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Randomized Double Blind Trial of Amitriptyline versus Placebo in Treatment of Chronic Laryngopharyngeal Neuropathy- Preliminary Results

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Abstract

Objective: A neuropathic etiology has been suggested for patients with chronic laryngopharyngitis symptoms without visible structural pathology. Prior studies have shown that treatment with neuro-modulating medications is beneficial, but it is unknown if this was due to placebo effect. Our objective was to compare the efficacy of amitriptyline versus placebo in treating chronic laryngopharyngeal neuropathy.

Study Design: Prospective, randomized placebo-controlled trial.

Methods: Patients were randomized to receive placebo or amitriptyline for 8 weeks. Primary outcome was change in modified Reflux Symptom Index (mRSI) score. Secondary outcomes were change in Voice Handicap Index-10 (VHI) scores, rates of adverse effects, and overall symptom severity.

Results: Eighteen patients completed the study. The average difference in mRSI and VHI scores after treatment were not significantly different between study arms. However, more subjects taking amitriptyline felt their symptoms had subjectively improved (6 out of 9, 67%), while the remainder noted no change. In the placebo group, only 4 out of 9 subjects (44%) felt their symptoms were better and 2 felt worse. Subjects took an average of 25 mg of amitriptyline or placebo daily by the end of the 8-week treatment period. No serious adverse effects were noted.

Conclusion: Although there was a trend toward greater subjective improvement in overall symptoms with amitriptyline, interpretation is limited due to the small sample size. Larger randomized controlled trials to determine the efficacy of neuro-modulating agents in the treatment of chronic laryngopharyngeal neuropathy, as well as better metrics to characterize this disorder are warranted.

Keywords: Cough; Laryngitis; Chronic laryngopharyngeal neuropathy; Amitriptyline

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Introduction

Chronic laryngopharyngitis can present with a myriad of symptoms including cough, hoarseness, throat clearing, foreign body sensation, throat pain, sensation of excessive phlegm, and difficulty swallowing [1,2]. These symptoms can significantly impact quality of life, with patients often reporting impaired ability to perform their job, embarrassment, discomfort, and avoidance of social settings [3-4]. Common causes for these symptoms include GERD, rhinosinusitis-induced post-nasal drainage, direct allergic effect, smoking, and other environmental causes. However, despite treatments for these conditions, some patients fail to improve.

A neuropathic etiology has been suggested for these refractory cases of chronic laryngitis. Some investigators have speculated that this condition may occur as a post-viral complication [5-8]. Diagnosis of this condition, also known as Chronic Laryngopharyngeal Neuropathy (CLN), remains one of exclusion, since there is currently no diagnostic test for this. Multiple medications used in other specialties for the treatment of neuropathic disorders have been used to treat CLN, with many patients reporting relief of symptoms. Specifically, uncontrolled trials of amitriptyline, nortriptyline, gabapentin, and pregabalin have shown to have some benefit, but it is unknown if the improvement in symptoms seen in these studies was due to a response to the medication or placebo effect alone [9-13]. In clinical experience here at the authors' institution, amitriptyline has been found to be well-tolerated by patients diagnosed with CLN, with symptomatic relief generally outweighing the side-effects. However, it is critical that the effectiveness of amitriptyline for the treatment of CLN be proven using a placebo controlled trial

We therefore initiated a randomized, double-blind, placebo controlled study to ascertain amitriptyline's effectiveness in treating CLN. Our hypothesis was that amitriptyline would be significantly superior to placebo as a treatment for this condition with respect to symptomatic relief of laryngitis.

Materials and Methods

Study design and Enrollment

This study was conducted at a large urban academic medical center in the northeastern United States. The study protocol was approved by the Boston Medical Center Institutional Review Board prior to beginning subject enrollment. Informed consent was obtained from all subjects. Patients who presented to the otolaryngology clinic at Boston Medical Center with the symptoms of chronic laryngopharyngitis were considered for the study. All subjects were treated with a proton-pump inhibitor (omeprazole 20 mg BID) for a minimum of 2 months to rule out gastro-esophageal reflux prior to discussion of study enrollment, and structural lesions (e.g. cancer) were ruled out using flexible laryngoscopy. Prior to enrollment, all subjects were also checked for allergies. If history or exam was concerning for allergies, subjects underwent treatment with a nasal steroid (fluticasone) and systemic oral antihistamine. Additional inclusion criteria were age 18 or older, and ability to speak and read English. Exclusion criteria included any history of environmental allergies, urinary retention, major depressive order, or allergy to a tricyclic antidepressant; smoking within the past 5 years, use of monoamine oxidase inhibitors (MAOIs) within the past 4 weeks; any prior amitriptyline use; and presence of upper respiratory infection or current diagnosis of gastroesophageal reflux (GERD). Women 18-55 years of age without a history of menopause who were currently nursing or pregnant, planning to become pregnant or unwilling to utilize contraception (barrier or hormonal methods) were also excluded.

The reflux symptom index (RSI) was previously designed to measure symptoms of laryngopharyngeal reflux (LPR) [14]. Although LPR and CLN may represent distinct etiologies, overlap in symptoms has been noted in our experience. In the absence of a previously validated metric to assess CLN symptoms, we used a modified RSI (mRSI) score as our primary outcome (see Intervention for details on modifications).

Prior studies validating the RSI were used to determine the sample size for this study. Belafsky "et al." [14] showed that the mean RSI for subjects with LPR improved from 20.9 to 12.8 after anti-reflux treatment [5]. We estimated a 20% improvement for the placebo group, using the estimate for continuous indicators from Hróbjartsson "et al." [15] meta-analysis of placebo effects. Thus, we predicted the final RSI for the placebo patients to be 16.72. The difference between these values (3.92) divided by the anticipated standard deviation (10.0, using the value from Belfasky "et al." [14]. for the final RSI value post-treatment) results in a standardized effect size of 0.392. Using this standardized effect size with a two tailed t-test, α=0.05 and a desired power level of 0.8, the resulting sample size was 100 for each study arm (200 overall).

Intervention

Enrolled subjects were assigned a study subject number and assigned to either placebo or amitriptyline for an 8-week treatment period. A random number generator was used to determine which subject numbers would be assigned to each treatment arm, in a 1:1 ratio. Assignments were made by nurse practitioners not involved in data analysis. Patients and investigators involved in data analysis (J.P.N., S.R., M.J.) were blinded to treatment assignment during the 8-week period.

Amitriptyline capsules were compounded with Avicel, biologically inert cellulose filler for a total of 12.5 mg of amitriptyline per capsule. Placebo capsules contained Avicel alone. All patients were counseled to start by taking 1 capsule at bedtime for 1 week, and to increase the dose by 1 additional capsule each week if symptoms persisted at the prior dose, for a maximum of 4 capsules nightly (i.e., maximum dose of 50 mg of amitriptyline or placebo). If a higher dose was not tolerated due to side effects, subjects were instructed to decrease the number of capsules to the last dose that was tolerated. All subjects were asked to complete a pre-treatment questionnaire, which included the Voice Handicap Index-10 (VHI-10) and modified Reflux Symptom Index (mRSI) scales to assess the baseline severity of symptoms. The RSI was modified to assess two additional symptoms, "throat pain or burning" and "pain with swallowing", and removed the symptom "difficulty swallowing foods, liquids, or pills". Subjects were contacted every 2 weeks by telephone by nurse practitioners after study enrollment, to confirm treatment start date, adherence, and any adverse effects.

At the completion of the 8-week treatment period, subjects returned to the otolaryngology clinic to complete a post-treatment questionnaire, again consisting of the VHI and mRSI scales, as well as questions assessing side effects, overall symptom severity, and perceived degree of change in symptoms. Both subjects and investigators were unblinded at the conclusion of the 8-week treatment period, after subjects had completed the post-treatment survey.

Statistical analysis

Primary outcome was change in mRSI score after treatment compared to baseline. Other secondary outcomes were change in VHI-10 score after treatment compared to baseline, side effects and rate of discontinuing treatment, and overall severity of symptoms on a Likert-type scale. Patients were also asked to subjectively rate by percentage, in 10-point increments, whether their symptoms were overall better, worse, or the same after treatment. Changes in modified RSI, VHI-10, and overall symptom severity scores, as well as percent change in symptoms were analyzed using two-tailed t-tests with equal variances to compare the mean differences between the two groups. Because outcomes between two independent subject populations were compared, and the study was not designed as a crossover or a matched case-control, unpaired two-tailed t-tests were used.

We compared the mean baseline score in each question of the mRSI to determine if certain symptoms may be more specifically associated with CLN. Pearson's correlation coefficient was used to determine whether there was a significant correlation between the outcome variable, change in RSI score, and independent variables pretreatment: score of overall severity, and average dose of amitriptyline. Additionally, multiple linear regressions was used to determine the association between the outcome variable, RSI score, and the independent variables dose of medication and pretreatment symptom severity scale while adjusting for age of subject. Microsoft Excel (Redmond, WA) was used for all statistical analyses. Significance

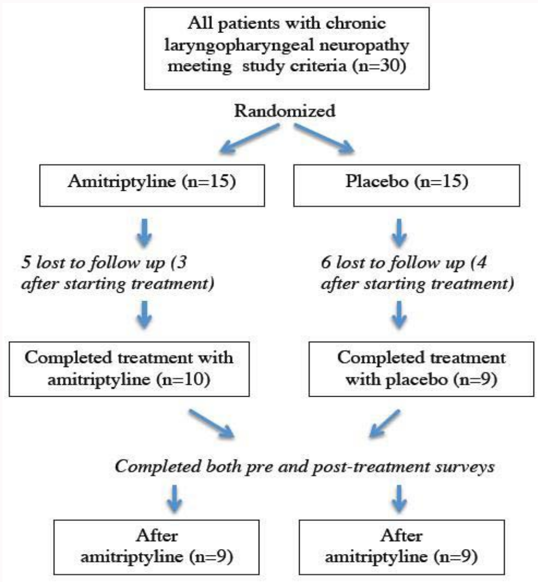

Figure 1: Study design algorithm.

was determined if the p-value was less than 0.05.

Results

Patients were enrolled from December 2013 through January 2015. Study enrollment was paused at this point for interim analysis. A total of 30 patients were consented and enrolled. Eleven subjects were lost to follow up after enrollment. Seven subjects had started treatment, 1 had not, and 3 had been mailed prescriptions but it was unknown if they had started treatment. Of the 7 who had started treatment, then dropped out, 3 had been assigned to the amitriptyline arm and 4 to the placebo arm. Of the 19 subjects that completed treatment, 18 completed both pre- and post-treatment questionnaires (Figure 1).

The demographics of the study group at enrollment were representative of the patient population at Boston Medical Center. Equal numbers of men and women were enrolled. The average age was 47.8 years (median 50.5 years, range 21-67). The majority of respondents identifying themselves as Black/African American (n=11), followed by white (n=6), other (n=5, including Cape Verdean, Haitian, and Brazilian), Asian (n=4), Hispanic (n=3), and Native American/Alaskan (n=1). In a prior demographic study of outpatient visits at Boston Medical Center, 119,458 unique patients over 18 years of age were studied, of whom 57.8% were women and 42.2% were male, and the most common ethnicities identified were white (32.24%), Black/African American (29.9%), Hispanic (17.8%), Other (8%), Declined (5.8%), and Asian (4.2%). Data from the 18 subjects who completed both pre- and post-treatment questionnaires were analyzed. There were no significant demographic differences between the two treatment arms (Table 1).

In terms of symptom duration at time of enrollment, the majority of respondents reported that they first experienced symptoms more than one year ago (71%, n=28), and 57% of respondents also stated their current episode had been ongoing for more than one year.

The mean mRSI score improved in the amitriptyline arm after treatment by 2.7 points from 18.7 to 16.0 (standard deviation 7.1) and worsened in the placebo arm by 0.4 points from 21.3 to 21.6 (standard deviation 12.0). When comparing the change in mean mRSI scores from pre- to post-treatment between the two arms, the difference was not statistically significant with an unpaired two-tailed t-test (p= 0.5). There was also no significant difference in pre-treatment mean mRSI scores between groups (amitriptyline 18.7±8.0, placebo 21.3±7.4, p=0.5).

The mean pre-intervention VHI score for the amitriptyline group was 2.3±1.3 while the pre-intervention VHI score for the placebo group was 8.9±10.7; however, there was no significant difference between groups (p=0.07). The mean post-intervention VHI score for the amitriptyline group was 5.3±3.9 while the post-intervention VHI score for the placebo group was 8.9±12.1. There was no significant difference in change in VHI score between the amitriptyline group and the placebo group (p=0.27).

When questioning the subjects on overall severity of symptoms (on a 0-10 scale) over the past week the mean value for pre-intervention in the amitriptyline group was 6.0 (standard deviation 2.0) while the mean value for severity of symptoms in the placebo group was 7.0 (standard deviation 1.9) with no significant difference between groups (p=0.1). There was no significant change in overall symptom severity before and after intervention between the two study groups (p=0.6) (Table 1).

The most distressing symptoms identified via the modified RSI prior to beginning treatment were frequent throat clearing (mean 3.0, standard deviation 1.6), globus (“sensation of something sticking in your throat or a lump in your throat”) (mean 2.9, standard deviation 1.9), excess throat mucus or postnasal drip (mean 2.8, standard deviation 1.6), reflux (“Heartburn, chest pain, indigestion, or stomach acid coming up”) (mean 2.4, standard deviation 1.7) and throat pain or burning (mean 2.4, standard deviation 1.9). Voice symptoms were

Table 1: Demographics and outcomes in amitriptyline vs. placebo arms.

	Amitriptyline (n=9)	Placebo (n=9)	P value*
Male Gender	6	5	1.0
Age in years	42 (17)	49 (18)	0.4
Pre-treatment RSI score	18.7 (8.0)	21.3 (7.4)	0.5
Change in RSI score	-2.7 (7.1)	+0.3 (12.0)	0.5
Pre-treatment VHI score	2.8 (4.1)	8.9 (10.7)	0.1
Change in VHI score	+3.7 (6.1)	0 (4.3)	0.2
Pre-treatment symptom severity (on scale of 0-10)	6.0 (2.0)	7.0 (1.9) (n=8)	0.1
Change in symptom severity	-1.0 (1.4) (n=7)	-0.3 (3.3) (n=7)	0.6

*For gender, Fisher’s exact test with 2 tails was used; t-test with 2 tails was used for all other variables. Equal variance between treatment arms was assumed. Mean (standard deviation) displayed for all variables except gender.

Table 2: Severity of symptoms before and after treatment*.

Symptom (Mean ± standard deviation)	Amitriptyline Pre-Treatment	Amitriptyline Post-Treatment	Placebo Pre-Treatment	Placebo Post-Treatment
Overall Symptom Severity	6.0±2.0	5.3±2.1 (n=7)	7.0±1.9 (n=8)	6.7±2.6 (n=7)
Modified RSI (Severity: 0=none, 5=severe)				
Hoarseness or a problem with your voice	1.5±1.8 (n=8)	1.2±1.6	1.8±2.2	2.1±2.5
Clearing your throat	2.9±1.3	2.8±1.0	2.4±2.1	2.8±1.9
Excess throat mucus or post-nasal drip	2.3±1.8	2.2±1.3	2.7±1.7	2.0±1.9
Coughing after you ate or after lying down	1.0±1.7	0.7±1.1	2.3±2.2	1.4±2.0
Breathing difficulties or choking episodes	0.8±1.4	0.4±0.8	1.3±1.5	0.9±1.8
Troublesome or annoying cough	1.7±1.4	0.8±1.2	1.7±1.7	2.2±2.1
Sensations of something sticking in your throat or a lump in your throat	3.3±2.1	2.8±1.9	2.0±2.1	2.3±2.2
Heartburn, chest pain, indigestion, or stomach acid coming up	1.7±1.5	1±1	3.6±1.5	3.8±1.8
Throat pain or burning	2.1±1.5	2.3±1.3	2.0±2.2	2.7±2.0
Pain with swallowing	1.6±1.1	1.8±1.5	1.8±2.1 (n=8)	1.4±2.2
Average Total mRSI score	18.7±8.0	16.0±7.4	21.3±7.4	21.7±7.4
VHI-10 (0=never, 4=always)				
My voice makes it difficult for people to hear me.	0.2±0.4	1.1±1.1	0.9±1.3 (n=8)	1.0±1.3
People have difficulty understanding me in a noisy room.	0.6±0.9	0.8±0.8	1.2±1.5	1.3±1.4
My voice difficulties restrict personal and social life.	0.6±0.9	0.9±1.1	1.1±1.7	0.4±0.9
I feel left out of conversations because of my voice.	0.3±0.5	0.3±0.7	0.8±1.4	0.8±1.3
My voice problem causes me to lose income	0	0.1±0.3	0.4±0.7 (n=8)	0.7±1.3
I feel as though I have to strain to produce voice.	0.1±0.3	0.8±1.0	0.8±1.4	0.9±1.5
The clarity of my voice is unpredictable	0.6±0.9	0.9±1.2	1.2±1.9	1.0±1.3
My voice problem upsets me.	0.3±0.7	0.8±1.4	1.3±1.7	1.3±2.0
My voice makes me feel handicapped.	0	0.1±0.3	0.5±1.0 (n=8)	1.1±1.8
People ask, “What’s wrong with your voice?”	0.1±0.3	0.7±1.4	0.9±1.2	0.3±1.0
Average Total VHI-10 score	2.8±4.1	6.4±6.6	8.9±10.7	8.9±12.7

*n (number of responses)=9 for each value, except where otherwise noted. Omitted responses were excluded from average value calculations for overall symptom severity and individual VHI-10 and mRSI questions. In calculating total VHI-10 and mRSI scores, a 0 was substituted for omitted responses for single questions within each scale.

infrequent, and patients rarely felt that their voice symptoms were a handicap. When present, the most common voice symptom was unpredictable clarity of voice (Table 2).

When asked whether their symptoms had subjectively improved, stayed the same, or worsened after treatment, the majority of patients in the amitriptyline group felt their symptoms had improved (6 out of 9, 66.7%), while the remainder felt their symptoms remained the same (Figure 2). For those who improved, average subjective percentage improvement was 38% (range 10-80%, median 30%). Of note, one subject wrote that symptom severity felt the same post-treatment, then wrote that symptoms were 30% improved compared to prior to treatment, so the response was interpreted as having improved. In the placebo group, only 44.4% (4 of 9) felt their symptoms were better, while another 3 felt the same, and 2 actually felt worse. Of those who improved, average percentage improvement was 48% (range 20-80%, median 45%).

The percentage of patients experiencing side effects was higher in the amitriptyline arm (6 of 9, 66.7%) vs. the placebo arm (2 of 9, 22.2%). In the amitriptyline arm, dizziness (4 of 9, 44.4%) was the most frequent side effect, followed by fatigue (3 of 9) and dry mouth (1 of 9). In the placebo arm, the 2 patients complained of both dry mouth and dizziness, and one of the two patients also noted increased fatigue. Subjects took an average of 2.1 pills daily by the end of the 8 week treatment period (median 2, range 1-4) in the amitriptyline arm, vs. 2.25 (median 2, range 1-4) in the placebo arm. Most patients confirmed that they took the pills daily, but may have missed a few doses. In the placebo arm, one patient took the pills every other day instead, and another patient took pills in the morning and evening. In the amitriptyline group, 4 patients thought they were taking

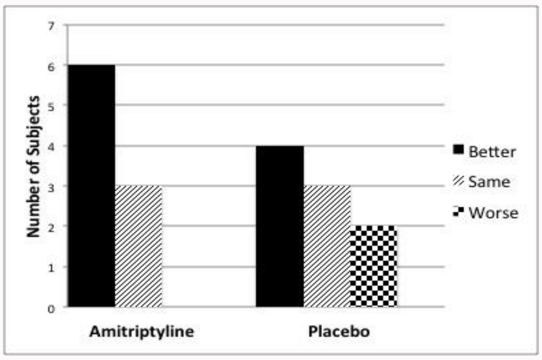

Figure 2: Change in overall symptom severity.

placebo, 3 thought they were taking amitriptyline, and 2 did not respond. In the placebo group, 4 patients thought they were taking amitriptyline, 2 placebo, and 3 did not respond. Using Pearson's correlation coefficient, there was no significant correlation between change in RSI score and pre-treatment scores of overall symptom severity (p=0.83). Analyzing the subjects in the amitriptyline group (n=9), there was no significant correlation between change in RSI and average dose of amitriptyline (p=0.7264). Multiple linear regressions did not reveal a significant association between change in RSI score and pre-treatment scores of overall symptom severity and age. The overall model was not significant (p=0.8860; R^2=0.0160). Individual variables within the model were also not significant: subjective pre-treatment overall symptom severity scores (scale 0-10) (β= -0.4529; p=0.6452); age (β=-0.01365; p=0.9323). A different model including dose and age as the independent variables to predict change in RSI was also determined to not be significant (p=0.7987, R^2=0.034). Analysis of individual variables within the model demonstrated that both variables were not significantly associated with change in RSI: dose (β= 0.0238; p=0.7931) and age (β= -0.09935; p=0.5264).

Discussion

Although there is a trend toward greater subjective improvement in overall symptoms with amitriptyline, interpretation is limited due to the small sample size thus far. This study will continue with some modifications. Adverse side effects in this study were those commonly noted with amitriptyline, including fatigue, dizziness, and dry mouth. There were no known serious adverse side effects, and the rate of loss to follow up was the same in both amitriptyline and placebo arms, suggesting that side effects were not the primary reason for subject drop out.

Analysis of individual questions in the modified RSI and VHI-10 scores also revealed that certain symptoms may be much more specific to patients with presumed CLN, such as throat clearing, globus, sensation of excess throat mucous, acid reflux, and throat pain. Interestingly, despite symptoms such as throat pain and globus, pain with swallowing was rare, further supporting the idea that these patients are not experiencing anatomic or functional obstruction, and are rather experiencing neuropathic pain. Voice symptoms were uncommon. This suggests that better metrics are needed to characterize CLN.

In addition to small sample size, results may have been affected by subject adherence to dosing schedules, as well as undertreatment of CLN based on the doses of amitriptyline used in this study. Although subjects were contacted every 2 weeks to discuss dosing regimen and adverse side effects, errors in dosing may have still occurred (i.e., missed doses), and we relied on subjects to accurately recall the regimen they followed over the prior 8 weeks. The amitriptyline dose range for this study was chosen based on current FDA guidelines and prior literature results. For its on-label use for outpatient treatment of depression in the United States, amitriptyline is prescribed at 25-50 mg PO qHS initially and increased by 25 mg every 5-7 days up to a maximum dose of 100-200 mg/day. Prior studies of amitriptyline in chronic laryngopharyngeal neuropathy used doses of 10 mg qHS (6,10) or 25 mg PO daily (9). Other known off label uses of amitriptyline include postherpetic neuralgia, migraine prophylaxis, and eating disorders, with prescribed doses ranging from 10-150 mg qHS.

Although the diagnosis of CLN is ultimately one of exclusion, it is possible that there may have been other confounding factors causing subjects' symptoms, despite our efforts to exclude them. For instance, although subjects with a prior history of major depression were excluded, and all patients had previously failed at least a 2- month course of treatment with proton-pump inhibitor, patients could have had as-of-yet undiagnosed underlying psychiatric disorders, or not maximized medical therapy for GERD (i.e., use of various anti-reflux medications, escalation to maximum dose, and lifestyle changes). If symptoms were attributable to a non-neuropathic etiology that was undertreated, it is possible that improvement in some patients with CLN alone could have been masked by patients with other etiologies that could not be treated by amitriptyline. There is no way to prove that diagnostic entity that we call CLN exists, but hopefully more studies like this will help with this determination.

Conclusions

Although there was a trend toward greater improvement in symptom severity with amitriptyline vs. placebo, the difference between treatment arms was not statistically significant due to small sample size. This study highlights the need for larger randomized controlled trials to determine the efficacy of neuropathic agents in the treatment of chronic laryngopharyngeal neuropathy, as well as a need for better metrics to characterize and diagnose this disorder.

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Registration

ClinicalTrials.gov Identifier NCT 02434523.

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