ORIGINAL ARTICLE

The Clinical Efficacy of a Pure Alginate Formulation (Lamina G) for Controlling Symptoms in Individuals with Reflux Symptoms: A Randomized Clinical Study

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Background/Aims: Bicarbonate-containing alginate formulations are reported to be effective for controlling reflux symptoms. However, the efficacy of Lamina G alginate without gas production has not been reported. The aim is to evaluate the efficacy of a non-bicarbonate alginate in individuals with reflux symptoms without reflux esophagitis. **Methods:** Participants who had experienced heartburn or regurgitation for 7 consecutive days were randomized to one of the following treatment groups: proton pump inhibitors (PPI) plus alginate (combination) or PPI plus placebo (PPI only). In addition, as a reference group, patients received placebo plus alginate (alginate only). The primary endpoint compared the percentage of patients with complete resolution of symptoms for the final 7 days of the treatment. Secondary endpoints compared changes in symptom score, symptom-free days during the treatment period, the Reflux Disease Questionnaire, Patient Assessment of Upper Gastrointestinal Disorders (PAGI)-Quality of Life and PAGI-Symptoms Severity Index scores, the investigator's assessment of symptoms, and incidence of adverse events. **Results:** Complete resolution of heartburn or regurgitation was not significantly different between the combination and PPI only groups (58.7% vs 57.5%, p=0.903). The secondary endpoints were not significantly different between the two groups. Complete resolution of heartburn or regurgitation, did not differ between the alginate only reference group and the PPI only group (75.0% vs 57.5%, p=0.146). **Conclusions:** The addition of non-bicarbonate alginate to PPI was no more effective than PPI alone in controlling reflux symptoms. **(Gut Liver 2019;13:642-648)**

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a representative gastrointestinal disease with a multifactorial pathophysiology.[1] Proton pump inhibitors (PPIs) have previously been shown to be the most effective treatment for GERD. However, other medications based on pathophysiology have also been investigated as treatments for GERD. One of the pathophysiologies typical of GERD is the presence of an acid pocket. The acid pocket is an area containing unbuffered, highly acidic gastric secretions that are located in the proximal stomach after meals. This zone acts as a reservoir from which acid can enter the esophagus when the esophagogastric junction opens.[2] Thus, the acid pocket represents an effective target for the treatment of GERD.[2] Alginate-based formulations act primarily on these acid pockets by forming a physical barrier. That is, when contacting with gastric acid, alginate rapidly forms a gel "raft" of near-neutral pH as a protective mechanical barrier above the acidic gastric contents.[3] Several studies have investigated the efficacy of sodium alginate, in particular the branded antacid product Gaviscon, in the alleviation of symptoms associated with GERD.[1,3-6]

Most alginate formulations, including Gaviscon, consist of three chemical components: sodium alginate; sodium bicarbonate, which reacts with stomach acid to yield carbon dioxide; and calcium carbonate, which reacts with stomach acid to yield free calcium ions.[7] This combination of components results in the production of an alginate antacid raft with gas produc-

tion.[7-9] Although pure sodium alginate without gas production can act as a gel raft of matrix-forming polymers,[8,9] there is no evidence that pure sodium alginate can be effective in controlling reflux symptoms on its own. Thus, the aim of study was to evaluate the efficacy of a non-bicarbonate alginate (Lamina G; Taejoon Pharm Co, Seoul, Korea) in reducing reflux symptoms in individuals with reflux symptoms without evidence of reflux esophagitis in endoscopy.

MATERIALS AND METHODS

1. Study design

A randomized, double-blind, parallel-group, comparative study was conducted over 4 weeks in the outpatient Gastroenterology Clinics of Severance and Gangnam Severance Hospitals, Seoul, Korea, between July 2014 and August 2016. The study was conducted involving patients with heartburn or regurgitation symptoms without evidence of reflux esophagitis in a screening endoscopy.

Patients received one of the following treatments for 4 weeks: 20 mg omeprazole once daily plus placebo (PPI only group) or 20 mg omeprazole plus 20 mL sodium alginate suspension (Lamina G, Taejoon Pharm Co.) three times daily (t.i.d.) (50 mg/mL) (combination group). A reference group of patients received placebo plus 20 mL sodium alginate suspension t.i.d. (50 mg/mL) (alginate only group).

The primary aim was to assess the percentage of patients with complete resolution of heartburn or regurgitation symptoms over the final 7 days of the 4-week treatment. The secondary aim was to assess symptom-free days or overnight symptom-free days over the 4-week treatment period. Any change from the baseline Reflux Disease Questionnaire (RDQ),[10,11] Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL)[12] and PAGI-Symptoms Severity Index (PAGI-SYM)[13] scores, as well as the clinical investigator's assessment for symptoms, were also assessed. The safety profile of subjects was investigated based on the incidences of adverse events (AEs).

Subjects were enrolled to participate in the study during 1-week screening and 4-week treatment period. After the initial screening period, subjects who met the inclusion criteria without exclusion criteria were randomized and assigned to treatment groups. Subjects received the study drug on day 1 and returned to scheduled clinic appointments at week 4 for assessment of GERD symptoms based on patient diaries; RDQ, PAGI-QOL, and PAGI-SYM scores; concomitant medication use; and the incidences of AEs. The remaining study medication was collected at week 4. All subjects had a physical examination with blood tests at both the initial appointment and the end of week 4. Female subjects had pregnancy tests performed at the initial and the week 4 appointments, and results were documented. The protocol was approved by the institutional review boards of each institution. Written informed consents

were obtained. The study was registered at cris.nih.go.kr (No. KCT0002297).

2. Patients

Subjects who met the inclusion criteria were eligible to participate in the present study: males and females of Korean ethnicity aged 20 to 80 years old; outpatients who had a history of episodes of heartburn or regurgitation symptoms for at least 3 months without evidence of reflux esophagitis in a screening endoscopy; symptoms of heartburn or regurgitation during the 1-week screening period (either ≥4 days of mild symptom or ≥ 2days of moderate to severe symptoms); and agreement to sign the informed consent form. The severity of symptoms was documented on a 4-point scale: 0=none (no symptoms), 1=mild (easily tolerated symptoms; symptoms were minimal and did not disturb normal activities), 2=moderate (symptoms disturbed normal activities), and 3=severe (symptoms markedly disturbed normal activities).[1]

Patients were ineligible to participate in the study when one or more of the following conditions were present: erosive reflux disease, Barrett's esophagus or esophageal stricture; active or healing gastroduodenal ulcer with the exception of evidence of a healed ulcer with scarring; history of esophageal, gastric, or duodenal surgery; any kind of malignant disease; ischemic heart disease by electrocardiogram; pregnant or nursing mothers; allergic history to the study drugs; alcohol or drug abuse; clinically significant liver problems (AST/SGOT, ALT/SGPT >2.5 upper limits of normal); clinically significant renal problems (serum creatinine >1.5 mg/dL); using a PPI within 2 weeks before screening, or use of prokinetics, H2-blocker, or antacids within 3 days before screening; participation in another clinical study within 4 weeks before screening; and any condition that an investigator considered to be inappropriate for the study (for example, reflux-like symptoms according to other organic disease).

3. Treatment allocation

Treatment allocation was done according to a computer-generated randomization code list provided by a statistician. Randomization was performed at the investigational sites. Participants were randomly assigned to receive one of the treatments for 4 weeks with a 2:2:1 ratio (PPI only group: combination group: alginate only group). The prescribed treatment schedule included a 20 mg omeprazole capsule before breakfast and 20 mL (50 mg/mL) Lamina G t.i.d. before meals. All processes were performed using a double-blind approach. The compliance with the medication was checked by counting the residual study drugs during every visit. If the final compliance rate was less than 80%, the data of the patient was excluded in the per protocol analysis.

4. Efficacy evaluation

The primary efficacy endpoint was measured as the percentage of subjects with complete resolution of reflux symptoms over the final 7 days of the treatment based on the patient diary.

The secondary efficacy endpoint was evaluated by the following: (1) changes of symptom score (patient diary) from the baseline, (2) symptom-free days during the 4-week treatment period (%, patient diary), (3) overnight symptom-free days during the 4-week treatment period (%, patient diary), changes from the baseline (4) RDQ, (5) PAGI-QOL, (6) PAGI-SYM scores, and (7) the clinical investigator's assessment of symptom improvement.

Safety was assessed by vital signs and physical examinations, including blood tests, at both the initial appointment and the end of week 4. All AEs were recorded including the onset date, end date, severity, the relationship with study drugs, the treatment modification, and outcomes.

5. Sample size calculation

Sample size calculation was based on the assumption the combination group had a higher adequate heartburn-relief rate than the PPI only group (56.7% vs 25.7%, respectively).[4] The following formula was used to calculate the sample size for each group:

$$n=(1.96+0.84)^2 \times (25.7 \times 74.3 + 56.7 \times 43.3)/(25.7-56.7)^2$$

More than 36 patients were required per group for a 5% significance level and a statistical power of 80%. Therefore, we decided to enroll at least 48 patients in each group (PPI only and combination group) with an estimated drop-out rate of 25% due to follow up loss and protocol violations. Given the 2:2:1 group ratio used in this study, 24 patients were recruited for the reference group.

6. Statistical analysis

Baseline characteristics were summarized according to treatment groups. Quantitative data were reported as means and standard deviation, whereas categorical data were expressed as proportions. The chi-square and Fisher exact tests were used to evaluate the associations among various categorical variables, and the t-test or Wilcoxon rank sum tests was used to compare non-categorical variables. All analyses were performed using SAS 9.2 (SAS institute Inc., Cary, NC, USA), and a p-value <0.05 was considered to indicate statistical significance.

RESULTS

1. Participant demographics and baseline characteristics

One hundred twenty patients were enrolled and randomized (Fig. 1). Two patients did not take any study drug resulting in a population of 118 patients. All subjects (46 in the combination group and 47 in the PPI only group) reported some efficacy data and the outcomes were analyzed (intention-to-treat population). The demographic and baseline characteristics among the study groups, including the reference group, are summarized in Table 1.

2. Primary efficacy analysis

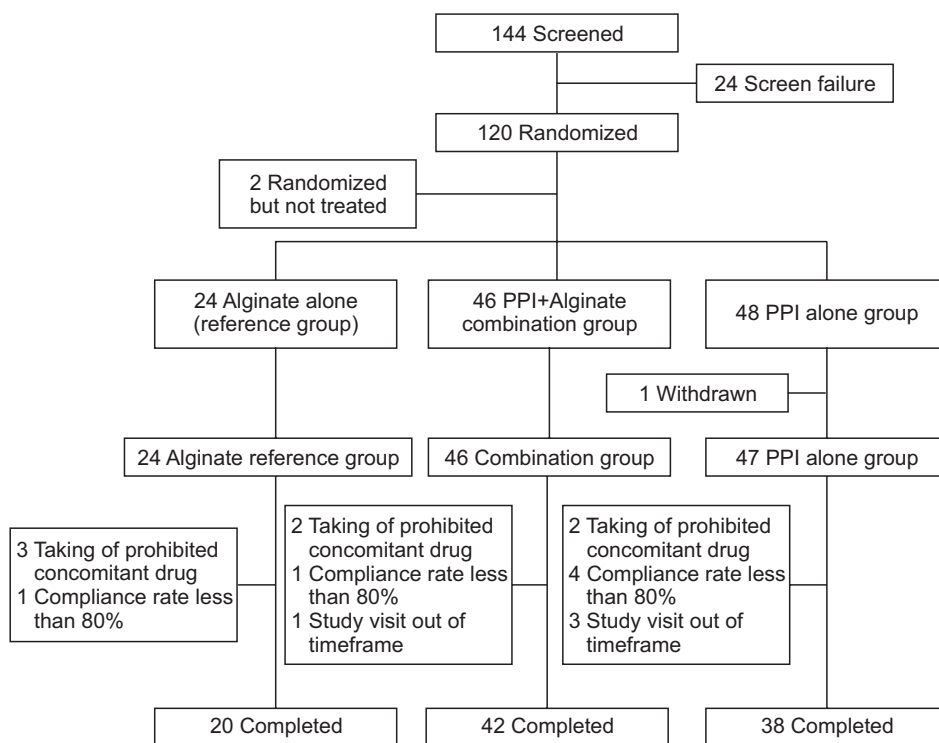The primary endpoint compared the percentage of patients

Fig. 1. Patient flowchart.
PPI, proton pump inhibitor.

Table 1. Baseline Patient Characteristics

Characteristic	PPI+alginate	PPI	Alginate	p-value*	p-value[†]
Male sex	8 (17.4)	11 (23.4)	4 (16.7)	0.472	0.511
Age, yr	49.2±12.1	47.7±12.1	50.4±10.8	0.583	0.361
Weight, kg	57.3±8.2	59.1±10.4	56.5±8.8	0.410	0.240
BMI, kg/m^2	22.2±2.3	22.3±2.8	22.0±3.2	0.892	0.733
Heartburn					
Day per week	6.4±1.4	5.7±2.3	6.2±1.8	0.460	0.422
Sum of score[‡]	8.7±4.0	7.8±4.7	8.0±3.8	0.341	0.615
Acid regurgitation					
Day per week	6.3±1.7	6.0±2.1	5.9±2.0	0.593	0.538
Sum of score[‡]	8.8±4.3	7.7±4.3	7.4±3.4	0.199	0.875

Data are presented as number (%) or mean±SD.
PPI, proton pump inhibitor; BMI, body mass index.
*p-value (PPI+alginate vs PPI); [†]p-value (PPI vs alginate); [‡]Score: none (0), mild (1), moderate (2), and severe (3).

Table 2. Percentage of the Patients with Complete Resolution of Symptoms for the Last 7 Consecutive Days

	PPI+alginate	PPI	Alginate	p-value*	p-value[†]
Heartburn	21 (45.7)	20 (47.6)	13 (54.2)	0.853	0.609
Regurgitation	20 (45.5)	23 (52.3)	10 (45.5)	0.522	0.602
Heartburn or regurgitation	27 (58.7)	27 (57.5)	18 (75.0)	0.903	0.146

Data are presented as number (%).
PPI, proton pump inhibitor.
*p-value (PPI+alginate vs PPI); [†]p-value (PPI vs alginate).

Table 3. Changes in Symptom Score from Baseline

	PPI+alginate	PPI	Alginate	p-value*	p-value[†]
Heartburn & regurgitation[‡]	7.3±8.7	5.2±6.6	5.2±7.3	0.218	0.639
Changes of symptom score[§]	−10.2±8.4	−10.4±8.4	−10.2±9.2	0.951	0.879
p-value (intragroup)	<0.0001	<0.0001	<0.0001		

Data are presented as mean±SD.
PPI, proton pump inhibitor.
*p-value (PPI+alginate vs PPI); [†]p-value (PPI vs alginate); [‡]Sum of symptom scores for the last 7 consecutive days; [§]From the sum of symptom scores at baseline.

with complete resolution of symptoms over the final 7 days of treatment (Table 2). Complete resolution of heartburn or regurgitation was not significantly different between the combination and PPI only groups (58.7% vs 57.5%, p=0.903). In addition, complete resolution of heartburn or regurgitation was also not significantly different between the PPI only and the alginate only groups (57.5% vs 75.0%, p=0.146).

3. Secondary efficacy analysis

The symptom scores were significantly lower than the baseline in all study groups, including the reference group (Table 3). However, the changes in symptom scores from baseline were not significantly different between the combination and PPI only groups (−10.2±8.4 vs −10.4±8.4, p=0.951). There was also no significant difference between the alginate only refer-

ence group and the PPI only group (−10.2±9.2 vs −10.4±8.4, p=0.879).

Other factors, including symptom-free days during treatment period (Table 4), the change in RDQ, PAGI-QOL, and PAGI-SYM scores (Table 5), and the clinical investigator's assessment of symptoms (data not shown), were not significantly different between the combination and PPI only groups. There was also no significant difference when comparing all secondary endpoints of the alginate only reference group with those of the PPI only group.

The incidence of AEs was investigated. Seven patients (14.9%) in the combination group, 12 patients (25.5%) in the PPI only group, and six patients (25.0%) in the alginate only group reported mild to moderate AEs. However, no severe AEs were reported in any of the treatment groups, and the incidence of AEs

Table 4. Symptom-Free Days during the 28-Day Treatment Period

	PPI+alginate	PPI	Alginate	p-value*	p-value[†]
Heartburn-free days, %	44.7±34.7	57.4±37.4	56.6±37.9	0.102	0.937
Regurgitation-free days, %	50.8±38.0	57.8±35.3	56.2±34.1	0.317	0.733
Overnight symptom-free days, %	74.8±33.1	83.7±21.3	80.7±28.1	0.454	0.915

Data are presented as mean±SD.
PPI, proton pump inhibitor.
*p-value (PPI+alginate vs PPI); [†]p-value (PPI vs alginate).

Table 5. RDQ, PAGI-QOL, and PAGI-SYM Survey Score Change

	PPI+alginate	PPI	Alginate	p-value*	p-value[†]
RDQ					
Baseline	17.5±5.4	15.5±4.9	15.8±4.7	0.046	0.562
28-day	9.3±8.5	6.0±5.9	5.9±5.7	0.074	0.955
Change from baseline	−8.2±7.6	−9.5±5.7	−9.8±7.2	0.421	0.747
PAGI-QOL					
Baseline	35.5±26.3	29.9±25.9	34.1±25.4	0.240	0.375
28-day	17.0±20.3	12.3±17.0	12.6±16.6	0.212	0.750
Change from baseline	−18.4±21.5	−17.7±20.8	−21.5±20.5	0.969	0.193
PAGI-SYM					
Baseline	32.3±21.0	23.2±16.3	27.2±17.6	0.036	0.371
28-day	16.5±17.1	10.8±12.9	11.8±13.2	0.047	0.956
Change from baseline	−15.9±17.3	−12.4±11.9	−15.4±14.7	0.562	0.555

Data are presented as mean±SD.
RDQ, Reflux Disease Questionnaire; PAGI-QOL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; PAGI-SYM, PAGI-Symptoms Severity Index; PPI, proton pump inhibitor.
*p-value (PPI+alginate vs PPI); [†]p-value (PPI vs alginate).

was not significantly different among treatment groups. One patient in the PPI only group withdrew from the study treatment due to an AE of mild dyspepsia.

DISCUSSION

This study showed that the addition of a non-bicarbonate alginate (Lamina G) together with PPI was not more effective than a PPI regime on its own in the alleviation of reflux symptoms. However, when analyzing the data from the reference group, a pure alginate regimen may be as effective as a PPI regimen on its own in reducing reflux symptoms without evidence of reflux esophagitis in endoscopy.

Since a longer and more robust treatment is necessary for successful mucosal healing,[14-17] initial PPI treatment is often recommended for more than 8 weeks in erosive reflux disease patients.[14-17] Conversely, the treatment goal of nonerosive reflux disease (NERD) patients is only symptom relief. Previous studies have reported symptom relief in GERD patients without evidence of reflux esophagitis following 4 weeks of PPI treatment.[17-20] Furthermore, patients with NERD are not treated well despite taking high-dose PPI. Considering the risks of long-term

PPI use, the shortest duration or the lowest dose of PPI is an important factor when managing GERD treatment.[21,22] Effective alternatives to PPI for symptom relief in GERD patients without evidence of reflux esophagitis would thus also be clinically valuable. Although further evidence is required to validate our data, the present study showed that monotherapy with an alginate alone can provide reflux symptom reduction in GERD patients without evidence of reflux esophagitis comparable to that with PPI treatment alone.

Pathophysiological mechanisms of GERD are categorized into factors that promote the occurrence of reflux and/or increase the perception of reflux.[23] The latter can be of particular importance in patients without diagnosed esophagitis.[23] An alginate acts on both mechanisms; the acid pocket as the factor promoting the occurrence of reflux, and mucosal integrity as the factor increasing the perception of reflux.

A floating drug-delivery system can act as a physical barrier against the acid pocket. Floating drug-delivery systems are divided into effervescent and noneffervescent systems.[8,24] The effervescent system includes gas-generating treatments such as the Gaviscon formulation, whereas the noneffervescent system includes matrix-forming polymers such as sodium alginate used

in the present study.[8,24] To the best of our knowledge, no study has evaluated the effectiveness of noneffervescent, pure sodium alginate treatment in GERD patients. Our study is the first to investigate the efficacy of pure sodium alginate in GERD patients. According to a previous report, raft formation was observed by endoscopy after 28 seconds of infusion with Lamina G.[24] Considering this rapid raft formation, sodium alginate could be an effective therapy for rapid symptom relief in GERD patients.

Microscopic impairment of the esophageal epithelium can be a pathophysiological factor of symptoms in GERD patients, explained as a relationship between impaired mucosal integrity and sensitivity to acid.[23,25] Recent studies measuring mucosal integrity by baseline esophageal impedance (mean nocturnal baseline impedance, MNBI)[23,26] highlight an important tool in predicting experimental sensitivity to acid. MNBI was significantly lower in NERD patients than in healthy control patients.[26,27] According to the previous studies, the esophageal mucosa in NERD patients showed distinct vulnerability when exposed to acids/weak acids, and vulnerable mucosa could be protected by an alginate-containing topical solution.[28,29] That is, alginates have bioadhesive potential, and can be prescribed as a topical treatment to maintain esophageal mucosal integrity against acid reflux from the stomach.[28-30]

Based on our findings here, pure sodium alginate may be an effective monotherapy for symptom relief in GERD patients without evidence of reflux esophagitis. However, we designed the study to compare a PPI treatment with a combination treatment (PPI and alginate), not with alginate only group. The alginate only group was designed arbitrarily as a reference group to show whether alginate monotherapy could be effective in GERD patients without evidence of reflux esophagitis. Thus, further study is required to validate the efficacy of pure sodium alginate in GERD patients without evidence of reflux esophagitis.

Our study is the first to evaluate the effect of pure sodium alginate in controlling reflux symptoms. However, it has several limitations. First, the study participants were selected to have reflux symptoms without evidence of reflux esophagitis in endoscopy. Ambulatory pH monitoring was not performed to exclude functional heartburn or hypersensitive esophagus. This may be one of the reasons not to show additional effect of pure sodium alginate to PPI in the study. Second, rescue medications for uncontrolled symptoms were not planned in the study. Thus, the possibility of self-rescue medication was not fully excluded. Third, the alginate only group was designed arbitrarily as a reference group without statistical evidence. Thus, further study is required to evaluate the efficacy of pure sodium alginate in GERD patients without evidence of reflux esophagitis. Fourth, psychiatric disorders such as depression and anxiety may play a role in GERD symptom manifestation. However, the use of psychiatric medication or a history of psychiatric disorder was not evaluated.

In conclusion, the addition of pure sodium alginate to PPI was no more effective than PPI alone in GERD patients without evidence of reflux esophagitis. Further study designed to compare pure sodium alginate with PPI only is necessary in the future.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Data analysis and interpretation, drafting of the manuscript: J.H.K. Study concept and design, critical revision of the manuscript for important, obtained funding, study supervision: Y.C.L. Revising it critically for important intellectual content: E.H.K., J.C.P., S.K.S., S.K.L., D.H.J., J.J.P., Y.H.Y., H.P.

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