

ORIGINAL ARTICLE

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성혜정, 정우철, 노지웅, 최수아, 강윤구, 홍소림, 조강원
가톨릭대학교 의과대학 내과학교실

Prediction of the Response to Proton Pump Inhibitor Treatment Using Wireless Ambulatory pH Monitoring in Patients with Globus Sense

Hea Jung Sung, Woo Chul Chung, Ji Woong Roh, Sooa Choi, Yoon Goo Kang, So Lim Hong and Kang Won Cho
Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background/Aims: Globus is a persistent or intermittent non-painful sensation of a lump or foreign body in the throat and a commonly encountered clinical condition. We aim to evaluate the prevalence of gastroesophageal reflux disease (GERD) and to determine the parameters for predicting the response to treatment with proton pump inhibitor (PPI) using wireless pH monitoring in patients with globus sense.

Methods: We retrospectively reviewed the medical records of 37 patients with atypical GERD symptoms. A total of 27 patients with dominant globus sense were enrolled. Endoscopic examination and 48-hour wireless esophageal pH monitoring were performed, and the patients underwent a therapeutic trial of full dose PPIs daily over a period of 4 weeks.

Results: Both typical and atypical GERD symptoms co-existed in 14 patients (51.9%, 14/27). According to ROME III criteria, 19 patients (70.4%, 19/27) were diagnosed as GERD. Twelve patients (44.4%, 12/27) were PPI responders. A significant difference in the frequency of symptom index (+) or symptom associated probability (+) was observed between the PPI responder group and the non-responder group ($p < 0.01$).

Conclusions: In patients with globus sense, 70.4% were diagnosed with GERD. Symptom index/symptom associated probability in wireless ambulatory pH monitoring was a good objective parameter for PPI responder. (*Korean J Gastroenterol* 2015;65:85-89)

Key Words: Gastroesophageal reflux; Globus; Esophageal pH monitoring

INTRODUCTION

Globus is a persistent or intermittent non-painful sensation of a lump or foreign body in the throat and a commonly encountered clinical condition. The etiology of globus appears to be multifactorial; gastroesophageal reflux disease (GERD), abnormalities of the upper esophageal sphincter, psychological disorder, structural head and neck disease,

cervical heterotopic gastric mucosa, and *Helicobacter pylori* infection. Although data are conflicting, GERD had been suggested to be a major etiology of this symptom, potentially accounting for 23-68% of globus patients.¹

Modalities used to establish the diagnosis of esophageal disease include upper endoscopy, esophageal manometry, ambulatory esophageal pH monitoring and an empirical trial with high-dose proton pump inhibitor (PPI). Due to the low

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교신저자: 정우철, 442-723, 수원시 팔달구 중부대로 93-6, 가톨릭대학교 의과대학 성빈센트병원 내과학교실

Correspondence to: Woo Chul Chung, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93-6 Jungbu-daero, Paldal-gu, Suwon 442-723, Korea. Tel: +82-31-249- 7138, Fax: +82-31-253-8898, E-mail: jwchulkr@catholic.ac.kr

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prevalence of esophageal mucosal findings, upper endoscopy has been suggested to have limited value in globus symptoms.^{2,3} Ambulatory pH monitoring is particularly helpful for detection of GERD in patients who underwent normal endoscopy and failed to respond to a therapeutic trial with PPI.⁴ However, in review of the literature, extraesophageal GERD symptoms improve more slowly than esophageal GERD symptoms following acid-suppressive therapy.⁵

To the best of our knowledge, data available for evaluation of the relationship between globus sensation and PPI treatment guided by objective parameters are limited. Parameters implicating GERD as the etiology of globus could be more helpful in predicting the response to anti-reflux therapy. The aims of the study were to evaluate the prevalence of GERD and the effectiveness of empirical treatment with PPI in patients with globus sensation and to determine the parameters for predicting the response to PPI.

SUBJECTS AND METHODS

1. Study population

Consecutive 37 patients with atypical GERD symptoms who underwent 48-hour wireless ambulatory esophageal pH monitoring at The Catholic University of Korea, St. Vincent's Hospital (Suwon, Korea) between October 2010 and October 2013 were reviewed retrospectively. Patients had undergone a comprehensive diagnostic evaluation by an oto-rhino-laryngologist in order to exclude the problems in the ear, nose, and throat. Before performing pH monitoring, symptoms were assessed by careful history taking.

The most common chief laryngeal complaints were globus (27), followed by throat discomfort or sore throat (10), chest pain (5) and hoarseness of voice (4). Globus was the dominant atypical GERD symptom, and a total of 27 patients were enrolled in this study. All patients underwent a therapeutic trial of full dose PPIs daily over a period of 4 weeks (mean 6.1 weeks, range 4 to 16 weeks) after pH monitoring. They were selected for further analysis of patient characteristics and reflux symptom association. Patients were asked to assess symptom improvement based on a 4 point Likert scale (0, no improvement; 1, mild; 2, moderate; 3, marked improvement) over a 4-week treatment period. Patients who showed moderate-marked improvement were deemed to have clinically significant improvement. Approval for this study was ob-

tained from the Catholic University of Korea Institutional Review Board (VC14 RIS10023).

2. Endoscopy and 48-hour wireless ambulatory pH monitoring

Forty-eight hour ambulatory esophageal pH monitoring was performed using the wireless pH capsule system (BRAVO pH System; Medtronic Inc., Shoreview, MN, USA) during at least 14 days off-PPI. All patients underwent endoscopy within 2 months before pH monitoring. The probe was placed at 5 cm from the squamo-columnar junction, after transoral introduction using a standard placement technique. Data were analyzed separately for each 24-hour period and the worst day was used for diagnosis.

3. Definition of GERD and parameter

GERD was classified as 1) erosive reflux disease (ERD); 2) pH + non-erosive reflux disease (NERD) with normal endoscopy and pathologic acid exposure; and (3) hypersensitive esophagus with normal endoscopy, normal distal esophageal acid exposure, and positive symptom association for acid reflux by ROME III criteria.⁶ Total 24-hour esophageal acid exposure (%) was defined as the total time at pH below 4 divided by time of monitoring. Total distal esophageal acid exposure less than 4.2% over 24 hours was considered normal. Symptom index (SI) was defined as the number of symptoms associated with reflux divided by the total number of symptoms. Symptom associated probability (SAP) was calculated as the probability that the observed distribution could occur by chance. SI and SAP were considered positive at $\geq 50\%$ and $\geq 95\%$, respectively.

4. Statistical methods

Data are shown in a descriptive manner; median (interquartile range) and number (percentage). Results in the GERD and non-GERD groups were compared using the Mann Whitney U-test. Fisher's exact test was used to determine differences between PPI response group and PPI non-response group. A p-value < 0.05 was considered statistically significant.

RESULTS

The patients consisted of 15 men (55.6%) and 12 women

(44.4%), with mean age of 53.2±10.48 years. In 14 patients, both typical (weak heartburn and/or acid regurgitation) and atypical GERD symptoms co-existed, whereas 13 patients had only atypical GERD symptoms. All patients had a grossly normal finding without erosion on endoscopic evaluation.

1. Prevalence of GERD

According to ROME III criteria, 19 patients (70.4%) who had positive results of esophageal pH monitoring NERD (n=11) and hypersensitive esophagus (n=8) were diagnosed with GERD, whereas 8 patients with negative results of esophageal pH monitoring were classified as non-GERD. The baseline characteristics of GERD and non-GERD patients are shown in Table 1. No significant differences with regard to presence of typical symptoms were observed between the GERD and non-GERD groups. Higher PPI response was observed in patients with GERD than in patients with non-GERD (10/19, 52.6% vs. 2/8, 25.0%, p=0.07).

2. Treatment response

Twelve (44.4%) patients showed marked or moderate improvement in their symptoms and were classified as PPI responders. Nine patients, however, showed mild improvement and the remaining 6 patients showed no change in their reflux symptom scores. Among PPI responders, 58.3% (7 of

12) had typical symptoms, whereas 46.7% of non-responders had typical symptoms (7 of 15). Significant differences in the frequencies of SI(+)/SAP(+) were observed between the PPI responder (10 of 12, 83.3%) and non-responder group (4 of 15, 26.7%; p < 0.01 by Fisher's exact test). Pathologic esophageal acid reflux did not differ significantly between PPI responder and non-responder (4 of 12, 33.3% vs. 7 of 15, 46.7%; p=0.48) (Table 2). The results of the PPI test correlated better with SAP than with abnormal acid exposure. The sensitivity and specificity of SI/SAP for PPI response were 83.3% and 73.3%, respectively.

DISCUSSION

To date, the effect of PPI in chronic laryngitis has been inconclusive. When the study was applied to patients with atypical symptoms, PPI therapy resulted in complete symptom resolution in 69% of the participants, 12% of the patients showed improvement of symptoms, and 20% showed minimal or no improvement.⁷ On the contrary, placebo-controlled trials and meta-analyses have failed to demonstrate any therapeutic benefit of PPIs.^{8,9} We thought that these conflicting data resulted from the non-uniformity of patients enrolled in previous studies. Laryngopharyngeal reflux (LPR) is a heterogeneous disorder with a wide spectrum of symptoms including

Table 1. Baseline Characteristics of the Enrolled Patients

Characteristic	GERD (n=19)	Non-GERD (n=8)	p-value ^a
Sex (M : F)	11 : 8	4 : 4	0.775
Age (yr)	52.8±11	53.7±10	0.440
Typical symptom (heartburn or acid regurgitation)	12 (63.2)	2 (25.0)	0.187
PPI response	10 (52.6)	2 (25.0)	0.070
Pathologic esophageal acid reflux	11 (57.9)	0	-
SI/SAP positive	14 (73.7)	0	-

Values are presented as n only, mean±SD, or n (%).

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; SI, symptom index; SAP, symptom associated probability.

^aGERD vs. non-GERD, Mann Whitney U-test.

Table 2. Factors and Improvement of Globus Symptoms Affecting Proton Pump Inhibitor (PPI) Response

Variable	PPI response(+) (n=12, 44.4%)	PPI response(-) (n=15, 55.6%)	p-value ^a
GERD	10 (83.3)	9 (60.0)	0.187
SI/SAP positive	10 (83.3)	4 (26.7)	0.003
Pathologic esophageal acid reflux	4 (33.3)	7 (46.7)	0.484
The presence of typical symptoms (heartburn, acid regurgitation)	7 (58.3)	7 (46.7)	0.547

Values are presented as n (%).

GERD, gastroesophageal reflux disease.

^aPPI response(+) vs. PPI response(-), Fisher's exact test.

throat discomfort, hoarseness of voice, cough, throat clearing and globus sensation. In addition, atypical manifestation of GERD shows different treatment response according to each symptom. In a previous study, hoarseness and throat clearing improved significantly, while throat pain, difficulty swallowing, and globus showed the same response in both treatment arms and placebo arms.¹⁰ In our result, prevalence of GERD was 70.4% of patients with globus and treatment response was 44.4%, which is a higher prevalence of GERD and a lower rate of treatment response compared with the published studies. It was noteworthy that the patients enrolled in this study had a dominant symptom of globus sense among laryngopharyngeal symptoms, so that our study had relative homogeneity.

In patients with laryngopharyngeal symptoms significant improvement is known to occur more slowly compared to those with esophageal symptoms following acid suppression therapy. It is widely accepted that extraesophageal GERD symptoms require more aggressive and prolonged therapy than typical GERD symptom.^{5,11,12} The precise pathophysiology of globus remains unclear. Several mechanisms have been proposed to explain the association between GERD and the globus sensation in previous reports: 1) direct irritation and inflammation of the laryngopharynx by gastric acid; 2) elevated UES pressure triggered by gastroesophageal reflux; acidification or distention of the distal esophagus.^{1,13,14} Thus, the incidence of heart burn or regurgitation in combination with a globus sensation might be much higher. In this study, we found that weak heartburn or regurgitation was more common in the GERD group than in the non-GERD group. The presence of classical reflux symptoms might be a risk factor for predicting GERD in patients with globus.

Most patients with LPR did not have erosive esophagitis endoscopically, nor show correlation with the presence of histological esophagitis. Endoscopy cannot be the method of choice for diagnosing LPR by itself.^{2,3} The pH monitoring study is a useful technique in confirming reflux. Pathological esophageal acid reflux (PEAR) suggests the presence of GERD, and correlation between reflux events and globus sensation is important to attributing GERD as the etiology of globus. SI/SAP is the most commonly used test for assessing reflux symptom association. In our results, PEAR was found in 40.7% and positive SI/SAP in 51.9%. Several studies reported that positive relationship between symptoms and re-

flux parameters such as positive SI and positive SAP could predict a good symptomatic response to medical as well as surgical therapy in GERD.^{15,16} In this study, marked symptomatic improvement was observed in 71.4% of patients having abnormal SI/SAP, suggesting that positive association of symptom and treatment response could be applied in patients with globus sensation. We expect that the remaining patients who have positive SI/SAP from pH monitoring would have relief with prolonged PPI treatments.

There were potential limitations of this study. First, due to the retrospective data, we could not account for all of the factors (e.g., smoking, alcohol, obesity) involved in symptom production of globus. However, in review of data from previous studies, there was no definite association with smoking, alcohol, or body mass index in globus sensation.⁴ Second, atypical reflux symptoms usually persist continuously. It is difficult for patients to mark a reflux event.¹⁷ In this study, we asked the patients to mark the time when they perceived aggravation of symptoms during pH monitoring. The symptom index was regarded as positive if an event was marked within 5 minutes after the onset of a reflux episode, and we tried to overcome the limitation.

To the best of our knowledge, this is the first study to investigate objective parameters for prediction of treatment response of PPI in patients with globus symptoms by means of 48-hour ambulatory pH monitoring and endoscopy. Our study showed that esophageal pH monitoring could discriminate patients as PPI responder and non-responder, and that symptom-reflux association could be a good predictor of PPI response in patients with globus.

In conclusion, SI/SAP in 48-hour ambulatory pH monitoring is a good objective parameter for positive PPI response in patients who present with globus symptoms. By exclusion of all other factors, along with pH monitoring, patients with globus will benefit from potent and prolonged PPI therapy.

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