Manuscript title:

Posterior nasal nerve neurectomy for the treatment of rhinitis: a systematic review and meta-analysis

Short running title:

Posterior nasal nerve neurectomy for rhinitis

Key Words

Allergy

Rhinology

Systematic Review

Chronic Rhinitis

Posterior Nasal Nerve Neurectomy

Abstract

Background

Posterior nasal nerve neurectomy (PNNN) is a surgical option for the treatment of refractory chronic rhinitis. It can be performed by surgical dissection, cryotherapy, or laser ablation.

Objective

This systematic review aimed to assess the effect of PNNN on Total Nasal Symptom Score (TNSS) in adults with chronic rhinitis.

Methods

A systematic review of EMBASE, MEDLINE, PubMed and ClinicalKey databases was conducted in November 2021. Studies reporting PNNN performed as a single procedure in adult patients with allergic, non-allergic or mixed chronic rhinitis, and TNSS as the outcome measure, were included.

Results

Database search identified 39 articles, of which 8 (463 patients) were included in the review. Two were randomised sham-controlled trials and six were prospective single-arm, unblinded and uncontrolled studies. Pooled analysis of data from the two randomized controlled trials found active treatment was associated with a significantly greater responder (≥30% reduction in TNSS from baseline) rate (OR 3.85, 95% CI 2.23 – 6.64, p<0.00001).

Conclusions

This systematic review identified there is some limited evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can improve TNSS in adult patients. However, this is from a limited number of trials with short follow-up. Future research should focus on prospective randomised controlled trials with larger numbers of participants and medium to long term follow up in order to help draw more valid conclusions regarding the true effectiveness of PNNN in this patient cohort.

Impact Statement

This systematic review shows there is some limited evidence to suggest posterior nasal nerve neurectomy can improve rhinitis symptoms in adult patients, and the incidence of serious adverse events associated with posterior nasal nerve ablation appears to be low.

Introduction

Rhinitis is chronic condition characterised by inflammation of the nasal mucosa, associated with symptoms of congestion, rhinorrhoea, sneezing, pruritis that are present for at least 12 weeks per year. It has a global prevalence of 30%[1], affecting 10-20% of adults in the United Kingdom (UK) and United States of America (USA) [2,3], and can lead to a significant reduction in quality of life and high health-care utilisation. Whilst medical therapy remains the mainstay of management, approximately 10-22% of patients will be refractory to such intervention[4]. Surgical options include inferior turbinate surgery in combination with vidian neurectomy (VN) or posterior nasal nerve neurectomy (PNNN), of which the latter two aim to eliminate the parasympathetic autonomic supply to the nasal mucosa[5]. PNNN differs from VN by targeting only the post-ganglionic posterior nasal branches as they exit the sphenopalatine foramen. This modification is thought to be a safer technique with a lower incidence of complications such as cheek and palatal numbness, and dry eyes[6].

PNNN can be performed either by surgical dissection and nerve resection, cryotherapy, radiofrequency, and laser ablation. These ablative techniques were first described in 2017 and are primarily performed endoscopically under local anaesthesia. The lateral nasal wall at the posterior middle meatus is targeted with either liquid nitrogen, radiofrequency energy, or a diode laser to produce local neural tissue ablation[7,8].

Total Nasal Symptom Score (TNSS) is a patient-assessed symptom questionnaire which evaluates the severity of the main symptoms of rhinitis; rhinorrhea, nasal congestion, nasal itching, and sneezing. The patient retrospectively reflects on the

severity of each symptom over the preceding 12 hours and evaluates it using a scale of 0 = No symptoms, 1 = Mild, 2 = Moderate, or 3 = Severe. The TNSS is calculated as the sum of the individual scores. When considering changes in TNSS, a reduction from baseline of ≥1 is considered the minimal clinically important difference (MCID)[9].

We aimed to evaluate the existing literature through a systematic review to assess the effect of PNNN on the TNSS in adult patients with chronic rhinitis, and the safety profile of this treatment when performed as a single procedure.

Materials and methods

Study design

A systematic review and descriptive analysis were performed of all published data related to the management of rhinitis with PNNN as a single procedure. The protocol for the systematic review was registered prospectively on the PROSPERO database in July 2021 (ID: CRD42021270486). We report our findings in accordance with PRISMA reporting guidelines[10].

Search strategy

Electronic searches of the following databases: EMBASE (1974 – January 2021), MEDLINE (1946 – January 2021), PubMed, Cochrane Library, ClinicalTrials.gov (via Cochrane) and ClinicalKey (1946–January 2021), were systematically conducted for articles written in English in November 2021. Databases were accessed through the

University of Hospitals Birmingham NHS Trust library with the assistance of an Information Specialist Librarian. The full search terms can be found in Table 1.

Study selection

Following the initial search, duplicated articles were excluded. All subsequent articles were independently screened by two authors (E.B/ A.D) according to their titles and abstracts for eligibility against the inclusion and exclusion criteria. Discrepancies were reviewed by a third author (K.K.G). All studies that reported data from any single modality of PNNN for adult patients with allergic, non-allergic or mixed rhinitis were included. Studies were included if they reported on procedure efficacy (comparison of pre- and post-operative TNSS) and safety (reported adverse events). Articles unavailable in English or as a full text, conference abstracts, combination procedures and articles reporting data in a paediatric population (<18 years) were excluded.

Data extraction

Data extraction was performed independently by two authors (E.B/ K.K.G), with any discrepancies resolved by a third author (A.D). Primary outcome measures were (1) a change in post- procedure TNSS (efficacy endpoint) and (2) reported adverse events (safety endpoint). Any other efficacy endpoints reported in the data were also extracted. Data was also extracted pertaining to study design, patient demographics, and procedure details.

Statistical analysis

A descriptive report with summary data tables was produced to summarize the literature. For the randomised controlled trials, a weighted estimate of the treatment effects across trials as odds ratios (OR) and respective 95% confidence intervals using a Mantel-Haenzel random-effects model for all outcome events was calculated. Results were deemed statistically significant at $p<0.05$. Heterogeneity was tested for using the I^2 statistic to quantify the percentage of total variation across studies. The amount of heterogeneity as 'low', 'moderate' or 'high' for I^2 values of 25%, 50% and 75% respectively. Statistical analysis and meta-analysis was performed using Review Manager 5.4.

Risk of Bias Scoring

Two reviewers (E.B/ K.K.G) independently assessed the non-randomized studies for risk of bias using the ROBINS-I tool[11] and the randomized studies for risk of bias using the RoB 2 tool[12]. Discrepancies were resolved with arbitration by a third reviewer (A.D).

Results

Study Selection

The study selection process is detailed in Figure 1. Our electronic database search identified 39 articles, with no duplicates. After primary screening based on the title and abstract, 12 articles remained for eligibility screening based on the full text. A further four articles were excluded based on the exclusion criteria. Eight full texts were subsequently included in our qualitative and quantitative analysis.

Study Characteristics

Study design and baseline characteristics are summarised in Table 2.

Six included studies were prospective, pre-post, single-arm studies and two were randomized, sham-controlled, single-blinded trials. Except for the single-centre study by Krespi et al[13], all were multi-centre studies. Del Signore et al used variable block size distribution by site with a 1:1 allocation[15]. Stolovitzky et al used a 2:1 site-stratified block randomization[16]. In both RCTs the patients were blinded to their assignment and blindfolded during the treatment. All were carried out in the USA and six out of the eight had industry sponsorship. Follow up periods varied between 3 months[13,14, 15, 16], 9 months[17], 12 months[18, 19], and 24 months[20].

Participants

The included studies represented 463 participants. In the seven studies that reported on patient demographics, the average age ranged from 53.3 years[18] to 60 years[14]. Gender split ranged from 35% male[16] to 50% male[19]. Chang et al[17] and Ow et al[20] reported results from the same patient cohort (pilot data and longer term follow up respectively).

All eight studies included patients with allergic, non-allergic or mixed sub-types of rhinitis, although. Stolovitzky et al included patients with chronic rhinitis >6 months, moderate-to-severe symptoms of rhinorrhoea, mild-to-severe nasal congestion and a total TNSS ≥6, and did not perform allergy testing[16]. Patients who had prior procedures or surgery for chronic rhinitis were excluded. Del Signore et al included patients with moderate-to-severe symptoms of chronic rhinitis and a total TNSS

≥4[15]. They also excluded patients who had prior procedures or surgery for chronic rhinitis. Chang et al[17] and Ow et al[20] specified that symptoms must have been present for a minimum of 6-months, with a total TNSS ≥4. Yen et al included patients with moderate-to-severe rhinorrhoea and mild-to-severe nasal congestion symptoms for at least 3 months[14]. Krespi et al included patients with chronic rhinitis and nasal congestion but did not detail a minimum required symptom duration[13]. Gerka Stuyt et al specified that patients must have had failure of trial of medical therapy for at least 3 months[19]. Four studies required patients to discontinue ipratropium bromide at least 3-days pre-procedure and throughout the follow up period[14, 15, 17, 20].

Intervention

Bilateral PNNN was performed as a single procedure in all studies, using a single surgical modality of either cryotherapy[14, 15, 17, 18, 19, 20], radiofrequency[16], or continuous wave laser[13] (Table 3). Five studies used ClariFix (Stryker ENT, Plymouth MN, USA) to perform the cryoablation endoscopically in line with the manufacturer's guidance[14, 15, 17, 18, 20]. In the sham control arm of the study by Del Signore et al the cryoprobe was held in place while a separate device with a canister loaded was held near the participant and activated to provide the sound of gas release[15]. Gerka Stuyt et al did not report details of the specific device they used for cryoablation[19]. Krespi et al used a 940nm diode laser (Epic-S, Biolase, Irvine CA) with a 400-micron malleable fibre tip, with continuous wave laser (5W, non-contact mode for 10-15seconds)[13]. Stolovitsky et al used the RhinAer System (Aerin Medical, Sunnyvale CA, USA) to perform radiofrequency neurolysis in patients in the active arm. For the patients in the sham arm the stylus was identically applied

to the tissue and sounds mimicking the treatment were played but no radiofrequency energy was delivered[16]. Procedures were performed primarily under local anaesthesia[13-20], however in the study by Krespi et al, a small cohort required sedation[13]. All studies involved bilateral treatment, either at single (posterior middle meatus)[13, 15, 17, 18, 19, 20] or multiple sites (middle and inferior meatus)[14, 16].

Primary Outcomes

In the pre-post single-arm studies the primary outcome was a change in TNSS from pre-operative baseline, to varying intervals of post-operative follow-up. Whereas in the two randomized sham-controlled trials the primary outcome was responder rate at follow-up, where a response was defined as a ≥30% improvement (decrease) in TNSS from baseline.

Gerka Stuyt et al adopted a 5-item TNSS, with an additional sub-domain focused on the effect on sleep, at each measure of TNSS they asked participants for one score based on a 12-hour period of retrospective reflection and one based on a 2-week period[19]. All other studies used a standard 4-item TNSS and did not specify the exact time frame patients were asked to reflect upon to calculate this[13, 14, 15, 16, 17, 18, 20]. All studies reported the occurrence of any adverse events (Table 4).

Change in the use of medication was measured at 12-months by Gerka Stuyt et al[19], at 90 days by Del Signore at al[15] and Stolovitzky et al[16], 60 days by Krespi et al[13], and at all follow up visits by Chang et al[17]. Timing of outcome measures ranged from 7 days to 2 years post-procedure.

Results of Individual Studies

Hwang et al reported the results of cryotherapy ablation at the posterior middle meatus in 27 patients[18]. Six patients were lost to follow up at 180 days and twelve patients at 365 days. Baseline mean TNSS was 6.2 (SD 0.5). They reported a statistically significant decrease between pre-operative and post-operative mean TNSS of -3.6 (SE 0.11) at 30 days, -3.5 (SE 0.12) at 90 days, -3.9 (SE 0.15) at 180 days, and -4.3 (SE 0.14) at 365 days. Baseline pre-operative TNSS for patients in the allergic rhinitis sub-group was not reported. In the non-allergic rhinitis sub-group (n=13) there was a statistically significant decrease between pre-operative and post-operative mean TNSS of -3.9 (SE 0.21) at 30 days, -4.1 (SE 0.22) at 90 days, -4.8 (SE 0.25) at 180 days, and -4.9 (SE 0.26) at 365 days. There were a total of 17 adverse events (Table 4).

Chang et al reported the results of cryotherapy ablation at the posterior middle meatus in 100 patients, with longer term follow up of these patients reported by Ow et al[17, 20]. Five patients were excluded and only 62 patients consented to long-term follow up, with a further 3 lost to follow up at 18 months and 24 months. Baseline mean TNSS was 6.1 (SD 1.9). Chang et al reported statistically significant reduction between pre-operative and post-operative mean TNSS of -3.2 (SE 0.27) at 30 days, -3.1 (SE 0.30) at 90 days, -3.1 (SE 0.29) at 180 days, and -3.1 (SE 0.31) at 270 days. Specific data for allergic and non-allergic rhinitis sub-groups was not included in the paper. In the post-operative period 21.4% (n=33) pre-operative medical therapies were discontinued. However, 59 medications were also newly initiated in the follow up period. Ow et al reported a statistically significant reduction in median TNSS of -3.0 (IQR 1.0 – 4.0) at 365 days, and of -4.0 (IQR 1.0 – 4.0) at

548 and 730 days. There was a statistically significant difference in median change between participants with pre-operative TNSS values of >7 compared to those with values <7, with higher pre-operative scores associated with increased reduction in median TNSS at all follow up time points except 365 days and 730 days. There was a total of 31 treatment-related adverse events reported (Table 4).

Yen et al reported the results of cryotherapy ablation at the middle and inferior meatus in 30 patients[14]. Baseline median TNSS was 7.0 (IQR 5.0 – 9.0). They reported a statistically significant reduction between pre-operative and post-operative median TNSS of -3.5 (IQR 2.0 – 6.0) at 30 days, and of -4.5 (IQR 2.0 – 5.0) at 90 days. They reported a total of 30 non-serious adverse events (Table 4).

Krespi et al reported the results of continuous wave laser ablation at the posterior middle meatus in 30 patients[13]. Baseline mean TNSS was 6.0 (SD 0.7). At 30 days follow-up they reported that there had been a 60% improvement in the TNSS but did not include the full data in their paper. They reported a statistically significant reduction between pre-operative and post-operative mean TNSS of -3.7 (SE 0.14) at 90 days. The authors reported that at 60 days follow up there had been a 60% reduction in medication use. There were no reported adverse events.

Gerka Stuyt et al reported the results of cryotherapy ablation at the posterior middle meatus in 24 patients[19]. Six patients were lost to follow up at 365 days. Baseline mean 12-hour TNSS was 6.92 (SD 2.8) and mean 2-week TNSS was 7.75 (SD 3.1). They reported a statistically significant reduction between pre-operative and post-operative mean 12-hour TNSS of -3.75 (SE 0.75) at 30 days, -4.0 (SE 0.64) at 90

days, and -3.84 (SE 0.85) at 365 days. There was also a statistically significant reduction between pre-operative and post-operative mean 2-week TNSS of -3.96 (SE 0.76) at 30 days, -3.87 (SE 0.72) at 90 days, and -3.99 (SE 0.85) at 365 days. In the allergic rhinitis sub-group (n=3), there was a statistically significant reduction between pre-operative and post-operative mean 2-week TNSS of -5.37 (SD 1.1) at 365 days. In the non-allergic rhinitis sub-group (n=16), they reported a statistically significant reduction between pre-operative and post-operative mean 12-hour TNSS of -4.1 (SE 0.92) at 30 days, -3.6 (SE 0.81) at 90 days, and -3.97 (SE 1.17) at 365 days. There was also a statistically significant reduction between pre-operative and post-operative mean 2-week TNSS of -3.54 (SE 0.99) at 30 days, -3.19 (SE 0.99) at 90 days, and -3.81 (SE 1.20) at 365 days. There were no reported adverse events.

Stolovitzky et al reported the results of radiofrequency neurolysis in 78 patients randomly assigned to the active treatment arm and a sham procedure in 39 patients assigned to the control arm. One patient was lost to follow up in the active treatment arm. At 3-months follow-up they reported a significantly higher percentage of responders in the active treatment arm versus the sham control: 67.5% (95% CI, 55.9% - 77.8%) vs. 41.0% (95% CI, 25.6% - 57.9%), P = 0.009. Baseline TNSS was similar between active (8.3, 95% CI, 7.9 – 8.7) and sham (8.2, 95% CI, 7.6 – 8.8) arms, but there was a significantly greater decrease in mean TNSS in the active treatment arm: -3.6 (95% CI, -4.2 to -3.0) vs. -2.2 (95% CI, -3.2 to -1.3), P = 0.013. The decrease in rhinorrhoea and congestion sub-scores at 3-months was significantly greater in the active treatment arm, while the decrease in nasal itching sub-score did not reach statistical significance. A total of 12 patients increased medication use during follow-up, 7 were in the active treatment arm and 5 in the

sham control arm. Assigning these patients as non-responders did not change the outcome of the primary endpoint analysis. Four adverse events were recorded (Table 4).

Del Signore et al reported the results of cryotherapy ablation in 68 patients randomly assigned to the active treatment arm and 65 assigned to the sham control. Six patients were excluded prior to follow-up. At 90-day follow-up there was a significantly higher percentage of responders in the active arm compared to the sham arm: 73.4% vs. 36.5%, P < 0.001. Baseline TNSS was similar between active (8.0 +/- 1.6) and sham (8.1 +/- 1.9) arms, but there was a significantly greater decrease in mean TNSS in the active treatment arm at 90-days: -3.7 (95% CI, -4.3 to -3.1) vs. -1.8 (95% CI, -2.5 to -1.1), P < 0.001. Repeated-measures multivariate analysis showed that only the treatment arm (OR for treatment vs sham: 3.43 [95% CI, 1.827 to 6.43, p = 0.0001]) and the TNSS value at baseline (OR 1.321 [95% CI, 1.095 to 1.593, p = 0/0036]) were associated with the primary outcome of ≥30% improvement in TNSS. There was no association with rhinitis sub-type. Evaluation of individual TNSS items showed significantly greater improvement in rhinorrhea and nasal congestion scores in the active arm, but no significant difference between arms for nasal itching and sneezing scores. At 90-day follow-up, there was a decrease in the percentage of patients using medications in both the active (47.1% to 40%) and sham (49.2% to 34.4%) arms.

In the pooled analysis of data from these two randomized controlled trials (Figure 2), active treatment was associated with significantly greater responder rate (OR 3.85, 95% CI 2.23 – 6.64, p<0.00001). There was no evidence of heterogeneity (I^2=0%).

Risk of Bias Within Studies

All six of the included non-randomized studies were deemed to be at an overall moderate risk of bias (Table 5). The studies were unblinded, uncontrolled and non-randomised and thus considered to have a serious risk of bias regarding the subjective outcome measures[13, 14, 17, 18, 19, 20].

Hwang et al and Gerka Stuyt et al were deemed to be at serious risk of bias due to confounding factors as they made no attempt at reporting or controlling concurrent medical treatment pre and post-intervention[18, 19]. The remaining four studies required patients to have discontinued Ipratropium Bromide prior to and throughout the study period but did not control other medications[13, 14, 17, 20].

Hwang et al and Gerka Stuyt et al were deemed to have moderate risk of bias due to missing data as both had significant numbers of patients lost to follow-up[18, 19]. The study by Ow et al was deemed to have serious risk of bias, with 44% of patients from the original cohort lost to follow up at the 548-day and 730-day time-points.

The two randomized sham-controlled trials were both deemed to be at an overall low risk of bias[15, 16] (Table 5).

Discussion

This systematic review identified some evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can lead to a higher patient

response rate and greater improvement in TNSS when compared to a sham control procedure. Observed improvements appeared to be greater for symptoms of rhinorrhoea and nasal congestion, as opposed to itching or sneezing. Medication use was not controlled for in any of the included studies and there were differing reports of both increased and decreased use across active treatment and control groups at follow-up. However, evidence for these conclusions on the effect of PNN ablation was limited to just two randomized controlled trials, both of which had a short duration of follow-up and relatively high baseline TNSS suggesting a patient group with severe and refractory symptoms.

While the remaining six non-randomized studies included within this review reported a reduction in the average post-operative TNSS sustained over longer periods of follow-up, these studies were deemed to have moderate-to-severe risk of bias across multiple domains that limits the ability to draw reliable conclusions from the data.

We found that while there was a reasonably high total number of reported adverse events (125 reported from 461 procedures), these were predominantly non-serious and transient[13-20]. The most commonly reported were ear blockage, headache, pain, palatal numbness, altered taste, and sinusitis, all of which had resolved at 90-day follow-up. There were three serious adverse events reported; one episode of epistaxis requiring electrocautery under general anaesthetia[18], one episode that required nasal packing[16], and one anxiety attack that required patient transfer to the emergency department[15]. The highest proportion of adverse events was reported by Yen et al, where there were 30 events reported in a cohort of 30

patients[14]. This was the only study to use cryotherapy ablation of multiple sites within the nasal cavity, increasing the number of sites and thus the area of mucosal damage in the nasal cavity may somewhat explain the higher relative numbers of adverse events reported.

Limitations

There are several limitations at a study, outcome, and review level that must be taken into consideration when interpreting these results. Six of the included studies had a similar broad design of a prospective, pre-post, single-arm trial and thus were all un-blinded, non-randomised and un-controlled. The risks of bias introduced by this design have been discussed in the relevant section above.

Both of the randomised sham-controlled trials cohorts were predominantly Caucasian patients with a selection criteria that required more severe symptoms at baseline. The reported baseline mean TNSS's in these two trials were higher than seen in the previous six single-arm studies. This may limit the external validity of these studies findings.

TNSS was used as a standard pre-operative and post-operative measurement of severity of rhinitis symptoms in each of the studies. However, there was variation in whether a 12-hour, 24-hour or 2-week retrospective reflective period was used, with some studies not giving any specific details. There may also be significant variation in a patient's score depending on the time of day they complete the TNSS, it was unclear whether this was accounted for in any of the studies.

It should also be noted that the six studies reporting outcomes after the use of the ClariFix (Stryker ENT, Plymouth MN, USA) cryoablation device or the RhinAer System (Aerin Medical, Sunnyvale CA, USA) were industry sponsored[14, 15, 16, 17, 18, 20].

At a review level, we were limited in terms of incomplete retrieval of identified research as the translated full text of one report was unavailable at our institution[21].

Conclusions

This is the first systematic review and meta-analysis of the current literature in this area of rhinology. It shows there is some limited evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can improve TNSS in adult patients. However, this is from a limited number of trials with short follow-up. The incidence of serious adverse events associated with posterior nasal nerve ablation appears to be low. Future research should focus on higher quality prospective randomised controlled trials with larger numbers of participants and medium to long term follow up in order to help draw more valid conclusions regarding the true effectiveness of PNNN in this patient cohort.

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Conflict of interest:

The authors declare that there is no conflict of interest.

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Figure Titles

Figure 1

Study selection process of included articles.

Figure 2

Association between posterior nasal nerve ablation and Total Nasal Symptom Score.

Table 1: Full electronic database search strategy

Database	Search term	Results
Medline	(posterior nasal nerve).ti,ab	364
	(endoscopic).ti,ab	159366
	ENDOSCOPY/	53772
	(2 OR 3)	183613
	(section).ti,ab	164990
	(ablation).ti,ab	97334
	(division).ti,ab	102612
	(5 OR 6 OR 7)	363030
	(1 AND 4 AND 8)	4
	(1 AND 4)	56
	(posterior nasal nerve).ti,ab [Humans]	238
	(posterior nasal neurectomy).ti,ab	22
	(endoscopic posterior nasal neurectomy).ti,ab	8
EMBASE	(posterior nasal nerve).ti,ab	29
	(endoscopic).ti,ab	257229
	ENDOSCOPY/	110560
	(section).ti,ab	220230
	(ablation).ti,ab	149430
	(division).ti,ab	122705
	(13 OR 14)	319841
	(15 OR 16 OR 17)	489353
	(12 AND 18 AND 19)	4
	(posterior nasal neurectomy).ti,ab	20
	(endoscopic posterior nasal neurectomy).ti,ab	7
PubMed	(posterior nasal nerve).ti,ab	31
	(section).ti,ab	509387
	(ablation).ti,ab	108215
	(division).ti,ab	1996906
	(endoscopic).ti,ab	470758
	(posterior nasal neurectomy).ti,ab	17
	(endoscopic posterior nasal neurectomy).ti,ab	5

Table 2: Study design and baseline characteristics of all included studies and participants

Study	Design	Funding/sponsorship	N =	Age (years)	Gender (M : F)	Inclusion Criteria	Allergic / Non-Allergic	Pre-procedure medical therapy (N, %)
Hwang, 2017	Pre-post study, prospective, single-arm	Arrinex Inc. (Stryker ENT)	27	53.3 +/- 3.3	10 : 17	Adult patients only TNSS rhinorrhoea score ≥2 TNSS nasal congestion score ≥2	Allergic: 13 Non-allergic: 13 Unknown: 1	Not reported
Chang, 2020	Pre-post study, prospective, single-arm	Stryker Corp.	100	58.6 +/- 16.2	35 : 63	Adult patients only Symptoms for >6 months Symptoms not controlled with ≥ 4 weeks INCS TNSS rhinorrhoea score 2 or 3 TNSS nasal congestion score 1, 2 or 3 Total TNSS ≥4	Allergic: 28 Non-allergic: 70	Oral steroid: 5 INCS: 40 Oral antihistamines: 33 Intra-nasal antihistamine: 8 Saline rinse: 39 Oral alpha-agonist: 8 Intra-nasal alpha-agonist: 6 Oral antileukotriene: 15 Ipratropium bromide discontinued 3 days before procedure and throughout follow up
Yen, 2020	Pre-post study, prospective, single-arm	Arrinex Inc. (Stryker ENT)	30	60 +/- 15.8	14 : 16	Adult patients only Moderate-to-severe rhinorrhoea Mild-to-severe nasal congestion Symptoms for >3 months	Allergic: 11 Non-allergic: 17	Not reported Ipratropium bromide discontinued 3 days before procedure and throughout follow up
Krespi, 2020	Pre-post study, prospective, single-arm	No financial support	32	Not reported	Not reported	Adult patients only Chronic rhinitis and nasal congestion	Allergic and non-allergic included Specific numbers not reported	Not reported
Ow, 2021	Pre-post study, prospective, single-arm	Stryker ENT	100	57.1 +/- 13.4	36 : 64	Adult patients only Chronic rhinitis for >6 months Failure of trial of medical therapy for >1 month	Allergic: 19 Non-allergic: 43	Not reported Ipratropium bromide discontinued 3 days before procedure and throughout follow up
Stuyt, 2021	Pre-post study, prospective, single-arm	No financial support	24	60 (25 – 91)	12 : 12	Adult patients only Failure of trial of medical therapy for >3 months	Allergic: 3 Non-allergic: 16 Mixed: 5	Anti-cholinergic: 13 Steroid: 14 Antihistamines: 9 Saline rinse: 5

Stolovitzky, 2021	Randomized, sham-controlled trial, multicentre, prospective, single-blinded	Aerin Medical	117 Active (78) Control (39)	Active treatment: 57.3 +/- 14.8 Sham control: 57.8 +/- 14.4	Active treatment: 28 : 49 Sham control: 13 : 26	Patients aged 18-85 years Chronic rhinitis for >6 months TNSS rhinorrhoea score 2 or 3 TNSS nasal congestion score 1, 2 or 3 Total TNSS ≥6 Excluded patients with prior procedures or surgery for chronic rhinitis	Allergy testing not performed. Seasonal allergic rhinitis excluded.	Active treatment arm Antihistamines: 56 (72.7) Decongestants: 22 (28.6) Oral leukotriene inhibitors: 4 (5.2) Intra-nasal steroid sprays: 34 (44.2) Intra-nasal anticholinergic sprays: 19 (24.7) Sham control arm Antihistamines: 28 (71.8) Decongestants: 10 (25.6) Oral leukotriene inhibitors: 3 (7.7) Intra-nasal steroid sprays: 26 (66.7) Intra-nasal anticholinergic sprays: 8 (20.5)
Del Signore, 2021	Randomized, sham-controlled trial, multicentre, prospective, single-blinded	Stryker ENT	133 Active (68) Control (65)	Active treatment: 52.3 +/- 15.8 Sham control: 58.3 +/- 16.4	Active treatment: 23 : 45 Sham control: 33 : 32	Patients aged ≥21 years Moderate-to-severe symptoms of chronic allergic or nonallergic rhinitis TNSS rhinorrhoea score ≥2 TNSS nasal congestion score ≥1 Total TNSS ≥4 Excluded patients with prior procedures or surgery for chronic rhinitis	Allergy test within 12 months of baseline Active treatment: Allergic 29 Non-allergic 39 Sham control: Allergic 28 Non-allergic 37	Active treatment arm Antihistamines: 20 (29.4) Antihistamine/steroid: 2 (2.9) Decongestant: 2 (2.9) Immunotherapy: 0 Intra-nasal steroid sprays: 16 (23.5) Ipratropium bromide: 0 Leukotriene inhibitors: 5 (7.4) Saline lavage: 5 (7.4) Sham control arm Antihistamines: 26 (40) Antihistamine/steroid: 0 Decongestant: 2 (3.1) Immunotherapy: 2 (3.1) Intra-nasal steroid sprays: 13 (20) Ipratropium bromide: 0 Leukotriene inhibitors: 3 (4.6) Saline lavage: 1 (1.5)

*TNSS: Total Nasal Symptom Score, INCS: intra-nasal corticosteroid

Table 3: Summary of results from individual studies.

Study	Surgical Modality	Site	Anaesthetic	Pre-operative TNSS	Post-operative TNSS	Follow up
Hwang, 2017	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 6.2 +/- 0.5 (n=27) --- Allergic: not reported (n=13) --- Non-allergic: 6.5 +/- 0.7 (n=13)	7d: 4.3 +/- 0.4* (n=27) 30d: 2.6 +/- 0.3* (n=27) 90d: 2.7 +/- 0.4* (n=27) 180d: 2.3 +/- 0.5* (n=21) 365d: 1.9 +/- 0.3* (n=15) --- 30d: 2.5 +/- 0.6* (n=13) 90d: 3.1 +/- 0.6* (n=13) 180d: 2.7 +/- 0.9 (n=10) 365d: 2.5 +/- 0.6* (n=6) --- 30d: 2.6 +/- 0.3* (n=13) 90d: 2.4 +/- 0.4* (n=13) 180d: 1.7 +/- 0.4* (n=10) 365d: 1.6 +/- 0.4* (n=9)	365 days
Chang, 2020	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 6.1 +/- 1.9 (n=98)	30d: 2.9 +/- 1.9* (n=97) 90d: 3.0 +/- 2.3* (n=96) 180d: 3.0 +/- 2.1* (n=95) 270d: 3.0 +/- 2.4* (n=92)	270 days
Yen, 2020	Cryotherapy	Middle meatus Inferior meatus Bilateral	LA	All patients: 7.0 (5.0-9.0) (n=30)	1 month: 3.5 (2.0-6.0)* (n=30) 3 months: 2.5 (2.0-5.0)* (n=30)	3 months
Krespi, 2020	Laser	Posterior middle meatus Bilateral	LA (n=21) Sedation (n=11)	All patients: 6.0 +/- 0.7 (n=32)	30d: "60% improvement in TNSS" (n=32) 90d: 2.3 +/- 0.4* (n=32)	90 days
Ow, 2021	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 6.0 (5.0-7.0) (n=91)	12 months: 3.0 (1.0-4.0)* (n=91) 18 months: 2.0 (1.0-4.0)* (n=57) 24 months: 2.0 (1.0-4.0)* (n=57)	24 months
Stuyt, 2021	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 12hr: 6.92 +/- 2.8 2wk: 7.75 +/- 3.1 (n=24) --- Allergic: 12hr: 6.67 +/- 3.2 2wk: 8.67 +/- 2.5 (n=3) --- Non-allergic: 12hr: 7.1 +/- 3.1 2wk: 7.75 +/- 3.6 (n=16) --- Mixed: 12hr: 6.4 +/- 2.1 2wk: 7.2 +/- 1.6 (n=5)	12hr TNSS 30d: 3.17 +/- 2.4* (n=24) 90d: 2.92 +/- 1.4* (n=24) 1yr: 3.08 +/- 2.6* (n=18) 2wk TNSS 30d: 3.79 +/- 2.1* (n=24) 90d: 3.88 +/- 1.8* (n=24) 1yr: 3.76 +/- 2.1* (n=18) --- 12hr TNSS 30d: 2.67 +/- 2.5 (n=3) 90d: 1.33 +/- 1.5 (n=3) 1yr: 2.6 +/- 0.6 (n=1) 2wk TNSS 30d: 2.33 +/- 2.5 (n=3) 90d: 1.67 +/- 2.0 (n=3) 1yr: 3.3 +/- 1.1* (n=1) --- 12hr TNSS 30d: 3.0 +/- 2.0* (n=16) 90d: 3.5 +/- 1.0* (n=16) 1yr: 3.13 +/- 3.0* (n=12) 2wk TNSS 30d: 4.21 +/- 1.7* (n=16) 90d: 4.56 +/- 1.7* (n=16) 1yr: 3.94 +/- 2.4* (n=12) --- 12hr TNSS 30d: 4.0 +/- 3.6 (n=5) 90d: 2.0 +/- 1.2* (n=5) 1yr: 3.2 +/- 2.2 (n=5) 2wk TNSS 30d: 3.4 +/- 3.0* (n=5) 90d: 3.3 +/- 0.8* (n=5) 1yr: 4.0 +/- 1.4* (n=5)	12 months
Stolovitzky, 2021	Radiofrequency	Posterior middle meatus Superior portion of posterior inferior turbinate Bilateral	LA	Active treatment arm: (n=77) Mean TNSS 8.3 +/- 1.9 Rhinorrhoea 3 (IQR 2-3) Congestion 3 (IQR 2-3) Itching 2 (IQR 1-2) Sneezing 2 (IQR 1-2)	Responder rate: Active arm 67.5% (95% CI, 55.9%-77.8%)* Sham control 41.0% (95% CI, 25.6%-57.9%)* Reduction in total TNSS: Active arm -3.6 (95% CI, -4.2 to -3.0)* Sham control -2.2 (95% CI, -3.2 to -1.3)*	3 months

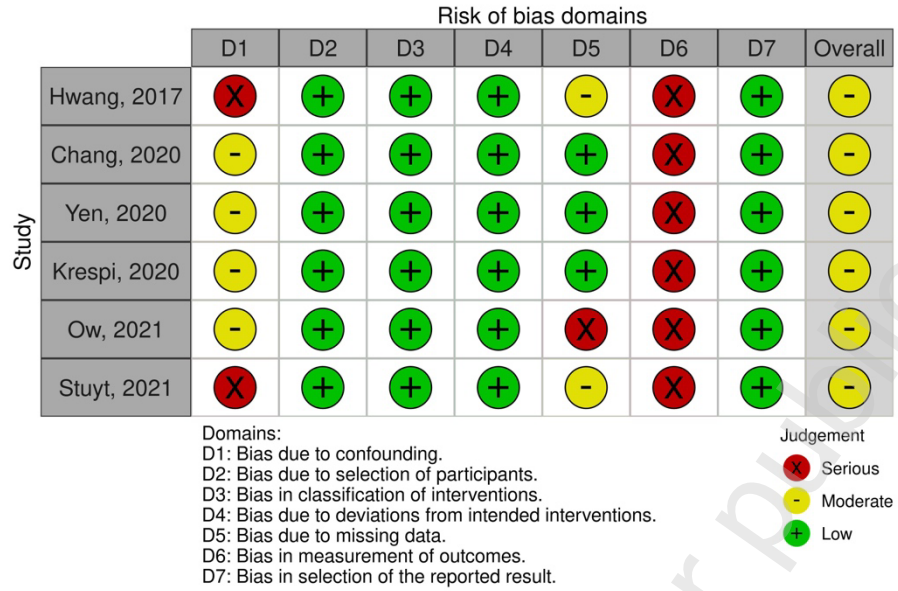
				Sham control arm: (n=39) Mean TNSS 8.2 +/- 1.8 Rhinorrhoea 3 (IQR 2-3) Congestion 3 (IQR 2-3) Itching 1 (IQR 1-2) Sneezing 2 (IQR 1-3)	Rhinorrhoea scores change at 3 months: Active arm -1 (IQR -2 to 0)* Sham control 0 (IQR -2 to 0)* Congestion scores change at 3 months: Active arm -1 (IQR -2 to 0)* Sham control 0 (IQR -1 to 0)* Itching scores change at 3 months: Active arm -1 (IQR -1 to 0) Sham control 0 (IQR -1 to 0) Sneezing scores change at 3 months: Active arm -1 (IQR -1 to 0) Sham control -1 (IQR -1 to 0)	
Del Dignore, 2021	Cryotherapy	Posterior middle meatus Bilateral	LA	Active treatment arm: (n=68) Mean rTNSS 8.0 +/- 1.8 Rhinorrhoea 2.6 +/- 0.5 Congestion 2.3 +/- 0.8 Itching 1.5 +/- 0.8 Sneezing 1.8 +/- 0.7 Sham control arm: (n=65) Mean rTNSS 8.1 +/- 1.9 Rhinorrhea 2.4 +/- 0.5 Congestion 2.4 +/- 0.7 Itching 1.5 +/- 0.9 Sneezing 1.8 +/- 0.8 Use of allergy/rhinitis medications: Active arm 32 (47.1%) Sham arm 32 (49.2%)	Responder rate: Active arm 47/64 (73.4%)* Sham control 23/63 (36.5%)* Reduction in total TNSS: Active arm -3.7 (95% CI, -4.3 to -3.1)* Sham control -1.8 (95% CI, -2.5 to -1.1)* Rhinorrhoea scores change at 90d: Active arm -1.2 (95% CI, -1.4 to -1.0)* Sham control -0.4 (95% CI, -0.6 to -0.2)* Congestion scores change at 90d: Active arm -1.2 (95% CI, -1.4 to -1.0)* Sham control -0.6 (95% CI, -0.8 to -0.4)* Itching scores change at 90d: Active arm -0.7 (95% CI, -0.9 to -0.5) Sham control -0.4 (-0.7 to -0.1) Sneezing scores change at 90d: Active arm -0.6 (95% CI, -0.8 to -0.4) Sham control -0.5 (95% CI, -0.7 to -0.2) Use of allergy/rhinitis medication: Active arm 26 (40.0%) Sham arm 22 (34.4%)	90 days

*TNSS: Total Nasal Symptom Score, LA: local anaesthetic *p<0.05

Table 4: Summary of all reported adverse events

Adverse Event	Number of patients		
Hwang, 2017	Ear blockage (n=13) Nasal dryness (n=3) Epistaxis* (n=1) Total events: 17		
Chang, 2020 & Ow, 2021	Bloody nasal discharge (n=1) Burning sensation in nose (n=1) Epistaxis (n=2) Hyperaemia (n=1) Middle turbinate haematoma (n=1) Increased mucous secretion (n=1) Newly noted ostia (n=2) Facial pain (n=1) Retained pledget (n=1) Synechiae (n=1) Facial pain (n=2) Headache (n=4) Dizziness (n=1) Dry eyes (n=2) Watery eyes (n=1) Altered taste (n=3) Teeth sensitivity (n=1) Dry mouth (n=1) Sinusitis (n=4) Total events: 31		
Yen, 2020	Headache (n=12) Pain (n=10) Palatal numbness (n=8) Total events: 30		
Krespi, 2020	No adverse events reported		
Stuyt, 2021	No adverse events reported		
Stolovitzky, 2021		Active arm	Sham control
	Pain	n=1	
	Sinusitis	n=1	
	Epistaxis		n=1**
	Dry eyes	n=1	
	Total events:	3	1
Del Signore, 2021		Active arm	Sham control
	Pain	n=25	n=1
	Headache	n=4	
	Nasal congestion	n=2	
	Palatal numbness	n=2	
	Vasovagal	n=1	n=1
	Epiphora	n=2	
	Anxiety	n=1	
	Dizziness	n=1	
	Drug reaction	n=1	
	Sinusitis	n=1	
	Vomiting		n=1
	Total events:	40	3
	*Required electrocautery in the operating theatre **Required nasal packing		

Table 5: Assessment of risk of bias within included studies using ROBINS-I tool and RoB-2 tool.



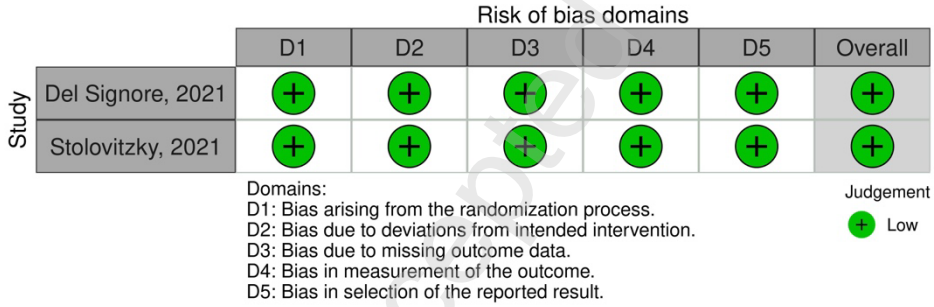


Figure 1. Study selection process of included articles.

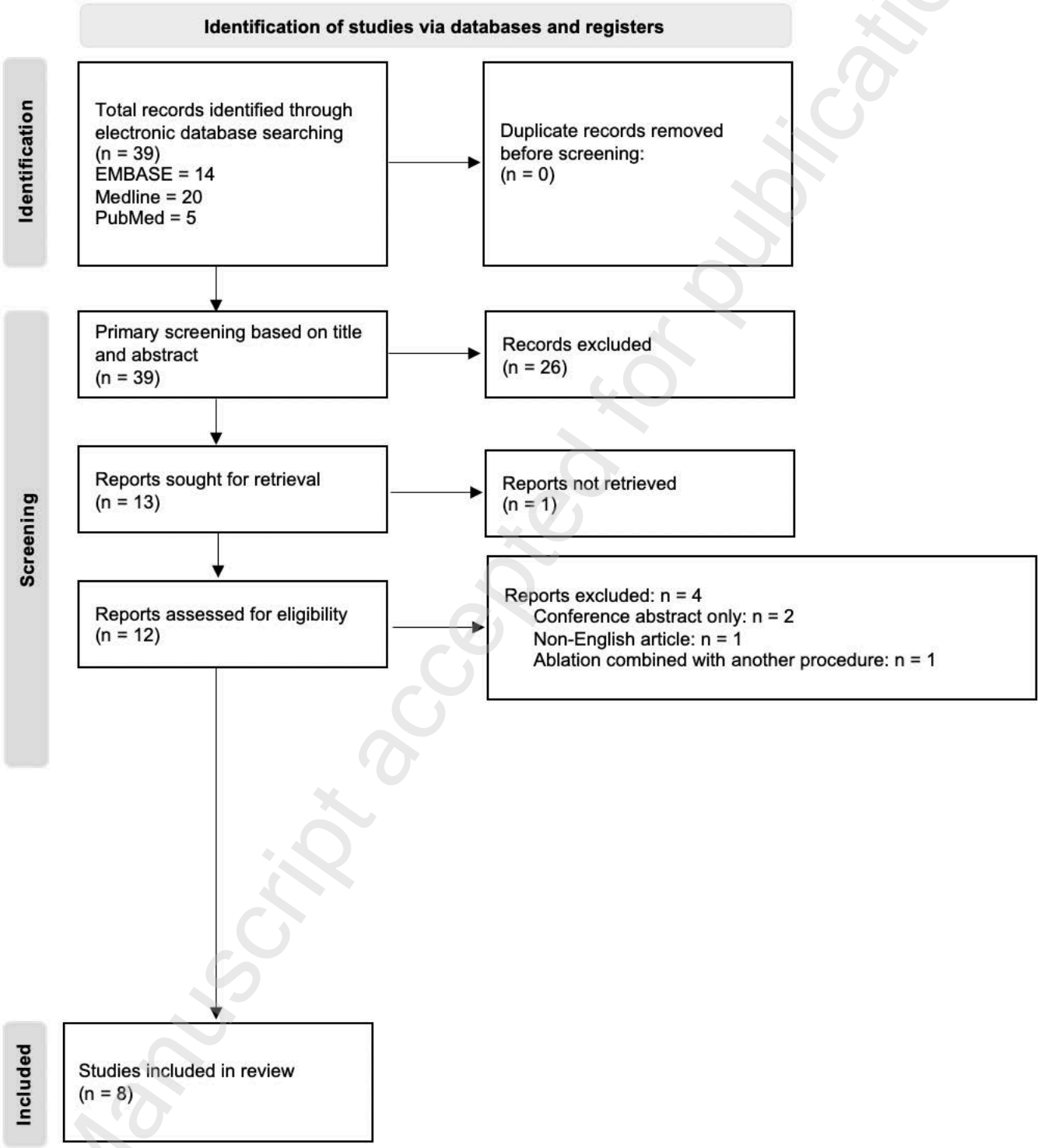


Figure 2. Association between posterior nasal nerve ablation and Total Nasal Symptom Score

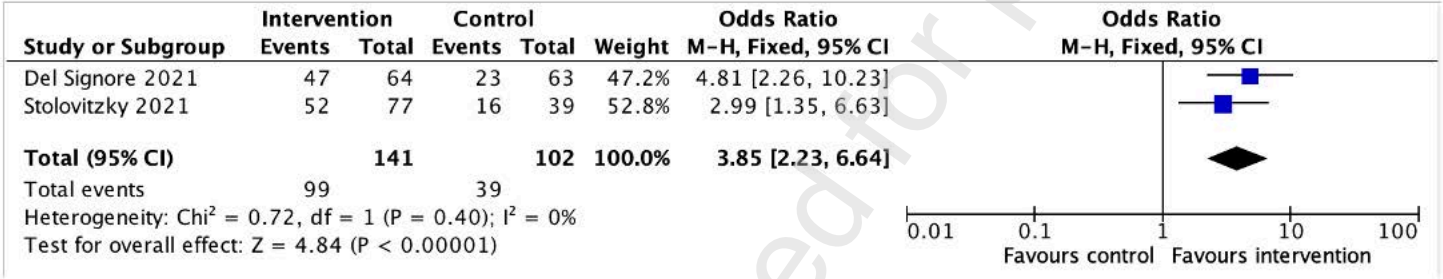


Figure 2 caption

Comparison: Posterior nasal nerve ablation versus sham control procedure

Outcome: Patient responder rate (≥30% improvement in TNSS from baseline) at 3-months follow-up