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A Preliminary Report on the Effect of Gabapentin Pretreatment on Peri-Procedural pain during In-Office Posterior Nasal Nerve Cryoablation

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Abstract

Background: Posterior nasal nerve (PNN) cryoablation is a novel surgical technique to address allergic and non-allergic rhinitis. Peri-procedural pain has been reported after PNN cryoablation and there are no standardized protocols for optimal in-office local anesthesia. This study seeks to evaluate the effect of gabapentin on patient discomfort following in-office PNN cryoablation.

Methods: Multi-institutional prospective analysis of patients undergoing in-office PNN cryoablation for allergic or non-allergic rhinitis between March 2018 and April 2019. Patients received local anesthesia with or without 600 mg oral Gabapentin one-hour pre-procedure. Rhinitis diagnosis, demographics, baseline disease specific quality of life (mini-Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), Total Nasal Symptom Score (TNSS)) were recorded. Patient discomfort was measured by the pain visual analogue scale (VAS) post treatment and rated 0–10 on an ordinal scale. Fisher's exact and Wilcoxon two sample tests were used to evaluate differences between the two groups.

Results: A total of 26 patients were enrolled (Gabapentin n=15, control=11). Baseline TNSS scores in the gabapentin vs control group were 10 (7.5–11.0) and 9 (6.0–10.0) ($p = .35$). Baseline Mini-RQLQ scores in Gabapentin vs. control groups were 3.21 (2.00–4.00) and 2.92 (2.78–4.35) ($p = .51$). The median VAS pain scores at five, twenty, and thirty minutes in the Gabapentin vs.

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control group were 0.0 (0.0–2.0) vs. 3.0 (1.0–4.0), 2.0 (0.0 – 3.0) vs. 8.0 (6.0–10.0), and 1.0 (0.0–1.0) vs. 5.0 (4.0–6.0) ($p=.02$, $.0043$, and $.003$ respectively).

Conclusion: Pre-procedure gabapentin significantly reduces immediate and delayed post procedural patient discomfort following PNN cryoablation.

Keywords

Rhinitis; Clarifix; Gabapentin; Cryoablation

Introduction

Chronic rhinitis can be characterized as allergic or non-allergic in nature based on the presence (allergic rhinitis) or absence (non-allergic rhinitis) of an allergen specific IgE mediated response. Allergic rhinitis (AR) has been estimated to affect up to 1.4 billion people globally and, when combined, allergic and non-allergic rhinitis (NAR) affects up to 60 million patients in the United States alone.^{1–4} AR and NAR cause significant detrimental impacts on health and quality of life (QOL), work productivity, social interaction and sleep.¹ Medical management of allergic and non-allergic rhinitis generally consists of topical intranasal medications (i.e. corticosteroids, antihistamines, anticholinergics), systemic antihistamines, and immunotherapy, while surgical/procedural therapies include inferior turbinate reduction, botulinum toxin injection, vidian neurectomy, posterior nasal neurectomy, and cryoablation of the posterior nasal nerve.

Posterior nasal nerve cryoablation (PNN) is a novel surgical technique to address allergic and non-allergic rhinitis via the targeted destruction of the posterior nasal nerve parasympathetic fibers. Preliminary data have demonstrated efficacy at reducing rhinitis symptoms as measured by the total nasal symptom score (TNSS).⁵ Patient tolerance of in-office procedures can be challenging in neurovascularly rich anatomic areas such as the posterior nasal cavity. Post-procedural headache (i.e. “brain freeze” or “ice cream headache”) and dental pain have been reported after PNN cryoablation. Discomfort is reduced through the use of topical anesthesia, submucosal injections, and oral analgesics (i.e. acetaminophen, ibuprofen, anxiolytics, and opiates), yet few guidelines exist regarding optimal anesthetic techniques.

Gabapentin 1-(1aminomethyl) cyclohexane acetic acid is a structural analogue of gamma-aminobutyric acid (GABA) that has demonstrated efficacy in reducing patient discomfort for rhinologic procedures.^{6–9} The primary objective of this study is to determine the effect of pre-procedure gabapentin on patient reported pain following in-office posterior nasal nerve cryoablation.

Materials and Methods

Study Participants

Adult patients age >18 years with a diagnosis of allergic or non-allergic rhinitis (defined by the International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis)¹⁰ were enrolled as a part of a prospective, multi-center, non-randomized observational cohort study

to evaluate peri-procedural pain following posterior nasal nerve cryoablation. Study enrollment sites consisted of rhinology and skull base surgery centers located within academic hospital systems within the United States, including the University of California Davis (Sacramento, CA, IRB#1430003–1) and the University of California Los Angeles (Los Angeles, CA IRB#19–001449). Study enrollment occurred between March 2018 and April 2019. Participants underwent in-office posterior nasal nerve cryoablation as a standalone procedure. Patients were excluded if they used narcotics as baseline therapy for medical conditions unrelated to their rhinitis. Atopy was confirmed with blood or skin testing. No study participants underwent inferior meatus cryotherapy.

Data Collection

Information on demographics, medical co-morbidities (i.e. chronic rhinosinusitis, anxiety/depression, primary headache disorder, temporomandibular joint dysfunction, facial pain syndrome), and prior medical therapies were collected at enrollment. Baseline measures of disease specific quality of life, collected as part of the standard of care, were used for investigational purposes. The Total Nasal Symptom Score (TNSS) is a validated symptom severity scoring system that measures each of the following symptoms: nasal congestion, nasal itching, sneezing, and rhinorrhea. A 4 point scale is used (0–3) for each question, where 0 indicates no symptoms and 3 indicates intolerable symptoms that interfere with daily activity.¹¹ TNSS is calculated by adding the sum of each score for a maximum of 12. The mini-Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a 14 question validated QOL measure of five rhinoconjunctivitis dimensions (activities, practical problems, nose symptoms, eye symptoms, and other symptoms) and utilizes a scale of 0–6 for each question.¹² A score of 0 indicates “not troubled” while a score of 6 indicates “extremely troubled”. The mini-RQLQ is scored by averaging each question for a maximum of 6.

Patient discomfort was measured using the pain visual analogue scale (VAS) at baseline (i.e. pre-treatment), and at the following intervals post-treatment: 5, 10, 20, and 30-minutes. Participants were instructed to choose a number from 0–10 on the VAS pain scale to indicate how much pain they might feel, with a score of 0 indicating no pain and a score of 10 indicating unbearable pain.

Procedural Anesthesia

PNN cryoablation was performed using the standard technique described by Hwang et al.⁵ The topical anesthetic regimen included 3 sprays of 4% lidocaine with oxymetazoline spray in each nostril, with 5 minutes allowed for the medication to take effect. Cottonoids soaked with 4% lidocaine with oxymetazoline were then placed along the inferior turbinate and into the inferior aspect of the middle meatus bilaterally for an additional five minutes (Figure 1). Finally, prior to the cryoablation, a sphenopalatine block with 1% lidocaine with 1:100k epinephrine was injected into the target intervention site, with 10 minutes allotted for the injection to take effect (Figure 2). Patient groups were divided into the control (no gabapentin) and the gabapentin treatment group. The treatment group received 600 mg per oral gabapentin one hour prior to procedure. Administration was confirmed at the time of the

procedure through patient interview. The control group did not receive oral analgesia prior to the procedure.

Statistical Analysis

Fisher's exact and Wilcoxon two sample test were used to examine differences between the two groups. SAS® software version 9.4 for Windows® was used in all analyses. A two-sided p-value less than .05 was considered significant.

Results

A total of 26 patients were enrolled (Gabapentin n=15, control=11). The mean age was 63 (SD =15.09), and male gender predominated at 69.3% (n=18). Non-allergic rhinitis was the predominant type of rhinitis at 81% (n=21). There was no statistically significant difference in patient comorbid conditions including chronic rhinosinusitis, primary headache disorder, temporomandibular joint disorder, facial pain syndrome, fibromyalgia, major depressive disorder, anxiety disorder, or tobacco abuse (P=.697). Patients in both the control and gabapentin treatment groups demonstrated similar use of topical nasal steroids, topical nasal antihistamines, topical nasal anti-cholinergic, topical saline irrigations, and proton-pump-inhibitors, (p = .99, .99, .09, .68, and .43) (Table 1).

TNSS in the Gabapentin vs. control group was [median (25th percentile – 75th percentile)] 10 (7.5–11.0) and 9 (6.0–10.0) (p = .35). Mini-RQLQ scores in the gabapentin vs control group were 3.21 (2.00–4.00) and 2.92 (2.78–4.35) (p = .51) (Table 1). The median VAS pain scores at five, twenty, and thirty minutes in the Gabapentin vs. control group were 0.0 (0.0–2.0) vs. 3.0 (1.0–4.0), 2.0 (0.0 – 3.0) vs. 8.0 (6.0–10.0), and 1.0 (0.0–1.0) vs. 5.0 (4.0–6.0) (p=.02, .0043, and .003 respectively) (Figure 3 and Table 2). Two patients in the control group experienced debilitating post procedural pain. One patient experienced a cold-stimulus headache (9/10 pain at 20- and 30-minutes post PNN) and the other experienced severe maxillary/dental pain (9/10 pain at 20 minutes and 6/10 pain at 30 minutes). There were no procedural complications and no epistaxis was noted during or after the procedure.

Discussion:

Modern surgical paradigm for medically refractory rhinitis has shifted away from vidian neurectomy to focus on addressing the down-stream parasympathetic nerve fibers delivered to the nasal cavity by the posterior nasal nerves. Nishijima demonstrated that prolonged denervation of the PNN resulted in nasal mucosal changes and decreased nasal secretion in an animal model.¹³ Terao first described PNN cryoablation for rhinitis in 1983¹⁴, followed by an endoscopic approach to resection of the PNN described by Kikawada in 2007.¹⁵ Hwang et al described a novel cryoprobe that selectively ablates soft tissue and posterior nasal nerve fibers with a predictable depth of penetration while preserving arterial supply.⁵ Disease specific QOL as measured by the TNSS was significantly improved at one year follow up. While the efficacy data for this novel cryoprobe is promising, few guidelines exist regarding optimal analgesic techniques and little is known about the patient's experience with discomfort immediately following posterior nasal nerve cryotherapy. We sought to

determine the effect of pre-procedural oral gabapentin on patient reported pain following PNN.

Study participants in both the gabapentin and control groups reported mild pain 5 minutes following PNN. Increasing discomfort was noted 20 minutes post procedure, followed by a reduction in discomfort at 30 minutes post-procedure. The increased discomfort seen at 20 minutes post-PNN may be related to the metabolism of the topical and submucosal lidocaine (effective duration 15–60 minutes).¹⁶ In this study, the 4% lidocaine/oxymetazoline pledgets are removed prior to cryoablation and it is likely that a portion of the increase in discomfort is a direct result of the diminished efficacy of the local anesthetic. Importantly, these data may help guide clinician counseling and patient treatment selection when deciding to pursue in-office treatment of recalcitrant rhinitis.

A significant reduction in patient discomfort was reported across all times points with pre-procedural administration of gabapentin. Gabapentin may be used preoperatively to protect the central nervous system from noxious stimuli thereby reducing hyperalgesia and pain, although the mechanism by which it does so is poorly understood. Gabapentin is widely used to treat neuropathic pain and is a therapy that is supported by multiple randomized clinical trials.^{6–9,17,18} Kazak et al investigated the role of a single pre-operative 600mg dose of gabapentin in endoscopic sinus surgery and septoplasty. Results from the 2009 study demonstrated decreased intraoperative pain medication requirements as well as improvement in postoperative pain scores and decreased oral pain medication requirements.⁸ Similarly, Turan et al showed that a single dose of 1200mg gabapentin significantly reduced intraoperative and postoperative pain scores in rhinoplasty and endoscopic sinus surgery patients.⁷ Unfortunately, the 1200mg dose of gabapentin was associated with dizziness in this cohort. Pandey et al demonstrated that increasing the dose of gabapentin beyond 600mg did not result in improvement in postoperative pain relief following lumbar discectomy.¹⁹ In concordance with the Kazak study methodology and Pandey results, our study used a pre-operative dose of 600mg gabapentin.

Clinical experience with PNN suggests that *severe* discomfort following posterior nasal nerve cryoablation manifests not as nasal pain, but rather as a cold stimulus headache or maxillary/dental pain, occurring shortly following the procedure. The cold stimulus headache is thought to be mediated through activation of the trigeminal nerve pathway.²⁰ Although the specific mechanism by which PNN cryotherapy may induce a cold stimulus headache is unknown, it is possible that the cooling of tissue near the pterygopalatine fossa may activate the trigeminal pathway. Similarly, we hypothesize that the neuromodulation that occurs with gabapentin administration may effectively reduce patient discomfort through the reduction of input to the trigeminal sensory pathway. Patient co-morbidities, including migraine, facial pain disorders, and anxiety/depression were selectively recorded to determine if there were any additional factors associated with pain/discomfort following PNN. These co-morbidities that were overtly chosen as data suggest that patients with migraine disorders experience cold-stimuli headaches at a higher rate than patients without migraine disorders.²¹ Post-procedural cold-stimulus headache was noted in 2/11 control group patients and 0/15 gabapentin patients. There were no statistically significant

differences in patient discomfort following PNN when stratified by medical comorbidities although a larger study population is needed to confirm these findings.

This study must be interpreted within the context of its limitations. The sample size in both the control group and intervention group was limited despite the multi-institutional nature of the study and results may not be generalizable to larger patient populations. Additionally, clinicians have a multitude of options for topical and submucosal anesthesia. Tetracaine and cocaine are both widely used esters that provide excellent topical anesthesia and results from this study may not align with alternative anesthetic regimens. While 600mg of gabapentin was chosen based on a priori research, the efficacy of varying doses of gabapentin is unknown. All study participants underwent middle meatus cryotherapy and the anesthetic regimen used in this study may not translate to improvement in reported pain for inferior meatus cryotherapy. Lastly, post-procedural VAS pain scale data were only recorded for 30 minutes postoperatively. This study does not exclude the development of peri-procedural pain beyond 30 minutes, although results suggest that patient discomfort appears to peak between 5- and 20-minutes post-procedure. Despite the limitations, this study demonstrates the efficacy of a non-opiate medication for the reduction of peri-procedural pain during in-office PNN cryoablation.

Conclusion:

Pre-procedure gabapentin reduces immediate and delayed post procedural patient discomfort following posterior nasal nerve cryoablation.

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Figure 1:
Endoscopic view of the left nasal cavity. Cottonoid soaked in 4% lidocaine with oxymetazoline is placed along the mucosa along the posterolateral wall of the nasal cavity near the posterior attachment of the basal lamella
* Middle turbinate
Nasal sidewall

Figure 2:
Endoscopic view of the left nasal cavity. 1% lidocaine with 1:100k epinephrine is infiltrated into the lateral nasal wall at the posterior attachment of the middle turbinate/basal lamella
* Middle turbinate
Nasal sidewall

Figure 3:

Box and Whisker plot of VAS pain scale scores at baseline, 5-, 10-, 20-, and 30-minutes post PNN cryoablation. The upper edge of the box represents the 75th quartile while the lower edge of the box is the 25th quartile. The line inside the box represents the mean and the large circle represents the median. The small circles beyond whiskers are values that fall outside $\pm 1.5 \times \text{IQR}$ (outliers).

Table 1:

Treatment group differences between control and gabapentin patients. *

N = 26	Control n = 11 (42.3%)	Gabapentin n = 15 (57.7%)	P value [#]
Age (mean +/- SD)	57.6 (16.7)	67 (12.9)	.14
Gender (% male)	72%	67%	1.0
Rhinitis			
Allergic	1 (9.1%)	1 (6.7%)	>.99
Non-allergic	9 (81.8%)	12 (80.0%)	
Mixed	1 (9.1%)	2 (13.3%)	
Comorbidities			
No medical comorbidity	2 (18.2%)	6 (40.0%)	.69
Chronic Rhinosinusitis	3 (27.3%)	4 (26.7%)	
Primary Headache Disorder	1 (9.1%)	0 (0.0%)	
Temporomandibular Joint Disorder	0 (0.0%)	0 (0.0%)	
Facial Pain Disorder	0 (0.0%)	0 (0.0%)	
Depression/Anxiety	4 (36.4%)	3 (20.0%)	
Smoker	1 (9.1%)	1 (6.7%)	
Primary Headache & Depression/anxiety	0 (0.0%)	1 (6.7%)	
Topical nasal steroid	9 (82.8%)	12 (80.0%)	>.99
Topical nasal antihistamine	5 (45.5%)	8 (53.3%)	>.99
Topical nasal anti-cholinergic	6 (54.6%)	13 (86.7%)	.09
Topical nasal saline	8 (72.7%)	9 (60.0%)	.68
Proton-pump-inhibitor	7 (63.4%)	6 (40.0%)	.43
TNSS ⁺ ; median (range)	9 (0–12)	10 (0–12)	.35 ^{\$}
Mini – RQLQ ^{>} ; median (range)	2.9 (0–6)	3.2 (0–6)	.51 ^{\$}

* Numbers are reported as n (%) unless otherwise noted.

[#] P-values generated from Fisher's exact test unless otherwise noted.^{\$} Wilcoxon rank sum test.⁺ Total Nasal Symptom Score

> Mini-Rhinoconjunctivitis Quality of Life Questionnaire

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Table 2:

VAS pain score differences between control and gabapentin patients.

N = 26	Control n = 11	Gabapentin n = 15	P value[#]
VAS Pain score 5 minutes; median (range)	3.0 (1.0–4.0)	0.0 (0.0–2.0)	.02
VAS Pain score 20 minutes; median (range)	8.0 (6.0–10.0)	2.0 (0.0–3.0)	.0043
VAS Pain score 30 minutes; median (range)	5.0 (4.0–6.0)	1.0 (0.0–1.0)	.003

[#]P-values generated from Fisher's exact test unless otherwise noted.