Venlafaxine in the Management of Vocal Cord Dysfunction

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A. Study Purpose and Rationale

Vocal cord dysfunction (VCD) is a condition characterized by closure of the vocal cords at the level of the larynx during inspiration, or early expiration resulting in symptoms of upper airway obstruction. Patients with VCD present with wheezing, dyspnea, and stridor. Their symptoms may be triggered by stress, exercise, cold air, inhalation of irritants, methacholine. The clinical presentation is similar to asthma. Patients with VCD are often misdiagnosed with refractory asthma since they does not respond to standard asthma therapy. The acute presentation can be dramatic, resulting in intubation or tracheostomy(1,2,3).

The overall prevalence of VCD in the population is unknown. A 1994 study by Newman *et al* (4) evaluated patients diagnosed with refractory asthma at a tertiary respiratory medicine clinic, and found VCD alone in 10% of patients, while an additional 30% of patients had both VCD and asthma. Morris *et al* followed a cohort of 40 military personnel with refractory dyspnea on exertion, wheezing and found 15% of them to meet criteria for VCD (5). In the retrospective study by Newman et al, the patients with VCD without asthma had been misdiagnosed for an average of 4.8 years, their medications were similar to those of the control group of patients with severe asthma, and 80% had received prednisone regularly at an average daily dose of 29 mg (6).

Patients with VCD have been shown to have flattening or truncation of the inspiratory limb of the flow-volume loop, however this is absent in the majority of patients (80%) without acute symptoms (6,7). Definitive diagnosis is made by direct visualization of vocal cord adduction with posterior "chinking" (a small opening at the posterior aspect of the cords) during either inspiration or early expiration while the patient is experiencing symptoms (7,8). There is a spectrum of laryngeal dysfunction especially in the setting of underlying lung disease. Asthmatics have glottic narrowing during expiration as a physiologic adaptation to their obstructive lung disease. This expiratory glottic narrowing may act to limit expiratory flow rates, thereby maintaining hyperinflation and preventing collapse of small airways (6). Where the transition from physiologic response to pathologic movement takes place is unclear. Nevertheless inspiratory closure of the vocal cords seen in VCD is clearly dysfunctional.

Certain characteristics have been found to be associated with VCD. Patients with VCD are predominantly women, in their twenties and thirties, often overweight and employed in the medical profession (6). Early reports of VCD cases suggested a close association with some types of psychiatric illnesses. Although, studies looking at incidence of psychopathology in these patients have reported the presence of major psychiatric and personality disorders, with the exception of anxiety-related disorders, no significant difference has been found when compared with the control group of asthmatics (6, 9).

Acute management has been achieved with a helium-oxygen mixture, anxiolytics, and relaxation techniques. Long-term management of patient with VCD includes speech therapy focusing on relaxed throat breathing, psychotherapy, biofeedback (3,5,7). Response rates of up to 70% have been reported after 2 years of follow up (10,11).

Given the high incidence of anxiety disorders among patients with VCD and documented response to psychotherapy typically used in anxiety disorders, this study will explore the effectiveness of Venlafaxine (Effexor), a first line drug for the treatment of generalized anxiety disorder in the long-term management of patients with VCD.

Hypothesis

Treating VCD patients with Venlafaxine will lead to symptomatic improvement and a decrease in emergency room visits.

B. Study Design and Statistical Analysis

This will be a prospective randomized double-blind placebo-controlled trial. Eligible patients will be randomized to one of two interventions: usual care plus Venlafaxine vs. usual care plus placebo. Venlafaxine will be administered at a starting dose of 37.5 mg po bid and titrated up every fourth day to a maximum dose of 150 mg per day as tolerated.

The primary outcome will be number of emergency room visits after 1 year of follow-up. Other information to be gathered include demographic data, frequency of symptoms, medications, whether or not subjects have received psychotherapy or speech therapy, and if so, how many hours of speech therapy or psychotherapy patients they have received. Information will be obtained through telephone interviews conducted every month. Chart review of ED visits will be conducted to confirm presenting symptoms and discharge diagnosis. Patients will be classified as having either mild or moderate to severe symptoms by a blinded reviewer based on their response to questions 6 through 9 on the questionnaire

The study will be designed with a sample size of 110 in each arm to provide 80% power to detect a difference of at least 30% in the number of ED visits between the control and test groups. This sample size was derived using the unpaired t-test with a type I error of 0.05 and an outcome measure of 9.7, with a standard deviation of 7.9 ED visits per year in the control group and an outcome measure of 6.5 ± 7.9 in the test group assuming a 70% response to Venlafaxine.

Patient characteristics will be summarized with means and standard deviations or frequencies and percentages. Comparisons of discrete characteristics between study groups will be assessed with the chi-squared test. Continuous characteristics will be compared with unpaired t-tests. All reported p values will be 2 sided with alpha of 0.05. Analysis will be based on the intention-to-treat principle in which patients will be analyzed in the original groups to which they were assigned regardless of compliance with the study drug.

C. Study Procedure

Clinical Examination

A complete history utilizing the American Thoracic Society (12) respiratory questionnaire will be obtained from each patient.

Pulmonary Function Tests

All recruited subjects will have pulmonary function tests performed that include spirometry and plethysmography. Spirometry will be performed using a volume displacement spirometer according the American Thoracic Society (ATS) recommendations (13). Spirometry will be used to measure FEV_1, FVC, FEV_1/FVC, and the flow volume loop. If there is evidence of airway obstruction these measurements will be repeated after administration of a bronchodilator. Body plethysmography will be used to determine TLC, RV. Diffusion capacity of the lung for carbon monoxide (DLCO) will be determined using the single breath CO technique. All measurements will be expressed as percentage of predicted (14). All PFTs will be performed when patient are without symptoms.

Bronchoprovocation testing

Airway reactivity will be assessed using standard bronchoprovocation testing. All patient will first inhale a saline placebo followed by five deep inhalations of increasing doses of methacholine mixed in normal saline solution at the following concentrations: 0.025, 2.5, 25 mg/ml. The patient will wait for 3 minutes and perform two FVC manoevers. This will be repeated for all concentration of methacholine until the maximal concentration is reached or there is a 20% drop in the FEV_1. If there is a > 10% decrease in FEV_1, the patient will receive two puffs of albuterol followed by repeat FVC manoevers five minutes after the administration of albuterol to evaluate responsiveness to the bronchodilator (8).

All patients with evidence of obstructive lung disease on PFT or following methacholine challenge will be excluded from the study. A list of the remaining patients will be generated and sent to the CPMC emergency room and the ENT department. Patients on this list who present to the ED with respiratory symptoms will undergo vocal cord evaluation.

Vocal cord Evaluation

All patient without evidence of obstructive disease who present with acute respiratory symptoms will undergo direct laryngoscopy using a flexible rhinolaryngoscope. Each patient will receive topical 2% viscous lidocaine in the nares for anesthesia. The posterior pharynx will not be anesthesized to avoid involvement of the vocal cords. The layngoscope will be directed to the posterior pharynx several centimeters above the glottis to prevent stimulation of the area and induce to prevent inducing vocal cord adduction. Videotape records of the vocal cord movement will be made (8). Confirmation of VCD will be made by a speech pathologist blinded to the identity of each patient.

Patients diagnosed with VCD will be randomized to Venlafaxine or placebo following management of the acute episode.

D. Study drugs

Venlafaxine at doses of 37.5 mg to 375 mg per day is FDA approved for the treatment of depression, anxiety disorder.

E. Medical device

N/A

F. F. Study Questionnaire

Telephone interview questionnaire

(i). ED visits

1. In the last month have you been seen in the emergency room?
2. If so, what symptoms were you having?
3. What medical management did you receive in the emergency room?
4. What was your discharge diagnosis?
5. What were your discharge medications?

(ii). Classification of symptoms

6. In the last month have you experienced any episodes of wheezing or shortness of breath (SOB)?
7. If so, how many episodes of wheezing, SOB have you experienced per week in the last month?
8. How many blocks can you walk?
9. What limits you exercise tolerance?

(iii). Medication review

10. What are you current medications?

(iv). Assessing usual Care

11. In the last month, have you been seen by a speech therapist, if so, for how many hours?
12. In the last month, have you been seen by a psychologist or a psychiatrist? If so, for what duration?

G. Study Subjects

Subjects to be screened will be patients 18 years and older, seen at the NYPH chest clinic who have been diagnosed with asthma and have demonstrated poor response to appropriate asthma regimen (based on the severity of asthma) despite medical compliance. Adequacy of response to standard asthma treatment will be judged by the referring physician.

Exclusion criteria : (i)known history of stroke, (ii) vocal cord polyps, (iii) laryngeal malignancy, (iv)myasthenia gravis, (v)history of ENT radiation therapy or surgery, (vi)more than one intubations, (vii)history of tracheostomy, (viii) inability to perform PFT manoevers, (ix)inability to undergo bronchoprovocation testing due to severe airway obstruction FEV1<50% predicted, MI in the past 3 months, aortic aneurysm, uncontrolled HTN (SBP>200, DBP>100)

H. Recruitment of Subjects

The patient's primary physician at the Chest clinic will assess if patient is suitable for the study and discuss patient's willingness to enroll in the study. Once a patient is deemed suitable and agrees to participate in the study, he/she will be contacted by study personnel.

I. Confidentiality of Study Data

All study data will be coded using a unique code generated for each participant. Data on all participants, included those who fail the screening tests, will be stored in a secure location accessible only to the investigators.

J. Potential Conflict of Interest

None

K. Location of the study

CPMC Chest Clinic, Pulmonary Function Testing lab, Emergency room.

L. Potential Risks

The goal of bronchoprovoction testing is to induce bronchoconstriction. The testing lab will have medications, resuscitative equipment as well as trained personnel to manage bronchospasm. There is no definitive data on the risk of complications associated with bronchoprovocation. In one study 4 of 88 patients failed to return to >90% of baseline FEV1 following beta-agonist treatment but none required a change in maintenance medications, and there were no adverse sequelae following challenge testing (15).

Laryngoscopy can lead to laryngeal edema and airway obstruction. Risk < 0.02% (16).

M. Potential benefits

If therapy is successful, patients will experience a decrease in the frequency of symptoms and ED visits**.**

N. Alternative Therapies

N/A

O. Compensation to subjects

None

P. Costs to Subjects

None

Q. Minors as Research Subjects

None

R. Radiation or radioactive Substances

None

S. References

1. Murray, D.M., Lawler, P.G. *All That Wheezes is Not Asthma. Anesthesia*. 1998; 53:1006 – 1010.
2. Appelblatt, N.H., Baker, S.R. Functional Upper Airway Obstruction: a new syndrome. Arch Otolaryngol. 1981; 107:305-306
3. Kellman RM, Leopold DA. *Paradoxical vocal cord motion: an important cause of stridor*. Laryngoscope 1982; 92: 58- 60.
4. Newman K .B., Dubester S.N. *Vocal Cord Dysfunction: Masquereder of Asthma*. Sem Resp Crit Care Med. 1994;15:161 – 167
5. Morris M. J., Deal L. E. Vocal Cord Dysfunction in patients with Exertional Dyspnea. Chest 1999;116:1676 –1682.
6. Newman K.B., Mason U.G., Schmaling K.B. *Clinical features of vocal cord dysfunction*. Am J Respir Crit Care Med 1995; 152: 1382 – 1386.
7. Christopher K.L., Wood R.P., Eckert C, et al. *Vocal cord dysfunction presenting as asthma*. N Eng J Med 1983; 308: 1566-1570.
8. O'Hallaren, M. T. Differential Diagnosis of Allergic Disease: Masqueraders of Allergy. Imm Allergy Clin N Am. 1996: 16(1): 69-76.
9. Gavin LA, Wamboldt M, Brugman S, et al. Psychological and family Characteristics of Adolescents with Vocal Cord Dysfunction. J of Asthma. 1998. 35(5), 409-417.
10. Link HW, Stillwell PC, Jensen VK, et al. Vocal Cord Dysfunction in the Pediatric Age Group. Chest 1998. 114 (4 suppl) 255S- 256S.
11. Sullivan MD, Heywood BM, Beukelmand DR. *A Treatment of Vocal Cord Dysfunction in female Athletes: An Outcome Study*. Laryngoscope. 2001; 111(10) 1751 – 1755.
12. Ferris BJ. *Epidemiology and Standardization Project*. Am Rev Respir Dis. 1978: 118:1-80.
13. American Thoracic Society. *ATS Statement – Snowbird workshop on standardization of spirometry*. Am Rev Respir Dis 1979; 119: 831-838.
14. Chemiack RM, Raber MD. Normal standards for ventilatory function using an automated wedge spirometer. Am Rev Respir Dis. 1972.106:38 – 46.
15. Cain H. *Bronchoprovocation Testing*. Clin Chest Med 2001. 22;4 651 – 660.
16. Koltai PJ, Parnes SM. Airway Complications from laryngoscopy and Panendoscopy. Ann Otol Rhinol Laryngol. 1987. 98:691-694.