ORIGINAL ARTICLE

Gut and Liver, Vol. 4, No. 4, December 2010, pp. 514-517

A Planned Prospective, Randomized, Placebo-Controlled Multicenter Trial Assessing the Effect of *Helicobacter pylori* Eradication on the Healing of Iatrogenic Ulcer after Endoscopic Resection of Gastric Neoplasm

Sang Gyun Kim*, Ho June Song†, Il Ju Choi‡, Joo Young Cho§, Hwoon-Yong Jung†, Bora Keum‖, Jae Hee Cheon¶, Yong Chan Lee¶, Jae Gyu Kim**, Sue K. Park††, Byung Joo Park††, and Hyun Chae Jung*; Korean College of *Helicobacter* and Upper Gastrointestinal Research

**Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, †Department of Internal Medicine, Ulsan University College of Medicine, Seoul, ‡Center for Gastric Cancer, National Cancer Center, Goyang, §Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, ‖Department of Internal Medicine, Korea University College of Medicine, Seoul, ¶Department of Internal Medicine, Yonsei University College of Medicine, Seoul, **Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, ††Department of Preventive Medicine, Seoul National University College of Medicine and Medical Research Collaboration Center, Seoul National University College of Medicine and Seoul National University Hospital, Seoul; Korean College of Helicobacter and Upper Gastrointestinal Research, Seoul, Korea*

Background/Aims: *Helicobacter pylori* eradication may facilitate the healing of iatrogenic ulcer after endoscopic resection of gastric neoplasm. This study involved designing a randomized, double-blinded, placebo-controlled, multicenter trial, performed by the Korean College of Helicobacter and Upper Gastrointestinal Research and the Medical Research Collaboration Center, Seoul National University Hospital. **Methods:** We intend to enroll up to 232 patients *H.-pylori*-positive patients who have gastric adenoma or early gastric cancer after endoscopic resection. The enrolled patients are being randomly allocated to the *H.-pylori*-eradication-plus-proton-pump-inhibitor group or the placebo-plus-proton-pump-inhibitor group based on their histology results and the size of the resected specimen. After random allocation, the iatrogenic ulcer size and stage are evaluated at 4- and 8-week follow-ups (with a window of ±7 days). The primary end point is the healing rate of the ulcer by stage, and the secondary end point is the rate of ulcer size reduction, relief rate from ulcer-related symptoms, and adverse-event rates. **Results:** More than 90% of the target subjects have already been enrolled into the study and are receiving ongoing periodic monitoring by the Medical Research Collaboration Center. **Conclusions:** Completion of the study should reveal whether *H. pylori* eradication can facilitate the healing of ulcer after endoscopic resection in Korea. **(Gut Liver 2010;4:514-517)**

Key Words: *Helicobacter pylori*; Iatrogenic ulcer; Endoscopic resection; Eradication; Medical Research Collaboration Center

INTRODUCTION

Endoscopic resection has been widely applied to gastric neoplasm such as gastric adenoma or early gastric cancer (EGC) as a curative treatment modality.[1] Since endoscopic submucosal dissection method has been introduced, complete en-bloc resection has been possible in larger-sized tumor rather than conventional endoscopic mucosal resection, but resulted in large iatrogenic ulcer. Although proton pump inhibitor has been administered for 4-8 weeks for the healing of iatrogenic ulcer, delayed healing has been observed in some portion of large-sized

Correspondence to: Hyun Chae Jung
Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 101 Daehangno, Jongno-gu, Seoul 110-744, Korea
Tel: +82-2-740-8112, Fax: +82-2-743-6701, E-mail: hyunchae@plaza.snu.ac.kr
Received on October 19, 2010. Accepted on November 8, 2010.
DOI: 10.5009/gnl.2010.4.4.514
Sang Gyun Kim and Ho June Song had equally contributed to study design and processing the manuscript as first author.

iatrogenic ulcer, especially by submucosal dissection method.

Helicobacter pylori (*H. pylori*) eradication has been reported to accelerate the healing of peptic ulcer as well as to prevent the recurrence.[2] *H. pylori* eradication can facilitate the healing process by improvement of microcirculation and expression of variable endogenous growth factors.[3] In the same manner with peptic ulcer, *H. pylori* infection may inhibit healing of iatrogenic ulcer after endoscopic resection of gastric neoplasm. Furthermore, larger iatrogenic ulcer by submucosal dissection method could be affected in the process of healing by *H. pylori* infection. Although *H. pylori* eradication may facilitate the healing of iatrogenic ulcer after endoscopic resection, there is no well-planned and designed study. Several studies have reported the effect of *H. pylori* eradication on iatrogenic ulcer, but had many limitations of nonplacebo-controlled trial, small sample size, small ulcer size, short-term follow-up, high drop-out rate or eradication before endoscopic resection.[4,5]

This randomized, double-blinded, placebo-controlled, multicenter trial has been planned and designed to elucidate the accurate sample size with statistical power, and monitored periodically with Medical Research Collaboration Center, Seoul National University Hospital. Over 90% among planned enrollment has been completed, and follow-up is still ongoing.

MATERIALS AND METHODS

1. Study subjects

From September 2008, patients who were considered eligible for endoscopic resection for gastric neoplasm including gastric adenoma or EGC have been enrolling from 6 general hospitals. Inclusion criteria are as follows; age 30-75 years, pathologically-confirmed gastric adenoma or EGC, tumor size 1-3 cm, EGC with differentiated histology, confined to mucosa and without evidence of distant metastasis, positive *H. pylori* infection.

The presence of *H. pylori* infection is determined by histologic examination with Wright-Giemsa stain on antrum lesser curvature and body lesser curvature, rapid urease test on antrum or urea breath test. *H. pylori* infection is defined as the cases with positive results on at least one test among the three tests.

Exclusion criteria are as follows; piecemeal endoscopic resection, positive tumor at resection margin in pathological mapping, history of medication such as proton pump inhibitor (PPI), H_2 receptor antagonist (H2RA), sucralfate, bismuth, prostaglandin within 2 weeks of enrollment, malignancy within 5 years of enrollment, current medication such as COX inhibitor, nonsteroidal anti-inflammatory drugs, aspirin, steroid, anticoagulants, anti-platelet agents, history of gastric surgery, serious complication with endoscopic resection, uncontrolled co-morbid diseases, history of allergic reaction to antibiotics or PPI. The Institutional Review Boards of the six hospitals approved the study protocol and all participants provided written informed consents for the study.

2. Sample size

Previous studies reported that the healing rate of iatrogenic ulcer was 70-85% in 8 weeks with 4 week-PPI treatment.[4-7] Based on these results, the required sample size was 97 patients for each arm on assumption of 75% healing rate in placebo arm and 90% in eradication when the significance level was defined at 5% and power at 80%. The patients for each arm should be acquired to 116 when the expected drop-out rate fixed 20% due to follow-up loss or protocol violation.

3. Endoscopic resection

Endoscopic resection included conventional endoscopic mucosal resection (EMR) such as strip biopsy method, EMR using cap, EMR with precutting and snare, or endoscopic submucosal dissection. After endoscopic resection, removed specimen was smoothed and fixed with 10% formalin. Pathological mapping was conducted at 2 mm thickness, and complete en-bloc resection was defined as negative tumor from lateral and vertical resection margin in one piece at pathological mapping. Ulcer size was calculated by multiplying the maximal diameter by the perpendicular diameter of specimen, and tumor size equally.

4. Randomization and blinding

At the day and next day of endoscopic resection, intravenous PPI is administered to prevent immediate complications such as bleeding or perforation. Patients satisfying the inclusion and exclusion criteria are stratified by two strata such as maximal diameter of ulcer on specimen (3 cm and more vs less than 3 cm) and pathologic diagnosis (EGC vs adenoma), and randomly allocated to eradication and placebo arms with random permuted block design by web-based randomization program in Medical Research Collaboration Center. At 3rd day of endoscopic resection, patients in the eradication arm take lansoprazole 30 mg twice a day, amoxicillin 1,000 mg twice a day, and clarithromycin 500 mg twice a day for 1 week, and patients in the placebo arm take lansoprazole and two placebos of amoxicillin and clarithromycin twice a day for 1 week. After 1 week of eradication, all patients take only lansoprazole 30 mg a day for 3 weeks. Patients are instructed

not to take any other medications that may affect ulcer healing such as PPI, H2RA, bismuth, or sucralfate. Intermittent rescue antacid is allowed to relieve ulcer-induced pain.

Medication package including amoxicillin, clarithromycin and lansoprazole is contained in one bottle. Placebo is same in size and color with amoxicillin or clarithromycin. Medication is packed and labeled, and information of medication is sealed up according to randomization by Medical Research Collaboration Center, Seoul National University Hospital.

5. End point and follow-up endoscopy

The primary endpoint for the study is iatrogenic ulcer healing rates by changes in stage, and the secondary endpoint is the reduction ratio of ulcer size, clinical symptom improvement rate and adverse event rates. Clinical visits are held at 2, 4, and 8 weeks after randomization. At 4 and 8 weeks, follow-up endoscopy is performed to evaluate iatrogenic ulcer healing and *H. pylori* eradication. Iatrogenic ulcer healing is assessed by measuring changes in both ulcer stage and ulcer size in follow-up endoscopy. Ulcer stage is assessed using a six-stage system by Sakita and Fukutomi: active (A1, A2), healing (H1, H2) and scar (S1, S2) stages.[8] Ulcer reduction ratio is determined by the ratio of initial ulcer size versus follow-up ulcer size at 4 and 8 weeks. The primary endpoint is evaluated from ulcer healing rate at 8 week-follow-up endoscopy.

Clinical symptoms are evaluated at 2, 4 and 8 weeks after randomization. Abdominal pain, epigastric soreness, acid regurgitation, epigastric discomfort, epigastric fullness, nausea and/or vomiting, diarrhea, changes of taste, headache and/or dizziness were recorded using scoring system (Table 1). The score 0 or 1 is defined as significant clinical symptom improvement. Compliance is evaluated by counting remained tablets, and patients who had taken less than 80% of prescribed medications are excluded from the per-protocol analysis.

H. pylori eradication is evaluated by urea breath test at 8 weeks after randomization. Thirty-eight mg of ^{13}C-urea powder dissolved in 50 mL of water is administered orally, and the second breath sample is collected at 30 minutes. A cut-off value of 4‰ is used.

Table 1. Clinical-Symptom Scoring

Grade	Severity
None (0)	Without any symptom
Mild (1)	Minimal epigastric symptom
Moderate (2)	Epigastric symptom without disruption of daily living activity
Severe (3)	Epigastric symptom with disruption of daily living activity

6. Statistical analysis

The intention-to-treat analysis will be preferentially conducted for the evaluation of primary and secondary endpoints for all randomized patients who received medication at least once. Per-protocol analysis will be performed for patients who would complete study protocol without any significant protocol violation. Significant protocol violation included inappropriate inclusion/exclusion criteria, compliance less than 80%, taking other medications that affect ulcer healing, and interim discontinuation of study.

Baseline characteristics are tested by the chi-square test, the Student t-test or the Mann-Whitney U-test. The changes in ulcer stage and ulcer reduction ratio are tested by the chi-square test and the Mann-Whitney U-test, respectively. Clinical symptom improvement and adverse event rates of both arms are compared using the chi-square test. p-value less than 0.05 will be considered to be statistically significant. Statistical analyses were performed using SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, USA) and SAS (version 9.1; SAS Inc., Cary, NC, USA).

RESULTS

Approval to conduct the study was received from the Institutional Review Board at 6 nationwide hospitals. A total of 202 patients were enrolled into the study between September 2008 and August 2010 with ongoing enrollment and follow-up. Interim periodic monitoring was conducted to maintain appropriate enrollment and follow-up by Medical Research Collaboration Center, and queries during monitoring has been solved by investigators.

Over 85% of among planned subjects has been completed, and the enrollment is expected to close in December 2010.

DISCUSSION

Although *H. pylori* eradication has been established in the treatment of peptic ulcer and reducing relapse of the disease, it has not been clarified that *H. pylori* eradication could facilitate healing of iatrogenic ulcer after endoscopic resection of gastric neoplasm. Since *H. pylori* eradication has not been considered to be inevitable in the management of iatrogenic ulcer after endoscopic resection, it has not been accepted for general clinical practice.

In early phase after endoscopic resection, healing of iatrogenic ulcer may be influenced by *H. pylori* infection as well as mechanical defect of gastric wall including mucosa and submucosa because *H. pylori* infection can interfere mucosal blood flow around the margin of iatrogenic ulcer, which results in delayed ulcer healing.[9] But in late phase of iatrogenic ulcer healing, most of iatrogenic ulcers can heal better rather than pathologic peptic ulcer irrespective *H. pylori* infection because *H. pylori* itself is not the main cause of diseases.

Previous studies have reported that *H. pylori* eradication facilitated ulcer healing in 4 weeks after endoscopic resection, but not in 8 weeks.[4,10,11] In one study, mean ulcer dimension was less than 2 cm^2, which could heal completely and not have any difference of healing rate in 4 weeks irrespective of *H. pylori* eradication.[4] In this study, because most patients stratified by 3 cm in maximal diameter of specimen had size over 3 cm, complete ulcer healing would not be achieved in 4 weeks and may have difference in ulcer reduction ratio. In 8 weeks after endoscopic resection, other studies has reported that there was not any difference in healing rate irrespective of *H. pylori* eradication, which may be influenced by long-standing PPI treatment.[10,11] In this study, because most initial ulcer size was larger than previous reports and PPI was administered for 3 weeks, there is a possibility of significant difference of ulcer reduction ratio after 8 weeks.

The advantages of this study are prospective planned design by multicenters and Medical Research Collaboration Center, large-scaled placebo controlled randomization, and accurate sample size calculation considering 20% drop-out. Furthermore, regular monitoring of appropriate enrollment and follow-up by Medical Research Collaboration Center would maintain good clinical trial with adequate feedback. This study will have the statistical power to demonstrate whether *H. pylori* eradication exerts any clinically relevant effect on accelerating healing of iatrogenic ulcer after endoscopic resection of gastric neoplasm.

ACKNOWLEDGEMENTS

This study was supported by a grant from Korea College of *Helicobacter* and Upper Gastrointestinal Research.

REFERENCES

1. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. Gastrointest Endosc 2003;57: 567-579.
2. Arkkila PE, Seppala K, Kosunen TU, et al. Eradication of *Helicobacter pylori* improves the healing rate and reduces the relapse rate of nonbleeding ulcers in patients with bleeding peptic ulcer. Am J Gastroenterol 2003;98:2149-2156.
3. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 2001;345:784-789.
4. Cheon JH, Kim JH, Lee SK, Kim TI, Kim WH, Lee YC. *Helicobacter pylori* eradication therapy may facilitate gastric ulcer healing after endoscopic mucosal resection: a prospective randomized study. Helicobacter 2008;13:564-571.
5. Ye BD, Cheon JH, Choi KD, et al. Omeprazole may be superior to famotidine in the management of iatrogenic ulcer after endoscopic mucosal resection: a prospective randomized controlled trial. Aliment Pharmacol Ther 2006;24: 837-843.
6. Lee SY, Kim JJ, Lee JH, et al. Healing rate of EMR-induced ulcer in relation to the duration of treatment with omeprazole. Gastrointest Endosc 2004;60:213-217.
7. Yamaguchi Y, Katsumi N, Tauchi M, et al. A prospective randomized trial of either famotidine or omeprazole for the prevention of bleeding after endoscopic mucosal resection and the healing of endoscopic mucosal resection-induced ulceration. Aliment Pharmacol Ther 2005; 21 Suppl 2:111-115.
8. Sakita T, Fukutomi H. Endoscopic diagnosis. In: Yoshitoshi Y, ed. Ulcer of stomach and duodenum. Volume 1. Tokyo: Nankodo, 1971:198-208.
9. Adachi K, Suetsugu H, Moriyama N, et al. Influence of *Helicobacter pylori* infection and cetraxate on gastric mucosal blood flow during healing of endoscopic mucosal resection-induced ulcers. J Gastroenterol Hepatol 2001;16: 1211-1216.
10. Kakushima N, Fujishiro M, Yahagi N, Kodashima S, Nakamura M, Omata M. *Helicobacter pylori* status and the extent of gastric atrophy do not affect ulcer healing after endoscopic submucosal dissection. J Gastroenterol Hepatol 2006;21:1586-1589.
11. Ueda H, Ito M, Tanaka S, et al. The effect of *Helicobacter pylori* eradication therapy on gastric ulcer healing after endoscopic mucosal resection. J Clin Gastroenterol 2006;40: 293-296.