

TREATMENT OF GASTROESOPHAGEAL REFLUX-RELATED COUGH WITH PROTON PUMP INHIBITORS AND PROKINETIC AGENTS

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ABSTRACT

Introduction: Gastroesophageal reflux-related cough cannot be well-treated with proton pump inhibitor (PPI) alone. This study aims to evaluate the differences of the curative effect of two drug on treating gastroesophageal reflux-related cough.

Case presentation: A randomized controlled trial design was used. Ninety patients with repeated cough, accompanying with heartburn, retrosternal pain, acid regurgitation and food regurgitation, were randomly assigned into two groups: experimental group and control group. These patients were orally given 20 mg of omeprazole bid or 20 mg of omeprazole bid + 5 mg of mosapride citrate dispersible tablets tid, with a course of treatment of 12 weeks. Then, the cough symptom score and reflux disease questionnaire (RDQ) score were determined. There were significant differences in cough symptoms scores and RDQ scores between the experimental group and control group before and after treatment ($P < 0.05$). The cough symptom scores in the experimental group decreased by 1.29 ± 0.19 , while the decreased value in the control group was 0.63 ± 0.38 , and the difference between these two groups was statistically significant ($P = 0.038$). The RDQ scores in the control group decreased by 3.55 ± 0.39 , while the decreased value in the experimental group was 6.22 ± 0.90 , and the difference between these groups was statistically significant ($P = 0.027$).

Conclusion: The results of the present study showed that the scores of these two groups after treatment significantly improved, when compared to those before treatment. These findings indicate that PPI combined with prokinetic agents has a good effect on gastroesophageal reflux-related cough. This study confirmed the effectiveness and worth popularizing in the treatment of acid-suppressing and gastrointestinal motility drugs. However, in terms of mental factors, sleep disorders, lifestyle and many other factors, it has not been further explored and involved, and needs other research.

Keywords: cough, gastroesophageal reflux disease, proton pump inhibitors, prokinetic agents, difference.

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Introduction

Gastroesophageal reflux disease (GERD) has become a common and even extremely harmful chronic disease^(1,2) and it refers to a series of symptoms of end-organ effects and (or) complications caused by the reflux of stomach contents in the esophagus, oral cavity (including the throat), and (or) lungs. Chronic cough is a common reason for the patients seeking treatment, and the common causes include post-nasal drip syndrome, cough variant asthma, gastroesophageal reflux cough (GERC), and eosinophilic bronchitis⁽³⁾.

Gastroesophageal reflux cough is a common cause of chronic cough. It is a special type of gastroesophageal reflux due to clinical syndromes, such as the reflux of gastric acid to the esophagus and cough induction⁽⁴⁾. The symptoms of chest distress, belching and acid regurgitation in patients with gastroesophageal reflux cough are milder, cough is more prominent, and it is easy to be confused with other respiratory diseases in clinical practice⁽⁵⁾. Cough mostly occurs in the day and in the erect position and it is related to eating. Dry cough or cough is accompanied with small amounts of white sticky sputum. The pathogenesis of GERC is complex, and

treatment is delayed due to misdiagnosis caused by the lack of typical reflux symptoms. The long-term clinical use of acid-making drugs, especially proton pump inhibitors (PPI), is not effective for treating GERC. The present study uses PPI or PPI combined with prokinetic agents to treat the patients with recurrent cough, accompanying with typical gastroesophageal reflux symptoms and clinically suspected gastroesophageal reflux-related cough, aiming to evaluate the efficacy of these two drug treatments, and improve the clinical treatment effect.

Materials and methods

Research objects

Patients with recurrent cough, accompanying with typical gastroesophageal reflux symptoms, were selected from patients in the Respiratory Medicine Department of Shanghai Pudan Hospital in Pudong New Area from January 2013 to September 2013 and the patients in the General Department of Shanghai Yingbo Community Health Service Center from October 2015 to December 2017.

Inclusion criteria:

(1) patients who complied with the GERD diagnostic criteria in the Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease (2013) issued by the American College of Gastroenterology (6);

(2) patients whose esophageal manometry indicates esophageal motor dysfunction; patients accompanying with reflux, heartburn, retrosternal pain and other symptoms,

(3) patients whose course of disease was more than two months.

Selection criteria:

(1) the course of cough was longer than eight weeks, and the patients have undergone anti-infection, antitussive, expectorant and bronchospasm relieving treatments, while the cough symptoms did not disappear or were not alleviated;

(2) the chest X-ray, lung CT and five sense organ examination revealed no abnormal findings;

(3) patients with typical gastroesophageal reflux symptoms, such as heartburn, retrosternal pain, acid regurgitation, and food regurgitation, and the reflux Disease Questionnaire (RDQ) score was ≥ 12 .

Exclusion criteria:

(1) patients with heart-lung, liver and kidney insufficiency, diabetes and other chronic diseases;

(2) pregnant or lactating women;

(3) patients who received acid-making drugs or

prokinetic agents within one week before the start of the test; (4) patients who were allergic to the test drug.

The difference in gender, age and disease course of these two groups of patients was not statistically significant ($P > 0.05$). The patients were prohibited to eat high-fat, spicy food and alcohol during the treatment period. These selected patients were randomly assigned into the two groups: experimental group and control group. Furthermore, these patients received PPI combined with prokinetic agents, or PPI treatment, respectively. The included patients were informed of the study and agreed to the test plan. This study obtained informed consent from patients, and approved by the Ethics Committee of Shanghai East Hospital ((2019) YYS No. 007).

Research medication

The control group was given 20 mg of omeprazole enteric-coated capsules bid (Brand Name: Omeprazole, 20 mg/grain; Changzhou Si Yao Pharmaceuticals Co., Ltd.; National Medicine Permission No. H10950086), which was orally taken before meals. The experimental group was given 10 mg of mosapride citrate dispersible tablets tid (Brand Name: Xinluna 5 mg/tablet; Chengdu Kanghong Pharmaceutical Group Co., Ltd.; National Medicine Permission No. H20031110) on the basis of the control group, which were taken orally before meals. The course of treatment of the both groups was 12 weeks.

Research method

The present study adopted a prospective, randomized controlled trial design. The gastroscopy was performed before treatment, and reflux esophagitis (RE) was graded according to the Los Angeles standard. Cough and gastroesophageal reflux symptoms were scored before and after treatment.

Cough symptom score

Daytime cough: 5 points, frequent coughs and inability to carry out daily activities; 4 points, frequent coughs with a certain impact on daily activities; 3 points, frequent coughs, but no impact on daily activities; 2 points, coughs for more than two times; 1 point, cough for 1-2 times; 0 point, no cough. *Nighttime cough:* 5 points, severe cough and inability to sleep; 4 points, frequent coughs at night; 3 points, frequent waking up at night caused by cough; 2 points, waking up early or waking up caused by cough; 1 point, cough that occurs only when awake or asleep; 0 point, no cough. The aver-

age score for daytime and nighttime cough was the cough symptom score⁽⁷⁾.

Gastroesophageal reflux symptom score

Under the guidance of a digestive physician, the patient carefully and completely filled out the RDQ⁽⁸⁾. According to the four symptoms of heartburn, retrosternal pain, acid regurgitation and food regurgitation, the scores were respectively scored. Seizure frequency: 0 point, no symptoms; 1 point, symptoms occurrence for <1 day/week; 2 points, symptoms occurrence for 1 day/week; 3 points, symptoms occurrence for 2-3 days/week; 4 points, symptoms occurrence for 4-5 days/week; 5 points, symptoms occurrence for 6-7 days/week. Severity: 1 point, the symptoms were not obvious, and found under doctor's warning; 3 points, the symptoms were obvious, and affected daily life and occasional medication; 5 points, the symptoms were very obvious and affected daily life, and there was a need to take medicine for a long time; symptoms between 1 point and 3 points were counted as 2 points; symptoms between 3 points and 5 points were counted as 4 points. The RDQ score is the sum of the frequency and severity score of four symptoms. A score ≥ 12 is helpful for the diagnosis of GERD.

Statistical analysis

SPSS 13.0 statistical software was used. The cough symptom score and RDQ score of the experimental group and control group were compared by independent sample t-test for inter-group comparisons and paired sample t-test for intra-group comparisons. $P < 0.05$ was statistically significant.

Results

General situation

A total of 90 patients with gastroesophageal reflux-related cough were included in the present study. Among these patients, 53 patients were male and 37 patients were female. Among the accompanying gastroesophageal reflux symptoms, 40 patients mainly suffered from heartburn, 23 patients suffered from retrosternal pain, 13 patients suffered from acid regurgitation, and 14 patients suffered from food regurgitation.

Furthermore, a total of 41 patients were diagnosed as RE under endoscopy, in which 27 patients were Grade A, 14 patients were Grade B, and none of the patients were Grade C or D. The other 49 patients were diagnosed as non-erosive reflux disease

(NERD), according to endoscopic findings and the RDQ score.

The control group comprised of 29 male patients and 16 female patients. The average age was 39.9 ± 1.5 years old, and the course of disease was 12.0 ± 0.2 weeks. The main symptoms of heartburn, retrosternal pain, acid regurgitation and food regurgitation were found in 17, 13, 9 and 6 patients, respectively. Furthermore, there were 27 patients with NERD, 12 patients with RE Class A, and 6 patients with RE Class B. In the experimental group, there were 24 male patients and 21 female patients. The average age of these patients was 40.6 ± 0.9 years old, and the course of disease was 12.0 ± 0.2 weeks. The main symptoms of heartburn, retrosternal pain, acid regurgitation and food regurgitation were found in 23, 10, 4 and 8 patients, respectively. Furthermore, 22 patients had NERD, 15 patients had RE Class A, and eight patients had RE Class B.

Groups	n	Dry Cough	With Sputum	Cough Related to Eating	Daytime Cough	Nighttime Cough	No Difference in the Day and Night
Control Group	45	33	9	26	28	17	0
Test Group	45	30	12	34	26	18	1
Total	90	63	21	60	54	35	1
Case difference	0	3	3	8	2	1	1
Ratio to total (%)	0	4.44	14.29	13.33	3.7	2.86	100

Table 1: The distribution of cough characteristics in the test group and control group (n).

Table 1 showed the distribution of cough properties in the experimental group and control group. The difference in gender composition, age, course of disease, cough symptom score and RDQ score before treatment in these two groups was not statistically significant. All patients completed 12 weeks of treatment and symptom assessments before and after treatment, and there were no cases of withdrawal or missed visits.

Cough symptoms

After treatment, the cough symptom scores of patients in these two groups were significantly lower than the scores before treatment. Furthermore, the decreased value in the control group was 0.63 ± 0.38 , while the decreased value in the experimental group was 1.29 ± 0.19 . The difference between the two groups has statistical significance ($P = 0.038$, Table 2). According to different cough characteristics, the scores of these two groups after treatment significantly improved, when compared to those before treatment (Table 3).

Groups		n	Cough Symptom Scores	RDQ Scores
Control Group	Before Treatment	45	2.20±0.34	14.38±0.52
	After Treatment	45	1.57±0.02	10.91±0.13
Test Group	Before Treatment	45	2.88±0.17	15.26±0.78
	After Treatment	45	1.66±0.07	9.01±0.90

Table 2: Comparison of cough symptom scores and RDQ scores between the test group and control group before and after treatment ($\bar{x} \pm s$).

Groups		n	Dry Cough	With Sputum	Cough Related to Eating	Daytime Cough	Nighttime Cough	No Difference in the Day and Night
Control Group	Before Treatment	45	3.01±0.30	2.95±0.29	1.17±0.43	3.19±0.26	1.21±0.91	-
	After Treatment	45	2.21±0.41	2.04±0.12	0.61±0.22	2.01±0.85	0.19±0.23	-
Test Group	Before Treatment	45	3.87±0.71	3.83±0.16	2.71±0.07	3.27±0.69	1.76±0.75	3
	After Treatment	45	1.15±0.30	2.38±0.57	1.70±0.26	1.18±0.22	0.84±0.13	1

Table 3: Comparison of cough symptom scores before and after treatment in patients with cough of different nature ($\bar{x} \pm s$).

Gastroesophageal reflux symptoms

After treatment, the RDQ scores of these two groups were significantly lower than those before treatment. Furthermore, the decreased value in the control group was 3.55 ± 0.39 , while the decreased value in the experimental group was 6.22 ± 0.90 , and the difference between these groups was statistically significant ($P=0.027$, Table 2). According to different GERD types, the scores of these two groups after treatment significantly improved, compared to those before treatment (Table 4).

Groups	Gender (M/F)	Average age	Heartburn	Retrosternal pain	Acid regurgitation	Food regurgitation	NERD	RE	
								Grade A	Grade B
Control Group	29/16	39.9±1.5	17	13	9	6	27	12	6
Test Group	24/21	40.6±0.9	23	10	4	8	22	15	8
Total	53/37	-	40	23	13	14	49	27	14

Table 4: The gastroesophageal reflux symptoms of the two groups.

Security

Patients in the experimental group and control group well-tolerated the treatment drugs, and no adverse events occurred during the treatment.

Discussion

GERD refers to a disease, in which the reflux of stomach contents into the esophagus causes discomfort and (or) complications, including NERD, RE and Barrett esophagus^(8,9). Up to 75% of gastroesophageal reflux-related cough patients lack typical gastroesophageal reflux symptoms⁽¹⁰⁾, and some GERD patients even have chronic cough as their only clinical manifestation. According to the main types of gastroesophageal reflux causing cough, GERD can be divided into two types: acid type and non-acid type⁽¹¹⁾. Present studies have considered the

following possible mechanisms of GERD in causing chronic cough: the minor aspiration of reflux and stimulation of cough can both cause airway mucosal epithelial damage, which in turn may lead to neutrophil granulocyte inflammatory reactions. However, the inflammatory reaction may aggravate airway mucosa inflammation and cough reflex, and cough may also induce gastroesophageal reflux, resulting in a vicious cycle of reflux-cough-inflammation⁽¹²⁾.

According to the "Guidelines for the Diagnosis and Treatment of Cough" formulated by the Chinese Thoracic Society, the relevant diagnostic criteria for gastroesophageal reflux cough were as follows⁽¹³⁾: (1) patients with chronic cough, and the course of disease was more than eight weeks, and the Chest X-ray revealed no significant lesions; (2) patients with sternal burning sensation, belching, acid regurgitation and other symptoms; (3) patients with the main cause of cough of eating; (4) patients whose gastroscopy examination revealed changed in reflux esophagitis; (5) patients with post-nasal drip syndrome, cough variant asthma and other diseases were excluded; (6) after receiving anti-reflux treatment, the cough of the patient was obviously relieved or disappeared.

The 24-hour esophageal PH is < four-time percentage $\geq 4\%$, indicating esophageal acid exposure. In a small number of patients with combined or mainly non-acid reflux (e.g. bile reflux), such as GERD caused by duodenal content reflux, the 24-hour PH monitoring can be negative. Hence, 24-hour PH monitoring can no longer be used as the "gold" standard for diagnosing GERD (14). Therefore, the diagnosis of gastroesophageal reflux-related cough based on relevant clinical data can also overcome the limitations of medical unit conditions.

In this group, 60.0% (54 patients) of the patients had daytime cough, 70.0% (63 patients) had dry cough, and 66.7% (60 patients) had cough related to eating. Studies have shown that the main mechanism of gastroesophageal reflux in both upright and supine positions is transient lower esophageal sphincter relaxation (tLESR) (15). LES pressure reduction and tLESR weaken the anti-reflux barrier, and trace gastric acid or other gastric contents in the reflux are mistakenly inhaled into the airway, stimulating the acid-sensitive receptors in the airway mucosa to excite the vagus nerve, resulting in increased airway sensitivity, and bronchospasm and cough.

Eating can directly reduce LES pressure or cause tLESR through stomach distension, while tLESR and esophageal-bronchial reflex can be

suppressed during sleep⁽¹⁶⁾. The above mechanism explains the clinical characteristics of gastroesophageal reflux-related cough mainly in daytime and upright positions, and is correlated to eating, which is consistent with the distribution of cough characteristics in this group of patients.

According to the Asia - Pacific consensus on GERD treatment (updated version), patients with chronic cough and typical GERD symptoms should be treated twice daily with PPI⁽¹⁷⁾. PPI omeprazole can specifically inhibit the H⁺-K⁺-ATP enzyme, which is the last link of acid secretion in the parietal cells. Hence, H⁺ cannot be transported from parietal cells to the outside of the gastric cavity to form gastric acid. This inhibits acid and prevents gastric acid from stimulating the esophageal and tracheal mucosa. Oribe et al.⁽¹⁸⁾ found that in addition to relieving gastroesophageal reflux-related cough by inhibiting acid secretion, PPI may also directly inhibit the increase in antigen-induced cough reflex sensitivity. This is also the possible reason for PPI having an obvious curative effect on GERD.

Many studies have pointed out that GERD patients have peristaltic disorder in the lower part of the body, with an incidence ranging from 48.3% to 84.1%^(19,20). According to XIE and other reports⁽²¹⁾, the esophagogastric junction contractile integral (EGJ-CI), which evaluates the esophagogastric junction contractile function and reflects the anti-reflux barrier function, in GERD patients were significantly lower than in the normal control group, while EGJ-CI in patients with esophageal hiatus hernia was lower. In addition, the main dynamic obstacles at the esophagogastric junction were divided into two: LES pressure reduction and transient lower esophageal sphincter relaxation (TLESR). The study revealed that the LES length of GERD patients was shorter than that of non-GERD⁽²²⁾, and LES resting pressure was lower than that of non-GERD, which may be one of the important factors leading to the recurrence of GERD after treatment. JIANG et al.⁽²³⁾ reported that ineffective esophageal motility (IEM) is closely correlated to esophageal acid exposure, abnormal weak acid reflux and long-term acid reflux, and it plays an important role in the pathological mechanism of refractory gastroesophageal reflux disease.

Different scholars have also proven that with the increase in the severity of the disease, its low-amplitude contraction was also more common. Some of GERD's effects on traditional anti-reflux therapy were not good, and some studies indicated that its

effective rate was 39.6% (21/53)-42.9% (12/28)⁽²⁴⁾.

Over the past 10 years, non-acid and/or weak acid reflux represents a special nosogeny, explaining the etiology of the treatment of patients with invalid GERD in approximately 90% PPI⁽²⁵⁾. The clinical treatment of GERD was based on anti-reflux. The study pointed out that the curative effect of the treatment of esophageal motor dysfunction, with the use of anti-acid drugs on the base of the prokinetic agents, was significantly better than the simple acid-inhibiting treatment⁽²⁶⁾.

Mosapride citrate dispersible tablets are a selective 5-hydroxytryptamine 4 receptor agonist, which can effectively excite the 5-hydroxytryptamine 4 receptor agonist in the nervous plexus and intercalary neuron from the cholinergic muscle of the gastrointestinal tract. It is beneficial in enhancing the peristaltic function of the esophagus and gastrointestinal tract, releasing acetylcholine, promoting the emptying of the contents of the upper gastrointestinal tract, shortening the exposure time of esophageal acid, further improving the motility of the gastrointestinal tract, and coordinating the function of upper gastrointestinal tract transportation, and this will not affect the secretion of gastric acid^(27,28).

Mosapride citrate increases the pressure of the lower esophageal sphincter, strengthens esophageal peristalsis and accelerates gastric emptying, which is beneficial to prevent the reflux of gastric contents, and thereby effectively reducing reflux time and the time for GERD patients, and preventing toxic side effects on the extrapyramidal system caused by this type of receptor block⁽²⁹⁾. In the treatment of reflux esophagitis, mosapride can promote the release of acetylcholine, stimulate the gastrointestinal tract of patients, help to restore the gastric motility of patients to normal, and further improve the relevant clinical manifestations of patients^(30,31).

After 12 weeks of treatment, in the experimental group (PPI combined with prokinetic agents) and control group (PPI alone), the overall average score, cough nature, cough symptom score (group difference is statistically significant: $P=0.038$) and RDQ scores in the present study were significantly lower than those before treatment (group difference is statistically significant: $P=0.027$), showing that these two schemes had a good affect in relieving GERD clinical symptoms. Furthermore, group difference has statistical significance, and it is proven that the effect PPI combined with prokinetic agents is more significant, and should be widely used in clinic. In a word, medical units that do not need to rely entirely on esoph-

ageal 24-hour pH monitoring and other inspection methods can combine this with symptom association probability (SAP) between reflux and cough, observe the relationship between cough onset and time, as well as posture and food intake, and provide PPI treatment combined with prokinetic agents to patients with gastroesophageal reflux-related cough, in order to relieve clinical symptoms as soon as possible⁽³²⁾.

Conclusion

The high incidence of gastroesophageal reflux disease and the multiple evolution of clinical symptoms are due to a variety of pathogenic factors. Accelerated rhythm of life, increased mental pressure, esophageal hypersensitivity, lower esophageal sphincter relaxation and induced acid reflux. In addition, sleep disorder causes autonomic nervous dysfunction, which decreases vagal nerve activity, increases sympathetic nerve activity and abnormal brain-intestinal axis function, increases esophageal sensitivity, decreases esophageal acid tolerance and increases the incidence of gastroesophageal acid reflux. This study confirmed the effectiveness and worth popularizing in the treatment of acid-suppressing and gastrointestinal motility drugs. However, in terms of mental factors, sleep disorders, lifestyle and many other factors, it has not been further explored and involved, and needs other research.

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