

Effects of orthognathic surgery with maxillary impaction plus septoplasty and total turbinectomy on breathing

Efeitos da cirurgia ortognática com impactação maxilar mais septoplastia e turbinectomia total na respiração

Efectos de la cirugía ortognática con impactación maxilar más septoplastia y turbinectomía total sobre la respiración

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Abstract

Complete removal of hypertrophied inferior nasal turbinates may favour the occurrence of the empty nose syndrome (ENS). Some surgeons recommend partial turbinectomy in order to minimize the occurrence of ENS. However, little is known about whether total removal of the inferior nasal turbinate is associated with ENS. The aim of the present study was to evaluate the effects of total turbinectomy and septoplasty on the breathing of individuals undergoing orthognathic surgery with maxillary impaction. A total of 20 individuals participated in this cross-sectional study, in which the relationship between exposure (maxillary orthognathic surgery) and outcome (nasal respiratory function) was investigated. The Empty Nose Syndrome 6-Item questionnaire and Nasal Obstruction Symptom evaluation scale were applied to investigate the ENS. A three-dimensional assessment of the piriform opening was performed pre- and postoperatively by computed tomography in order to measure the volume of the nasal cavities using the Dolphin Imaging software. ENS was detected in 35% of patients, while 13 reported improved breathing. Symptoms of ENS such as dryness, suffocation, nose feels too open and nasal crusting were mentioned. The mean nasal cavity volume was 7477.15 mm³ greater in the initial evaluation ($p < 0.05$). In summary, the occurrence of ENS does not constitute an absolute contraindication of total turbinectomy, a procedure that contributed to the improvement of airway permeability.

Keywords: Computed tomography; Nasal cavity; Nasal obstruction; Orthognathic surgery; Otorhinolaryngology.

Resumo

A remoção completa dos cornetos nasais inferiores hipertrofiados pode favorecer a ocorrência da síndrome do nariz vazio (SNV). Alguns cirurgiões recomendam a turbinectomia parcial para minimizar a ocorrência da SNV. No entanto, pouco se sabe se a remoção total da concha nasal inferior está associada à SNV. O objetivo do presente estudo foi avaliar

os efeitos da turbinectomia total e da septoplastia na respiração de indivíduos submetidos à cirurgia ortognática com impactação maxilar. Um total de 20 indivíduos participaram deste estudo transversal, no qual a relação entre exposição (cirurgia ortognática maxilar) e desfecho (função respiratória nasal) foi investigada. O questionário *Empty Nose Syndrome 6-Item* e a escala de avaliação *Nasal Obstruction Symptom* foram aplicados para investigar a SNV. A avaliação tridimensional da abertura piriforme foi realizada no pré e pós-operatório por meio de tomografia computadorizada para mensuração do volume das cavidades nasais por meio do software *Dolphin Imaging*. A SNV foi detectada em 35% dos pacientes, enquanto 13 relataram melhora da respiração. Sintomas da SNV como secura, asfixia, nariz muito aberto e crostas nasais foram mencionados. O volume médio da cavidade nasal foi 7.477,15 mm³ maior na avaliação inicial ($p < 0,05$). Em resumo, a ocorrência da SNV não constitui contraindicação absoluta da turbinectomia total, procedimento que contribuiu para a melhora da permeabilidade das vias aéreas.

Palavras-chave: Cavidade nasal; Tomografia computadorizada; Obstrução nasal; Cirurgia ortognática; Otorrinolaringologia.

Resumen

La extirpación completa de los cornetes nasales inferiores hipertrofiados puede favorecer la aparición del síndrome de nariz vacía (SNV). Algunos cirujanos recomiendan la turbinectomía parcial para minimizar la aparición del SNV. Sin embargo, poco se sabe si la extirpación total del cornete inferior está asociada con el SNV. El objetivo del presente estudio fue evaluar los efectos de la turbinectomía total y la septoplastia sobre la respiración de individuos sometidos a cirugía ortognática con impactación maxilar. Un total de 20 individuos participaron en este estudio transversal, en el que se investigó la relación entre la exposición (cirugía ortognática maxilar) y el resultado (función respiratoria nasal). Se aplicó un cuestionario *Empty Nose Syndrome 6-Item* y la escala de calificación *Nasal Obstruction Symptom* para investigar el SNV. La evaluación tridimensional de la apertura piriforme se realizó pre y post-operatoriamente mediante tomografía computarizada para medir el volumen de las fosas nasales mediante el software *Dolphin Imaging*. Los síntomas del SNV fueron detectados en el 35% de los pacientes, mientras que 13 informaron una mejor respiración. Se mencionaron los siguientes síntomas del SNV: sequedad, ahogo, nariz muy abierta y costras nasales. El volumen medio de la cavidad nasal fue 7.477.15 mm³ mayor en la valoración inicial ($p < 0,05$). En resumen, la aparición del SNV no constituye una contraindicación absoluta para la turbinectomía total, procedimiento que contribuyó a mejorar la permeabilidad de la vía aérea.

Palabras clave: Cavidad nasal; Tomografía computarizada; Obstrucción nasal; Cirugía ortognática; Otorrinolaringología.

1. Introduction

The care of patients with facial deformities requires attention in order to improve upper airway obstruction, facial shape, and malocclusion. With the proper planning of orthognathic surgery treatment, the maxillofacial surgeon can contribute to the patient's quality of life, especially in the presence of respiratory and sinus difficulties that coexist with facial deformities (Posnick; Kinard, 2019). Nasal septoplasty plays a role in the surgical correction of septal thickening and deflections and generally improves nasal airflow and sinus drainage (Kridel; Delaney, 2019). In addition, the enlarged lower turbinate also obstructs nasal breathing and interferes with drainage of the maxillary sinus (van Egmond *et al*, 2019).

Empty nose syndrome (ENS) has been associated with a reduction in the size of the nasal turbinate and has been long diagnosed in an empirical manner (Gandomi; Bayat; Kazemei, 2010). The incidence of this condition is unknown, since validated diagnostic criteria are sparse and therefore difficult to measure (Talmadge *et al*, 2019). When the turbinate is excessively reduced during sinus surgery, there is evidence that its function can be altered (Manji *et al*, 2019). However, the prevention of ENS, avoiding excessive reduction of the nasal turbinate, is still not a consensus (Gill *et al*, 2019). The Empty Nose Syndrome 6-Item questionnaire (ENS6Q) is a tool for the diagnosis of this condition (Velasquez *et al*, 2017). Moreover, using the Nasal Obstruction Symptom Evaluation (NOSE) scale, it is also possible to investigate nasal obstruction and airway permeability (Stewart *et al*, 2004).

With the advancement of imaging technology, three-dimensional (3D) virtual planning has consolidated itself as an auxiliary device that provides accurate surgical results, allowing new possibilities for the treatment of facial deformities. The software predicts the repercussions of surgical movements on adjacent soft tissues (Tonin *et al*, 2020). However, a high failure rate has been reported for surgical procedures performed in order to correct nasal obstruction due to the lack of objective and reliable clinical parameters that would assist the surgeon during preoperative planning (Burgos *et al*, 2018).

It has been hypothesized that complete removal of the hypertrophied inferior nasal turbinates favours the occurrence of ENS. Some surgeons, particularly otolaryngologists, advocate that partial turbinectomy should be performed in order to minimize the occurrence of ENS (Sozansky; Houser, 2015). Therefore, the present study was undertaken in order to investigate whether total removal of the inferior nasal turbinate is associated with ENS. We analysed the effects of total turbinectomy and septoplasty on the breathing of patients undergoing maxillary impaction. Airway permeability and volume were assessed by computed tomography (CT) and the ENS6Q questionnaire and NOSE scale were also applied.

2. Methodology

2.1 Study design, patients and ethical issues

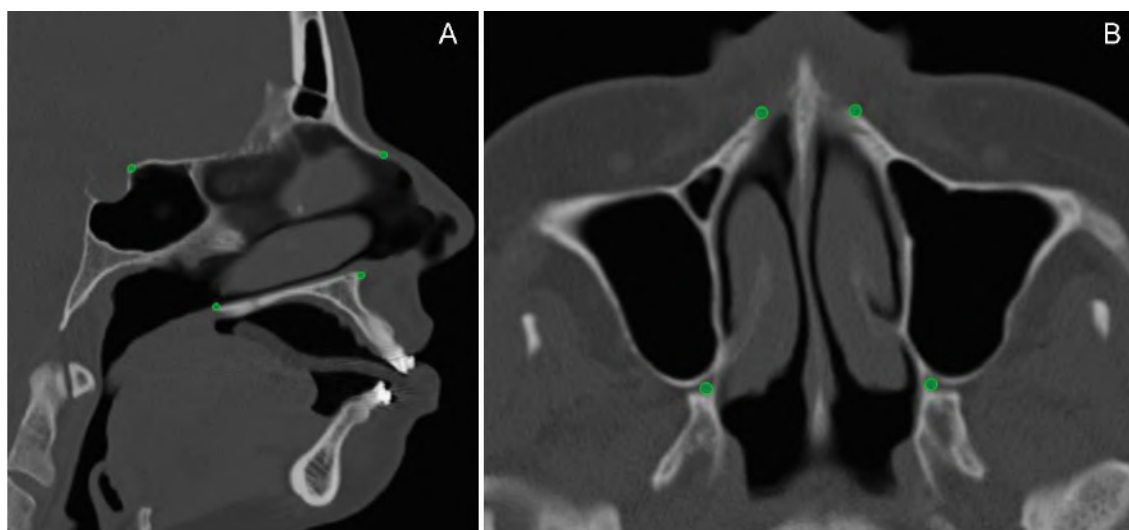
In this cross-sectional study, the exposure (maxillary orthognathic surgery) and outcome (nasal respiratory function) relationship was investigated after a 6-month follow-up in individuals ≥ 18 years old undergoing maxillary impaction following Le Fort I osteotomy. The subjects were selected at two services: the Department of Oral and Maxillofacial Surgery, University of Pernambuco, and the Service of Oral Surgery and Maxillofacial Surgery of a private hospital (Recife, Brazil) between June 2019 and December 2019. Individuals who had previously undergone functional nasal surgery were excluded from the study.

The study was approved by the Ethics Committee of the University of Pernambuco (No. 17712919.8.0000.5207), and all subjects gave written informed consent to participate, in agreement with the Declaration of Helsinki. The study is in accordance with the previously published methodology (Setia, 2016). Also, the reporting of this study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology checklist and statement (Knottnerus; Tugwell, 2008).

2.2 CT assessment and volume analysis

For this study, the nasal cavity area in profile was established as a quadrilateral region between the nasion, anterior nasal spine, posterior nasal spine, and anterior clinoid process (Figure 1A). In the axial view, the nasal cavity area was included between the midpoints of the pyriform opening and the pterygopalatine fossae (Figure 1B).

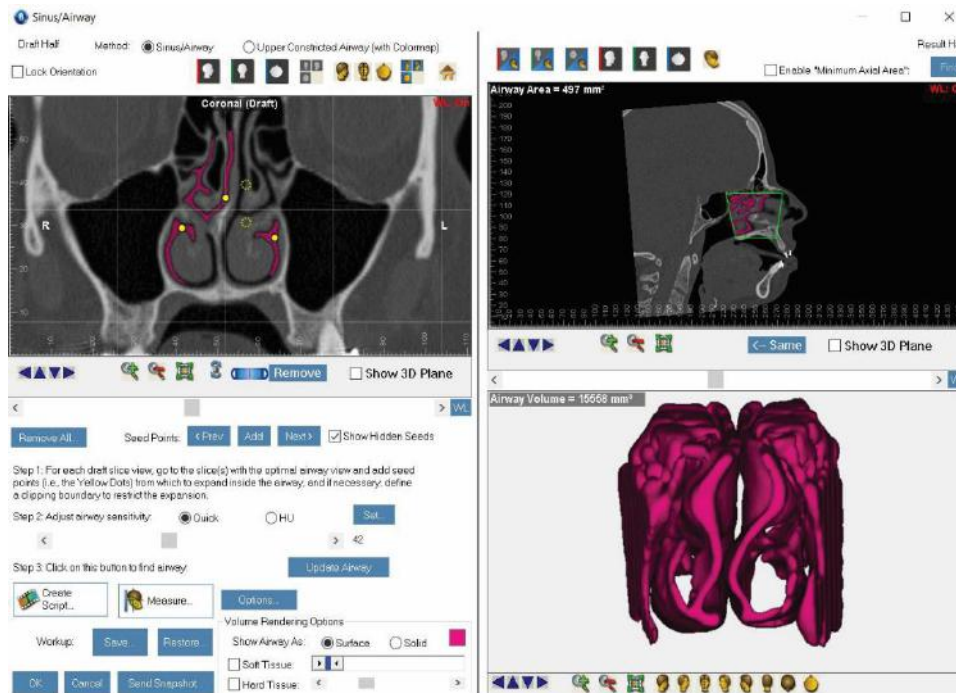
Figure 1. (A) The nasal cavity area in profile was established as a quadrilateral region between the nasion, anterior nasal spine, posterior nasal spine, and anterior clinoid process. (B) Axial view of the nasal cavity area, which was included between the midpoints of the pyriform opening and the pterygopalatine fossae



Source: Authors.

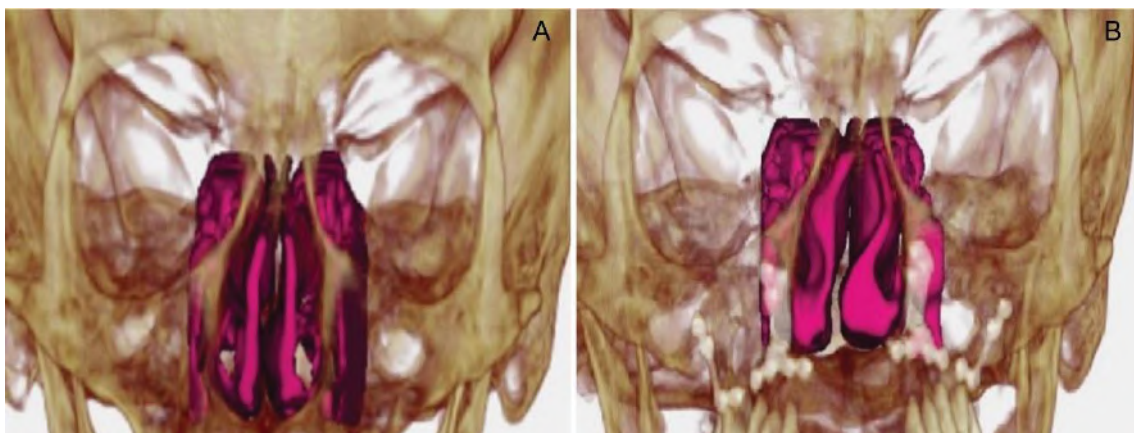
3D assessment of the nasal cavity volume was performed using the Dolphin Imaging software (version 11.95, Canoga Park, CA, USA) (Figure 2). CT of the sinuses was obtained preoperatively, and the initial volume of the nasal cavity was calculated (Figure 3A). Six months after orthognathic surgery with turbinectomy (a reasonable period for the reduction of intranasal oedema), a new CT was performed to calculate the nasal cavity volume and to compare the initial and final volumes (Figure 3B). Clinicodemographic data were collected from all participants.

Figure 2. Three-dimensional assessment of the nasal cavity volume was performed using the Dolphin Imaging software



Source: Authors.

Figure 3. (A) Computed tomography (CT) of the sinuses was obtained preoperatively, when the initial volume of the nasal cavity was measured. (B) Six months after orthognathic surgery with turbinectomy, a new CT was requested for a new calculation of the nasal cavity volume



Source: Authors.

2.3 Surgical procedure

Under general surgery conditions with nasal intubation and after infiltration of local anaesthesia with vasoconstrictor agents (xylocaine and epinephrine, 1:200,000), access to the maxillary vestibule was obtained on both sides with a cautery. The periosteum was raised with a dissector in the region of the anterior wall of the maxillae, pyriform opening and behind the maxillary zygomatic bone. Le Fort I type osteotomy was then performed bilaterally and the cartilaginous nasal septum was separated with a septum chisel. Last, the maxilla was separated from the pterygoid process with the aid of a delicate curved chisel. After the down fracture, a parallel incision was made in each inferior turbinate under direct view. The elevated flaps of the nasal mucosa exposed the enlarged inferior turbinate. The resection of the hypertrophic turbinate was completed with the use of straight mayo scissors. After resection in each inferior turbinate, the nasal mucosa was closed using resorbable sutures.

2.4 ENS6Q assessment

The ENS6Q was used to further evaluate the occurrence of ENS (Velasquez *et al*, 2017). The nasal symptoms perceived by the participants (dryness, sense of diminished nasal airflow, suffocation, nose feels too open, nasal crusting, and nasal burning) were classified according to the severity and frequency of each problem. The scale consists of six statements that assess how the respondent generally feels, including “no problem/not applicable”, “very mild”, “mild”, “moderate”, “severe”, and “extremely severe”. When the patient answered “no problem/not applicable”, “very mild” and “mild”, we considered ENS to be absent, whereas when they answered “moderate”, “severe” and “extremely severe”, we considered ENS to be present.

2.5 NOSE scale evaluation

The NOSE scale was applied to evaluate patients with nasal obstruction based on the following conditions: nasal congestion or stuffiness, nasal blockage or obstruction, trouble breathing through the nose, trouble sleeping, and unable to get air through the nose during exercise (Stewart *et al*, 2004). The scale consists of five statements that assess how the respondent generally feels, including “not a problem”, “very mild problem”, “moderate problem”, “fairly bad problem”, and “severe problem”. When the patient answered “not a problem” or “very mild problem”, we considered ENS to be absent, whereas when the patients answered “moderate problem”, “fairly bad problem” or “severe problem”, we considered ENS to be present.

2.6 Data analysis

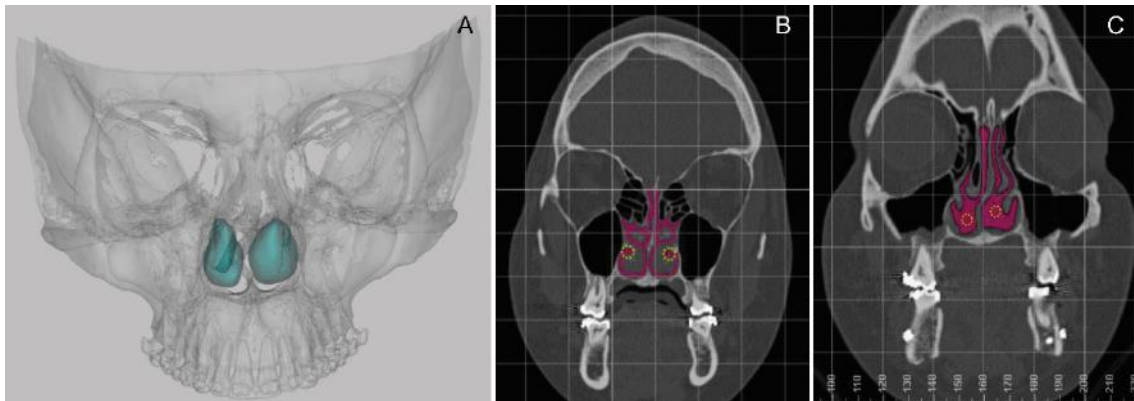
Data were analysed using the Statistical Package for the Social Sciences (SPSS, SPSS Inc., version 23.0, Armonk, USA). A descriptive analysis was performed using the absolute and relative values of the clinicodemographic data collected. For the numerical variables, the paired t-Student test was employed to compare the assessments and the t-Student test with equal variances or Mann-Whitney test was used to compare two categorical variables. Pearson’s or Spearman’s correlation coefficient and the t-Student test specific for the null correlation hypothesis were applied to assess the grade of the relationship between two numerical variables. Normality was determined by the Shapiro-Wilk test and the equality of variances by the Levene’s test. For all analyses, the level of significance was set at <0.05.

3. Results

Twenty patients were included in the study. Women were more affected (n=16; 80%) than men (n=4; 20%). Patient age ranged from 18 to 44 years, with a mean age of 30.3 ± 6.9 years. The individuals were diagnosed as having class II (50%) and III (50%) deformities. All patients underwent total turbinectomy, 70.0% of them with counter-clockwise rotation and 30.0% with clockwise rotation (Figure 4A).

The mean and median values were correspondingly higher for the final occlusal plane (FOP) than for the initial occlusal plane (IOP), while they were higher for the posterior nasal spine (PNS) than for the anterior nasal spine (ANS). The mean and median volumes were correspondingly higher in the initial than in the final evaluation (Figure 4B and 4C). The mean volume value was 0.19 greater in the FOP than in the IOP. The mean volume was 7477.15 mm³ greater in the initial evaluation and the PNS was 0.72 higher than ANS; however, there was a significant difference in volume between evaluations ($p < 0.001$) (Table 1).

Figure 4. (A) Three-dimensional reconstruction of hypertrophy of the inferior nasal turbinates before turbinectomy was performed. (B) Initial volume - area without a preoperative obstacle. (C) Final volume - area with no obstacle after surgery.



Source: Authors.

Table 1. Computed tomography features and volume results before and after orthognathic surgery with turbinectomy

Variable	Mean \pm SD	Median (P25; P75)
IOP	8.28 \pm 5.87	6.75 (3.68; 14.46)
FOP	8.47 \pm 1.56	8.36 (8.13; 9.14)
Difference (FOP - IOP)	0.19 \pm 6.40	1.09 (-6.22; 4.96)
<i>p</i> value*	0.897	
Initial volume	22894.20 \pm 3321.69	22598.00 (21448.00; 25269.75)
Final volume	15417.05 \pm 3019.22	15129.00 (12373.75; 17784.75)
Difference (initial and final volume)	7477.15 \pm 3397.61	8680.00 (4043.50; 10698.75)
<i>p</i> value*	<0.001	
ANS	3.89 \pm 2.65	3.74 (1.31; 5.26)

PNS	4.62 ± 3.15	5.50 (1.33; 7.30)
Difference (PNS - ANS)	0.72 ± 4.87	-0,01 (-3.67; 5.29)
p value*	0.514	

*Paired t-Student test. ANS, anterior nasal spine; FOP, final occlusal plane; IOP, initial occlusal plane; PNS, posterior nasal spine. Source: Authors.

Except for initial volume, final volume and difference between the volume evaluations, the other variables differed significantly between the two types of rotation ($p < 0.05$). The mean and median IOP and ANS were correspondingly higher for counter-clockwise rotation. Furthermore, the mean and median FOP and PNS were correspondingly higher for clockwise rotation. The mean FOP and IOP difference was positive for clockwise rotation and negative for counter-clockwise rotation. Similarly, the mean PNS-ANS difference was positive for clockwise rotation and negative for counter-clockwise rotation (Table 2).

Table 2. Analysis of numerical variables according to rotation type

Variable	Rotation type		p value
	Clockwise rotation	Counter-clockwise rotation	
	Mean ± SD Median (P25; P75)	Mean ± SD Median (P25; P75)	
IOP¹	2.45 ± 2.27 1.54 (0.71; 4.45)	10.78 ± 5.09 10.38 (6.08; 14.97)	0.001
FOP²	9.69 ± 1.62 9.48 (8.49; 11.27)	7.94 ± 1.25 8.17 (8.10; 8.45)	0.015
Difference between FOP and IOP¹	7.25 ± 2.16 7.55 (4.96; 8.97)	-2.84 ± 5.03 -2,37 (-7.20; 2.28)	0.001
Initial volume¹	22525.67 ± 1332.75 21991.50 (21502.00; 23757.75)	23052.14 ± 3918.33 23040.50 (20633.75; 25940.25)	0.755
Final volume¹	15080.67 ± 3219.57 14925.50 (11960.25; 17981.50)	15561.21 ± 3043.27 15129.00 (12805.00; 17902.25)	0.754
Difference between initial volume and final volume¹	7445.00 ± 3624.24 9140.00 (3466.50; 10000.00)	7490.93 ± 3437.88 7843.50 (4071.00; 10777.25)	0.979
ANS¹	1.72 ± 1.60 1.24 (0.41; 3.22)	4.83 ± 2.49 4.99 (3.10; 7.37)	0.012
PNS²	7.07 ± 3.17 8.16 (5.18; 9.07)	3.57 ± 2.58 2.21 (1.25; 5.96)	0.041
Difference between PNS and ANS¹	5.35 ± 3.93 5.90 (3.01; 8.60)	-1.26 ± 3.83 -1.67 (-3.91; 2.48)	0.002

¹t-Student test with equal variances. ²Mann-Whitney test. ANS, anterior nasal spine; FOP, final occlusal plane; IOP, initial occlusal plane; PNS, posterior nasal spine. Source: Authors

The results of the ENS6Q and NOSE questionnaires are shown in Table 3. Symptoms of ENS such as dryness, suffocation, nose feels too open and nasal crusting were mentioned by one (15%) patient. Regarding the NOSE scale, symptoms such as nasal congestion or stuffiness, nasal blockage or obstruction, trouble breathing through the nose, trouble sleeping, and

unable to get air through the nose during exercise items were reported by four (20%) patients each. Thus, ENS was present in three patients, corresponding to 35.0% of all patients.

Table 3. Assessment by the Empty Nose Syndrome 6-Item questionnaire (ENS6Q) and Nasal Obstruction Symptom Evaluation (NOSE) scale

Variable	n (%)
ENS6Q	
Dryness	
No	19 (95)
Yes	1 (5)
Sense of diminished nasal airflow	
No	20 (100)
Yes	-
Suffocation	
No	19 (95)
Yes	1 (5)
Nose feels too open	
No	19 (95)
Yes	1 (5)
Nasal crusting	
No	19 (95)
Yes	1 (5)
Nasal burning	
No	20 (100)
Yes	-
Empty nose syndrome diagnosis	
No	17 (85)
Yes	3 (15)
NOSE scale	
Nasal congestion or stuffiness	
No	16 (80)
Yes	4 (20)
Nasal blockage or obstruction	
No	16 (80)
Yes	4 (20)
Trouble breathing through the nose	
No	16 (80)
Yes	4 (20)
Trouble sleeping	
No	16 (80)
Yes	4 (20)

Unable to get air through the nose during exercise

No	16 (80)
Yes	4 (20)

Empty nose syndrome diagnosis

No	13 (65)
Yes	7 (35)

Source: Authors.

4. Discussion

Correction of defects in airway obstruction and deformity is possible with the use of Le Fort I osteotomy, which is commonly employed in orthognathic surgery to correct vertical excess of the maxilla, due to favourable access to the nasal septum, lower concha, pyriform openings, and nasal floor (Posnick; Agnihotri, 2010). This was confirmed in the present study since this type of osteotomy was performed in all patients in order to correct the maxillary defect. Also, a direct view of the lower nasal turbinates permitted the execution of total turbinectomy and septoplasty, contributing to improved patient breathing in 13 of the 20 patients investigated. Thus, it can be seen that total turbinectomy and septoplasty are effective in improving nasal permeability in individuals who present respiratory complaints and who undergo maxillary suspension.

ENS is a rare complication of surgical removal of hypertrophy of the lower nasal turbinates. The pathophysiology remains unknown, but possibly involves a disorder caused by excessive nasal permeability, affecting neurosensitive receptors and the functions of humidification and conditioning of inhaled air (Scheithauer, 2010). The most common symptoms of ENS are excessive formation of nasal crusting, “paradoxical” nasal obstruction, and odour of the nasal cavity (Coste; Dessi; Serrano, 2012). In addition, other features may include facial pain, headache, dryness of the mucosa, dyspnoea, epistaxis, sleep disorders, and occasional mucopurulent rhinorrhoea (Coste; Dessi; Serrano, 2012). The feeling of “not getting enough air” is not relieved by mouth breathing and often has a negative impact on psychological well-being, which manifests as anxiety, depression, anger, frustration, irritability, and fatigue (Hong; Jang, 2016). Herein, each of the symptoms of ENS such as dryness, suffocation, nose feeling too open and nasal crusting was mentioned by only one patient. Notably, a study reported that patients with ENS have a warmer and drier nasal mucosa since these anatomical changes alter the local temperature and humidity of the nasal cavity, effectively preventing the nasal mucosa from functioning physiologically (Scheithauer, 2010). In our study, only one individual reported nasal dryness.

Although not all patients who receive turbinectomy develop ENS, individuals who have a relatively preserved part of the turbinate may develop this condition. In this context, there is a difficulty in diagnosing individuals based only on the degree of turbinate reduction. The diagnosis is made according to surgical history and the relevant symptoms (Houser, 2007). In the current study, we used the ENS6Q and NOSE scale as diagnostic aids for individuals with ENS, which permitted us to make the most reliable diagnosis (Stewart *et al*, 2004; Velasquez *et al*, 2017). Furthermore, we estimated the nasal cavity volume by CT prior to and six months after surgery, with significant differences being observed between evaluations. When impacting the maxilla, the volume of the nasal fossa did not increase, even when total turbinectomy was performed. The volume was definitely reduced because the removal of hypertrophy of the lower nasal turbinates associated with maxillary impaction caused a reduction of the volume of the nasal cavity. In this respect, there is no way to prove for sure that the improvement in breathing was due to the turbinectomy. Nevertheless, by performing maxillary impaction in individuals with hypertrophy of the lower nasal turbinates who present respiratory complaints without performing turbinectomy, there could be a degree of worsening in patient breathing. This finding is in line with the study by Posnick and Kinard (2019), who reported that patients with pre-existing nasal obstruction

who undergo orthognathic surgery should also be submitted to turbinectomy as an adjunct to orthognathic surgery for a better quality of life. In contrast, the presence of hypertrophied inferior turbinates in reduced pyriform openings complicates the passage of air and hinders respiratory function (Posnick; Fantuzzo; Troost, 2007). The surgical techniques used to reduce the soft tissue of the turbinates have been reported to cause proven improvement in nasal obstruction, but may induce mucosal necrosis, crusting and bleeding (Roithmann, 2018). In the present study, only one patient had nasal crusting after the surgery.

Functional abnormalities that affect nasal breathing (i.e., deviated septum, nasal constriction and enlarged lower nasal concha) have been documented in individuals with maxillary deformities (Bezerra *et al*, 2011). This was also observed in our study, in which patients with maxillary defects had some degree of difficulty in breathing. In addition, the NOSE scale may be used to assess the improvement of breathing in individuals who undergo surgical procedures, including septoplasty and nasal valve surgery combined with maxillary surgery (Kahveci *et al*, 2012). In the present study, this scale was used to assess airway permeability in individuals who underwent maxillary orthognathic surgery combined with removal of the lower nasal turbinates. Assessment of the respiratory quality of these individuals confirmed that maxillary surgery produces beneficial effects on nasal airway function (Erbe *et al*, 2001; Payne, 2009; Williams *et al*, 2013).

The upper repositioning, known as maxillary impaction, is described as a suspension manoeuvre that may be associated or not with removal of a bone fragment of the maxilla, and that is later completed by internal fixation with the patient in occlusion. Its main indications are for individuals with vertical excess of the maxilla (Posnick; Agnihotri, 2010; Posnick; Fantuzzo, 2007; Posnick; Kinard, 2019). In our study, all patients underwent maxillary impaction movement with rotation of the occlusal plane in a clockwise or counter-clockwise direction. There were significant differences between the two types of rotation, showing that the switch in the occlusal plane interferes considerably with the final position of the anterior and posterior nasal spine due to the type of rotation. Nonetheless, prospective studies with robust samples should be performed to confirm our results.

5. Conclusion

In summary, total turbinectomy of the inferior nasal turbinate with septoplasty contributes to improved breathing. The occurrence of ENS does not constitute an absolute contraindication of total turbinectomy. The volume of the nasal cavity was smaller after the surgical procedure. Certainly, surgery for the removal of hypertrophy of the lower nasal turbinates contributed to airway permeability in these patients, but this issue should be investigated in future controlled study.

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