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Significance of Non-erosive Minimal Esophageal Lesions in Gastro-esophageal Reflux Disorder

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Background : Non-erosive reflux disorder, which represents more than 60% of gastro-esophageal reflux disorders, lacks objective parameters for diagnosis. The purpose of this study was to evaluate the correlation between non-erosive minimal lesions at the lower esophagus and gastro-esophageal reflux disorder.

Methods : Patients were asked to answer a symptom questionnaire. The endoscopic findings were either graded by LA classification or recorded as non-erosive minimal lesions. Patients with minimal lesions were treated with rabeprazole or a placebo and responses were evaluated at weeks 1 and 4.

Results : In 8 centers, 3454 patients were screened. In patients with heartburn or acid regurgitation as the most bothersome symptom, 23.7% had endoscopy negative reflux disorder, 40.1% showed minimal lesions, and 36.2% had mucosal break esophagitis. Thirty-four percent of patients with minimal lesions and 39.1% of patients with LA 'grade A' mild esophagitis reported typical reflux symptoms as their main symptom. In patients with minimal lesions, medication with rabeprazole reduced symptoms significantly at weeks 1 and 4, but not with the placebo.

Conclusion : Patients with non-erosive minimal esophageal lesions had similar reflux symptoms comparable to those with mild erosive reflux esophagitis, and reflux symptoms were improved with a short-term proton pump inhibitor. Thus, non-erosive minimal esophageal lesion constitutes a great part of gastro-esophageal reflux disorder.

Key Words : Gastro-esophageal Reflux Disease; Endoscopes, Gastrointestinal

INTRODUCTION

Gastro-esophageal reflux disorder (GERD) is diagnosed by the presence of esophageal mucosal break or reflux-related symptoms that are severe enough to impair the quality of life. The spectrum of endoscopic findings in GERD ranges from normal through erosions to ulceration or stricture. Endoscopic mucosal break has a high specificity, but lacks sensitivity, for GERD. However, about 60% of patients with GERD do not have detectable evidence of esophagitis[1] and 24-hr esophageal pH monitoring is also not a confirmative method of GERD[2]. Since subjective symptoms are the main diagnostic factor, physicians may come into conflict with health insurance agencies about treatment strategy in patients with non-erosive reflux disorder (NERD).

Patients with mild grade esophagitis are more common in

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the proportion of population than those with moderate or severe grade lesions[3]. Non-erosive minimal lesions were also found in some patients with reflux symptoms. Hetzel-Dent scale[4] and suggestion[5] by Hoshihara and Hashimoto included the non-erosive minimal mucosal lesions in the endoscopic grading system of reflux esophagitis (RE). Agreements between experienced endoscopists were sufficient for the recognition of minimal endoscopic lesions of reflux esophagitis[6]. This study investigated the frequency of endoscopic non-erosive minimal lesions and their correlation with reflux symptoms, and treatment response to the proton pump inhibitor.

MATERIALS AND METHODS

This was a multi-center prospective study performed from September 2002 to November 2002 in Sungnam city, South Korea. Sungnam is a satellite city of Seoul. Three hospitals that treated referred patients as well as primary patients, and 5 clinics operated by gastroenterologyists joined this study.

Patients in the out patient clinic who planned to undergo gastroscopy were enrolled. The exclusion criteria included patients with peptic ulcer, gastrointestinal bleeding, cancer, previous gastric surgery, follow-up procedure within 1 year, medication history of proton pump inhibitors or H_2 receptor antagonists within 1 month, or those undergoing gastroscopy for the purpose of health screening.

Patients were asked to fill out a symptom questionnaire before the procedure. Symptoms were grouped into 4 categories such as GERD typical, atypical, epigastric pain, and discomfort symptoms. Heartburn and acid regurgitation were classified as typical symptoms. Atypical symptoms included hoarseness, globus sensation on throat, non-cardiac chest pain, and chronic cough. Symptom severity was graded as 1, 2, and 3. Mild symptom without bother was designated as 1, and moderate symptom with disturbance on the quality of life as 2, and severe symptom with disturbance on sleep as 3.

Endoscopic findings of reflux esophagitis were graded according to the Los Angeles classification or as minimal change lesions. Minimal change lesions were divided into 5 categories; blurring of esophago-gastric (EG) Z-line, coarseness or thickening of EG junction, discoloration, erythema, and hyperemic mucosal islet at lower esophagus (Figure 1). Endoscopic pictures of patients with minimal lesions were collected and evaluated again by 3 investigators from each hospital.

The study protocol was summarized in Figure 2. Patients with typical GERD symptoms were all selected, but those with atypical symptoms, epigastric pain, or discomfort were treated only in cases with endoscopic findings of minimal lesions or mucosal breaks.

Patients with minimal lesions were randomly treated with a placebo or rabeprazole 10 mg once daily, but those with mucosal breaks were treated with rabeprazole only. Prokinetic drugs

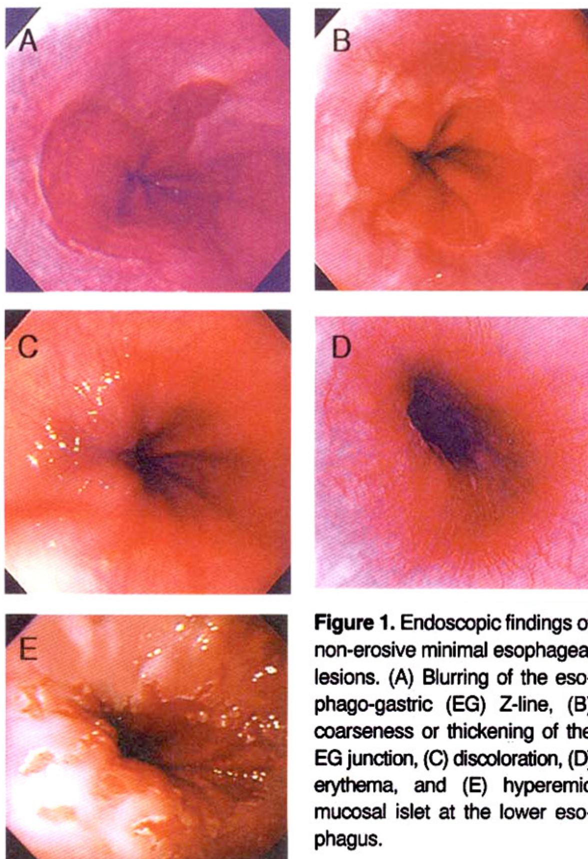

Figure 1. Endoscopic findings of non-erosive minimal esophageal lesions. (A) Blurring of the esophago-gastric (EG) Z-line, (B) coarseness or thickening of the EG junction, (C) discoloration, (D) erythema, and (E) hyperemic mucosal islet at the lower esophagus.

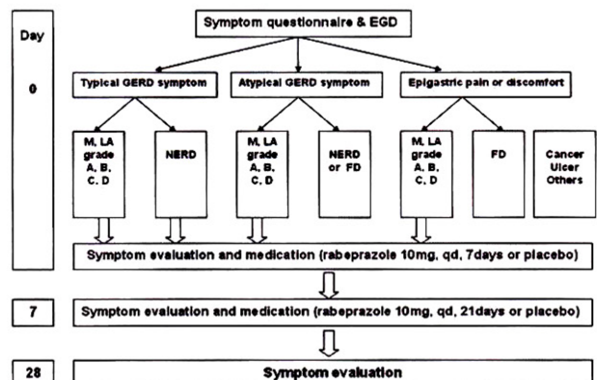

Figure 2. Study protocol. Patients were asked to answer a symptom questionnaire before endoscopy. Patients with typical GERD symptoms were all selected, but those with atypical symptoms, epigastric pain, or discomfort were treated only in cases with endoscopic findings of minimal lesions or mucosal breaks. Symptoms were evaluated again at weeks 1 and 4 after medication. M: minimal lesion, FD: functional dyspepsia.

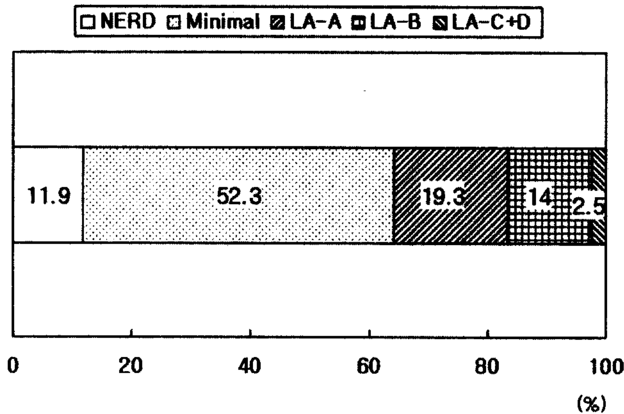

Figure 3. Frequency of patients with minimal esophageal lesions. Among 472 patients with GERD, the number of patients with endoscopy negative reflux disease was 56 (11.9%) and those with non-erosive minimal lesions and mucosal breaks were 247 (52.3%) and 169 (35.8%), respectively.

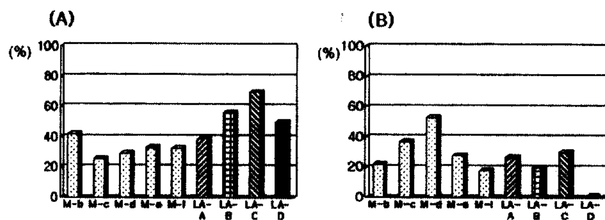

Figure 4. Symptoms in patients with each grade of reflux esophagitis. The proportion of typical (A) or atypical (B) reflux symptoms in patients with each grade or minimal lesion is illustrated. M: minimal lesion, b: blurring, c: coarseness, d: discoloration, e: erythema, I: islet.

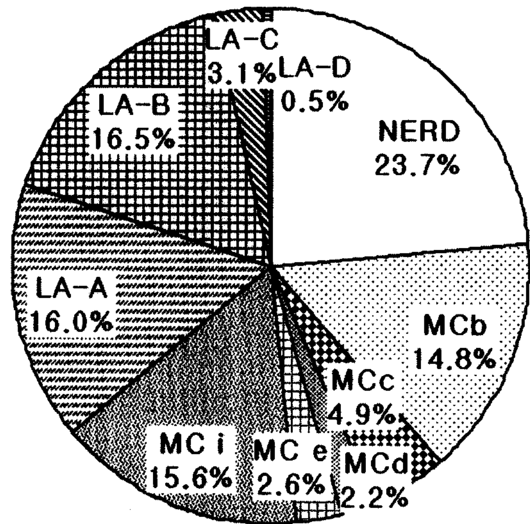

Figure 5. The proportion of each endoscopic grade in patients with typical reflux symptoms as a most bothersome symptom. Patients with minimal lesions accounted for 40.1%.

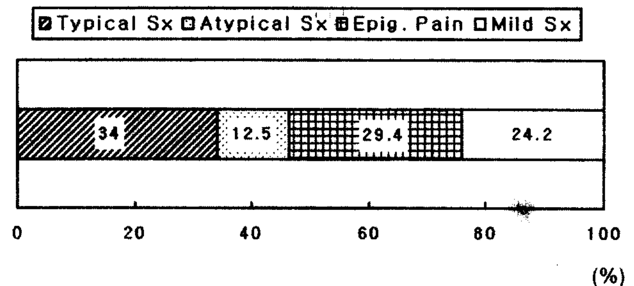

Figure 6. Main symptom pattern of patients with minimal esophageal lesions. Thirty-four percent of patients had typical reflux symptoms and 12.5% of those had atypical symptoms as their main symptom.

were not prohibited in either the rabeprazole or placebo groups. Symptoms were evaluated again at weeks 1 and 4 after medication.

Changes in symptoms after the medication were analyzed using Wilcoxon rank sum and signed rank test with the SAS program.

RESULTS

Among the 3,454 screened patients, 472 (13.7%) patients were selected for therapeutic trial with rabeprazole or placebo. Mean age of these selected patients was 48 (20~83) years old. There were more male than female patients (M:F=255:217).

1. Frequency of patients with non-erosive minimal esophageal lesions

Among the 472 selected patients, there were 56 (11.9%) patients with endoscopy negative reflux disease. Including 18 patients who had 2 kinds of minimal lesion, 247 (52.3%) patients had non-erosive minimal esophageal lesions. There were 80 (16.9%) patients with blurring at the esophago-gastric Z-line; and 44 (9.3%) with coarseness, 17 (3.6%) with discoloration, 18 (3.8%) with erythema, and 106 (22.5%) with islet lesions. According to the concept of conventional NERD, 64.2% of patients belonged to NERD. Reflux esophagitis of LA grade A was found in 91 (19.3%) patients; 66 (14.0%) patients had grade B, 10 (2.1%) patients had grade C, and 2 (0.4%) had grade D (Figure 3).

2. Symptoms of patients with non-erosive minimal esophageal lesions

The proportion of patients with typical reflux symptoms such as acid regurgitation or heartburn in each esophageal lesion is illustrated in Figure 4 (A) and those with atypical reflux symptoms in Figure 4 (B). The incidence of symptoms in patients with

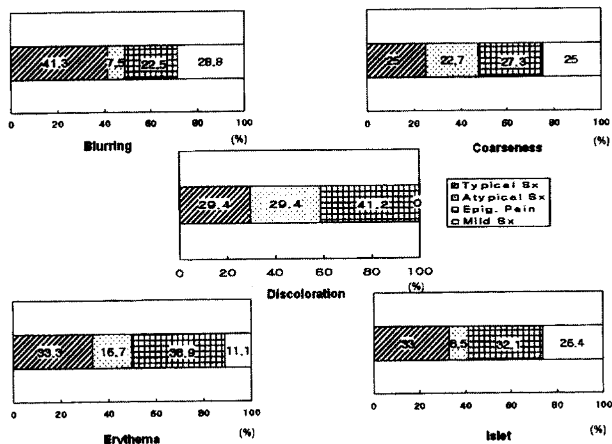

Figure 7. Symptom pattern for different types of minimal lesion. Typical reflux symptom was most common in patients with blurring at the EG Z-line. Atypical symptoms were most common in patients with discoloration at the lower esophagus.

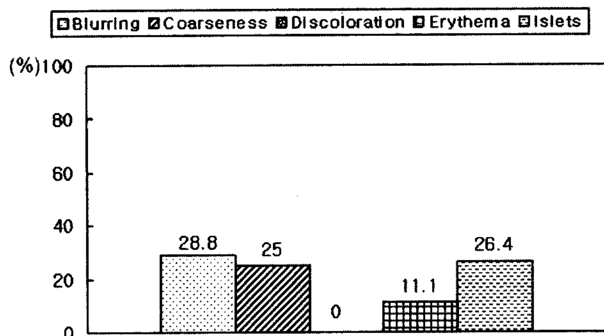

Figure 8. The proportion of mild symptoms (symptom score 1) in patients with minimal lesions. The severity of symptoms in all patients with discoloration was greater than or equal to 2.

minimal change lesions was similar to the incidence of mild erosive lesions. In patients with mild esophagitis of LA 'grade A', 39.1% of patients complained of typical reflux symptoms as their main symptom and 27% complained of atypical symptoms.

Figure 5 shows the proportion of each endoscopic grade in patients with typical reflux symptoms as their most bothersome symptom. Patients with non-erosive minimal lesions accounted for 40.1%. The proportion of NERD and erosive esophagitis in patients with typical reflux symptoms were 23.7% and 36.1%, respectively. Based on reflux symptoms, 63.9% of patients with typical reflux symptoms also belonged to conventional NERD.

In patients with non-erosive minimal lesions, 34% and 12.5% of patients had typical and atypical reflux symptoms as their main symptom. Thus, 46.5% of patients had reflux-related symptoms before endoscopy (Figure 6). Symptom pattern for different types of minimal lesions is illustrated in Figure 7. Typical reflux symptoms were most common in patients with

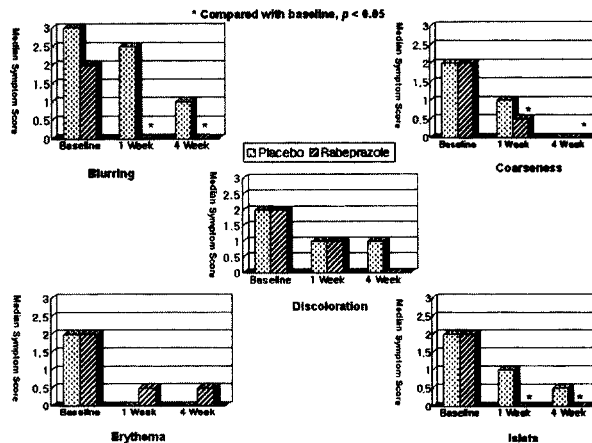

Figure 9. Therapeutic trial for patients with minimal lesions. Compared with the baseline, rabeprazole significantly reduced symptom score at weeks 1 and 4 in patients with blurring, coarseness, and islet lesions. Also, in patients with discoloration and erythema, the symptom score at weeks 1 and 4 showed decreasing trends. There was no significant symptom reduction with the placebo.

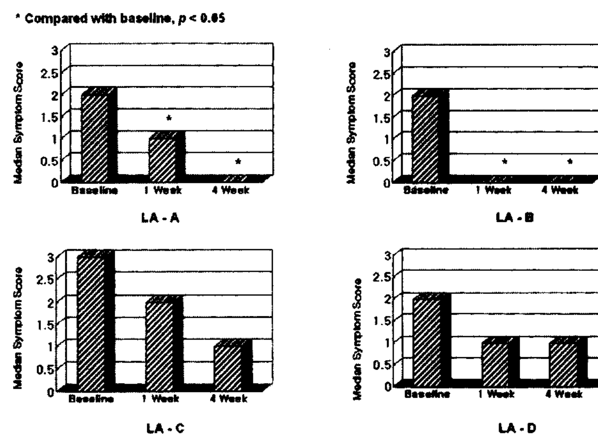

Figure 10. Treatment response in patients with esophageal mucosal breaks. In patients with LA grades A and B, symptoms decreased significantly with rabeprazole 10mg once per day. But, in patients with grades C and D, symptom reductions were insignificant.

blurring at the EG Z-line. Atypical symptoms were most common in patients with discoloration at the lower esophagus. The proportion of mild symptoms (symptom score 1) in patients with minimal lesions is shown in Figure 8. The severity of symptoms in all patients with discoloration was greater than or equal to 2.

3. Therapeutic trial for patients with non-erosive minimal esophageal lesions

Among patients with minimal lesions, 182 patients were treated with rabeprazole and 83 patients with a placebo. The number of patients treated for each type of minimal lesions was

as follows; rabeprazole or placebo was prescribed in 58 and 22 patients with blurring, 31 and 13 patients with coarseness, 12 and 5 patients with discoloration, 11 and 7 patients with erythema, and 70 and 36 patients with islet lesions. Compared with the baseline, rabeprazole significantly reduced the symptom score at weeks 1 and 4 in patients with blurring, coarseness, and islet. Also, in patients with discoloration and erythema, the symptom score at weeks 1 and 4 showed a decreasing trend. The number of patients with discoloration and erythema was not enough to make significant symptom changes with medication. There was no significant symptom reduction with the placebo (Figure 9).

4. Treatment response in patients with esophageal mucosal breaks

All patients with mucosal breaks at the lower esophagus were treated with rabeprazole and the treatment responses are shown in Figure 10. In patients with LA grades A and B, symptoms decreased significantly with rabeprazole 10 mg once a day. But, in patients with grades C and D, symptom reductions were insignificant.

DISCUSSION

The majority of patients with symptoms of gastro-esophageal reflux have no endoscopic evidence of esophagitis. Therefore, endoscopy has a low sensitivity for GERD. Some minimal changes of the lower esophagus may be encountered in practice, regardless of reflux symptoms. Non-erosive minimal lesions of the lower esophagus are not accepted as evidence of reflux esophagitis following the Los Angeles classification, but the Hetzel-Dent scale includes a grade of hyperemia or friability, and the Japanese Society for Esophageal Diseases proposed JSED '96 classification that includes grade 1 as the discoloring type of esophagitis[7]. This study included minimal changes as a part of reflux esophagitis in order to increase the sensitivity of endoscopy in GERD and evaluated the association with reflux symptoms. Improvement in sensitivity could imply a decreased specificity, potentially resulting in a weak association between minimal lesions and the symptoms of GERD. However, patients with NERD are similar to patients with esophagitis in symptom severity[8-10].

The inter- and intraobserver reproducibility in the endoscopic scoring of esophagitis was good for expert endoscopists when Hetzel-Dent scales were used in addition to LA classification.[11] Agreements among experienced endoscopists were also acceptable for both non-erosive minimal lesions and mucosal breaks[6]. Although we did not check the kappa value for evaluating esophageal severity in this study, all investigators in this study had finished gastroenterology fellowships in university hospitals and were experts in endoscopy. Three investigators from each hospital together reviewed all still images of minimal lesions to confirm agreement of minimal lesions. The agreements among endoscopists were similar for still images and video recordings[6].

Non-erosive minimal lesions include friability, erythema, blurring, discoloration, and thickening. Five items indicating minimal lesions, blurring, coarseness, discoloration, erythema, and islet, were selected in this study. Friability was excluded because it was subjective and difficult to define. Instead, we enrolled islet lesions to elucidate its association with GERD. Unexpectedly, about 1/3 of patients with islet lesions had typical reflux symptoms and also 15.6% of patients with typical reflux symptoms were those with islet lesions. These results implied that the symptom pattern in patients with islet lesions was not much different than other minimal change lesions. Thus, islet lesion was also acceptable as one of the endoscopic patterns of GERD. The overall incidences of typical reflux symptoms in patients with each type of minimal lesion were similar to those of patients with grade A esophagitis of LA classification.

The incidence of GERD with reflux esophagitis, defined by the presence of definite mucosal break, was 35.8% of all patients with GERD. The proportion of conventional NERD, a combination of endoscopy negative and non-erosive minimal lesion, was 64.2% in this data, and was similar to another study[1]. If we accept the minimal endoscopic lesion as a clue for the presence of reflux esophagitis, the sensitivity of endoscopic diagnosis in patients with GERD will increase to 88.1%.

Therapeutic trial is also a method of confirmative diagnosis. Patients with non-erosive minimal lesions were treated with either a proton pump inhibitor or a placebo. Compared with the baseline, rabeprazole significantly reduced reflux symptoms, but the placebo did not. Unfortunately, paired comparison between the rabeprazole group and the placebo group was insignificant.

Among 5 minimal lesions, the proportion of patients who had mild symptoms (symptom score ≤ 1) was lower in patients with discoloration or erythema. This finding was correlated with the results of therapeutic trials with rabeprazole in minimal lesions. The symptom reduction after rabeprazole treatment was insignificant in cases with discoloration and erythema, which could suggest that these two types of lesions may need more intensive acid suppression. The clinical response to treatment with proton pump inhibitor in non-erosive minimal lesions indicated that the minimal lesions deserve treatment.

All patients with mucosal breaks were treated with the actual medication, rabeprazole, and without placebo for ethical reasons. Symptoms in patients with mild reflux esophagitis such as grade A or B of the LA classification were controlled well with rabeprazole 10 mg once per day, but in patients with

severe reflux esophagitis such as grade C or D, the rabeprazole 10 mg once a day treatment did not result in significant symptom reduction. This finding justified the treatment with double doses in severe cases.

In summary, about 2/3 of patients with GERD have no detectable endoscopic evidence of esophagitis. But, patients with non-erosive minimal esophageal lesions accounted for 40% of all patients with reflux symptoms. Patients with minimal lesions were similar in symptom severity to those with mild esophagitis. Short-term therapy with a proton pump inhibitor also significantly reduced the reflux symptoms of patients with minimal lesions. Non-erosive minimal lesions should be re-evaluated as evidence of reflux esophagitis, in order to increase the sensitivity of endoscopy in the diagnosis of GERD.

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