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Journal

Ear, Nose & Throat Journal, 102(10)

ISSN

0145-5613

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Publication Date

2023-10-01

DOI

10.1177/01455613211018576

HHS Public Access

Author manuscript

Ear Nose Throat J. Author manuscript; available in PMC 2022 December 15.

Published in final edited form as:

Ear Nose Throat J. ; : 1455613211018576. doi:10.1177/01455613211018576.

The Impact of Surgical Posterior Nasal Nerve Cryoablation on Symptoms and Disease Specific Quality of Life in Patients with Chronic Rhinitis.

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Abstract

Objective—Preliminary data have demonstrated long term efficacy of posterior nasal nerve (PNN) cryoablation in reducing rhinitis symptoms for patients with allergic rhinitis (AR) and non-allergic rhinitis (NAR). We sought to evaluate the impact of procedural cryoablation of the posterior nasal nerve on quality of life in patients with AR and NAR.

Methods—Adult patients undergoing posterior nasal nerve cryoablation for AR or NAR after appropriate medical therapy were included for analysis. Demographics, medical therapies, baseline rhinitis symptom (TNSS) and disease specific quality of life (mini-RQLQ) questionnaires were recorded. The Wilcoxon signed rank test was used to test for significant changes in baseline test scores post treatment. Absolute and relative improvement in outcomes was determined for each participant. Secondary outcomes were assessed with univariate and multivariate analysis.

Results—Fourteen patients were enrolled with a mean follow up of 16.5 weeks. TNSS and mini-RQLQ scores significantly improved after PNN cryoablation (median deltas (IQR): −4 (3), −1.61 (1.08) respectively; both p=.0002). The minimal clinically important difference for the TNSS and mini-RQLQ was obtained in 92.9% of patients in each category. Relative mean percentage (%) improvement after PNN cryoablation in the TNSS and mini-RQLQ was 40.7% and 40.5% (stdev=24.9, 29.5 respectively), respectively for all patients. NAR patients (n=10) reported mean improvement of 41.3% (29.1) as measured by the TNSS and 49.6% (25.9) by mini-RQLQ. AR patients reported mean percentage improvement in TNSS and mini-RQLQ scores of 39.5% and 24.6% (12.1; 28.5) respectively. Patients who had been prescribed a nasal anticholinergic for management prior to PNN cryoablation had statistically significantly increased improvement in mini-RQLQ scores from pre- to post-procedure (p=.0387).

Conclusion—Surgical cryoablation of the PNN significantly improves both symptoms and disease specific QOL in majority of patients with AR and NAR.

Keywords

Allergic rhinitis; non-allergic rhinitis; mixed rhinitis; chronic rhinitis; posterior nasal nerve; cryoablation; quality of life

INTRODUCTION

Chronic rhinitis affects over 80 million individuals in the US, and through extrapolation of prevalence studies, approximately 450 million people worldwide.[1–3] The magnitude of the population affected by this disease process results in a well-documented economic impact. Over 3 billion dollars of direct medical cost, and over 11 billion dollars of treatment cost were attributed to allergic rhinitis alone in the early 2000s.[4] This is further compounded by the loss of productivity, with nearly a quarter of all lost productivity in the US could be attributed to this condition.[5] For patients who have exhausted medical therapies, there have traditionally been limited surgical options. Therefore, definitive or lasting treatments for chronic rhinitis are a pressing topic of research given the both the individual patient and societal implications.

Chronic rhinitis is traditionally divided into three categories: allergic rhinitis (AR), non-allergic rhinitis (NAR), and mixed rhinitis. There is significant overlap in the presentations and symptomatology of these disease processes, creating a challenge in distinguishing the contributing etiologies to a patient's symptoms.[2] A consensus definition of allergic rhinitis per the 2015 Clinical Practice Guidelines for allergic rhinitis is the following: "an immunoglobulin E (IgE)–mediated inflammatory response of the nasal mucous membranes after exposure to inhaled allergens."[6] In contrast, NAR is characterized by symptoms that are not a result of IgE-mediated responses.[3] Mixed rhinitis includes those patient's with etiologies falling into both categories.

An accurate diagnosis portends a favorable regimen for patients with chronic rhinitis by providing a treatment that is targeted at the etiology of the disease. A number of topical therapies are available for use such as decongestants, steroids, anticholinergics, and antihistamines. However, compliance amongst patients with chronic rhinitis is poor; the literature has demonstrated that almost two-thirds of patients do not take their medications regularly, and up to one-third believe the medications to be ineffective.[7] Historically, definitive surgical treatment has been vidian neurectomy, with the goal of eliminating the parasympathetic innervation to the nasal mucosa. This is an operative procedure requiring general anesthesia and may result in postoperative sequelae such as xerophthalmia.[8]

More recently, posterior nasal nerve (PNN) cryoablation has emerged as a low morbidity alternative to vidian neurectomy. It involves an in-office procedure that spares patients general anesthesia and the potential sequelae associated with transecting the vidian nerve. Contemporary sponsored studies have demonstrated improvements in the quality of life of patients with chronic rhinitis undergoing PNN cryoablation.[9] While these data are promising, there remains a relative paucity of surgical outcomes for this novel therapy. Our objective was to evaluate the impact of PNN cryoablation on both the symptomatology and disease specific quality of life of patients with allergic and non-allergic rhinitis.

PATIENTS AND METHODS

Institutional Review Board (IRB) approval (ID# 1563028–2) was obtained for this retrospective study at the University of California Davis Medical Center. Sequential patients

undergoing PNN cryoablation for allergic rhinitis, mixed rhinitis, or non-allergic rhinitis between October 2018 and January 2020 were retrospectively analyzed in this single institution study. Patients who had persistent AR or NAR were considered candidates for the procedure and included in this study. AR was determined by blood or skin prick testing with an IgE mediated response. Patients who did not fill out the total nasal symptom score (TNSS) or the mini rhinoconjunctivitis quality of life (mini-RQLQ) questionnaires or had follow up less than 6 weeks were excluded. Patients undergoing simultaneously in-office procedures such as inferior turbinate reduction or balloon sinuplasty were excluded.

All patients underwent an in-office procedure with a single surgeon via cryoprobe application against the lateral nasal wall (Figure 1) with an anesthetic regimen as previously described by Steele et al.[10] The inferior meatus was not treated in any of the analyzed patients. Demographics, comorbidities (chronic rhinosinusitis (CRS), primary headache disorder, TMJ dysfunction, facial pain syndrome, depression/anxiety, smoker), and prior medical therapies were recorded. Baseline and follow up measures of disease-specific QOL, collected as part of the standard of care, were used for investigational purposes. TNSS is a validated symptom severity scoring system that measures each of the following symptoms: nasal congestion, nasal itching, sneezing, and rhinorrhea. A 4-point scale is used (0 to 3) for each question, where 0 indicates no symptoms and 3 indicates intolerable symptoms that interfere with daily activity. TNSS is calculated by adding the sum of each score for a maximum of 12. The mini-Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a 14-question validated QOL measure of 5 rhinoconjunctivitis dimensions (activities, practical problems, nose symptoms, eye symptoms, and other symptoms) and uses a scale of 0 to 6 for each question. A score of 0 indicates “not troubled” whereas a score of 6 indicates “extremely troubled.” The mini-RQLQ is scored by averaging each question for a maximum of 6. TNSS and mini-RQLQ were collected on the day of surgery and at subsequent follow up visits.

The Wilcoxon signed rank test was used to test for significant improvement from baseline for both tests. Absolute and relative improvement in outcomes was determined for each participant. Potential variation in baseline QOL status was considered further when evaluating postoperative improvements by calculating the mean percentages (%) of absolute relative improvement in QOL outcomes determined for each participant using the algorithm: [(mean preoperative score − mean postoperative score) / mean preoperative score] × 100.

Clinical significance for outcome measures was determined by the minimal clinically important difference (MCID) of 0.55 and 0.4 for the TNSS and mini-RQLQ, respectively.[11]

Secondary outcome measures evaluated outcome variation based on the type of rhinitis (allergic versus mixed versus non-allergic), comorbidities, length of follow-up, gender, or age to the differences noted in the pre- and post-intervention TNSS and mini-RQLQ scores. Atopy was confirmed with blood or skin testing. The Wilcoxon sum rank test or Kruskal-Wallis test were used for categorical variables. Spearman’s correlation was used for numerical variables. The variables that were significant at 0.1 level were included in a multiple linear regression model for both TNSS and mini-RQLQ outcome measures.

All statistical analyses were conducted using SAS® software for Windows® version 9.4 (SAS® Institute Inc, Cary, NC). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographics

Fourteen patients were enrolled with a mean follow up of 16.5 weeks. Four of the patients had allergic or mixed rhinitis. The remaining 10 had non-allergic rhinitis. Age and gender were also recorded. (Table 1) Three patients were excluded due to lack of follow up and incomplete patient reported outcome measure forms.

Comorbidities

Comorbidities surveyed for included CRS, primary headache disorder, TMJ dysfunction, facial pain syndrome, depression/anxiety, or smoking history as demonstrated in Table 1.

Medical Management

Majority of patients presenting to our clinic initially underwent attempts with medical management prior to being offered PNN cryoablation. The types of therapies trialed for each patient is outlined in Table 2.

Outcome Measures

TNSS and mini-RQLQ scores significantly improved after posterior nasal nerve cryoablation among all patients (−4 (3), −1.61 (1.08) respectively; both p=.0002) (Figure 2). Utilizing the MCID of 0.55 and 0.4 for the TNSS and mini-RQLQ, respectively, 13 out of the 14 patients obtained clinically important difference (92.9%; two separate patients did not obtain MCID, one for the TNSS and one for the mini-RQLQ). Relative mean percentage (%) improvement for all patients was 40.7% and 40.5% (stdev=24.9, 29.5 respectively) as measured by the TNSS and mini-RQLQ respectively. Patients with NAR (n=10) reported mean improvement of 41.3% (29.1) as measured by the TNSS and 49.6% (25.9) by mini-RQLQ. Patients with allergic or mixed rhinitis reported mean percentage improvement in TNSS and mini-RQLQ scores of 39.5% and 24.6% (12.1; 28.5) respectively.

Univariate and Multivariate Analysis

Univariate analysis did not show a statistically significant effect of the patient demographics (age and gender), length of follow up, type of rhinitis, nor associated comorbidities on the post-procedural outcome on either the TNSS or the mini-RQLQ. Patients who had been prescribed a topical nasal anticholinergic (TNAC) for medical management prior to proceeding with PNN cryoablation had statistically significantly increased improvement on the change in mini-RQLQ scores from pre- to post-procedure (p=.0387). (Tables 3 and 4)

After controlling for baseline TNSS (p=.0004) in the multivariate analysis, patients without depression/anxiety tended to have higher post-TNSS scores by an average of 1.52 (se=0.89) points, though this was not statistically significant (p=.1164). For the mini-RQLQ multiple

regression, after controlling for baseline (p=.0002), a prior trial on a TNAC increased improvement by an average of 0.93 (se=0.35) points (p=.025). (Tables 5 and 6)

DISCUSSION

Differentiating between the subtypes of chronic rhinitis is critical in establishing a first-line treatment response to give patients the best chance of improving symptoms and overall quality of life. Clinical Practice Guidelines for AR make a strong recommendation for topical intranasal steroid use, with the option supplement with combination therapy for patients who fail monotherapy.[6] The British Society for Allergy and Clinical Immunology has updated treatment recommendations for non-allergic rhinitis, an entity with several etiologies and more complex treatment approach.[12] This includes treatment with topical intranasal steroid, intranasal ipratropium, and topical antihistamines.[12] Despite these therapies, many patients remain symptomatic. In our patient cohort, majority were trialed on at least monotherapy of topical medication, with most of those receiving some type of combination therapy as well (Table 2). Patient reported disease specific QOL as measured by the TNSS and mini-RQLQ remained poor despite these medical therapies and all patients elected to undergo posterior nasal nerve cryoablation.

Prior to procedural surgical cryoablation, there were limited long-term options available to patients with recalcitrant symptoms of chronic rhinitis short of vidian neurectomy, the sequelae of which are well-documented.[8, 13, 14] Although there are reports of botulinum toxin injection for the treatment of rhinitis, this intervention is also procedural with limited data and short duration of action.[15] Posterior nasal nerve cryoablation is potentially a superior alternative to these treatment methods for chronic rhinitis, though head to head comparisons have not been performed. By targeting the postganglionic parasympathetic fibers of the vidian nerve via the posterior nasal nerve, the complications that are observed with vidian neurectomy are avoided.[16] In addition, improvement has been noted to be significant at as early as 6-weeks post-procedure, and the effects have been shown to be long-lasting with at least nine months of durable symptom control demonstrated.[9] In this context, our cohort included patients with at least 6-weeks of post-procedural data. With an average follow up of 4.5 months, including three patients with at least eight months of follow-up demonstrating continued clinical improvement, our study further substantiates previous findings.

The magnitude of the response demonstrated after PNN cryoablation was calculated via relative mean percentage improvement in the TNSS and mini-RQLQ scores, a measurement not previously studied. The patients treated in this study demonstrated approximately 40% improvement in their symptoms and quality of life. These data may help to inform both surgeons and patients during the pre-procedural shared decision-making process. The robust response observed in both the non-allergic and allergic/mixed rhinitis groups is notable, with meaningful clinical improvement observed in all but one patient in regard to both the symptomatology and quality of life as measured by the TNSS and mini-RQLQ, respectively. These findings corroborate the results from industry sponsored studies.[9] The potential implication of both the NAR and AR/mixed groups benefitting from this procedure is that the downstream effect of the numerous etiologies of chronic rhinitis may be mediated

through the posterior nasal nerve. One prior study showed significant reduction in the density of nasal glands and inflammatory cell infiltration after PNN resection, suggesting the physiological mechanism of the response to chronic rhinitis of all types as seen after PNN cryoablation.[17]

This study is unique in that the patients included underwent topical therapy not limited to a single pharmacologic class and were deemed to be medically recalcitrant prior to proceeding with PNN cryoablation, a criteria not required for candidacy in prior studies.[9, 18–21] One patient did not receive any topical therapy due to such severe, incapacitating osteoarthritis that limited application of a nasal spray. Even so, based on inclusion criteria in prior research, this patient was able to be included in this study while maintaining the applicability of these results. Overall, a positive response was demonstrated after PNN cryoablation in this series of patients with chronic rhinitis.

We noted that medical management trial with TNAC led to better response based on post-procedural mini-RQLQ scores, but this did not hold true for the post-procedural TNSS. This finding is supported by literature demonstrating pre-procedure patient response to topical nasal anticholinergics as predictive of response to PNN cyroablation.[21] In our patient cohort, the post-procedural relative mean percentage improvement in TNSS and mini-RQLQ scores was especially prominent in patients with NAR, suggesting a potential physiologic benefit in the mediation of their rhinitis symptoms. This may further correlate to the benefit seen in patients trialed on TNACs.

Anxiety and depression are common comorbid conditions in patients with sinonasal inflammatory disorders. While the incidence of anxiety/depression in this particular cohort is greater than what may be expected (20–25% of chronic rhinosinusitis patients), this could be attributed to sampling error.[22] Future study with larger sample sizes is needed to further elucidate this correlation. Patients with depression/anxiety report greater improvement based on the post-procedural TNSS and mini-RQLQ questionnaires after PNN cryoablation while controlling for their baseline responses. This is contradictory to data from studies evaluating patients with chronic rhinosinusitis and comorbid depression in which the depression exerts a negative impact on symptom burden.[22] It is possible that patients with comorbid depression may perceive symptoms worse than patients without comorbid depression and once disease specific symptoms improve, the patient reported outcome measures may drop more significantly than those without comorbid psychiatric illness. This multiple regression analysis is insufficient to draw firm conclusions in this aspect but suggests avenues for further research in gauging the candidacy of patients with depression/anxiety for PNN cryoablation.

Our study was limited by a few factors including the lack of a control group. However, the patient population we studied served as their own control group prior to the intervention. In addition, there are potential confounders, especially when considering topical therapy use. While we tracked pre-procedural therapies, the instructed use of either topical or oral medications was not recorded after the procedure. Further, the small sample size of our cohort, and the robust response likely contributed to identification of fewer predictive factors with statistical significance. Even so, over 65% of patients (155 out of 236) studied who

underwent PNN cryoablation for rhinitis were included in industry-sponsored studies, and the 14 patients in this series are a meaningful addition to the non-sponsored study data pool.[9, 10, 18, 19, 21] Future directions for evaluating the use and benefit of posterior nasal nerve cryoablation will include a focus on increasing time of follow up, distinguishing the benefit of the procedural cryoablation from the ongoing use of intranasal therapeutics, and further categorizing rhinitis subtypes and the patients' response to PNN cryoablation. Posterior nasal nerve cryoablation reduces total nasal symptom score and demonstrates improvement in mini-RQLQ in patients with both AR and NAR by approximately 40% in this cohort. PNN is an option in the treatment algorithm when escalating therapy from conservative/therapeutic management to surgical management.

CONCLUSION

This study demonstrates that PNN cryoablation significantly improves symptoms and disease specific quality of life in patients with allergic and non-allergic rhinitis as measured by TNSS and mini-RQLQ.

Acknowledgement:

The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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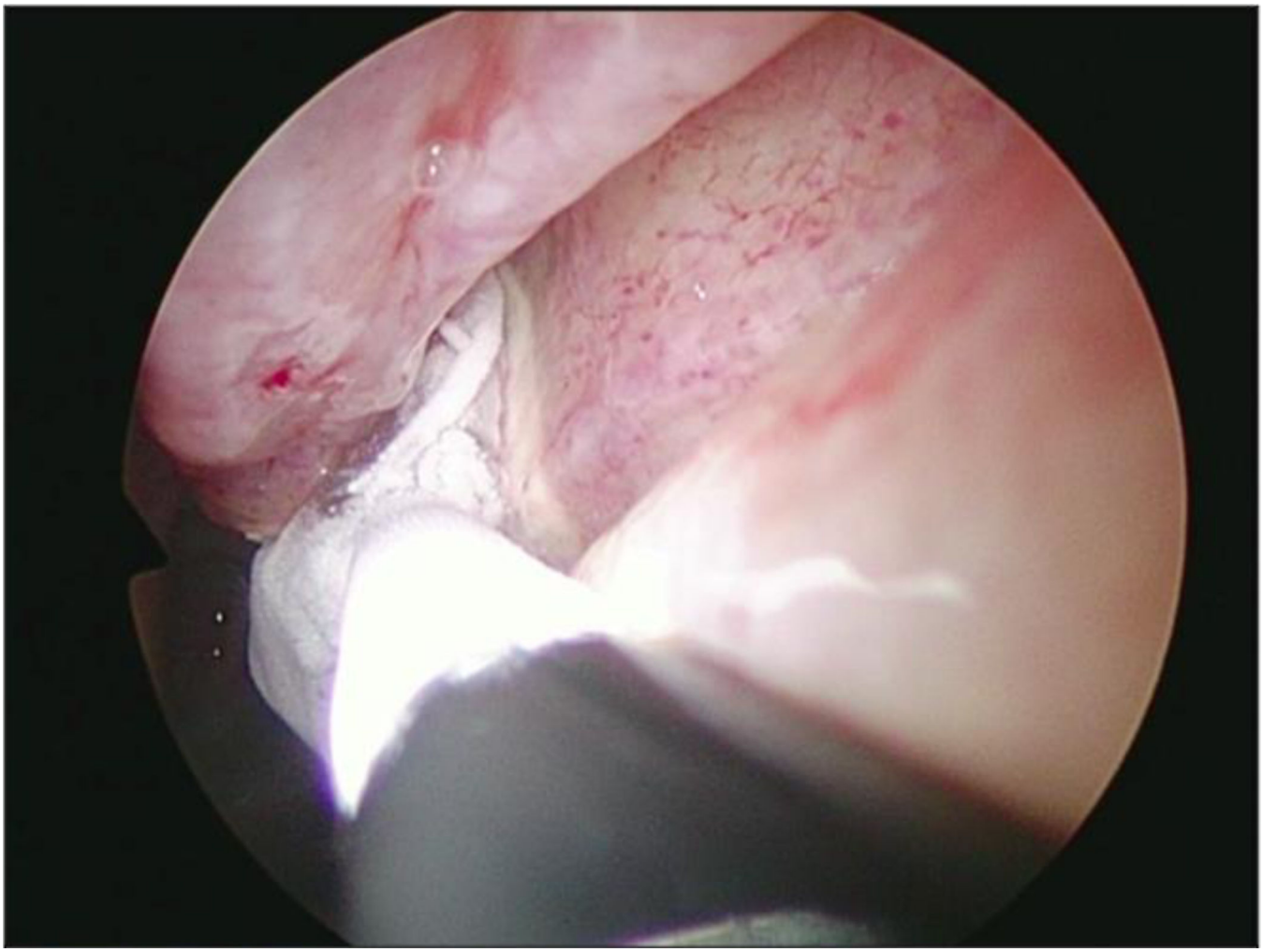

Figure 1: In office Posterior Nasal Nerve Cryoablation

The cryoprobe is held against the lateral nasal wall at the location where the posterior nasal nerve branches exit the pterygopalatine fossa.

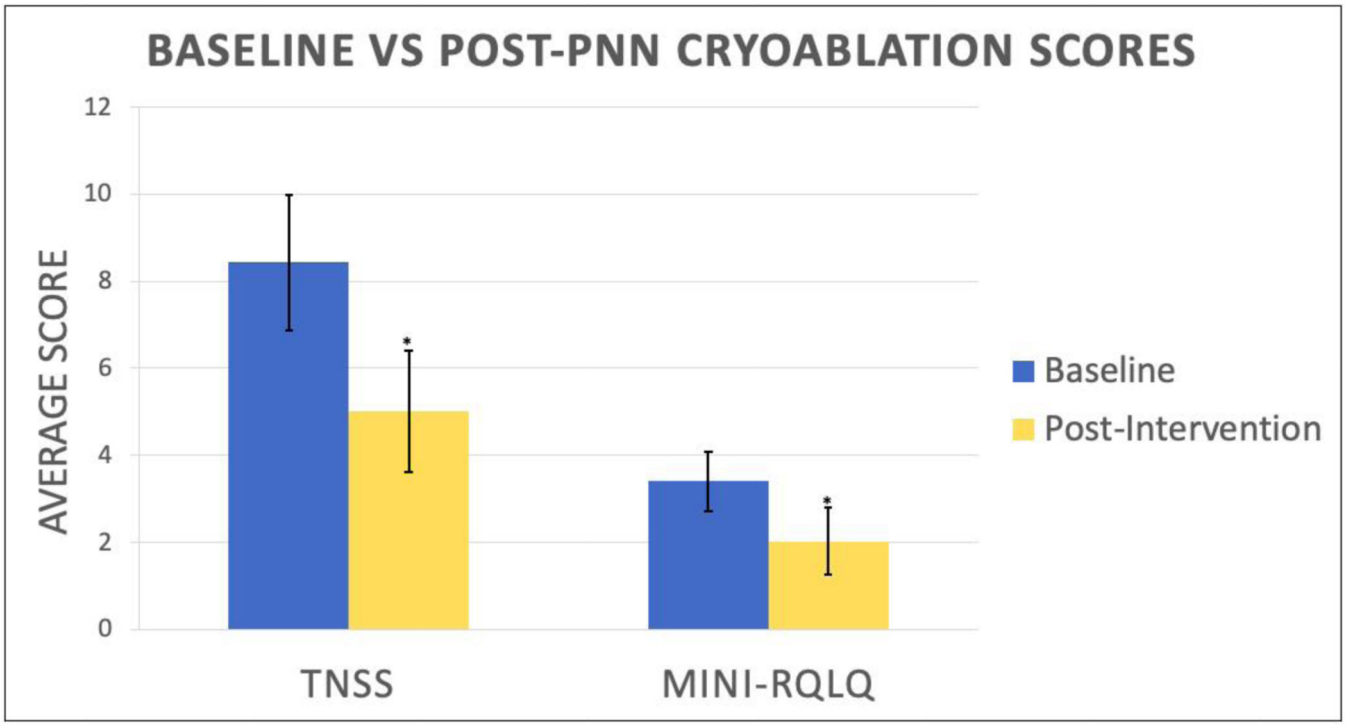

Figure 2: Observed change in TNSS and mini-RQLQ after PNN cryoablation.
(* = statistical significance).

TABLE 1:

Patient Demographics.

Patient ID	Length of Follow Up (weeks)	Age	Gender	Rhinitis type	Comorbidities
1	12	68	M	NAR	Depression/Anxiety
2	13	73	M	NAR	Depression/Anxiety
3	14	70	M	NAR	Depression/Anxiety
4	16	65	M	NAR	Smoker
5	32	39	F	AR	Depression/Anxiety
6	6	69	M	NAR	None
7	36	34	F	AR	Primary headache disorder
8	11	75	M	NAR	Depression/Anxiety
9	6	40	F	Mixed	Primary headache disorder, Depression/Anxiety
10	6	74	M	NAR	Smoker
11	6	61	F	NAR	None
12	20	72	M	NAR	Depression/Anxiety
13	17	48	M	NAR	Depression/Anxiety
14	36	40	F	AR	Depression/Anxiety

M: male; F: female; NAR: non-allergic rhinitis; AR: allergic rhinitis

TABLE 2:

Rhinitis type and pharmacologic treatment prior to PNN cryoablation.

Rhinitis type	TNS	TNAH	TNAC	Saline	PPI
AR	Yes	Yes	-	Yes	1
AR	Yes	Yes	-	Yes	-
AR	Yes	Yes	-	Yes	Yes
Mixed	Yes	Yes	Yes	Yes	-
NAR	Yes	Yes	Yes	Yes	Yes
NAR	Yes	-	Yes	Yes	Yes
NAR	Yes	-	-	Yes	Yes
NAR	Yes	-	Yes	-	Yes
NAR	Yes	Yes	-	Yes	Yes
NAR	Yes	-	Yes	-	Yes
NAR	-	-	-	-	-
NAR	Yes	Yes	Yes	Yes	Yes
NAR	-	-	Yes	-	-
NAR	Yes	Yes	-	Yes	-

TNS: topical nasal steroid; TNAH: topical nasal antihistamine; TNAC: topical nasal anticholinergic; PPI: proton pump inhibitor

TABLE 3:

Univariate Analysis for change in TNSS and mini-RQLQ.

Demographic Variable	Change in TNSS Rho	p-value	Change in mini-RQLQ Rho	p-value
1. Age	−.00112	.9970	−.35204	.2171
2. Length of follow up	−.33070	.2482	.23361	.4215

Spearman's Rho Correlation Coefficients for age and length of follow up.

diffTNSS: difference between pre-procedural TNSS and post-procedure TNSS; diffMRQLQ: difference between pre-procedural mini-RQLQ and post-procedure mini-RQLQ

TABLE 4:

Univariate Analysis for change in TNSS and mini-RQLQ.

Demographic Variable	Change in TNSS		Change in mini-RQLQ	
	Median (IQR)	p-value	Median (IQR)	p-value
1. Gender				
■ Male (n = 9)	−4 (−4, −2)	.8941	−1.65 (−1.72, −1.1)	.5166
■ Female (n = 5)	−4 (−5, −3)		−0.89 (−1.86, −0.43)	
2. Rhinitis Type				
■ Non-allergic rhinitis (10)	−3.5 (−4, −2)		−1.61 (−1.72, −0.89)	
■ Allergic rhinitis (3)	−4 (−5, −3)	.4025	−0.43 (−1.86, 0.29)	.2064
■ Mixed rtiinitis (1)	−5 (−5, −5)		−2.29 (−2.29, −2.29)	
3. Headache				
■ Yes (2)	−5.0 (−5, −5)	.1381	−1 (−2.29, 0.29)	.9287
■ No (12)	−3.5 (−4, −2)		−1.61 (−1.79,−0.835)	
4. Depression/Anxiety				
■ Yes (9)	−4 (−5, −4)	.1011	−1.72 (−2,−1.57)	.1067
■ No (5)	−2 (−3, −1)		−0.89 (−1.1,−0 65)	
5. Smoking History				
■ Yes (2)	−2.5 (−3, −2)	.3253	−1.405 (−1.71. −1.1)	1.000
■ No (12)	−4 (−5, −2.5)		−1.61 (−1.93,−0.715)	
6. TNS				
■ Yes (12)	−4 (−4.5, −2.5)	1.000	−1.61 (−1.79,−0.715)	.6556
■ No (2)	−3.5 (−5, −2)		−1.55 (−2, −1.1)	
7. TNAH				
■ Yes (8)	−3.5 (−4.5, −1.5)	.4084	−0.835 (−1.79, −0.54)	.1983
■ No (6)	−4 (−5, −3)		−1.68 (−2,−1.57)	
8. TNAC				
■ Yes (7)	−4 (−5, −3)	.2889	−1.72 (−2.29,−1.65)	.0387
■ No (7)	−3 (−4,−2)		−0.78 (−1.57, −0.43)	
9. Saline				
■ Yes (10)	−4 (−5, −2)	1.000	−1.23 (−1.72,−0.65)	.1614
■ No (4)	−3.5 (−4.5, −2.5)		−1.855 (−2.46, −1.405)	
10.PPI				
■ Yes (8)	−3.5 (−4, −2)	.4445	−1.61 (−1.715, −0.77)	.8494
■ No (6)	−4.5 (−5, −2)		−1.48 (−2, −0.78)	

Wilcoxon Sum Rank Test for gender, headache, depression/anxiety, smoking history.Kruskal-Wallis Test for rhinitis type.

Change in TNSS: difference between pre-procedural TNSS and post-procedure TNSS; Change in mini-RQLQ: difference between pre-procedural mini-RQLQ and post-procedure mini-RQLQ; TNS: topical nasal steroid; TNAH: topical nasal antihistamine; TNAC: topical nasal anticholinergic; PPI: proton-pump inhibitor.

TABLE 5:

Multiple Regression Analysis.

	R^2	Model p-Value	Predictor Variable		
				Estimate	p-Value
Multiple Regression Model	.6942	.0015	BLTNSS Depression/Anxiety	0.822 −1.516	**.0004** .1164

Dependent Variable: Post-procedural TNSS

BLTNSS: Baseline TNSS

TABLE 6:

Multiple Regression Analysis.

	R^2	Model p-Value	Predictor Variable		
				Estimate	p-Value
Multiple Regression Model	.8517	.0002	BLMRQLQ TNAC Depression/Anxiety	0.966 −0.93 −0.691	**.0002** **.0246** .1317

Dependent Variable: Post-procedural mini-RQLQ

BLMRQLQ: Baseline mini-RQLQ; TNAC: Topical nasal anticholinergic