. Studies showed that recurrence of *H. pylori* infection more frequently occurred in patients treated with a low-efficacy treatment regimen than in those treated with a high-efficacy regimen. It seems that low-efficacy therapy does not actually cure *H. pylori* infection in the gastric mucosa but only temporarily suppresses it and does not completely eradicate it from the host[3,5,15,17].

In our study 16/241 patients (6.6%) showed recurrence of *H. pylori* within 1 year post-eradication and this rate was higher than in any previous reports[3]. There was no significant difference between regimens in recrudescence and, in addition, there was no significant difference between regimens in recurrence rate. Recent investigations have suggested that long-term effectiveness of antimicrobial therapy may be limited by high rates of recrudescence and reinfection, due to high levels of antibiotic resistance and pressure from high levels of infection[3,12].

The eradication of *H. pylori* infection results in a marked reduction of ulcer relapse. Many studies have shown that peptic ulcer recurrence is usually caused by *H. pylori* reinfection[6,13]. However, in our study, no recurrence of peptic ulcer was detected at the follow up endoscopy. Probably the reason why no such recurrence was detected in our study was that the initial stages of ulcer activity, which we observed at initial endoscopy,

were mostly at scar status. Since there was no recurrence of ulcers, we should carefully consider that *H. pylori* eradication might not be necessary at the ulcer scar stage of disease.

Some reports have shown a significantly lower prevalence of *H. pylori* infection among patients with gastroesophageal reflux disease than among those without this disease, suggesting that *H. pylori* infection might protect against reflux esophagitis[18]. However, in our study, there was no difference in incidence of this disease between *H. pylori*-cured patients and *H. pylori*-recurred patients. This suggests that there is no relationship between *H. pylori* infection and reflux esophagitis.

H. pylori infection may have a role to play in the progression of atrophy and intestinal metaplasia. The rate of glandular atrophy and intestinal metaplasia was found to be higher in *H. pylori*-positive patients but it was very low in those without *H. pylori* infection[19-25]. There was no significant difference in atrophic mucosal change between *H. pylori*-recurred and *H. pylori*-cured groups in our study. This could suggest that *H. pylori* reinfection does not affect the progression of the atrophy. We suggest the need for a comparative study of *H. pylori*-positive patients, *H. pylori*-recurred patients, *H. pylori*-negative patients and *H. pylori*-cured patients with regard to endoscopic and histologic findings. Also, polymorphic DNA fingerprinting is needed to detect whether the reinfecting strain is the identical or a different strain.

In conclusion, the reinfection rate in Korea is 9.1%, which represents a decreasing trend, but this is still higher than in the developed countries[25]. This may be due to the high prevalence of *H. pylori* infection which may influence high rates of reinfection after eradication. The endoscopic mucosal changes, including reflux esophagitis, metaplasia or atrophy, showed no significant differences between the *H. pylori*-recurred group and *H. pylori*-cured group. There was no incidence of recurred or aggravated ulcers.

COMMENTS

Background

Successful eradication of *Helicobacter pylori* (*H. pylori*) is important for the prevention of recurrent peptic ulcer disease and gastric cancer. Reinfection rate of *H. pylori* infection after successful eradication is also an important problem in the management of peptic ulcer disease.

Research frontiers

The reinfection rate after eradication therapy for *H. pylori* is extremely low in developed western countries. In contrast to this, high recurrence rates have been reported in developing countries such as Peru, Brazil, Chile, Vietnam and Bangladesh, which are countries with a high prevalence of *H. pylori* infection. The high prevalence of *H. pylori* infection may possibly be associated with high rates of reinfection after eradication because of the high risk of re-exposure to infection. In this study, the authors demonstrate the *H. pylori* reinfection rate and endoscopic changes after successful eradication in Korea.

Innovations and breakthroughs

The high prevalence of *H. pylori* infection in Korea suggests the possibility that the reinfection rate might be higher than western countries. This study showed that the reinfection rate is 9.1% in Korea and that the endoscopic mucosal changes, including reflux esophagitis, metaplasia or atrophy, showed no significant differences between the *H. pylori*-recurred group and *H. pylori*-cured group.

Applications

The reinfection rate in Korea is 9.1% which represents a decreasing trend but which is still higher than in the developed countries. This may be due to the high prevalence of *H. pylori* infection which may influence high rates of reinfection after eradication. *H. pylori* infection may have a role to play in the progression of atrophy and intestinal metaplasia, but there was no significant difference in atrophic mucosal changes between *H. pylori*-recurred and *H. pylori*-cured groups which suggests that *H. pylori* reinfection does not affect the progression of the atrophy.

Terminology

Recurrence of *H. pylori* is thought to occur *via* two distinct mechanisms, recrudescence and reinfection. Recrudescence means reappearance of the original strain of *H. pylori* following its temporary suppression rather than successful eradication. Reinfection occurs when a patient becomes infected with either the original strain or a new strain of *H. pylori* after successful eradication. Demonstrated *H. pylori* negativity for 1 year post-treatment is a reliable indicator of successful eradication without recrudescence.

Peer review

This manuscript describes an endoscopic cohort study of patients infected with *H. pylori* receiving eradication therapy. The authors aimed to investigate the reinfection rate after eradication therapy and the endoscopic findings after eradication, after a mean follow-up of 41 mo. They observed a reinfection rate of 9% per year, after confirmation of eradication at 1 year follow-up.

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