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2021

Bachour , A , Bäck , L & Pietarinen , P 2021 , ' No changes in nocturnal respiration with hypoglossal neurostimulation therapy for obstructive sleep apnoea ' , The Clinical Respiratory Journal , vol. 15 , no. 3 , pp. 329-335 . https://doi.org/10.1111/crj.13303

http://hdl.handle.net/10138/353232
https://doi.org/10.1111/crj.13303

acceptedVersion

Title page

No changes in nocturnal respiration with hypoglossal neurostimulation therapy for obstructive sleep apnea

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All authors have seen and approved the manuscript.

Running title

HGNS, AHI and ODI4

Authorship Statement

- Adel Bachour: Wrote the study protocol, collected data, analyzed data and wrote the manuscript.
- Leif Bäck: Participated in writing the study protocol, in analyzing data and in writing the manuscript.
- Petra Pietarinen: Participated in writing the study protocol, in collecting data, in analyzing data and in writing the manuscript.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CRJ.13303

Disclosure Statement

- Adel Bachour has received financial support from the Helsinki University Research Fund to perform this study. The University hospital has no influence on data collection or reporting the results. The financial support was offered to promote science. There are no connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated including pertinent commercial or other sources of funding for the individual authors or for the associated departments or organizations, personal relationships, or direct academic competition for each author.
- Petra Pietarinen: No financial support. No conflict of interest
- Leif Bäck: No financial support. No conflict of interest.

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Article type : Original Article

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Adel Bachour, Leif Bäck and Petra Pietarinen

Abstract

Study Objectives: We initiated Hypoglossal Neurostimulation therapy (HGNS) at the Helsinki University Hospital in late 2014. Here, we report our experience.

Methods: We included all 15 HGNS patients. All patients had previously failed both CPAP and oral appliance therapy for sleep apnea. Overnight polysomnography parameters were analyzed before and at 1.5 years with HGNS.

Results: Mean ± SD patient age was 53 ± 6 years; 2 women and 13 men were included. Mean ± SD efficient CPAP level was 11.4 ± 3.4 cmH_2O. Implantation technically succeeded in all patients. There were no significant changes of AHI and ODI4 after HGNS [median (quartile) 29.2/h (19.8-38.7) vs. 30.1/h (15.6-52.6) and 15.0/h (5.9-20) vs. 12.5/h (6.9-30.2) respectively].

Conclusion: We did not observe significant changes in AHI and ODI4 indices with HGNS therapy. Larger multicenter randomized controlled trials are necessary before wider international use of HGNS.

Keywords:

Upper airway stimulation, sleep apnea, CPAP failure, pacemaker, oral appliance, CPAP pressure

Introduction

The most widely accepted treatment for obstructive sleep apnea (OSA) is nasal continuous positive airway pressure (CPAP). However, long-term use for many patients is suboptimal and adherence may vary between 39% to 70%.[1, 2]

Cranial nerve stimulation of the hypoglossal nerve (Hypoglossal Neurostimulation; HGNS) was approved by the Food and Drug Administration in 2014 for the treatment of moderate and severe OSA in adults. The selection criteria for HGNS included a body mass index (BMI) <32 kg/m^2, lack of central apnea, and a favorable pattern of palatal collapse during drug-induced sedation endoscopy (DISE).[3, 4] The short-term results from feasibility trials were favorable.[5] A withdrawal randomized study, in already successful patients, supported effectiveness at 13 months and at 18 months.[6] Three-year improvements in objective respiratory parameters were maintained.[7] Moreover, HGNS therapy was reported to be cost-effective when compared with no treatment.[8] A very recent study[9] in patients outside the US Food and Drug Administration guidelines for HGNS revealed outcomes similar to those from the 1-year STAR trial.[5]

As oral appliance (OA) therapy is reported to be non-invasive and efficacious for sleep apnea, we decided not to propose HGNS to sleep apnea patients who did not attempt OA therapy.

We initiated HGNS therapy in late 2014 at the Helsinki University Hospital. We used the same implantation device (upper Airway Stimulation system, Inspire Medical Systems, Maple Grove, MN, USA) as previously reported.[3-10] We applied the same inclusion and exclusion criteria, with the exception that we added a previous oral therapy failure to the inclusion criteria.

We wanted to share our experience with other centers to aid the medical community in optimizing the selection criteria for this innovative therapy.

The aim of this study was to report the changes of apnea and hypopnea index (AHI) and oxygen desaturation index of 4% (ODI4) with HGNS.

Methods

We included all 15 patients from our center since October 2014 in whom HGNS was performed.

Inclusion Criteria

$15 \leq AHI \leq 65$, BMI < 35 kg/m^2, no concentric collapse at palate via DISE, CPAP therapy failure, and OA therapy failure or contraindication.

Exclusion Criteria

Unresolved complete concentric collapse at the level of the soft palate, radiotherapy or ablation therapy of the head, neck, or both; surgical resection for cancer or congenital malformations of the larynx, tongue, or throat (with exception of tonsillectomy, adenoidectomy, or both); previous surgery within 3 months performed on soft-palate tissue; and any chronic medical illness that contraindicates implant use as judged by the physician.

Drug-induced sedation endoscopy:

Before inclusion, all patients underwent a DISE evaluation under propofol sedation using the VOTE classification.[11] All DISE videos were reviewed with the Inspire team. Only patients with no concentric collapse were included.

Sleep studies

An overnight polysomnography (Embla N7000, Denver, CO, USA, and NOX A1, Nox Medical, Reykjavík, Iceland) was performed before implantation, at 2 to 3 months from implantation (for titration purposes), and thereafter at 12 months. We used a stimulating device (Inspire, Medtronic Inc, Minneapolis, MN). An expert from Inspire Medical Systems attended all implantations and all titration polysomnographies. We applied the AASM criteria for scoring.[12] One physician expert in sleep medicine analyzed all the sleep studies. We followed the recent recommendation of reporting the full-night efficacy and the oxygen desaturation index of 4% in evaluating HGNS outcomes.[13] When available, a simultaneous transcutaneous CO_2 measurement was performed by a capnograph (Sentec AG, Therwil, Switzerland) during the in-lab overnight polysomnography.

At the last follow-up visit, patients were asked to indicate their global satisfaction with the HGNS therapy on a scale from zero (corresponding to very unsatisfied) to 100 (corresponding to very satisfied).

Previous CPAP pressure levels were obtained from the CPAP device.

The Helsinki University Hospital research committee approved the study and the patient's written consent (§20. June 15th, 2017. HUS/24/2017)

Statistical analysis

For continuous variables with normal distribution, we reported data as mean and standard deviation. For non-parametric continuous variables with abnormal distribution, we used the Mann-Whitney U test to compare two samples and reported data as median and lower-upper quartile. The effect size was calculated and the Eta squared value was reported with its significance (small, median, and large). Pearson correlation for correlation tests was used. The alpha risk was set at 0.05. We used the Bonferroni correction for multiple comparisons yielding a significant *P*-value at <0.005. IBM SPSS Statistics software version 25 was used.

Results

Patients:

We included 15 patients, of which two were women. Mean age was 53 years; the order of patients in the tables does not correspond to the order of implantation (Table 1).

CPAP therapy was proposed to all patients prior to HGNS. Three patients did not tolerate CPAP; therefore, the efficient CPAP pressure remained undefined. For the remaining patients, the mean efficient CPAP pressure level was 11.4 cm H_2O. Only one patient (number 5) had an efficient CPAP pressure level <8 cm H_2O (Table 1).

OA therapy for sleep apnea was proposed when CPAP therapy failed. For one patient (number 6), OA was not indicated because of a dental problem. For 5 patients, OA was not efficient in controlling sleep apnea (persistence of snoring,

apneas and sleep apnea symptoms). OA was not tolerated in the remaining patients.

Although patients gained weight during the follow-up period, this gain was not statistically significant. BMI increased from a median 30.1 kg/m^2 (baseline) to 30.4 kg/m^2 (*P*=.653), which corresponds to an increase of approximately 6 kg.

The time of surgery to implant the first HGNS was 6 hours and 31 minutes, thereafter, it decreased to a mean of 2 hours and 52 minutes.

Results of HGNS:

We reported the results of the most recent sleep study that was performed at a mean ± SD period of 1.5 ± 0.8 years from implantation. Table 2 shows the HGNS polysomnography outcomes. The median (quartile) AHI was 29.2/h (19.8-38.7) at baseline and with HGNS 30.1/h (36.5 ± 23.8), which indicates the absence of a significant modification (*P*=0.902, Eta squared = 0.008, small effect size). Similar results were observed concerning the oxygen desaturation index of 3% (ODI3), the oxygen desaturation index of 4% (ODI4) (Figure 1), the cumulative time spent with oxygen saturation <90% (CT90), the transcutaneous CO_2 values ($TcCO_2$), and the percentage of snoring time (Table 2). Epworth sleepiness scale values (ESS) changed with HGNS (from a median at 11.0 to 7.0, *P*=0.037). The median total sleep time was not statistically significantly at baseline than with HGNS (319 vs. 289 minutes; *P*=0.285).

Follow up and adherence to HGNS:

Polysomnographies with HGNS were performed at a mean ± SD period of 1.5 ± 0.8 years from implantation (Table 2). Data on adherence to HGNS were collected at the last follow-up visit 2.1 ± 1.3 years from implantation. Patients used their HGNS therapy for a mean ± SD time of 3:35 ± 2:01 (hours:minutes) per day.

Satisfaction:

The mean ± SD satisfaction score was 68 ± 26, indicating good satisfaction with HGNS therapy. We did not observe a significant correlation between the satisfaction score and modifications in AHI scores (*P*=.519) or ESS (*P*=.219).

Discussion

The novelty of this study is that HGNS therapy failed to ameliorate the AHI and ODI4 indices of our patients, in contrast with previously reported studies.[3-10]

Our results are less favorable than those of Strollo et al.[5] This previous study included 126 patients (83% men, mean age 54.5 years, BMI 28.4) and revealed a 68% reduction in median AHI score at 12 months of HGNS therapy. In contrast, here we report an 11% increase in AHI values with HGNS at 16 months of therapy.

There are several possible explanations for this difference. Our patients gained a mean of 6 kg after implantation of HGNS. Tuomilehto et al[14] reported that a weight reduction of 5 kg from the initial body weight was associated with a reduction in AHI of 2.0 units. We did not find any studies that described the effect of BMI increase on AHI values in HGNS. We may expect that weight gain is not the dominant mechanism for the observed outcomes.

We included patients with failed or inefficient OA therapy for sleep apnea. Both OA therapy and HGNS effectively aim to push the tongue forward and thus leave more space behind. We may expect a similar effect with HGNS when the OA is inefficient. Our hypothesis does not agree with the recently published study by Mulholland and Dedhia[15] who studied the effect of mandible advancement maneuver (MA) during DISE on upper airway obstruction. These investigators concluded that patients having significant airway improvement in the upper pharynx with MA appeared less likely to succeed with HGNS.

Recently, it has been reported that CPAP therapy levels $\geq$8 cmH_2O are associated with a greater probability of lower HGNS responsiveness.[16] Only one of our patients had an efficient CPAP pressure level <8 cmH_2O, which is consistent with the findings of Lee et al.[16] This may explain our poor outcomes with HGNS. We downloaded the 95th percentile pressure from the CPAP device smart card as performed by Lee et.al.[16]

In a recent study,[16] it has been reported that women, patients with lower BMI, and those of older age are more likely to respond to HGNS. In this study, we had

only 2 women and our patients were a mean of 6 years younger than those reported by Heisser et al.[17]

Despite the absence of changes in polysomnography parameters with HGNS therapy, our patients had good satisfaction with HGNS therapy and their ESS scores decreased significantly. When considering the low adherence and total sleeping time with HGNS, we believe that HGNS disturbed the sleep of our patients. The good satisfaction score could be partially explained by a placebo effect. Recently, Baptista et al.[18] reported in a review article that some HGNS patients were satisfied with their clinical improvement despite treatment failure indicated by polysomnographic data. One explanation for this paradox in our population is that patients were thankful for their care regardless of the outcome; they felt privileged to receive an advanced therapy without additional financial cost. In Finland, the National Health Care Institution covers the medical costs for every citizen without supplemental insurance. As patient satisfaction is important in any therapy, perhaps outcomes other than polysomnography results should be considered.

HGNS therapy was reported to be long-term cost-effective when compared with no treatment.[8] Although we did not perform a cost-effectiveness analysis, we share the opinion of Skirko and Weaver,[19] who considered the results of the long-term cost-effectiveness of HGNS as very preliminary.

Our study has some limitations. Our sample size was low and thus reduces the possibility of drawing solid conclusions. Moreover, there was no comparison group treated with HGNS that had not failed OA; this fact does not allow determination of the effect of OA failure. Finally, in any surgical procedure, surgeon experience is associated with reduced side effects and improved outcomes. All our patients had a technically successful implantation and the surgery time stabilized after the first implantation. Several studies have aimed to help match sleep apnea treatment modalities to patients. Although various phenotypes and endotypes such as loop gain, arousal threshold, and anatomic burden have been identified for the best therapeutic modality, application of these measures is hampered by methodological complexity.[16, 20] We were not aware of the effect of CPAP pressure levels on HGNS outcomes at the time of the inclusion.

Our HGNS methodology uses unilateral nerve stimulation. Recently, a bilateral hypoglossal nerve stimulation for treatment of adult obstructive sleep apnea has been developed with promising results.[21]

It is important to mention that the STAR trial [5] was a randomized therapy-withdrawal trial in already successful patients, and not a regular randomized controlled trial. We therefore, recommend large multi-center randomized controlled trials before wider international use of HGNS.

In conclusion:

We did not observe favorable outcomes in a short series of consecutive patients treated with HGNS at our center. Several questions remain unanswered regarding this failure. One of these is related to patient selection, particularly in those with a previous high CPAP pressure demand and those with an OA therapy failure. Large multi-center randomized controlled trials are necessary before wider international use of HGNS.

Abbreviations

AHI = apnea and hypopnea index

BMI = body mass index

CPAP = continuous positive airway pressure

CT90 = cumulative time spent with oxygen saturation <90%

ESS = Epworth sleepiness scale

DISE = drug-induced sedation endoscopy

HGNS = hypoglossal neurostimulation

ODI3 = oxygen desaturation index of 3%

ODI4 = oxygen desaturation index of 4%

$TcCO_2$ = transcutaneous CO_2

TST = total sleep time

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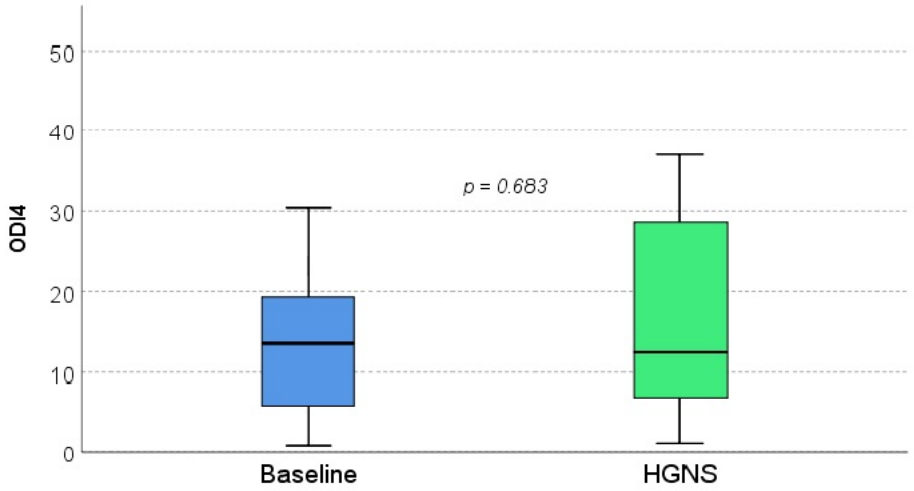
Legends for figure 1: Differences between oxygen desaturation index of 4% (ODI_4) at baseline and with Hypoglossal Neurostimulation (HGNS)

Table 1: Patient characteristics and follow up data.

Patient	Gender	Age	CPAP	oral appliance	Polysomnography	Follow up	Adherence	Satisfaction score	Previous head and
			pressure	history	HGNS	time	daily use	100 = satisfied	neck surgery
		years	cm H_2O		time in years	years	hh:mm	0 = unsatisfied	
	mean	**53**	**11.4**		**1.5**	**2.1**	**3:35**	**68**	
	SD	**6**	**3.4**		**0.8**	**1.3**	**2:01**	**26**	
1	man	56	9.8	not tolerated	1.5	1.6	6:44	61	Cyst ablation from the right maxillar region
2	man	45	11.9	not tolerated	0.4	0.7	4:25	.	None
3	woman	55	10.2	inefficient	2.0	2.0	0:44	45	None
4	man	60	10	inefficient	2.4	2.4	4:42	90	Uvulopalatopharangeoplasty, tonsillectomy
5	man	54	5.9	inefficient	1.0	1.0	5:45	100	Tonsillectomy
6	man	58	14.6	non suitable	0.5	2.7	4:00	99	Bimaxillary osteotomy, Inferior turbinate reduction
7	woman	58	not tolerated	not tolerated	2.2	2.9	7:14	60	Right-side Caldwell-Luc
8	man	50	8.5	not tolerated	1.2	1.2	4:16	90	Tonsillectomy
9	man	61	14	not tolerated	0.9	0.9	2:35	70	None
10	man	42	not tolerated	not tolerated	1.2	1.3	1:07	70	None
11	man	50	19.1	not tolerated	1.6	1.6	2:34	55	Septoplasty and inferior turbinate reduction
12	man	49	12	inefficient	3.2	4.2	1:51	0	None
13	man	51	not tolerated	inefficient	0.8	0.8	4:00	65	Hyoid bone suspension; Palatoplasty; Radiofrequency ablation of the tonsils and the tongue base
14	man	62	9	not indicated	2.4	4.6	1:00	75	lacrymal duct dilation, Right eye perforation trauma
15	man	42	11.4	not tolerated	1.1	4.2	3:00	75	Septoplasty

Patient	BMI		AHI		ODI3		ODI4		CT90		$TcCO_2$		TST		ESS		Snoring time	
	baseline	HGNS	baseline	HGNS	baseline	HGNS	baseline	HGNS	baseline	HGNS	baseline	HGNS	baseline	HGNS	baseline	HGNS	baseline	HGNS
	kg/m^2		/hour		/hour		/hour		%		kpa		minutes				%	
Median	30.1	30.4	29.2	30.1	18.1	23.7	15.0	12.5	2.7	4.1	5.3	5.5	319	289	11.0	7.0	47	23
Percentile 25	28.7	28.7	19.8	15.6	9.3	13.4	5.9	6.9	0.3	0.7	5.0	5.0	261	215	8.0	4.0	23	5
Percentile 75	30.5	32.4	38.7	52.6	35.3	44.8	20.0	30.2	9.2	18.1	5.5	6.0	371	336	14.0	11.0	67	60
p	*0.653*		*0.902*		*0.461*		*0.683*		*0.454*		*0.368*		*0.285*		*0.037*		*0.106*	
Eta squared	*0.018*		*0.008*		*0.017*		*0.007*		*0.017*		*0.029*		*0.087*		*0.156*		*0.068*	
Effect size	*small*		*small*		*small*		*small*		*small*		*small*		*median*		*large*		*median*	
1	28.7	28.7	30.8	28.5	29.8	13.7	20	7.1	2	0	5.41	6.01	251	101	11	11	12	36
2	28.9	29.7	38.7	15.6	35.3	10	19.3	6	0	1	.	.	196	181	8	4	47	65
3	30.5	32.4	65.1	83.9	59.8	62.1	30.4	28.6	9	1	5.4	5.93	261	314	14	13	67	45
4	20.3	20.7	19.8	26.6	9.3	23.7	6.8	14.3	0	1	.	5.88	258	269	17	4	23	1
5	29.8	29.7	49.7	11.6	35.4	13.4	16.1	6.7	3	2	4.92	5.55	385	394	11	4	11	5
6	30.5	28.7	19.6	8.7	16.7	13.9	15.2	6.9	7	10	.	.	371	392	12	1	62	9
7	22.8	22.8	13.8	3.3	9.2	1.9	4.5	1.1	0	0	.	5.32	306	217	9	6	28	1
8	31.9	27.8	17.6	58.3	7.2	34.2	2.6	16.7	0	6	5.1	4.62	319	314	17	16	65	5
9	30.1	30.4	28.8	30.1	13.1	20.8	0.8	9.3	0	1	5.07	4.62	475	393	8	11	74	22
10	31.2	39.7	31	52.6	15	42.5	.	36.9	.	.	.	.	360	336	14	11	38	39
11	29.7	31	32	46.7	29.9	45	26.9	.	11	24	.	5.12	346	215	12	5	80	60
12	28.7	34.6	69.2	72.4	67.2	74.9	63.1	67.3	53	31	.	5.53	384	142	17	14	86	93
13	33	34.1	29.2	48.3	24.8	44.8	14.1	35.1	10	16	5.93	6.1	310	292	8	7	52	62
14	30.1	30.4	21.3	40	18.1	41.5	9.8	24.4	3	44	.	.	263	267	4	4	34	17
15	30.5	31.4	28.3	20.2	8.8	11.9	5.9	10.6	1	10	.	.	354	289	11	10	14	23

Abbreviations: BMI = body mass index; AHI = apnea and hypopnea index; ODI_3 = oxygen desaturaion index of 3%;
ODI4 = oxygen desaturation index of 4%; $TcCO_2$ = transcutaneous CO_2; TST = total sleep time; ESS = Epworth sleepiness scale;



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