Cryosurgical Ablation for Treatment of Rhinitis: A Prospective Multicenter Study

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Objective: To assess the efficacy and safety of cryoablation of the posterior nasal nerve (PNN) for treatment of chronic rhinitis.

Methods: This was a prospective single-arm trial of 98 adult patients at six U.S. centers with chronic allergic and nonallergic rhinitis. PNN cryoablation was performed in-office under local anesthesia using a handheld device. Patients discontinued use of intranasal ipratropium 3 days prior to treatment and throughout the study period. Reflective Total Nasal Symptom Score (rTNSS) was measured at pretreatment baseline and posttreatment at 1 month, 3 months, 6 months, and 9 months. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was completed at pretreatment and 3 months post-treatment. Adverse effects and postprocedure medication usage were recorded.

Results: Ninety-eight procedures (100%) were successfully completed. rTNSS significantly improved over pretreatment baseline (6.1 ± 1.9) at 1 month (2.9 ± 1.9, *P* < 0.001), 3 months (3.0 ± 2.3, *P* < 0.001), 6 months (3.0 ± 2.1, *P* < 0.001), and 9 months (3.0 ± 2.4, *P* < 0.001) postprocedure. Nasal congestion and rhinorrhea subscores improved significantly at all time points (*P* < 0.001). Both allergic and nonallergic rhinitis subcohorts showed improvement (*P* < 0.001), with a comparable degree of improvement between groups. RQLQ significantly improved over pretreatment baseline (3.0 ± 1.0) at 3 months (1.5 ± 1.0, *P* < 0.001), and all RQLQ subdomains demonstrated improvement. Of 54 patients using intranasal medication at baseline, 19 (35.2%) were able to discontinue use. Twenty-nine adverse effects were reported, including headache, epistaxis, and sinusitis.

Conclusion: Cryoablation of the PNN for chronic rhinitis is safe and can result in relief of nasal symptoms and improvements in quality of life.

Key Words: Rhinitis, cryosurgery, cryoablation, rhinorrhea, congestion, posterior nasal nerve.

Level of Evidence: 4

INTRODUCTION

Chronic rhinitis affects an estimated 60 million people in the United States. Rhinitis is commonly treated with a wide array of medications, including intranasal anticholinergics, antihistamines, and decongestants. Although medication use improves symptoms for the majority of patients, 10% to 22% of patients continue to have rhinitis refractory to medical treatment and may warrant consideration of other treatment modalities. Surgical treatment for medically refractory rhinitis has classically been via dissection, with the aim to disrupt preganglionic parasympathetic innervation to the nasal mucosa. Postganglionic nerve fibers via the posterior nasal nerve (PNN) has also been considered as a surgical alternative for refractory rhinitis. Although efficacious, these surgical procedures must be performed in an operating room under general anesthesia. Recently, an office-based approach to cryoablation of the PNN was described using a novel cryotherapy device. A pilot study demonstrated that PNN cryoablation was effective in reducing rhinitis symptoms and could be performed safely in an office setting under local anesthesia. Here, we prospectively study a larger cohort of patients undergoing PNN cryoablation with a focus on rhinologic outcomes, quality of life, concurrent medication use, and adverse effects.

MATERIALS AND METHODS

Study Design

This prospective, multicenter, single-arm, open-label clinical trial was conducted to evaluate the safety and effectiveness of PNN cryoablation in adults with chronic rhinitis. Six U.S. study centers enrolled patients; all protocols were institutional review board–approved prior to initiation. All site investigators were board-certified otolaryngologists. The study was publicly registered on clinicaltrials.gov (NCT03181594).

Subject Selection

Subjects were recruited between February 2017 and April 2018 from the investigators’ clinical practices. Subjects gave
written informed consent prior to enrollment. Subjects were adults with chronic rhinitis (allergic or nonallergic) whose symptoms were not adequately controlled with a minimum of 4 weeks of topical nasal steroid treatment. Key inclusion and exclusion criteria are listed in Table I. Study eligibility was confirmed via medical history, baseline clinical assessment, and endoscopic examination. Subjects were instructed to not use nasal anticholinergic sprays (e.g., ipratropium) at least 3 days before the procedure and throughout study participation. Patients were determined to have allergic rhinitis versus nonallergic rhinitis based on skin prick or serum IgE-antibody testing.

Device and Procedure

The handheld cryoablation device (Stryker Corporation, Kalamazoo, MI) is a single-use disposable device that uses nitrous oxide as the cryogen to freeze mucosal tissue in a targeted fashion in the nasal cavity. The target tissue lies at the posterior aspect of the middle meatus (Fig. 1), adjacent to the sphenopalatine foramen and corresponding to the trajectory of the posterior nasal nerve as it emerges from the pterygopalatine fossa. The cryoprobe’s surface reaches −60 to −80°C, and treatment is estimated to achieve −20°C cryoablation to a depth of 3 millimeters.

Clinical Endpoints

Prior to the procedure, subjects rated baseline severity of their nasal symptoms using the Reflective Total Nasal Symptom Score.
Scale (rTNSS). The primary clinical endpoint was the post-procedure change in rTNSS relative to baseline. Subjects completed rTNSS at follow-up visits at 30, 90, 180, and 270 days postprocedure. Quality of life was assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), administered at pretreatment and 90 days posttreatment. Concomitant medication use was also recorded at all study visits. If a subject resumed use of ipratropium during the study period, the subject’s subsequent scores were excluded from data analysis.

The primary safety endpoint was the incidence of procedure- or device-related adverse events occurring during the study period, as noted by site investigators based on a postprocedure phone call to the patient the following day, as well as an in-person review at each office visit. During the study, periprocedural pain was not assessed in a standardized fashion by all site investigators. Therefore, to more thoroughly characterize periprocedural tolerance and discomfort, a follow-up telephone questionnaire was administered to subjects by an independent third party between December 2018 and February 2019. Pain scores were rated on a scale of 0 to 10.

**Data Analysis**

Study data were recorded, stored in compliance with local regulations, and monitored by the study sponsor for quality and completeness. Descriptive statistics were calculated with no data
imputation. Unless otherwise noted, data are expressed as means ± standard deviations. Hypothesis testing employed paired sample t tests or Wilcoxon signed-rank tests as appropriate, accepting P < 0.05.

RESULTS

A total of 98 patients were included in this study (Table II). The cohort had a mean age of 58.6 ± 16.2 years; 64.3% patients were female; and 91.8% patients identified as Caucasian. Within this cohort, 70 (71.4%) patients had nonallergic rhinitis (NAR) and 28 (28.6%) patients had allergic rhinitis (AR). There were five device malfunctions reported during this study, all involving the lack of cryogen flow from the device cannister. However, each device malfunction was immediately resolved by the replacement of a new cryogen canister; thus, all 98 (100%) procedures were able to be completed. Four were lost to follow-up at or prior to 270 days. Three were excluded because of ipratropium use at day 90, day 180, and day 270, respectively.

\[ \text{rTNSS mean scores (Fig. 2A) improved significantly between preoperative baseline (6.1 ± 1.9) and 30 days postprocedure (2.9 ± 1.9, } \ P < 0.001, \text{ and they remained improved at all subsequent posttreatment time points: 90 days (3.0 ± 2.3, } \ P < 0.001, \text{ 180 days (3.0 ± 2.1, } \ P < 0.001, \text{ and 270 days (3.0 ± 2.4, } \ P < 0.001). \text{ The minimal clinically important difference (MCID) for rTNSS has been defined as 30% reduction in baseline score.} \]

Using this MCID threshold, 76 of 97 (78.4%) patients had clinically meaningful improvement at 30 days, 71 of 96 (74.0%) at 90 days, 75 of 95 (78.9%) at 180 days, and 65 of 92 (70.7%) at 270 days (Fig. 2B).

\[ \text{rTNSS total scores improved significantly at all time points for both the NAR subcohort (} \ P < 0.001 \text{ at all time points) and AR subcohort (} \ P < 0.001 \text{ at all time points) (Fig. 2A). The degree of improvement in rTNSS over baseline was statistically comparable between the NAR and AR subcohorts at 30 days (} \ P = 0.338, \text{ 90 days (} \ P = 0.593, \text{ 180 days (} \ P = 0.718, \text{ and 270 days (} \ P = 0.228. The rates of symptom improvement exceeding the MCID for the NAR and AR subcohorts are described in Figure 2B.} \]

Fig. 3. Significant changes in rTNSS subscores were observed following the cryoablation procedure across all subjects. Error bars represent standard deviation. Statistically significant improvements from baseline (P < 0.001) are identified by: *All domains. rTNSS = Reflective Total Nasal Symptom Score.

Fig. 4. Significant changes in RQLQ total and domain scores were observed following cryoablation procedure. Markers represent means ± standard deviation. Statistically significant improvements from baseline (P < 0.001) are identified (*). rTNS = Reflective Total Nasal Symptom Score.
For the overall cohort, a significant improvement was seen at each time point for all rTNSS subscores (Fig. 3): rhinorrhea \((P < 0.001)\), congestion \((P < 0.001)\), sneezing \((P < 0.001)\), and nasal itchiness \((P < 0.001)\). When analyzing subscores by atopic status, the NAR subcohort showed significant improvement in each of the rTNSS subscores at all time points \((P < 0.05)\), whereas the AR subcohort showed improvements in rhinorrhea \((P < 0.001)\) and congestion \((P < 0.001)\), as well as sneezing \((P < 0.05)\) at 90 days and 180 days. The AR subcohort did not show significant improvement in sneezing at 30 days or 270 days, and it showed no improvement in nasal itchiness at any time point.

RQLQ mean scores (Fig. 4) demonstrated significant improvement from baseline \((3.0 \pm 1.0)\) to 90 days \((1.5 \pm 1.2)\, P < 0.001\). Analysis of RQLQ subdomains—activities, sleep, non–hayfever symptoms, practical problems, nasal symptoms, eye symptoms, and emotions—demonstrated significant improvement in each \((P < 0.001)\). Significant improvement in RQLQ total score and domain scores were observed in both the NAR subcohort \((P < 0.001)\) and AR subcohort \((P < 0.001)\). The magnitude of RQLQ improvements were statistically comparable between the NAR \((1.4 \pm 1.1)\) and AR \((1.8 \pm 1.3)\) subcohorts \((P = 0.114)\).

Twenty-nine adverse events were reported to be possibly related to the device and/or procedure (Table III). There were two reported instances of epistaxis. One severe case of epistaxis occurred on posttreatment day 19 following the retrieval of a pledget inadvertently left in the nasal cavity from the day of treatment. Bleeding was noted from the posterior aspect of the inferior turbinate and required control in the operating room with suction cautery. A second case of mild epistaxis from the anterior septum occurred 36 days following treatment and resolved with in-office cautery. Two patients reported eye dryness in the posttreatment period. The first was the same patient mentioned above with a retained pledget, whose eye dryness began following treatment of epistaxis and persisted at 270 days. The other case of eye dryness started at 90 days and resolved by 30 days. In two cases, investigators reported new ostia (one new uncinate process perforation, one new maxillary sinus accessory os) not seen on the initial endoscopy. Nasal synechiae was noted in one patient. Four headaches were reported as adverse effects, two of which occurred within 1 day following treatment. Three sinus infections were reported, occurring at 5 days, 8 days, and 40 days following treatment.

Seventy-two of 98 (73.5%) study patients completed a retrospective telephone questionnaire about procedure-related discomfort. Of these 72, 16 (22.2%) reported no pain or discomfort, whereas 56 (77.8%) endorsed some degree of pain or discomfort. Headache was the most common type of pain, reported in 28 (38.9%) patients, followed by nasal pain \((N = 10, 13.9%)\) and sinus pain \((N = 4, 5.5%)\). Of 28 patients reporting headache, 17 reported a severe pain score \((7 to 10)\), and 20 reported headaches lasting over 1 hour. Five of 10 patients reporting nasal pain had a severe pain score, and two of four patients reporting sinus pain had a severe pain score.

Concurrent medication use during the study period is reported in Table IV. Importantly, this study sought to report patterns in medication use following cryotherapy rather than use concurrent medication usage as a proxy for treatment success or failure. In this patient cohort, the most common medications used at baseline were intranasal corticosteroids (INCS) in 40.8% of patients, intranasal saline rinses \((39.8\%)\), oral antihistamines \((33.7\%)\), and oral leukotriene inhibitors \((15.3\%)\). Of 154 medications that 98 patients were using at baseline, 33 \((21.4\%)\) medications were discontinued during the study period, with 121 \((78.6\%)\) medications that continued to be used. Medications with largest rates of discontinuance were INCS \((17 of 40, 42.5\%)\) and intranasal antihistamines \((3 of 8, 37.5\%)\). Medications with the highest continued usage rate were intranasal alpha agonists \((6 of 6, 100\%)\), oral leukotriene antagonists \((14 of 15, 93.3\%)\), and intranasal saline \((35 of 39, 89.8\%)\). The most common medications initiated during the study period were intranasal

### TABLE III.

| Adverse Event (Total N = 29) | Severity | Time Postprocedure (days) |
|-------------------------------|----------|--------------------------|
| Nasal (N = 12)                |          |                          |
| Bloody discharge              | Mild     | 11                       |
| Burning sensation             | Mild     | 4                        |
| Epistaxis                     | Severe   | 19                       |
| Epistaxis                     | Mild     | 36                       |
| Hyperemia                     | Mild     | 28                       |
| Middle turbinate hematoma     | Mild     | 34                       |
| Mucous                        | Severe   | 3                        |
| Ostia newly noted (accessory maxillary) | Mild | 67                       |
| Ostia newly noted (uncinate)  | Mild     | 77                       |
| Pain                          | Moderate | 1                        |
| Retained pledget              | Mild     | 1                        |
| Synechiae                     | Mild     | 26                       |
| Head/face (N = 6)             |          |                          |
| Facial pain                   | Mild     | 7                        |
| Facial pain                   | Moderate | 1                        |
| Headache                      | Moderate | 1                        |
| Headache                      | Severe   | 1                        |
| Headache                      | Moderate | 17                       |
| Migraine                      | Mild     | 16                       |
| Ocular (N = 3)                |          |                          |
| Dry eyes                      | Mild     | 30                       |
| Dry eyes                      | Moderate | 26                       |
| Watery eyes                   | Moderate | 23                       |
| Oral (N = 5)                  |          |                          |
| Bad taste                     | Mild     | 1                        |
| Numbness                      | Moderate | 1                        |
| Swollen sensation             | Mild     | 30                       |
| Teeth sensitivity             | Mild     | 1                        |
| Dry mouth                     | Mild     | 90                       |
| Sinus (N = 3)                 |          |                          |
| Sinusitis                     | Mild     | 40                       |
| Sinusitis                     | Mild     | 8                        |
| Sinusitis                     | Moderate | 5                        |
saline (21 of 60, 35%) and oral antihistamines (10 of 67, 14.9%). At the study start, no patients were on intranasal ipratropium as required by inclusion criteria. However, three (3.1%) patients, all within the NAR subcohort, started ipratropium use for persistent rhinitis symptoms during the follow-up period. As described earlier, they were subsequently excluded.

**DISCUSSION**

Although its etiology is not precisely understood, rhinitis is thought to arise from a dysregulation of the autonomic innervation of the nasal mucosa leading to increased vascular permeability, mucus secretion, and edema. Given the pathophysiology, targeting the parasympathetic innervation of the nasal mucosa has been the treatment strategy for several decades whether accomplished through topical medications, botulinum toxin injection, or surgical neurectomy. Although each modality has been shown to be efficacious, there are challenges associated with each. Medical management typically involves intranasal anticholinergics and INCS. Although these measures are noninvasive, they require daily use and may still incompletely control patient symptoms. Botulinum toxin injection has been shown to be effective in rhinitis treatment, presumably through its widespread adoption has been limited by need for general anesthesia. Cryoablation of the PNN is a minimally invasive fashion under local anesthesia in the office.

This study demonstrated favorable treatment responses to cryoablation for chronic rhinitis. The present study built on the prior published pilot data for cryoablative treatment with the Clarifix device, adding a larger patient cohort, more rigorous capture of longer-term follow-up timepoints, a validated quality-of-life outcome measure, and tracking of medication usage. Although the pilot study reported statistically significant improvements in posttreatment rTNSS scores, the current study builds on those findings and includes an analysis of patients demonstrating clinically meaningful improvements in rTNSS scores. The rate of patients exceeding the MCID at 6 months of 78.9% found in the current is comparable to the findings of the previously published pilot study, which noted symptomatic improvement in 74% patients at 6 months.

It is noteworthy that cryoablation appeared to benefit patients with both AR and NAR. This effect was also noted in the pilot study, although treatment numbers were smaller in the pilot study. Despite the fact that improvement in AR symptoms might be unexpected at first glance, prior surgical outcomes studies have demonstrated that patients with AR who underwent posterior nerve neurectomy experienced significant improvements in their rhinitis symptoms. Tissue sampling of the inferior turbinate following surgical ablation of the PNN has revealed a reduction in the number of infiltrating neutrophils, eosinophils, and lymphocytes, suggesting that disruption of the autonomic innervation may reduce the inflammatory cell populations that are pathologic in both AR and NAR. In our study, we observed that improvements in overall rTNSS score in AR patients were mostly due to improvements in nasal congestion and rhinorrhea, with minor improvements in sneezing and no change in nasal itchiness. The improvements observed in the AR subcohort of this study suggest a potential role of cryotherapy in treatment of AR. However, owing to the binary classification of our patients into NAR or AR subcohorts, we cannot rule out the possibility that some AR patients actually had mixed rhinitis and theoretically could have benefited from treatment of the NAR component of their rhinitis. Additionally, this study is limited in that we did not further subclassify NAR subjects into rhinitis subtypes. Further study is warranted regarding the potential indications of PNN cryoablation for specific rhinitis subtypes, such as vasomotor or senile rhinitis.

Because rhinitis has been shown to adversely affect quality of life, including sleep disturbance, daytime somnolence, and decreased work productivity, we sought to characterize...
changes in disease-specific quality of life through the RQLQ-validated outcome measure. The improvements in RQLQ observed in this study are comparable to those previously documented in patients undergoing vidian neurectomy.\textsuperscript{25} Despite the fact that improvement in RQLQ nasal subdomain might have been expected, it is notable that the eye subdomain (along with every other RQLQ subdomain) also demonstrated improvement after cryotherapy. Although not readily explained, the improvement in eye symptoms associated with improvements in rhinitis may be attributable to suppression of a common underlying inflammatory pathophysiology. This phenomenon has been supported by other studies; for example, a randomized double-blinded placebo-controlled medication trial demonstrated significant improvement in ocular symptoms of AR with use of only intranasal fluticasone.\textsuperscript{24}

Whereas the pilot study had fairly substantial dropout rates beyond 6 months postprocedure, the present study was able to capture outcomes in 93.9\% of the cohort through 9 months postprocedure. rTNSS scores showed that the full effect of symptom improvement was achieved by 1 month postprocedure and that improvements after cryoablation remained durable through 9 months. Although these outcomes are still relatively short-term, it is notable that surgical treatment by posterior nasal neurectomy has demonstrated improvement of symptoms for 3 years.\textsuperscript{25}

The cryoablation procedure was generally well tolerated and able to be completed in 100\% of patients, indicating its suitability for an office-based setting. The most common side effect reported by patients was headache. From our experience, patients most often describe this as an "ice cream headache", suggesting a transient temperature-induced sphenopalatine neuralgia affecting a minority of patients. There was a large discrepancy between the number of investigators reporting pain as an adverse effect during the study period (4 of 98, 4.1\%) and the number of patients endorsing headache when assessed in the retrospective survey (26 of 72 patients, 38.9\%). This is likely due to the lack of standardization of reporting periprocedural pain as an adverse event during the study. Because the follow-up phone questionnaire took place up to 22 months after the procedure, the introduction of recall bias must also be considered. Nonetheless, the risk of developing a headache immediately postprocedure should certainly be disclosed when offering this therapy to patients. Future studies with standardization assessment of periprocedural pain are warranted to better specify patient comfort with cryotherapy.

A recent systematic review identified 15 studies of cryoablation in rhinitis;\textsuperscript{12} however, the authors noted that the majority of articles were published between 1977 and 1997, with the only study published in the last 5 years being the pilot study for this device.\textsuperscript{5} Excluding the pilot study for the Clarifix device, no prior studies have used a validated symptom scoring system. The findings of our study using the rTNSS are consistent with multiple prior studies demonstrating improvement after cryotherapy. Although the durability of improvement beyond 9 months remains to be seen.

This study has several limitations. Foremost, our study lacked a control treatment arm. In addition, the study was not blinded for either the provider or the patient, which may have introduced bias from both parties when reporting outcomes. Future randomized controlled studies, perhaps incorporating a sham treatment arm, would be helpful to further validate the efficacy of PNN cryoablation. Additionally, the inclusion criteria required that patients had failed 4 weeks of INCS but did not explicitly require treatment failure with ipratropium or other nonsteroidal medications. Although many patients had tried other forms of medication in addition to INCS, we acknowledge the possibility that some included study patients may still have benefited from other classes of intranasal medications as an alternative to cryosurgical treatment. Furthermore, although there was significant improvement in quality-of-life outcomes by RQLQ at 90 days, RQLQ scores were not tracked beyond this time point, thus limiting our ability to ascertain whether RQLQ improvements remained durable in parallel with the improved rTNSS scores noted beyond 90 days. Although it may be reasonable to assume that disease-specific quality of life correlates with rhinitis symptom metrics and thus would remain improved at later time points, future studies would benefit from tracking long-term quality-of-life outcomes in addition to long-term symptom outcomes. We also acknowledge that three patients were excluded during the study period from subsequent outcome analysis upon resumption of ipratropium use. Although excluded from the statistical analyses to avoid confounding effects of ipratropium use, these patients may have represented additional treatment failures. Despite the study's limitations, its results suggest that cryoablation is a safe, effective, and feasible treatment option for medically refractory allergic and nonallergic rhinitis.

CONCLUSION
Cryoablation of the PNN for chronic rhinitis is safe, can decrease nasal symptoms of rhinitis, and can improve disease-specific quality of life.

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BIBLIOGRAPHY
1. Settipane RA, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. Clin Allergy Immunol 2007;19:21–34.
2. Lieberman P, Kaliner MA, Wheeler WJ. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. *Curr Med Res Opin* 2005;21:611–618.

3. Golding-Wood PH. Observations on petrolatum and vidian neurectomy in chronic vasomotor rhinitis. *J Laryngol Otol* 1961;75:232–247.

4. Kanaya T, Kikawada T. Endoscopic posterior nasal neurectomy: an alternative to Vidian neurectomy. *Clin Exp Allergy Rev* 2009;9:24–27.

5. Hwang PH, Lin B, Weise R, Atkins J, Johnson J. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. *Int Forum Allergy Rhinol* 2017;7:952–956.

6. US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: Allergic rhinitis: Developing drug products for treatment. Guidance for industry 2018. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm071293.pdf. Accessed August 26, 2019.

7. US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: Nonallergic rhinitis: Developing drug products for treatment. Guidance for industry 2018. Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm486105.pdf. Accessed August 26, 2019.

8. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinosinusitis Quality of Life Questionnaire. *J Allergy Clin Immunol* 1999;104:364–369.

9. Meltzer EO, Wallace D, Dykewicz M, Shneyer L. Minimal clinically important difference (MCID) in allergic rhinitis: agency for healthcare research and quality or anchor-based thresholds? *J Allergy Clin Immunol Pract* 2016;4:682–688.e6.

10. Bernstein JA. Nonallergic rhinitis: therapeutic options. *Curr Opin Allergy Clin Immunol* 2013;13:410–416.

11. Baranuk JN, Silver PB, Kaliner MA, Barnes PJ. Perennial rhinitis subjects have altered vascular, glandular, and neural responses to bradykinin nasal provocation. *Int Arch Allergy Immunol* 1994;105:202–206.

12. Kompelli AR, Janz TA, Rowan NR, Nguyen SA, Soler ZM. Cryotherapy for the treatment of chronic rhinitis: A qualitative systematic review. *Am J Rhinol Allergy* 2018;32:491–501.

13. Kim RS, Kim SS, Yoon JH, Han JW. The effect of botulinum toxin type A injection for intrinsic rhinitis. *J Laryngol Otol* 1998;112:248–251.

14. Braun T, Garkov R, Kramer MF, Krause E. Septal injection of botulinum neurotoxin A for idiopathic rhinitis: a pilot study. *Am J Otolaryngol* 2012;33:64–67.

15. Ozenberger JM. Cryosurgery for the treatment of chronic rhinitis. *Laryngoscope* 1973;83:508–516.

16. Terao A, Meshitsuka K, Suzuki H, Fukuda S. Cryosurgery on postganglionic fibers (posterior nasal branches) of the pterygopalatine ganglion for vasomotor rhinitis. *Acta Otolaryngol* 1983;96:139–148.

17. Girdhar-Gopal H, Okurwalski L, Strume M. An assessment of postganglionic cryoneurolysis for managing vasomotor rhinitis. *Am J Rhinol* 1994;8:157–164.

18. Robinson SR, Wormald PJ. Endoscopic vidian neurectomy. *Am J Rhinol* 2006;20:197–202.

19. Kikawada T. Endoscopic posterior nasal neurectomy: An alternative to vidian neurectomy. *Oper Tech Otolaryngol Head Neck Surg* 2007;18:297–301.

20. Halderman A, Sindwani R. Surgical management of vasomotor rhinitis: a systematic review. *Am J Rhinol Allergy* 2015;29:128–134.

21. Ikeda K, Yoka H, Saito T, Kawano K, Yao T, Purukawa M. Effect of resection of the posterior nasal nerve on functional and morphological changes in the inferior turbinate mucosa. *Acta Otolaryngol* 2008;128:1337–1341.

22. Yan CH, Hwang PH. Surgical management of nonallergic rhinitis. *Otolaryngol Clin North Am* 2018;51:945–955.

23. Tan G, Ma Y, Li H, Li W, Wang J. Long-term results of bilateral endoscopic vidian neurectomy in the management of moderate to severe persistent allergic rhinitis. *Arch Otolaryngol Head Neck Surg* 2012;138:492–497.

24. Ratner P, Van Bavel J, Mohar D, et al. Efficacy of daily intranasal fluticasone propionate on ocular symptoms associated with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2015;114:141–147.

25. Ogawa T, Takeno S, Ishino T, Hirakawa K. Submucous turbinatectomy combined with posterior nasal neurectomy in the management of severe allergic rhinitis: Clinical outcomes and local cytokine changes. *Auris Nasus Larynx* 2007;34:319–326.

26. Kobayashi T, Hyodo M, Nakamura K, Komobuchi H, Honda N. Resection of peripheral branches of the posterior nasal nerve compared to conventional posterior neurectomy in severe allergic rhinitis. *Auris Nasus Larynx* 2012;39:593–596.

27. Marshall T, Yun WK, Hazout C, Sacks R, Harvey RD. A systematic review of the evidence base for vidian neurectomy in managing rhinitis. *J Laryngol Otol* 2016;130:suppl 4:eS7–S28.