Received: 8 July 2019 | Revised: 19 September 2019 | Accepted: 9 November 2019

DOI: 10.1111/coa.13483

CORRESPONDENCE: OUR EXPERIENCE

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Intranasal trigeminal training in empty nose syndrome: A pilot study on 14 patients

1 | INTRODUCTION

Empty nose syndrome (ENS) is a rhinological disorder first described in 1994 and considered as a rare, debilitating complication of turbinal surgery.[1] Clinical symptoms usually comprise paradoxical nasal obstruction, local dryness, nasal crusting, intranasal pain and burning, sleep disorder, breathing difficulty and suffocation, often leading to profound psychological distress. The underlying pathophysiology is unknown and most likely multifactorial, encompassing anatomical and neurosensory alterations.

Thermal activation of moderate cold trigeminal receptors (TRPM8) by inhaled air is thought to be the main mechanism linking nasal airflow to perception of nasal patency.[2] Therefore, neurosensory disruption might play a bigger role than previously thought in the cognitive perception of nasal obstruction. It has been shown that mucosal surface area cooling by inhaled air, and subsequent trigeminal activation, better correlates with subjective nasal patency than measuring the anterior nasal resistance or total nasal airflow.[3,4] ENS patients may thus suffer from nasal obstruction not only because airflow patterns were altered but also because trigeminal function is deficient.

Current management of ENS focuses mainly on surgical restoration of preoperative nasal anatomy, thus somewhat neglecting the neurosensory side of ENS. The aim of this study is to subject ENS patients to a chronic multidaily TRPM8 stimulation, or trigeminal training, to observe the effects on subjective nasal obstruction (primary outcome) and quality of life (secondary outcome).

2 | MATERIALS AND METHODS

2.1 | Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki on biomedical research for human subjects and was approved by the Ethics Committee of the Erasmus Hospital. All patients provided written informed consent, which described the study's aim, protocol, potential benefits and side effects, and the patient's right to withdraw from the study at any time.

2.2 | Study design and patients

This clinical prospective study was conducted between October 2018 and April 2019 in the department of otorhinolaryngology of Erasmus Hospital, Brussels, Belgium. Patients were recruited from the otorhinolaryngology department and from the French-speaking Empty Nose Syndrome Association.[1] The inclusion criteria consisted of: a history of bilateral turbinate surgery, symptoms consistent with ENS, and a minimum of 11/30 on the validated Empty Nose Syndrome 6-Questionnaire (ENS6Q).[5] The exclusion criteria consisted of: the presence of an active rhinological pathology (eg, polyposis, sinusitis and neoplasia) and allergy to trigeminal stimulants (levomenthol and eucalyptol). Fourteen patients matched our criteria and were included in the study. As in most studies, time frame is hard to establish because many patients have had multiple turbinate procedures and symptoms arise progressively. In this study, half of our patient cohort had more than one turbinate procedure.

2.3 | Pre-training assessment

A nasal endoscopic examination, an anterior active rhinomanometry and a trigeminal lateralisation test were performed. The trigeminal lateralisation test was used to assess intranasal trigeminal function.[6] Two 50 mL brown glass bottles were presented simultaneously to the nostrils of blind-folded patients who were asked to inhale for a few seconds and lateralise the trigeminal stimulus. One bottle contained levomenthol crystals (trigeminal stimulant) dissolved in glycol propylene (1 g/1 mL) and the other contained only glycol propylene, a non-olfactory non-trigeminal solvent. Twenty pseudorandomised stimulations were performed, and the test score was established as the number of correct lateralisations.

2.4 | Intranasal trigeminal training

The trigeminal training protocol was similar to the one proposed by Oleszkiewicz et al in 2018.[7] As for trigeminal stimulants, we decided to use levomenthol and eucalyptol as they induce a potent yet well-tolerated cooling sensation by chemically activating the same trigeminal receptor (TRPM8) which elicits subjective nasal patency,

[1] www.syndromedunezvide.com, F. Lepaisant.

to mirror physiological pathways as much as possible. Two 30 mL brown glass bottles were provided to the participant: (a) 10 mL of levomenthol crystals dissolved in glycol propylene (1 g/1 mL); (b) 10 mL of pure eucalyptol solution. Participants were asked to inhale the content of both bottles three times a day for at least 10 seconds per inhalation. The training duration was first established as 60 days (inspired from Oleszkiewicz et al) but was adjusted to a minimum of 30 days, based on a realistic assumption that a longer duration may deter ENS patients to take part in the study.

As nasal obstruction was our primary outcome, participants were asked to fill in the Nasal Obstruction Symptom Evaluation (NOSE) questionnaire before and after completion of the trigeminal training. In addition, SNOT-22 and ENS6Q questionnaires were also given to assess trigeminal training impact on quality of life and ENS-specific symptoms, respectively.

Keypoints

- Empty nose syndrome is a rare and debilitating complication of turbinate surgery, with varying symptoms of which paradoxical nasal obstruction is typical.
- Trigeminal training consisting of three-times daily levomenthol and eucalyptol inhalations for at least 30 days were associated with improved subjective nasal patency and quality of life.
- Trigeminal training is an outpatient, low-cost, easy-to-do, non-invasive and non-harmful treatment modality that can be proposed to ENS patients as a preliminary step before considering surgery.
- Trigeminal lateralisation testing seems to be a more reliable diagnostic tool than rhinomanometry in ENS.

2.5 | Statistical analysis

Pre-training and post-training questionnaire scores were compared using Wilcoxon signed-rank tests. Mann-Whitney rank-sum tests were used to compare non-paired samples. Statistical significance was fixed at α = 0.05. All tests were performed with Statistical Packages for Social Sciences® Version 20.0. (IBM).

3 | RESULTS

3.1 | Pre-training assessment

The mean age of participants was 41 years old with a sex ratio of 1/1 (Table 1). Medical histories revealed surgery on inferior turbinates in 13 patients and on middle turbinates in one patient. Surgical techniques varied among patients and were sometimes combined; they included partial and radical turbinectomy, bipolar and monopolar cauterisation, and radiofrequency. Total nasal airflow resistance mean was 0.32 and 0.26 Pa/cm^3/s after vasoconstriction (P = .93). Trigeminal lateralisation mean score was 9.1/20. Nasal endoscopy excluded alternative diagnoses and showed absent or minimal crusting in all patients.

TABLE 1 Baseline characteristics and pre-training assessment of 14 patients with empty nose syndrome. Data are shown in mean

	Statistics (n = 14)
Age	41 (23-77)
Sex ratio	7M:7F
Rhinomanometry (Pa/cc/s)	0.322
Rhinomanometry after decongestion (Pa/cc/s)	0.266
Lateralisation test (0-20)	9.1
NOSE (0-20)	12.1
ENS6Q (0-30)	17.1
SNOT-22 (0-110)	60

3.2 | Post-training outcomes

Trigeminal training results are shown in Table 2. Seven patients duly completed the training, five participants dropped in the first 12 days and two were lost to follow-up. The NOSE score was significantly reduced from 12.4 to 9.8/20 (P = .027; Figure 1). The ENS6Q score showed no difference. The SNOT-22 score was significantly reduced from 63.7 to 50.7/110 (P = .028), mainly in particular subdomains: nasal obstruction, sleep disturbances and emotional status (Figure 2). There was no difference in all three questionnaire scores between the participants who completed the training and those who did not.

TABLE 2 Trigeminal training duration and post-training questionnaire scores for each participant

Participants (n = 14)	Duration (d)	NOSE (0-20)	ENS6Q (0-30)	SNOT-22 (0-110)
1	42	6	4	24
2	37	11	8	60
3	Lost to follow-up			
4	12			
5	63	20	24	76
6	3			
7	39	5	10	38
8	37	6	15	48
9	42	14	21	65
10	30	7	15	44
11	3			
12	1			
13	10			
14	Lost to follow-up			
Mean	41.4	9.8	13.8	50.7

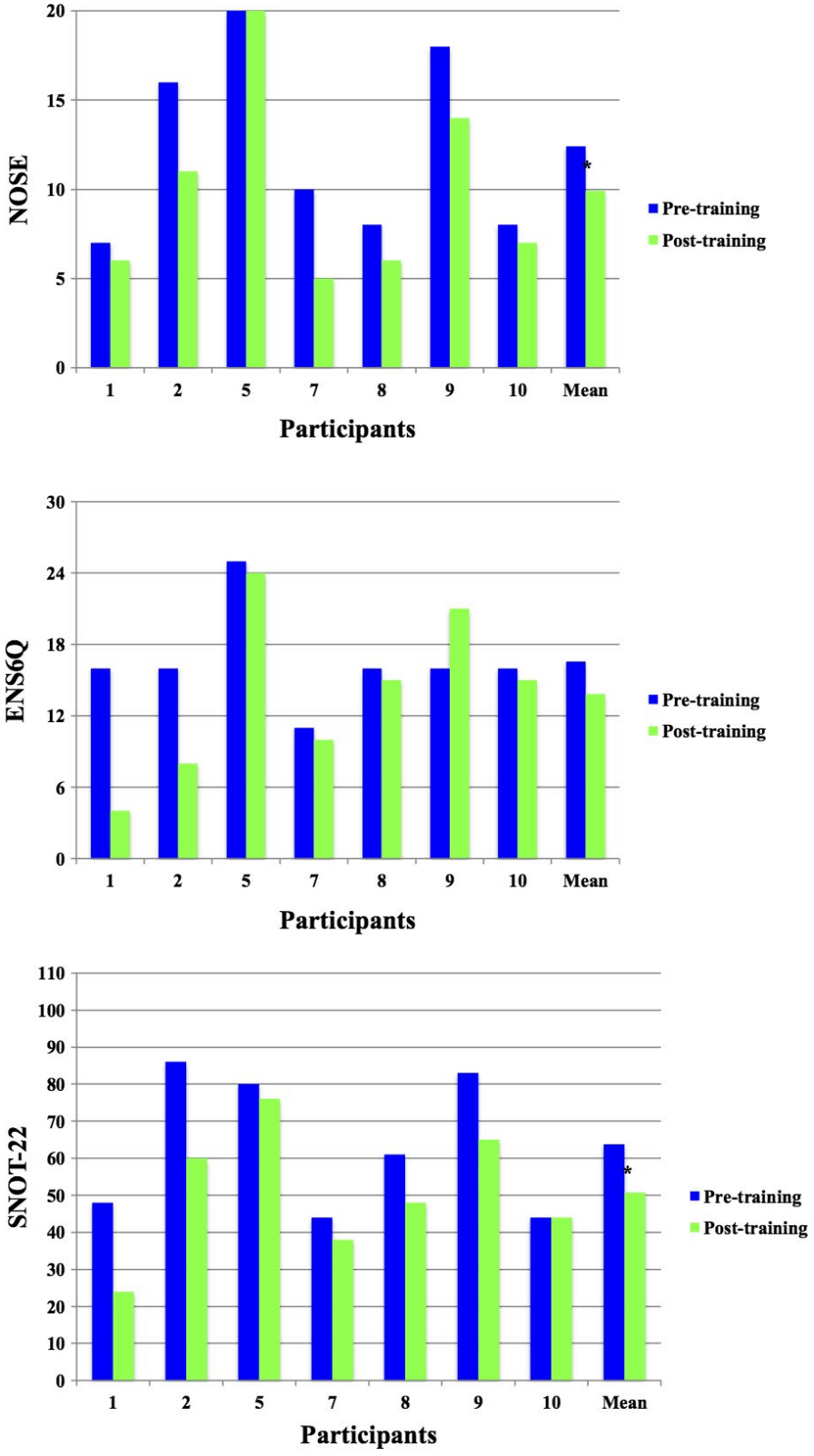

FIGURE 1 Pre- and post-trigeminal training scores for NOSE, ENS6Q and SNOT-22 questionnaires for participants who completed the training (n = 7)

4 | DISCUSSION

Although alterations in both nasal anatomy and neural sensitivity are generally accepted as the main contributors to ENS, current management is mainly targeted at filling-in the patient's empty nose. A systematic review by Leong in 2015 reported surgical studies with varying success with autologous and allologous grafts, implants and injections, with an improvement of symptoms up to 12 months.[8] However, they also found that 21% of patients reported only mild improvement after surgery. Moreover, these surgeries concern

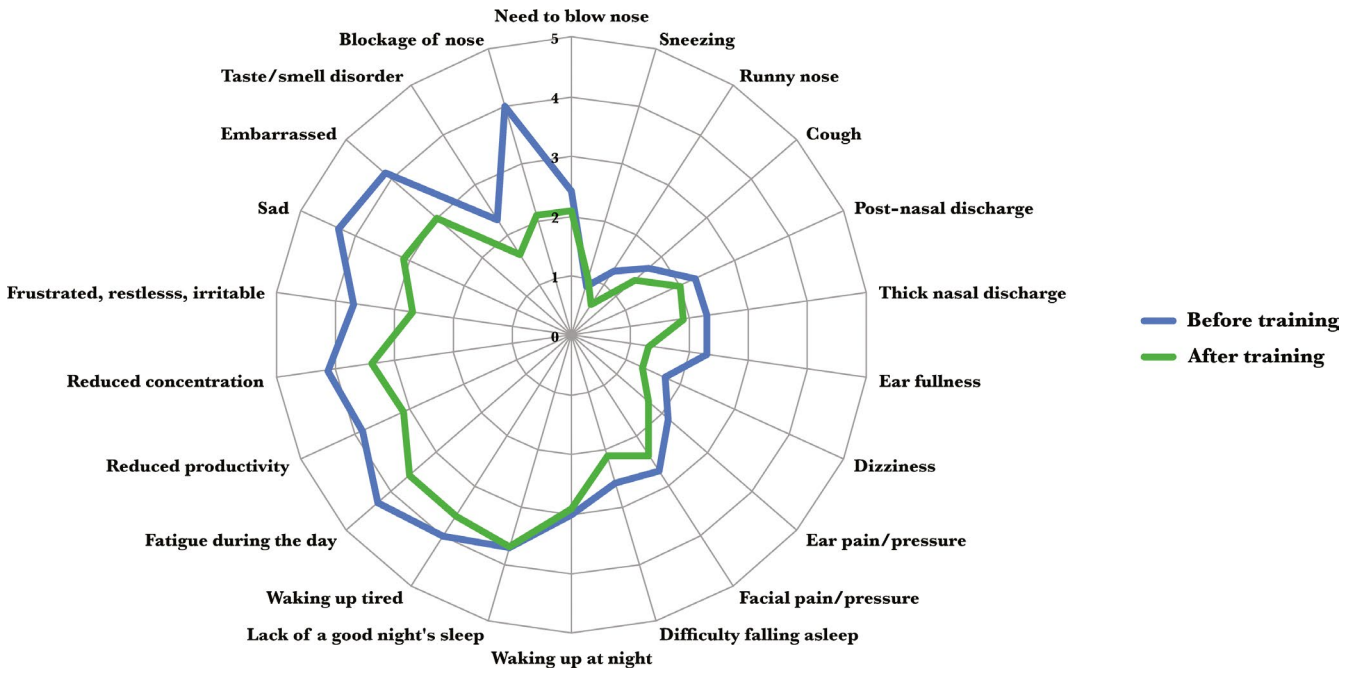

FIGURE 2 Radar plot showing each SNOT-22 item score (min = 0, max = 5) before and after trigeminal training (n = 7)

patients with resected turbinates and do not account for ENS patients who still have turbinates. The inhaled airflow volume, resistance and distribution can be modified and improved by reshaping nasal anatomy but if the sensing mechanism is disrupted, the information of adequate airflow will not be transmitted to the brain. To date, no studies have explored the neurosensory aspect of ENS in order to improve patient outcomes.

The main result of this study is the significant reduction of the NOSE score after a mean of 41 days of three-times daily trigeminal training by levomenthol and eucalyptol. The SNOT-22 score, of which nasal obstruction is just one of 22 items, aims to assess quality of life in sinonasal diseases. The observed decrease in this study suggests that intranasal trigeminal stimulation could indirectly alleviate the burden on the quality of life of ENS patients, especially nasal obstruction, sleep disturbances and emotional status. As for ENS6Q score, the absence of difference suggests that the severity of ENS symptoms does not depend solely on nasal obstruction. Indeed, some items, as nasal crusting and nasal dryness, are presumably more linked to disrupted intranasal climate than trigeminal sensing, although in this study crusting is unlikely to have played a major role as it was minimal on endoscopy. Interestingly, two out of seven patients had a sharp decrease in their ENS6Q score (8 and 12 points) beyond the minimal clinically important difference value set at 7 point as calculated by Thamboo et al.[9]

Trigeminal lateralisation and rhinomanometry results from our 14 ENS patients were consistent with the study of Konstantinidis et al.[6] These authors showed that trigeminal function was significantly reduced in ENS patients (scoring at 10.9/20) compared to patients with inferior turbinectomy without ENS (14.9/20) and to unoperated controls (17.2/20), whereas intranasal resistance was similar across all three groups. Rhinomanometry resistance results in this study were also within normal limits for healthy individuals.[10] Although lower values might have been expected, considering that some ENS patients had no more inferior turbinates, this is not observed. These findings reinforce the idea that rhinomanometry poorly correlates with perceived nasal patency and is not recommended as a diagnostic tool for ENS patients.

One limitation of our study was the high number of patients who did not duly complete the trigeminal training. Reasons of training cessation via phone follow-up included lack of immediate symptom improvement and fear of nasal mucosa irritation in the long term. However, selection bias was partially reduced by observing no difference between the group who finished training and those participants who did not. Another limitation was compliance to the training. Although it was reported by participants as ranging between 50% and 75%, it is ultimately unknown. Finally, long-term effects of trigeminal training are unknown and are likely to dwindle. However, the same could be said about surgical filling for which there is no evidence of longlasting effect.[8] Trigeminal training could offer a cheap, non-invasive, simple, outpatient treatment modality before considering surgery and general anaesthesia. Moreover, the maintenance of an effect can be envisaged not necessarily through a strict training regime but by ad hoc courses of inhalation, dependent on patient symptoms. Some of our ENS patients manifested their wish to pursue inhalations on a regular basis.

For future studies, authors recommend adding control groups by comparing ENS patients with healthy individuals and patients with total inferior turbinectomy but no ENS symptoms. Furthermore, larger cohorts of ENS patients will allow clustering them into radical and conservative turbinate surgery groups to

assess whether the effects of trigeminal stimulation is proportional to turbinate resection. Finally, our study focused solely on subjective symptom improvement rather than objective score changes. Further studies may benefit from a post-training assessment with trigeminal lateralisation test and rhinomanometry to assess whether subjective symptom improvement correlates with objective score changes.

5 | CONCLUSION

To our knowledge, this is the first study to explore a neurostimulating approach to ENS management. Our results suggest that an intranasal trigeminal training for at least 30 days improved self-rated evaluation on nasal patency (NOSE) and, to a lesser extent, general quality of life (SNOT-22) in ENS patients. These pilot results prompt a focus on the neurosensitive aspect of ENS and supports further research towards this novel method of treating these patients.

CONFLICT OF INTEREST

All authors declare that they do not have conflict of interest in relation to this work.

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