World Journal of Otorhinolaryngology-Head and Neck Surgery (2021) 7, 40—44

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Research Paper

Predictors of success in hypoglossal nerve stimulator implantation for obstructive sleep apnea

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Received 28 August 2019; received in revised form 21 January 2020; accepted 16 February 2020
Available online 30 June 2020

KEYWORDS
Obstructive sleep apnea;
Hypoglossal nerve stimulator;
Drug-induced sleep endoscopy;
Treatment;
Predictor

Abstract *Objective:* Current guidelines for hypoglossal nerve stimulator (HGNS) implantation eligibility include drug-induced sleep endoscopy (DISE) findings and other patient characteristics but lead to highly variable rates of surgical success across institutions. Our objective was to determine whether additional factors seen on preoperative evaluation could be used as predictors of surgical success.
Study design: Retrospective chart review.
Setting: Single-institution academic tertiary care medical center.
Subjects: and Methods:This study included patients with obstructive sleep apnea (OSA) who underwent HGNS implantation between 2015 and 2018. Surgical success was defined as a postoperative apnea-hypopnea index (AHI) of less than 20 events per hour and an AHI reduction of at least 50%. Preoperative polysomnogram (PSG) results, DISE findings, and physical parameters were compared between surgical successes and failures.
Results: A total of 68 patients were included in the analysis. The overall surgical success rate was 79.4% (54/68). Elevated preoperative AHI was associated with an increased likelihood of treatment failure, with an AHI of (36.9 $\pm$ 16.8) events/hour in the success group compared to (49.4 $\pm$ 19.6) events/hour in the failure group ($P = 0.05$). Patients observed to have partial lateral oropharyngeal collapse on DISE was more frequently associated with the treatment failure group than in the success group ($P = 0.04$).
Conclusion: Patients who underwent HGNS implantation overall had a very high treatment response rate at our institution. Factors that may predispose patients to surgical failure

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.wjorl.2020.02.007

included the presence of lateral oropharyngeal collapse and a significantly elevated preoperative AHI. These should be considered when determining surgical candidacy for HGNS implantation.

Introduction

Hypoglossal nerve stimulator (HGNS) is a non-ablative surgical treatment for patients with obstructive sleep apnea (OSA) with difficulty tolerating continuous positive airway pressure (CPAP). The fully-implantable device consists of a sensing lead to detect the phase of respiration, an impulse generator, and a stimulation lead placed around the protrusor branches of the hypoglossal nerve. This activates the genioglossus muscle and allows the tongue to move forward during inspiration, thereby opening the retroglossal and retropalatal areas and prevent airway obstruction.

An integral component of the preoperative evaluation for candidacy is drug induced sleep endoscopy (DISE). This allows for analysis of the structural elements of airway collapse during sleep. There are several limitations to DISE, including low interrater reliability, questions of its relevance to natural sleep, and a lack of an agreed-upon grading system.[1] Of these systems, the VOTE criteria, measuring collapse at the velum, oropharynx, tongue base, and epiglottis, is the most commonly used in the literature.[2] This system characterizes the directionality and severity of collapse at each of these sites.

Currently, the only finding on DISE that is a contraindication for HGNS implantation is complete concentric collapse of the palate.[3] Other recommendations include BMI less than 32 kg/m^2, apnea-hypopnea index (AHI) 15—65 events per hour, and a lack of central apneas. The STAR trial, which assessed clinical safety and effectiveness of HGNS implantation using the Inspire Upper Airway Stimulation (UAS) system, used the criteria of BMI less than 32 kg/m^2, AHI greater than 20 events per hour and less than 50 events per hour, absence of central apneas, and absence of complete concentric palatal collapse. This study reported a success rate of 66%, which was defined as a reduction in AHI of at least 50% from baseline and a postoperative AHI of less than 20 events per hour.[4] Follow up trials have demonstrated success rates of 64% at 18 months and 74% at 36 months.[5,6] Other series using Inspire UAS have reported success rates of 35%—73%.[7—10]

Clearly, a wide range of response rates to HGNS implantation exists. We hypothesize that after excluding patients with complete circumferential palatal collapse, other DISE characteristics may predict treatment failure or success and can be used as additional tools for assessing surgical candidacy.

Methods

The study was performed after approval from the University of Pennsylvania Institutional Review Board was obtained (protocol #827948). The current study was performed independently and was not industry-supported.

Patients who underwent drug-induced sleep endoscopy (DISE) and subsequent HGNS implantation with the Inspire Upper Airway Stimulation system (Inspire Medical Systems, Minneapolis, Minnesota) between 2015 and 2018 by a single surgeon at an academic tertiary care center were included in the analysis. Age, sex, body mass index (BMI), pre- and post-operative AHI, pre- and post-operative oxygen saturation nadir, and DISE characteristics were recorded. Preoperative sleep study values were obtained from laboratory polysomnograms (PSG) and home sleep testing (HST). Patients were excluded from HGNS implantation eligibility if they demonstrated complete concentric collapse on DISE. Strict BMI and AHI cutoffs were not used and surgical eligibility based on these factors was at the discretion of the surgeon. Values for postoperative AHI and oxygen saturation nadir were obtained from the patient's most recent sleep study, which included PSGs, HSTs, and laboratory titration PSGs. Formal PSGs or HSTs were typically unavailable for patients who obtained satisfactory results on initial titration PSG and did not require follow-up testing. Therefore, the results for postoperative AHI and oxygen saturation nadir were obtained from the titration sleep study in these patients. Sleep endoscopy results were characterized using the VOTE system, which scores the degree and directionality of collapse at the velum, oropharynx, tongue base, and epiglottis.[11]

Data analysis was conducted using XLSTAT software (Addinsoft, New York, NY). Data were compared using *t* tests, Mann—Whitney, or Fisher's exact tests as dictated by data set normality. A *P* value of 0.05 was considered significant.

Results

Demographics

A total of 68 patients were included in the analysis. 89.7% of patients were male. Treatment success was defined as a postoperative AHI of less than 20 events per hour and an AHI reduction of at least 50%. The success rate was 79.4%. The mean age between the success and failure groups was

significantly different [(62.5 ± 10.5) years and (55.2 ± 10.0) years, respectively; $P = 0.03$]. There was no significant difference in mean BMI between successes and failures [(29.9 ± 4.2) kg/m^2 and (29.4 ± 3.0) kg/m^2, respectively]. Eligibility cutoffs for BMI and AHI were less stringent compared to those described in the STAR trial. However, there was no significant difference in the number of patients who would not have met the traditional eligibility criteria (BMI < 32 kg/m^2 and AHI < 65 events/hour) between treatment successes and failures. Preoperative OSA severity demonstrated a significantly lower AHI in the success group [(36.9 ± 16.8) events/hour] compared to the failures [(49.4 ± 19.6) events/hour; $P = 0.05$]. There was no significant difference in preoperative oxygen saturation nadir between successes and failures (75.9% ± 13.8% and 76.9% ± 10.3%, respectively).

Sleep endoscopy characteristics

The total number of patients comparing degrees of collapse in the treatment success and failure groups based on the VOTE criteria is shown in Table 1. Sleep endoscopy characteristics at the level of the velum, tongue base, or epiglottis were not significantly different between groups (Table 2). Patients with partial lateral oropharyngeal collapse were more likely to fail treatment compared to patient without lateral OP collapse or those with complete OP collapse ($P = 0.04$). No patients demonstrated concentric or lateral collapse of the velum or lateral collapse of the epiglottis. There was no significant difference between the number of levels of collapse between successes and failures (2.4 ± 0.8 and 2.5 ± 0.9, respectively), nor in the total combined severity of collapse (3.8 ± 1.4 and 3.6 ± 1.3, respectively) (see Table 3).

Across all subjects, AHI improved from (39.5 ± 18.2) events/hour preoperatively to (10.4 ± 15.1) events/hour postoperatively ($P < 0.001$). Oxygen saturation nadir improved from 76.1% ± 13.2% preoperatively to 85.9% ± 11.4% postoperatively ($P < 0.001$) (Table 4). The average AHI for patients with surgical success was 4.2 events/hour postoperatively, compared to an AHI of 34.2 events/hour in the failure group. The success group demonstrated an average improvement in AHI of 89% (a reduction of 32.8 events/hour), whereas the failure group improved by 30% (an average reduction of 15.2 events/hour). The oxygen saturation nadir improved on average by 11.1% in the success group and 5.1% in the failure group.

More treatment failures had home or in-lab polysomnograms ($P = 0.007$) compared to successes, who were more likely to have a titration study only. Seven patients of the 14 treatment failures initially had titration studies that suggested a good response to HGNS therapy, achieving an AHI less than 20 events/hour and an AHI reduction by greater than 50% compared to their preop AHI. Treatment failures, including those who initially had a successful titration study, typically pursued additional testing following the initial titration study due to continued OSA symptoms or device intolerance, whereas treatment successes frequently responded to well to initial device titration and did not require further workup. Only one patient in the treatment success group would have been characterized as a treatment failure based on her initial titration sleep study. Patients who underwent formal PSG or HST, regardless of treatment failure or success, had a significantly higher AHI [(20.5 ± 18.1) events/hour vs. (5.8 ± 11.0) events/hour, $P < 0.001$] and lower oxygen saturation nadir (82.8% ± 5.0% vs. 87.3% ± 13.2%, $P < 0.001$) compared to those who had a titration study alone.

Table 1 Demographic characteristics of treatment success and failure groups (Mean±SD).

Demographics	Success	Failure	*P* value
Sex (M/F)[a]	13/1	48/6	0.660
Age (years)	62.5 ± 10.5	55.2 ± 10.0	0.030
BMI (kg/m^2)	29.8 ± 4.2	29.4 ± 3.0	0.680
Preop AHI (events/hour)	36.9 ± 16.8	49.4 ± 19.6	0.048
Postop AHI (events/hour)	4.2 ± 5.2	34.2 ± 16.2	<0.001
Preop O_2 nadir (%)	75.9 ± 13.8	76.9 ± 10.3	0.760
Postop O_2 nadir (%)	86.9 ± 12.2	82.1 ± 5.3	0.030

[a] The number of cases.

Discussion

HGNS has been shown to be an effective, non-ablative surgical therapy for OSA in patients who are unable to tolerate CPAP with durable results.[5,6]Preoperative evaluation plays a critical role in determining candidacy for implantation, considering factors such as BMI, polysomnogram results, and drug-induced sleep endoscopy findings. DISE is used primarily to exclude complete concentric collapse of the palate in HGNS candidates but is also able to determine the severity and directionality of collapse in other areas of the aerodigestive tract and support the recommendation for certain surgical modalities.[1,3]

In terms of preoperative characteristics higher AHI was more likely to be correlated with treatment failure. We did not find a correlation between treatment success and BMI, though prior work has suggested that patients with a BMI of less than 32 kg/m^2 are more likely to respond.[12] These results were consistent with findings from others suggesting patients with AHI greater than 50 are more likely to be non-responders.[12]Though the STAR trial limited inclusion criteria to patients with AHI between 20 and 50 events per hour, current indications for HGNS have broadened the range to an AHI between 15 and 65 events per hour.[13]

Our findings demonstrate that though patients were more likely to experience treatment failure in patients with an elevated AHI, these patients still achieved some benefit from HGNS. In patients with an AHI greater than 50, those who failed still had an average improvement in AHI of 20 events per hour. These patients did demonstrate a significant improvement in AHI, though not enough to meet the definition of success. This may reflect the fact that in such patients, a tolerable level of HGNS may be insufficient to overcome such a high degree of structural collapse. Therefore, patients with an elevated AHI should be counseled regarding the expected benefit of HGNS and the possibility of continued need for additional OSA therapy.

Table 2 Degrees of collapse by VOTE criteria between treatment success and failure [n(%)].

Degree of collapse	Success			Failure		
	None	Partial	Complete	None	Partial	Complete
Velum	0 (0)	8 (11.8)	46 (67.6)	1 (1.5)	3 (4.4)	10 (14.7)
Oropharynx	44 (64.7)	7 (10.3)	3 (4.4)	8 (11.8)	6 (8.8)	0 (0)
Tongue base	18 (26.5)	26 (38.2)	10 (14.7)	4 (5.9)	6 (8.8)	4 (5.9)
Epiglottis	23 (33.8)	16 (23.5)	15 (22.1)	8 (11.8)	5 (7.4)	1 (1.5)

Younger patients were also more likely to experience treatment failure. This is corroborated by findings in a study of the ADHERE registry, which found that AHI reduction was greater in older adults.[14] It has been suggested that increased airway collapsibility due to neuromuscular decline may play a role in the development of OSA in older patients.[15] Therefore, HGNS, which specifically targets muscular tone, may be more effective in this population. In contrast, younger patients may develop OSA as a result of more sensitive ventilatory control mechanisms, which may require different treatment approaches to fully address.

When using DISE to determine HGNS candidacy, aside from excluding complete concentric palatal collapse, confirming the presence of anterior-posterior palatal or tongue base collapse is often used to support the surgeon's decision to proceed with HGNS implantation. However, these results suggest that these factors may be insufficient to determine whether the patient will ultimately respond to treatment. Amongst DISE observations, only partial lateral oropharyngeal collapse was found to be significantly correlated with treatment failure. Lateral oropharyngeal collapse may be physiologically and functionally similar to circumferential palatal collapse, with a component of hypertrophy or overactivity of the palatopharyngeus muscle.

All surgical failures with lateral OP collapse were partial. In addition to partial lateral OP collapse, all of these patients had anteroposterior collapse at the palate, tongue base, or both. Complete lateral OP collapse was not found to be associated with treatment failure. The reliability of this finding may be impacted by the low number of patients with complete lateral collapse ($n = 3$), all of whom responded successfully to HGNS implantation. Further investigation is needed to determine whether a correlation between complete lateral OP collapse and treatment response exists.

This study is limited by the availability of postoperative formal non-titration sleep study data for many surgical successes, as such patients frequently obtained their titration sleep study and did not require additional follow up testing due to continued effectiveness of HGNS. Using data from titration sleep studies as a surrogate for formal PSG data may increase our reported rate of surgical success and may not reflect their actual postoperative AHI and oxygen saturation nadir.

Table 4 Comparison of baseline and postoperative apnea-hypopnea index (AHI) and oxygen saturation nadir for all patients (Mean±SD).

Measure	Preoperative	Postoperative	*P* value
AHI (events/hour)	39.5 ± 18.2	10.4 ± 15.1	<0.001
O_2 nadir (%)	76.1 ± 13.2	85.9 ± 11.4	<0.001

Patients experiencing continued OSA symptoms postoperatively are more likely to warrant further workup after their initial titration study, whereas patients experiencing subjective benefit from HGNS are unlikely to pursue additional testing. As half of treatment failures initially had a successful titration sleep study, this may not adequately screen for patients who do not experience long-term benefit from the device. Based on our data, the positive and negative predictive values of the titration study were both approximately 88%. Nevertheless, the titration study may be less accurate in reporting the magnitude of change in AHI and oxygen saturation compared to formal studies. To fully assess the true treatment effect of HGNS, we hope to use validated measures to assess OSA symptoms on all patients postoperatively, using HST or PSG testing as necessary in the future.

Our surgical response rate of nearly 80% is one of the highest reported in the literature, which may be due to appropriate patient selection. This response rate may also be affected by the lower rate of formal postoperative PSGs in surgical success patients compared to surgical failures. Apart from excluding patients with complete concentric collapse, these findings suggest that lateral OP collapse

Table 3 Correlation between treatment outcome and DISE characteristics (Mean±SD).

Structure	Success ($n = 54$)	Failure ($n = 14$)	*P* value
Velum (AP)	1.9 ± 0.3	1.6 ± 0.6	0.17
Oropharynx (Lat)	0.2 ± 0.5	0.4 ± 0.5	0.04
Tongue base (AP)	0.9 ± 0.7	1.0 ± 0.8	0.74
Epiglottis (AP)	0.9 ± 0.8	0.5 ± 0.6	0.30

may also predict decreased efficacy of HGNS. Additionally, patients with an elevated AHI are more likely to fail treatment. These results may offer additional guidance in determining candidacy for HGNS implantation and predicting postoperative treatment response.

Conclusion

The goal of this study was to determine predictors for the success or failure of HGNS implantation based on preoperative parameters. In addition to complete concentric collapse of the palate, which is currently the only DISE finding that is an exclusion criterion for HGNS implantation, the presence of lateral oropharyngeal collapse may also decrease the treatment response rate. Patients with a significantly elevated AHI preoperatively may also be at risk of failing to meet the standard definition of surgical success. These factors should be considered when determining surgical candidacy for HGNS implantation in patients with OSA.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tiffany Chao; No conflicts of interest to disclose. Erica Thaler; Previous research funding from Inspire Medical Systems. Participation in ADHERE study funded by Inspire Medical Systems.

CRediT authorship contribution statement

Tiffany N. Chao: Conceptualization, Validation, Formal analysis, Data curation, Writing - original draft. **Erica R. Thaler:** Conceptualization, Methodology, Validation, Resources, Investigation, Writing - review & editing, Supervision, Project administration.

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Edited by Jie Gao