

Double-blinded randomized prospective trial of intranasal capsaicin treatment for nonallergic rhinitis

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Background: Nonallergic rhinitis (NAR) is currently a diagnosis of exclusion with an unclear pathophysiologic mechanism and limited treatment options. In patients diagnosed with NAR based on symptoms, negative skin testing and positive optical rhinometry (ORM), the study's objective was to evaluate the therapeutic action of intranasal capsaicin in the management of rhinitic symptoms and the effect on ORM readings.

Methods: Patients with a history of NAR underwent screening by a diagnostic intranasal capsaicin challenge with ORM and skin-prick testing. Twenty-two NAR patients were enrolled and randomized to either treatment with 0.1mM capsaicin (n = 11) or placebo (n = 11). Treatment consisted of 5 consecutive intranasal applications separated by 1 hour with follow-up at 4 and 12 weeks. At each visit, subjects underwent intranasal capsaicin challenge with ORM reading and a visual analog scale scoring of rhinitis symptoms.

Results: Treatment with intranasal capsaicin resulted in a median change with improvement in total symptom score (TSS) of -5 from baseline vs an increase of 2 with placebo

at 4 weeks, which remained significantly different between the groups at 12 weeks ($p = 0.03$). At 12 weeks posttreatment, 60% of the intervention group vs 80% of placebo-treated patients still met objective criteria for NAR by ORM.

Conclusion: Using ORM in the objective diagnosis of NAR, this trial showed that intranasal 0.1mM capsaicin not only improved rhinitic symptoms but also objectively reduced nasal reactivity and nasal congestion with a 40% responder rate at 12 weeks as noted by ORM. © 2020 ARS-AAOA, LLC.

Key Words:

intranasal capsaicin; nasal congestion; nonallergic rhinitis; optical rhinometry; vasomotor rhinitis; TRPV-1

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Rhinitis describes inflammation of the membranes lining the nose, which presents with common symptoms including itching, rhinorrhea, sneezing, or nasal congestion. It is a chronic illness found worldwide associated with significant burden on quality of life. The definition of rhinitis may be simple, but the diagnosis and management can be far from it.

Rhinitis is divided into 2 broad categories: allergic rhinitis (AR) and nonallergic rhinitis (NAR). Although a

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diagnosis of AR can be confirmed with skin or blood testing, NAR is currently a diagnosis of exclusion. It is defined as rhinitis symptoms in the absence of an identifiable allergy, structural abnormality, or sinus disease. Although the exact pathophysiology is still unknown, it has previously been described as an imbalance in the autonomic nervous system in response to a non-immunologic stimuli within the environment such as changes in temperature, strong odors, and airborne irritants. This is in contrast to AR, which is triggered by an immunoglobulin E (IgE)-mediated response.¹ With a better understanding of pathophysiology and the disease process of NAR, treatment can be directed more appropriately.

The nasal mucosa is innervated by autonomic and sensory neurons (C and A δ) that are mediated by the trigeminal system. When activated by environmental stimulants, these sensory neurons release pro-inflammatory neuropeptides, resulting in rhinitic symptoms.

A known receptor of the trigeminal system is the transient receptor potential cation channel subfamily V member 1 (TRPV-1) vanilloid receptor found on C-sensory fibers within the nasal mucosa. These receptors are activated by noxious temperatures, low extracellular pH, and capsaicin.² In animal studies, capsaicin has been shown to stimulate sensory C-fibers releasing substance P and calcitonin gene-related peptide (CGRP), both potent vasodilators.² However, repeated stimulation caused desensitization and degeneration of C-fibers, which is the basis for capsaicin usage in pain treatment for several diseases including post-herpetic neuralgia, diabetic peripheral neuropathy, and arthritis-related pain.³

Previous studies have shown that repeated administration of intranasal capsaicin decreased nasal symptoms in NAR patients.⁴ Additionally, studies have repeatedly shown that capsaicin therapy can improve symptoms of patients historically identified with NAR via visual analogue scale (VAS) rating of symptoms surveys. These studies defined NAR patients as those with rhinitic symptoms and negative allergy skin testing to exclude AR. To date, there are no studies in which the diagnostic criteria of NAR involves a positive result of an objective criteria and the effects of treatment on this objective criteria.^{5,6,7}

Previously, nasal provocation testing (NPT) has been used to determine nasal response to specific irritants that have been introduced directly to the nose. Several technologies are available to measure the nasal response to the NPT including acoustic rhinometry, rhinomanometry, and rhinostertometry. However, these current technologies have several limitations including inability to monitor response to nasal irritant continuously, not being well-tolerated in a clinical setting, or limited due to nasal anatomy. Consequently, NPT has yet to be widely adopted in clinical practice.

Recently, 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.⁸ Additionally, ORM coupled with NPT has been investigated as an objective means of diagnosing NAR. It also

represents a clinically viable tool as it consists of only a spectacle-like frame with an optical emitter and detector probe that is placed across the nasal dorsum. A 808-nm wavelength is emitted that corresponds to the isosbestic point of hemoglobin, thereby providing a means of measuring changes in total nasal blood volume via change in optical density (OD). The frame is linked to any computer with the software to collect the data.⁵

The utility of ORM coupled with NPT was first described in 2010. A prospective pilot study evaluated ORM as an objective measure of nasal patency in response to NPT. This was evaluated in patients with AR, in response to histamine challenge. A positive correlation between ORM readings and subjective symptom scores for nasal congestion with NPT with intranasal histamine was noted.⁵

Multiple studies have addressed incorporating ORM as an objective tool in addition to negative skin test and rhinitis symptoms in the diagnostic criteria for NAR.^{5,6} In 2012, Lambert et al.⁶ studied 6 rhinitic patients negative for allergy skin testing and 6 health controls. Each underwent NPT with increasing concentrations of intranasal capsaicin (0.005 mM, 0.05 mM, and 0.5 mM). All NAR patients exhibited a dose-dependent increase in change of maximal OD by ORM, reflecting an increase in nasal blood flow, from baseline with increasing capsaicin concentrations. These changes in ORM correlated with numeric analog scores of the rhinitic symptom of nasal congestion. This was not reproduced in healthy control patients without NAR. Consequently, this was the first study to publish the combination of an intranasal capsaicin challenge and ORM as a possible objective clinical diagnostic tool for NAR.

Building on these previously published findings, this study has 2 goals: (1) to use ORM in addition to rhinitic symptoms with negative allergy skin test as the diagnostic criteria for NAR, and (2) to evaluate the therapeutic action of intranasal capsaicin in the management of rhinitic symptoms and on the effect on ORM readings.

Patients and methods

Subjects

Twenty-two patients with NAR were recruited through the outpatient Otorhinolaryngology clinic associated with the McGovern Medical School at the University of Texas Health Science Center at Houston (UTHSC-H). The study was approved by the UTHSC-H Institutional Review Board (MS-14-0173). Informed consent was obtained prior to enrollment.

Inclusion and exclusion criteria

The study population consisted of participants between 18 and 70 years of age diagnosed with NAR, defined by a history of 2 or more intermittent or constant symptoms of nasal congestion, rhinorrhea, or sneezing and negative allergy skin-prick testing for at least 1 year. In addition, enrolled patients tested positive (change in OD of at least 0.2

from baseline) on NPT with 0.05mM capsaicin based on ORM assessment, previously reported by Lambert et al.⁶ in 2016. ORM provides continuous measurement of blood flow in nasal vessels as an indirect assessment of nasal congestion. A greater change in OD from baseline generally notes more nasal blood flow and hence increased congestion. Prior to enrollment, participants had to discontinue intranasal steroids for at least 4 weeks, intranasal or systemic antihistamines for 3 days, and intranasal or systemic decongestants for 3 days. Participants with previous history of sinonasal surgery, chronic rhinosinusitis, inflammatory, or granulomatous diseases, asthma, AR, immunocompromised state, or radiation to the head and neck were excluded from the study.

Study procedure

This study was registered at ClinicalTrials.gov (NCT02493257). This study was a double-blinded, randomized, placebo-controlled trial involving 5 treatments separated by 1 hour with either 0.1mM intranasal capsaicin or a placebo.

The study consisted of a total of 4 clinical visits.

1. At the first visit, participants underwent skin-prick testing to 6 common allergens including dust mite, mixed mold extract, cat hair, grass pollen, insect extracts, and Bermuda grass, along with a positive and negative control to exclude AR. Those confirmed with negative skin-prick testing then underwent NPT with 0.05mM capsaicin analyzed by ORM. A positive response was defined by ≥ 0.2 OD change from baseline by ORM after NPT. Only participants with both a negative skin-prick test and positive NPT response to capsaicin as noted by ORM were eligible for the study.
2. At the second visit, blinded participants were randomized into 1 of 2 groups:
 - a. Group A: treated intranasally with placebo, 1% ethanol in 0.9% saline solution;
 - b. Group B: treated intranasally with 0.1 mM capsaicin, which was prepared using the formula previously reported by Van Rijswijk et al.⁹; (0.1 mmol/L) capsaicin diluted in ethanol and 0.9% normal saline.
3. Five consecutive intranasal applications of 0.1mM capsaicin or placebo were administered intranasally with a mucosal atomizer device with 1 hour between each application. The investigator who was administering the intranasal treatment was blinded. Prior to each treatment, the nasal mucosa of all participants were anesthetized with 100 μ L of 1% lidocaine in each nasal cavity via an atomizer. The lidocaine does not alter the nasal mucosa reaction to capsaicin, and causes a mild stinging sensation, masking the effects of intranasal capsaicin. The masking effects of lidocaine allow the subjects to be also be blinded to the treatment.
4. Participants followed up at 4 weeks and then again at 12 weeks after treatment. During the follow-up appointments, participants had symptoms assessed by

VAS and underwent a diagnostic NPT with 0.05mM capsaicin with ORM assessment.

Outcomes measured

The primary outcome of the study was the median change in OD by ORM from baseline after NPT with the diagnostic 0.05mM capsaicin between pre-treatment and 4 weeks and 12 weeks posttreatment.

Additionally, all subjects at the initial visit were asked to rate the typical nasal symptoms of NAR, including sneezing, nasal irritation, nasal obstruction, and nasal congestion utilizing the VAS. The symptom score is based on a commonly used rhinitis rating system recommended by the U.S. Food and Drug Administration (FDA) for clinical trial studies on NAR. The VAS scale ranges from 0 (none, no distress) to 10 (agonizing, unbearable distress). The score for each nasal symptom was added together to calculate a total symptom score (TSS, max = 40). A baseline TSS was obtained at initial visit, and then again at the 4-week and 12-week follow-up. The change in TSS at 4 weeks and 12 weeks from baseline was calculated for each patient and median change with interquartile range (IQR) in TSS was reported. VASs have been previously validated in other diseases including anxiety, chronic pain, and cancer. In 2007, Bousquet et al.¹⁰ reported that VAS is a simple and easy method to evaluate the severity of symptoms in AR. In 2009, Bousquet et al.¹¹ went further and showed the utility of VAS when used to evaluate the change in symptoms and responsiveness during treatment. However, the VAS score has not been validated specifically in NAR.

Statistical analysis

Due to the small sample size and non-Gaussian distribution of data, a 2-sample Wilcoxon rank-sum (Mann-Whitney) test was used to compare the median change in OD in response to intranasal capsaicin challenge pretreatment and posttreatment in both the placebo and treatment group. A Wilcoxon signed-rank test was used to compare median change in OD and TSS at 4 weeks and 12 weeks from baseline within each treatment group.

Results

A total of 65 subjects were screened, with 22 subjects meeting eligibility criteria, which included negative skin-prick testing and a positive response to intranasal capsaicin by ORM. Both the placebo and intervention group started with 11 subjects, and both had 1 patient lost to follow-up for the 12-week visit. Figure 1 includes the study flow diagram and Table 1 includes the demographics and baseline symptom scores for both the intervention and placebo groups.

Power analysis was based on previous study published by Lambert EM et al.⁶ in 2013, evaluating the diagnostic utility of ORM for NAR. Based on this previous study, to

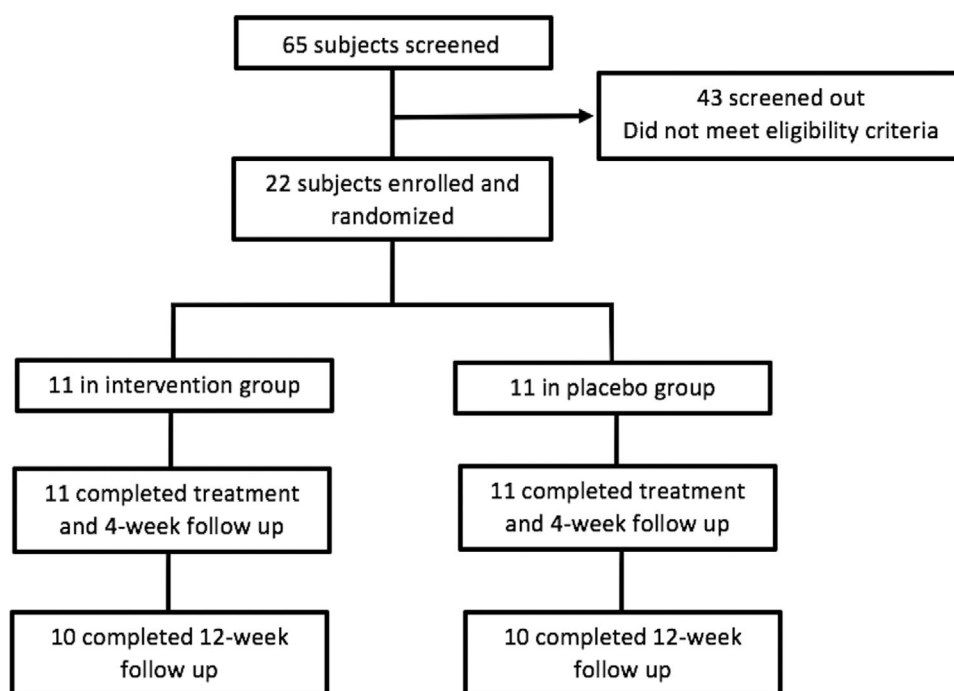


FIGURE 1. Study flow diagram. Illustrates subject disposition beginning from screening and enrollment through 12-week follow-up is completed.

TABLE 1. Baseline demographics and clinical characteristics by treatment group

Characteristic	Intervention	Placebo
Subjects, n	11	11
Male, n	8	5
Female, n	3	6
Mean age (years), mean $\pm$ SD	40 $\pm$ 16	33 $\pm$ 8
Mean TSS	17	13
Sneezing, n	2	2
Secretions, n	5	3
Irritation, n	5	3
Obstruction, n	5	5

SD = standard deviation; TSS = total symptom score.

adequately power the trial it required at least 11 subjects in each treatment arm. The subjects were randomized to each group. At 12 weeks, the data was underpowered because there was a patient in each treatment arm that was lost to follow-up.

The primary endpoints were the median change in maximal OD after NPT with 0.05mM capsaicin using ORM from baseline to 4 weeks and 12 weeks after treatment. Secondary endpoints were the median change in TSS from baseline to 4 weeks and 12 weeks after treatment.

Table 2 lists the median point and IQR for the TSS and maximal OD for each group at the 3 time periods. Table 3

highlights the median change with IQR in OD and TSS at 4 weeks and 12 weeks in comparison to baseline within each treatment group. Although there was not a statistically significant difference in the change in OD in the intervention group at 4 weeks, the distribution of data points was primarily <0 with the upper limit of the IQR at 0.04, noting most patients had a decrease in nasal reactivity to diagnostic concentrations of capsaicin by ORM. There was a statistically significant difference in the median change in TSS in the intervention group at 12 weeks from baseline (median change in the intervention group: decrease 4.5, $p = 0.03$).

Figure 2 highlights the decrease in median TSS in the intervention group at 4 weeks and 12 weeks posttreatment,

TABLE 2. Median optical density in response to capsaicin challenge and VAS total symptom score

Parameter	Placebo	Intervention
Optical density, median (IQR)		
Baseline (n = 11)	0.26 (0.2–0.42)	0.34 (0.25–0.46)
At 4 weeks (n = 11)	0.2 (0.18–0.36)	0.26 (0.08–0.31)
At 12 weeks (n = 10)	0.26 (0.2–0.37)	0.27 (0.15–0.39)
VAS TSS, median (IQR)		
Baseline (n = 11)	12 (10–21)	16 (10–22)
At 4 weeks (n = 11)	12 (10–16)	11 (3–17)
At 12 weeks (n = 10)	13 (11–28)	9.5 (4–12)

IQR = interquartile range; TSS = total symptom score; VAS = visual analogue scale.

TABLE 3. Median change in optical density in response to capsaicin challenge and VAS TSS in comparison to baseline

Parameter	Placebo	Intervention	<i>p</i>
Optical density change, median (IQR)			
4 weeks vs baseline	−0.05 (−0.12 to 0.12)	−0.05 (−0.38 to 0.04)	0.38
12 weeks vs baseline	−0.05 (−0.13 to 0.17)	−0.08 (−0.41 to 0.15)	0.33
VAS TSS change, median (IQR)			
4 weeks vs baseline	2 (−4 to 3)	−5 (−12 to −2)	0.07
12 weeks vs baseline	1.5 (−2 to 8)	−4.5 (−13 to 0)	0.03

IQR = interquartile range; TSS = total symptom score; VAS = visual analogue scale.

which was not seen in the placebo group. There was a clinically significant difference in the median change of TSS between the 2 posttreatment time periods from baseline in the intervention group. At both time periods, the median change of TSS was >0 , indicating more severe symptoms posttreatment in the placebo group. The intervention group had a median change of -5 vs a 2-point increase in the placebo group at 4 weeks in TSS ($p = 0.07$). The trend was similar at week 12, at which the median change from

baseline in the intervention group was -4.5 vs a 1.5-point increase seen in the placebo group ($p = 0.03$).

The median OD in response to diagnostic concentration of capsaicin (0.05 mM) in the intervention group decreased from baseline of 0.34 to 0.26 at 4 weeks and remained decreased; it was 0.27 at 12 weeks (Tables 2 and 3) ($p = 0.10$ and $p = 0.24$, respectively). This change was even less in the placebo group with no change in median OD at baseline to 12 weeks, staying at 0.26 in response to NPT with 0.05 mM

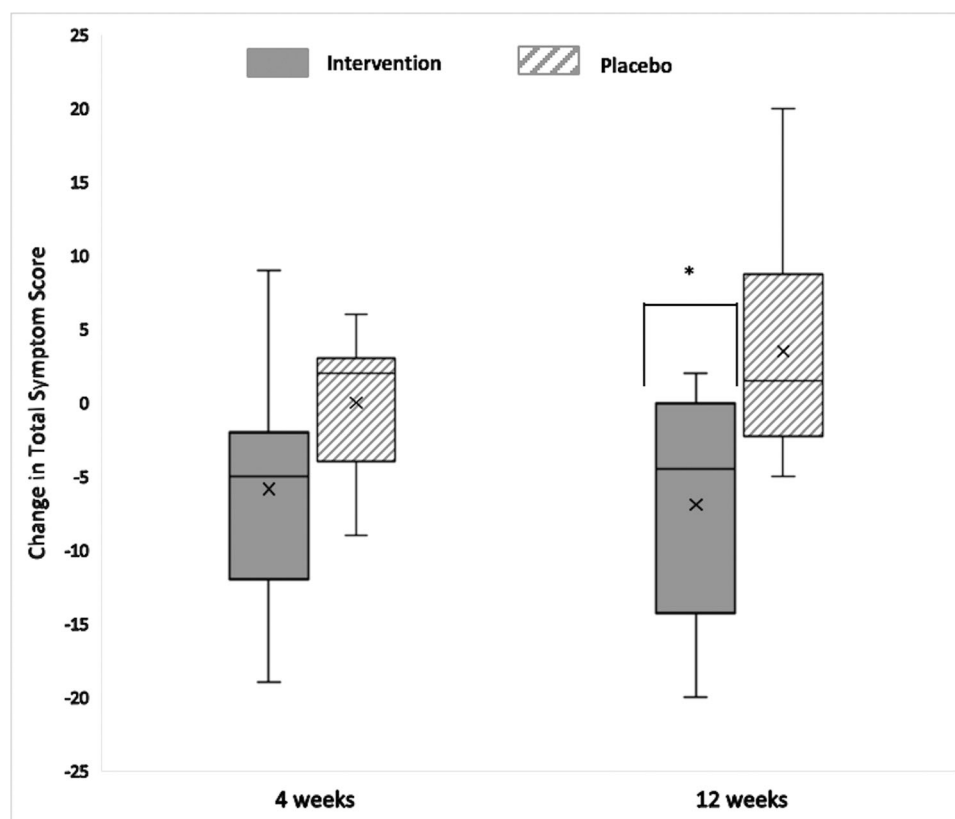


FIGURE 2. Box-and-whisker plot of change in TSS at baseline, 4 weeks, and 12 weeks posttreatment for both groups. The maximum score for TSS is 40 utilizing the visual analogue scale. The top of the box denotes the 75th percentile and the bottom of the box denotes the 25th percentile, which is the IQR. The line in the middle denotes the median. The X denotes the mean and the whiskers represent the highest and lowest values. This highlights the decrease in median TSS in the intervention group at 4 weeks and 12 weeks posttreatment, which is not seen in the placebo group. $*p < 0.05$. IQR = interquartile range; TSS = total symptom score.

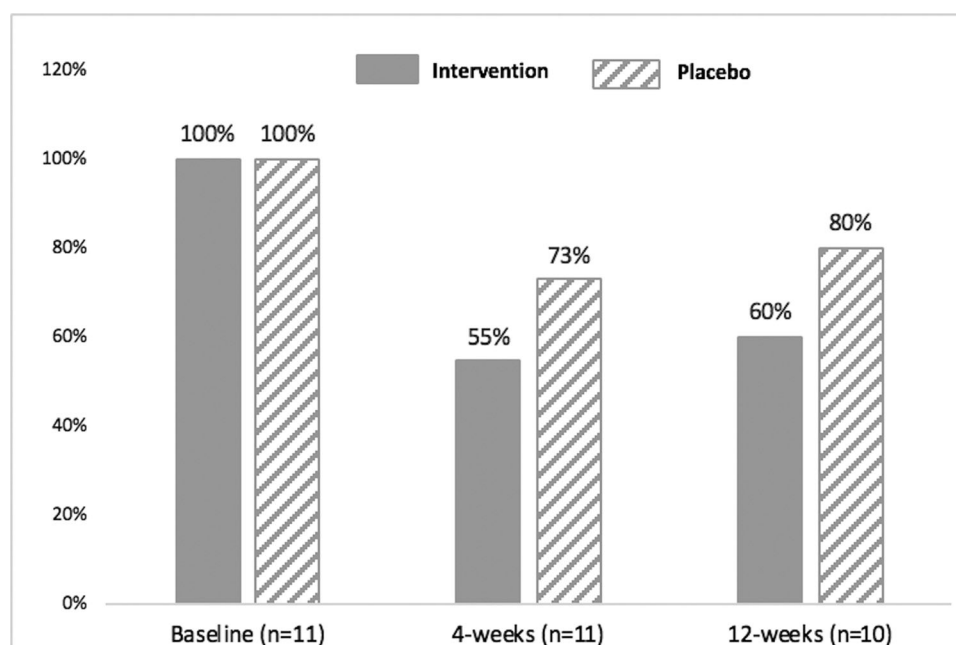


FIGURE 3. Percentage of subjects that met diagnostic criteria of NAR at baseline, 4 weeks, and 12 weeks. Diagnostic criteria base on maximum change in response to intranasal capsaicin nasal provocation testing analyzed by optical rhinometry. NAR = nonallergic rhinitis.

capsaicin. The TSS had a more significant trend, in which the intervention group at both 4 weeks and 12 weeks had a persistent decrease in symptoms from 16 at baseline to 11 and 9.5, respectively (Tables 2 and 3). In the placebo group, median TSS score did not change much from a baseline of 12 at 4 and 12 weeks (12 and 13, respectively).

In the intervention group, 55% (6/11) of the subjects had a decrease in OD at 4 weeks, with a median change in OD of -0.35 with an IQR of -0.42 to -0.28 . At 12 weeks, 83% (5/6) of those subjects had a persistent decrease in OD from baseline, and the sixth subject was lost to follow-up at 12 weeks. In Figure 3, the percentage of subjects that continued to meet the diagnostic criteria of NAR based on OD by ORM in response to 0.05mM capsaicin is shown. In the intervention group, 45% of the subjects that initially met criteria for the diagnosis of NAR based on ORM would no longer be diagnosed with NAR 4 weeks posttreatment. This response rate of 40% persisted at 12 weeks to the 5 treatments of intranasal 0.1mM capsaicin compared to the placebo of 20%.

Discussion

This is the first study to use an inclusive objective means, ORM after NPT with intranasal capsaicin, in addition to history and exclusion of AR to define patients with NAR. In this study with a specifically defined NAR population, we confirmed that repeated challenges with 0.1mM intranasal capsaicin resulted in significant reduction in TSS from baseline at both 4 weeks and 12 weeks posttreatment. However, the unique aspect of this study was the utilization of ORM as a means of determining if treatment with

intranasal capsaicin resulted in patients no longer meeting this objective criteria for NAR.

Patients with NAR are more reactive to intranasal capsaicin than healthy controls resulting in vasodilation and hence increased blood flow into the nasal mucosa in response to intranasal capsaicin nasal provocation. This increased blood flow can be detected by ORM as an increase in OD. A positive response to a nasal provocation with intranasal capsaicin has been determined to be a change in OD from baseline of 0.2 OD or greater. We observed a decrease in median change in OD in the intervention group at 4 weeks that was persistent at 12 weeks relative to baseline, with no change noted in the placebo group. The more clinically relevant observation was that by definition, 100% of enrolled patients met criteria for NAR diagnosis by ORM. At 4 weeks, only 55% of the intervention group met criteria by ORM for the diagnosis of NAR, and there was a 40% response rate at 12 weeks posttreatment. In the 5 subjects no longer meeting criteria by ORM at 4 weeks, 80% had a decrease in the TSS. The median change in TSS was -5 , with an IQR of -17 to -2 . In the 4 subjects no longer meeting criteria by ORM at 12 weeks, 100% had either a decrease or no change in the TSS from baseline. The median change in TSS is -11.5 , with an IQR of -18.5 to -3.75 . This is in contrast to the placebo group in which 20% at 12 weeks posttreatment no longer met criteria for the diagnosis of NAR based on ORM. One of the 2 subjects in the placebo group no longer meeting criteria at 12 weeks had an OD of 0.19 , a 0.03 decrease from baseline OD. However, at 12 weeks they remained symptomatic, with an increase in TSS of 11. The second subject in the placebo group no longer meeting criteria had an OD of 0.07 at 12 weeks, a 0.13 decrease

from baseline OD. At 12 weeks, the TSS had decreased by 5 from baseline, and no longer reported symptoms. A potential explanation for the objective decrease in OD in these placebo subjects is there exposure to intranasal capsaicin at both the first visit and again at 4 weeks, albeit at a lower concentration than the treatment dose. These subjects may be more sensitive to intranasal capsaicin even at a lower concentration.

Currently, NAR is diagnosed by history and excluding AR with either skin-prick or blood testing for antigen-specific IgE levels. ORM with NPT with 0.05mM capsaicin can be feasibly incorporated clinically and provides positive objective means of an inclusive criteria for the diagnosis of NAR. In addition, combined with symptoms, ORM may be used to monitor responses to treatment.

In 1991, Lacroix et al.⁴ was 1 of the first studies to use laser Doppler flowmetry to objectively show an improved vascular response to repeated challenge with intranasal capsaicin in patients identified by history with NAR. However, laser Doppler flow monitoring after NPT with capsaicin cannot be readily incorporated into clinical practice. The study nonetheless supported the use of repeated intranasal capsaicin challenge for the treatment of NAR. Since then, other placebo-controlled trials have evaluated different application schedules of intranasal capsaicin as a treatment option for NAR. In 2003, Van Rijswijk et al.⁹ concluded that undergoing 5 doses of intranasal capsaicin in 1 day is equivalent to undergoing a 2-week course. In 2014, Van Gerven et al.¹² found positive molecular and cellular changes (decrease in TRPV-1 expression and substance P) to repeated intranasal capsaicin in NAR patients.

Although the literature has consistently shown that intranasal capsaicin is an effective treatment option for NAR, these studies failed to offer a clear NAR population amenable to treatment, as these trials defined NAR by exclusion with a history of rhinitic symptoms and a negative either skin or allergy blood test. Our study offered ORM as a positive objective means of evaluating changes to nasal vascular response to nasal provocation with intranasal capsaicin as a diagnostic criterion for NAR. In addition, this study showed how ORM to capsaicin challenges provides a clinical means of assessing treatment response. Combined with symptoms, incorporating ORM clinically into the di-

agnosis of NAR may allow physicians to identify responders and nonresponders to intranasal capsaicin. In addition, this study suggests that in this specifically defined NAR population, repeated intranasal capsaicin may be effective in managing NAR in ~40% of patients.

Limitations

A limitation of the study is the small sample size, which was compounded by 2 patients being lost to follow-up at 12 weeks, making it difficult to detect a statistically significant posttreatment change. Similar analysis with a larger sample size and longer duration will allow for a better assessment of long-term effects of intranasal capsaicin. Also, the use of history, negative allergy skin or blood test, and positive response to intranasal capsaicin fails to identify those NAR patients with elevated local IgE levels. As such, this may contribute to limited improvement in some NAR patients in the intervention group. Future studies evaluating the effectiveness of intranasal capsaicin in the treatment of NAR should address means of identifying patients with local elevated IgE levels and to evaluate the duration of capsaicin effectiveness.

Conclusion

In this randomized clinical trial with an inclusively defined NAR population by NPT with intranasal capsaicin and optical rhinometry monitoring, we confirmed that treatment with repeated capsaicin significantly improves symptom scores. Additionally, optical rhinometry monitoring of NPT provided a clinically applicable means of objectively evaluating nasal reactivity. Using optical rhinometry, we found clinically meaningful reduction in OD to capsaicin challenge in the intervention group, but not in the placebo group. optical rhinometry, along with symptoms, may better identify responders to intranasal capsaicin treatment. ❧

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