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Alimentary Tract

The effects of paroxetine and amitriptyline on the upper esophageal sphincter (UES) pressure and its natural history in globus pharyngeus

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ABSTRACT

Background: Antidepressant agents have been shown to be an effective and safe treatment method for patients with globus. However, there are few clinical trials dedicated to studying the effects of antidepressant agents on the natural history and upper oesophageal sphincter (UES) pressure of treated globus patients.
Aims: To evaluate the effect of paroxetine and amitriptyline to prevent relapses in patients with globus, the simultaneous relationship between changes in UES pressure and improvement of globus symptoms were measured.
Methods: Globus patients were randomised into amitriptyline, paroxetine and lansoprazole groups for a 6-week treatment period, and follow-up was extended to 12 additional months. Efficacy was evaluated in terms of the Glasgow-Edinburgh Throat Scale (GETS), and UES pressure was measured by standard oesophageal manometry.
Results: Paroxetine therapy resulted in a higher withdrawal rate due to symptom relapse (15.9% *vs* 44.1%, $P = 0.01$; 15.9% *vs* 64.7, $P = 0.001$) than amitriptyline and lansoprazole. Furthermore, globus symptoms were alleviated with the decrease of UES pressure after paroxetine and amitriptyline treatment ($r = 0.620$, $P = 0.02$; $r = 0.575$, $P = 0.03$)
Conclusions: This follow-up study indicates that paroxetine may alter the natural history of globus and can effectively be used for the long-term management of patients with the disease. Apart from the clinical benefits, paroxetine and amitriptyline can potentially decrease UES pressure.

1. Introduction

Globus pharyngeus is a long-lasting recurrent disease, in which patients commonly describe the sensation of a ball being lodged in their throat. Globus sensation is not an uncommon symptom. According to our recent study [1], the overall lifetime prevalence of globus was 21.5%, with a peak age at disease onset of 35–54 years. Although many possible aetiologies for globus have been proposed, its exact pathogenesis remains obscure. In addition to psychogenic factors, gastroesophageal reflux disease (GERD) [2,3] and hypertonicity of the oesophageal body [4], conflicting reports exist regarding a relationship with increased upper oesophageal sphincter (UES) pressure. Some studies [5–8] have suggested that globus is caused by hypertonicity of UES pressure. Tokashiki et al. [9] found that 13 of the 20 subjects complained of globus at approximately the same time as the UES pressure increased with distal oesophageal acid perfusion; however, Sun et al. [10] failed to demonstrate increased prevalence of UES hypertonicity in patients with globus sensation.

While the most appropriate standard medication for globus pharyngeus has not been established, the usual medical care often shows inadequate response [11–13]. However, antidepressant agents are gradually becoming more widely accepted as treatment options. In recent years, antidepressant agents have shown consistent evidence of efficacy on functional gastrointestinal disorders (FGIDs), even for refractory FGIDs [14–16]. According to our previous study, low-dose amitriptyline (AMT) is effective and

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well-tolerated for globus patients [13]. Paroxetine (PAR) therapy is more efficacious than low-dose AMT therapy in alleviating globus symptoms [12]. Despite several studies in the literature showing the efficacy of antidepressants for the treatment of this disorder, to date, relatively limited data has evaluated the effect of PAR and AMT to prevent relapses in patients with globus. Moreover, little research has been conducted to investigate the effect of antidepressants on oesophageal function.

Previously, we reported on the short-term efficacy of PAR and AMT for globus patients. The present study had two goals. First, we aimed to elucidate the natural history of globus patients who demonstrated treatment response after 6 weeks of treatment. Second, we attempted to identify the effect of antidepressants on UES pressure.

2. Materials and methods

2.1. Patients

Patients over the age of 18 years of age with the globus sensation of a lump or foreign body in the throat were enrolled from either the department of gastroenterology or Ear, Nose and Throat (ENT) Clinics at Guangzhou Nansha Central Hospital, from September 2014 to August 2016. Globus was diagnosed in accordance with Rome III consensus criteria [17]. Investigations into both the upper GI and laryngo-oesophageal endoscopy were performed for globus in all subjects. The inclusion criteria of endoscopy were normal gastric and oesophagus mucosa without the presence of any organic disease. The exclusion criteria included: (1) age below 18 or above 80 years; (2) use of any proton pump inhibitor (PPI) or histamine type 2 receptor antagonist during the last 2 months; (3) use of tranquilisers or antidepressants that may affect oesophageal motor function; (4) prior foregut surgery or histopathology-based motor disorders; (5) known allergy to lansoprazole (routine treatment, RT), AMT or PAR; (6) severe hepatic or renal dysfunction; (7) prostatic disease; (8) pregnancy or breastfeeding; exclusion criteria related to endoscopy were endoscopy not permitted; gastric or duodenal peptic ulcer; gastroesophageal reflux (GERD); gastric and oesophageal neoplasm; any precancerous gastric and oesophagus lesions; gastric and oesophageal polyp; and hiatal hernia.

2.2. Study design and procedures

This was a prospective, randomised controlled trial for globus pharyngeus (clinical trial number: Chi-CTR-TRC-14005097), which was approved by the hospital ethics committee. Prior to the study, written informed consent was obtained, and demographical data, previous medication use and medical histories were collected from all subjects. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in *a priori* approval by the institution's human research committee.

Recruited outpatients were randomised to treatment with RT, AMT or PAR using a computerised random number generator. The staff generating the list and preparing the opaque sealed envelopes were not involved in any of the data collection. Blinding of participants and observers was not possible due to the nature of the intervention; however, the patients were notified of which medicine they would take after randomisation. Only the study statistician was blinded to the allocation of intervention or control arms. In the RT group, patients were treated with lansoprazole (Takepron; 30 mg/tablet; Takeda Pharmaceutical Company, Osaka, Japan) 30 mg twice daily, one tablet in the morning and another tablet in the afternoon. In the AMT group, patients were treated with AMT (25 mg/tablet; Hunan Dongting Pharmaceutical Co., Ltd. HuNan, China) 12.5 mg once daily before bedtime. In the PAR group, patients were treated with PAR (Seroxat; 20 mg/tablet; GlaxoSmithKline Pharmaceutical Co., Ltd.) 20 mg once daily before bedtime. The dose of each allowed drug and the duration of treatment with these drugs were recorded in detail.

Before and during the last day of treatment, high-resolution manometry and the following questionnaires were performed: GETS, the Pittsburgh Sleep Quality Index and the Hamilton Rating Scale Anxiety/Depression.

Patients who responded to treatment at the end of the 6-week treatment trial entered post-treatment follow-up for 12 months without receiving any drug therapy. No rescue medication was provided for this trial. Treatment response [13] was defined as a >50% reduction in the GETS score. The response was calculated as the formula: (|(score at treatment – score at baseline) |/score at baseline) × 100%. The treatment responses of these three groups were calculated separately.

Follow-up visits were performed at two-week intervals by phone or a return visit to the treating clinician. At each follow-up visit, the GETS and visual analogue scale (VAS) were administered by investigators. We then evaluated the relapse time in each of these three groups. Relapse was defined as a patient who reported at least five episodes of globus sensation per week, GETS score ≥ score at baseline or VAS ≥ 50. The patient was removed from the study once relapsed, and the time interval of symptom relapse was measured in weeks since the initiation of follow-up.

2.3. Sample size

Previously, we reported that the treatment response of low-dose AMT for globus patients was 75%, significantly higher than that of 35.7% in RT groups. Moreover, we performed a preliminary trial before conducting the present study to evaluate the efficacy of PAR for globus patients and found that 80% (16/20) of globus patients showed a treatment response. With a two-sided significance level $\alpha = 0.05$, a power of 90%, and an estimated loss to follow-up of 10%, the total required sample size of 190 was large enough to provide safety and effectiveness data reflecting the actual reality of treatment with PAR, AMT and RT.

2.4. Evaluation of globus symptoms

The severity of globus symptoms was measured by making a mark on the GETS questionnaire [18], which is based on 10 questions, with a maximum possible score of 70. Patients subjectively indicated the severity of their symptoms for each question on a 7-point Likert scale, with 0 representing "none" and 7 representing "unbearable".

2.5. High-resolution manometry protocol

After an 8-h fasting period, manometry was performed with the patients in a supine position, using a water-perfused catheter of 4 mm in diameter (Ninbo Maida Medical Device Inc., Ningbo, China). The catheter has 24 channels with recording side-holes. Hole 1, which starts at the most distal point, is 5 cm from hole 2. Holes 2–5 are 1 cm from each other. Side-holes 6–24 are 1.5 cm from each other. The oesophagogastric junction (EGJ) was explored through side-holes 2–5. A 30-s period of basal recording was obtained after positioning the catheter. Later, the patients were asked to swallow 5 ml of water and repeat this for a total of 10 times, separated by 30-s intervals. Lastly, multiple rapid swallows (generally 5 swallows of 2 mL of water spaced at 2- to 3-s intervals) were performed. UES resting pressure, UES residual pressure and lower oesosphageal sphincter (LES) resting pressure were analysed. All tests were performed by a single investigator.