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Failure of a Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of *H. pylori* Eradication in *H. pylori*-Infected Patients with Functional Dyspepsia

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Background/Aims: The role of *Helicobacter pylori* eradication in patients with functional dyspepsia (FD) is still uncertain. We originally planned a randomized clinical study to observe dyspeptic symptoms after *H. pylori* eradication therapy. However, we failed to complete the study; therefore, we analyzed the factors that affected the failure of the study. **Methods:** Interviews and questionnaire surveys were conducted to analyze the factors that induced early termination from the study. **Results:** Many patients were screened by gastroenterologists at 11 tertiary referral hospitals between July 2009 and August 2010; however, only 4 patients met the enrollment criteria. Most patients who visited our clinics had been experiencing FD symptoms for less than 6 months or were already taking medication. They also demanded to continue taking medications and using other drugs. Only 3 of the 4 patients signed informed consent. **Conclusions:** The application of the current Rome III criteria to FD is difficult to evaluate in Korean patients with dyspeptic symptoms because of the early medical evaluation. Most Korean patients who were diagnosed with FD by the Rome III criteria did not overcome their fear of being unable to use rescue medications during the study period. **(Gut Liver 2011;5:468-471)**

Key Words: *Helicobacter pylori*; Dyspepsia; Symptom

INTRODUCTION

The pathophysiological mechanisms of functional dyspepsia (FD) are associated with multifactorial causes such as delayed gastric emptying, impaired gastric accommodation to a meal, hypersensitivity to gastric distention, altered duodenal sensitivity to lipids or acid, abnormal duodenojejunal motility, psychosocial factors, environmental factors, and autonomic dysfunction.[1] *Helicobacter pylori* status has also been proposed to be involved in generating FD symptoms. The Maasricht III consensus report recommended *H. pylori* eradication for patients with *H. pylori* infection and investigated nonulcer dyspepsia.[2] In the second Asia-Pacific Consensus Guidelines for *H. pylori* infection, *H. pylori*-infected patients with FD were candidates for *H. pylori* eradication.[3] A systemic review showed that *H. pylori* eradication therapy had a small but statistically significant effect in *H. pylori* positive nonulcer dyspepsia.[4] However, the role of *H. pylori* eradication in patients with FD is still controversial because the benefits of *H. pylori* eradication have not been fully evaluated.

FD has been evaluated again since the Rome III classification

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was published in 2006.[5] FD was redefined as symptoms located in the epigastric region, including pain or burning, postprandial fullness, or early satiation. No studies have been conducted in Korea to evaluate the effect of *H. pylori* eradication in *H. pylori*-infected patients with FD. Therefore, we planned a randomized placebo-controlled study to evaluate the clinical usefulness of *H. pylori* eradication therapy in Korean patients with *H. pylori* infection and FD. However, we failed to enroll sufficient numbers of patients for the study. The aim of the present study was to evaluate the causes of enrollment failure.

MATERIALS AND METHODS

1. Overview of original study design

A randomized, double-blind, placebo-controlled study was designed for patients who were diagnosed with FD using the Rome III criteria. The study protocol was developed by the *H. pylori* and dyspepsia study group of Korean College of Helicobacter and Upper Gastrointestinal Research from November 2007 to March 2008. The protocol was reviewed by the Medical Research Collaborating Center (MRCC) at Seoul National University College of Medicine. It was approved by the Institutional Review Boards of 11 medical centers in Korea and the Korean Food and Drug Administration (KFDA).

2. Study population

We enrolled FD patients met the Rome III criteria for FD according to inclusion criteria: 1) patients of age 20 to 70 seeking medical care for dyspeptic symptoms; 2) patients who had normal endoscopic findings and *H. pylori* infection (positive rapid urease test and/or positive result on histology). We excluded the following patients: 1) who had reflux symptoms, bowel symptoms suggestive of irritable bowel syndrome, hematemesis, or any other symptoms and signs indicating serious disease; 2) who were treated by histamine-receptor antagonists, proton pump inhibitors, prostaglandins, prokinetics, bismuth-containing compounds, or antibiotics during 4 weeks before the study began; 3) who had concomitant diseases that might be the causes of dyspeptic symptoms, such as gallstones or pancreatic disease, depression or psychosomatic disorders as assessed by the Beck Depression Inventory (BDI) and the Somatosensory Amplification Scale (SSAS), and the histories of an abdominal operation.

3. Planned endoscopy and *H. pylori* evaluation

Endoscopy was performed before the screening period, and biopsies were taken for the rapid urease test and histology. If a patient had a positive rapid urease test or a positive histological examination for *H. pylori*, the patient was considered to have *H. pylori* infection.

4. Designed study protocol

1) Run-in period

After endoscopy, patients were evaluated for FD using the Rome III criteria. Patients diagnosed with FD received diary cards and were asked to record eight dyspeptic symptoms and their health-related quality of life for a run-in period of 14 days. The 8 dyspeptic symptoms were selected from among the 15 symptoms of the Nepean Dyspepsia Index-Korean version (NDI-K) and included pain in the upper abdomen, discomfort in the upper abdomen, burning in the upper abdomen, inability to finish a regular meal, fullness after eating, pressure in the upper abdomen, bloating in the upper abdomen, and nausea.[6] The 8 symptoms were estimated by rating frequency (5 subscales), intensity (6 subscales), and bothersomeness (5 subscales).

The NDI-K questionnaire measuring health-related quality of life consisted of 25 questions and 5 areas of life including; tension/sleep (9 items), interference with daily activities (6 items), eating/drinking (3 items), knowledge/control (4 items), and work/study (3 items).[6] For most of the areas, the impact of the illness was considered to interfere with a patient's ability to do something or with their enjoyment of that area of life. These items were measured using 5-point Likert scales where zero, not at all or not applicable; 1, a little; 2, moderately; 3, quite a lot; and 4, extremely. The NDI-K quality-of-life score ranges from 0 to 99, with higher scores indicating a worse quality of life.

2) Treatment period

After the run-in period, patients were randomized, with the help of computer-generated randomization codes, to receive either *H. pylori* eradication using triple therapy (30 mg lansoprazole twice daily, 500 mg clarithromycin twice daily, and 1 g amoxicillin twice daily) for 1 week or a placebo triple therapy for 1 week. Compliance with medication was defined as the consumption of at least 80% of the medication.

3) Follow-up period

The patients were reevaluated for their symptoms and health-related quality of life at 4 and 8 weeks after finishing the test medication. Diary cards for a given week were collected at that week's visit. At the week 8 visit after finishing the test medication, the patients underwent a ^{13}C-urea breath test to check *H. pylori* infection status.

4) Assessment of symptoms

Efficacy was assessed at 8 weeks after taking the study medications using the patient global assessment of efficacy, which had 5 grades: symptom-free, markedly improved, moderately improved, not changed, and deteriorated. Three secondary efficacy parameters were used in the study. The first parameter was a patient's global assessment of efficacy at 4 weeks. At 8 weeks after the medication was completed, improvement in the 8 se-

lected NDI-K dyspeptic symptoms was considered the second parameter, and 4 grades were used to evaluate decreases in the total symptom scores: prominent effect (more than 75% reduction), moderate effect (50% to 75% reduction), mild effect (25% to 50% reduction), and no effect (less than 25% reduction). This parameter was changed to a disease-specific quality-of-life score using the validated NDI-K.[6]

5) Statistical analysis

Sample sizes were measured prospectively in the basis of intension-to-treat approach. Our calculations were based on the results of a previous double-blind placebo-controlled study of itopride for FD.[7] The placebo response rate of the study was 41.2% when the patient's global assessment of efficacy was used. To detect a 15% increase in response in the active treatment group, a sample size of 173 per group would give us a power of 0.8, a standardized difference (the difference divided by the standard deviation) of 0.4, with an alpha significance level of 0.05 (two-sided). All variables were examined using the chi-square test, Fisher's exact test, or repeated measures analysis of variance. A two-tailed p-value under 0.05 was considered statistically significant for all analyses.

5. Surveys for the investigators after closing the study

We prepared a questionnaire for the investigators to evaluate the causes of failed patient enrollment. The questionnaire consisted of 4 questions: How many patients did you plan to enroll in the study? How many patients did you enroll in the study? What were the causes of failed enrollment? What did you think about other considerations for successful termination in a future study?

RESULTS

Many patients were screened by gastroenterologists at 11 tertiary referral hospitals from July 2009 to August 2010, but only four patients met the criteria for enrollment. The excluded patients either had symptoms consistent with irritable bowel syndrome or gastroesophageal reflux disease, responded to acid-suppressive agents, or were already taking *H. pylori* eradication therapy, anti-depressant/anti-anxiety drugs, or prokinetics at primary clinics. A significant number of screened patients also had short-duration dyspeptic symptoms and wanted to be considered for an early diagnosis and treatment for their symptoms. Only 3 among the 4 patients signed the informed consent. One patient, who refused the informed consent, shunned the placebo triple-therapy group. They also demanded to have rescue prokinetics or other medications. Two patients finished the study according to the study protocol. None of the patients had any evidence of depression or psychosomatic disorders as assessed by the BDI and the SSAS. However, two is not a sufficient sample of patients to satisfy the study goals. This study was finally abandoned by the *H. pylori* and dyspepsia study group of Korean College of Helicobacter and Upper Gastrointestinal Research in August 2010. We investigated the factors for enrollment failure using a questionnaire survey for researchers. The factors that promoted premature closure of this trial were as follows. Many patients who had dyspeptic symptoms revealed shorter symptom duration than required by the Rome III criteria for FD, so they could not participate. Some avoided joining the study due to demands on time or concerns about treatment uncertainty. Many patients were already taking medications to control dyspeptic symptoms before visiting one of our tertiary hospitals.

DISCUSSION

The Rome III criteria were published in 2006,[5] and the revision included changes in the concept of FD. Rome I and Rome II defined FD as pain or discomfort located in the upper abdomen without a definite structural or biochemical elucidation. However, no unique single symptom has been found in the vast majority of patients with FD in subsequent studies. Moreover, most symptoms of patients with FD failed to explain physiological abnormalities. Under these circumstances, FD was sub-classified into epigastric pain syndrome and postprandial distress syndrome in the Rome III criteria.[8] Many new studies to explore the underlying pathophysiological disturbances of the newly classified FD are expected with introduction of the Rome III criteria.

Some patients with FD respond to acid-suppressing drugs, and the prevalence of nonerosive reflux disease (NERD) with FD has not been clarified.[9] However, the Rome III criteria have a limitation, namely the overlap between NERD and FD.[10,11] An overlap of NERD with FD is important in a study of *H. pylori* eradication. Therefore, the impact of *H. pylori* eradication in patients with FD cannot be precisely evaluated.

The prevalence of *H. pylori* is high in Korea.[12] We planned this study to evaluate the response after *H. pylori* eradication in patients with FD and *H. pylori* infection. A randomized, double-blind, placebo-controlled study was designed for patients who were diagnosed with FD by the Rome III criteria. The study protocol was developed by the *H. pylori* and dyspepsia study group of the Korean College of Helicobacter and Upper Gastrointestinal Research from November 2007 to March 2008. The protocol was reviewed by MRCC at Seoul National University College of Medicine and approved by the KFDA and the Institutional Review Board. The enrollment of patients started in July 2009.

Unfortunately, we failed to enroll enough patients with FD and *H. pylori* infection into our study. We assume that the enrollment difficulty depended on several factors. First, the diagnosis of FD in the Rome III criteria requires that the onset of FD symptoms be longer than 6 months.[8] Most patients who visited our clinics had symptom durations shorter than 6 months. A similar situation was reported recently by Manabe

et al.[13] in Japan. Our Korean dyspeptic patients, like the Japanese patients, had visited the hospital for an evaluation sooner than the 6 months defined in the Rome III criteria. We made an effort to maintain the Rome III diagnostic criteria for FD during the entire study period. Second, many patients were taking medicines before visiting our tertiary clinics. We recommended to the patients that they interrupt their medications for 2 weeks to participate in the study. However, most of them wanted continuous prescriptions for prokinetics or other agents to control their symptoms. This was a critical barrier in this study. Many candidates for the study were middle-aged patients who had jobs. They also felt burdened by demands on their time imposed by participation in this study.

In conclusion, the current Rome III criteria for FD were difficult to apply to Korean dyspeptic patients, most of whom had symptom durations shorter than 6 months. The majority of patients who were diagnosed with FD by the Rome III criteria did not overcome fears that they could not use rescue medications during the study period, even though they did not have depression or a psychosomatic disorder.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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