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Electrical Stimulation of the Genioglossus in Patients with Residual Obstructive Sleep Apnea Post-UPPP Surgery

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Abstract

Objective: Genioglossus is a major upper-airway dilator muscle, which leads to upper-airway obstruction when its activity is decreased. We evaluated the effect and safety of genioglossus stimulation for patients with residual mild-to-moderate obstructive sleep apnea (OSA) after uvulopalatopharyngoplasty (UPPP).

Methods: We enrolled 23 patients diagnosed with OSA by polysomnography (PSG) 6 months after UPPP, who underwent nightly transcutaneous genioglossus stimulation (TGS) therapy. Apnea hypopnea index (AHI), microarousal index (MAI), the ratio of duration of SpO2 < 90% to total sleep time (T90) and Epworth sleepiness scale (ESS) before and during TGS treatment were compared. We first observed the overall effect of TGS, and then compared its influence on patients with mild and moderate sleep apnea.

Results: Compared with non-TGS therapy, there was a significant decrease in AHI, MAI, T90, and ESS (9.15 ± 4.21 vs. 17.90 ± 6.85, $p < 0.0001$; 6.33 ± 3.75 vs. 10.93 ± 4.90, $p < 0.0001$; 4.87 ± 4.02 vs. 9.13 ± 4.24, $p < 0.0001$; 8.65 ± 3.35 vs. 9.30 ± 3.10, $p = 0.002$, respectively), and a significant increase in mean SpO2 and minimal SpO2 (mini SpO2) (95.52% ± 0.95% vs. 94.43% ± 1.12%, $p < 0.0001$; 88.74% ± 2.94% vs. 85.17% ± 4.67%, $p < 0.0001$, respectively) during TGS treatment. Patients in the mild and moderate groups had the same variation trend between TGS and non-TGS therapy nights. However, the moderate group had a higher absolute value of changed AHI (AHI; 11.12 ± 3.95 vs. 5.66 ± 1.70, $p < 0.05$) and MAI (MAI; 5.8 (3.3, 8.6) vs. 2.5 (1.05, 5.6), $p < 0.05$) than the mild group. There were no significant differences in absolute changed mean SpO2 (mean SpO2), absolute changed miniSpO2 (miniSpO2), changed T90 (T90) and absolute changed ESS (ESS) between the two groups. Moreover, the percentage of AHI was not different between the two groups (47.89% ± 13.79% vs. 51.04% ± 13.32%, $p = 0.587$). There was no perceived discomfort during TGS therapy and no procedure-related adverse events.

Conclusion: Submental transcutaneous electrical stimulation of the genioglossus led to a significant reduction in AHI and improvement of daytime sleepiness for existing mild-to-moderate OSA patient's post-UPPP surgery.

Keywords: Transcutaneous electrical stimulation; Obstructive sleep apnea syndrome; UPPP

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common health disorder, affecting approximately 4% of men and 2% of women [1]. It is characterized by repeated upper airway collapse due to loss of pharyngeal muscle tone, leading to intermittent oxyhemoglobin desaturations and arousals from sleep. Evidence suggests that intermittent hypoxemia and sleep disruption contribute to sudden cardiac death, stroke, hypertension, and metabolic dysregulation (nonalcoholic fatty liver disease glucose intolerance and hyperlipidemia) [2,3].

Continuous positive airway pressure (CPAP) is the most effective treatment for OSAS; however, many patients are inadequately treated owing to poorly tolerated CPAP. Some patients who were not willing to use or were tolerant to CPAP accepted UPPP, but some of them still had residual disordered breathing postoperatively. Patients were exposed to a significantly increased risk of cardiovascular and metabolic disease with no effective therapy. Thus, further research is required to explore new therapeutic options for these patients.

Electrical stimulation has emerged as a rapidly developing and promising treatment alternative in obstructive sleep apnea (OSA), including hypoglossal nerve stimulation (HGNS) and transcutaneous genioglossus stimulation (TGS). HGNS and TGS have been piloted as treatments for obstructive sleep apnea [4-6] which can protrude the tongue and mitigate airflow obstruction during sleep [7].

Increases in inspiratory airflow can account for observed reductions in sleep apnea severity during HGNS and TGS. To the best of our knowledge, there are no studies on this approach to treat patients with residual OSA post-UPPP.

UPPP can address obstruction at the soft palate but not at the tongue base. We hypothesize that non-invasive method of TGS may improve the level of obstruction at the tongue and lead to improvements in residual OSA post-UPPP.

We aimed to explore the feasibility, efficacy, and safety of TGS for persistent OSA after UPPP.

Materials and Methods

Subjects and outcome measures

Twenty-three patients diagnosed with persistent OSA post-UPPP were recruited between February 2013 and January 2014 at the First Affiliated Hospital with Nanjing Medical University. Inclusion criteria were as follows: (i) age 18–70 years; (ii) 30 > apnea hypopnea index (AHI) > 5 indicated by overnight polysomnography 6 months after UPPP surgery; (iii) without abnormal nasal cavity structure and resistance; (iv) gap after the tongue < 11 cm on computed tomography. Exclusion criteria were as follows: (i) patients with acute illness; (ii) lung disease (e.g. asthma, COPD); (iii) pregnancy or lactating; (iv) history of allergy to the electrode sheet and/or alcohol; (v) patients with rhinitis; (vi) current enrollment in another clinical study that may confound the results of the present study; (vii) structural abnormalities of the airway (e.g. nasal polyps, cancer, significant deflection of the nasal septum).

All patients provided informed consent prior to study participation; the study protocol was approved by and performed according to institutional and ethics policies of the Patient Ethics Committee of The First Affiliated Hospital of Nanjing Medical University.

Overnight polysomnography (PSG) testing was performed the first night to determine the presence and severity of OSA; patients underwent TGS therapy the first night and PSG monitoring the second night. All recording sensors were attached to patients non-invasively. PSG variables were monitored simultaneously and continuously.

Primary outcome measures included nocturnal AHI, microarousal index (MAI), and ratio of duration of SpO2 < 90% to total sleep time (T90). Secondary outcome measures included daytime sleepiness before and after treatment, assessed according to the Epworth sleepiness scale (ESS). Patients were divided into two groups according to AHI (mild and moderate). Comparisons were made to observe the effect of treatment on PSG parameters and daytime ESS between the two groups.

PSG Technique

An evaluation of daytime sleepiness based on the ESS [8] was performed prior to sleep study. All participants underwent a nocturnal, in-laboratory polysomnography (Compumedics E-64, Australia) and were monitored for at least 7h overnight before and during treatment. Sleep was monitored using five electroencephalographic channels (EEG; C4–M1, F4–M1, O2–M1, E2–M2 and E12–M2) and a submental electromyogram. Nasal airflow was measured by continuously recording the nasal pressure, snoring, body position and pulse oximetry, as well as chest and abdominal effort. We used the 2012 standard of the American Academy of Sleep Medicine for scoring sleep apnea events: [9] The apnea/hypopnea index (AHI) is used as a predictor of OSAS severity and graded as "mild" (5–15/h), "moderate" (15–30/h), or "severe" (>30/h) according to AASM guidelines [10].

TGS Technique

The instrument (produced by Yacheng Biological Technology Co. Ltd., Zhengzhou, China) consists of the body of instrument treatment, electrodes, patches, cable, AC power supply and other accessories. Patches were placed over the submental area between the mandible prominentia laryngea (Figure1). The important part of the study was to determine a suitable stimulation frequency and intensity that patients could tolerate. Transcutaneous stimulation of genioglossus was performed for the enrolled patients and a comfortable stimulation level was established. The stimulation intensity when the patients showed response to stimulation and muscle contraction was the basic strength and the stimulation intensity was the maximal tolerable stimulation strength when the patients felt discomfort and unbearable. Stimulation frequency of 30 Hz was titrated to ensure it could achieve an effective muscle contraction.

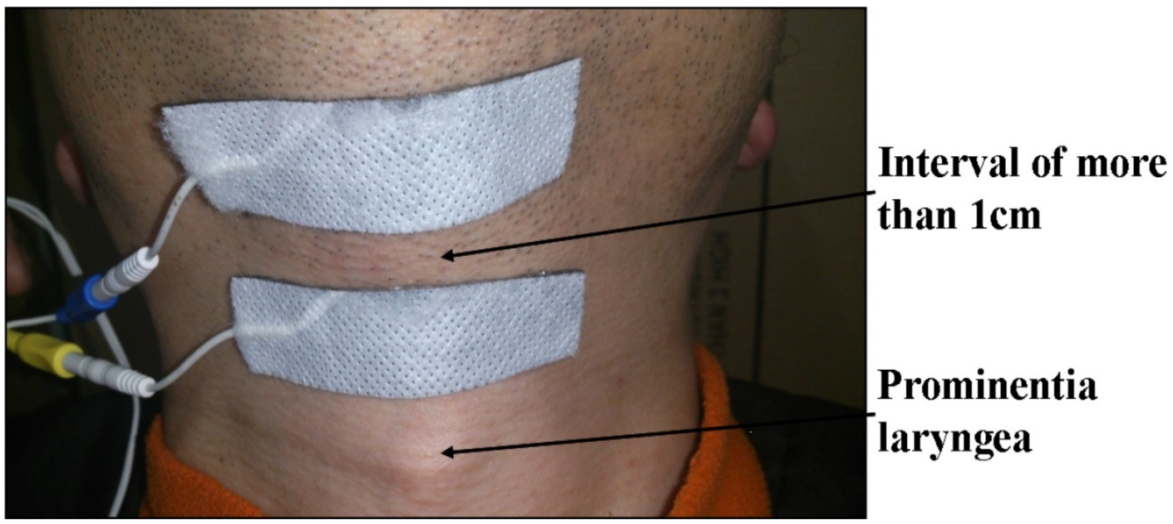

Figure 1: Frontal view of patch placement. One patch was placed below the mandible and the other above the prominentia laryngea, greater than 1 cm from the first patch. Patches were connected with cables to the stimulation device.

Statistical Analysis

Values are presented as the mean ± standard deviation for normally distributed data and as the median (interquartile range) for non-normally distributed data.

A Student's t-test was performed for normally distributed date and the nonparametric test for non-normally distributed data.

SPSS version 16.0 statistical software was used for analysis, with a p-value of less than 0.05 considered statistically significant.

Results

Twenty-three patients (17 males and 6 females) aged 25 to 63 years (mean 50.50 ± 7.78) were analyzed. Compared with non-therapy nights, significant improvements in apnea and hypopnea, oxygen saturation, and sleep fragmentation occurred during and after TGS therapy.

AHI, MAI, T90, and ESS were remarkably reduced and mean SpO2 and minimal SpO2 (miniSpO2) were remarkably increased with stimulation (Table 1).

In the mild group, nocturnal AHI, MAI, T90, and ESS were all significantly reduced, while mean SpO2 and miniSpO2 were all significantly elevated.

The same trends were seen in the moderate group (Table 2).

The absolute change in AHI (AHI) and MAI (MAI) in the moderate group decreased to a greater extent than in the mild group;

However, there were no statistically significant differences in the absolute change in mean SpO2 (meanSpO2), miniSpO2 (miniSpO2), T90 (T90), and ESS (ESS) between the two groups (Table 3).

Moreover, there was no significant difference in the percentage of AHI between groups (Table 4).

Furthermore, OSA events were eliminated while electrical stimulation was delivered (Figure 2).

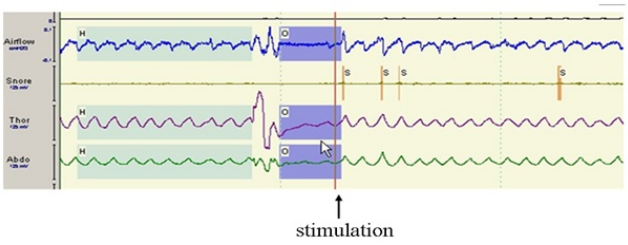

Figure 2: Elimination of OSA events by electrical stimulation.

Variables	Before treatment	After treatment	t	p-value
AHI	17.90 ± 6.85	9.15 ± 4.21	10.1	0
Mean SpO2 (%)	94.43 ± 1.12	95.52 ± 0.95	–4.10	0
MiniSpO2 (%)	85.17 ± 4.67	88.74 ± 2.94	–4.31	0
Basis SpO2 (%)	96.17 ± 0.98	96.48 ± 0.95	–1.16	0.259
MAI	10.93 ± 4.90	6.33 ± 3.75	6.98	0
T90	9.13 ± 4.24	4.87 ± 4.02	4.9	0
ESS	9.30 ± 3.10	8.65 ± 3.35	3.54	0.002

Table 1: Overall comparison before and after treatment.

Variables	Before treatment	After treatment	t/z	p-value	Before treatment	After treatment	t	p-value
AHI	11.19 ± 1.81	5.53 ± 2.03	10.5	0	23.05 ± 4.16	11.93 ± 3.19	10.15	0
Mean SpO2 (%)	94.70 ± 0.95	96.10 ± 1.00	–2.94	0.016	94.23 ± 1.24	95.08 ± 0.64	–2.86	0.014
MiniSpO2 (%)	86.80 ± 4.59	90.60 ± 2.84	–2.87	0.018	83.92 ± 4.50	87.31 ± 2.18	–3.09	0.009
Basis SpO2 (%)	96.40 ± 1.07	96.40 ± 1.26	0	1	96.00 ± 0.91	96.54 ± 0.66	–1.85	0.089
MAI	6.31 ± 2.72	3.24 ± 2.05	4.05	0.003	14.48 ± 2.63	8.71 ± 2.93	6.42	0
T90	6.8 (1.1,8.9)	1.4 (0.0,5.3)	–2.19	0.028	11.63 ± 2.12	6.81 ± 3.86	4.25	0.001
ESS	6.58 ± 1.50	5.80 ± 1.32	3.26	0.01	11.38 ± 2.26	10.85 ± 2.70	2.01	0.068

Table 2: Comparison of mild and moderate groups before and after treatment.

Variables	Mild group	Moderate group	t/Z	p-value
AHI	5.66 ± 1.70	11.12 ± 3.95	4.47	0
mean SpO2	1.0 (0.75, 1.5)	1.0 (0.0, 2.0)	–0.40	0.692
miniSpO2	3.5 (0.75, 8.3)	2 (0.0, 7.0)	–0.25	0.803
MAI	2.5 (1.05, 5.6)	5.8 (3.3, 8.6)	–2.05	0.041
T90	1.7 (0.15, 8.3)	3.1 (1.9, 8.2)	–1.12	0.264
ESS	1.0 (0.0, 1.2)	0.0 (0.0, 1.5)	–0.70	0.485
AHI, MAI, T90, and ESS = Pre-treatment date minus during or after treatment date. Calculation of mean SpO2 and miniSpO2: During treatment date minus before treatment date				

Table 3: Comparison of absolute changed variations between groups.

Variables	Mild group (%)	Moderate group (%)	t	p-value
Percentage of AHI (%)	51.04 ± 13.32	47.89 ± 13.79	–0.55	0.587
Percentage of AHI = (Pre-treatment AHI minus during treatment AHI)/Pre-treatment AHI				

Table 4: Percentage of absolute change of AHI (AHI) between groups.

Discussion

The application of TGS in patients with mild-to-moderate OSA after UPPP led to clinically and statistically significant improvements in upper airway ventilation. The neuromuscular responses to airflow obstruction are blunted, and fail to compensate for obstruction and restore airway patency during sleep. The mechanism of TGS on reducing AHI may be that such stimulation trains dilator muscles and improves their endurance to prevent collapse of the upper airway. In animal studies, exogenous electrical stimulation of the genioglossus muscle augmented the activity of this pharyngeal dilator and restored airway patency [11]. Moreover, several studies showed that electrical stimulation of the genioglossus may improve pharyngeal stability and prevent upper-airway collapse during sleep in patients with OSA, playing an important role in treatment [12-14].

Edmonds et al. [15] investigated transcutaneous electrical stimulation of the genioglossus in patients with OSA, different from those of Miki et al. [16] They found that transcutaneous electrical stimulation during upper airway collapse was not effective and caused arousal. However, the intensity of stimulation in their study was relatively high and difficult to tolerate for patients. In our study, we first maintained the range for basic and maximum stimulation intensity. The MAI in our research was reduced compared with pre-treatment data, demonstrating that patients were not aroused from sleep. According to the findings of Miki et al. [16] we found TGS to be an effective and feasible treatment for persistent mild-to-moderate OSA post-UPPP surgery.

The development of pharyngeal obstruction during sleep has been widely attributed to a loss of pharyngeal neuromuscular activity, Oliven et al. studied [14] electrical stimulation of the genioglossus, using fine wire electrodes that were inserted intraorally into the muscle, and measured upper airway caliber and critical occlusion pressure, their study revealed one-half of the tested patients with OSAS to have improved pharyngeal patency with stimulation. Besides, Research [17] indicated stimulating its motor nerve can lead to the contraction of genioglossus muscle, The branches of the hypoglossal nerve that dominate the genioglossus predominantly contain efferent (motor) fiers, stimulation of those branches activates the genioglossus muscle with minimal afferent (sensory) feedback. Those all show neuromuscular stimulation is feasible to treat OSAS. Giuseppe Lanza et al. [18] found OSAS patients showed an impairment of central motor conductivity to the genioglossus according to transcranial magnetic stimulation (TMS). TMS might be considered as a valuable tool in assessment the effect of therapy to stimulation and bring new vision to understanding the neuromuscular stimulation in future research. TGS relieved the severity of residual OSA in both the mild and moderate groups. However, further analyses were performed to compare additional factors; we found that the moderate group had a greater AHI than the mild group, implying that TGS exerted a greater effect than in the mild group. However, the percentages of AHI between the two groups were without statistical significance, indicating that the moderate group gained no benefit over the mild group.

Additionally, improvement in sleep respiratory disturbances did not occur (the reduction in AHI was approximately 50%). The possible reasons for this observation are as follows: (1) A basic stimulation intensity is not strong enough to eliminate recurrent apnea or hypopnea, 7 while a higher stimulation intensity can rouse patients from sleep; (2) OSA is often more severe during REM than NREM and genioglossus activity decreases during REM; this may cause apnea or hypopnea that requires a different stimulus threshold at different sleep stages [19]; (3) When esophageal pressure is greater than –10 cm H_2O, transcutaneous electrical stimulation fails to prevent or improve sleep-disordered breathing [20]; and (4) We assessed acute (only one night) upper airway responses to TGS, and did not address factors associated with chronic use of the therapy, which may affect the evaluation of the treatment. A multicenter, prospective, single-group, cohort study by Strollo et al. [21] showed that AHI significantly decreased when patients received 12 months' of upper-airway stimulation to treat OSA. Because our experimental time was short, whether long-term effectiveness was better, and whether stimulation can cause muscle fatigue are not well established. Further studies are required to answer these questions.

If UPPP is applied when little or no obstruction is noted at the retrolingual area (base of tongue), its success is reasonably good. We

selected patients with mild-to-moderate OSA after UPPP because their retropalatal areas were enlarged by removing excess portions of the palatal edge, tonsils, and uvula. If OSA persists post-UPPP, obstruction at the retrolingual area is likely, requiring repeat treatment [22] Stimulating the genioglossus can make the tongue advance, increasing the posterior airway space. However, severe OSA usually has more than one site of obstruction; the response to stimulation treatment is usually worse than for mild-moderate OSAS. Thus, we did not select patients with severe OSA to avoid the negative effect on evaluation of results.

We chose a frequency of 30 Hz based on the observation that for all skeletal muscles, tension is frequency-dependent and stimulation frequencies of 20 Hz to 30 Hz generate about two-thirds the maximum tension, which is well maintained for long periods [23].

CPAP is considered "standard treatment" for OSAS [24], but the adherence to therapy is often poor and remains a challenge for both patients and clinicians, 17 despite efforts to improve acceptance. UPPP can remove redundant soft palate and uvula, and is used to treat the retropalatal region for snoring and OSAS. UPPP, when performed conservatively, is overall an excellent surgical procedure for treating obstruction at the retropalatal level. However, surgery cannot improve obstructions at other levels. As additional methods to solve this problem require further exploration, TGS therapy can provide another choice. In addition, TGS can also help to identify responders and nonresponders prior to implanting HGNS systems.

TGS therapy also has limitations. First, stimulation frequency, waveform, ramp profile during initiation of stimulation, current intensity, and duration of stimulation require more thorough investigation. Second, stimulation can sometimes be uncomfortable and may lead to arousal from sleep, which can limit the clinical applicability of this technique. Third, patients received one night of treatment, which may have affected the results. It is also possible that stimulating the hypoglossus nerve chronically exerts long-term trophic effects on lingual muscles, including changes in muscle fiber strength and type, 11 which may enhance their ability to maintain pharyngeal patency during sleep. Research indicates that the stimulation intensity may have needed to be increased over time to offset elevations in upper airway collapsibility with increasing age and weight [25-27]. Despite these limitations, TGS is considered a new therapy for select patients with OSA who have difficulties with CPAP therapy or residual OSA post-UPPP. More definitive randomized, controlled research to verify this treatment is necessary.

Conclusion

TSG decreases pharyngeal collapsibility and leads to increase of airflow while concomitantly improving sleep apnea without arousing patients from sleep. Thus, it can be considered as an alternative treatment for residual OSA post-UPPP.

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