


Long-term Outcomes Following Temperature-Controlled Radiofrequency Neurolysis for the Treatment of Chronic Rhinitis



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Abstract

Background: Temperature-controlled radiofrequency neurolysis of the posterior nasal nerve has been shown to reduce the symptom burden of patients with chronic rhinitis.

Objectives: To evaluate the long-term safety and effectiveness of temperature-controlled radiofrequency neurolysis of the posterior nasal nerve for the treatment of chronic rhinitis.

Methods: A prospective extension of a 12-month single-arm study, where reflective total nasal symptom score (rTNSS) and the responses to a study-specific quality of life questionnaire and patient satisfaction survey were collected at 24 months.

Results: Forty-seven patients completed initial 12-month follow-up after treatment with the study device, of which 34 patients were re-consented and completed 24-month follow-up. The mean rTNSS of the long-term follow-up patients improved from 8.4 (95% confidence interval (CI), 7.7 to 9.0) at baseline to 2.9 (95% CI, 2.1 to 3.6), $P < .001$ at 24 months, a 65.5% improvement. On a 6-point scale (0-5), postnasal drip improved from a mean of 4.1 (95% CI, 3.6 to 4.6) to 2.1 (95% CI, 1.7 to 2.5) and chronic cough improved from 3.2 (95% CI, 2.7 to 3.6) to 0.9 (95% CI, 0.5 to 1.3) from baseline through 24 months; $P < .001$ for both measures. The proportion of patients achieving a minimal clinically important difference of 30% improvement from baseline at 24 months was 88.2% (95% CI, 73.4%-95.3%). At 24 months, 24% of patients were taking overall fewer and 15% taking overall more rhinitis medication classes than at baseline. Patients reported a higher quality of life in terms of sleep, well-being, and lower oral medication/nasal spray use at 24 months. There were no serious adverse events considered related to the procedure in the 12-24-month period.

Conclusion: Temperature-controlled radiofrequency neurolysis results in a significant and durable reduction in the symptom burden of chronic rhinitis and patients reported improved quality of life through 24 months postprocedure.

Keywords

rhinitis, rTNSS, rhinorrhea, congestion, posterior nasal nerve, neurectomy, temperature-controlled, radiofrequency ablation, allergic, neurolysis

Introduction

Posterior nasal nerve (PNN) neurectomy has been shown to be effective in the treatment of chronic rhinitis,^{1,2} and is an option for patients dissatisfied by the results of medical management. Minimally invasive treatment options targeting the PNN for the treatment of chronic rhinitis include a device for temperature-controlled radiofrequency (TCRF) neurolysis. Radiofrequency energy devices are widely used in otolaryngology,^{3–5} but TCRF is unique in that the temperature of the treatment area is continually measured and energy delivery to

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the tissue is varied to maintain a tissue temperature of 60 °C. Consequently, TCRF neurolysis enables focused treatment without significant damage to overlying mucosa and adjacent tissue. The RhinAer System (Aerin Medical, Inc., Sunnyvale, CA, USA) received marketing clearance for the treatment of chronic rhinitis from the United States Food and Drug Administration in 2019 and *conformité européenne* marking in 2020. The RhinAer Stylus is applied and TCRF energy is delivered to the portion of the nasal cavity mucosa overlying the PNN region in the posterior middle meatus and along the posterior inferior turbinate.

PNN and Vidian nerve neurectomy are thought to block efferent parasympathetic stimulation and blocking parasympathetic innervation has been shown to reduce submucosal glands secretion, blood flow in the submucosa, and stromal edema.⁶ Moreover, the administration of intranasal botulinum toxin A on the mucosal lining of the nose is thought to suppress parasympathetic nerves in the nasal mucosa.^{7,8} TCRF neurolysis of the PNN demonstrated superiority over a sham procedure at 3 months postprocedure in a randomized controlled trial.⁹ In a separate single-arm study, the procedure showed a significant reduction in rhinitis symptom burden (efficacy) through 12 months, as measured by the reflective total nasal symptom score (rTNSS).¹⁰ Here, we report safety and efficacy results of long-term follow-up of that same single-arm study at 24 months, in addition to patient quality of life (QoL) data and the extent of patient satisfaction with the procedure.

Methods

This study was an extension of a prospective, single-arm, open-label, multicenter study¹⁰ with enrollment at 5 centers in the United States, designed to collect long-term outcomes for patients undergoing TCRF neurolysis of the PNN for the treatment of chronic rhinitis. The study extension was approved by Western Institutional Review Board (reference 20202529) and registered at clinicaltrials.gov (NCT04684875). All patients gave written informed consent to participate in the study extension. All investigators were board-certified otolaryngologists.

Patients were treated between October 2018 and June 2019 and 24-month data were collected through May 2021. Key inclusion criteria for treatment were chronic rhinitis symptoms of at least 6 months duration with inadequate response to at least 4 weeks usage of intranasal steroids, a 12-hour rTNSS ≥ 6 , as well an rTNSS subscore of ≥ 2 for rhinorrhea and an rTNSS subscore of ≥ 1 for congestion. The rTNSS questionnaire is shown in the Supplemental Material. Patients were excluded for treatment if they had nasal anatomic abnormalities or obstructions that could restrict access to the treatment site, rhinitis medicamentosa, active nasal/sinus infection, history of nose bleeds, ocular allergic symptoms, or history of dry eye. Patients were

invited to consent for the study extension if they completed 12-month follow-up of the original study.

The RhinAer System is a combination of the Aerin Console and the RhinAer Stylus. The console generates power, which is transmitted to the stylus. The stylus is a single-use, disposable, handheld device that delivers 60 °C temperature-controlled bipolar radiofrequency energy to the PNN region. Treatment conditions with short and mid-term results for the patients included in this report have previously been described.¹⁰ The treatment protocol involved bilateral treatment at 1-3 non-overlapping positions in the PNN region. Device settings were 60 °C at 4 W for 12 seconds of treatment time at each position. No repeat/touch-up procedures were performed throughout the 24-month follow-up period.

At 24 months, patients completed the rTNSS questionnaire and recorded postnasal drip and chronic cough symptom scores on a 6-point scale (0 = no problem and 5 = severe symptoms). In addition to rTNSS, the percentage of patients achieving a minimal clinically important difference (MCID) of ≥ 1 point improvement from baseline¹⁰⁻¹³ and $\geq 30\%$ improvement over baseline^{12,14} were determined. At baseline (preprocedure) and 24 months, patients were asked the same series of questions about their QoL. A satisfaction survey was performed at 3, 12, and 24 months post-procedure. The QoL questions and the satisfaction survey are shown in the Supplemental Material. Responses to the QoL questions were provided on an ordered 5-category scale with descriptors (Never, rarely, occasionally, frequently, very frequently). Responses to the satisfaction survey were provided on a 10-point scale with anchor and midrange word descriptors (10 being the best outcome). Midrange (5-6 points) descriptors for treatment tolerability and recovery were "It was tolerable". Midrange (5-6 points) descriptors for breathing, satisfaction, and recommendation were "About the same", "Neither satisfied nor dissatisfied", and "Perhaps", respectively. Although medications indicated for rhinitis were not controlled during this pragmatic study, the use of specific medication classes (anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists) were recorded. Adverse events were captured based on patient interview and medical record review, as available, during the 12-24-month interval and classified based on relatedness to the device and/or procedure.

Data in this report are from the patients participating in the study extension (N = 34), unless stated otherwise. Descriptive statistics were calculated with no data imputation. Unless stated otherwise, continuous data are presented as mean and 95% confidence intervals (CI), and categorical data as number and percentages of total. This study extension was intended to examine duration of treatment effect on rTNSS through 24 months. Outcomes were assessed using linear mixed effect model to test for an overall change over time, with Dunnett's test used for comparison of follow-up

Table 1. Patient Demographics, Baseline, and 12-Month Follow-up Data for the Population (i) Treated in the Original Study, (ii) Enrolled in the Study Extension Through 24 Months, and (iii) That did not Enroll in the Study Extension.

	Treated (N = 50)		24-month follow-up (N = 34)		Non-enrolled in study extension (N = 16)		P value ^a
Female sex	29	(58)	21	(62)	8	(50)	.543
Age (years)	57.9	± 11.9	58.7	± 12.6	56.1	± 10.5	.466
Race							
White	47	(94)	32	(94)	15	(94)	>.999
Asian	2	(4)	1	(3)	1	(6)	
American Indian or Alaska Native	1	(2)	1	(3)	0	(0)	
Body mass index (kg/m ²)	29.8	± 6.4	30.7	± 6.4	27.9	± 6.2	.152
Rhinitis type							
Allergic	21	(42)	13	(38)	8	(50)	.131
Nonallergic	17	(34)	10	(29)	7	(44)	
Unknown	12	(24)	11	(32)	1	(6)	
Rhinitis symptoms >1 year	50	(100)	34	(100)	16	(100)	-
rTNSS							
Baseline	8.5	± 1.8	8.4	± 1.9	8.8	± 1.5	.401
12-month ^b	3.6	± 2.3	3.4	± 2.5	3.9	± 1.8	.525
Responder rate at 12 months ^{b,c}							
≥1-point improvement	47	(100)	34	(100)	13	(100)	-
≥30% improvement	38	(81)	26	(76)	12	(92)	.410

rTNSS = reflective total nasal symptom score.

Continuous data are presented as mean ± standard deviation. Categorical data are presented as number (percent of total) of each population.

^aComparing the population enrolled in the 24-month follow study extension to the population that did not enroll in the study extension. Continuous data were compared by *t* tests and categorical data were compared by Fisher exact tests.

^bn = 47 for the original (treated) population. n = 13 for the population non-enrolled in the study extension.

^cResponder rate at 12 months is the proportion of patients with ≥1-point or ≥30% improvement in rTNSS from baseline. n = 13 for the population non-enrolled in the study extension.

visits to baseline and Tukey-Kramer comparisons between follow-up visits. Adjusted (least square) means are presented for postnasal drip and cough data. Additional post-hoc analyzes using linear mixed models were conducted with respect to rhinitis etiology and the satisfaction survey. Results from the QoL questions are presented as the number (% of total), where the results were converted to a binary outcome by combining the best two categories reflecting a higher QoL for each question (never/rarely or very frequently/ frequently) and the remaining categories. The QoL baseline responses were compared to 24-month responses using 2-sided Fisher exact tests.

Results

Fifty patients were treated in the original study and 47 patients reached 12-month follow-up. Of the patients that reached 12-month follow-up, 34 were reconsented for the study extension and completed the 24-month follow-up visit. Patient disposition is shown in the Supplemental Material. The population that completed 24-month follow-up was not significantly different from the population that did not enroll in the study extension (Table 1). Furthermore, the baseline and 12-month mean rTNSS of the 24-month population were not significantly different from those of

the original population ($P = .740$ for baseline and $P = .803$ for 12-month rTNSS, *t* test). At 12 months, of the 13 patients that declined to participate in the 24-month study extension, 13 (100%) were reporting an MCID of ≥1 point improvement in rTNSS over baseline and 12 (92.3%) were reporting an MCID of ≥30% improvement in rTNSS over baseline.

The mean rTNSS at 24 months remained significantly improved from baseline (Figure 1); the mean change in rTNSS was -5.5 (95% CI, -6.4 to -4.6), $P < .001$, which represented a 65.5% improvement. There was no difference between the results obtained at each follow-up time point (all $P > .05$). At 24 months, the proportion of patients reporting an MCID of ≥1-point improvement in rTNSS from baseline was 97.1% (95% CI, 85.1%-99.5%). Using a more stringent MCID, 88.2% (95% CI, 73.4%-95.3%) exhibited ≥30% improvement from baseline at 24 months. There were no adverse events, serious or otherwise, considered related to the device or procedure in the 12-24-month extended follow-up period.

At 24 months, significant improvement in each rTNSS subscore (rhinorrhea, nasal congestion, nasal itching, and sneezing) was maintained (Figure 2), $P < .001$ for all time points. Postnasal drip and chronic cough scores remained significantly improved from baseline through 24 months (Figure 3), $P < .001$ for all time points.

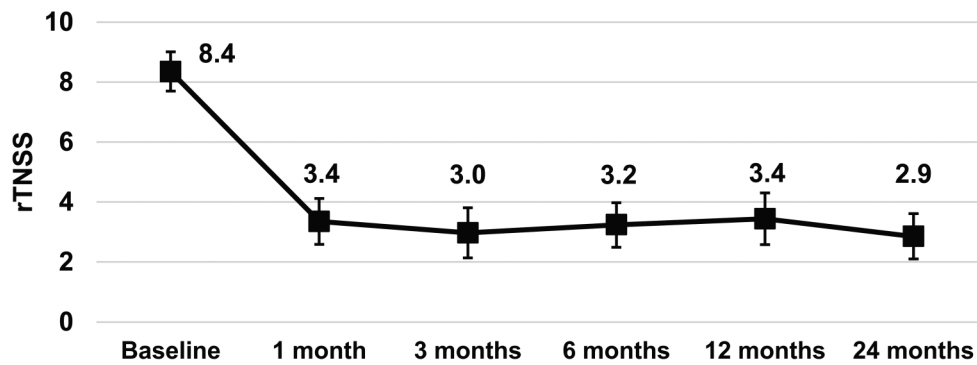


Figure 1. Mean reflective total nasal symptom score (rTNSS) over time (N = 34 at all time points). Bars represent 95% confidence intervals. All follow-up values were significantly improved from baseline ($P < .001$ at all time points).

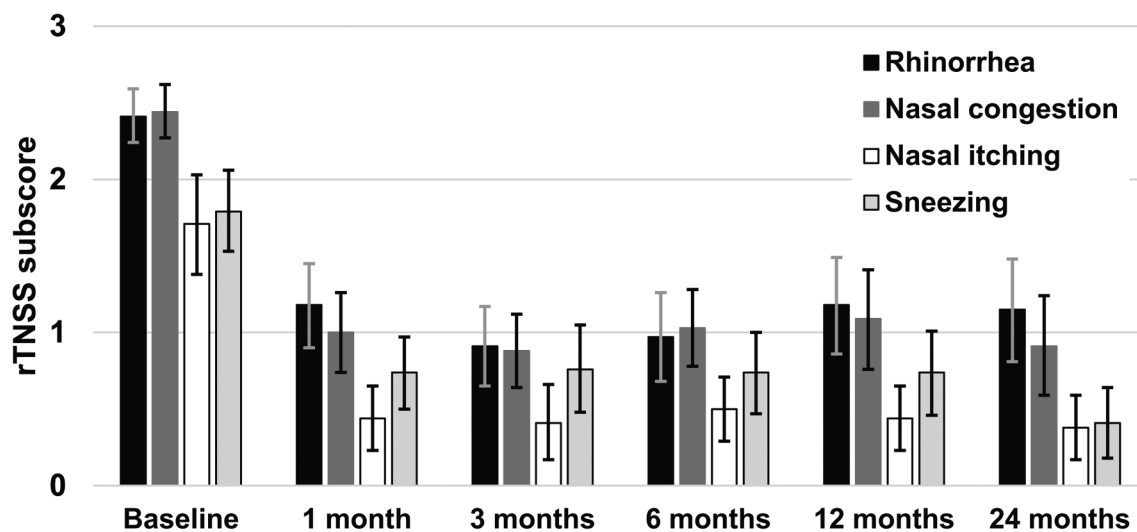


Figure 2. Mean reflective total nasal symptom score (rTNSS) subscores over time (N = 34 at all time points). Bars represent 95% confidence intervals. All follow-up values were significantly improved from baseline ($P < .001$ at all time points).

The stratification of patients based on rhinitis subtype was based on prior knowledge (patient report or physician assessment). At 24 months, all patients, regardless of rhinitis subtype (allergic, non-allergic, unknown), exhibited a significant improvement in mean rTNSS compared to baseline: allergic -4.8 (95% CI, -6.1 to -3.5), nonallergic -6.1 (95% CI, -8.5 to -3.7), unknown -5.8 (95% CI, -7.4 to -4.3), $P < .001$ for all subtypes. Furthermore, there was no difference between the improvement observed with each subtype ($P = .875$).

Compared to baseline responses, a significantly larger percentage of patients responded positively to the series of QoL questions, indicating an increase in QoL at 24 months (Figure 4). Significantly more patients were never/rarely having difficulty falling asleep ($P < .001$), very frequently/frequently having good sleep throughout the night ($P = .045$), never/rarely feeling fatigued during the day ($P = .018$), never/rarely having feelings of frustration/restlessness/irritability ($P < .001$), never/rarely having feelings of

embarrassment or self-consciousness about their chronic rhinitis ($P = .002$), very frequently/frequently having a good sense of well-being ($P = .009$), and rarely/never using nasal sprays ($P = .008$). Fewer patients reported use of oral medications and nasal breathing strips to help with symptoms of chronic rhinitis, although the difference between baseline and 24 months did not reach significance ($P = .071$ and $.191$, respectively).

Patient satisfaction with the procedure and result was high and was consistent from 3 through 24 months (Figure 5). There was no significant difference in the response to each question from 3 through 24 months [$P = .549$ (tolerable procedure), $P = .202$ (ease of procedure), $P = .709$ (change in breathing through the nose), $P = .736$ (satisfaction with the procedure), and $P = .544$ (likely to recommend to a friend)].

In addition to the forms of medication collected as part of questions on QoL (Figure 4), the use of medication classes commonly prescribed to treat rhinitis was also recorded. At

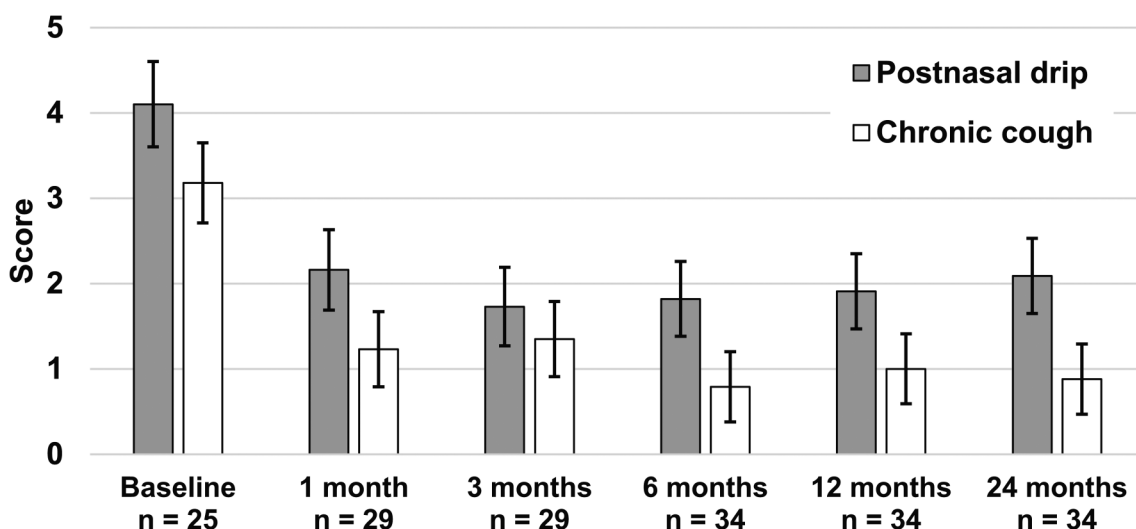


Figure 3. Adjusted mean postnasal drip and cough scores over time. Bars represent 95% confidence intervals. All follow-up values were significantly improved from baseline ($P < .001$ at all time points).

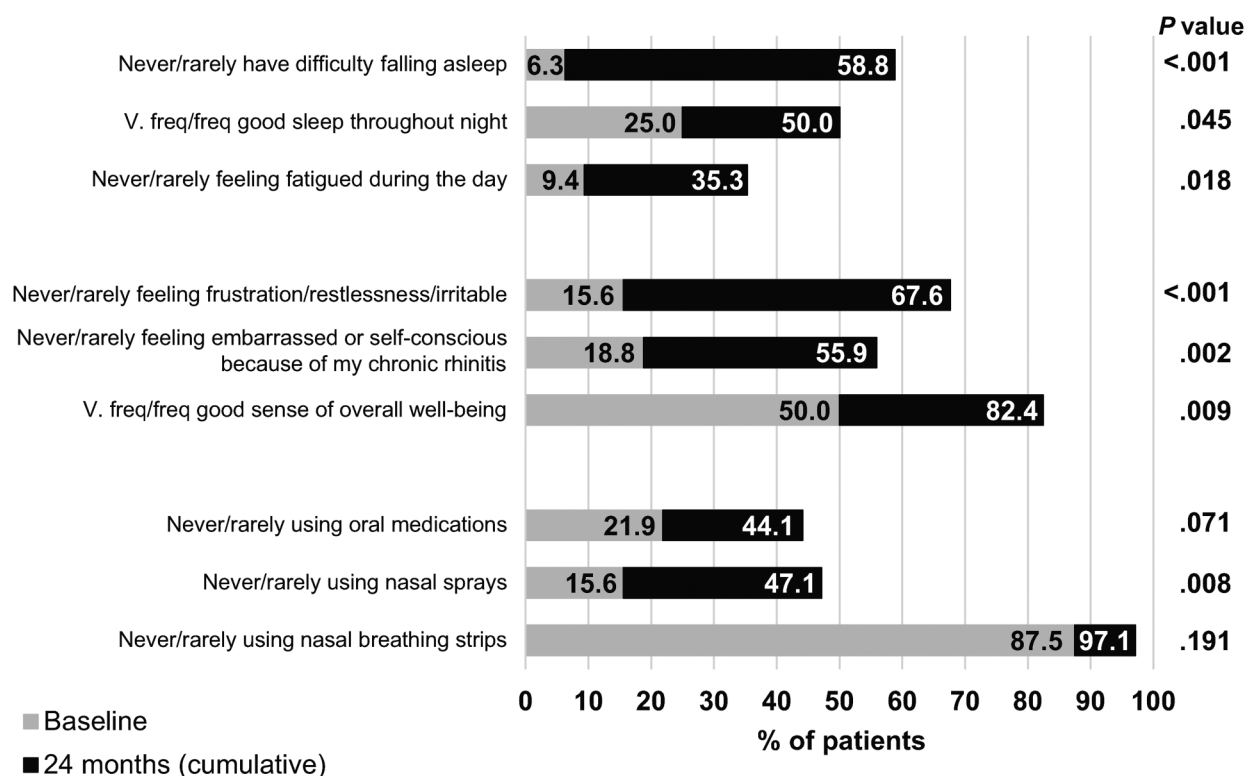


Figure 4. The percentage of patients answering a series of questions consistent with an increase in quality of life from baseline (gray bars/black numbers) through 24 months (cumulative gray and black bars/white numbers). V. freq/freq = very frequently/frequently. $n = 32$ at baseline and $n = 34$ at 24 months. P values compare baseline to 24 months.

baseline, 4 (12%) patients were taking anticholinergics, 21 (62%) antihistamines, 21 (62%) corticosteroids, 4 (12%) decongestants, and 3 (9%) leukotriene receptor antagonists. Comparing 24 months to baseline, 8 (24%) patients reported

an overall decrease and 5 (15%) reported an overall increase in the number of rhinitis medication classes taken. In each medication class: 2 (6%) stopped and 2 (6%) started anticholinergic use, 5 (15%) stopped and 2 (6%) started antihistamine use, 6

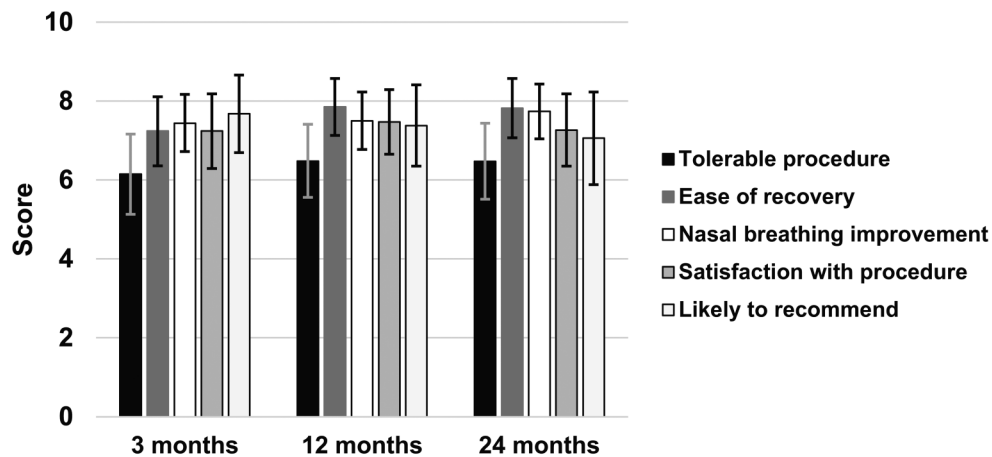


Figure 5. Mean score on a patient satisfaction survey at 3, 12, and 24 months. Bars represent 95% confidence intervals. N = 34, except n = 33 for tolerable procedure at 12 months. There was no significant difference in the response (score) to each question over time (all $P > .05$).

(18%) stopped and 3 (9%) started corticosteroid use, 0 (0%) stopped and 6 (6%) started decongestant use, and 2 (6%) stopped and 0 (0%) started leukotriene receptor antagonist use.

Ipratropium bromide (anticholinergic) use may be a confounding variable to the treatment effect and therefore, changes in rTNSS and responder rates (based on MCIDs) were calculated after removing patients using ipratropium bromide from the analysis. A total of 7 of the 34 patients were using ipratropium bromide at some point from baseline through 24 months. At 24 months, the mean change in rTNSS from baseline of the 27 patients not using ipratropium bromide at any time during the original study and study extension was -5.6 (95% CI, -6.5 to -4.8). The proportion with an MCID of ≥ 1 -point improvement from baseline was 100% (95% CI, 87.5%-100%) and the proportion with $\geq 30\%$ improvement from baseline was 92.6% (95% CI, 76.6%-97.9%).

Discussion

This report details the long-term safety and efficacy of TCRF neurolysis of the PNN using the RhinAer System. Long-term data is important because nerves regenerate, and peripheral nerve regeneration has been reported to occur at a rate of 1-6 inches per month.^{15,16} Furthermore, surgical PNN neurectomy has demonstrated relief of symptoms for 3 years.¹⁷ The patient-reported outcomes in this 24-month study indicate TCRF neurolysis of the PNN results in a durable improvement in chronic rhinitis symptoms. All but one patient (97.1%) was exhibiting an MCID of ≥ 1 -point improvement in rTNSS from baseline^{11-13,18} and all but 4 patients (88.2%) were exhibiting $\geq 30\%$ improvement from baseline^{12,14} at 24 months. The MCIDs used in this study are widely used in literature reports on devices targeting the PNN area.¹⁹⁻²³ For comparison, in a study evaluating cryoablation of the PNN, 80.7% of patients were exhibiting an

MCID of ≥ 1 -point improvement in rTNSS at 24 months.¹⁹ The long-term safety profile of the TCRF device is good and there were no events that raised safety concerns in the 12-24-month period.

The 3-month results of a randomized controlled trial comparing active treatment with the TCRF device to a sham procedure for patients with chronic rhinitis demonstrated that all symptoms measured by the rTNSS instrument were improved from baseline, and that improvements in rhinorrhea and nasal congestion were significantly greater in the active treatment arm than in the sham arm.⁹ A durable reduction in all symptoms (rhinorrhea, nasal congestion, nasal itching, and sneezing) was observed in this long-term single-arm study. While postnasal drip and chronic cough are not part of the rTNSS instrument, these symptoms are commonly experienced by patients with chronic rhinitis and the durable reduction in these symptoms observed in this study likely contributes to the improvement in patient QoL after the procedure.

Patients with allergic, nonallergic, and rhinitis of unknown origin exhibited a durable improvement in symptoms through 12 months¹⁰ and 24 months, supporting the hypothesis that the treatment effect is also independent of rhinitis subtype.

The study design was pragmatic in that medication use was not dictated by the protocol and changing medication prescriptions is commonplace in the management of chronic rhinitis. While this study was not specifically designed to evaluate medication use, medication class analysis showed more patients had an overall decrease (than overall increase) over baseline in the number of medication classes they were taking at the end of the study extension at 24 months. Ipratropium bromide is an anticholinergic drug that inhibits parasympathetic nerve conduction by antagonizing the action of acetylcholine. To ensure any ipratropium bromide use was not confounding the evaluation of

the treatment effect, the primary endpoint¹⁰ and long-term data analyzes in this study were repeated after removing any patients using the drug at any time during the study. This subgroup analysis showed that the observed effect is not enhanced by ipratropium bromide use; there was still a significant decrease in symptom burden over the long term in patients who had never used ipratropium bromide.

Chronic rhinitis is widely accepted to contribute to a reduction in patient QoL.^{24,25} The responses to the QoL questions indicated patients were experiencing better sleep quality at 24 months postprocedure. Patient-reported feelings of frustration and embarrassment related to chronic rhinitis symptoms were reduced, and patients reported a better sense of well-being. With the significant and durable reduction in all rhinitis symptoms, it is not surprising patients reported an increase in QoL from baseline. Patient satisfaction with the procedure was high just 3 months after the procedure and this sentiment was maintained over the long term.

The limitations of this study are the lack of control arm, lack of medication control, and the fact that only a subset of the patients in the original 12-month study consented to the extension through 24 months. However, the population that enrolled in the study extension was not significantly different from the one that did not enroll. Furthermore, rTNSS results of the long-term cohort at baseline and 12 months were not significantly different from those of the original study. Although concurrent medication usage was evaluated in this pragmatic study, future studies that employ a medication control strategy could be useful to explore any confounding effects of medication changes.

Conclusions

TCRF neurolysis of the PNN results in a significant and durable reduction in the symptom burden of chronic rhinitis through 24 months postprocedure. Patients reported improved QoL in terms of better sleep quality, personal feelings and well-being, and lower oral medication/nasal spray use. At 24 months, a larger percentage of patients had decreased the number of rhinitis medication classes they were taking since baseline than had increased their medication use during the study. Patient-reported satisfaction with the procedure remained high through 24 months postprocedure.

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Jeremy P. Watkins: Investigation; Writing – review & editing.

V. Vasu Kakarlapudi: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: xxxxxxxx. Dale Ehmer and V. Vasu Kakarlapudi are consultants for Aerin Medical. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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Ethical Approval

The study extension was approved by Western Institutional Review Board (reference 20202529).


Informed Consent

All patients gave written informed consent to participate in the study extension.

Trial Registration

The study was registered at clinicaltrials.gov (NCT04684875).

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Supplemental material

Supplemental material for this article is available online.

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