

"SLOW": an effective strategy for treating suspected gastroesophageal reflux cough

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Research article

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Abstract

Background Patients with gastroesophageal reflux cough were always given drugs treatment to relieve symptoms. But most of these patients were found to have unhealthy dietary habits. To develop a new strategy to assist drugs therapy, the study was conducted.

Objective To explore the clinical significance of “SLOW” strategy in the treatment of suspected gastroesophageal reflux cough.

Methods A prospective study was conducted to select 122 patients diagnosed with chronic cough and suspected with gastroesophageal reflux cough who were admitted to Qilu hospital of Shandong University (Qingdao) from January 2015 to December 2017. Patients were randomly divided into experimental group (n=72) and control group (n=50). The experimental group was given omeprazole 20mg bid po + domperidone 10mg tid po + “SLOW” strategy, while the control group was only given omeprazole 20mg bid po + domperidone 10mg tid po. Hsu cough scoring system was used to analyze and evaluate the efficacy after 4 weeks of treatment.

Results Among the 72 patients in the experimental group, 56 were effective (77.8 %), of which 44 cases were completely alleviated (61.1 %). Of the 50 control group patients, 27 were effective (54.0 %), of which 19 were in complete remission (38.0 %). The Hsu cough score showed a significant decrease in the scores of the experimental group, which was statistically significant compared with that of the control group ($P<0.05$).

Conclusion The “SLOW” strategy, as a supplement to drug therapy, can increase the efficiency of treatment and significantly reduce the Hsu cough score.

Introduction

Chronic cough is a common disease among respiratory outpatients, and the incidence rate among adults is as high as 10–40 %, among which gastroesophageal reflux cough accounts for about 20 % [1]. The members of this study found an obvious phenomenon in their daily work. Patients who experience chronic cough often have unhealthy eating habits, which include eating fast and much, preference for sugary desserts, liquid food, carbonated drinks and so on. These eating habits promote acid reflux of the stomach contents, which not only leads to gastroesophageal reflux cough (GERC), but also exacerbates chronic cough caused by other reasons. Currently, diagnosis of GERC requires 24-hour esophageal pH and multichannel impedance monitoring, which is rejected by many outpatients due to inconvenience and economic reasons. Clinical treatment of GERC mainly relies on drugs to inhibit gastric acid secretion and promote gastric peristalsis, while dietary guidance is relatively simple. Therefore, from the perspective of dietary habits, this study summarized the “SLOW” strategy, which means, to prevent chronic cough in patients with the above-mentioned dietary habits. For the “SLOW” strategy, “S” refers to slow and relaxed, which requires eating slowly and relaxedly. “L” specifies no liquid and sweet food. “O” indicates no overeating, especially during dinner, to ensure stomach is empty before going to bed. “W”

means no water while eating which requires the participants to drink water at least 30 minutes before each meal or one to two hours after meals.

Methods

1 Subjects

Select patients diagnosed with chronic cough in Qilu Hospital of Shandong University (Qingdao) from January 2015 to December 2017, and the cause of chronic cough is suspected to be gastroesophageal reflux cough.

1.1 Inclusion criteria

(1). The duration of cough was more than 8 weeks, and gastroesophageal reflux cough was suspected clinically; (2). Chest radiography showed no active or organic disease; (3). Cough SUPPRESSANTS and antibiotics were not effective; (4). Non-smokers or patients who have quit smoking for 2 or more years; (5). No history of dust exposure, no history of heart disease; (6). No history of upper respiratory tract infection within two months; (7). No application history of angiotensin converting enzyme inhibitors. In addition, participants need to have at least one of the following four eating habits: (1). Food needs to be consumed within 7 minutes, or less; (2). Preference for liquid foods, such as porridges, noodles, etc. or food containing more than 250ml liquid per meal, or having cooked rice soaked in water or soup, or have cookies soaked in milk before serving. (3). Participants with an inclination towards sweeter foods, such as desserts, sugar, sugary beverages, sweet potato, etc; (4). Overeating, especially at night, accounts for more than 50 % of daily intake.

1.2 Exclusion criteria

(1). Chest radiography suggests active or organic lesions; (2). New signs and symptoms of infection appeared during the study period; (3). The combination of cardiovascular and cerebrovascular emergencies; (4). Unable to cooperate with researchers for other reasons.

2 Therapeutic schedule

The enrolled patients were randomly divided into the experimental group (n = 72) and the control group (n = 50). The experimental group was given omeprazole 20mg bid po + domperidone 10mg tid po + "SLOW" strategy. The control group was only given omeprazole 20mg bid po + domperidone 10mg tid po. Weekly follow-up calls were conducted to observe the effects of treatment on the symptoms of the chronic cough. The study was approved by the ethics committee of Qilu Hospital of Shandong University (Qingdao) and we have obtained the consent from the patients.

3 Observation indicators

3.1 Hsu's 6-level scoring system was used for cough scoring [2], and 0–5 points were scored according to the frequency of cough. The details are shown in table 1.

3.2 Efficacy criteria

The criteria for treatment effectiveness are classified into four categories: (1). *complete remission*: cough symptoms disappeared; (2). *markedly improved*: cough symptom scores decreased by at least two points; (3). *improved*: cough symptom scores decreased by 1 point; (4). *invalid*: no change in score, or cough symptoms aggravate. Cough scores were given at the time of first visit, followed up weekly by telephone and cough scores were recorded.

3.3 Analysis of other interfering factors

In order to further verify that the treatment effect of patients in the experimental group is related to the treatment strategy rather than other factors, including age, gender, cough duration and cough symptom score, etc. We conducted a multi-factor analysis of patients in the experimental group, especially those with complete remission of symptoms.

4 Statistical methods

The effective rate and complete response rate were expressed as percentages. Age and course of disease were tested by t test while chi-square (χ^2) test was used for sex. Non-parametric test (rank sum test) was used for the comparison between groups before and after treatment. Non-parametric test (two relevant samples) was used for intra-group comparison before and after treatment.

Results

5.1 Case information

A total of 122 patients were selected, randomly divided into the experimental group ($n = 72$) and the control group ($n = 50$). The mean age of the experimental group was 54.51 ± 17.05 while control group was 56.38 ± 14.88 . The mean course of disease in the experimental group was 61.44 ± 38.45 months, while that in the control group was 56.72 ± 31.65 months. There were 33 males (45.8 %) and 39 females (54.2 %) in the experimental group with 24 males (48.0 %) and 26 females (52.0 %) in the control group. There was no statistically significant difference in the age, course of disease and gender between the two groups ($P > 0.05$). The details are shown in table 2.

5.2 Therapeutic efficiency and complete remission rate

After 4 weeks of treatment, 56 cases (77.8 %) in the experimental group showed improvement, of which 44 cases (61.1 %) were completely alleviated. In the control group, 27 cases (54 %) were effective, of which 19 cases (38 %) were completely relieved. The details are shown in table 3.

5.3 Changes in Hsu cough score

Before treatment there was no significant difference in Hsu cough scores between the experimental group and the control group ($P > 0.05$). After 4 weeks of treatment, the Hsu cough scores decreased significantly both in the control and experimental group ($P < 0.01$). However, the difference in Hsu cough scores between the experimental group and the control group was also statistically significant ($P < 0.05$), which was shown in table 4.

5.4 Factors influencing turnaround time

The turnaround time is not related to various factors such as age, gender, cough duration time, and cough symptom scores.

5.5 Factors influencing cure time

We checked the 44 patients whose cough was completely eliminated, and we revealed that the cure time is not related to age, gender, cough duration time and cough symptom score.

Discussion

Both esophagus and trachea originate from fetal foregut in the process of tissue development, and their autonomic nerves have homology. Reflux and acidic gas stimulate various mechanical and chemical receptors in the esophagus, and then affect the trachea through the vagus reflex [3]. When the esophageal mucosa is stimulated by gastric contents (acidic or non-acidic), the trachea will produce the reflex stimulation which is called "esophagus-bronchial reflex". The vagus nerve afferent pathway on the surface of the esophagus is also an important cough regulating nerve. When stimulated, it can directly lead to cough or increase cough excitability via the central nervous system.

Chronic cough patients with the abovementioned characteristics are prone reflux of gastric contents into the esophagus. Although no further definite diagnosis has been made, they are the suspected GERC patients. Symptoms of chronic cough can be caused by inhalation of the gastric contents into the lung by mistake or indirect stimulation into the throat. Moreover, esophagobronchial reflex can also be caused by the reflux of gastric contents, resulting in long-term cough due to the high sensitivity of the esophageal mucosa to various irritations [4].

Currently, the routine treatment of GERD mainly involves the intervention of direct stimulation of gastric contents on the lungs and throat. Regimens generally include proton pump inhibitors (PPI), gastric motility agents, and gastric acid neutralizers, with few interventions targeting esophagobronchial reflex and esophageal hypersensitivity. Therefore, the treatment effect of some patients is not ideal, and refractory gastroesophageal reflux disease (RGERD) even occurs [5].

In untreated GERD, acid reflux and non-acid reflux accounted for 50 % respectively, while among GERD patients receiving PPI treatment, 4 % coughs were associated with acid reflux, 74 % with weak acid reflux, and 17 % with weak base reflux [6]. In adults, reflux of gastric acid into the throat and irritation of the cough is rare. However, 24-hour esophageal pH monitoring found that most GERD patients only had distal reflux, suggesting that some cough causes were significantly correlated with distal reflux. Meanwhile, through the MII multi-conductor impedance electrode, it can be known that non-acidic reflux is also closely correlated with GERD [7]. At this time, gastroscopy does not necessarily reveal abnormal esophageal mucosa, which is called gastroscopy-negative GERD or non-erosive reflux disease (NERD). When we do gastroscopies, we don't necessarily find abnormalities in the esophagus mucosa, called gastroscopy-negative GERD or non-corrosive re-disease NERD, and the current consensus holds that NERD is a subtype of GERD [8]. NERD is divided into three subtypes: (1) Abnormal acid exposure; (2) The esophageal mucosa is highly sensitive (the physiological amount of acid reflux can cause heartburn symptoms); (3) The production of symptoms has nothing to do with acid reflux [9].

So any stomach contents entering the esophagus, whether weak acid or even basic reflux, can also cause intractable cough, and stimulation of the esophageal mucosa leading to pain in the anterior chest or back. Preventing food reflux to the esophagus and reducing irritation to the esophagus may be effective in relieving the cough of such patients, rather than just reducing the acidity of the esophagus. To this end, we have developed a "SLOW" strategy based on the following considerations:

"S" stands for slowly and relaxed, which is the focus of this strategy because eating fast could aggravate GERD in three aspects: (1) Food first reaches the gastric fundus after eating. If food is eaten too fast for a long time, it will be swallowed in large lumps, which will not only cause the expansion of the esophagus, but also cause the expansion of the gastric fundus, stimulate the stretch receptors in the gastric fundus and stimulate the transient relaxation of the esophageal sphincter [10]. (2) Eating too fast, saliva cannot be secreted in time, and the decrease in saliva volume leads to the decrease in the concentration of epidermal growth factor, which can inhibit gastric secretion [11]. Therefore, the decrease of the amount of saliva, can lead to increased gastric acid secretion, easy to aggravate the stimulation of the esophagus. (3) Eating too fast, the mood is often a state of tension and anxiety, and mood has a significant impact on the stomach. Psychosocial stimuli can aggravate acid reflux symptoms in patients with gastropathy, and the potential mechanisms may include: exacerbating the frequency and degree of esophageal acid exposure, inhibiting gastric acid drainage, or hypersensitivity of esophageal mucosa generated by stimulation [12].

“L” is for no liquid and sweat food. There are three possible reasons: (1) Liquid food contains much water, the required chewing frequency is low and chewing intensity is small, these can inhibit the secretion of saliva. Decreased levels of epidermal growth factor and amylase in saliva can increase gastric acid production. (2) Gastric emptying requires the muscles of the pylorus to wrap the food and deliver it downward. If the food is too thin, it will be difficult to wrap it tightly, resulting in up-down turbulence and delayed emptying, which will also increase the possibility of reflux. (3) Sparse foods tend to flow back into the esophagus, while irritant fluids, such as coffee and carbonated drinks, can aggravate the incidence of gastroesophageal reflux [13].

“O” means no overeating. If you eat too much, the emptying will become slower, which will naturally increase the chances of reflux [14]. So we recommend that patients go on a diet and stop eating 3 hours before bedtime.

“W” means no water while eating correctly. This is the same as eating liquid food. Drinking a lot of water reduces the production of saliva and slows the emptying of the stomach. We recommend drinking water 1–2 hours after meals.

Kahrilas *et al*/believe that acid-inhibiting therapy has a definite therapeutic effect on chronic cough, but how to screen patients is the key [15]. This study can provide reference for screening patients who benefit. Dietary intervention is currently a weak link in the treatment of cough. This strategy requires no additional drugs, has no economic burden and no side effects, is easily understood and accepted by patients, and is easy to be promoted in medical institutions at all levels. Therefore, for chronic cough patients who have the habit of eating fast, preferring sweets and liquids, overeating and drinking water while eating, it is recommended to empirically apply the strategy of “SLOW”, and try to supplement the current drug treatment of chronic cough, especially GERD.

Declarations

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS

The datasets used during the current study are available from the corresponding author on reasonable request.

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AUTHORS' CONTRIBUTIONS

Guangqiang Wang, Meiling Ding designed the study. Guangqiang Wang, Meiling Ding, Wei Zhang, Baoyi Liu were responsible for case collections and follow-up. Meiling Ding, Xiaojie Song, Liqun Wu contributed to analyzing the data. Guangqiang Wang, Meiling Ding, Liqun Wu drafted and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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References

1. Janson C, Chinn S, Jarvis D, Burney P. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. *Eur.Respir.J.*2001 Oct;18(4):647-654.

DOI:10.1183/09031936.01.00098701.

2. Hsu JY, Stone RA, Logan-Sinclair RB, Worsdell M, Busst CM et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour using ambulatory recorder. *Eur.Respir.J.*1994 July;7(7):1246-1253.

DOI:10.1183/09031936.94.07071246.

3. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest.*2006 Jan; 129 (1 Suppl): 80S-94S.

DOI:10.1378/Chest.129.1-suppl.80s

4. Smith JA, Decalmer S, Kelsall A, et al. Acoustic cough from-reflux associations in chronic cough: potential triggers is used of mechanisms.2010 Sep;139(3):754-762.

DOI:10.5009/gnl.2012.6.2.197

5. LV HJ, Qiu ZM. Refractory chronic cough due to gastroesophageal reflux: definition, mechanism and management. *World Methodol* 2015;5;1 49-56

DOI:10.5662/wjm.v5.i3.149.

6. Xu X, LV H, Yu L, Chen Q, Ling S, QIU Z. A stepwise protocol for the treatment of refractory gastroesophageal reflux-induced chronic cough. *J. Thorac. Dis* 2016;8(1):178-185

DOI:10.3978/j.issn.2072-1439.2016.01.50

7. Qiu Z, Yu L, Xu S, Liu B, Zhao T, Lü H, Qiu Z. Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. *Respirology*. 2011 May; 16 (4) :645-652.

DOI:10.1111/j.1440-1843.2011.01952.x.

8. Modline IM, Hunt RH, Malfertheiner P, et al. Non-erosive, reflux disease-defining the entity and delineating the management. *Digestion*, 2008,78 Suppl1 :1-5.

DOI:10.1159/000151248.Epub 2008 Oct 2.

9. Ates F, Francis DO, Vaezi MF. refractory gastroesophageal reflux disease: advances and treatment. *Expert. Rev Gastroenterol Hepatol* 2014;8:657-67

DOI:10.1586/17474124.2014.9.10454.Epub 2014 Apr 19.

10. Carmagnola S, Cantu P, et al. Mechanoreceptors of the proximal stomach and perception of gastric distension. *Am J* 2005 Aug;100 (8) :1704-10.

DOI:10.1111/j.1572-0241.2005.41350.x

11. Vaezi MF. Chronic cough and gastroesophageal reflux disease :how do we establish a causal link? *Chest* 2013;143:587-9.

DOI:10.1378/chest.12-2682

12. Jang SH, Ryu HS, et al. Psychological factors influence the overlap syndrome in functional gastrointestinal disorders and their effect on quality of life among firefighters in South Korea. *J Dig Dis*. 2016 Apr;14(4);236-43

DOI:10.1111/1751-2980.12330

13. Fass R, Quan SF, O'Connor GT, Ervin A, Iber C. Predictors of heartburn during sleep in a large prospective cohort study. *Chest*. 2005 May; 127 (5) :1658-1666.

DOI:10.1378/chest.127.5.1658

14. Xu X, Yang Z, Chen Q, et al. Comparison of clinical characteristics of chronic cough due to non-acid and acid gastroesophageal reflux. Clin Respir J 2015;9:196-202

DOI:10.1111/crj.12124

15. Kahrilas PJ, et al. Response of chronic cough to acid-suppressive therapy in patients with gastroesophageal reflux disease. Chest 2013;143(3):605-612.

DOI:10.1378/chest.12-1788

Tables

Table 1 Cough scores and their corresponding symptom details

Scores	Symptom details
0	No cough (fully recovered)
1	One paroxysmal cough per day
2	At least two paroxysmal coughs per day, but no night cough
3	Frequent cough, but does not affect daily activities, or night cough and wake once
4	Frequent cough and affect daily activities, night cough and wake often
5	Most of the time cough, or cannot sleep at night

Table 2. Comparison of case data between the two groups

	experimental group	control group	t value	P value
age	54.51±17.05	56.38±14.88	0.728	0.407
disease course	61.44±38.45	56.72±31.65	0.742	0.460
sex			0.056	0.814
male	33[45.8%]	24[48.0%]		
femal	39[54.2%]	26[52.0%]		

Table 3. Comparison of efficiency and complete remission rates between the two groups

	experimental group	control group
An efficient	77.8 %	54.0 %
Full Remission rate	61.1 %	38.0 %

Table 4. Changes in HSU cough scores between the two groups

	Prior treatment	Post treatment	Z2	P2
Experimental Group	3(2,4)	0(0,2)	6.588	0.000
Control Group	4(3,4)	2(0,4)	4.550	0.000
Z1	1.260	3.123		
P1	0.208	0.002		