

ORIGINAL ARTICLE

Cryotherapy for treatment of chronic rhinitis: 3-month outcomes of a randomized, sham-controlled trial

Anthony G. Del Signore MD, PharmD¹ | Joshua B. Greene MD² |
Joseph L. Russell MD³ | David M. Yen MD⁴ | Ellen M. O'Malley MS⁵ |
Rodney J. Schlosser MD⁶

¹ Mount Sinai Hospital System, New York, NY

² Ascension St. Vincent Anderson, Anderson, IN

³ National Allergy & ENT, North Charleston, SC

⁴ Specialty Physician Associates, Bethlehem, PA

⁵ Clinical Affairs, Stryker ENT, Plymouth, MN

⁶ Medical University of South Carolina, Charleston, SC

Correspondence to: Anthony G. Del Signore, MD, PharmD, Mount Sinai Hospital, 10 Union Square East, New York, NY 10003.

Email:

anthony.delsignore@mountsinai.org

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Abstract

Background: The purpose of this study was to test whether cryotherapy is superior to a sham procedure for reducing symptoms of chronic rhinitis.

Methods: This study was a prospective, multicenter, 1:1 randomized, sham-controlled, patient-blinded trial. The predetermined sample size was 61 participants per arm. Adults with moderate/severe symptoms of chronic rhinitis who were candidates for cryotherapy under local anesthesia were enrolled. Participants were required to have minimum reflective Total Nasal Symptom Scores (rTNSSs) of 4 for total, 2 for rhinorrhea, and 1 for nasal congestion. Follow-up visits occurred at 30 and 90 days postprocedure. Patient-reported outcome measures included the rTNSS, standardized Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ(S)], and Nasal Obstruction Symptom Evaluation (NOSE) questionnaires. Adverse events were also recorded. The primary endpoint was the comparison between the treatment and sham arms for the percentage of responders at 90 days. Responders were defined as participants with a 30% or greater reduction in rTNSS relative to baseline.

Results: Twelve US investigational centers enrolled 133 participants. The primary endpoint analysis included 127 participants (64 active, 63 sham) with 90-day results. The treatment arm was superior at the 90-day follow-up with 73.4% (47 of 64) responders compared with 36.5% (23 of 63) in the sham arm ($p < 0.001$). There were greater improvements in the rTNSS, RQLQ(S), and NOSE scores for the active arm over the sham arm at the 90-day follow-up ($p < 0.001$). One serious procedure-related adverse event of anxiety/panic attack was reported.

Conclusion: Cryotherapy is superior to a sham procedure for improving chronic rhinitis symptoms and patient quality of life.

KEYWORDS

chronic rhinitis, cryotherapy, quality of life, randomized, controlled trial, sham-control

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Disruption of the parasympathetic innervation to the nasal mucosa through procedures such as vidian neurectomy and posterior nasal neurectomy can reduce nasal drainage.¹⁻⁶ Despite their demonstrated efficacy, these surgical techniques were previously invasive, required general anesthesia and specialized instrumentation, and could be associated with potentially devastating complications.⁷

The direct application of cold to destroy tissue (cryotherapy) is universally practiced and has been applied in a variety of fields, including ophthalmology, gynecology, neurosurgery, cardiology, oncology, and dermatology.^{8,9} This technology can also be used for the same purpose as the vidian neurectomy or posterior nasal neurectomy but in a less invasive manner, allowing it to be performed under local anesthesia.⁷ Throughout the 1970s, 1980s, and 1990s, various articles were published on the use of cryotherapy to treat rhinitis, but the technology was not broadly adopted.¹⁰⁻¹²

In 2016, the US Food and Drug Administration cleared the (ClariFix) cryotherapy device (Stryker ENT, Plymouth, MN)¹³ for the destruction of unwanted tissue, including in adults with chronic rhinitis. Several nonrandomized clinical studies of this device have demonstrated clinical improvement in rhinitis symptoms after treatment¹⁴⁻¹⁸; however, those studies were not randomized, and the patient-reported outcomes used to evaluate efficacy were subject to recall bias. This study was undertaken to provide high-level evidence from a patient-blinded, randomized, controlled trial to test whether cryotherapy is superior to a sham procedure for reducing symptoms of chronic rhinitis.

1 | PATIENTS AND METHODS

1.1 | Study design and population

This is a prospective, multicenter, randomized, sham-controlled, patient-blinded study. Eligible participants were randomized 1:1 to active treatment or sham-control. Participants were adults (≥ 21 years) with moderate to severe symptoms of chronic allergic or nonallergic rhinitis who were candidates for cryotherapy under local anesthesia. A minimum baseline total reflective Total Nasal Symptom Score (rTNSS) of 4 was required, with a minimum score of 2 for rhinorrhea and 1 for nasal congestion. All participants were required to have a skin or blood allergy test within 12 months of baseline. A positive radioallergen sorbent test or skin test results were the basis for determination of allergic rhinitis status. However, in a small number of participants with mixed rhinitis, the investigator determined the predominant rhinitis type based on additional clinical information. Exclusion criteria were

sinus/nasal surgery within 6 months, active sinus/nasal infection, and plans to undergo an ear/nose/throat procedure concurrently or within 3 months of the study procedure. Nasal obstruction that limited access to the posterior nose excluded participants, as did previous cryotherapy or surgical procedures for rhinitis. History of chronic epistaxis, rhinitis medicamentosa, cold sensitivities (eg, Raynaud disease, cryoglobulinemia) were further exclusion criteria. Participants were also required to discontinue ipratropium bromide (IB) at ≥ 14 days before baseline and through the 90-day follow-up.

Review and approval of the protocol was provided by the Advarra (Columbia, MD) institutional review board (IRB) or the local site IRB. All participants provided written informed consent to participate. The study has been registered at www.clinicaltrials.gov with the unique identifier NCT04154605.

1.2 | Randomization

Randomization assignments were generated by an independent statistician using variable block size distribution by site with a 1:1 allocation to active or sham treatment. Randomization was stratified by allergy subgroup (allergic, nonallergic). The randomized assignment was obtained by the sites from the electronic database randomization module at the time of the procedure after all baseline data were collected and eligibility was confirmed.

1.3 | Procedure

All participants were expected to undergo a bilateral procedure using the ClariFix device in accordance with the manufacturer's instructions. To support blinding, all participants wore blindfolds during the procedure to limit any visual clues that could suggest the treatment assignment. Topical and local anesthesia regimens were the same for both treatment arms and included oral prophylactic pain medication, decongestant spray, topical anesthetic spray, anesthesia-soaked pledgets, and injected local anesthetic. Active procedures were performed according to the manufacturer's instructions with the posterior middle meatus of each side treated with a 30-second freeze/60-second thaw cycle. A second freeze/thaw cycle was allowed per side at the physician's discretion. The sham procedure was conducted in the exact same manner as the active procedure, except a cryogen canister was not loaded in the device. The cryoprobe of the device was placed in the posterior middle meatus of the participant's nasal cavity. While the cryoprobe was in place, a separate device with a canister loaded was held near the participant and activated for

30 seconds to provide the sound of gas release from the canister. The cryoprobe was then held in place in the participant's posterior middle meatus for an additional 60 seconds to simulate the thaw cycle. This process was then repeated on the opposite side. A standardized script was used during both active and sham procedure to promote blinding. No concurrent procedures were permitted. All patients were monitored subsequent to the procedure for postprocedure pain and symptoms. Patients were then discharged after 30 minutes of monitoring. Postprocedure regimens, including frequency and duration of nasal saline lavages, and resumption of intranasal steroids, antihistamines (intranasal or oral) were determined at each site by that physician's standard practice and, as such, varied by site. However, at each site, both active and sham participants received the same postprocedure regimen.

1.4 | Assessments

Participants attended follow-up visits at 30 and 90 days postprocedure. At each follow-up visit, participants completed validated questionnaires. Validated questionnaires included the rTNSS,¹⁹ the standardized Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ(S)],²⁰ and the Nasal Obstruction Symptom Evaluation (NOSE).^{21,22} Adverse events were also recorded and were adjudicated by an independent medical monitor for seriousness and relatedness. Initially, rhinoscopy examinations were also required at each follow-up, but, due to COVID-19 restrictions, the protocol was amended and rhinoscopy examinations were not required.

The primary endpoint was the comparison between treatment arms for the percentage of responders at 90 days. Responders were defined as participants with a $\geq 30\%$ reduction in rTNSS relative to baseline.²³

The minimum clinically important difference (MCID) for the RQLQ(S) was defined as ≥ 0.5 point.²⁰ A NOSE responder was defined as a participant with at least 1 NOSE class improvement or reduction of $\geq 20\%$ compared with baseline.^{22,24}

1.5 | Statistical analysis

Summary statistics were calculated for all study endpoints. Categorical variables were summarized using frequency distributions, and continuous variables were summarized with mean and standard deviation (for normal distributions) or median and interquartile range (for non-normal distributions). The 95% confidence interval (95% CI) was computed for the change from baseline for the patient-reported outcomes. The primary efficacy endpoint was

tested at a one-sided alpha level of 0.025 using a chi-square test. The secondary endpoints were tested using the Student *t* test or signed-rank test for change from baseline within arm and two-sample *t* test or Wilcoxon test for change from baseline between arms. An alpha level of 0.05 was considered statistically significant.

The hypothesis tested for superiority of the response rate of the active over the sham treatment using a one-sided *Z* test of 2 proportions. The sample size was calculated with 90% power and a 2.5% one-sided type 1 error rate based on the assumptions of 1:1 randomization allocation and response rates of 73.5% (95% CI, 63.6-81.9%) in the active arm and 45% in the sham arm. A total sample size of 122 randomized participants (61 per arm) was considered adequate to test the hypothesis.

The primary endpoint was evaluated on the per-protocol cohort, meaning any participants unblinded before the 90-day visit or with significant protocol deviations (eg, inclusion/exclusion criteria, did not received treatment as randomized) were not included in the analysis of the primary endpoint. Adverse events were evaluated on all participants by the actual treatment received. Adverse events were adjudicated for seriousness and relatedness by an independent physician.

A repeated-measures multivariate logistic regression analysis was performed to determine predictors of rTNSS primary endpoint. The analysis was adjusted for by treatment arm and follow-up visit, as well as the following covariates of clinical interest: age, sex, rhinitis type, IB response, previous sinonasal procedure(s), and baseline rTNSS.

The statistical analysis was performed by an independent statistician using SAS version 9.4 (SAS Institute, Cary, NC), unless noted otherwise.

2 | RESULTS

A total of 133 participants (68 active, 65 sham) were enrolled at 12 investigational centers in the US. The flow of participants through the 90-day follow-up is shown in Figure 1. Four participants were excluded from the per-protocol analysis cohort due to not meeting minimum baseline rTNSS scores ($n = 1$), unblinded by the investigator after the procedure and discontinued follow-up ($n = 1$), and canceled procedures ($n = 2$). One procedure was canceled when a sham participant had a vasovagal reaction and the other because the active participant's nasal anatomy prevented access to the treatment site. In addition, 1 active and 1 sham participant missed the 90-day follow-up visit.

Demographic and other baseline data are presented by study group in Table 1. On average, the participants in

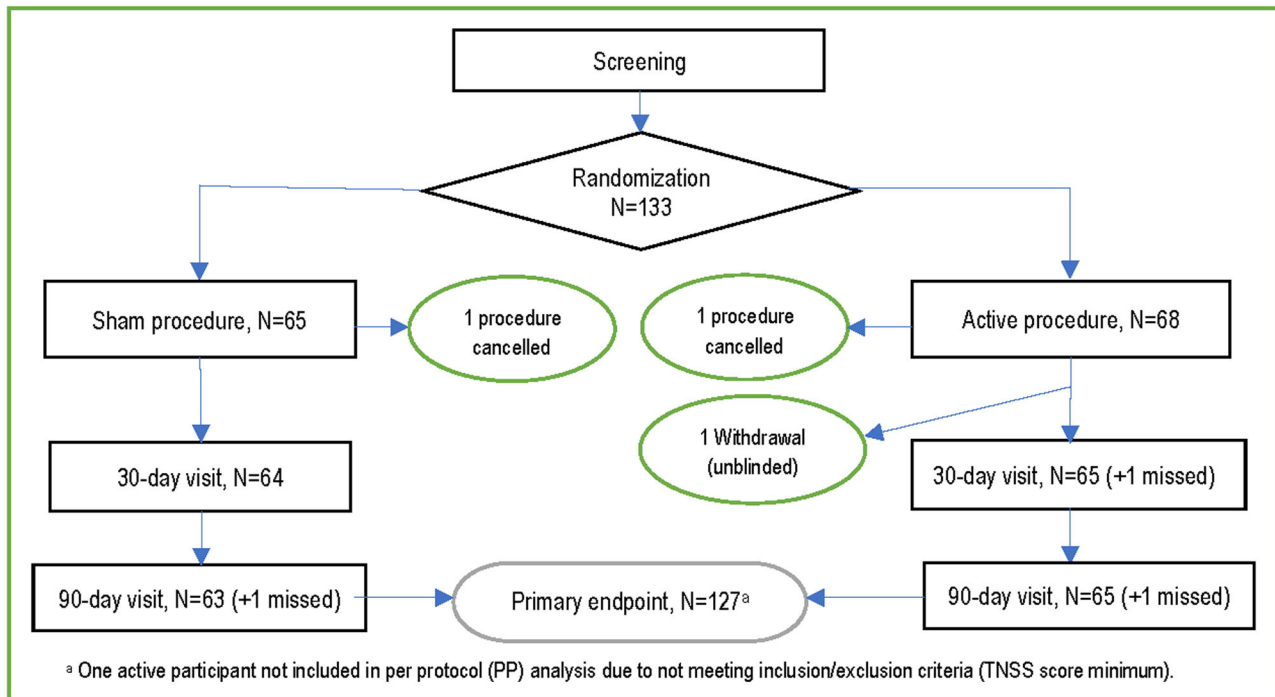


FIGURE 1 Per-protocol participant flow through the 90-day follow-up (primary endpoint).

the active arm were 6 years younger than those in the sham arm (mean age, 52.3 vs 58.3 years; $p = 0.032$). Otherwise, baseline characteristics were not statistically different between treatment arms. Fifty-seven percent of participants had nonallergic rhinitis and 43% had allergic rhinitis. Nearly all participants (94.0%) had a rhinitis duration of >2 years. Approximately half of the participants (66 of 133) had documented responses to a previous trial of ipratropium bromide. The percentages of participants taking allergy and/or rhinitis medications at baseline and 90-day follow-up are presented in Table S1. For the most part, medications were stable, with small numbers of participants in each arm discontinuing medications during the 90-day follow-up period. The differences between arms at 90 days were not statistically significant (all $p > 0.05$).

At the 90-day follow-up, the active arm had 73.4% (47 of 64) responders compared with 36.5% (23 of 63) in the sham arm (Fig. 2). This difference was statistically significant ($p < 0.001$)—the primary endpoint was met, demonstrating superiority of cryotherapy over the sham procedure.

The rTNSSs at baseline and follow-up visits are presented in Table 2 and Figure 3. The active arm improved from 8.0 ± 1.6 at baseline to 4.3 ± 2.4 at 90 days and the sham group improved from 8.1 ± 1.9 at baseline to 6.3 ± 2.5 at 90 days. Although both arms demonstrated statistically significant mean changes from baseline, the active arm showed significantly greater improvement over the sham arm at the 90-day follow-up (active change: -3.7 [95% CI,

-4.3 to -3.1], sham change: -1.8 [95% CI, -2.5 to -1.1]; between arms $p < 0.001$).

Evaluation of the individual rTNSS items demonstrated significantly greater improvement for rhinorrhea and nasal congestion in the active arm compared with the sham arm ($p < 0.001$ for both items) (see Table S2). The mean change (95% CI) for rhinorrhea was -1.2 (-1.4 to -1.0) in the active arm vs -0.4 (-0.6 to -0.2) in the sham arm at 90 days postprocedure. The mean change (95% CI) for nasal congestion was -1.2 (-1.4 to -1.0) in the active arm vs -0.8 (-1.0 to -0.6) in the sham arm at 90 days postprocedure. Nasal itching and sneezing were not significantly different between the treatment arms.

The repeated-measures multivariate analysis assessed the association of the primary endpoint outcome ($\geq 30\%$ improvement in the rTNSS) and the following covariates: treatment arm, rTNSS at baseline, age, sex, rhinitis type, previous ipratropium bromide response, previous sinonasal procedure(s), and visit. The multivariate model showed that only the treatment arm (odds ratio for treatment vs sham: 3.430 [95% CI, 1.827 to 6.43; $p = 0.0001$]) and the rTNSS value at baseline (odds ratio: 1.321 [95% CI, 1.095 to 1.593; $p = 0.0036$]) were associated with the outcome (Table 3). The remaining covariates were not significantly associated with the outcome. With regard to the IB response, it is important to note that there were only 5 IB nonresponders in the active arm and 6 in the sham arm. Of these, 3 of the 5 (60%) active participants and 4 of the

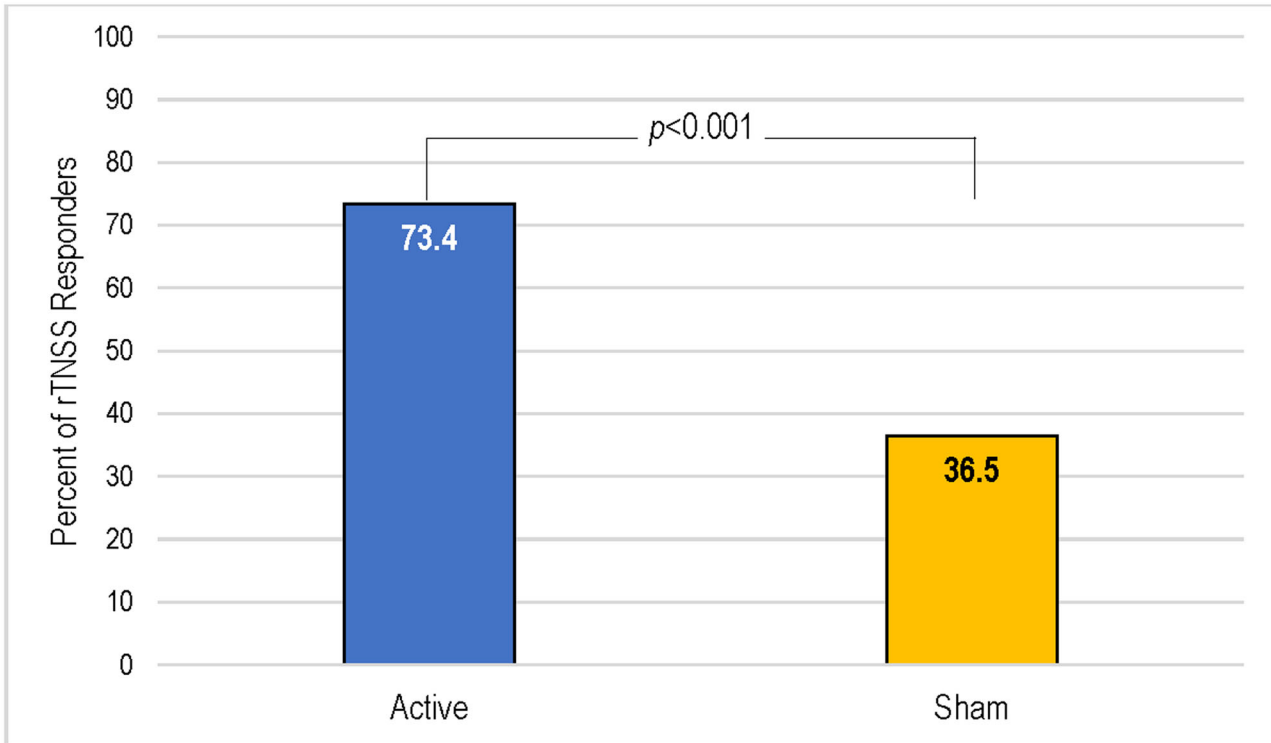


FIGURE 2 Primary endpoint. Comparison of rTNSS responders by treatment arm at 90-day follow-up. Responders are defined as participants with a $\geq 30\%$ reduction in rTNSS relative to baseline. $p < 0.025$ considered statistically significant. rTNSS = reflective Total Nasal Symptom Score.

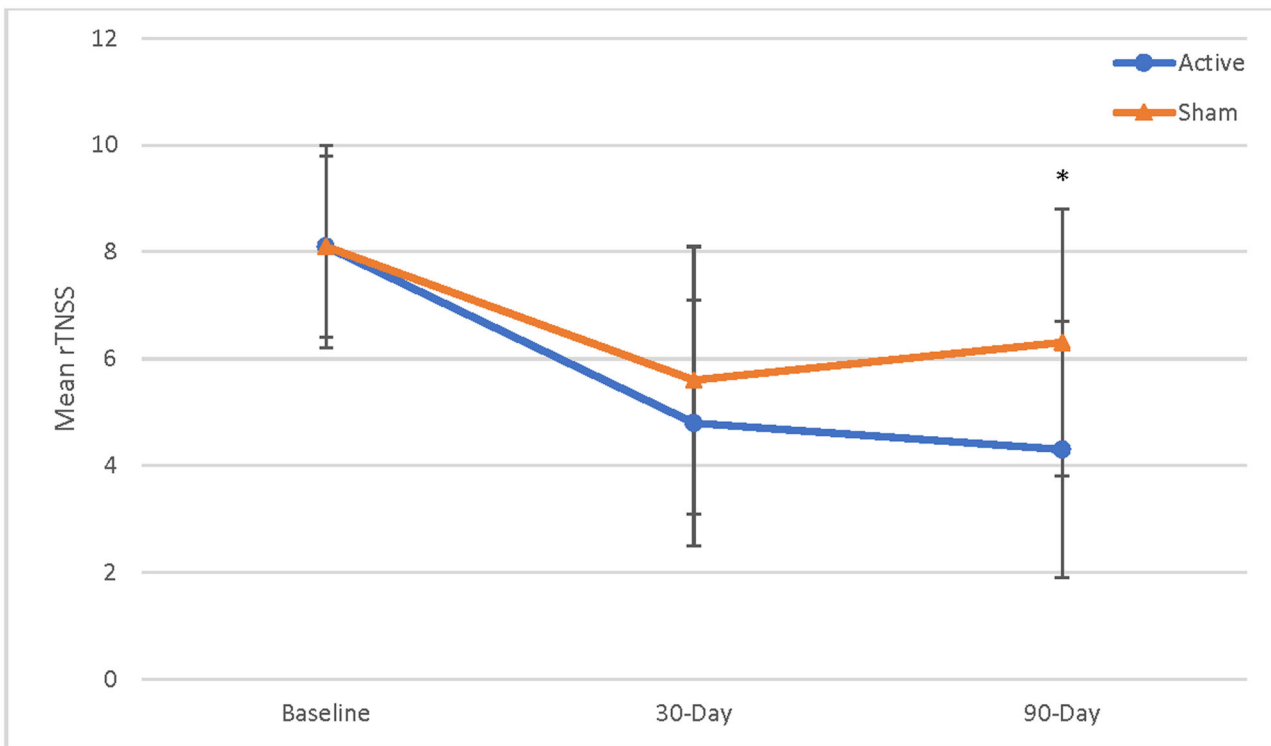


FIGURE 3 Change in mean rTNSS by treatment arm. Error bars indicate standard deviations. Asterisks indicate statistical significance ($p < 0.001$) for the difference between treatment arms. rTNSS = reflective Total Nasal Symptom Score.

TABLE 1 Demographics and baseline characteristics*

Characteristic	Active (n = 68)	Sham (n = 65)	All participants (N = 133)
Age (years)	52.3 ± 15.8	58.3 ± 16.4	55.2 ± 16.3
Sex			
Female	66.2% (45)	49.2% (32)	57.9% (77)
Male	33.8% (23)	50.8% (33)	42.1% (56)
Race			
White/Caucasian	89.7% (61)	87.7% (57)	88.7% (118)
Native Hawaiian/other Pacific Islander	0.0% (0)	0.0% (0)	0.0% (0)
Black/African American	4.4% (3)	7.7% (5)	6.0% (8)
Asian	2.9% (2)	3.1% (2)	3.0% (4)
American Indian/Alaskan Native	1.5% (1)	0.0% (0)	0.8% (1)
Other	1.5% (1)	1.5% (1)	1.5% (2)
Ethnicity			
Not Hispanic or Latino	92.6% (63)	87.7% (57)	90.2% (120)
Hispanic or Latino	7.4% (5)	12.3% (8)	9.8% (13)
Rhinitis type			
Allergic	42.6% (29)	43.1% (28)	42.9% (57)
Nonallergic	57.4% (39)	56.9% (37)	57.1% (76)
Completed previous IB trial	47.1% (32 of 68)	52.3% (34 of 65)	49.6% (66 of 133)
Previous IB response			
Nonresponder	15.6% (5 of 32)	17.6% (6 of 34)	16.7% (11 of 66)
Responder	81.3% (26 of 32)	82.4% (28 of 34)	81.8% (54 of 66)
Unknown	3.1% (1 of 32)	0.0% (0 of 34)	1.5% (1 of 66)
Using IB at screening visit	4.4% (3)	10.8% (7)	7.5% (10)
Previous sinonasal procedure(s)	36.8% (25 of 68)	43.1% (28 of 65)	39.8% (53 of 133)
Mean baseline rTNSS score	8.0 ± 1.8	8.1 ± 1.9	8.1 ± 1.8
Mean baseline RQLQ(S) score	2.7 ± 1.1	2.8 ± 1.1	2.7 ± 1.1

IB = ipratropium bromide; RQLQ(S) = standardized Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS = reflective Total Nasal Symptom Score.

*Data expressed as mean ± standard deviation or as percent (n). Numbers indicate whether different from the expected total. *p* values are based on two-sample *t* test or Wilcoxon test for continuous parameters and chi-square or Fisher exact test for categorical parameters. *p* values in italics are from the Wilcoxon test.

^aOther races include: Nilo-hamite and multiracial.

6 (67%) sham participants were TNSS responders. These numbers, although small, support our multivariate analysis that IB responsiveness does not predict TNSS response.

Both treatment arms showed statistically significant improvement over baseline for the RQLQ(S) (Table 4 and Fig. 4); however, the active arm showed significantly greater improvement over the sham arm at the 90-day visit (active change: -1.5 [95% CI, -1.8 to -1.2], sham change: -0.8 [95% CI, -1.1 to -0.5]; between arm $p < 0.001$). At the 90-day visit, 82.8% (53 of 64) of the active-arm participants achieved the MCID of ≥ 0.5 -point improvement in the RQLQ(S) compared with 52.4% (33 of 63) of sham participants. RQLQ(S) domain scores were more improved in the active arm compared with the sham arm for 5 of the 7 domains (non-hay fever symptoms: $p = 0.007$; practical problems: $p = 0.002$; nasal symptoms: $p < 0.001$; eye symptoms: $p = 0.020$; emotions: $p < 0.001$) and approached statistical significance for sleep ($p = 0.050$).

Active-arm participants also demonstrated significantly greater improvement in NOSE scores than sham-arm participants at the 90-day visit (active change: -29.9 [95% CI, -35.8 to -24.0], sham change: -14.8 [95% CI, -21.2 to -8.4]; between arm $p < 0.001$) (Table 5 and Fig. 5). The NOSE responder rate was 81.3% (52 of 64) for the active arm vs 54.0% (34 of 63) for the sham arm.

There was 1 procedure-related serious adverse event. One active participant had an anxiety/panic attack while still in the clinic after a successful study procedure. Vital signs were normal. The participant was transported by ambulance to the emergency room where a computed tomography scan was performed and showed normal findings. The participant remained under observation for 23 hours and was then released. The event was considered resolved and no sequelae were reported.

Thirty-five participants (32 active, 3 sham) reported a total of 43 nonserious related adverse events (see

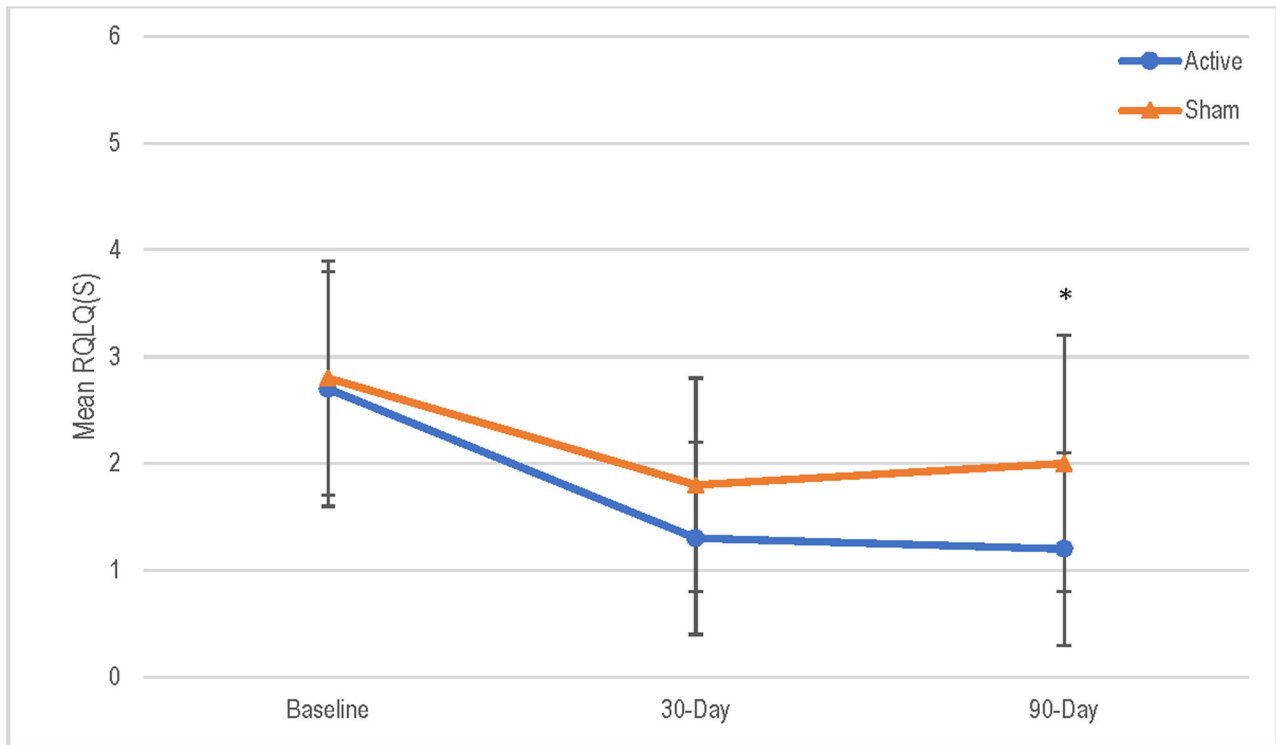


FIGURE 4 Change in mean RQLQ(S) score by treatment arm. Error bars indicate standard deviations. Asterisks indicate statistical significance ($p < 0.001$) for the difference between treatment arms. RQLQ(S) = Rhinoconjunctivitis Quality of Life Questionnaire standardized.

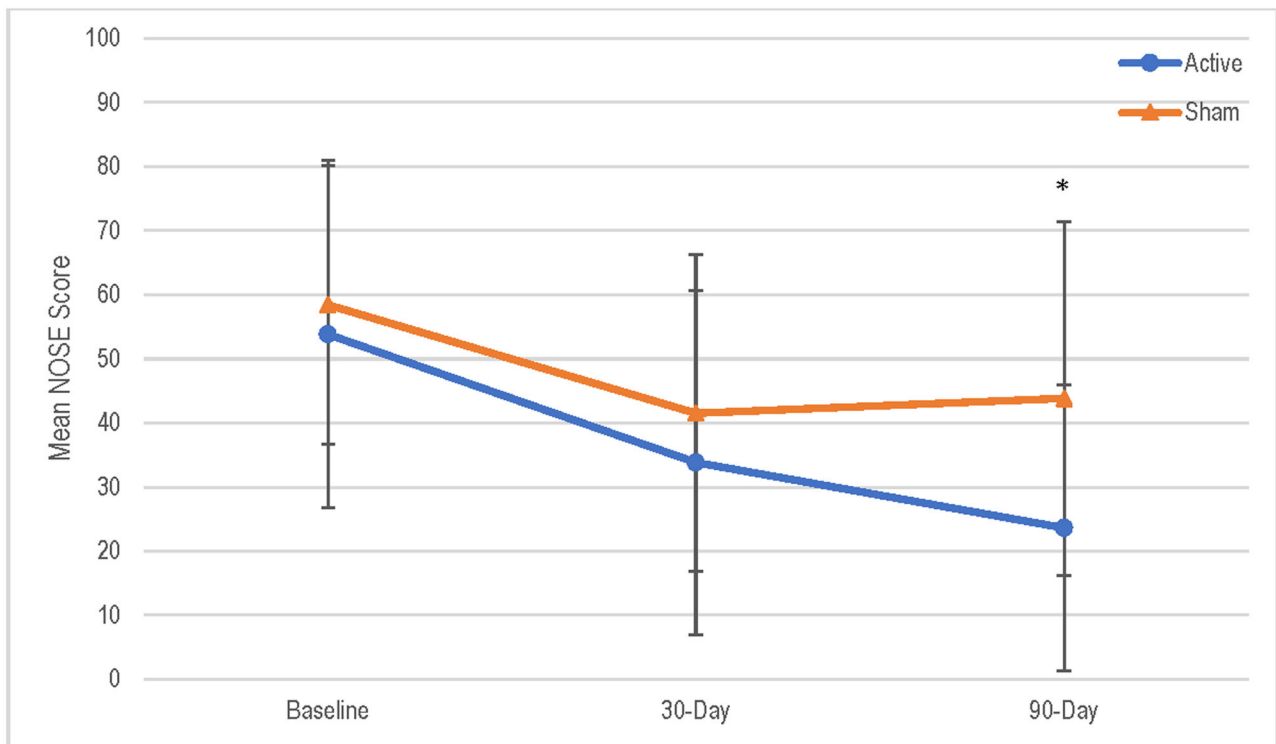


FIGURE 5 Mean change in NOSE score by treatment arm. Error bars indicate standard deviations. Asterisks indicate statistical significance ($p < 0.001$) for the difference between treatment arms. NOSE = Nasal Obstruction Symptom Evaluation.

TABLE 2 Total rTNSSs*

Follow-up period	Active				Sham						
	N	Baseline rTNSS score	Follow-up rTNSS score	Change in rTNSS score (95% CI)	Within-arm p value ^a	N	Baseline rTNSS score	Follow-up rTNSS score	Change in rTNSS score (95% CI)	Within-arm p value ^a	Between-arm p value ^b
30 days	64	8.1 ± 1.7	4.8 ± 2.3	-3.2 (-3.9 to -2.6)	<0.001	64	8.1 ± 1.9	5.7 ± 2.5	-2.5 (-3.1 to -1.8)	<0.001	0.088
90 days	64	8.0 ± 1.6	4.3 ± 2.4	-3.7 (-4.3 to -3.1)	<0.001	63	8.1 ± 1.9	6.3 ± 2.5	-1.8 (-2.5 to -1.1)	<0.001	<0.001

CI = confidence interval; rTNSS = reflective Total Nasal Symptom Score.

*Data expressed as mean ± standard deviation (n). Changes data expressed as mean (95% CI).

^ap values based on Student *t* test or signed-rank test for change from baseline within arm. p values in italics from signed-rank test.

^bp values based on two-sample *t* test or Wilcoxon test for change from baseline between arms. p values in italics from Wilcoxon test.

Table S3). The most common events were postprocedure pain/discomfort at the treatment site (26 participants) and headache (4 participants). These events were typically resolved within 1 to 2 hours of the procedure and common interventions included over-the-counter pain medications and warm beverages.

3 | DISCUSSION

Chronic rhinitis is widely prevalent in the US, affecting up to 30% of the adult population in some form, and accounting for more than \$4.6 billion in annual health-care expenditures.^{25,26} Chronic rhinitis is commonly subdivided as allergic or nonallergic. Medical treatments that are used as first-line therapy for all types of rhinitis include intranasal corticosteroids, antihistamines, and ipratropium bromide; oral antihistamines; and nasal saline sprays and irrigation. Immunotherapy is an additional option for patients with allergic rhinitis. Unfortunately, 10% to 22% of patients with chronic rhinitis fail to respond to medical treatment.²⁷ Historically, vidian neurectomy to disrupt parasympathetic innervation of the nasal mucosa was an effective surgical option for these recalcitrant cases of chronic rhinitis. However, this procedure never attained widespread use due to a high rate of dry eye from simultaneous disruption of parasympathetic innervation to the lacrimal gland.⁶ The posterior nasal nerve was later identified as a better target for surgical intervention to focally disrupt only nasal parasympathetic innervation, as it is distal to the parasympathetic fibers for lacrimal innervation.⁷ More recently, selective cryoablation of the posterior nasal nerve has shown promise in nonrandomized studies for reducing rhinorrhea and nasal congestion in patients with allergic and nonallergic rhinitis, but the lack of a control arm has limited interpretation of the data from these trials.¹⁴⁻¹⁸ The present study was designed to address this limitation by including a randomized, sham-controlled arm.

To our knowledge, this is the first randomized, prospective, sham-controlled trial of cryotherapy as a treatment for chronic rhinitis. We showed the treatment was superior to sham for the 90-day rTNSS responder rate (73.4% vs 36.5%, $p < 0.001$). The results of this study validate the use of cryoablation of the posterior nasal nerve as an effective treatment for chronic rhinitis. In comparison with previous studies on cryoablation of the posterior nasal nerve, our baseline rTNSS score of 8.1 was higher than those previously described by Hwang et al¹⁴ (6.2), Chang et al¹⁵ (6.1), and Yen et al¹⁶ (7.0), and similar to that described by Gerka Stuyt et al¹⁸ (7.8). Despite our participants having more severe baseline symptom scores, our 90-day active treatment change (-3.7) was similar to changes in those

TABLE 3 Repeated-measures multivariate analysis for rTNSS responder rate*

Covariate	Comparison	Beta estimate	SE of beta	p value	Odds ratio (95% CI)
Intercept		-3.4486	1.0299	0.0008	0.032 (0.004-0.239)
Treatment	Active vs sham	1.2325	0.3213	0.0001	3.430 (1.827-6.438)
Age (years)	1-unit increase	0.0148	0.0092	0.1050	1.015 (0.997-1.033)
Sex	F vs M	-0.0958	0.3451	0.7812	0.909 (0.462-1.787)
Rhinitis type	Allergic vs nonallergic	-0.2242	0.3192	0.4825	0.799 (0.428-1.494)
rTNSS (total) at baseline	1-unit increase	0.2782	0.0955	0.0036	1.321 (1.095-1.593)
IB response	No response vs response	0.2330	0.6770	0.7308	1.262 (0.335-4.758)
IB response	Unknown/NA vs response	0.0372	0.3224	0.9081	1.038 (0.552-1.952)
Previous sinonasal procedure/s	No vs yes	0.1737	0.3131	0.5790	1.190 (0.644-2.197)
Visit	1 month vs 3 months	0.0360	0.2235	0.8720	1.037 (0.669-1.606)

*Data based on a repeated-measures logistic regression by modeling the odds of $\geq 30\%$ improvement in rTNSS. Generalized estimating equations were used to obtain parameter estimates.

CI = confidence interval; F = female; IB = ipratropium bromide; M = male; NA = not available; rTNSS = reflective total nasal symptom score; SE = standard error.

TABLE 4 Total standardized RQLQ(S) scores

Arm	Follow-up period	N	Baseline RQLQ(S) score	Follow-up RQLQ(S) score	Change from baseline	Within-arm p value ^a	Between-arm p value ^b	≥ 0.5 point improvement
Active	30-day	64	2.7 \pm 1.1	1.3 \pm 0.9	-1.4 (-1.7 to -1.1)	<0.001	0.060	79.7% (51)
	90-day	64	2.7 \pm 1.1	1.2 \pm 0.9	-1.5 (-1.8 to -1.2)	<0.001	<0.001	82.8% (53)
Sham	30-day	64	2.8 \pm 1.1	1.8 \pm 1.0	-1.0 (-1.2 to -0.7)	<0.001		67.2% (43)
	90-day	63	2.8 \pm 1.1	2.0 \pm 1.2	-0.8 (-1.1 to -0.5)	<0.001		52.4% (33)

CI = confidence interval; RQLQ(S) = standardized Rhinoconjunctivitis Quality of Life Questionnaire.

*Data expressed as mean \pm standard deviation or percent (n or N). Changes expressed as mean (95% CI). RQLQ(S) scores can range from 0 (no impairment) to 6 (severe impairment). Change of ≥ 0.5 point considered the minimum clinically important difference.

^ap values based on Student *t* test or signed-rank test for change from baseline within arm. p values in italics based on signed-rank test.

^bp values based on two-sample *t* test or Wilcoxon test for change from baseline between arms. p values in italics based on Wilcoxon test.

other studies (-3.5, -3.1, -4.0, and -3.9, respectively). Furthermore, we showed a greater improvement in the 90-day rTNSS score in the treatment vs the sham arm (-3.7 vs -1.8, $p < 0.001$). In addition, the difference in change from baseline in NOSE score between our treat-

ment and sham arms (-29.9 vs -14.8) supports the use of cryoablation as an additional treatment for nasal obstruction. The NOSE change from baseline in the treatment arm reported here is similar to that reported by Yen et al¹⁶ (-31.4).

TABLE 5 Total NOSE scores*

Arm	Follow-up period	N	Baseline NOSE score	Follow-up NOSE score	Change from baseline	Within-arm p value ^a	Between-arm p value ^b	NOSE responder rate ^c
Active	30 days	64	53.8 \pm 27.1	33.8 \pm 26.9	-20.1 (-27.4 to -12.8)	<0.001	0.493	67.2% (43)
	90 days	64	53.5 \pm 27.3	23.6 \pm 22.3	-29.9 (-35.8 to -24.0)	<0.001	<0.001	81.3% (52)
Sham	30 days	64	58.4 \pm 21.8	41.5 \pm 24.7	-17.0 (-22.4 to -11.5)	<0.001		62.5% (40)
	90 days	63	58.6 \pm 21.9	43.8 \pm 27.6	-14.8 (-21.1 to -8.4)	<0.001		54.0% (34)

CI = confidence interval; NOSE = Nasal Obstruction Symptom Evaluation.

*Data expressed as mean \pm standard deviation or percent (n). Changes expressed as mean (95% CI).

^ap values based on Student *t* test or signed-rank test for change from baseline within arm. p values in italics based on signed-rank test.

^bp values based on two-sample *t* test or Wilcoxon test for change from baseline between arms. p values in italics based on Wilcoxon test.

^cResponder defined as a participant with at least 1 NOSE class improvement or a NOSE score reduction of $\geq 20\%$ vs baseline.

Through multivariate analysis, we found that only the treatment arm and rTNSS value at baseline were associated with the outcome. The rTNSS value at baseline was also shown to be associated with the primary endpoints in the study by Ow et al, with higher scores associated with greater improvement.¹⁷ Likewise, in agreement with our findings, other studies also found no association with the type of rhinitis (allergic vs nonallergic).^{14,15,17,28} We did not identify any association with a previous response to IB. This is in contrast to findings by Yoo et al, who found IB response to be the only predictor of cryoablation success when using the Runny Nose Score from the 22-item Sino-Nasal Outcome Test.²⁸ The difference in findings may be the result of different outcome tools as well as different ratios of IB responders/nonresponders in the 2 studies, as we had a lower proportion of nonresponders in our study. Our results suggest that cryoablation is a viable option for patients regardless of previous response to IB.

The strengths of this study include its prospective, multicenter, randomized, sham-controlled, single-blind design using several validated patient-reported outcome measures. This is unique among most procedural interventions in rhinology due to the difficulty performing sham procedures, thus it lends further support to the true efficacy of cryotherapy for chronic rhinitis. The fact that participants in the sham arm actually perceived benefit at 30 days over baseline supports the concept of a placebo effect for procedural interventions and the need to include such sham arms in future studies for other procedures. In addition, the multicenter design indicates these results are likely to be broadly applicable to other otolaryngology practices. Another strength of our study involves the patient population. Nearly all participants in the study had rhinitis for 1 year or longer, had often undergone previous sinonasal procedures, and had variable responses to nasal sprays such as IB. There was nearly equal distribution between allergic and nonallergic rhinitis, with similar response rates. Thus, cryotherapy appears to be effective in these highly symptomatic patients who have been refractory to other medical and surgical therapies, regardless of the etiology of their rhinitis.

There are several weaknesses in our study. One is the racial homogeneity of the study population (88% Caucasian). Future studies should aim to study a broader racial diversity of participants. In addition, although objective rhinoscopy examinations were part of the original protocol, restrictions on rhinoscopies during the COVID-19 pandemic required a protocol amendment to remove the rhinoscopy requirement, which precluded a meaningful evaluation of this objective endpoint. This study was industry-sponsored; however, all authors had access to the study data and final approval of the manuscript contents,

an independent physician reviewed adverse events, and an independent statistician conducted the data analyses. Finally, we reported a relatively short-term duration of follow-up (90 days), yet extended follow-up is currently being conducted on these participants.

In conclusion, this randomized, controlled trial has provided high-level evidence demonstrating that cryotherapy performed in the office setting under local anesthesia is superior to a sham procedure for improving patients' chronic rhinitis symptoms and quality of life.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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