Double-Blinded Randomized Prospective Trial of Intranasal Capsaicin Treatment for Non-Allergic Irritant Rhinitis

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Protocol Title: Double-Blinded Randomized Prospective Trial of Intranasal Capsaicin Treatment for Non-Allergic Irritant Rhinitis

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Population: The study population will consist of patients with non-allergic irritant rhinitis (NAIR) as defined by history (symptoms of nasal congestion, rhinorrhea, nasal itching or sneezing upon exposure to nasal irritants) and positive optical rhinometer (Rhinolux™, Rhios GmbH, and Germany) response with intranasal challenge with capsaicin. Participants will be sought from those presenting to the outpatient Otolaryngology clinic at the University of Texas Medical School at Houston. Patients included in the study will be between the ages of 18 and 70 with no history of sinonasal surgery, intranasal steroid use for more than 4 weeks, intranasal or systemic antihistamine for 3 days, intranasal or systemic decongestants for 3 days, chronic rhinosinusitis, inflammatory or granulomatous diseases, asthma, allergic rhinitis, immunocompromised state or radiation to the head and neck.

Sample size: 11 participants will need to be recruited to each group (experimental and control) to detect a significant post-treatment change. In order to reach our target enrollment of 22 participants we expect to screen 60 subjects.

Number of sites: single site

Study duration: 13 weeks

Subject duration: 13 weeks

General Information: The proposed study seeks to investigate the effect of intranasal capsaicin treatment in patient with Non-allergic irritant rhinitis (NAIR), as well as evaluate optical rhinometry (ORM) as a means to quantify symptomatic improvement in NAIR patients during and after treatment.

Background Information:

Rhinitis is defined as inflammation of the membranes lining the nose, characterized by symptoms including itching, rhinorrhea, and/or nasal congestion. It is a common clinical illness throughout the world and is consistently ranked among the most frequent of chronic illnesses, significantly affecting the quality of life of patients and their families. Non-allergic rhinitis is defined as rhinitis symptoms in the absence of an identifiable allergy, structural abnormality, or sinus disease. Non-allergic irritant rhinitis (NAIR) affects as many as 17 million Americans, and approximately 22 million suffer a combination of allergic rhinitis (AR) and NAIR (1).

The pathophysiology of NAIR is largely unknown. It is described as a non-specific nasal hyper-reactivity that occurs on exposure to non-immunologic stimuli including changes in temperature, strong odors, and airborne irritants. Nasal mucosa is innervated by autonomic and

sensory neurons. Such stimulation of sensory fibers (C and Aδ) can lead to the irritative effects including sneezing, itching, rhinorrhea, and pain (2). Such effects are believed to be mediated by the trigeminal system.

The trigeminal nerve fibers in the nasal cavity respond to a wide variety of chemical stimuli. One known receptor is the TRPV-1 vanilloid receptor. Capsaicin is one such ligand of the TRPV-1 receptor; however, the receptor is also activated by noxious temperatures and low extracellular pH (3). Stjarne et al showed that although capsaicin acts as an irritant in controls and rhinitic patients, those with NAIR reported increased rhinorrhea and nasal congestion (4). In animal studies, capsaicin has been shown to stimulate sensory C-fibers releasing substance P and calcitonin gene related peptide (CGRP), both potent vasodilators (5). However, repeated stimulation showed desensitization and degeneration of C-fibers (6), which is the basis for capsaicin usage in pain treatment.

Currently, intranasal steroids are the only FDA approved agents used in NAIR. Topical applications of capsaicin have been used in the treatment of pain particularly in post-herpetic neuralgia, post mastectomy pain, and hypersensitivity disorders of the lower urinary tract (7-9). LaCroix et al has shown that repeated administration of intranasal capsaicin decreased nasal symptoms in NAIR patients (10). Although multiple studies using intranasal capsaicin have been shown to improve nasal symptoms of NAIR patients (11-13); there have been no studies in which NAIR patients were objectively identified and symptom improvement was objectively monitored.

Optical rhinometry (ORM) has been proposed to be a useful instrument in the assessment of nasal blood flow, as an indirect measurement of nasal congestion (14). A positive correlation has been made between optical rhinometry and symptom scores for nasal congestion in nasal provocation testing (15). ORM has also been shown to correlate with changes in nasal cavity cross sectional area measured via acoustic rhinometry (16). In addition, our group recently reported that ORM following 0.05 mM capsaicin challenge can be utilized to identify NAIR patients (17).

A study by Lambert et. al. (2012) was able to objectively identify patients with NAIR by intranasal capsaicin challenge followed by assessment with optical rhinometry (17). Studies have shown that capsaicin therapy can improve symptoms of patients historically identified with NAIR via visual analog scale (VAS) rating of symptoms and symptom surveys; however, there has been no study evaluating the capsaicin therapy on patients objectively identified as NAIR patients.

Multiple studies have demonstrated that intranasal capsaicin can improve nasal symptoms of NAIR patients (11-13). Regarding the usage of capsaicin, there is a product on the market: Sinus Buster which has capsaicin as the active ingredient. Numerous research papers have evaluated the efficacy and safety of Sinus Buster for the treatment of congestion in non-allergic rhinitis patients (5, 12). However, the diagnosis of NAIR in these previous studies was based primarily on history. In addition, the primary outcome in these studies was symptomatic without any objective evaluation. The goal of this study will be two-fold: with patients objectively identified as NAIR patients via the optical rhinometer, we will re-evaluate the therapeutic action of intranasal capsaicin on the management of rhinitic symptoms. We expect that the patients will show significant improvement in their symptoms. We will then use optical rhinometry as a means to objectively monitor changes in symptoms in NAIR patients. We expect that post treatment, patients will no longer have the positive response previously seen on intranasal capsaicin challenge before receiving treatment. We hope to be able to establish optical

rhinometry as an objective measurement of symptom improvement for NAIR symptoms, along with the subjective patient surveys.

Objectives:
1. To establish optical rhinometry as an objective means of evaluating changes of NAIR symptoms after treatment.
2. To re-evaluate the therapeutic action of intranasal capsaicin on the management of rhinitic symptoms in objectively defined NAIR patients.

Study Design:

The study will consist of patients with non-allergic irritant rhinitis (NAIR) as defined by history (symptoms of nasal congestion, rhinorrhea, nasal itching or sneezing upon exposure to nasal irritants) and positive optical rhinometer (Rhinolux™, Rhios GmbH, and Germany) response with intranasal challenge with capsaicin (17). Participants will be sought from volunteers and those presenting to the outpatient Otolaryngology clinic at the University of Texas Medical School at Houston. Patients included in the study will be between the ages of 18 and 70 with no history of sinonasal surgery, intranasal steroid use for more than 4 weeks, intranasal or systemic antihistamine for 3 days, intranasal or systemic decongestants for 3 days, chronic rhinosinusitis, inflammatory or granulomatous diseases, asthma, allergic rhinitis, immunocompromised state or radiation to the head and neck.

Allergy Testing to Identify and Exclude Subjects with Allergic Rhinitis

All previously consented subjects with history consistent with NAIR will be screened with a skin prick test (Multi-Test II Lincoln Diagnostics, Decatur, IL USA) to 6 common allergens including dust mite, mixed mold extract, cat hair, grass pollen, insect extracts, and bermuda grass extract to exclude allergic rhinitis. Those with confirmed negative skin prick testing will be eligible for the study.

Capsaicin Challenge and Optical Rhinometry

The optical rhinometer apparatus is applied to either side of the nasal dorsum according to the manufacturer's instructions. A one-minute baseline recording will be obtained and averaged. Capsaicin solution (Sigma Chemical, St. Louis, MO USA) will be diluted in 1% ethanol vv and 0.9% normal saline. 1% ethanol in 0.9% normal saline will serve as the vehicle solution. A mucosal atomizer device (MAdomizer, Wolfe Tory Medical, Inc Salt Lake City, UT USA delivering a 100 µl solution will be used to deliver a dose of capsaicin totaling 1.5 µg of caspsaicin (0.05 mM) to the anterior face of the inferior turbinate of each nare. The maximum change in optical density (OD) will be recorded. Patients with a maximum change in OD of at least 0.2 will be considered a positive response and included in the study.

A composite symptom score will be recorded based a commonly used rhinitis rating system as recommended by the FDA for clinical trial studies on allergic rhinitis (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf). Each of the following 4 symptoms: nasal itching/tingling, nasal congestion, sneezing and rhinorrhea, will be rated on a 0-3 scale of severity (Appendix B) and a summed composite score will be recorded for each subject.

Capsaicin Treatment Concentration

The capsaicin solution will be prepared by using the formula previously reported by Van Rijswijk et al; (0.1mmol/l) diluted in ethanol and 0.9% normal saline (19). Using the MAD, 0.8mL will be delivered to each nasal cavity for a total of 24.4 ug per nasal cavity.

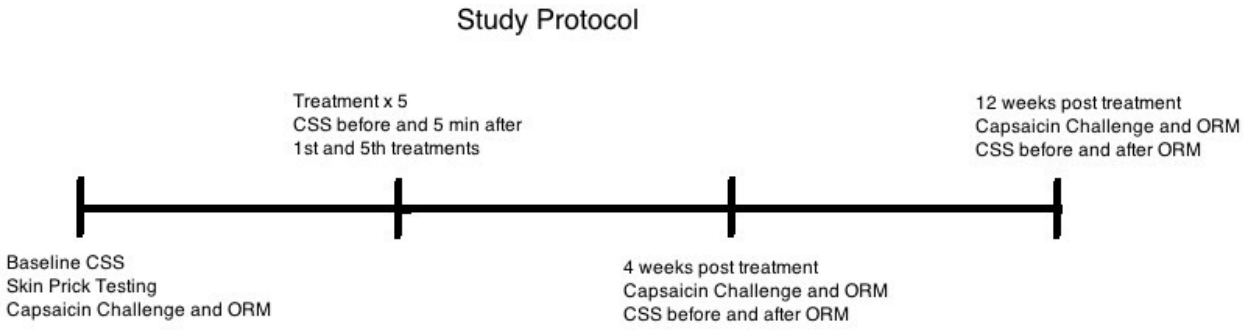
Study Procedure:

There will be a total of 4 visits. On the first visit, patients will be consented and undergo skin prick testing, the capsaicin challenge and Optical Rhinometry. Prior to undergoing the capsaicin challenge, a composite symptom score will be recorded. Patients with confirmed negative skin prick testing, and positive response on ORM will be eligible for the study and will be asked to return for treatment. Those who are not eligible will not be responsible for any costs associated with screening and will be compensated for parking as well as $25.00 for their time.

At the second visit, the NAIR patients will have been randomized and blinded into two groups: Group A will be treated with vehicle spray; and Group B will be treated with the capsaicin spray. The PI will be blinded to the treatment. A member of the research team, which consists of Drs. Amber Luong, Martin Citardi, Samer Fakhri, and Faramarz Ashoori (research coordinator), will assist during the randomization and distribution of appropriate pre-made medications so that the PI and subjects remain blinded.

5 consecutive applications of capsaicin or placebo will be administered intranasally, with 1 hour between each application. Fifteen minutes prior to each application of medication, the nasal mucosa will be anesthetized with 100 ul of 1% lidocaine will be applied to each nasal cavity via MAD for all study participants. The lidocaine should not alter the nasal mucosa reaction to capsaicin; and is meant to anesthetize the area from the mild stinging of capsaicin. In fact, because lidocaine has a very mild stinging sensation at times; it can serve to mask the stinging one may get with intranasal capsaicin. Using the MAD, 100 µL of 1% ethanol in 0.9% saline solution (Group A) or 0.8 mL solution with (0.1mmol/l) of capsaicin in 1% ethanol in 0.9% saline (Group B) will be delivered to each nasal cavity. On this day, they will not need to undergo optical rhinometry. Patients will fill out composite symptoms scores before and five minutes after 1st and 5th treatments. Patients who complete this portion of the experiment will receive $50 dollars in compensation as well as parking.

Patients will then follow up 4 and 12 weeks after initiating treatment. At the 4 week and 12 week follow-up appointments, subjects will undergo capsaicin challenge followed by ORM and composite symptom score of nasal symptoms will be reported. Patients who complete both follow up visits will receive $25 dollars in compensation as well as parking.



Compensation:

In summary, patients that undergo the screening process and complete the skin prick testing and intranasal capsaicin challenge and ORM will be compensated $25 as well as parking validation. Patients that undergo the treatment will be compensated $50 plus parking for completing that day. Patients that complete the study and return 4 and 12 weeks post treatment, will be compensated $25 plus parking.

Data and Safety Monitoring:

Previous studies have shown that the concentration of capsaicin that will be used is generally well tolerated.

Regarding the lidocaine, it is administered routinely in our clinic prior to nasal endoscopy and flexible laryngoscopy exams. Side effects can include minor stinging and burning when applied to the nose. Because it is an intranasal spray, there is a risk that patients will swallow it and may have difficulty swallowing for up to 45 minutes after application. We express to patients that they should avoid eating or drinking anything up to 45 minutes after the lidocaine application.

Regarding skin prick testing, patients may have mild discomfort where the skin is pricked. They may have symptoms such as itching, a stuffy nose, red watery eyes, or a skin rash. Rarely, people can have anaphylaxis, but this usually only occurs with intradermal testing, which we will not be performing. If patients become short of breath, we do have oxygen available in the clinic.

Patients will be educated to call the outpatient Otolaryngology clinic at the University of Texas Medical School at Houston if there are any adverse effects.

Human Subjects:

Participants will be sought from those presenting to the outpatient Otolaryngology clinic at the University of Texas Medical School at Houston. Patients included in the study will be between the ages of 18 and 70 with no history of sinonasal surgery, intranasal steroid use for more than 4 weeks, intranasal or systemic antihistamine for 3 days, intranasal or systemic decongestants for 3 days, chronic rhinosinusitis, inflammatory or granulomatous diseases, asthma, allergic rhinitis, immunocompromised state or radiation to the head and neck.

This is a small study of only 22 subjects total and as addressed previously we anticipate screening 60 subjects in order to complete our enrollment. . Our practice consists of adult patients with a majority of who speak and read English. Therefore, it is unlikely to exclude a subject from the study because they do not speak or read English

Statistical Analysis:

Justification of sample size:

Using Dr. Lambert's paper (17) : his article showed the average maximum optical density in NAIR patients was 0.2 (SD 0.051), seen when using the 0.05 mM concentration of capsaicin during the capsaicin challenge and ORM. Healthy control subjects had a mean maximal OD change of 0.174 (SD 0.034). This was significant to p=0.01. Based on this data, 11 patients will need to be recruited to detect a significant post-treatment change.

Student's t-test will be used to compare the mean change in composite symptom scores pre and post-treatment in both groups. Student's t-test will also be used to compare changes in maximal optical density in response to capsaicin challenge pre- and post-treatment in both

groups. Statistical significance will result if $p < 0.05$. The Spearman Rank Correlation will be used to analyze associations between composite symptom scores and changes in OD.

Ethics:
IRB approval will be sought from CPHS

Data Handling and Record Keeping: In order to maintain confidentiality, a data sheet with patient's names and data collected for the study (see data sheet) will be stored in a locked file cabinet within the department of Otorhinolaryngology. Access to data sheets in patient will be limited to co-investigators and research coordinator. Only de-identified data or collective data will be shared.

Quality control and assurance: In order to confirm that the diagnosis of non-allergic irritant rhinitis is accurate and made in an unbiased manner, a history of rhinitic symptoms will be confirmed with objective skin testing.

All datasheets will be recorded by PI and reviewed by at least one of the other 3 co-investigators to ensure accuracy in the recording of clinical data.

Publication Plan: This study has been funded by the American Association of Otolaryngic Allergy (AAOA) Foundation Grant. Results from this study will be presented at a future AAOA national meeting and initial publication rights will be given to the International Forum of Allergy and Rhinology.

All enrolled subjects will be notified of any publication resulting from this study, but these publications will present data on only the aggregate group.

REFERENCES

1. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: A critical evaluation of the literature. Pharmacoeconomics 2004;22:345-361.
2. Hummel T. Assessment of intranasal trigeminal function. Int J Psychophysiol. 2000 May;36(2):147-55.
3. Silver WL, Clapp TR, Stone LM, Kinnamon SC. TRPV1 receptors and nasal trigeminal chemesthesis. Chem Senses. 2006 Nov;31(9):807-12.
4. Stjärne P, Lundblad L, Lundberg JM, Anggård A. Capsaicin and nicotine-sensitive afferent neurones and nasal secretion in healthy human volunteers and in patients with vasomotor rhinitis. Br J Pharmacol. 1989 Mar;96(3):693-701.
5. Blom HM, Van Rijswijk JB, Garrelds IM, Mulder PG, Timmermans T, Gerth van Wijk R. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. Clin Exp Allergy. 1997 Jul;27(7):796-801.
6. Ciabatti PG, D'Ascanio L. Intranasal Capsicum spray in idiopathic rhinitis: a randomized prospective application regimen trial. Acta Otolaryngol. 2009 Apr;129(4):367-71.
7. Sicuteri F, Fusco BM, Marabini S, Campagnolo V, Maggi CA, Geppetti P, Fanciullacci M (1989) Beneficial effect of capsaicin application to the nasal mucosa in cluster headache. Clin J Pain 5 : 49-53
8. Watson CPN, Evans RJ, Watt VR (1988) Post-herpetic neuralgia and topical capsaicin. Pain 33 : 333-340
9. Watson CPN, Evans R J, Watt VR (1989) The post-mastectomy syndrome and the effect of topical capsaicin. Pain 38:177-186
10. Lacroix JS. Buvelot JM. Polla BS. Lundberg JM, Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy 1991; 21:595-600.
11. Bernstein JA, Davis BP, Picard JK, Cooper JP, Zheng S, Levin LS. A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of nonallergic rhinitis. Ann Allergy Asthma Immunol. 2011 Aug;107(2):171-8.
12. Blom HM, Severijnen LA, Van Rijswijk JB, Mulder PG, Van Wijk RG, Fokkens WJ. The longterm effects of capsaicin aqueous spray on the nasal mucosa. Clin Exp Allergy. 1998

Nov;28(11):1351-8.
13. Marabini S, Ciabatti PG, Polli G, Fusco BM, Geppetti P. Beneficial effects of intranasal applications of capsaicin in patients with vasomotor rhinitis Eur Arch Otorhinolaryngol. 1991;248(4):191-4.
14. Hampel U, Schleicher E, Wüstenberg EG, Hüttenbrink KB. Optical measurement of nasal swellings. IEEE Trans Biomed Eng. 2004 Sep;51(9):1673-9.
15. Luong A, Cheung EJ, Citardi MJ, Batra PS. Evaluation of optical rhinometry for nasal provocation testing in allergic and nonallergic subjects. Otolaryngol Head Neck Surg. 2010 Aug;143(2):284-9.
16. Cheung EJ, Citardi MJ, Fakhri S, Cain J, Batra PS, Luong A. Comparison of optical rhinometry to acoustic rhinometry using nasal provocation testing with Dermatophagoides farinae. Otolaryngol Head Neck Surg. 2010 Aug;143(2):290-3.
17. Lambert EM, Patel C, Fakhri S, Citardi MJ, Luong A. Optical rhinometry in non-allergic irritant rhinitis (NAIR): A capsaicin challenge study. Presented at the 2012 American Academy of Otolaryngic Allergy Fall Meeting in Washington, D.C.
18. Mittenzwey H, Wustenberg EG, Leupold W. Optical rhinometry: applicationon children and adolescents for nasal provocation tests. Pedatr Allergy Immunol. 2007 Aug;18(5):372-7.
19. Van Rijswijk JB, Boeke EL, Keizer JM, Mulder PGH, Blom HM, Fokkens WJ. Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinits: a double-blind randomized application regimen study. Allergy. 2003. 58:754-61.