

## ORIGINAL

# Efficacy of proton pump inhibitor in combination with rikkunshito in patients complaining of globus pharyngeus

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**Abstract :** Objective : Globus pharyngeus (GP) is a common symptom of laryngopharyngeal reflux disease (LPRD), and proton pump inhibitor (PPI) and rikkunshito, a traditional Japanese medicine having prokinetic effect improve LPRD symptoms. In the present study, we examined the efficacy of high-dose PPI in combination with rikkunshito in patients complaining of GP. Methods : 106 patients complaining of GP without any organic endoscopic findings were enrolled. Results : Patients were first administrated with high-dose PPI alone for 4 to 8 weeks and the symptom was improved in 65 patients. Among 41 patients with PPI-refractory GP, 22 patients were administrated with high-dose PPI in combination with rikkunshito, and the symptom was improved in 14 of 22 patients 4 weeks later. The average value of a modified reflux symptom index of the responders was similar to that of non-responders. Only a few patients had positive values in reflux finding scores in both groups. Conclusion : The present findings suggest the existence of a high prevalence of LPRD in patients complaining of GP. The data also suggest that gastroesophageal dysmotility is involved in GP, in addition to excessive acid reflux. The pre-therapeutic laryngopharyngeal symptoms and endoscopic findings could not predict the efficacy of the treatment for GP. *J. Med. Invest.* 63 : 227-229, August, 2016

**Keywords :** globus pharyngeus, laryngopharyngeal reflux disease, proton pump inhibitor, rikkunshito

## INTRODUCTION

Globus pharyngeus (GP), a constant or intermittent perception of a lump or a foreign body in the throat, is a common chief complaint in the otolaryngologist's office and one of the symptoms of laryngopharyngeal reflux disease (LPRD) (1). Since proton pump inhibitors (PPIs) have been accepted as the standard treatment for LPRD (2), they are proved effective in controlling GP, and it is considered that there is causal relationship between LPRD and GP. On the other hand, rikkunshito, a traditional Japanese medicine that stimulates gastrointestinal movements is used as prokinetic to treat the symptoms of gastroesophageal reflux disease (GERD) (3). It was reported that adding prokinetic agents that accelerate gastric emptying to PPIs improved symptoms of LPRD in the patients refractory to the standard PPI therapy (4).

In the present study, in order to clarify the prevalence of LPRD in patients complaining of GP, an attempt was made to examine the efficacy of the combination of rabeprazole, a PPI with rikkunshito in controlling this sensation. We first examined the efficacy of rabeprazole alone in patients with GP. In the patients who did not respond to rabeprazole, the efficacy of rabeprazole in combination with rikkunshito was then examined. Finally we examined whether the initial symptoms and endoscopic findings evaluated with a modified laryngopharyngeal reflux symptom index (RSI) (5, 6), and the pre-treatment laryngopharyngeal reflux finding scores (RFS) (7) could predict the efficacy of a PPI in combination with rikkunshito.

## PATIENTS AND METHODS

### Patients

The present study includes 106 patients (41 males and 65 females ; mean age :  $62.5 \pm 14.1$  years, range : 21-87 years old) complaining of GP. They did not have any findings as glottic/subglottic stenosis, carcinoma, leukoplakia or paradoxical vocal fold motion to examination with a video rhinolaryngoscope system equipped with a flexible fiber optic endoscope of 3.1-mm-diameter (VNL-100s, Pentax, Japan). This study was approved by the Committee for Medical Ethics of Kochi National Hospital, Kochi Red Cross Hospital and JA Kochi Hospital, and an informed consent was obtained from each patient prior to the study.

### Study design

All patients were first treated with rabeprazole alone at a dose of 20 mg/day for 4 weeks. Respondents continued to be treated with the same regimen for additional 4 weeks. Non-respondents then treated with a combination of rabeprazole at the same dose, and rikkunshito at a dose of 7.5 g/day for additional 4 weeks.

### Evaluation

The feeling of GP was evaluated by visual analogue scale (VAS) ranging from 0, no symptom to 100, presence of symptom at the first visit. VAS scores were then measured 2, 4 and 8 weeks after the treatment. The efficacy of the treatment on the symptom of GP was determined in patients with more than 50% reduction in VAS (8).

Before the treatment, the initial laryngopharyngeal symptoms and endoscopic findings were evaluated with a modified RSI and RFS. Belasfsky *et al.* developed RSI, a nine-item questionnaire for assessment of symptoms in patients with LPRD (5). It was modified to a four-item questionnaire by Oritate *et al.*, which is usually used clinically in Japan (6) (Table 1). RFS was also developed by Belasfsky

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Table 1 Laryngopharyngeal Reflux Symptom Scores

Within the last month, how did the following problems affect you?	0=no problem			5=severe problem		
	0	1	2	3	4	5
1. Clearing your throat or an annoying cough	0	1	2	3	4	5
2. Hoarseness or a problem with your voice	0	1	2	3	4	5
3. Sensation of something sticking in your throat or a lump in your throat Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
4. Heartburn, chest pain, indigestion, or stomach acid reflux	0	1	2	3	4	5

et al. to evaluate eight endoscopic findings that are commonly observed in patients with LPRD (7) (Table 2). The video-images of laryngopharynx were recorded by the video rhinolaryngoscope system with a flexible fiber optic endoscope of 3.1-mm-diameter (VNL-100s, Pentax, Japan). They were then evaluated by another otolaryngologist blind to clinical data and independent from the examiner. A total RFS score of 7 or more was considered positive.

Table 2 Reflux Finding Score (RFS)

Reflux Finding Score (RFS)	
subglottic	0=absent 2=present
Ventricular	0=partial 2=copmplete
Erythema/hyperemia	2=arytenoids only 4=diffuse
Vocal fold edema	1=mild 2=moderate 3=severe 4=polypoid
Diffuse laryngeal edema	1=mild 2=moderate 3=severe 4=obstructing
Posterior commissure hypertrophy	1=mild 2=moderate 3=severe 4=obstructing
Granuloma/granulation tissue	0=absent 2=present
Thick endolaryngeal mucus	0=absent 2=present

### Statistics

Wilcoxon signed-ranks test were used for statistical analysis with Statcel 3 and  $p < 0.05$  was considered significant.

## RESULTS

A hundred and six patients complaining of GP were first administered with rabeprazole alone at a dose of 20 mg/day. The symptom of GP improved in 45 patients (42.5%) after treatment for two weeks and in 65 patients (61.3%) for four weeks. All these patients received an additional 4-week administration of rabeprazole with a lasting improvement of their symptom. The remaining 41 patients were considered to have rabeprazole-refractory GP. Among them, 22 patients were administered rabeprazole at the same dose in combination with rikkunshito at a dose of 7.5 g/day and 19 who

refused further treatment dropped out. Four weeks after the combination therapy, the symptom of GP was improved in 14 of 22 patients. Accordingly, a total of 79 patients (74.5%) responded to either PPI therapy alone or to the combination of PPI and rikkunshito (Fig. 1).

The initial value of the modified RSI was  $5.57 \pm 4.07$  in the 79 patients who responded to either PPI therapy alone or to its combination with rikkunshito. It was similar to the RSI value of  $6.00 \pm 10.84$  in the 8 patients who were refractory to both therapies. Among the 79 patients who responded to either PPI therapy alone or to its combination with rikkunshito, the initial endoscopic findings were evaluated using RFS in 60 patients and 3 patients showed positive RFS. Among the 8 patients who did not respond to both therapies, the initial endoscopic findings were evaluated using RFS in 6 patients and a patient showed positive RFS.

## DISCUSSION

LPRD is caused by retrograde flow of acidic gastric contents via esophagus into the larynx, and PPI is generally accepted as the standard treatment for LPRD (1, 2). Moreover, it was reported that higher dose PPI therapy for longer period was more effective in patients with LPRD (9). Because GP is a common symptoms of LPRD, in the present study, PPI therapy with rabeprazole at a high dose of 20 mg/day was administrated in patients complaining of GP and 61% of them showed improvement of the symptom 4 to 8 weeks later. The finding suggests that in more than half of patients complaining of GP, the underlying cause is LPRD. This observation is indicative of a high prevalence of LPRD in patients complaining of GP.

Prokinetic agents that stimulate anterograde movements through the gastrointestinal tract is used to treat the symptoms of GERD (10). It was also reported that an addition of prokinetic agents to PPI therapy improved symptoms of LPRD in patients who were refractory to the standard PPI therapy (4). Therefore, it is suggested that in addition to excessive acid reflux, dysmotility of the esophagogastrintestinal tract is involved in the pathophysiology of LPRD. Because rikkunshito enhances gastroesophageal clearance (11), it is used for the treatment of PPI-refractory patients with both GERD and LPRD (3, 12). In the present study, 14 of 22 PPI-refractory patients complaining of GP responded to the combination therapy of high dose rabeprazole with rikkunshito. This finding suggests that gastroesophageal dysmotility is also involved in the development of GP. But, in the remaining patients who were refractory to both PPI alone and the combination therapy of PPI with rikkunshito, their GP may be caused by psychiatric disease, allergies or postnasal drip.

Several studies showed only a weak correlation between LPRD-like laryngopharyngeal symptoms, endoscopic findings, hypopharyngeal pH monitoring (13, 14). This is the reason why patients initially diagnosed as LPRD based on their symptoms and signs, often do not respond to PPI therapy. In fact, it was reported that no pretherapeutic predictors of response to high dose PPI therapy

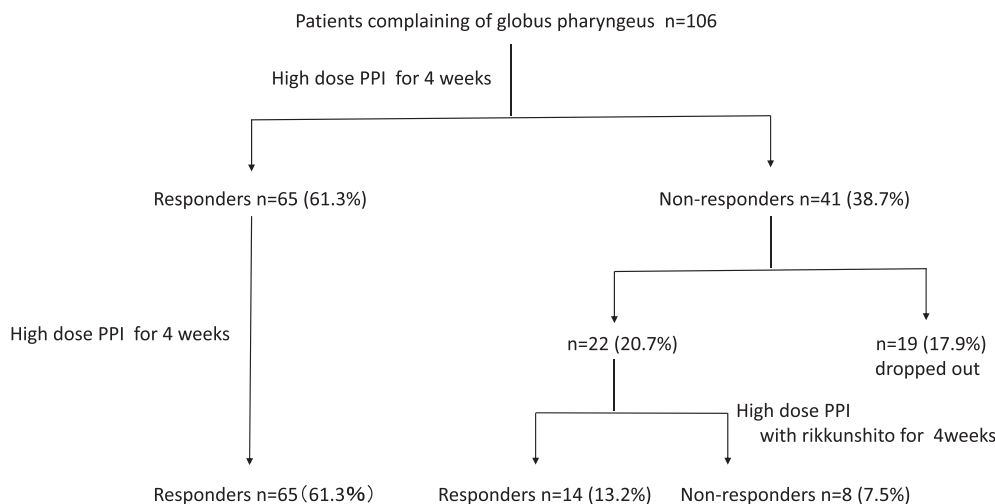


Fig. 1 : Disposition flow chart showing the number of responder or non-responder patients complaining of globus pharyngeus to PPI therapy with rabeprazole at a dose of 20 mg/day or to combination therapy of rabeprazole at a dose of 20 mg/day with rikkunshito at a dose of 7.5 g/day. PPI : proton pump inhibitor.

such as symptoms, pH monitoring or esophageal manometry was identified in patients with LPRD (9). The present study shows that in patients complaining of GP, the pretherapeutic value of a modified RSI or positive RFS also did not predict the efficacy of PPI alone or in combination with rikkunshito.

In conclusion, the present study suggests a high prevalence of LPRD in patients complaining of globus pharyngeus. Because the response to PPI therapy was unpredictable with neither laryngopharyngeal symptoms nor endoscopic findings, we propose that patients complaining of GP should be first treated with high dose PPI therapy for more than 4 weeks. We also propose that in case of PPI-refractory GP, patients should be then treated with the combination therapy of high dose PPI with rikkunshito.

## CONFLICT OF INTEREST

We declare that we have no conflicts of interest.

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