Helicobacter pylori Eradication in Patients with an Iatrogenic Ulcer after Endoscopic Resection and Peptic Ulcer

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Background/Aims: We aimed to compare the outcomes and timing of *Helicobacter pylori* eradication in patients with iatrogenic and peptic ulcers.

Materials and Methods: This was a retrospective study of 183 patients treated between 2012 and 2015 with 7-day standard triple therapy after endoscopic resection (ER). The patients were enrolled as the iatrogenic ulcer group and assigned to an early treatment group (n=139, *H. pylori* eradication initiated 2 days after ER) and a late treatment group (n=44, 8 weeks after ER). During the same period, 152 patients with peptic ulcer were assigned to the peptic ulcer group.

Results: Successful *H. pylori* eradication was achieved in 141 patients (77.0%) in the iatrogenic ulcer group and 114 (75.0%) in the peptic ulcer group ($P=0.661$). Among the ER patients, the eradication rate was 79.9% (n=111) in the early treatment group and 68.2% (n=30) in the late treatment group ($P=0.109$). The adverse event rate was significantly higher in the peptic ulcer group than in the iatrogenic ulcer group (13.8% vs. 4.9%, $P=0.005$). Compliance and adverse events did not significantly differ between the early and late treatment groups.

Conclusions: In iatrogenic ulcer, *H. pylori* eradication can be performed with a relatively lower adverse event rate, regardless of treatment timing, than that in peptic ulcer. (**Korean J Helicobacter Up Gastrointest Res 2018;18:30-37**)

Key Words: Endoscopic mucosal resection; Endoscopic submucosal dissection; *Helicobacter pylori*; Peptic ulcer

INTRODUCTION

The detection rate of gastric neoplasms, including early gastric cancers (EGCs), has been gradually increasing, primarily because of the widespread use of endoscopy. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are widely employed as curative treatments for gastric neoplasms such as EGCs and adenomas in many centers.¹⁻⁴ After the endoscopic resection (ER) of these lesions, a larger artificial ulceration is created and treatment with proton pump inhibitors (PPIs) is generally recommended for 4~8 weeks.^{5,6}

According to the Korean guidelines, peptic ulcer disease with *Helicobacter pylori* infection requires acid-sup-

pressing therapy with a PPI for 4~8 weeks, which is considered as the *H. pylori* eradication period.⁷ However, *H. pylori* eradication for iatrogenic ulcers has not been strongly recommended thus far; instead, based on the Maastricht IV/Florence Consensus Report, *H. pylori* eradication should be considered based on the risk stratification of patients with premalignant gastric conditions.⁸

Previous studies have shown that *H. pylori* eradication after ER of EGCs has a prophylactic effect on metachronous gastric cancer,^{9,10} and Cheon et al.¹¹ reported that *H. pylori* eradication might improve the ulcer healing rate after ER. However, in cases of iatrogenic ulcers, the optimal timing of eradication therapy after ER remains unclear.

In the present study, we aimed to compare the *H. pylori* eradication rate, compliance, and side effects between peptic ulcer and iatrogenic ulcer patients after ER. In the iatrogenic ulcer patients, we also attempted to identify the difference in outcomes based on the timing of eradication between patients who started *H. pylori* eradication on the discharge day after ER and patients who started *H. pylori* eradication after iatrogenic ulcer treatment with

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PPI (≥ 8 weeks).

MATERIALS AND METHODS

1. Patients

Between January 2012 and December 2015, 679 patients underwent ER of gastric low-grade adenoma, high-grade adenoma, EGC, and polyps by a single endoscopist (J.Y.A) at Asan Medical Center, Seoul, Korea. Of these patients, 285 received *H. pylori* eradication therapy (Fig. 1). We excluded 39 patients who received sequential therapy or triple therapy with a treatment duration of >7 days. The remaining patients ($n=246$) underwent 7-day standard triple therapy (amoxicillin [1 g], twice daily; clarithromycin [500 mg], twice daily; and standard dose PPI, twice daily). Among the remaining 246 patients, 56 were excluded due to the lack of revisits at the outpatient clinic or due to the presence of inappropriate follow-up tests after eradication therapy. The reasons for these exclusions were as follows: additional surgery after ER, no confirmation test of *H. pylori* eradication due to second ER, and confirmation test of *H. pylori* eradication within 4 weeks. We also excluded 7 patients who started eradication therapy on 2~8 weeks after ER. Finally, we enrolled 183 patients who were assigned to the early treatment group (*H. pylori* eradication initiated 2 days after ER) and the late treatment group (*H. pylori* eradication initiated after 8 weeks of PPI treatment for iatrogenic ulcer; Fig. 1).

During the same period, we enrolled 152 patients with

peptic ulcer disease associated with *H. pylori*, who underwent 7-day standard triple therapy approximately 2 weeks after detection. This study was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2016-0905).

2. Methods

A retrospective review of the electronic medical records for each patient was performed to collect data on their baseline clinical characteristics. In particular, information on age, sex, body mass index, smoking history, alcohol history, drug history, indications for ER, methods of *H. pylori* detection, and bleeding events was collected.

The diagnostic methods for *H. pylori* infection included the rapid urease test (CLO test[®]; Asan Pharm Co., Ltd., Seoul, Korea), urea breath test (UBiT; Otsuka, Tokyo, Japan), and histopathologic examination (Giemsa stain or Warthin-Starry stain) of the resected specimen. When ≥ 1 tests indicated positive results, the patient was considered to be infected with *H. pylori*. Moreover, *H. pylori* eradication was confirmed after 4 weeks, following completion of the therapy, through methods such as the rapid urease test, urea breath test, and/or histopathologic examination.

For patients who received *H. pylori* eradication therapy, data on the eradication regimen, compliance, and adverse event with drug treatment were also collected.

Fig. 1. Patient enrollment flowchart. ER, endoscopic resection.

3. Definition

Successful *H. pylori* eradication was defined as the presence of all negative results on performed confirmation tests. Patients with failure of 7-day standard triple therapy subsequently received second-line eradication, which involved quadruple eradication (PPI [standard dose], twice daily; bismuth subsalicylate [524 mg], 4 times daily; metronidazole [250 mg], 4 times daily; and tetracycline [500 mg], 4 times daily) over 7~14 days. Compliance was defined as the percentage of doses taken during the 7 days following the first dose. Arbitrarily, patients were considered to be good compliers if they had taken at least 12 out of 14 doses of each medicine (compliance >85%) during the assessed time period.¹²

Immediate bleeding was considered in cases where post-ER bleeding was detected within 24 hours, early delayed bleeding was considered in cases where post-ER bleeding was detected between 24 hours after EMR/ESD and the initiation of second-look endoscopy (the second day after the procedure), and late delayed bleeding was considered in cases where bleeding was detected between the time of the second-look endoscopy and 1 month after the procedure.¹³

4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 23.0 for Windows (IBM Co., Armonk, NY,

USA). With regard to comparison between the groups, continuous variables were analyzed using the Student's t-test and categorical variables were analyzed using the χ^2 test or exact test. Significance was considered when the *P* value was <0.05.

RESULTS

The median intervals from ER to the initiation of eradication therapy were 2.0 days (interquartile range [IQR], 2.0~2.0 days) in the early treatment group, and 79.0 days (IQR, 75.8~116.8 days) in the late treatment group. Also, the median interval from diagnosis to the initiation of eradication therapy was 14.0 days (IQR, 7.0~32.0 days) in the peptic ulcer treatment group.

1. Baseline clinical characteristics of the study patients

1) Comparison between the iatrogenic ulcer and peptic ulcer treatment groups

Table 1 presents a comparison of the baseline characteristics for the iatrogenic ulcer and peptic ulcer treatment groups. Patients in the iatrogenic ulcer treatment group were significantly older than those in the peptic ulcer treatment group (median age, 62 years *vs.* 55 years; *P*<0.001). Moreover, men were more frequent in the iatrogenic ulcer treatment group than in the peptic ulcer treatment group (67.8% *vs.* 56.6%; *P*=0.035). The in-

Table 1. Patient Characteristics in the Iatrogenic Ulcer and Peptic Ulcer Treatment Groups

Characteristic	Iatrogenic ulcer treatment group (n=183)	Peptic ulcer treatment group (n=152)	<i>P</i> value
Median age (yr)	62 (55~67)	55 (45~64)	<0.001
Male	124 (67.8)	86 (56.6)	0.035
Body mass index (kg/m ²)	24.7±3.0	24.0±3.3	0.055
Smoking			0.082
Never	93 (50.8)	88 (57.9)	
Ex-smoker	61 (33.3)	34 (22.4)	
Current smoker	29 (15.8)	30 (19.7)	
Alcohol			0.088
Never	83 (45.4)	65 (42.8)	
Past	35 (19.1)	44 (28.9)	
Current	65 (35.5)	43 (28.3)	
Use of nonsteroidal anti-inflammatory drugs or anti-platelet agents	37 (20.2)	32 (21.1)	0.851
Bleeding events	15 (8.2)	20 (13.2)	0.139

Values are presented as median (interquartile range), number (%), or mean±standard deviation.

cidence of bleeding events was 8.2% in the iatrogenic ulcer treatment group and 13.2% in the peptic ulcer treatment group ($P=0.139$); these cases were all treated via endoscopic bleeding control, without any serious complications.

2) Comparison between the early and late treatment groups

Table 2 provides a comparison of the baseline characteristics between the early and late treatment groups in the patients with iatrogenic ulcers. In the early treatment group, the indications for ER were EGC in 54 (38.9%), adenoma in 67 (48.2%), and polyps in 16 (11.5%) patients, whereas in the late treatment group, the indications for ER were EGC in 15 (34.1%), adenoma in 21 (47.7%), and polyps in 6 (13.6%) patients. Two patients in each group received eradication therapy for gastric mucosa-associated

lymphoid tissue (MALT) lymphoma. Moreover, 8 and 7 patients exhibited post-ER bleeding in the early and late treatment groups, respectively (5.8% vs. 15.9%, $P=0.053$). In particular, early and late delayed bleeding was noted in 12 and 3 patients, respectively. Of these, 4 patients received medication such as anti-platelet agents, and 1 patient who exhibited late delayed bleeding, underwent dialysis for chronic kidney disease.

2. Comparison of the rates of *H. pylori* eradication, compliance, and adverse events

Table 3 and Fig. 2 illustrate the comparison of the rates of *H. pylori* eradication, compliance, and adverse events between the peptic ulcer and iatrogenic ulcer treatment groups. Moreover, the patients in the early and late treatment groups were also compared. *H. pylori* was success-

Table 2. Patient Characteristics in the Early and Late Treatment Groups

Characteristic	Early treatment group (n=139)	Late treatment group (n=44)	P value
Median age (yr)	61 (55~67)	63 (57~66)	0.230
Male	93 (66.9)	31 (70.5)	0.661
Body mass index (kg/m ²)	24.7±3.0	25.0±3.1	0.498
Smoking			0.874
Never	72 (51.8)	21 (47.7)	
Ex-smoker	45 (32.4)	16 (36.4)	
Current smoker	22 (15.8)	7 (15.9)	
Alcohol			0.790
Never	63 (45.3)	20 (45.5)	
Past	28 (20.2)	7 (15.9)	
Current	48 (34.5)	17 (38.6)	
Use of nonsteroidal anti-inflammatory drugs or anti-platelets	26 (18.7)	11 (25.0)	0.365
Bleeding events	8 (5.8)	7 (15.9)	0.053

Values are presented as median (interquartile range), number (%), or mean±standard deviation.

Table 3. Comparison on the Rates of *Helicobacter pylori* Eradication, Compliance, and Adverse Events in All Groups

Outcomes	Peptic ulcer treatment group (n=152)	Iatrogenic ulcer treatment group			P value
		Total (n=183)	Early treatment group (n=139)	Late treatment group (n=44)	
Successful eradication	114 (75.0)	141 (77.0)	111 (79.9)	30 (68.2)	0.661 ^a 0.109 ^b
Compliance (%)	96.4±9.9	97.3±8.8	97.2±9.4	97.3±6.9	0.397 ^a 0.985 ^b
Adverse events	21 (13.8)	9 (4.9)	9 (6.5)	0 (0)	0.005 ^a 0.117 ^b

Values are presented as number (%) or mean±standard deviation.

^aComparison between the peptic ulcer treatment group and the iatrogenic ulcer treatment group.

^bComparison between the early treatment group and the late treatment group.

Fig. 2. Comparison of *Helicobacter pylori* eradication (A) and adverse event rates (B).

Table 4. Adverse Events during the Treatment Period

Adverse events	Iatrogenic ulcer treatment group		Peptic ulcer treatment group
	Early treatment group	Late treatment group	
Diarrhea	2 (22.3)	0 (0)	5 (23.8)
Dyspepsia	3 (33.3)	0 (0)	1 (4.8)
Epigastric soreness	3 (33.3)	0 (0)	1 (4.8)
Nausea or vomiting	0 (0)	0 (0)	10 (47.6)
Bitter taste	0 (0)	0 (0)	2 (9.5)
General weakness	0 (0)	0 (0)	1 (4.8)
Central nervous system effects	1 (11.1)	0 (0)	1 (4.8)
Total	9 (100.0)	0 (0)	21 (100.0)

Values are presented as number (%).

fully eradicated from 141 (77.0%) patients in the iatrogenic ulcer treatment group and 114 (75.0%) patients in the peptic ulcer treatment group ($P=0.661$). There was no significant difference in compliance between the 2 groups. However, patients in the peptic ulcer treatment group (21, 13.8%) experienced more adverse events than those in the iatrogenic ulcer treatment group (9, 4.9%, $P=0.005$). The rates of *H. pylori* eradication were 79.9% ($n=111$) in the early treatment group and 68.2% ($n=30$) in the late treatment group ($P=0.109$). Compliance did not significantly differ between these groups. Although there was no significant difference in the adverse event rate during treatment, the patients in the early treatment group experienced more adverse events (9, 6.5%) than those in the late treatment group (0, 0.0%, $P=0.117$).

Table 4 lists the adverse events that arose during

treatment. These included diarrhea, dyspepsia, epigastric soreness, nausea or vomiting, bitter taste, general weakness, and central nervous system effects including dizziness and somnolence. The most common adverse events were dyspepsia (33.3%) and epigastric soreness (33.3%) in the early treatment group, and nausea or vomiting (47.6%) in the peptic ulcer treatment group.

3. Second-line treatment after the failure of first-line treatment

The 7-day standard triple therapy failed in 38 patients (25.0%) in the peptic ulcer treatment group, 28 patients (20.1%) in the early treatment group, and 14 patients (31.8%) in the late treatment group. Of these, a total of 36 patients (45.0%) subsequently underwent treatment with a quadruple regimen, and 23 (28.8%) achieved suc-

successful eradication, 7 (8.7%) exhibited failure of quadruple therapy, and 6 (7.5%) were lost to follow up.

DISCUSSION

In the present study, we found that the rate of adverse events was lower in the iatrogenic ulcer treatment group than in the peptic ulcer treatment group (4.9% vs. 13.8%, $P=0.005$), and that the rates of *H. pylori* eradication and compliance did not differ between these 2 groups. In the iatrogenic ulcer patients, the rates of *H. pylori* eradication, compliance, and adverse events did not significantly differ between the early and late treatment groups (79.9% vs. 68.2%, $P=0.109$; 97.2% vs. 97.3%, $P=0.985$; and 6.5% vs. 0.0%, $P=0.117$). Thus, based on these findings, we believe that the timing of *H. pylori* eradication after ER can be determined based on the patient's symptoms and the status of the iatrogenic ulcer.

In Korea, ER is commonly performed for patients with noninvasive low-grade neoplasia with risk factors, noninvasive high-grade neoplasia, and differentiated or undifferentiated invasive neoplasia in the stomach.^{3,14-16} These broad indications for ER can be attributed to the development of ESD, which is superior to EMR due to the higher en bloc and complete resection rates.^{3,17} With the enhancements in endoscopic interventions, the interest in iatrogenic ulcers after ER has gradually increased. Iatrogenic ulcers can occasionally cause significant bleeding or abdominal pain, similar to that caused by peptic gastric ulcers. Acid-suppressing agents such as PPI or anti-ulcer agents are empirically administered to prevent bleeding and accelerate ulcer healing after ER.^{18,19} Previous studies have shown that *H. pylori* eradication, including PPI treatment, can improve the healing rate¹¹ and the quality of healing after ER in gastric ulcers.²⁰ Nevertheless, the optimal timing of *H. pylori* eradication after ER remains unclear.

Recently, Huh et al.²¹ reported that the early initiation of *H. pylori* eradication, within ≤ 2 weeks of ER of gastric tumors, is an independent predictor of eradication success (eradication success rate: 90.0% for early treatment [≤ 2 weeks], 76.2% for intermediate treatment [2~8 weeks], and 72.4% for late treatment [≥ 8 weeks]; $P <$

0.001). However, that study did not evaluate the side effects and completion rates of eradication therapy in each group. In the present study, we sought to compare the outcomes of *H. pylori* eradication between peptic ulcer and iatrogenic ulcer patients, and to identify the optimal timing of *H. pylori* eradication after ER. Contrary to previous reports, we found that the *H. pylori* eradication rate did not differ between the early and late treatment groups, and that the overall eradication rate of iatrogenic ulcer patients did not differ from those of peptic ulcer patients. Thus, the timing of *H. pylori* eradication after ER can be chosen based on the condition of the patients, as the eradication rate is not associated with the timing of therapy.

A recent study reported that the *H. pylori* eradication rate of standard triple therapy ranged from 80.0% to 81.4% between 2008 and 2010 in Korea.²² Although several studies have shown that the *H. pylori* eradication rate of iatrogenic ulcer cases ranged from 72.4% to 95.5%,^{11,21} to our knowledge, no study has compared *H. pylori* eradication between peptic ulcer and iatrogenic ulcer patients thus far. We considered that the mechanism of ulcer formation due to ER would differ from that due to *H. pylori* infection or nonsteroidal anti-inflammatory drugs administration. Therefore, we assumed that the outcomes of the iatrogenic ulcer treatment group might differ from those of the peptic ulcer patients. However, the *H. pylori* eradication rate did not differ between our peptic ulcer and iatrogenic ulcer treatment groups (77.0% vs. 75.0%, $P=0.661$). This result suggests that the eradication rate was not affected by the mechanism of ulcer formation.

Several factors are reportedly associated with a decreased efficacy of *H. pylori* eradication therapy, including antibiotic resistance, CYP2C19 polymorphisms, MDR1 C3435T polymorphism, eradication duration, smoking, and probiotics.²³⁻²⁸ Drug compliance was also found to be a risk factor of eradication failure.^{12,29} To minimize the effects of these factors, we chose the same regimen with a 7-day duration in all the patients. Accordingly, we found that drug compliance was high in all the groups (mean drug compliance rate: 96.4% in the peptic ulcer treatment group, 97.3% in the iatrogenic ulcer group, 97.2% in the early treatment group, and 97.3% in the late treatment

group) in the present study, possibly because the patients were provided a detailed explanation of the need for eradication and the importance of taking medication before eradication therapy, and because the patients were concerned about the severity of their disease and the therapeutic procedure. Hence, drug compliance did not affect the eradication rate of *H. pylori* in all the groups. A fuller explanation before eradication treatment could have increased patient compliance with the medication regimen.

Adverse events were reported in up to 50% of patients receiving triple therapy.³⁰ Most of the adverse events were mild, and did not lead to the discontinuation of therapy. In particular, antibiotic administration is often associated with gastrointestinal side effects, such as diarrhea, nausea, vomiting, bloating, and abdominal pain. Similarly, patients after ER often experience nausea, dyspepsia, or abdominal pain. In a previous report, the key mechanism underlying post-ER pain was found to involve hypersensitivity to acid and another was found to involve peristaltic contractions of edematous and inflamed ulcers.³¹ In the present study, we found that the adverse events in the iatrogenic ulcer treatment group were less frequent than those in the peptic ulcer treatment group (4.9% vs. 13.8%, $P=0.005$). One possible reason for this finding was that the pathogenesis of iatrogenic ulcers was completely mechanical, rather than as a result of gastric mucosa degradation by gastric juice or apoptosis due to *H. pylori* infection, and that the basal stomach of peptic ulcer patients might be damaged to a greater extent than that of iatrogenic ulcer patients. Thus, basal gastrointestinal symptoms and antibiotic sensitivity might be more common and severe in peptic ulcer patients than in pre-ER patients. Nevertheless, further studies are needed to explain these differences.

We found also from our current analysis that although there was no significant difference in the adverse event rate between the early and late treatment groups (6.5% vs. 0.0%, $P=0.117$), the rate of adverse events was lowest in the late treatment group. We believe that this finding is related to the pre-eradication use of PPI, which reduced gastrointestinal symptoms by decreasing the sensitivity to acid.

Our study had several limitations of note. First, as the analysis was retrospectively performed in a single referral center, a possible selection bias cannot be excluded. Second, we did not perform tests for antibiotic resistance, which is an important factor affecting the *H. pylori* eradication rate. Third, the most important factor in iatrogenic ulcer healing is the size of ulcer, but this was not evaluated in our present study. Fourth, we could not distinguish between early and late peptic ulcer treatment groups. The ulcer stage and formation time were clear in cases of iatrogenic ulcer, while the peptic ulcer stages found with endoscopy varied. Because of these differences, the peptic ulcer group could not be classified according to the time of *H. pylori* eradication. Despite these limitations, this is the first study to compare the results of *H. pylori* eradication, compliance, and adverse events between iatrogenic ulcer and peptic ulcer patients and evaluate the appropriate timing of eradication therapy in iatrogenic ulcer patients.

In conclusion, in iatrogenic ulcer patients after ER, *H. pylori* eradication with a 7-day standard triple therapy can be performed with a relatively lower number of adverse events, as compared to that in patients with peptic ulcer. Moreover, the timing of eradication after ER can be chosen based on the condition of the patients.

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