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Double-Blind, Placebo-Controlled Study With Alginate Suspension for Laryngopharyngeal Reflux Disease

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Objective: Treatment for laryngopharyngeal reflux disease (LPRD) is challenging because of delays in recognition and poor responsiveness to proton-pump inhibitor therapy. The aim of this study was to determine the efficacy and safety of liquid alginate suspension for treating LPRD.

Methods: A double-blind, placebo-controlled, prospective study comparing 8 weeks of treatment with Alginos Oral Suspension (TTY Biopharm Co. Ltd., Taipei, Taiwan) (sodium alginate 1,000 mg three times daily) with a placebo was conducted on patients who fulfilled the criteria of at least one symptom consistent with LPRD, a total reflux symptom index (RSI) score of > 10, and a total reflux finding score (RFS) of > 5. Those with erosive gastroesophageal reflux disease, as evidenced through screened transnasal upper gastrointestinal endoscopy, were excluded. Efficacy was assessed by RSI, RFS, and ambulatory multichannel intraluminal impedance and pH (MII-pH) monitoring.

Results: A total of 80 patients aged 22 to 72 years were enrolled. Compared with baseline, both Alginos (TTY Biopharm Co. Ltd.) and the placebo significantly reduced the total RSI ($P < 0.001$) and the total number of reflux episodes shown by MII-pH monitoring ($P < 0.05$) after 8 weeks of treatment. However, liquid alginate suspension was unable to show superiority over the placebo. The incidence of various adverse events from Alginos (TTY Biopharm Co. Ltd.) was relatively low (7.7%) and mild.

Conclusion: This study showed that liquid alginate suspension was well tolerated by LPRD patients. It effectively improved symptoms and reflux numbers but was unable to show superiority over placebo. As observed in previous studies, a great placebo effect was present. The importance of lifestyle modification could not be overlooked.

Key Words: Laryngopharyngeal reflux disease, alginates, gastroesophageal reflux disease, multichannel intraluminal impedance and pH monitoring.

Level of Evidence: 2.

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INTRODUCTION

Laryngopharyngeal reflux disease (LPRD), an extraesophageal variant of gastroesophageal reflux disease (GERD), refers to the retrograde flow of gastric content to the laryngopharynx.[1] Most patients with LPRD do not exhibit the classic heartburn symptoms and acid regurgitation commonly associated with GERD.[2] Based on a study of pH-monitoring-confirmed LPRD cases, Belafsky et al. developed a self-administered tool called the reflux symptom index (RSI)[3] and also a reflux finding score (RFS) based on endolaryngeal signs.

LPRD is known to have poorer responsiveness to proton-pump inhibitor (PPI) therapy and delay in recognition compared to GERD.[4] LPRD can be diagnosed using the following three approaches: 1) symptomatic responses to empirical treatment, 2) direct endoscopic or laryngoscopic observation of mucosal injury, and 3) objective demonstration of reflux events through multichannel impedance and pH (MII-pH) monitoring.[5] Empirical therapy involves a trial of acid-suppressing agents such as PPIs or histamine-2 antagonists. In patients who have ongoing symptoms despite taking PPIs twice daily, reflux monitoring approaches such as MII-pH monitoring can be highly effective for further characterizing refractory patients. MII-pH monitoring enables the measurement of acid and nonacid reflux and has emerged as the gold standard for measuring gastroesophageal reflux.[6,7] Evidence increasingly shows that

Additional supporting information may be found in the online version of this article

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the addition of MII technology improves diagnostic accuracy for LPR events.[5]

However, studies using the MII-pH for the diagnosis of LPRD remain limited and there is a lack of consensus for the reference normative values for proximal esophageal measurements.[8,9] Recently, a novel compound called Alginos Oral Suspension (TTY Biopharm Co. Ltd., Tapei, Taiwan) containing alginate sodium has been introduced to the market. Alginates precipitate in forming a gel in which CO_2 converted from bicarbonates is entrapped. The alginate raft then serves as a pH-neutral barrier over the gastric content and esophageal mucosa. There were clinical studies, reviews, and meta-analyses indicating that alginates are more effective than placebo or antacids for treating GERD.[10–12] However, few studies have investigated whether Alginos (TTY Biopharm Co. Ltd.) could be used for treating LPRD. McGlashan et al. conducted a pilot study on liquid alginate suspension (Gaviscon Advance, Gaviscon, Slough, U.K.) and showed statistically significant decreases in the RSI and RFS with profound placebo effects.[13] Thus, in this present study, the primary objective was to evaluate the efficacy and safety of Alginos Oral Suspension (TTY Biopharm Co. Ltd.) for treating adult patients with LPRD, as documented by the most commonly used inclusion criteria based on laryngeal symptoms and laryngoscopic findings used in previous studies. Meanwhile, in addition to the conventional diagnostics of the RSI and RFS, we used the MII-pH monitoring as the most objective parameters to demonstrate the reflux changes before and after treatment.

MATERIALS AND METHODS

Study Participants and Design

We conducted a randomized, double-blind, placebo-controlled prospective study at National Taiwan University Hospital (NTUH), Taipei, Taiwan, a single tertiary medical center, from October 2011 to January 2015. Patients aged 22 to 75 years who had exhibited at least one symptom of LPRD, including hoarseness, throat clearing, throat pain, globus sensation in the throat, or chronic cough for 4 weeks or longer, were eligible for enrollment. Other inclusion criteria were a total RSI score of >10 and total RFS of >5, as in the previous study.[13] The study protocol was approved by the Ethical Committee of NTUH (201106058MA) and registered at ClinicalTrials.gov (NCT01450748). All participants provided written informed consent. Patients with any of the following conditions were excluded: viral or bacterial laryngitis; erosive GERD as evidenced by upper gastrointestinal endoscopy; or laryngeal, esophageal, or gastric cancer. In addition, patients were excluded if they had a history of neck radiation therapy; uncontrolled hypertension or moderate to severe renal impairment; esophageal or gastric surgery, with active pulmonary infection as evidenced by chest plain film; endotracheal tube intubation within 2 months before entering this study; or allergies to any of the drugs used in this study. Patients who had been under any alginate preparations within 2 days before screening, acid-suppressive agents or any prokinetic agents within 7 days before screening, or PPIs within 14 days before screening were also excluded. Cigarette smoking was categorized as current smokers and nonsmokers. Significant alcohol consumption was defined as alcohol intake >20 g/day for men and >10 g/day for women.

All participants received an RSI recording by a trained nurse and an RFS recording by an experienced otorhinolaryngologist on day 0. Participants were then randomly assigned to the study or control group. Permuted block randomization method was applied to generate randomization codes.

All participants were instructed to take 20 mL three times daily after meals throughout the 8-week study period. Practical education regarding diet control and lifestyle modifications was provided for all study participants by the study nurse. Compliance to medication and adherence to lifestyle recommendations were evaluated by the study nurse on follow-up visits. Alginos Oral Suspension (TTY Biopharm Co. Ltd.) contains 50 mg of sodium alginate, 26.7 mg of sodium bicarbonate, and 16 mg of calcium carbonate per mL, whereas the placebo suspension was prepared identically in appearance, taste, and fluidity. The placebo did not exhibit the ability to form the aforementioned alginate raft that served as a pH-neutral barrier over the gastric content and esophageal mucosa. The first 24-hour ambulatory MII-pH readings (days 0–1) served as the baseline value. The second 24-hour readings (days 1–2) were used to assess the acute effects of the study medications. Further RSI recordings were obtained on days 2 and 29 ± 3, and RFS recordings were obtained on day 29 ± 3. At the final visit, RSI and RFS recordings were obtained and 24-hour MII-pH monitoring was performed to assess the treatment responses (Fig. 1).

The primary efficacy endpoint was a mean reduction in the total RSI from baseline to week 8. The secondary efficacy endpoints were 1) a mean reduction in RSI from baseline to day 2 and week 4; 2) mean reduction in the total RFS; 3) mean change in the individual component of RSI; 4) mean change in the individual component RFS from baseline to weeks 4 and 8; and 5) the total number of reflux episodes measured by 24-hour ambulatory MII-pH monitoring, including the mean acute change from baseline to day 2 and mean change from baseline to week 8.

Reflux Symptom Index

The RSI is a validated nine-item, self-administered questionnaire to assess the severity and responses to treatment of LPRD-associated symptoms[3] (Table I). Each component is scored between 0 (no problem) and 5 (severe problem), with a maximum total score of 45. An RSI greater than 10 is considered abnormal.

Reflux Finding Score

The RFS is a validated[14] rating scale developed to quantify the degree of laryngeal involvement in LPRD during fiberoptic laryngoscopy (Table I). Scores range from 0 to 26, with scores greater than 7 considered pathological.

Multichannel Intraluminal Impedance and pH Monitoring

A modified MII-pH monitoring probe with six impedance segments and three pH electrodes was used (Ohmega Ambulatory Impedance-pH Recorder, Medical Measurement Systems, Enschede, Netherlands). The catheter was introduced transnasally. The six impedance segments defined the six zones along the esophagus, Z1 to Z6, which were centered at 17, 15, 9, 7, 5, and 3 cm above the lower esophagus sphincter, respectively, with Z1 being most proximal to the upper incisor. The three pH electrodes were located in the stomach, 5 cm above the lower esophageal sphincter and 21 cm above the lower esophageal

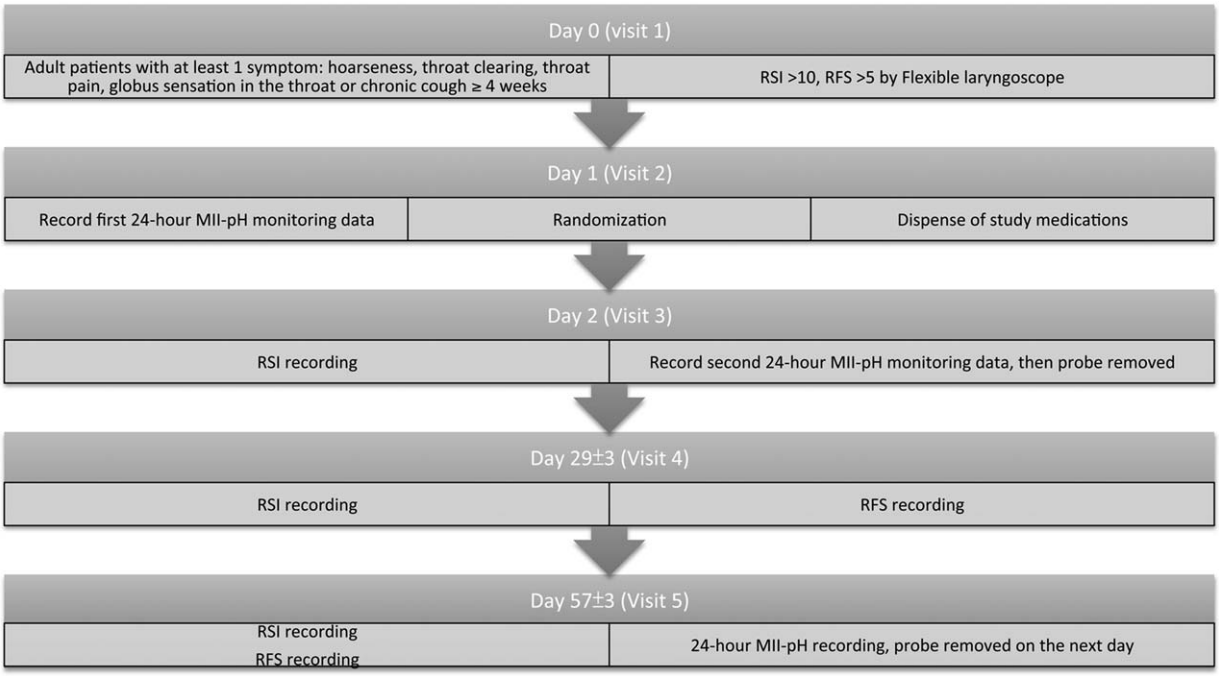

Fig. 1. Study design: double-blind, randomized, placebo-controlled.
MII-pH = multichannel intraluminal impedance and pH; RFS = reflux finding score; RSI = reflux symptom index.

sphincter.[15] All of the segments and electrodes were assumed to locate in the esophagus. A length of time exceeding 4.0% of the 24-hour recording spent below pH 4.0 was selected as the definition of pathological acid reflux. A positive 24-hour pH-metry was defined as pathological acid reflux or a symptom index of $\geq 50\%$. Other parameters such as DeMeester scores and symptom association probability (SAP) were also recorded.

Statistical Analysis

Reductions in mean RSI scores by 7 (placebo) and 12 (alginates) over 2-month treatment periods have been observed in the literature.[13] A sample size of 56 patients was estimated based on a two-sided 5% significance test and 90% power to demonstrate the superior treatment efficacy of liquid alginate suspension over the placebo. The dropout rate was assumed to be 30% considering the use of MII-pH monitoring. Therefore, it was determined that approximately 80 patients would be enrolled.

For efficacy analysis, a paired t test was conducted to compare the scores before and after treatment. Correlations between RSI and parameters of MII-pH monitoring were calculated using Pearson's correlation coefficient, Spearman's rank correlation coefficient, and P values, with $P < 0.05$ considered to be statistically significant.

RESULTS

Patients' Demographic and Baseline Multichannel Intraluminal Impedance-pH Monitoring Data

A total of 80 patients comprising 30 men and 50 women were enrolled. Participant disposition is shown in Figure 2. Baseline characteristics between the two study groups were comparable. One patient in the alginate group did not take any study medication and was excluded. Finally, 79 patients completed MII-pH data collection on randomization visits, and 76 patients attended the final visit at week 8, of whom 49 patients completed the follow-up MII-pH data collection. Detailed demographic features and summary of disease status at baseline are shown in Tables II and III.

Correlation Between Reflux Symptom Index/ Reflux Finding Score and Multichannel Intraluminal Impedance-pH Monitoring Data

To further evaluate the presence of any association between the subjective symptomatic questionnaire and objective signs of the two mainstay diagnostic tools of

TABLE I.
Items in RSI and RFS.

RSI	RFS
Hoarseness or voice problems	Subglottic edema
Throat clearing	Ventricular obliteration
Excess throat mucus or postnasal drip	Erythema or hyperemia
Difficulty swallowing food, liquid, or pills	Vocal fold edema
Coughing after eating or lying down	Diffuse laryngeal edema
Breathing difficulties or choking episodes	Posterior commissure hypertrophy
Troublesome or annoying cough	Granuloma or granulation tissue
Sensation of something sticking in the throat or a lump in the throat	Thick endolaryngeal mucus
Heartburn, chest pain, indigestion, or stomach acid being pushed upward	

RFS = reflux finding score; RSI = reflux symptom index.

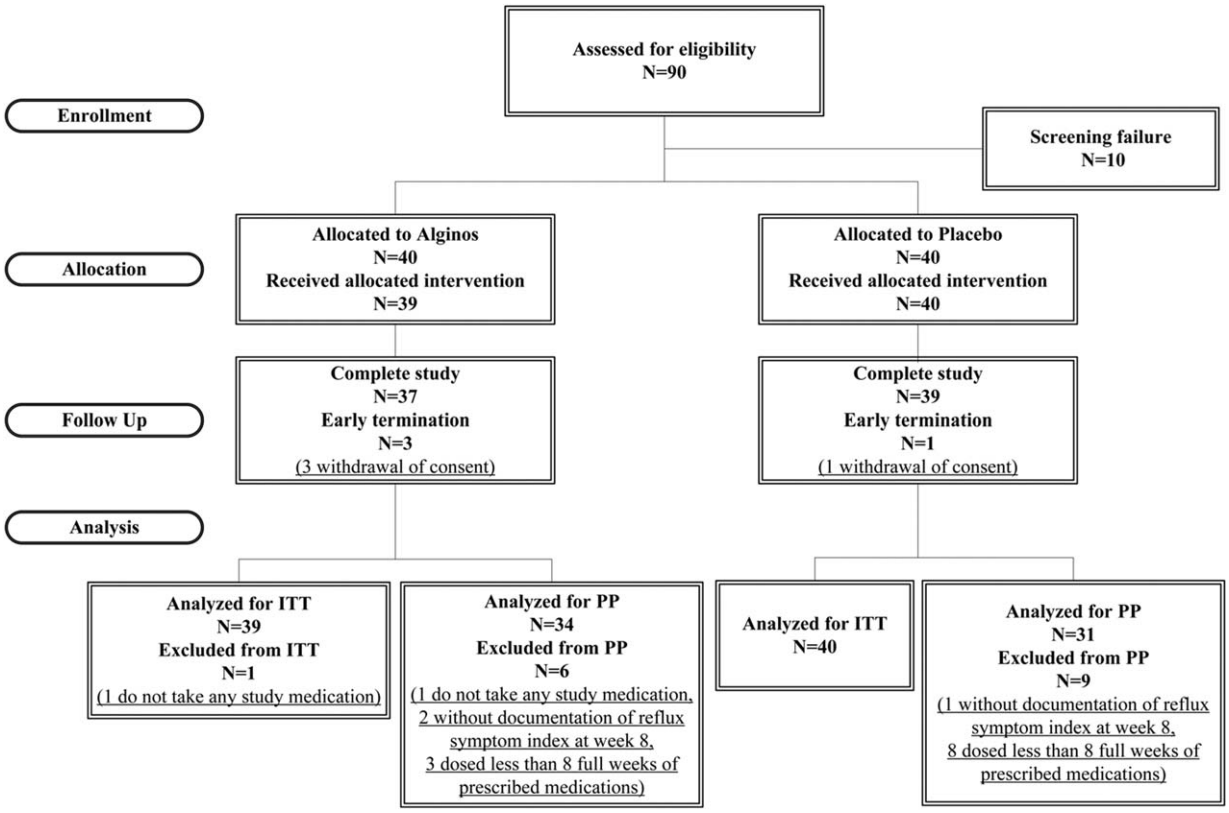

Fig. 2. Participant disposition: enrollment, allocation, follow-up, and analysis (N = 79).
ITT = intention-to-treat; PP = per-protocol.

LPRD, correlations between RSI scores and MII-pH monitoring parameters were calculated at baseline, end of study, and after treatment course. However, neither SAP nor SI showed significant correlation with RSI and RFS. Similarly, no significant correlation of the RSI-pH monitoring results was shown.

Regarding the total RSI score and various impedance parameters, a weak positive correlation was observed between the total RSI and mixed reflux at baseline (correlation coefficients 0.3129, $P = 0.0286$). As with RFS, % of time pH < 4 in proximal impedance segments, that is, Z1 and Z2, showed weak positive correlation (correlation coefficient Z1: 0.3904, P = 0.0056; Z2: 0.3058, $P = 0.0326$). Complete data of correlation between RSI/RFS and MII-pH monitoring parameters were shown in Supporting Table SII (Correlation of MII-pH Parameters and RSI at Baseline) and Supporting Table SIII (Correlation of MII-pH Parameters and RFS at Baseline).

Comparison of Reflux Symptom Index, Reflux Finding Score, and Multichannel Intraluminal Impedance-pH Parameters Between the Alginos and Placebo Groups: Primary and Secondary Efficacy Endpoints

I. Primary Efficacy Endpoint. The time course of the mean total RSI scores is shown in Figure 3. The intention-to-treat (ITT) and per-protocol (PP) groups had similar results. The statistical analysis results revealed that the participants in the alginate group had significant ($P < 0.0001$) improvement after 8 weeks in terms of total RSI score reduction (from 21.18 ± 7.53 at baseline to 10.14 ± 6.77 at week 8). However, the placebo group also showed comparable total RSI score reduction. Although liquid alginate suspension seemed to yield a greater reduction in total RSI score than did the placebo, the difference was not statistically significant (-10.78 ± 6.17 vs. -7.92 ± 7.02, $P = 0.12$).

II. Secondary Efficacy Endpoints. The total RSI score was significantly reduced after 4 weeks in the alginate group (21.18 ± 7.53 vs. 12.64 ± 6.33, $P < 0.001$). However, the placebo group also showed similar reductions in total RSI ($P = 0.11$).

For the alginate group, the total RFS significantly declined from 8.44 ± 3.21 at baseline to 5.97 ± 3.13 by week 4 and further to 4.49 ± 2.82 by week 8 (both $P < 0.001$). However, the total RFS in the placebo group also significantly decreased by a similar extent. The analysis of covariance test results indicated no significant differences between the treatment groups at week 4 ($P = 0.78$) or 8 ($P = 0.32$).

The mean change in the individual RSI components from baseline to week 4 and week 8 was calculated to assess which components were sensitive to the study medication intervention. The results showed that only one component (sensation of something sticking in the throat or a lump in the throat) was sensitive to liquid

TABLE II.
Summary of Demographic Characteristics.

Demographics	Sodium Alginate (n = 39)	Placebo (n = 40)
Age, years	49.3 ± 13.8	46.5 ± 12.9
Female gender	26 (66.7%)	23 (57.5%)
Weight, kg	60.9 ± 11.4	62.2 ± 10.1
Height, cm	161.2 ± 7.4	163.1 ± 7.7
BMI, kg/m^2	23.4 ± 3.7	23.3 ± 3.1
Alcohol drinking	2 (5.1%)	0 (0.0%)
Smoking	3 (7.7%)	6 (15%)
RSI at screening	21.2 ± 7.5	19.0 ± 7.2
RFS at screening	8.4 ± 3.2	7.5 ± 1.5
MII-pH parameters	Sodium Alginate (n = 25)	Placebo (n = 24)
% time pH < 4		
Upper E	0.10 ± 0.19 (0.00,0.80)	0.30 ± 0.94 (0.00,4.40)
Upright	0.16 ± 0.30 (0.00,1.30)	0.20 ± 0.61 (0.00,2.70)
Supine	0.01 ± 0.04 (0.00,0.20)	0.04 ± 0.20 (0.00,1.00)
Lower E	5.01 ± 6.89 (0.00,27.40)	7.85 ± 16.66 (0.00,76.10)
Upright	4.72 ± 4.79 (0.00,14.70)	9.42 ± 16.01 (0.00,69.10)
Supine	5.77 ± 13.39 (0.00,53.90)	4.76 ± 17.03 (0.00,83.10)
Acid reflux	2.44 ± 3.28 (0.00,10.00)	4.83 ± 15.27 (0.00,73.00)
Weak acid reflux	26.44 ± 3.20 (2.00,87.00)	18.50 ± 16.15 (3.00,78.00)
Nonacid reflux	23.20 ± 32.48 (0.00,148.00)	18.33 ± 18.35 (0.00,69.00)
Liquid reflux	8.04 ± 10.97 (0.00,54.00)	6.17 ± 4.30 (0.00,16.00)
Mixed reflux	44.04 ± 33.57 (7.00,145.00)	35.50 ± 28.21 (8.00,135.00)
Total reflux episodes	52.08 ± 41.38 (7.00,166.00)	41.67 ± 30.80 (12.00,151.00)
Z1 (%)	20.08 ± 13.52 (3.00,46.00)	12.67 ± 12.08 (0.00,50.00)
Z2 (%)	32.68 ± 15.45 (4.00,62.00)	25.46 ± 14.87 (8.00, 73.00)
Z3 (%)	79.44 ± 12.89 (50.0,100.0)	77.46 ± 11.29 (53.00,94.00)
Total symptom episodes	23.00 ± 73.50 (0.00,372.0)	18.08 ± 29.34 (0.00,99.00)
SI (%)	15.92 ± 22.30 (0.00,66.70)	15.08 ± 23.11 (0.00,100.00)
SAP (%)	46.50 ± 57.32 (0.00,200.0)	50.72 ± 45.29 (0.00,100.00)

Data are presented as mean ± standard deviation or numbers with the associated percentages in parentheses. For the MII-pH parameters, data are presented with mean ± standard deviation with the minimal and maximal values in parentheses.

BMI = body mass index; lower E = lower esophagus; MII-pH = multichannel intraluminal impedance and pH; RFS = reflux finding score; RSI = reflux symptom index; SAP = symptom association probability; SI = symptom index; upper E = upper esophagus; Z = zone.

alginate suspension treatment for 4 weeks in the ITT ($P = 0.035$) and PP ($P = 0.034$). The remaining eight components all significantly improved, but the intergroup differences were not statistically significant.

Regarding the eight individual RFS components. The alginate group showed significantly reduced erythema or hyperemia, vocal fold edema, diffuse laryngeal edema, and posterior commissure hypertrophy. However, liquid alginate suspension was unable to exhibit a significant difference compared with the placebo.

Significant reduction in total symptom episodes, mixed reflux, and total reflux episodes was noted in both liquid alginate suspension (from 23.00 ± 73.50 to 7.68 ± 13.20, $P = 0.0242$; 44.04 ± 33.57 to 32.00 ± 22.50, $P = 0.0092$; 52.08 ± 41.38 to 38.20 ± 30.89, $P = 0.0110$, respectively) and placebo group (from 18.08 ± 29.34 to 8.96 ± 15.17, $P = 0.0020$; 35.50 ± 28.21 to 24.92 ± 17.12, $P = 0.0001$; 41.67 ± 30.80 to 29.88 ± 18.36, $P = 0.0002$, respectively). However, the reduction was not significantly different between the groups. Complete data of MII-pH results before and after treatment was shown in Supporting Table SI (MII-pH Results Before and After Treatment Course).

Adverse Events

This study found liquid alginate suspension to be well tolerated. Four adverse events were reported in three (7.7%) patients in alginate group, whereas three adverse events were experienced by two (5.0%) patients in the placebo group. All adverse events were mild in severity and unrelated to the study medications.

DISCUSSION

Currently, there is no gold standard for the diagnosis of LPRD due to the lack of pathognomonic diagnostic criteria. The most commonly used approaches include subjective symptom improvement after a short course of empirical pharmacological treatment, also known as the PPI test; direct endoscopic observation of mucosal injury;

TABLE III.
Summary of Disease Status at Baseline.

Laryngopharyngeal Reflux History		Sodium Alginate (n = 39)	Placebo (n = 40)	*P* Value
Hoarseness	Yes	23 (59.0%)	23 (57.5%)	1.0000*
	No	16 (41.0%)	17 (42.5%)	
	Duration (week)	51.3 ± 51.3	53.3 ± 60.7	0.9066†
Throat clearing	Yes	30 (76.9%)	35 (87.5%)	0.2515*
	No	9 (23.1%)	5 (12.5%)	
	Duration (week)	79.7 ± 87.2	58.1 ± 61.5	0.2477†
Throat pain	Yes	5 (12.8%)	7 (17.5%)	0.7555*
	No	34 (87.2%)	33 (82.5%)	
	Duration (week)	36.8 ± 37.9	39.4 ± 34.2	0.9025†
Globus sensation in the throat	Yes	33 (84.6%)	36 (90.0%)	0.5179*
	No	6 (15.4%)	4 (10.0%)	
	Duration (week)	74.5 ± 84.9	65.8 ± 65.0	0.6311†
Chronic cough	Yes	19 (48.7%)	22 (55.0%)	0.6549*
	No	20 (51.3%)	18 (45.0%)	
	Duration (week)	48.8 ± 47.6	74.5 ± 68.9	0.1797†
Receive medical intervention	Yes	8 (20.5%)	12 (30.0%)	0.4391*
	No	31 (79.5%)	28 (70.0%)	

*Fisher's exact test.
†Two-sample *t* test.

and objective demonstration of reflux events through ambulatory MII-pH monitoring.[5] However, the rate of response to the PPI test was significantly higher among patients with typical GERD than among patients with LPRD.[16] Moreover, the various signs of mucosal injury observed in endoscopic examinations, such as edema and hyperemia, are all related to acute or chronic inflammation, and thus could be caused by viral infection or chemical irritation not limited to LPRD. In 1969, Spenser reported the first case of intraesophageal pH monitoring as a GERD-confirmatory test.[17] In a subsequent study, MII-pH monitoring was introduced to help circumvent some of the limitations of conventional pH monitoring systems. Impedance measuring devices enabled the assessment of the presence, proximal extent, and consistency of the refluxate. MII-pH monitoring was found to be superior to pure impedance measuring devices, pH monitors, and endoscopy for diagnosing atypical GERD.[8] In our study, MII-pH monitoring was able to detect reflux events in patients who were negative for GERD according to endoscopic examinations. The average percentage of time below pH 4 in the lower esophagus (5 cm) was 5.01 ± 6.89 in liquid alginate suspension group and 7.85 ± 16.66 in placebo group ($P = 0.6571$), and in the upper esophagus (21 cm) was 0.10 ± 0.19 in liquid alginate suspension group and 0.30 ± 0.94 in placebo group ($P = 0.5089$) at baseline. MII monitoring also exhibited a total reflux episode of 52.08 ± 41.38 in liquid alginate suspension group, 41.67 ± 30.80 in placebo group ($P = 0.3952$) per 24 hours. Without proper diagnosis, effective treatment may be hindered. In the present study, the correlation between RSI scores and impedance results exhibited a trend of increasing positive correlation from Z6 to Z1, or in other words, from the lower esophagus to the upper esophagus (Fig. 4). The reflux event to the upper esophagus detected by the multichannel impedance meter provides evidence of irritation in proximal esophagus and could further aid in the diagnosis of LPRD. Further studies may be required in the future.

Published studies on the effect of acid-suppressing therapy on chronic laryngitis have yielded conflicting results[18] (Table IV). Reichel et al. reported that 20 mg of esomeprazole twice daily for 3 months demonstrated a significant improvement in total RSI (14.27 ± 1.58 vs. 7.79 ± 1.74, $P < 0.05$) and total RFS (4.60 ± 0.63 vs. 2.32 ± 0.76, $P < 0.05$).[19] Lam et al. reported a significantly decreased total RSI in a twice-daily rabeprazole 20 mg group compared with that in a placebo group; however, no significant differences in RFS were observed between the two groups.[20] MacGlashan et al. reported that administering 10 mL of liquid alginate preparation four times daily yielded a significantly greater reduction in total RSI than that observed in a no treatment control group after 2 ($P = 0.005$) and 6 ($P = 0.008$) months of treatment for patients with laryngopharyngeal reflux.[13] However, Noordzij et al. reported that 40 mg of omeprazole twice daily for 2 months failed to demonstrate therapeutic efficacy over a placebo in patients with reflux laryngitis.[21] Wo et al. reported that, although total laryngeal symptom scores significantly improved in two groups administered 40 mg of pantoprazole daily for 12 weeks and a placebo, no significant differences were observed ($P = 0.89$). No significant improvement in hypopharyngeal reflux was observed in either study group.[22] There are several possible reasons for such discrepant results. One may be the lack of consensus regarding the diagnosis of LPRD, with the RSI, RFS, and even

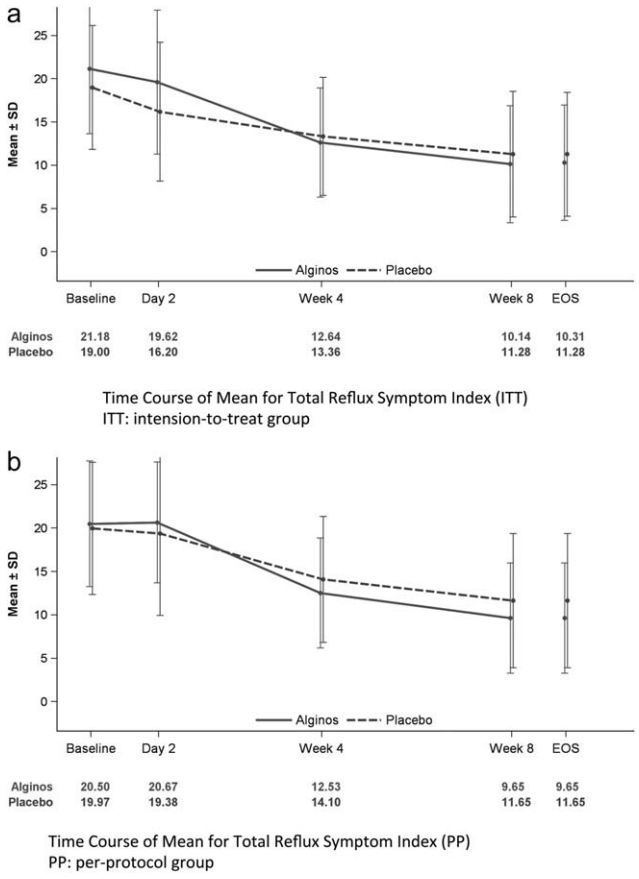

Fig. 3. Time course of mean for total RSI. (a) ITT group; (b) PP group. The ITT and PP populations had similar results. Participants in the Alginos (TTY Biopharm Co. Ltd., Taipei, Taiwan group had a significant ($P < 0.0001$) improvement after 8 weeks of treatment in terms of total RSI score reduction (from 21.18 ± 7.53 at baseline to 10.14 ± 6.77 at week 8) in the ITT group. However, the placebo group also exhibited a comparable total RSI score reduction. Although Alginos (TTY Biopharm Co. Ltd.) seemed to produce a greater reduction in the total RSI score than did the placebo, the difference was not statistically significant (−10.78 ± 6.17 vs. −7.92 ± 7.02, $P = 0.12$).
EOS = end of study; ITT = intention-to-treat; PP = per-protocol; RSI = reflux symptom index; SD = standard deviation.

different cutoff points in pH and reflux episode values. Studies that have included patients based on RSI and RFS results (Reichel et al.[19] and Lam et al.[20] but not pH testing (Noordzij et al.[21] and Wo et al.[22]) have tended to demonstrate significant improvements in treatment groups over placebo groups. Studies with pH testing documented evidence of refluxate to the hypopharynx and more accurately identified patients with LPRD, who had lower response rates to PPI treatment.[4] Another explanation is that other nonacidic gastric irritants such as pepsin and bile are harmful to laryngeal mucosa and may play a significant causative role.[23]

Similar to several of the aforementioned studies, in the present study the liquid alginate suspension failed to yield a reduction in total RSI superior to that yielded by the placebo.[20–22] A pronounced placebo effect was observed, especially when the placebo suspension and liquid alginate suspension were made to be identical in appearance. A placebo effect was hypothesized to be more likely to occur when LPRD is evaluated based on subjective rather than objective findings.[24] Steward et al. conducted a study on 42 patients with chronic laryngopharyngitis treated with lifestyle modifications to compare 20 mg of rabeprazole twice daily with placebo control for 8 weeks. The results failed to demonstrate any significant differences between the groups.[24] Notably, further analysis of lifestyle modification data revealed a significant improvement for the entire patient population, with avoidance of oral intake within 2 hours of bedtime and lying down with blocks placed under bedposts to raise the head of the bed by at least 6 inches, and with a reduction in caffeine consumption. Thus, education on lifestyle modification is essential for treating patients with LPRD.

Strengths and Limitations of the Present Study

In addition to the conventional diagnostics of the RSI and RFS, we introduced MII-pH monitoring to document reflux events in the participants. Furthermore, MII-pH monitoring was performed before and after treatment to aid the diagnosis of LPRD as well as treatment evaluation. This comprehensive data provided a more objective evaluation of the treatment efficacy. Nevertheless, the baseline MII-pH results were not used as the selection criteria in the present study, which may be the crucial reason that the two groups did not differ in the treatment response. Future pharmaceutical studies integrating the MII-pH results provided by the present study as the selection criteria may help to identify the true LPRD patients and then demonstrate the true drug efficacy. In addition, our study excluded patients with

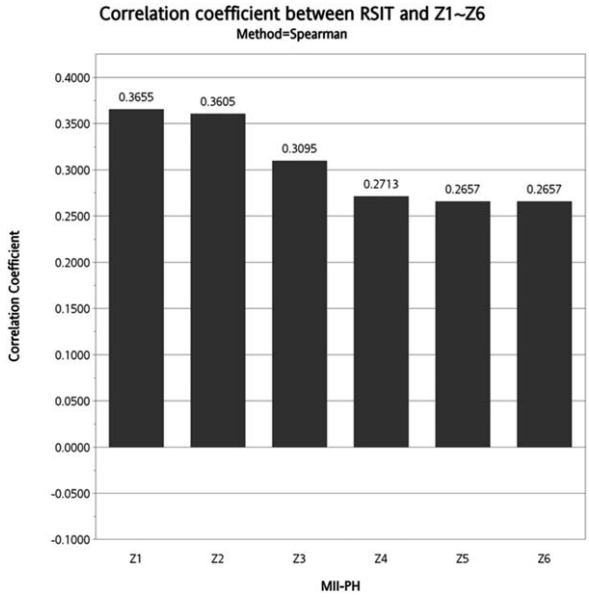

Fig. 4. Correlation between RSI score and impedance result (episode) from Z1 to Z6. A trend of increasing positive correlation from Z6 to Z1, or in other words, from the lower esophagus to the upper esophagus, was observed.
RSI = reflux symptom index; RSIT = total RSI score.

TABLE IV.
Comparison of Randomized Controlled Trials for Treatment of LPRD.

Author	Medication	Country/ Population	Education*	No. of Patients	Inclusion Criteria	Endpoint	Duration, Weeks	Result
Vaezi et al.[28]	Esomeprazole vs. placebo	U.S.A.	N	95:50	Laryngeal symptoms	Symptom resolution	16	PPI therapy of no therapeutic benefit compared with the placebo.
Reichel et al.[19]	Esomeprazole vs. placebo	Germany	N	30; 28	RSI, RFS	Total RSI, RFS	12	Reductions of total RSI and RFS were significantly higher in the treatment group than in the placebo group ($P < 0.05$).
Steward et al.[24]	Rabeprazole vs. placebo	U.S.A.	Y	21:21	Laryngeal symptoms and signs	Laryngeal symptoms and signs	8	Lifestyle modification with or without therapy significantly improves symptoms. PPI demonstrated no superiority over the placebo.
Lam et al.[20]	Rabeprazole vs. placebo	Hong Kong	N	42; 40	Laryngeal complaints, RFS	RSI, RFS	12	Significant reduction in total RSI noted in the treatment group but not the placebo group. No significant differences in RFS between two groups.
McGlashan et al.[13]	Liquid alginate suspension vs. no treatment	U.K.	Y	24; 25	RSI, RFS	RSI, RFS	8	Significant differences between the treatment and control groups observed for RSI and RFS.
Noordzij et al.[21]	Omeprazole vs. placebo	U.S.A.	N	15; 15	Laryngeal complaints, positive 24-hour dual-channel pH probe test	Symptom scores Endoscopic Laryngeal signs	8	Omeprazole failed to demonstrate superiority over the placebo, although improvements were noted in both groups.
Langevin et al.[29]	Omeprazole vs. placebo	Canada	N	14:16	pH-monitoring documented GERD, laryngeal symptoms	Laryngeal symptoms	12	Significant improvement in laryngologic symptoms with omeprazole compared with the placebo.
Wo et al.[22]	Pantoprazole vs. placebo	U.S.A.	N	20; 19	Laryngeal complaints, positive triple-sensor pH test	Laryngeal symptom score, RFS, reflux episode on pH test	12	Total RSI significantly improved in both study groups, without significant differences between them.
El-Serag et al.[30]	Lansoprazole vs. placebo	U.S.A.	N	12:10	Laryngeal symptoms and signs	Laryngeal symptoms and signs	12	lansoprazole achieved significantly better symptomatic response than did the placebo.

*Diet control and lifestyle modification.

GERD = gastroesophageal reflux disease; LPRD = laryngopharyngeal reflux disease; N = no; PPI = proton-pump inhibitor; RFS = reflux finding score; RSI = reflux symptom index; Y = yes.

erosive GERD based on transnasal esophagoscopy (GIF-XP260N; Olympus Optical Co., Tokyo, Japan) performed by experienced endoscopists and focused on the group for which promising treatment is still lacking and urgently needed. The limitation was the 8-week follow-up period, which might be insufficient considering that chronic inflammation signs in the larynx may take longer to resolve. Moreover, the modified MII-pH monitoring probe used in the present study measured the pH and impedance data confined to the upper and lower esophagus but not the pharyngeal data, as demonstrated in previous studies using the pharyngeal pH sensors.[4,25–27] Future studies incorporating the pharyngeal sensors to the present MII-pH probes may help clarify the pathophysiological changes of LPRD and associated treatment responses. Finally, placebo effect has been observed in previous studies and in the present study. Lifestyle modifications, including avoidance of oral intake within 2 hours of bedtime and lying down with blocks placed under bedposts to raise the head of the bed by at least 6 inches, and with a reduction in caffeine consumption, improve larygopharyngeal symptoms.[24] In our study, all patients were educated on lifestyle modification by study nurses; therefore, the effect of lifestyle modification alone could not be clearly demonstrated. Future studies including a third comparison group,

lifestyle modifications alone, would further delineate the impact of lifestyle modification on the treatment of LPRD.

CONCLUSION

This study showed that liquid alginate suspension (Alginos Oral Suspension, TTY Biopharm Co. Ltd.) was well tolerated by LPRD patients. It was unable to show the superiority over placebo for the treatment of LPRD, although it effectively improves symptoms scores and reflux numbers. As observed in previous studies, a great placebo effect was present. The importance of lifestyle modification could not be overlooked. With MII-pH monitoring, we demonstrated evidence of refluxate irritation to proximal esophagus that could aid in diagnosing LPRD. Future studies are required to explore the proper diagnosis and treatment of LPRD.

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Authors contributions. Wei-Chung Hsu: guarantor of the article and in charge of study design, performing the study, data acquisition, interpretation, and manuscript revision; Wen-Hsuan Tseng: manuscript draft, data acquisition; Ping-Huei Tseng: study design, performance of study, data acquisition; Jia-Feng Wu: study design, performance of study, data acquisition; Ya-Chin Hsu: data acquisition; Ting-Yi Lee: data acquisition; Yen-Hsuan Ni: study design, interpretation; Hsiu-Po Wang: study design, interpretation; and Tzu-Yu Hsiao: study design, interpretation. All authors have approved the final version of the manuscript.

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