Original Article

Effect of Rebamipide Combined with Omeprazole on Symptom Improvement in Non-*Helicobacter pylori* Gastritis

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ABSTRACT

Background: Non-ulcer dyspepsia (functional dyspepsia) was a very common disorder in clinical practice. Non-ulcer dyspepsia can be classified into functional dyspepsia and non-*Helicobacter pylori* gastritis. Unfortunately, treatment of dyspepsia in non-*H. pylori* gastritis does not complete symptoms resolution.

Objective: To evaluate effect of rebamipide combined omeprazole on symptom improvement compared with placebo combined omeprazole.

Patients and Methods: This study was a double-blinded, randomized placebo-controlled, single-center study, with concealed allocation. Patient with dyspeptic symptoms of 4 weeks or longer were randomized to receive rebamipide 100 mg.t.i.d. combined with omeprazole 20 mg.o.d. (Group A) or an identical placebo combined with omeprazole (Group B). All patients had esophagogastroduodenoscopic biopsy for the evidence of non-*H. pylori* gastritis, such as a negative rapid urease test and negative histology for *H. pylori*. Symptom improvement was evaluated in terms of symptom-score and global assessment score at before treatment and 2 weeks, 4 weeks and 8 weeks after treatment.

Results: Twenty-four patients were enrolled. There were 14 patients in group A (placebo combined omeprazole) and 10 patients in group B (rebamipide combined omeprazole). Group A mean age was 49.10 ± 11.06 yrs. There were 20% male and symptom score was 11.10 ± 5.55. Group B mean age was 47.71 ± 10.99 yrs. There were 21.43% male and symptom score was 10.14 ± 4.75. The symptom improvement was significantly superior in group A in term of symptom score ($p = 0.001$, 95%CI = 2.74-8.55) and global assessment ($p < 0.001$, 95%CI = 1.60-3.40) compare with group B.

Conclusion: Rebamipide combined with omeprazole resulted in a significant reduction in the overall symptom scores, bloating symptom, and improvement of the global assessment improvement score at 8 weeks after treatment. In non-*H. pylori* gastritis subjects, rebamipide is useful as an adjunctive agent in combination with omeprazole in the treatment of functional dyspepsia .

Key words : rebamipide, omeprazole, gastritis, dyspepsia

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INTRODUCTION

Non-ulcer dyspepsia (functional dyspepsia) is a very common disorder in clinical practice, accounting for up to 66.2% in patients presenting with dyspeptic symptom. In one study, non-ulcer dyspepsia was found in functional dyspepsia (38.2%) and in non-*Helicobacter pylori* gastritis (28%)[1]. Treatment of dyspepsia in non-*H. pylori* gastritis does not really end at the time of symptom resolution. Continuation of symptoms contributes to follow in a long time.

The proposed pathogenesis of non-ulcer dyspepsia (functional dyspepsia) includes physiological disorders such as abnormal motility disorders, hypersecretion of gastric acid, maldigestion or malabsorption of carbohydrates, augmented perception of visceral pain (visceral hypersensitivity), *H. pylori* infection, inflammation, brain-gut interaction and psychosocial factor. These pathogenesis factors may combine to produce various symptoms of dyspepsia. Inflammation involving the enteric mucosa or the neural plexus can produce symptoms[2] by way of peripheral sensitization and/or hypermotility stimulated by the induction of mucosal inflammatory cytokines[3]

Rebamipide is a mucosal protective agent that is widely used in Japan for the treatment of peptic ulcers and chronic gastritis. Rebamipide improves symptoms as well as mucosal histology. Mucosal protective agents generally facilitate mucosal blood flow,[4] increase prostaglandin synthesis[5,6], increase gastric mucus[7,8] thus enhancing mucosal protection for the gastric mucosa, decrease gastric mucosal inflammation by suppressing free radicals[9,10] and inhibiting inflammatory cells infiltration.[11,12]

In a double-blind, dose finding (50 mg. vs 100 mg. t.i.d.), multicenter study in 116 patients with acute gastric mucosal lesions and/or subepithelial hemorrhages, rebamipide 100 mg. t.i.d. resulted in healing rate of 50% after 2 weeks and 61% after 4 weeks of treatment, with improvement of symptoms[13] compared with placebo treatment. In another study with 20 patients with benign chronic gastritis and peptic ulcer, rebamipide 100 mg. t.i.d. for 8 weeks resulted in symptom improvement of 50% and effectiveness of 80%.[14] In another report, involving 86 patients with *H. pylori* chronic gastritis, rebamipide 300 mg daily in comparison with placebo wasv shown to be effective with regard to decreased neutrophil infiltration in the mucosa and decreased i-nos production.[11]

Meta-analysis study assessing treatment of symptoms in functional dyspepsia, encompassing functional dyspepsia with no demonstrable lesions by gastroduodenoscopy as well as non-*H. pylori* gastritis with abnormal gastroduodenoscopic lesions, has demonstrated that proton pump inhibitors, e.g. omeprazole, appear to be the best effective agents, but symptom improvement is only about 50%.

The aim of this study was to compare the efficacy of rebamipide combined with omeprazole and a placebo combined with omeprazole on symptom improvement in non-*H. pylori* gastritis after 8 weeks of treatment.

MATERIALS AND METHODS

Patients

Thai patients aged ≥18 with dyspeptic complaints ≥4 weeks, with or without pervious treatment for dyspeptic symptom, who attended outpatient departments of Srinakarin Hospital, Khon Kaen, between June 2007 and June 2008 were recruited initially. A total of 24 dyspeptic patients were enrolled. All subjects underwent esophagogastroduodenoscopy and tested negative for *H. pylori* by rapid urease test, with biopsy pathology compatible with gastritis, and with symptom score more than 2 point.

Exclusion criteria included a positive gastric biopsy for *H. pylori*, previous upper abdominal surgery, diabetes, congestive heart failure, renal disease, thyroid disease, liver disease, gallstone, pregnancy or current breast feeding ,diagnosed of gastric ulcer or duodenal ulcer, psychologic disorder, history of NSAIDs or aspirin ingestion in the preceding 2 weeks, and history of allergy to omeprazole. The study was approved by the local ethical committee, and all patients gave written informed consent to participate in the study.

Method

Patients were advised to stop taking omeprazole or ranitidine and can receive only liquid antacid (30 ml. t.i.d.) for 1 week before undergoing EGD. If endoscopic gastritis was evident, biopsy from antrum and body mucosa was taken, 3 specimens at each site, for evaluation of *H. pylori* by rapid urease test (CLO® test) and by histopathologic confirmation.

Twenty-four patients were randomly assigned to receive either the rebamipide and omeprazole combination (14 patients; Group A) or placebo and omeprazole combination (10 patients; Group B).

Rebamipide (100 mg, t.i.d.) plus omeprazole (20 mg. o.d) for 8 weeks were prescribed to Group A. An identical placebo (1 tablet t.i.d) plus omeprazole (20 mg. o.d.) were prescribed for the same duration to Group B.

Patients were requested to complete a standard questionnaire on dyspeptic symptom score (adapted from Gastrointestinal Symptom Rating Scale [GSRS] and Global Assessment Improvement Rate) before starting treatment and again at 2 weeks, 4 weeks and 8 weeks after completion of treatment. Follow-up visits were scheduled at 2 weeks, 4 weeks and at completion of treatment. Medical interview was focused on symptoms and medication compliance (including pill counting), and self-completed questionnaire was collected. Questions were also asked concerning any additional self-taken medications, patient's impression of the prescribed drugs, and whether the patients wanted to continue taking the study medication or not.

Randomization key was disclosed after the last visit of the latest enrolled patient. Changes in the scores for dyspeptic symptoms and Global Assessment Improvement Rate before and after treatment were analyzed.

Evaluation of symptom score and Global Assessment Improvement Rate

Dyspeptic symptoms were assessed from the self-recorded questionnaires. Patients were given detailed instruction before answering the questionnaires. The questionnaires were focused on 6 upper gastrointestinal symptoms, namely epigastric pain/discomfort, nausea or vomiting, bloating, early satiety, and belching symptoms. Symptoms were rated at seven levels with regard to intensity, frequency, in last 2 weeks duration and impact on daily life according to 3 grades with half steps between each rating as categorical scale (Likert Scales); grade 0, absence symptom; grade 1, mild intensity with 1-3 attacks in 1 week; grade 2, mild intensity with more than 4 attacks in 1 week; grade 3, moderate intensity with 1-3 attacks in 1 week; grade 4, moderate intensity with more than 4 attacks in 1 week; grade 5, severe intensity with 1-3 attacks in 1 week; grade 6, severe intensity with more than 4 attacks in 1 week. Symptom scores were recorded by the patient reflecting the general status over the preceding 2 weeks. Dyspeptic symptoms were recorded before treatment and, at 2 weeks, 4 weeks and 8 weeks after treatment. Global Assessment Improvement Rate was assessed from the self-recorded questionnaires. Patients were likewise given detailed instruction before answering the questionnaire. Global Assessment Improvement Rate questionnaire was focused on global improvement of any symptoms, and the quality of life in over last 2 weeks, and consisted of visual analogue scale (VAS) from 0 (normal) to 10 point (very severe symptom). Global assessment was recorded before treatment and, at 2 weeks, 4 weeks and 8 weeks after treatment.

Study design

This study was a double-blinded, randomized placebo-controlled, single-center study, with concealed allocation. Data analysis was carried out using STATA for Window version 8. The continous data such as age, weight and height were calculated and reported as mean, standard deviation, minimum and maximum range. Categorical data were recorded as number in each group. Gender; smoking and drinking data were reported as frequency shown in number and percentages in each group.

Data analysis was shown in three parts, the first part covered baseline characteristics. The second part of data analysis concerned the main outcome analysis. The mean pre- and post-sum scores of the dyspeptic symptoms were compared along an intention-to-treat principle. As a subgroup analysis, improvements in each item were compared between group A and group B. Regarding the Global Assessment Improvement Rate, the differences in the mean of sum scores between pre- and post-treatment were compared in both groups. Distribution of the continuous data variables was tested for normality by using the Kolmogorov-Smirnov test. The third part of data analysis was related medication side effects during the 8 study weeks. For statistical analysis, student's *t*-test, chi-squared test for parametric data, and Mann-Whitney *U*-test for non-parametric data were used. *P*-values of less than 0.05 were regarded as statistically significant by two-tailed and 95 percent confidence intervals

RESULTS

Baseline characteristics of the patients

Fourteen patients were allocated to the rebamipide-omeprazole group (group A) and 10 patients to the placebo-omeprazole group (group B). No patients in both groups were excluded from analysis. Two patients in the placebo-omeprazole group with-

Table 1. Base-line Characteristics of the 24 patients with gastritis

Characteristic		Treatment group (group A) (N = 14)	Placebo group (group B) (N = 10)
Male (%)		21.43%	20%
Age (yr)	Mean ± SD	47.71 ± 10.99	49.10 ± 11.06
	Range	27-71	33-65
Current smoker (%)		0	10
Alcohol use (%)		0	0
BMI (kg/m^2)	Mean ± SD	23.12 ± 4.25	24.69 ± 3.04
	Range	18.36 - 30.93	19.72 - 30.44
Symptom score		10.14 ± 4.75	11.10 ± 5.55
	Range	2-17	3-18
Location of gastritis			
	antrum:body:pangastritis (%)	57.14 : 0 : 42.86	60 : 0 :4
Severity of gastritis			
	mild, moderate, severe (%)	71.43 : 28.56 : 0	100 : 0 : 0
History of proton pump inhibitor (%)		85.70	80
Stop drug regimen before 8 weeks (%)		0	20

Table 2. Change in symptom score before and after 8 week of the therapy (mean ± SD)

	Before treatment		After treatment		*p*-value (95%CI)**
	Symptom score	*p*-value (95% CI)*	Symptom score	*p*-value (95% CI)*	
Symptom score total					
Placebo	11.10 ± 5.55	0.65 (-3.42 to 5.33)	7.10 ± 7.14	0.27 (-2.20 to 7.40)	0.19 (-2.36 to 10.36)
Treatment	10.14 ± 4.75		4.50 ± 4.18		0.001 (2.74 to 8.55)
Epigastrium pain/discomfort					
Placebo	2.90 ± 1.73	0.27 (-2.11 to 0.63)	1.60 ± 1.90	0.55 (-0.92 to 1.69)	0.18 (-0.72 to 3.32)
Treatment	3.64 ± 1.50		1.21 ± 1.19		<0.001 (1.50 to 3.35)
Nausea					
Placebo	0.80 ± 1.03	0.11 (-0.13 to 1.16)	0.30 ± 0.67	0.47 (-0.28 to 0.60)	0.14 (-0.20 to 1.20)
Treatment	0.29 ± 0.47		0.14 ± 0.36		0.43 (-0.24 to 0.53)
Vomiting					
Placebo	0.10 ± 0.32	0.81 (-0.22 to 0.28)	0.00 ± 0.00	-	0.34 (-0.13 to 0.33)
Treatment	0.070.27		0.00 ± 0.00		0.34 (-0.08 to 0.23)
Bloating					
Placebo	3.00 ± 1.70	0.77 (-1.68 to 1.25)	2.00 ± 1.83	0.36 (-0.79 to 2.08)	0.16 (-0.47 to 2.47)
Treatment	3.21 ± 1.72		1.36 ± 1.55		0.004 (0.73 to 2.99)
Early satiety					
Placebo	2.60 ± 2.46	0.08 (-0.22 to 3.42)	1.80 ± 2.10	0.07 (-0.10 to 2.56)	0.43 (-1.35 to 2.95)
Treatment	1.00 ± 1.84		0.57 ± 1.02		0.11 (-0.11 to 0.97)
Belching					
Placebo	1.70 ± 1.89	0.75 (-1.73 to 1.27)	1.40 ± 1.26	0.74 (-0.98 to 1.35)	0.71 (-1.49 to 2.09)
Treatment	1.93 ± 1.64		1.21 ± 1.42		0.25 (-0.55 to 1.98)

* compare placebo group and treatment group

** compare before and after treatment

drew at 4 and 7 weeks because of severe abdominal pain. No patients were lost to follow up. Questionnaires were completed by all remaining patients. Analysis of symptom scores was performed in 14 patients of the rebamipide-omeprazole and in 10 patients of placebo-omeprazole group, respectively. The baseline characteristics did not differ significantly between the two groups (Table 1).

Changes in symptoms

There was no statistical significance in the distribution of symptom scores between the two groups, either at baseline or after medication (Table 2). In a subgroup analysis, the rate of improvement in symptom score total for each item was investigated. The improvement in total symptom score before treatment and after treatment was significantly greater in rebamipide-omeprazole group than in the placebo-omeprazole group for three items, namely symptom score total, epigastric pain and bloating (Table 2 and Figure 1-3)

Changes in the Global Assessment Improvement Rate (score)

Improvement in the Global Assessment Improvement Rate (score) was evaluated before treatment and after treatment in both groups (Table 3). In compari-

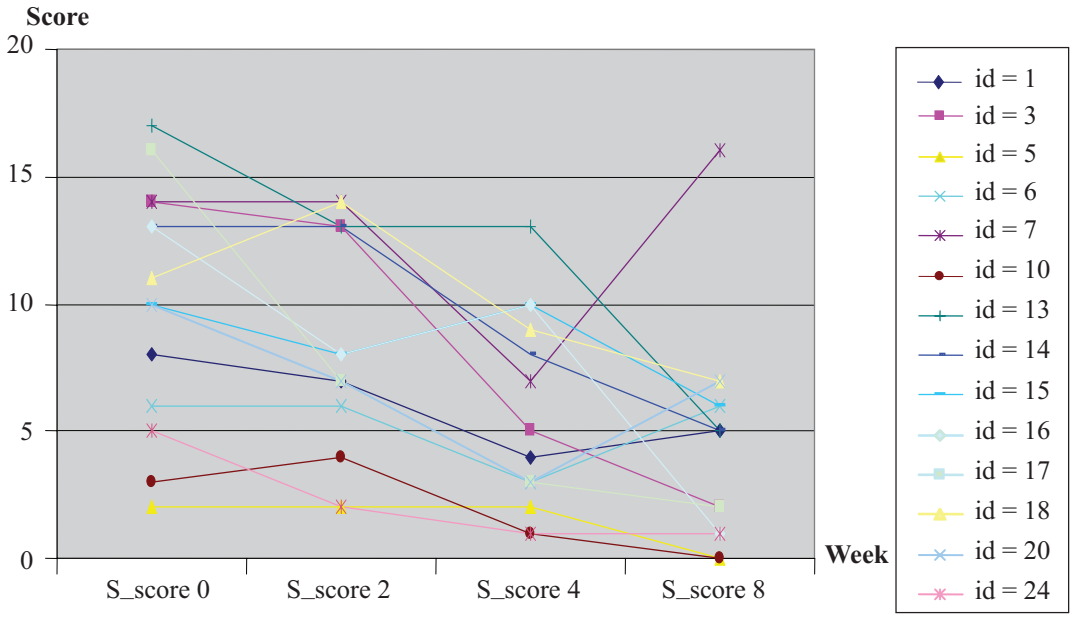

Figure 1. Symptom score in drug group

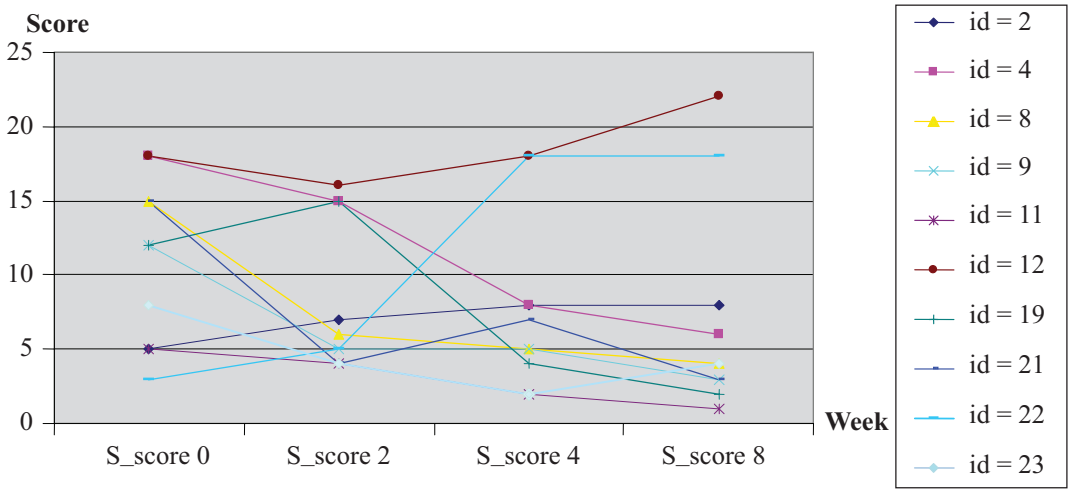

Figure 2. Symptom score in placebo group

son with the placebo-omeprazole group, the rebamipide-omeprazole group showed a significant improvement both before and after treatment. (Table 3 and Figure 4-6)

Safety assessment

No patients in either group stopped the medications or withdrew from the study due to side-effects during the study period. (Table 4)

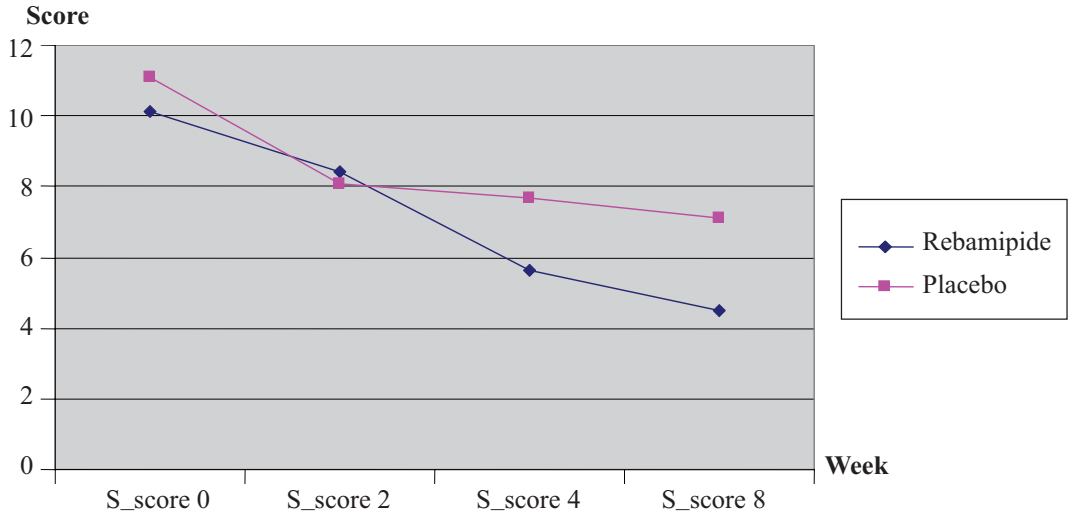

Figure 3. Symptom score comparison between rebamipide and placebo

Table 3. Change in the Global Assessment Improvement Rate (score) before and after the 8 weeks of therapy (meanSD)

	Before treatment		After treatment		*p*-value (95%CI)**
	Global score	*p*-value (95%CI)*	Global score	*p*-value (95%CI)*	
Global score					
Placebo (N = 10)	5.20 ± 2.30	0.94 (-1.53 to 1.65)	3.10 ± 2.60	0.63 (-1.48 to 2.40)	0.02 (0.47 to 3.73)
Rebamipide (N = 14)	5.14 ± 1.81		2.64 ± 1.98		<0.001 (1.60 to 3.40)

* compare placebo group and treatment group
** compare before and after treatment

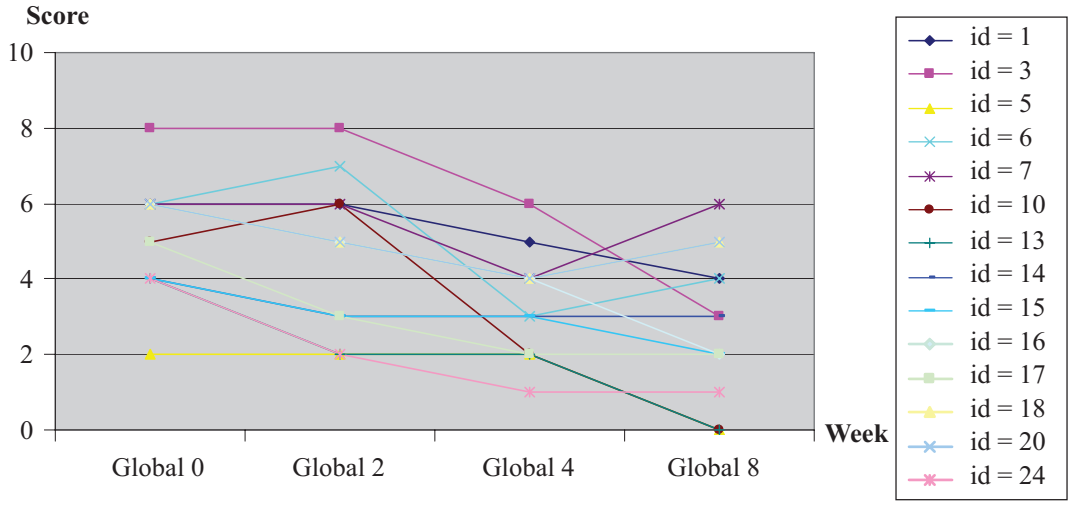

Figure 4. Global score in drug group

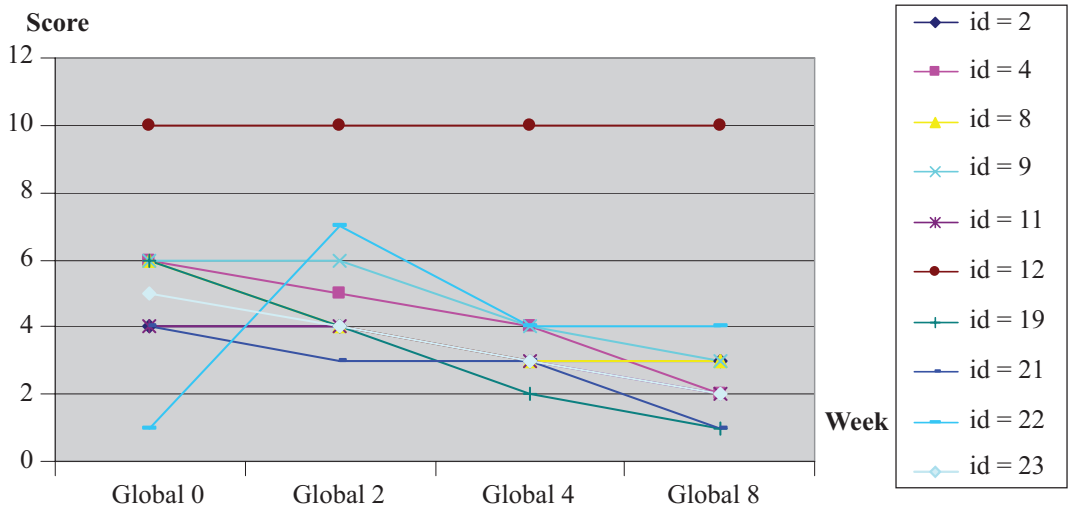

Figure 5. Global score in placebo group

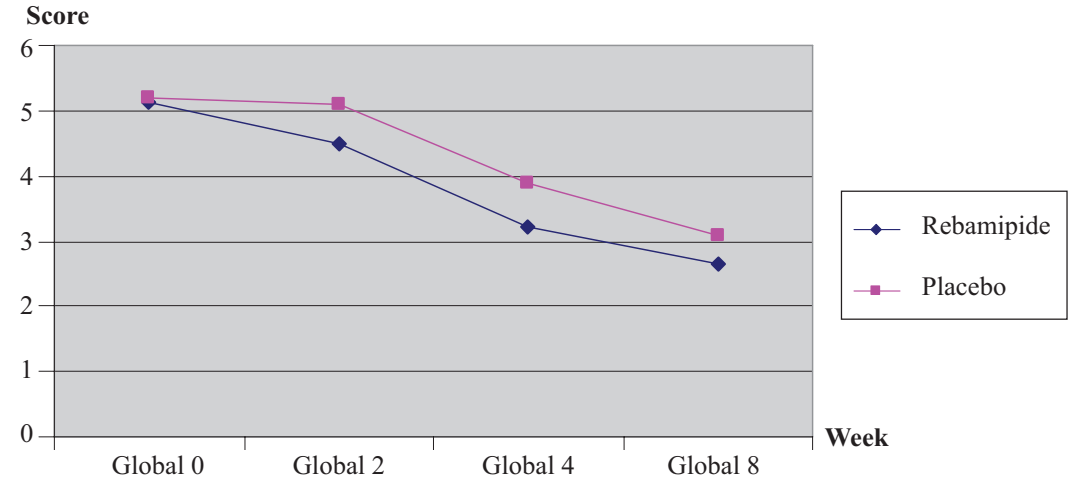

Figure 6. Global score comparison between rebamipide and placebo

Table 4. Side effect characteristics of the 24 patients with gastritis.

Side effect	Treatment group (N = 14)	Placebo group (N = 10)
Constipation (N, %)	1 (0.71)	0 (0)
Diarrhea (N, %)	0 (0)	1 (10)

DISCUSSION

Preliminary analysis of our data from this study in Thai patients with non-*H. pylori* gastritis indicated that there was improvement in the overall symptoms after 8 weeks of combined rebamipide-omeprazole treatment (group A) with regard to nausea, vomiting, early satiety and bloating, although the improvement was not reach the statistically different from the placebo-omeprazole group (group B). The improvement in symptom score was, nevertheless, significantly greater in the group A than in the group B regarding epigastric pain and bloating. Group A regimen was also superior to group B with regard to the improvement of the Global Assessment Improvement Rate (score).

There are differences in the prevalence and the symptoms of FD (non-*H. pylori* gastritis included in this group) among various populations in differing geographic regions. In Western areas, ulcer-like dyspepsia, characterized by upper abdominal pain, is most predominant[15,16] whereas dysmotility-like dyspepsia, characterized by nausea, fullness and early satiety is

most frequently observed in Japan.[17,18] In Japan, mucosal protective agents are commonly used in general practice for the relief of upper gastrointestinal symptoms. Taking these aspects into consideration, we have conducted this study to evaluate the efficacy of such agents in the treatment of Thai patients with non *H. pylori* gastritis. Rebamipide is a very commonly used gastric mucosal protective agent in Japan and Korea. It enhances gastric mucosal protection and suppresses gastric mucosal inflammation.[19,20] As gastric mucosal inflammation has been reported to alter the level of visceral pain, rebamipide can possibly exhibit efficacy in non-*H. pylori* gastritis.

A double-blind, placebo-controlled multicenter study of rebamipide for FD patients with or without *H. pylori* infection was conducted in the USA. In that study, rebamipide failed to show significant improvement in individual symptoms after 8 weeks of treatment. However, a significant reduction in the belching score compared with placebo at 2 weeks was observed in *H. pylori*-positive patients.[21] Although improvement was not remarkable in the US study, a positive effect may be possible in other patient populations.

Finding from our study were similar regarding the change in the overall symptom score which did not differ significantly between the rebamipide and the placebo treatment groups.[22] Confounding factors such as a high placebo effect, inclusion of dyspeptic symptoms in GERD and dysmotility symptomatology, may account for failure to obtain a significant reduction of symptom severity after rebamipide treatment. The symptom score total was included 11 symptoms as heartburn, retrosternal discomfort, epigastric discomfort, nausea or vomiting, bloating, early satiety, appetite loss, belching, morning discomfort, epigastric pain, pain or discomfort relieved after a meal for evaluating effect of rebamipide added on omeprazole compared with placebo.

In this study, statistical significance was reached in the overall symptom score and the improvement of the Global Assessment Improvement Rate (score), although four individual symptoms (nausea, vomiting, early satiety and belching) were not significantly improved in the subgroup analysis in group A, as shown in Table 2. Rebamipide is not a prokinetic agent and does not affect gastric emptying,[23] so these mechanisms supported this study result.

Our study is first to show that a mucosal protective agent, rebamipide in combination with omeprazole, is associated with improvement in symptom score and the improvement of the Global Assessment Improvement Rate (score) in non-*H. pylori* gastritis patients. Further study in large numbers of patients is needed to confirm this observation.

Conclusion; rebamipide combined with omeprazole produces a significant reduction in the overall symptom scores, bloating symptom and the improvement of the Global Assessment Improvement Rate (score) after 8 weeks of treatment in Thai patients with non-*H. pylori* gastritis.

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