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BRIEF ARTICLE

Rikkunshito improves globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux

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Abstract

AIM: To investigate the effect of rikkunshito on laryngopharyngeal reflux (LPR) symptoms and gastric emptying in patients with proton-pump inhibitor (PPI)-refractory LPR.

METHODS: In total, 22 patients with LPR were enrolled. Following a 2-wk treatment with PPI monotherapy, PPI-refractory LPR patients were randomly divided into two treatment groups (rikkunshito alone or rikkunshito plus the PPI, lansoprazole). LPR symptoms were assessed using a visual analog scale (VAS) score, gastrointestinal symptoms were assessed using the gastrointestinal symptom rating scale (GSRS), and gastric emptying was assessed using the radio-opaque marker method prior to and 4 wk following treatments.

RESULTS: The 4-wk treatment with rikkunshito alone and with rikkunshito plus the PPI significantly decreased the globus sensation VAS scores. The VAS score for sore throat was significantly decreased following treatment with rikkunshito plus PPI but not by rikkunshito alone. Neither treatment significantly changed the GSRS scores. Rikkunshito improved delayed gastric emptying. We found a significant positive correlation between improvements in globus sensation and in gastric emptying (r^2 = 0.4582, P < 0.05).

CONCLUSION: Rikkunshito improved globus sensation in patients with PPI-refractory LPR, in part, because of stimulation of gastric emptying. Thus, rikkunshito is an effective treatment for PPI-refractory LPR.

Key words: Laryngopharyngeal reflux; Gastroesophageal reflux disease; Globus sensation; Gastric emptying; Rikkunshito

Core tip: Regarding the treatment of laryngopharyngeal reflux (LPR) symptoms such as globus sensation and a scratchy feeling, proton pump inhibitors (PPIs) are considered the mainstay. We investigated the effects of rikkunshito on globus sensation and gastric emptying in patients with PPI-refractory LPR.

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INTRODUCTION

Symptoms or complaints of globus sensation ("globus"), a "lump in the throat" feeling located between the upper edge of the sternum and the cricoid region, are common. Recently, gastroesophageal reflux disease (GERD) has been identified as a major cause of globus[1-3]. Stom-

ach acid reflux produces a number of extraesophageal symptoms in the laryngopharynx, commonly referred to as laryngopharyngeal reflux (LPR)[1,2], which include a hoarse voice, cough, a scratchy feeling in the throat, and globus[1-3]. However, the etiology of globus remains unclear. Recent studies have suggested the condition may be caused by hypertonicity in the upper esophageal sphincter (UES)[4,5]. We have demonstrated that elevated UES pressure resulting from gastroesophageal reflux without direct exposure of the hypopharynx to acid can cause the globus sensation[6].

Proton-pump inhibitors (PPIs) are considered the mainstay treatment for LPR[7]. However, LPR requires more aggressive and prolonged therapy than GERD, and PPIs do not improve extraesophageal symptoms in the laryngopharynx in all cases[7,8]. Furthermore, increasing evidence suggests that duodeno-gastroesophageal reflux may be related to several laryngeal disorders[9]. Thus, stimulation of gastric emptying or esophageal clearance in addition to inhibition of gastric acid secretion may be an effective treatment for LPR. Ezzat *et al*[10] reported that adding prokinetics, such as cisapride and itopride, to PPIs to treat LPR reduced the recurrence of symptoms. However, few studies have investigated the efficacy of prokinetics in the treatment of LPR.

Rikkunshito, a traditional Japanese medicine, is widely used to treat upper gastrointestinal symptoms such as gastroesophageal reflux[11,12] and dyspepsia[13,14]. Rikkunshito has been shown to accelerate gastric emptying in functional dyspeptic patients[13,14] and rats[15]. Furthermore, rikkunshito improved upper gastrointestinal symptoms in PPI-refractory GERD patients[12]. Thus, we investigated the effects of rikkunshito on globus sensation and gastric emptying in patients with PPI-refractory LPR.

MATERIALS AND METHODS

Subjects

In total, 22 patients with PPI-refractory LPR were enrolled at Tokyo Medical University Hospital, from March, 2007 to December, 2008. PPI-refractory LPR was defined as the presence of LPR symptoms (globus sensation, sore throat, excessive throat clearing) despite therapy using a standard dose of PPI for 2 or more weeks. Enrolled patients met the following inclusion criteria: (1) 20-76 years of age; (2) received standard-dose therapy with a PPI for at least 2 wk prior to commencement of the study; (3) a score of three or higher than the average gastrointestinal symptom rating scale (GSRS) score for acid reflux, abdominal pain, or indigestion; (4) had LPR symptoms (globus sensation, sore throat, or excessive throat clearing); and (5) provided written informed consent for study participation. Exclusion criteria were: (1) use of an antipsychotic drug, skeletal muscle relaxant, anti-ulcer drug (with the exception of a PPI), digestive drug, or antacid within 2 wk of the start of the present study; (2) patients who had globus sensation, laryngopharyngeal pain, or chronic cough due to an organic disease; (3) cervical spine disease; (4) sinusitis; (5) bronchial asthma; (6) patients with serious complications; (7) a history of drug hypersensitivity; (8) females who were pregnant or wished to become pregnant during the study or follow-up period, and lactating females; and (9) patients who were considered unsuitable by the chief investigator.

Study design

This prospective, randomized, comparative parallel group study examined the efficacy and safety of a therapeutic strategy using rikkunshito in patients with PPI-refractory LPR. The study was conducted according to ethical guidelines for clinical studies and with consideration of patients' human rights and privacy. The protocol was approved by the Institutional Review Board of Tokyo Medical University.

Study procedures

All patients were treated with a standard-dose PPI for at least 2 wk prior to obtaining written informed consent. After obtaining written informed consent, LPR symptoms and gastrointestinal symptoms were evaluated using a visual analog scale (VAS) score and the GSRS scores. Following treatment with the PPI, lansoprazole (30 mg/d, *qd*), for at least 2 wk, patients with PPI-refractory LPR who met the inclusion and none of the exclusion criteria were enrolled in the study. Enrolled patients were randomly divided into two groups using the envelope method: rikkunshito (7.5 g/d, *tid*) alone and rikkunshito (7.5 g/d, *tid*) plus a standard dose of lansoprazole (30 mg/d). We used a powdered extract of rikkunshito (Tsumura & Co., Tokyo, Japan) obtained by spray drying a hot water extract mixture of the following eight crude herbs: *Atractylodis lanceae Rhizoma* (4.0 g), *Ginseng radix* (4.0 g), *Pinelliae tuber* (4.0 g), *Hoelen* (4.0 g), *Zizyphi fructus* (2.0 g), *Aurantii nobilis pericarpium* (2.0 g), *Glycyrrhizae radix* (1.0 g), and *Zingiberis rhizoma* (0.5 g). LPR symptoms, gastrointestinal symptoms, and gastric emptying were evaluated before and after a 4-wk treatment regimen using rikkunshito or rikkunshito plus PPI.

Assessment of LPR symptoms and gastrointestinal symptoms

LPR symptoms of globus sensation, sore throat, and excessive throat clearing were assessed using a VAS scale. Gastrointestinal symptoms were assessed using the GSRS, a 15-item questionnaire used to assess general gastrointestinal symptoms[16]. Each GSRS item is rated on a seven-point Likert scale, from no discomfort (1) to very severe discomfort (7). According to a factor analysis, the 15 GSRS items are divided into five domains: abdominal pain (abdominal pain, hunger pain, and nausea), reflux syndrome (heartburn and acid regurgitation), diarrhea syndrome (diarrhea, loose stools, urgent need for defecation), indigestion syndrome (borborygmus, abdominal distension, eructation, increased flatus), and constipation syndrome (constipation, hard stools, feeling of incomplete evacuation).

Table 1 Subjects' characteristics

	Rikkunshito	Rikkunshito + PPI
Number of patients	11	11
Mean age (range)	55.9 (39-76)	56.6 (25-76)
Sex (male/female)	4/7	4/7
Smoking (yes/no)	5/6	3/8

There is no significant difference between the rikkunshito and rikkunshito + proton-pump inhibitor (PPI) groups (Fisher's exact test or Wilcoxon's rank sum test).

Measurement of gastric emptying using radio-opaque markers

Radio-opaque markers were used to evaluate gastric emptying according to the method proposed by Cremonini *et al*[17]. Briefly, 18 subjects swallowed a capsule containing 40 radio-opaque markers (Sitzmarks, Konsyl Pharmaceuticals, Fort Worth, TX, United States) before and after 4 wk treatment with rikkunshito or rikkunshito plus PPI. A plain abdominal radiograph was obtained 3 h after intake of the capsule, and the number of markers in the stomach was counted.

Adverse events, safety and tolerability

Safety and tolerability were assessed by recording all adverse events, and changes in hematological and clinical laboratory variables were measured at the screening visit. An adverse event was defined as any unfavorable or unintended sign, whether or not it was considered to be causally related to the drugs used in this study.

Compliance

Treatment compliance was defined as the percentage of the test drug used. A treatment compliance of at least 66.6% was considered acceptable.

Statistical analysis

Within-group treatment responses in were evaluated according to pre- and post-treatment VAS and GSRS scores using a paired *t* test or the Wilcoxon signed-rank test. Mean the pre- and post-treatment scores were compared between groups using the Wilcoxon rank-sum test. Between-group age and demographic factors were compared using the Wilcoxon rank-sum test, and the distributions of sex and smoking status were compared using Fisher's exact test. We calculated the correlation between change in globus sensation and change in gastric emptying values using the non-parametric Spearman's *r* correlation. *P* values < 0.05 were considered to indicate statistical significance. All data are expressed as mean ± SD.

RESULTS

Patient characteristics

We found no marked differences in age, sex, or smoking status between the groups (Table 1). No difference was found between pre- and post-PPI monotherapy for globus sensation (VAS score, 58.7 ± 25.2 and 56.7 ± 20.1, respectively) or gastrointestinal symptoms (overall GSRS score, 2.2 ± 0.9 and 2.0 ± 0.7, respectively) in the enrolled patients.

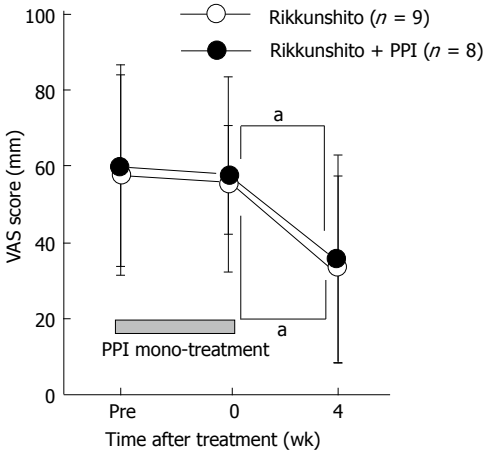

Figure 1 Effects of proton-pump inhibitor monotherapy and subsequent treatment with rikkunshito alone or rikkunshito plus proton-pump inhibitor on visual analog scale scores for globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. Proton-pump inhibitor (PPI) monotherapy was delivered for at least 2 wk prior to the experiment. Each value represents the mean ± SD. $^{a}P < 0.05$, significantly different from the visual analog scale (VAS) score at week 0 in each group (paired *t* test). No significant between-group differences were found at any time point.

Changes in LPR and gastrointestinal symptoms after rikkunshito or rikkunshito plus PPI treatment

The 4-wk treatment regimen significantly decreased the globus sensation VAS scores in both treatment groups (Figure 1). Furthermore, the post-treatment VAS scores were not significantly different between treatment groups.

The effects of rikkunshito alone or rikkunshito plus PPI treatments on sore throat and excessive throat clearing in patients with PPI-refractory LPR are shown in Table 2. The VAS scores for sore throat and excessive throat clearing did not decrease following the 2-wk PPI monotherapy. The VAS score for sore throat decreased after treatment with rikkunshito plus PPI but not after rikkunshito alone. The VAS score for excessive throat clearing did not change in either treatment group.

Neither the rikkunshito alone nor rikkunshito plus PPI treatment group showed a significant change in the overall GSRS or five subscale scores following the 4-wk treatment period (Table 3).

Changes in gastric emptying following rikkunshito alone or rikkunshito plus PPI treatment

Changes in gastric emptying following rikkunshito or rikkunshito plus PPI treatment are shown in Figure 2. The number of markers in the stomach tended to decrease after treatment with rikkunshito alone, but the difference was not statistically significant. However, the number of markers in the stomach was significantly decreased following treatment with rikkunshito plus PPI. We found no between-group difference in the number of markers in

Table 2 Effects of rikkunshito and rikkunshito plus proton-pump inhibitor treatments on sore throat and excessive throat clearing in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux

	Week	Visual analog scale score (mean ± SD)		
		A: Rikkunshito	B: Rikkunshito + PPI	*P* (A *vs* B)
Sore throat		(*n* = 4)	(*n* = 5)	
	-2	35.4 ± 21.6	44.3 ± 30.5	0.730
	0	24.0 ± 28.1	45.2 ± 28.4	0.234
	4	24.8 ± 32.8	31.8 ± 30.2[a]	0.538
Excessive throat clearing		(*n* = 4)	(*n* = 8)	
	-2	48.0 ± 12.8	40.8 ± 32.5	1.000
	0	37.2 ± 21.5	45.7 ± 25.0	0.514
	4	39.8 ± 34.9	25.7 ± 24.2	0.569

Each value represents the mean ± SD. [a]*P* < 0.05, significantly different from the visual analog scale score at week 0 in each group (paired *t* test). No significant differences were found between the rikkunshito and rikkunshito plus proton-pump inhibitor (PPI) treatments at any time point.

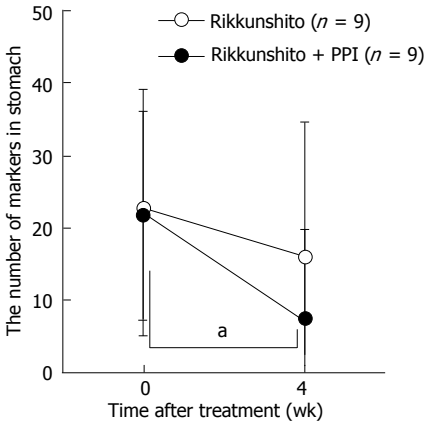

Figure 2 Effects of rikkunshito alone and rikkunshito plus proton-pump inhibitor on gastric emptying in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. Each value represents the mean ± SD. [a]*P* < 0.05, significantly different from the number of markers at week 0 in the rikkunshito + proton-pump inhibitor (PPI) group (Wilcoxon signed-rank test). We found no significant difference between treatment groups after the 4-wk treatment period (Wilcoxon rank-sum test).

the stomach following the 4-wk treatment period.

Correlation between improvement in globus sensation and improvement in gastric emptying

The correlation between improvement in globus sensation and improvement in gastric emptying is shown in Figure 3. A marked improvement in globus sensation was observed in patients with PPI-refractory LPR as gastric emptying improved. The correlation analysis revealed a significant positive correlation between the improvement in globus sensation and the improvement in gastric emptying ($r^2 = 0.4582$, $P < 0.05$).

Safety of rikkunshito

No adverse event/reaction requiring treatment occurred in any patient during the study period.

DISCUSSION

As no diagnostic gold standard is available for LPR, few studies have investigated this condition. However, previous reports indicate that 74.4% of GERD patients experience extraesophageal or atypical manifestations with prevalences of globus sensation and laryngitis/pharyngitis in GERD patients of 38.7% and 19.9%, respectively[8]. LPR requires more aggressive and prolonged therapy than GERD, and several cases in which PPIs did not improve extraesophageal symptoms in the laryngopharynx have been reported[7,8]. We examined PPI-refractory patients whose LPR symptoms of globus sensation, sore throat, or excessive throat clearing did not improve after at least 2 wk of PPI treatment. Rikkunshito has been shown to improve upper gastrointestinal symptoms in PPI-refractory GERD patients[12]; thus, we investigated the efficacy of rikkunshito in improving extraesophageal symptoms in patients with PPI-refractory LPR. Our findings indicate that a 4-wk treatment regimen of rikkunshito alone or rikkunshito plus PPI improved globus sensation in patients with PPI-refractory LPR. Two theories of LPR pathogenesis have been proposed. According to the direct impairment theory, LPR occurs when stomach acid acts directly on the hypopharynx, whereas the reflex theory holds that acid reflux in the lower esophagus causes coughing or other symptoms through a vagal reflex[1-3]. Moreover, we demonstrated previously that globus sensation can be caused by elevated upper esophageal sphincter pressure resulting from gastroesophageal reflux without direct exposure of the hypopharynx to acid[6]. Thus, acid secretion control alone is not sufficient for the treatment of LPR, which is caused by several factors. Unlike the PPIs, rikkunshito does not have an antisecretory effect[18], and, thus, may improve the globus sensation via a different mechanism. Kawahara *et al*[11] reported that rikkunshito reduced esophageal acid exposure through improved esophageal acid clearance in GERD patients. The hesperidine and atractylodin, components of rikkunshito, have been shown to improve delayed gastric emptying in L-NNA-administered rats[15,19], and rikkunshito improved upper GI symptoms *via* stimulation of gastric emptying in functional dyspeptic patients[13,14] and in patients who had undergone pylorus-preserving gastrectomy[20]. A recent study showed that rikkunshito stimulated secretion of a ghrelin, which has stimulatory effects on appetite and gastrointestinal motor activity[21,22]. Furthermore, rikkunshito and atractylodin enhance reactivity of its receptor[23]. Nahata *et al*[24] found an association between impaired ghrelin signaling and gastrointestinal motility dysfunction and demonstrated that rikkunshito restored gastrointestinal motility by improving the ghrelin response in rat GERD models. If rikkunshito reduces gastric contents, it seems reasonable that a subsequent reduction in the reflux volume may reduce acid exposure in the esophagus, pharynx, and larynx. We calculated the correlation between improved globus sensation and improved gastric emptying to investigate the association between rikkunshito-induced stimulation of gastric emptying improved globus sensation. We found

Table 3 Gastrointestinal symptom rating scale scores after 4 wk treatments of rikkunshito with or without proton-pump inhibitor

	Week	Rikkunshito (mean ± SD)	Test[1] *P* value	Rikkunshito + PPI (mean ± SD)	Test[1] *P* value	Test[2] *P* value
Overall scores	-2	2.25 ± 1.06	0.232	2.19 ± 0.73	0.375	1.000
	0	2.12 ± 0.85	-	1.96 ± 0.50	-	0.778
	4	1.83 ± 0.84	0.148	1.73 ± 0.37	0.195	0.736
Subscale scores						
Reflux syndrome	-2	2.25 ± 1.06	0.055	2.79 ± 0.91	0.170	0.369
	0	2.23 ± 1.60	-	2.45 ± 1.42	-	0.540
	4	1.94 ± 1.16	1.000	1.94 ± 0.86	0.106	0.801
Abdominal pain	-2	2.27 ± 1.29	0.168	2.33 ± 1.12	0.058	0.658
	0	1.87 ± 0.86	-	1.77 ± 0.85	-	0.914
	4	1.59 ± 0.78	0.250	1.50 ± 0.40	0.223	0.805
Indigestion syndrome	-2	2.40 ± 1.04	0.615	2.54 ± 1.29	0.551	0.844
	0	2.30 ± 1.03	-	2.20 ± 0.86	-	1.000
	4	2.17 ± 1.22	0.201	1.94 ± 0.75	0.139	0.961
Diarrhea syndrome	-2	1.77 ± 1.05	0.750	1.71 ± 0.71	1.000	0.878
	0	1.61 ± 0.68	-	1.77 ± 0.75	-	0.661
	4	1.41 ± 0.49	0.098	1.71 ± 0.68	0.866	0.345
Constipation syndrome	-2	1.77 ± 1.05	0.341	1.71 ± 0.71	0.784	0.138
	0	1.61 ± 0.68	-	1.77 ± 0.75	-	0.254
	4	1.41 ± 0.49	0.134	1.71 ± 0.68	1.000	0.883

0 week: Baseline. Test[1]: There is also no significantly different compared from gastrointestinal symptom rating scale score at week 0 (Wilcoxon's signed rank test); Test[2]: There is no significant difference between the rikkunshito with or without plus proton-pump inhibitor (PPI) treatment at each period (Wilcoxon's rank sum test).

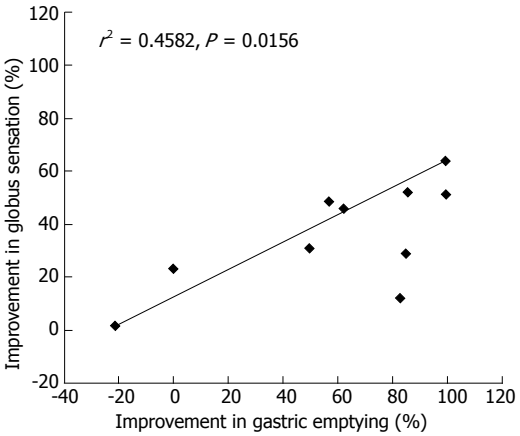

Figure 3 Correlation between improvement in globus sensation and improvement in gastric emptying. The improvement in globus sensation calculation based on pre- and post-treatment visual analog scale (VAS) scores using the following formula: Improvement (%) = [(pre-score) - (post-score)]/(post-score) × 100. Pre-score: VAS score before the start of rikkunshito or rikkunshito + proton-pump inhibitor treatment; Post-score: VAS score after the 4-wk treatment period. Improvement in gastric emptying was calculated based on the number of markers in the stomach before and after treatment.

a significant positive correlation between improved globus sensation and improved gastric emptying. Thus, the improvement in globus sensation following treatment with rikkunshito may be the result, at least in part, of improved gastric emptying. In addition to the globus sensation, patients with LPR typically experience sore throat or excessive throat clearing. Treatment with rikkunshito plus PPI, but not with rikkunshito alone, improved the tingling sensation in patients with PPI-refractory LPR in the present study, suggesting that acid may play a greater role in causing a sore throat than in globus sensation. Moreover, the LPR symptoms of globus sensation, sore throat, and excessive throat clearing may be induced by different mechanism. Johnston *et al*[25] reported absence or decreased expression of mucosal-protective proteins in laryngeal epithelial cells in 64% of patients with LPR. Thus, reducing the gastric content that passes into the laryngopharyngeal tissue *via* mucosal defenses may be an effective treatment for LPR. Rikkunshito has an effect on mucosal defenses in the gastroesophageal region, although the effect in the laryngopharynx is unclear[26,27]. In addition to the inhibitory effects of PPIs on acid, rikkunshito-induced stimulation of gastric emptying and effects on mucosal defense may contribute to the improvement in sore throat in the laryngopharynx.

The present study demonstrated that rikkunshito did not improve gastrointestinal symptoms in patients with PPI-refractory LPR assessed using the GSRS. In contrast, rikkunshito has been shown to improve upper gastrointestinal symptoms in PPI-refractory GERD patients assessed using the frequency scale for the symptoms of GERD score[12]. This discrepancy may be related to differences in the pathology and/or assessment tools used in the two studies.

In conclusion, rikkunshito treatment improved the globus sensation in patients with PPI-refractory LPR. The effect may be the result, at least in part, of the stimulation of gastric emptying. Rikkunshito plus PPI therapy may be an effective novel therapeutic strategy for PPI-refractory LPR symptoms, including globus sensation and sore throat.

COMMENTS

Background

Regarding the treatment of laryngopharyngeal reflux (LPR) symptoms such as globus sensation and a scratchy feeling, proton pump inhibitors (PPIs) are considered the mainstay. However, cases exist in which extraesophageal symp-

toms in the laryngopharynx are not improved by PPI.

Research frontiers

Recently, gastroesophageal reflux disease (GERD) has been considered a major cause of globus. However, the etiology of globus remains unclear. The authors have demonstrated that the cause of the globus sensation is elevated upper esophageal sphincter pressure, resulting from gastroesophageal reflux without direct exposure of the hypopharynx to acid.

Innovation and breakthroughs

Stimulation of gastric emptying or esophageal clearance in addition to inhibition of gastric acid secretion may also be efficacious in the treatment of LPR. It has been reported that addition of prokinetics, such as cisapride and itopride, to PPIs in the treatment of LPR reduced the recurrence of symptoms. However, there are few reports of the efficacy of prokinetics in the treatment of LPR.

Applications

Rikkunshito, a traditional Japanese medicine, has a dual action on the stomach: relaxation of the proximal stomach and contraction of the distal stomach. Recently, it was reported that rikkunshito improved upper gastrointestinal symptoms in PPI-refractory GERD patients. This was a prospective, randomized, parallel comparative study performed to examine the efficacy and safety of a therapeutic strategy using rikkunshito in patients with PPI-refractory LPR.

Peer review

The authors examined the effect of an herbal medicine "rikkunshito" on symptoms and gastric emptying in patients with LPR. The outcome of the study is interesting and important for the care of patients with PPI-refractory LPR.

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