Trigeminal endonasal perception – an outcome predictor for septoplasty*

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Abstract

Background: No adequate test exists to predict outcome after septoplasty. Despite adequate surgery, patients still might experience nasal breathing impairment. The aim of this study was to determine if pre-operative trigeminal sensitivity can predict satisfaction after septoplasty.

Methods: Single centre prospective cohort study in tertiary referral centre with follow-up time of 6 weeks postoperatively. Patients scheduled for septoplasty or septorhinoplasty with turbinoplasty were consecutively selected the day before surgery. Standard preoperative examinations (acoustic rhinometry and Sniffin' Sticks 12 test), the evaluation of nasal obstruction on a visual analogue scale (VAS) and the trigeminal lateralisation task were performed before and 6 weeks after surgery. Biopsies were taken during surgery and TRPV1 mRNA expression was measured by PCR.

Results: Thirty patients were included with a median age of 29 years and equal gender distribution. Trigeminal perception and sensation of nasal obstruction showed a significant correlation: preoperative lateralisation test scores, representing endonasal trigeminal sensitivity, correlated significantly with the mean VAS change scores, which demonstrate subjective improvement. A lateralisation test score of 31.5 and more had a sensitivity of 88% to predict an improvement of more than 3 VAS points. Additionally, high TRPV1 mRNA expression was linked with good postoperative VAS scores.

Conclusion: The preoperative evaluation of the trigeminal sensitivity could improve patients' selection for septoplasty with a higher rate of satisfaction. Endonasal trigeminal sensitivity is directly linked with subjective outcome. Therefore, patients with low trigeminal sensitivity should undergo septoplasty only after thorough counselling.

Key words: trigeminal, sensitivity, septoplasty, outcome

Introduction

Nasal obstruction due to a deviated septum is a common problem in rhinology. To improve nasal airflow, septoplasty with or without turbinoplasty is frequently carried out. In a great part of the patients a significant improvement in nasal symptoms [(1)] and quality of life [(2)] can be achieved. Still, a relevant number of patients report ongoing subjective nasal obstruction although objectively showing free anatomical passage [(3-5)]. This mismatch between objective and subjective outcome indicates the importance of sensory perception in nasal obstruction. Different studies already concluded a meaningful role of trigeminal sensitivity for the perception of nasal airflow and the sensation of a "patent nose" [(6-8)]. Without altering nasal inner space a subjective relief of nasal congestion was provided with menthol

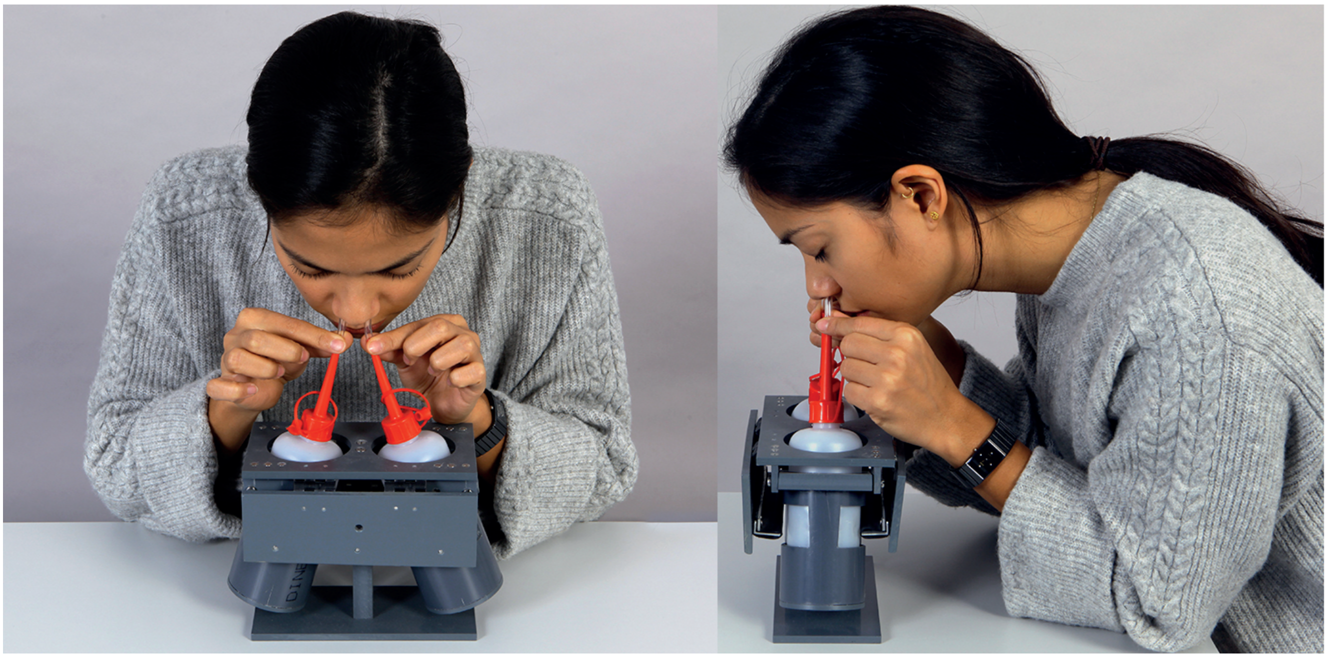

Figure 1. Trigeminal sensitivity detection device.

by triggering trigeminal nerves and cold receptors [9]. Still, the exact correlation between nasal resistance to airflow and nasal sensation of airflow, is not completely understood yet. But since the important role of trigeminal sensitivity in nasal function is well-known [10], its impairment could contribute to the persisting sensation of nasal obstruction after septoplasty. Therefore, the aim of this study was to examine whether trigeminal sensitivity can be used to predict patients' satisfaction after septoplasty.
A clinical tool that correlates well with the subjective nasal congestion could result in less inconsistent outcomes and better selection of patients [11].

Material and methods

All patients planned for primary septoplasty or functional septorhinoplasty with turbinoplasty were asked to participate in this prospective study. The indication for surgery was given by the complaints of a patient that matched the clinician's observation upon anterior rhinoscopy and nasal endoscopy. Standard preoperative examinations of our institution including acoustic rhinometry and Sniffin' Sticks 12 test were performed. Additionally, participants were asked to evaluate the extent of nasal obstruction on a visual analogue scale (VAS) from 0-10 (0 no nasal obstruction; 10 complete obstruction) and for each side of the nose separately. Trigeminal sensitivity was then assessed by the lateralisation task. Therefore, abstinence from smoking, eating or drinking anything other than water for at least one hour prior to testing was requested.
All measurements were performed twice, before and 6 weeks after surgery. Exclusion criteria were neurological conditions that could impair endonasal trigeminal sensitivity.

Lateralisation test

The patient's task was to lateralize trigeminal stimuli presented randomly to either the left or right nostril.
This was assessed by using a previously described method as shown in Figure 1 [12, 13]. The device was built of 2 removable squeeze bottles with a total volume of 250ml. One bottle contained 30ml of odorous eucalyptol as an activator of the trigeminal system, while the other bottle was filled with 30ml of odour-less propylene glycol [14]. Each bottle was prepared with a spout directing the smell separately to each nostril. Blindfolded participants held onto the spouts to prevent movements that might cause mechanical activation of the trigeminal nerve and therefore any interference with odour lateralisation abilities.
Forty stimuli were randomly applied to the nostrils at an interstimulus interval of approximately 30s. After each stimulus patients had to identify the nostril to which eucalyptol was presented.

Surgical procedure

Standard septoplasties or septorhinoplasties both in open and closed technique were performed by different surgeons with the primary aim to restore function by straightening the nasal septum on its entire length. Any technique of resection, replacement and scoring of cartilage was allowed. In those patients where rhinoplasty was performed at the same time, again no restrictions were applied. All patients underwent mucosal sparing inferior turbinate surgery with removal of the anterior parts of the turbinate bone and laterofracture. A small biopsy from the inferior turbinate was taken for PCR analyses.
All patients received overnight non-adhering nasal packing and were regularly seen one week postop, followed by an individual

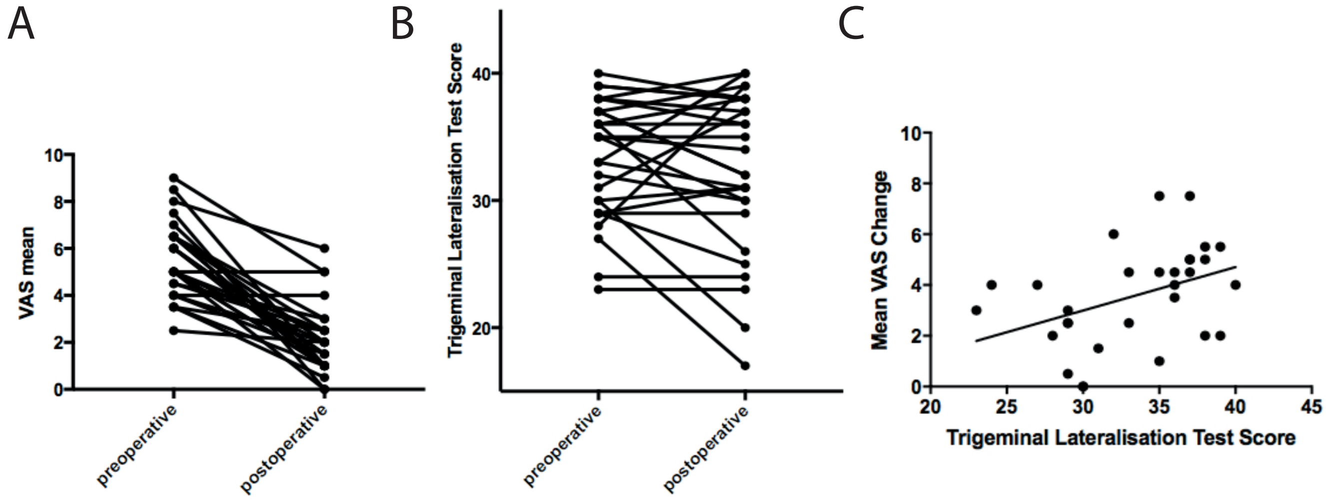

Figure 2. a) Comparison of mean VAS pre and postoperatively (Paired t-test, n=30). b) Comparison of pre and postoperative lateralisation test scores (Paired t-test, n=30). c) Linear regression analysis of trigeminal sensitivity and mean VAS change: A clear linear correlation is ob-served (Linear regression: n=30, p=0.03, r=0.40).

treatment algorithm.

PCR

Inferior turbinate biopsied from the first 20 subjects were stored in RNAlater (Quiagen, Hilden, Germany) frozen until RNA extraction. Biopsies were then shredded with beads (Precellys, LabForce, Switzerland) and mRNA was extracted using the RNeasy mini kit (Qiagen), according to the manufacturer's instructions. Reverse transcription was done with the use of reverse transcription reagents containing random hexamers (Fermentas). A taqMan®-PCR (Applied Biosystems, USA) based system was used for TRPV1, TRPM8 and TRPA1 mRNA. Beta-actin was chosen as the housekeeping gene. PCR quantification was performed on an ABI PRISM 7000 Sequence Detection System (Applied Biosystems) and interpreted using the 2-δδCT formula as described previous works.

Statistical analysis

Graph Pad Prism and SPSS was used for statistical analyses. Initially, lateralisation test results and mean VAS were compared pre and postoperatively (two-tailed paired t-test). Further, correlations between preoperative lateralisation test results and mean VAS changes were examined using a linear regression test. The groups were arbitrarily divided in benefit (mean VAS difference > 3) and non-benefit (mean VAS difference =< 3). Validity and cut off value of the lateralisation test were then assessed by using ROC in SPSS. At the end, two groups identified by the ROC curve were formed to compare significant differences among each other (two tailed t-tests).

Results

A total of 39 patients participated in the study out of which 30 were included with full follow-up. The median age at the time of treatment was 29 and gender distribution was equal. Thirteen patients underwent septoplasty with turbinoplasty, while 17 patients (57%) received additional rhinoplasty. Reasons for exclusion were non-compliance and change of operative procedure to other than septo-/rhinoplasty i.e. sinus surgery (Table 1).
Table 1 summarises the demographics and all mean test results before and after surgery. Generally, a significant improvement of subjective and objective nasal obstruction was achieved after septoplasty in terms of mean VAS score ($p < 0.001$) (Figure 2a) and cross sectional area measurements in acoustic rhinometry (MCA1 $p < 0.01$). However, comparing clinical examinations before and after surgery, subjective outcome did not correlate well with objective clinical findings. Correlations of cross sectional area measurements (MCA1) and mean VAS scores did not show significant results (p=0.77). However, correlation analysis of trigeminal perception and sensation of nasal obstruction was significant: preoperative lateralisation test scores, representing endonasal trigeminal sensitivity, correlated significantly with the mean VAS change scores, which demonstrate subjective improvement (r=0.40, p=0.03, Figure 2c). Comparing lateralisation test scores and therefore trigeminal sensitivity before and after surgery, no significant changes emerged (p= 0.27) (Figure 2b). Finally, two groups were formed (benefit vs. non-benefit group). Regarding age, gender, Sniffin' Sticks 12 test results, rhinomanometry, cross sectional area measurements and the distribution of patients receiving rhinoplasty, no significant differences appeared between the groups (Table 1). A ROC analysis (Figure 3) was then performed to evaluate the validity and representative value of the lateralisation test, therefore representing trigeminal sensitivity, as an outcome predictor. Results revealed a fairly good test (AUC=0.747) with a sensitivity of 88% and specificity

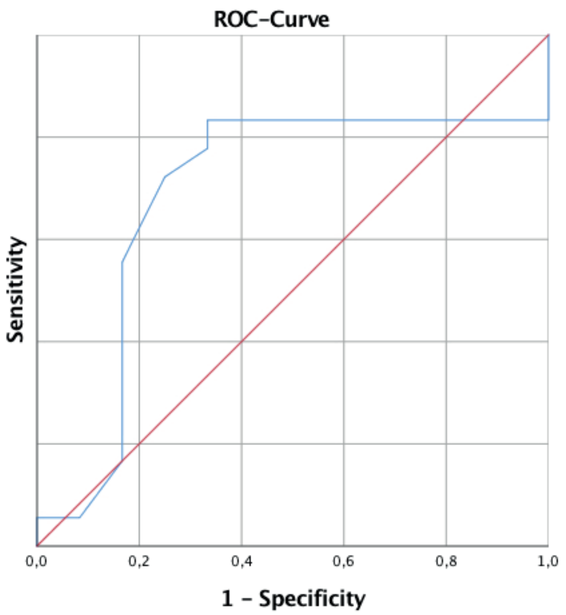

Figure 3. ROC analysis of the lateralisation test: Selecting patients with a score of more than 31.5 upon trigeminal testing will identify 90% of patients with an increase in VAS by 3 or more points.

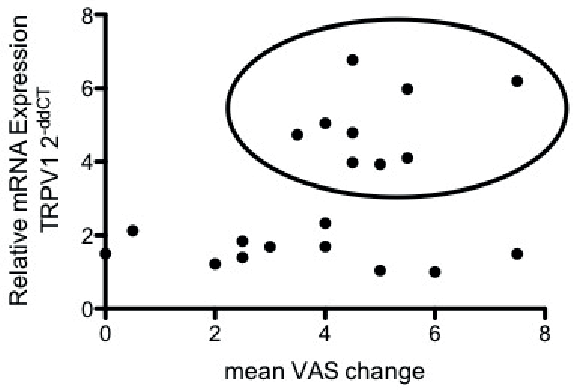

Figure 4. Relative TRPV1 mRNA expression shows no correlation with VAS values. High expression however, is associated with high VAS changes.

of 70% to identify patients who would benefit from septoplasty. A cut off value of 31.5 points in the lateralisation test was identified. The trigeminal sensitivity and deltaVAS were significantly different between the benefit and non-benefit group (p=0.02 for both parameters in t-test).

Semiquantitative PCR showed very low expression for TRPM8 and TRPA1 and therefore these channels could not be used for further analyses. TRPV1 mRNA expression was seen in all samples, however, no correlation between mRNA expression and VAS scores nor with trigeminal testing could be observed. Interestingly, patients with higher expression levels of TRPV1 (>3) uniformly had better outcome in terms of meanVAS change and postoperative mean VAS value (Figure 4). The positive predictive value and specificity here was 100%, while sensitivity accounted to only 64%. Since only 2 patients suffered from rhinitis, no subgroup analyses was performed.

Discussion

Results of the present study indicate that trigeminal endonasal sensitivity can be used as a predictive factor for the subjective outcome of septoplasty. Although clearly not being the only reason for a failed functional improvement, analyses revealed a significant correlation between subjective outcome and endonasal trigeminal sensitivity. Importantly, patients with a low sensitivity to trigeminal stimuli did subjectively benefit less from a septoplasty. Further, trigeminal sensitivity did not show relevant changes in patients before and after surgery confirming previous studies [15-17].

Current diagnosis and treatment of nasal obstruction are still mostly based on patient's subjective opinion as rhinomanometry and acoustic rhinometry do not always correlate well with the sensation of nasal obstruction [3]. This lack of correlation was also observed in our cohort, where postoperative VAS score did not correlate with objective measures. This often results in inconsistent outcomes [6, 18]. Therefore, in order to make a more appropriate selection for nasal surgery, the sensation of nasal obstruction should be evaluated more adequately. As shown in this study, trigeminal sensitivity was directly linked with subjective improvement after surgery. Therefore, the assessment of endonasal trigeminal sensitivity could become a reliable clinical tool for selecting patients for septoplasty preoperatively. However, many and for some part still unknown other factors do influence nasal surgery outcome. Especially in patients with additional rhinoplasty, further attention has to be drawn on patient's satisfaction of the rhinoplasty outcome. Different studies also implied the relevance of gender [1] and age [19, 20]. However, investigating these potentially biasing parameters, we could not detect differences between patients who had a good or poor benefit from surgery (Table 1).

With regard to the trigeminal sensitivity, no relevant differences before and after septoplasty were seen, which were demonstrated in other studies before [15, 16]. A damage to the nerve or sensory epithelium, however, seems conceivable due to strong manipulation of the nasal mucosa during nasal surgeries and therefore cannot be excluded. But rather 6, than the 12 weeks described by Scheibe et al. seem to have been sufficient for trigeminal sensitivity to recover [17]. Nevertheless, the rather short follow-up should be mentioned as shortcoming. Long term results could be different as shown in different previous publications concerning satisfaction after septoplasty. To be able to compare trigeminal recovery and not to skew results by recall

Table 1. Comparison of olfaction among anosmia (A), hyposmia (B) and normosmic control (C).

Demographics	All	(N30)	Benefit	(N17)	Non-benefit	(N13)
Age	29 (SD 9,8)		30 (SD 7,3)		28 (SD 12,2)	
Gender (m:w)	20:10		11:06		09:04	
Additional rhinoplasty	17		8		7	
Objective nasal tests (mean)	**preoperative**	**postoperative**	**preoperative**	**postoperative**	**preoperative**	**postoperative**
Sniffin stick 12	10,2 (SD 2,2)	10,8 (SD 2,1)	9,9 (SD 2,5)	10,6 (SD 2,5)	10,7 (SD 1,5)	11 (SD 1,1)
Trigeminal	33,3 (SD 4,6)	32,4 (SD 6,2)	35.1 (SD 4,1)	33 (SD 6)	31 (SD 4,1)	31,5 (SD 6,2)
Mean VAS	5,4 (SD 1,5)	2 (SD 1,4)	6,5 (SD 1,1)	1,5 (SD 1,2)	4,4 (SD 1,3)	2,7 (SD 1,5)
MCA1 whole nose	0.40 cm^2 (SD 0,1)	0.52 cm^2 (SD 0,2)	0.36 cm^2 (SD 0,1)	0.51 cm^2 (SD 0,2)	0.45 cm^2 (0,1)	0.52 cm^2 (SD 0,1)

bias we chose a rather short postoperative period.

The important role of sensory perception in the sensation of a “patent nose” is well-known [6, 7]. Especially Eccles et al. analysed the positive effect of menthol stimulating trigeminal perception and improving subjective sensation of nasal airflow without altering inner nasal space [7, 21]. “Trigeminal training” may even improve CO2 sensitivity and the feeling of nasal patency, while not having a relevant impact on lateralisation scores [22]. In contrast, altering inner nasal space, as mentioned above, does not always improve subjective sensation of nasal airflow [6, 18]. But we do know that nasal anatomy influences trigeminal sensitivity depending on nasal size cavity [8]. The empty nose syndrome, where the pathogenesis is also no not clearly understood yet, describes perfectly this paradoxical sensation of nasal obstruction. Newer studies indicate that an impairment of trigeminal perception could lead to an empty nose syndrome [23, 24]. Thus, these findings of an important role of trigeminal sensitivity on the perception of nasal patency corroborate very well with the results of our study.

Lateralisation test using menthol for trigeminal sensitivity measurements were already used in previous studies [9, 12, 13]. It is even applicable to test trigeminal function in children [25]. Also, the different topographical distribution of trigeminal receptor in the nasal cavity appear non-relevant as the trigeminal stimuli should spread over the whole inner nasal space [10, 26]. Despite the common limitations of a psychophysical test, we feel that the lateralization task is a robust and easy-to-perform method that correlates well with trigeminal sensitivity. The advantage of performing a blinded test repeatedly 40 times reduces the potential risk of random results and also intraindividual variance.
A clear limitation includes difficulties in reproducing the results when not adhering strictly to the test protocol: we observed that the protocol needs to be followed meticulously with precise maintenance of the interstimulus interval of 30 sec in order to avoid habituation of the odour, which can lead to the impression of poor trigeminal performance. Unpublished results from partnerinstitutions which tried to adopt the method showed that lack of strict adherence to the protocol could result in false test results. Therefore, the test requires accurate performance of the examiner. The test relied strongly on the examiner’s performance. In fact, data from “too fast testing” yielded very low scores suggesting they were obtained by chance. A test relying less on the examiners performance would be the evaluation of CO2 threshold - a relatively pure trigeminal stimulus - [27] using an olfactometer to present CO_2 under controlled conditions [28, 29]. However, this complex and time-consuming method seems hardly realisable in a clinic setting and therefore does not present a practicable alternative. An evolution of the lateralisation test into a clinically useful tool would be desirable.

As for the correlation analyses the decision fell on VAS as it is a common parameter to evaluate subjective sensation of nasal obstruction. However, only the mean VAS change of pre and postoperative was used, as in our opinion the postoperative VAS alone would not have quantified the change properly.
Another limitation is that the criteria (VAS change > 3), in which the two groups were divided, based only on patient’s opinion and examiner’s presumption. There is not yet a study defining a successful septoplasty outcome on minimum VAS change. Even so, with the quantity of participants the results seemed representative and not by chance as shown by ROC analysis.
The definition of success in our study was based on the VAS change. It is interesting to see that the preoperative VAS scores were different between the benefit and non-benefit groups too. One could argue that the preoperative VAS is a good selection criterion, which would be much easier than measuring trigeminal sensitivity and has been shown earlier [30]. In our study, this statement would be daring, since the definition of success could bias this selection. However, these patients seemed to have a lower lateralisation score potentially explaining biologically the underlying cause.

PCR results revealed rather low expression levels for TRPM8 and TRPA1 mRNA which is in line with other publications [26, 31]. The perception of cold and menthol are mediated through these channels and we had hoped to see correlations to the trigeminal clinical test. Nevertheless, TRPV1 seems also to represent the trigeminal system in these patients as high expression was a perfect predictor for good subjective outcome. Due to its low sensitivity and invasiveness of the test, it unfortunately has a limited role as a screening tool preoperatively.

In the future, preoperative assessment of endonasal trigeminal sensitivity could help to appropriately select patients for septoplasty. In this case, patients with septal deviation and high endonasal trigeminal sensitivity could undergo septal surgery with a high probability of improving nasal breathing ability. However, patients with low trigeminal perception could be informed about their decreased chances of symptom improvement after surgery and need through counselling.

Conclusion

This is the first report to predict septoplasty outcome using sensitivity testing. We suggest implementing preoperative trigeminal function testing into routine assessments as they could help to predict outcome and thus counselling of patients.

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Authorship contribution

S.B. has conducted the study and written the manuscript, S.P. has equally contributed to the study and data collection and has co-authored the manuscript, S.K. has helped with study conduction and performed PCR and reviewed the manuscript, S.K and D.H. have collected data and reviewed the manuscript, A.D performed the PCR, C.A. has supervised PCR, M.S. has planned, designed and supervised the study and written the manuscript.

Conflict of interest

There are no conflicts of interest.

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