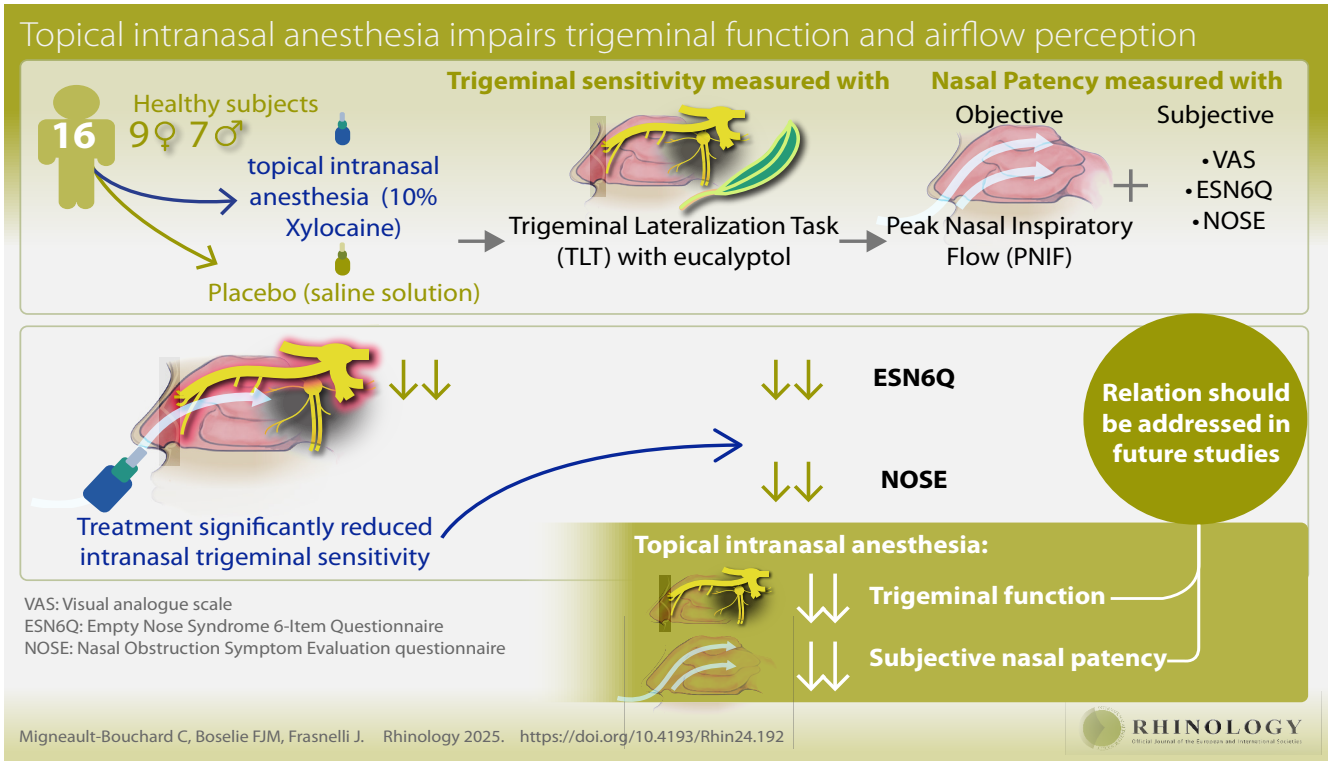
Topical intranasal anesthesia impairs trigeminal function and airflow perception

Chloé Migneault-Bouchard[1], Franciscus J.M. Boselie[2], Johannes Frasnelli[1,3]

Rhinology 63: 1, 85 - 91, 2024
https://doi.org/10.4193/Rhin24.192



Abstract

Background: Impairment of airflow perception by the intranasal trigeminal system may explain chronic nasal obstruction (CNO), especially in cases where no major deformity or mucosal inflammation can explain reduced airflow. We aim to characterize the effect of topical intranasal anesthesia on intranasal trigeminal sensitivity and consequently the sensation of nasal obstruction.

Methodology: We performed a crossover study of 16 healthy subjects, randomised for either treatment (topical intranasal anesthesia with 10% Xylocaine) or placebo (saline solution). We used the Trigeminal Lateralization Task (TLT) with eucalyptol to assess trigeminal sensitivity. We measured nasal patency objectively with Peak Nasal Inspiratory Flow (PNIF), and subjectively with a Visual Analog Scale (VAS), the Empty Nose Syndrome 6-Item Questionnaire (ENS6Q), and the Nasal Obstruction Symptom Evaluation (NOSE) questionnaire.

Results: Topical intranasal anesthesia significantly reduced intranasal trigeminal sensitivity. Further, after topical intranasal anesthesia, reduced trigeminal sensitivity was associated with the subjectively reduced nasal patency, as highlighted by ENS6Q and NOSE scores.

Conclusions: Topical intranasal anesthesia reduces intranasal trigeminal function resulting in subjectively reduced nasal patency. In future studies, the relation of reduced intranasal trigeminal function and subjective nasal obstruction needs to be addressed to open an avenue for potential interventions for an important portion of ENT patients.

Key words: topical intranasal anesthesia, trigeminal system, nasal obstruction

Introduction

Chronic nasal obstruction (CNO) is one of the most common complaints in clinical ENT practice [1], generating expenditures of $6 billion annually in the United States alone [2]. There are several aetiologies for CNO, including structural deformities, infections, and inflammation; the most common being acute, allergic, or chronic rhinitis [3]. Depending on the cause, CNO requires different diagnostic approaches and therapeutic strategies. However, conservative and/or surgical treatment attempts fail to resolve CNO in 23-37% of the cases [2]. In some cases, especially when no major anatomical deformity or obstructive mucosal inflammation can explain the reported CNO, and medical and surgical treatment fail to resolve it, CNO is labelled as treatment-refractory and anatomically inexplicable.

The pathophysiology of treatment-refractory and anatomically inexplicable CNO is not well understood. In these cases, alterations of afferent neural pathways responsible for the perception of intranasal airflow, namely the intranasal trigeminal system, is often suspected to cause reduced subjective nasal patency [4-6]. In fact, nasal airflow is perceived by the activation of multimodal receptors on the trigeminal nerve located on the nasal cavity's epithelium [7, 8]. These receptors respond to intranasal temperature changes caused by the inhaled air (e.g., low temperatures are associated with increased intranasal airflow) as well as chemical substances such as menthol or eucalyptus [9]. Consequently, inhaling these substances gives the impression of increased intranasal airflow, and therefore of reduced nasal congestion, even if objectively there are no changes in the degree of congestion [2, 5, 10, 11].

In turn, locally injecting an anesthetic into the nasal vestibule reduces the intranasal trigeminal function [12] and produces a sensation of nasal obstruction while having no effect on nasal resistance to airflow, demonstrated by anterior rhinomanometry [13, 14]. However, these studies were carried out before the introduction of validated patient rated outcome measures (PROMs) such as the Empty Nose Syndrome 6-item Questionnaire (ENS6Q) and the Nose Obstruction Symptom Evaluation (NOSE), and the evaluation of the intranasal trigeminal system was limited to the use of a visual analog scale.

This body of evidence suggests that topical intranasal anesthesia impairs intranasal trigeminal function and airflow perception.

Materials and methods

This study was carried out in the Department of Otorhinolaryngology of the Centre Hospitalier de Luxembourg (data collection) and in the Department of Anatomy of Université du Québec à Trois-Rivières (data analysis). We performed the study according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects; it was approved by the national and institutional ethics review boards, respectively (National Research Ethics Comittee, CNER approval No: 202206/02; Université du Québec à Trois-Rivières, IRB approval No: CER-23-295-10.04).

Participants

The study included 17 healthy participants. After exclusion of one participant that dropped out between the first and second test session, the sample consisted of 16 healthy participants (9 women, mean age of 37 ± 10; 7 men, mean age of 33 ± 6) without any rhinological symptoms. All participants underwent a full ENT evaluation by the ENT-surgeon (FJMB) including anterior rhinoscopy to exclude anatomical deformity, mucosal inflammation, and nasal disease. Participants with history of traumatic brain injury or head trauma, an upper respiratory tract infection with olfactory loss for more than one month, chemotherapy or radiotherapy for head and neck cancer, previous sino-nasal surgery, neurodegenerative disease, usage of any medication that could influence nasal sensitivity, pregnancy or breastfeeding and allergy to the anesthesia were excluded. All participants were recruited in the Centre Hospitalier du Luxembourg by the ENT-surgeon (FJMB).

Olfactory dysfunction is typically associated with reduced trigeminal sensitivity [15]. To exclude this confounder, we ascertained normal olfactory function in all participants by using the identification task of the Sniffin' Sticks test kit (Burghart, Germany) [16, 17]. In short, this test is based on felt-tip pen-like odor dispensing devices involving the identification of 16 common odorants using 4 descriptors for each odor. The sum of correct identifications was used to determine the eligibility of the participants to the study. A score of ≥12 was considered normal and used as an inclusion criterion.

Methods

The participants were tested on two different days. The testing sessions were separated by a minimum time of 24 hours for a wash-out period (1 to 14 days, n=8; 15 days and more, n=8). They were randomised for either anesthetic or placebo for the first study visit, and then were crossed over to the opposite treatment for the second study visit. The anesthesia and the placebo were applied by the ENT-surgeon (FJMB) according to a fixed protocol. The anesthesia was applied using standard nasal 10% Xylocaine which was sprayed in both nasal cavities (0.5ml both sides), and 1ml Xylocaine-soaked cotton balls, which were placed at the entrance of each nasal valve for 5 minutes. The placebo was applied equivalently but using NaCl 0.9% solution. Although the study was set up as a blind intervention, participants perceived the effect of the anesthesia immediately after the application.

Before and after performing topical intranasal treatment (anesthetic or placebo), we evaluated intranasal trigeminal function and nasal patency.

Intranasal trigeminal function

We assessed trigeminal function using the trigeminal lateralization task (TLT) [18, 19]. Specifically, we used two identical opaque glass bottles (total volume 60ml), one containing 10 cotton balls soaked with the mixed olfactory-trigeminal stimulus eucalyptol (target, 7 ml; eucalyptus odor, cooling sensation, agonist of the TRPM8 receptor [20], Sigma-Aldrich, Switzerland); the other one containing only 10 cotton balls (sham). The bottles had polyethylene caps with a diameter of approximately 2cm in which we had drilled 2 holes with a diameter of 5mm. In each hole, we inserted a tube with a length of approximately 4cm. This allowed us to simultaneously present the content of each bottle to only one nostril. The participants held the bottles to their noses, one of the holes was placed under the nostrils. They were invited to take a sniff and to then identify the nostrils to which the target had been presented (forced choice). Participants were blindfolded to not have any visual cues. We applied a total of 40 pseudo-randomized stimuli of the same concentration, at an interval of 30-40 s between each stimulation. The sum of correct identifications was used to estimate trigeminal sensitivity; scores can range between 0 and 40 (0 to 20 for each nostril).

Nasal patency

(A) Objective: We assessed nasal patency using the Peak Nasal Inspiratory Flow (PNIF) [21]. We employed a portable spirometer with a face mask adapted to the participant's mouth and nose. At the end of a maximal expiration followed by three medium deep breaths, we asked participants to perform a forced maximal inspiration with their mouth closed. We repeated the maneuver three times, and the highest value was recorded. This test represents the highest airflow achieved through both nostrils during maximum forced nasal inspiration.
(B) Subjective: We used three different methods to evaluate subjective nasal patency [1]. To rate nasal patency, we asked participants to use a Visual Analog Scale (VAS; ranging from 0: complete obstruction to 100: no obstruction) [2]. To directly assess nasal obstruction, participants filled out the Empty Nose Syndrome 6-Item Questionnaire (ENS6Q) [22], a clinical tool to assess symptoms of empty nose syndrome based on a series of 6 visual analog scales (ranging from "no problem/not applicable" to "extremely severe"). This questionnaire allows to identify patients suspected of empty nose syndrome; a condition characterised by diminished intranasal trigeminal sensitivity. We adapted the questionnaire to the study's context by changing the instructions from "in the last month" to "in the last 15 minutes" [3]. Finally, to assess the sensation of nasal obstruction, participants completed the Nasal Obstruction Symptom Evaluation (NOSE) [23, 24], a clinical tool consisting of 5 visual analog scales (ranging from "not a problem" to "severe problem") to assess nasal obstruction. Again, we changed the instructions from "in the last month" to "in the last 15 minutes".

Statistical analysis

We analysed data with SPSS 28.0 (SPSS Inc., Chicago, IL, USA) and set the alpha value to 0.05. All post hoc tests were Bonferroni corrected. We report average scores with standard deviations unless stated otherwise. Intranasal trigeminal function (TLT) and objective nasal patency (PNIF) data are normally distributed, while the subjective nasal patency (VAS, ENS6Q and NOSE) did not follow a normal distribution.
To examine the effect of anesthesia on intranasal trigeminal function and measures of nasal patency, we performed separate repeated-measures (rm) ANOVA on individual dependant variables (TLT scores for trigeminal function, PNIF for objective nasal patency as well as each VAS, ENS6Q scores, and NOSE scores for subjective nasal patency) with intervention (2 levels: anesthetic, placebo) and time (2 levels: before treatment, after treatment) as within subject factors. To disentangle interactions, we subsequently performed paired t-tests or Wilcoxon tests (depending on the normality of the distribution) with appropriate corrections for multiple comparisons.
Next, we analyzed the association between intranasal trigeminal function before and after topical application of nasal treatment by computing Pearson's correlations between TLT scores before and after topical intranasal treatment. Finally, we analyzed the association between intranasal trigeminal function and nasal patency by computing Spearman's correlations (not all data were normally distributed) between TLT scores and measurements of nasal patency (objective: PNIF; subjective: VAS, NOSE, ENS6Q) before and after administration of topical intranasal anesthesia. We repeated this analysis of an association between TLT and each separate question of NOSE and ENS6Q questionnaires with Bonferroni correction.

Results

We present descriptive statistics for intranasal trigeminal function before and after each intervention (anesthetic or placebo) in Table 1.

For intranasal trigeminal function, the rm ANOVA yielded significant effects of intervention [$F(1.15) = 4.699$; $p=0.047$], time [$F(1.15)=31.441$; $p<0.001$] and intervention*time [$F(1.15) = 16.063$;$p=0.001$]. To disentangle the interaction, we carried out paired two t-tests, one for each intervention (anesthetic, placebo). For the anesthetic condition, the paired t-test revealed a significant difference before and after treatment [$t(15) = 5.794$; $p<0.001$). In turn, for the placebo intervention, no significant difference was observed (Figure 1). In addition, we compared the effects of intervention (anesthetic vs placebo) with separate paired t-tests for both time points. This revealed a significant difference between anesthetic and placebo after the treatment [$t(15)=-3.082$;$p=0.004$], but not before the treatment.

Table 1. Descriptive statistics, mean scores and standard deviation for intranasal trigeminal function and nasal patency before and after each intervention (anesthetic or placebo).

	Anesthetic		Placebo	
	Before	After	Before	After
Intranasal trigeminal function				
TLT mean ± SD	32.94 ± 4.49	26.44 ± 5.28	33 ± 4.53	31.56 ± 5.61
Nasal patency				
PNIF mean ± SD	113.12 ± 45.53	107.50 ± 35.17	115.94 ± 35.37	110.63 ± 33.91
VAS mean ± SD	8.06 ± 1.35	8.09 ± 1.92	8.69 ± 1.40	8.75 ± 1.24
NOSE mean ± SD	1.31 ± 1.35	3.25 ± 5.37	2.06 ± 2.84	0.56 ± 1.09
ENS6Q mean ± SD	113.12 ± 45.53	107.50 ± 35.17	115.94 ± 35.37	110.63 ± 33.91

With regards to nasal patency, the rm ANOVA yielded a significant effect of intervention [$F(1.15) = 12.799$; $p=0.003$] as well as the interaction intervention*time [$F(1.15) = 14.694$; $p=0.002$] for the ENS6Q scores. To disentangle the interaction, we carried out two Wilcoxon tests, one for each intervention (anesthetic, placebo). For the anesthetic condition, the Wilcoxon test revealed a significant difference before and after treatment [$Z= -2.239$; $p=0.0245$], but not for the placebo (Figure 2). In addition, we compared the effects of intervention (anesthetic vs placebo) with separate Wilcoxon test for both time points. This revealed a significant difference between anesthetic and placebo after the treatment [$Z=-3.055$; $p<0.001$], but not before the treatment. We did not observe any significant effect for the other objective (PNIF) or subjective (VAS, NOSE) measurements of nasal patency.

We computed Pearson's correlations between TLT scores before and after the administration of the topical intranasal treatment. For both, anesthesia ($r=0.589$; $p=0.016$) and placebo ($r=0.852$; $p<0.001$), TLT scores before and after topical application were significantly correlated. We further investigated the correlation between intranasal trigeminal function and nasal patency, after topical anesthesia. This showed that TLT was correlated with the NOSE scores after topical intranasal anesthesia ($rho=-0.524$; $p=0.037$). We did not observe any other correlation. Finally, we computed Spearman's correlations between intranasal trigeminal function and each separate question of NOSE and ENS6Q questionnaires after topical anesthesia. This showed that TLT negatively correlated with the second item (sense of diminished nasal airflow (cannot feel air flowing through your nose)) of the ENS6Q questionnaire after topical intranasal anesthesia ($rho=-0.637$; $p=0.008$); no other significant results were observed.

Discussion

Here we report three main findings. First, topical intranasal anesthesia with 10% Xylocaine significantly reduced intranasal trigeminal function. Second, Xylocaine anesthesia induced higher ENS6Q scores. Third, after Xylocaine anesthesia, scores for trigeminal sensitivity and scores for NOSE items such as nasal congestion, obstruction and problems breathing were correlated.

Earlier studies evaluated the effect of topical intranasal anesthesia on nasal airflow, objectively by anterior rhinomanometry or subjectively by means of VAS [12-14]: Intranasal anesthesia produced a sensation of nasal obstruction but did not modify objectively measured nasal patency. This effect was suggested to be due to decreased intranasal trigeminal sensitivity induced by intranasal anesthesia [12], in line with our results. Together with our earlier studies [5], this suggests that the intranasal trigeminal system is crucially involved in the perception of nasal airflow. Here, we were able to objectify the effect of anesthesia on trigeminal sensitivity by using the TLT to assess sensitivity toward eucalyptol [20]. In fact, both cool temperatures and chemical substances such as eucalyptol and menthol activate the TRPM8 receptor [25]. This body of literature suggests that perception of nasal airflow is, at least partly, due to the activation of TRPM8 receptors [9, 26].

The present results contrast with previous studies on the effect of nasal anesthesia that showed a very pronounced feeling of nasal obstruction. Unlike previous studies, in this research local anesthesia was done by spraying, which led to a less pronounced feeling of nasal obstruction. It therefore seems that surface anesthesia has a far smaller effect than a locally injected anesthesia or an injury of the trigeminal nerve in a deeper layer. One may thus hypothesize that impairment of the trigeminal system can exhibit different degrees, depending on the underlying cause, e.g., deep injury after a surgery, inflammation, or varying expression levels of TRPM8 receptors.

We observed an effect of anesthesia on the ENS6Q, but not for VAS or NOSE. This is puzzling. Two non-exclusive hypotheses can be put forward why this discrepancy between different methods assessing nasal patency appears: first, even if we carried out a power analysis before running our experiment, it may still

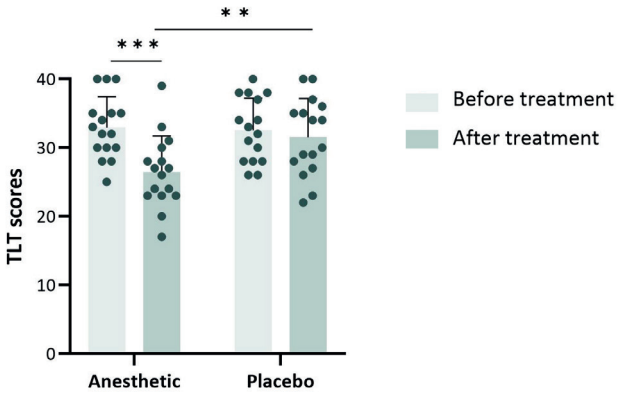


Figure 1. Trigeminal Lateralization Task (TLT) according to the time (before treatment and after treatment) for anesthetic and placebo condition. Error bars represent standard deviation (SD).

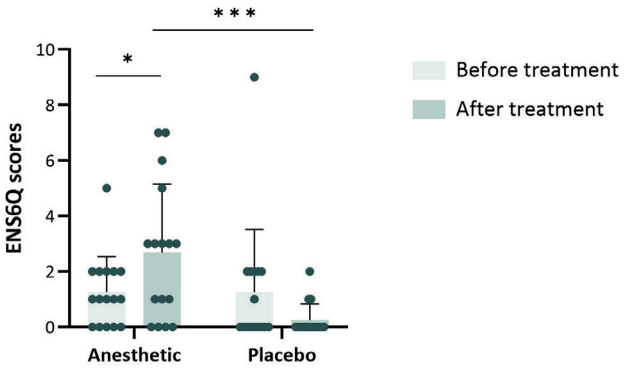


Figure 2. Empty Nose Syndrome 6-Item Questionnaire (ENS6Q) score according to the time (before treatment and after treatment) for anesthetic and placebo condition. Error bars represent standard deviation (SD).

be that our study is underpowered. To overcome this, future studies should include more participants. Second, the three different approaches do not measure exactly the same thing. The ENS6Q allows to identify symptoms related to Empty Nose Syndrome (ENS; e.g., dryness, lack of air sensation, suffocation, nose feeling too open, etc.), while the NOSE identifies symptoms related nasal obstruction (e.g., nasal congestion, obstruction, trouble breathing through the nose, etc.). Intranasal anesthesia led to higher ENS6Q scores; this effect was mainly driven by the second item (cannot feel air flowing through the nose)) that was negatively correlated with TLT, indicating that individuals who scored poorly at TLT reported a higher sense of diminished nasal airflow. This suggests that the ENSQ6Q is better suited to map the effects of intranasal anesthesia. In turn, after intranasal anesthesia, NOSE scores and TLT scores were significantly correlated, indicating that individuals who scored poorly at the TLT reported the most severe symptoms, even if there was no difference before vs after anesthesia, on a group level.

The empty nose syndrome is a paradoxical subjective nasal obstruction despite widely patent nasal cavity in clinical examination [27]. The pathophysiology of ENS is not yet fully understood, and is most likely multifactorial, including anatomical and neurosensory alteration. Altered perception of nasal airflow via impaired intranasal trigeminal function is often suspected to be a major contributing factor to this subjective nasal obstruction [27]. Importantly, ENS is characterised by diminished intranasal trigeminal sensitivity [27].

Xylocaine does not directly affect TRPM8 receptors, but rather anesthetises the nasal mucosa by the inhibition of action potentials via sodium channel blocking in vasoconstrictor (sympathetic) fibres [28]. Consequently, topical anesthesia causes a decrease of superficial nasal blood flow and nitric oxide levels [2]. In fact, TRPM8 is abundant in nasal mucosa within the subepithelium. More specifically, TRPM8 receptors are particularly located around the nasal blood vessels, in the vascular region, and may mediate neurovascular reflexes (8). The vasoconstriction produced by Xylocaine may therefore indirectly impede the activation of TRPM8 [2]. In summary, there is evidence that Xylocaine anesthesia crucially impairs TRPM8 activation.

The subjective appreciation of nasal obstruction is multifactorial. Nasal airflow can be influenced by many parameters, such as anatomical obstruction or inflammation. However, in some cases, no major anatomical deformity or obstructive inflammation is present to explain the reported nasal obstruction, and medical and surgical treatment failed to resolve it. The impairment of the intranasal trigeminal system seems to cause this subjective sensation of nasal obstruction. Regarding these cases, our results provide an interesting avenue to study impairment of nasal patency further. In fact, our approach could serve as a model to better understand the pathomechanism of impaired nasal airflow perception and could allow for the development of potential interventions. For example, stimulation with a TRPM8 agonist such as menthol or eucalyptol could be an alternative therapeutic approach in patients with CNO as the chemical stimulus combined with the somatosensory stimulus of the airflow may allow for the perception of airflow when the effect of the airflow alone is insufficient to evoke airflow perception; this may therefore relieve their symptoms of nasal obstruction.

The primary limitation of our hypothesis-generating study is the limited sample size due to the clinical aspect of the study. Even if we carried out a power calculation based on previous publications [11, 12], which established a required sample size of n=17, a larger sample may have allowed to observe additional results regarding the effect of topical nasal anesthesia on subjective measurement of nasal patency, e.g., by the NOSE questionnaire. A second limitation is the design. Although the study was set up as a blind intervention, the participants immediately and very obviously perceived the anesthetic effect of Xylocaine

application. A third limitation is the limited number of objective measurements in the data. Most tests used are questionnaires (VAS, ENS6Q and NOSE) which are prone to individual subjective severity bias. However, the NOSE and ENS6Q are validated patient rated outcome measures. Finally, while the effect of anesthesia resembled findings in patients with nasal obstructions from earlier reports, we did not directly compare them to patient data, as no patients were included in the study.

Conclusion

Our study shows that topical intranasal anesthesia with Xylocaine reduced intranasal trigeminal function and perception of nasal patency (e.g., sensation of nasal obstruction without any anatomical obstruction). The study of the trigeminal system may open an avenue for potential interventions for an important portion of ENT patients which eventually may considerably increase their quality of life. A previous study showed that a low intranasal trigeminal function seems to predict poor chances of symptom improvement after surgery [29], highlighting the involvement of the intranasal trigeminal system in airflow perception.

Acknowledgements

The authors would like to thank all the participants.

Authorship contribution

Conception or design of the work (all authors); data acquisition (CMB, FJMB); data analysis (CMB, JF), drafting work (all authors); final approval (all authors).

Conflict of interest

The authors declare no conflict of interest.

Funding

This study was supported by the Fonds de Recherche du Québec – Santé to CMB and JF (FRQS chercheur boursier senior #352197), Natural Sciences and Engineering Research Council of Canada (NSERC; RGPIN-2022-04813) and the Canadian Institutes of Health Research (CIHR; AFF_173514) to JF.

References

1. Macdonald KI, McNally JD, Massoud E. The health and resource utilization of Canadians with chronic rhinosinusitis. Laryngoscope. 2009;119(1):184-189.
2. Sozansky J, Houser SM. The physiological mechanism for sensing nasal airflow: A literature review. Int Forum Allergy Rhinol. 2014;4(10):834-838.
3. Corey JP, Houser SM, Ng BA. Nasal congestion: A review of its etiology, evaluation, and treatment. Ear Nose Throat J. 2000;79(9):690.
4. Saliba J, Fnais N, Tomaszewski M, et al. The role of trigeminal function in the sensation of nasal obstruction in chronic rhinosinusitis. Laryngoscope. 2016;126(5):E174-E8.
5. Migneault-Bouchard C, Boselie FJM, Hugentobler M, Landis BN, Frasnelli J. Trigeminal impairment in treatment-refractory chronic nasal obstruction. Rhinology. 2021. Jun 1;59(3):312-318.
6. Li C, Farag AA, Leach J, et al. Computational fluid dynamics and trigeminal sensory examinations of empty nose syndrome patients. Laryngoscope. 2017;127(6):E176-e184.
7. Filiou R-P, Lepore F, Bryant B, Lundström JN, Frasnelli J. Perception of Trigeminal Mixtures. Chem Senses. 2015;40(1):61-69.
8. Keh S, Facer P, Yehia A, Sandhu G, Saleh H, Anand P. The menthol and cold sensation receptor TRPM8 in normal human nasal mucosa and rhinitis. Rhinology. 2011;49:453-457.
9. Eccles R. Menthol: Effects on nasal sensation of airflow and the drive to breathe. Curr Allergy Asthma Rep. 2003;3(3):210-214.
10. Lindemann J, Tsakiropoulou E, Scheithauer MO, Konstantinidis I, Wiesmiller KM. Impact of menthol inhalation on nasal mucosal temperature and nasal patency. Am J Rhinol. 2008;22(4):402-405.
11. Malik J, Spector BM, Wu Z, et al. Evidence of nasal cooling and sensory impairments driving patient symptoms with septal deviation. Laryngoscope. 2022;132(3):509-517.
12. Eccles R, Jawad MSM, Morris S. Olfactory and trigeminal threshold ans nasal resistance to airflow. Acta Otolaryngol. 1989;108:268-273.
13. Jones AS, Crosher R, Wight RG, Lancer JM, Beckingham E. The effect of local anaesthesia of the nasal vestibule on nasal sensation of airflow and nasal resistance. Clin Otolaryngol Allied Sci. 1987;12(6):461-464.
14. Jones AS, Wight RG, Crosher R, Durham LH. Nasal sensation of airflow following blockade of the nasal trigeminal afferents. Clin Otolaryngol Allied Sci. 1989;14(4):285-289.
15. Migneault-Bouchard C, Hsieh JW, Hugentobler M, Frasnelli J, Landis BN. Chemosensory decrease in different forms of olfactory dysfunction. J Neurol. 2020;267(1):138-143.
16. Oleszkiewicz A, Schriever VA, Croy I, Hahner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2019;276(3):719-728.
17. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses. 1997;22(1):39-52.
18. Hummel T, Futschik T, Frasnelli J, Hüttenbrink K-B. Effects of olfactory function, age, and gender on trigeminally mediated sensations: a study based on the lateralization of chemosensory stimuli. Toxicol Lett. 2003;140-141:273-280.
19. Frasnelli J, Gingras-Lessard F, Robert J, Steffener J. The effect of stimulus duration on the nostril localization of eucalyptol. Chem Senses. 2017;42(4):303-308.
20. Hummel T, Frasnelli J. Chapter 8 - The intranasal trigeminal system. In: Doty RL, editor. Handb Clin Neurol. 164: Elsevier; 2019. p. 119-134.
21. Bermuller C, Kirsche H, Rettinger G, Riechelmann H. Diagnostic accuracy of peak nasal inspiratory flow and rhinomanometry in functional rhinosurgery. Laryngoscope. 2008;118(4):605-610.
22. Velasquez N, Thamboo A, Habib A-RR, Huang Z, Nayak JV. The Empty Nose Syndrome 6-Item Questionnaire (ENS6Q): a validated 6-item questionnaire as a diagnostic aid for empty nose syndrome patients. Int Forum Allergy Rhinol. 2017;7(1):64-71.
23. Stewart MG, Witsell DL, Smith TL, Weaver EM, Yueh B, Hannley MT. Development and validation of the Nasal Obstruction Symptom Evaluation (NOSE) scale. Otolaryngol Head Neck Surg. 2004;130(2):157-163.
24. Marro M, Mondina M, Stoll D, de Gabory L. French validation of the NOSE and RhinoQOL questionnaires in the management of nasal obstruction. Otolaryngol Head Neck Surg. 2011;144(6):988-993.
25. McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature. 2002;416:52.

26. Migneault-Bouchard C, Lagueux K, Hsieh JW, Cyr M, Landis BN, Frasnelli J. Trigeminal cold receptors and airflow perception are altered in chronic rhinosinusitis. Rhinology. 2024;62(1):63-70.
27. Konstantinidis I, Tsakiropoulou E, Chatziavramidis A, Ikonomidis C, Markou K. Intranasal trigeminal function in patients with empty nose syndrome. Laryngoscope. 2017;127(6):1263-1267.
28. Newton DJ, McLeod GA, Khan F, Belch JJF. Mechanisms influencing the vasoactive effects of lidocaine in human skin. Anaesthesia. 2007;62(2):146-150.
29. Soyka MB, Wawrzyniak P, Eiwegger T, et al. Defective epithelial barrier in chronic rhinosinusitis: The regulation of tight junctions by IFN-γ and IL-4. J Allergy Clin Immunol. 2012;130(5):1087-1096.e10.

Chloé Migneault-Bouchard
Department of Anatomy
Université du Québec à Trois-Rivières (UQTR)
3351, boulevard des Forges
Trois-Rivières (Québec) G8Z 4M3
Canada

Tel: +1(819) 376-5011 #3360
E-mail:
Chloe.Migneault-Bouchard@uqtr.ca

Chloé Migneault-Bouchard[1], Franciscus J.M. Boselie[2], Johannes Frasnelli[1,3]

[1] Department of Anatomy, Université du Québec à Trois-Rivières (UQTR), Trois-Rivières, QC, Canada

[2] Department of Otorhinolaryngology, Centre Hospitalier de Luxembourg, Luxemburg

[3] Research Center, Sacré-Coeur Hospital, Montréal, QC, Canada

Rhinology 63: 1, 85 - 91, 2024
https://doi.org/10.4193/Rhin24.192

Received for publication:
May 8, 2024
Accepted: September 9, 2024

Associate Editor:
Basile Landis