Effects of Radiofrequency Ablation of Posterior Nasal Nerves on Inflammatory Cytokines, Peak Nasal Inspiratory Flow, and Nasal Blood Flow in Patients with Chronic Rhinitis

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Protocol Title:	Effects of Radiofrequency Ablation of Posterior Nasal Nerves on Inflammatory Cytokines, Peak Nasal Inspiratory Flow, and Nasal Blood Flow in Patients with Chronic Rhinitis
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Study Coordinator:	Dr. David Z. Allen
Population:	Will be enrolling at least 36 patients of good health with chronic rhinitis. Patients will be eligible for intervention if they have chronic rhinitis symptoms for at least 6 months and have failed medical treatment. Patients will be enrolled at the Texas Medical Center in Houston, Texas.
Number of Sites:	Single site / UT Houston is the only site
Study Duration:	Twelve Months
Subject Duration:	14 weeks, 28 weeks if patients decide to participate in the optional last patient visit

General Information

Patients with chronic rhinitis (CR) often fail medical management. In-office radiofrequency ablation (RFA) of the posterior nasal nerve (PNN) has been established as an effective therapy for CR. However, understanding the objective response, such as nasal patency as determined by peak nasal inspiratory flow (PNIF) and changes to type 2 cytokine profiles, to this treatment has yet to be elucidated. We will be performing RFA of the PNN and evaluating the change in PNIF, patient symptom scores and cytokine changes thereafter in patients with CR.

Background Information

CR is inflammation of the nasal mucosa that leads to symptoms such as sneezing, congestion, and post-nasal drip that is separated by an allergic response - allergic rhinitis and non-allergic rhinitis (NAR). AR is an IgE-mediated inflammation of the nasal mucosa while NAR is non-IgE-mediated and has multiple etiologies including vasomotor, hormonal, and occupational among others. Overall, the condition affects 40 million people in the US annually and is a contributor to healthcare utilization and morbidity. Research has illustrated that contributors to AR are cytokines such as Interleukin (IL-) 3, 4, 5 whom stimulate immunoglobulin production and recruit inflammatory cells such as mast cells and eosinophils. In NAR, the pathophysiology is less clear and may be associated with irregularities of neural function. Regardless, AR treatment consists of a steroid and/or antihistamine spray, saline irrigations, and antihistamines. For NAR,

anti-cholinergic sprays in addition to broad-based therapies such as steroid/antihistamine sprays are utilized. In both, there is a high rate of persistent symptoms, treatment failure, and prolonged medication administration, thus forcing patients to seek procedural interventions. Historically, options have included septoplasty, turbinate reduction, vidian neurectomy and/or posterior nasal nerve (PNN) neurectomy. However, these procedures incur risks and are typically performed in the operating room. Recently, office-based procedures have been introduced to address symptoms of nasal congestion and drainage. Temperature-controlled radiofrequency ablation (RFA) is a safe in-office procedure that has been shown to decrease symptoms. However, no data has been reported on effects of RFA on objective variables associated with rhinitis. Peak nasal inspiratory flow (PNIF) is an objective outcome for nasal congestion which is a simple, cost-effective, and reliable measure that is performed in-office. To our knowledge, PNIF has not been studied as a measure of the effectiveness of RFA of PNN. We believe that this procedure will improve nasal patency and thus PNIF. Finally, RFA of PNN has been proposed as a therapeutic option for both AR and NAR, as it has shown to be effective in all types of chronic rhinitis, possibly by changing the underlying cytokine profile in the disease. For instance, type 2 cytokines are elevated in AR and are critical in its pathophysiology. We propose that the positive symptom effects of RFA in CR patients may be linked to changes in Type 2 cytokines and we seek to measure those levels. We will then attempt to correlate or understand the relationship that these objective values have with subjective patient scores that are well established in the literature such as reflective total nasal symptom score (rTNSS) and nasal obstruction symptom evaluation (NOSE) values.

Objectives

In summary, the primary outcome of this project is to determine how RFA of the PNN affects underlying cytokine profiles in addition to peak nasal inspiratory flow levels. The secondary outcomes of this study will be to assess how RFA of the PNN changes subjective symptom scores such as rTNSS and NOSE.

Study Design

This will be a prospective, single-arm single institution study with enrollment at the Texas Sinus Institute at The University of Texas Health Science Center at Houston. The patients will be enrolled through a 12-month time frame. Each patient will have a required 14-week participation window with an optional visit at 28 weeks as well. We will be assessing the objective and subjective response of RFA of the PNN in patients with rhinitis. At each post-procedure visit including the procedure visit, we will be assessing side effects and adverse events of the treatment. The primary outcome of this project is to determine how RFA of the PNN affects underlying cytokine profiles in addition to peak nasal inspiratory flow levels, which will be determined at weeks 0 and 12 for cytokine changes and weeks 0, 4, 12 and an optional 26 weeks for PNIF. The secondary outcomes of this study will be to assess how RFA of the PNN changes subjective symptom scores such as rTNSS and NOSE and this will be assessed at weeks 0, 4, 12 and an optional 26 weeks.

Study Population

Patients between the ages of 18-80 will be eligible for intervention if they have chronic rhinitis symptoms for at least 6 months (rhinorrhea, congestion, post-nasal drip), poor response to

medical management that was attempted for at least 4 weeks, a rTNSS score ≥6, as well as ≥2 for rhinorrhea, and ≥1 for congestion. Exclusion criteria consists of active sinusitis, rhinitis medicamentosa, recurrent and ongoing epistaxis, immunodeficiency as defined by an illness or a history of sinus surgery. We will perform a query within the electronic medical record to assist in finding patients with chronic rhinitis.

The following ICD-10 codes will be used:

- J30.9 Allergic Rhinitis
- J30 Vasomotor rhinitis
- R09.82 Post-nasal drip/Chronic Rhinitis
- J34.89 Rhinorrhea
- J30.81 Animal Dander rhinitis
- J30.89 Dust rhinitis
- J30.5 Food induced rhinitis
- J31 Atrophic rhinitis

Then we will reach out to them and offer them participation in the study.

Study Procedures

There will be a total of four required visits with an optional fifth visit. At the first visit, enrolled participates will be screened and stopped on all intranasal corticosteroids. The total clinic appointment should not exceed 30 minutes. At this visit, we will be obtaining all relevant demographic information for analysis such as age, gender, years of rhinitis symptoms, medical co-morbidities, types of medical management that had been trialed and for how long, history of other allergic symptoms, and specific allergic triggers or prior allergy test results. We will collect this through the electronic medical record and then collate and save this data on an encrypted hard drive. At the second visit (at least two weeks from the first visit), we will teach and train participants to perform PNIF for which we will take the highest of three repeated values, we will also collect rTNSS and NOSE values in addition to nasal secretions prior to the procedure. The patient will fill the symptom score evaluations out on handouts, and we will tabulate the responses on an encrypted drive. We will collect the PNIF values on the electronic medical record and then record and save them on an encrypted hard drive. Our laboratory has established a protocol utilizing a White Blood Cell Isolation Medium called Leukosorb (Pall Corporation, New York) for nasal secretions. The Leukosorb paper is an efficient way to collect nasal secretions for cytokine analysis. The 1 x 1 cm paper will be placed over the posterior aspect of the inferior turbinate near the treatment site under endoscopic visualization. The paper is left in place for 5 minutes and then retrieved into an Eppendorf tube on ice. The paper will be stored at -80 until processed. To process, the paper collected secretions are eluted from the Leukosorb paper by centrifugation and stored at -20C for analysis by Biolegend. For confidentiality, each patient will be assigned a study identification number and all samples collected will be labeled with a study identification number. The document key correlating patient to their study identification number will be stored in a password protected document on UT server. For the treatments, we will be using Neurent Medical's Neuromark™ system

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(Neurent, Ireland). This device has been approved by the FDA for treatment of chronic rhinitis. The NEUROMARK device is an in-office, disposable bipolar RFA device with a treatment tip consisting of micro electrodes which delivers RF energy while monitoring appropriate tissue contact to maximize delivery to posterior nasal nerve and its variable branching. After topical anesthesia consisting of oxymetazoline and 1% lido followed by 4% lidocaine, the device will be placed in the posterior inferior turbinate under endoscopic visualization. The device will be activated per manufacturer's instructions. After the procedure we will allow the patient to recover appropriately and ask for any adverse events or side effects at that time. We will detail these adverse events in the electronic medical record and record them in the encrypted hard drive. The second visit should take around 45-90 minutes. There will be subsequent visits at week four post procedure and week twelve post procedure. At week four we will be assessing side effects and adverse events in addition to obtaining rTNSS, NOSE, and PNIF values. This visit should not take more than 20-30 minutes. At week 12 post-procedure we will be obtaining rTNSS, NOSE, PNIF and nasal secretions for cytokine analysis. This visit should take around 30-45 minutes at most. The last optional visit, week 26 post-procedure, will be identical to week 4's visit, and should last no more than 30 minutes. The total clinic time required will be 150 minutes with an optional extra 30 (180 minutes) should patients want to participate in the final clinic visit. After week 12, statistical analysis and comparative analytics will be initiated.

Data and Safety Monitoring

Adverse events are not expected however should they occur patients will report them to the PI of the study. Any Adverse or unanticipated events will be reviewed monthly during regularly monthly meeting involving Drs. Luong, Citardi and Yao. The adverse events will be adjudicated by the committee. A log of these events will be kept. Any adverse event resulting from the device will be reported to the company.

Statistics

This study will be a prospective analysis. The primary endpoint is the change in PNIF from baseline after RFN treatment of the PNN at 12 weeks. Prior literature has shown that treatment of rhinitis can lead to an increase of PNIF in variable amounts depending on baseline. Literature suggests an average increase of PNIF to be around 25-35 L/min after treatment, with a standard deviation (SD) of approximately 30 L/min. With an average expected change of 30, SD of 30, and 80% power at alpha of 0.05, the minimum sample size should be 32. Assuming a 10% dropout rate, we seek to enroll 36 eligible subjects. We will also perform analyses of rTNSS and NOSE scores. As has been published, a patient will be considered a "responder" if they have at least 30% reduction of rTNSS at 12 weeks and ≥1 NOSE class improvement or a reduction in NOSE at least 20% from pre-treatment. Additionally, the minimum clinically important difference (MCID) for the RQLQ(S) is established at ≥0.5 points and 20 for PNIF. We will be performing statistical analysis after each post-procedure visit, but the primary objective will be evaluation of the PNIF and cytokine changes after week 12. However we will also assess how PNIF scores change at weeks 4 and 26 in addition to week 12. The secondary outcomes will be to assess how RFA of the PNN changes subjective symptom scores such as rTNSS and NOSE at weeks 4, 12,

and 26. Comparative analytics will be performed on all groups. Paired t-tests, Wilcoxon-Mann t-tests, chi-squared tests and ANOVA analysis will be used. Criteria for termination of the study could be poor recruitment in which the study could not be completed within 3 years.

Ethics

We will be obtaining a waiver of consent for every patient. Each patient will have a unique identifier without any identifiable medical information. There is a risk of data breech however all information will be stored on a HIPPA compliant database on a University of Texas server that will be de-identified. The patient information will be kept using a linking log and a unique patient identifier for each patient. All data will be saved on encrypted University of Texas computers using the HIPPA compliant database. Patient information and data will be stored for three years.

Data handling and record keeping

Only collaborators of this investigation will have access to the patient data and information. We will be ensuring that all patients have a unique identifier without any medical information. All data will be saved on an encrypted hard drive and encrypted data sheets. Human subjects will not be identifiable.

Quality control and assurance

An electronic medical record will be kept for each study visit. Data documents will be compared to electronic medical record to confirm accuracy of collected data. Audits of the source data will be performed by the faculty mentor on a minimum of annual basis. Source data will be audited by at least two members of the research team after each study visit.

Publication Plan

Findings will initially be presented at American Academy of Otolaryngic Allergy conference. Thereafter, we will seek to publish our results at a high-impact, and clinically relevant, journal.