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MISCELLANEOUS

Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience

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Abstract Selective upper airway stimulation (UAS) is a novel therapy for patients with obstructive sleep apnea (OSA). The aim of this study was to analyze the application and outcome of UAS in patients with moderate to severe OSA in the clinical routine of a tertiary referral center. The design of this study is single-center, prospective clinical trial. Thirty-one patients who received a UAS device (Inspire Medical Systems) were included. Treatment outcome was evaluated at 2, 3, 6, and 12 months after surgery. Data collection included demographics, body mass index (BMI), apnea hypopnea index (AHI), oxygen saturation and desaturation index (ODI), Epworth Sleepiness Score (ESS), adverse events, and adherence to therapy. Sher criteria were used to evaluate treatment response. The mean age was 59.6 years with thirty patients being male. Mean BMI was 28.8 kg/m^2. The mean pre-implantation AHI of 32.9/h could be reduced to 7.1/h after 12 months ($p < 0.001$). The mean pre-implantation ODI of 30.7/h could be reduced to 9.9/h after 12 months ($p = 0.004$). The mean pre-implantation ESS of 12.6 could be reduced to 5.9 after 12 months ($p = 0.006$). Serious adverse events did not occur. Therapy adherence was a usage of 6.6 h/night after 12 months. OSA severity and subjective daytime sleepiness were improved in patients with moderate to severe OSA after receiving UAS therapy. Patients maintained high adherence to therapy use after 12 months. It is encouraging that UAS has been shown to be successfully implemented in the routine clinical management of OSA outside of a clinical trial setting.

Keywords Obstructive sleep apnea · Sleep surgery · Upper airway stimulation · Hypoglossal nerve stimulation · Sleep apnea treatment

Introduction

Obstructive sleep apnea (OSA) is characterized as a clinical condition with recurrent upper airway (UAW) narrowing and collapse during sleep, which results in intermittent oxyhemoglobin desaturation and sympathetic activation. This results in excessive daytime sleepiness and impaired the quality of life. OSA represents the most common sleep-related breathing disorder with a rising prevalence of 6 % in women and 13 % in men in USA [1–5].

Furthermore, OSA is known to be an independent risk factor for hypertension, ischemic heart disease, stroke, congestive heart failure, diabetes, and metabolic syndrome. OSA is associated with an increased risk of motor vehicle accidents [6–11]. The gold standard in the therapy of patients with moderate to severe OSA is the nocturnal treatment with continuous positive airway pressure (CPAP). CPAP therapy is able to improve UAW obstructions effectively and has a positive impact on adverse health consequences [12]. Despite its efficacy, a limitation of CPAP therapy is the nonadherence of patients. Only 68 % of patients continue CPAP therapy after 5 years [13, 14]. Therefore, it is important to develop alternative treatment options for these patients with CPAP incompliance. Over a long period of time, conservative methods, such as oral appliance therapy or sleep positional training,

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and a variety of UAW surgery, that modify the soft tissue surrounding the pharynx either by tissue reduction or stabilization and advancement, were the common alternative treatment options. Side effects and the lack of resilient data on effectiveness limit the acceptance [15].

Recently, a new treatment option addressing the reduced activity of the UAW dilatator muscles during sleep—mainly the genioglossus muscle—has been developed. Unilateral respiration-synchronized stimulation of the hypoglossal nerve generates protrusion of the tongue and could demonstrate its beneficial effect in the treatment of patients with OSA [16, 17]. The STAR (Stimulation Treatment for Apnea Reduction) trial proved the effectiveness of selective upper airway stimulation (UAS) in patients with OSA and CPAP incompliance using a prospective multicenter single-group trial followed by a randomized therapy withdrawal trial [18]. Since then various centers in Europe and the United States of America incorporated UAS in their range of therapy alternatives for appropriate cases.

The aim of this prospective study was to analyze the application and outcome of UAS in patients with moderate to severe OSA in the clinical routine at a tertiary referral center in Germany.

Materials and methods

Patient selection

Patients with moderate to severe OSA [apnea hypopnea index (AHI) >15/h and <65/h, central apnea index <25 %] and nonadherence to CPAP treatment were eligible for enrollment. All consecutive patients from June 2014 to June 2015 who received an implantation of an UAS system (Inspire II Upper Airway Stimulation system, Inspire Medical Systems, Maple Grove, MN, USA) were included in this study. Screening included a home sleep polygraphy, an inpatient polysomnography, clinical examination, and a drug-induced sleep endoscopy (DISE) with propofol to characterize the pattern of upper airway obstruction according to the VOTE classification and to rule out a complete concentric collapse of the soft palate [19]. The Epworth Sleepiness Scale (ESS) was conducted for the evaluation of daytime sleepiness [20]. Patients were excluded if the body mass index (BMI) was above 35 kg/m^2. Patients were excluded if pronounced anatomical abnormalities preventing the effective use of assessment of the UAS were identified during clinical examination (e.g., enlarged tonsils). Further exclusion criteria were chronic obstructive pulmonary disease, New York Heart Association class III or IV heart failure, neuromuscular diseases, hypoglossal nerve palsy, recent myocardial infarction or severe cardiac arrhythmias, persistent uncontrolled hypertension despite medication use, active psychiatric disease, and the foreseeable requirement of magnet resonance imaging [18]. Informed consent was obtained from each patient. The study was approved by the local ethics committee (Fakultät für Medizin, Ethikkommission, Technische Universität München, Germany).

Upper airway stimulation system

Qualified participants underwent a surgical implantation of the UAS system. The UAS system was implanted on the patient́s right side under general anesthesia. Three surgical incisions are necessary for the placement of the components of the UAS device. A horizontal submandibular incision is required to place the stimulation lead around selected fibers of the hypoglossal nerve, which are responsible for a protrusion of the tongue. A nerve integrity monitoring system (NIM 3.0, Medtronic Xomed, Jacksonville, FL, USA) was used to detect the appropriate fibers. A second incision inferior to the clavicle is required to create a pocket superficial to the major pectoralis muscle to accommodate the implanted pulse generator (IPG). The sensing lead, which enables the detection of breathing maneuvers to generate synchronized hypoglossal nerve stimulation, is placed within a tunnel between external and internal intercostal muscles using a third incision on the right lateral thorax wall. Both stimulation and sense leads are connected to the IPG using a subcutaneous tunneling device. A proper functioning of the whole system was ascertained before closure [21–23]. All the patients were discharged on the third postoperative day. Postoperative examination with the removal of the stitches was performed within 1–2 weeks.

Follow-up

Follow-up visits were scheduled at month 1, 2, 3, 6, and 12. Table 1 and Fig. 1 illustrate the performed examination during the follow-up visits. At month 1 after surgery, the device was activated and patients were instructed in the use of the controller to initiate and terminate the therapy for nighttime home use. Patients were instructed to increase

Table 1 Summary of the examinations performed during the follow-up visits

	First turn on	ESS	PSG	PG	UAS titration
Month 1 (M1)	X				
Month 2 (M2)		X	X		X
Month 3 (M3)		X	X		X
Month 6 (M6)		X		X	
Month 12 (M12)		X		X	

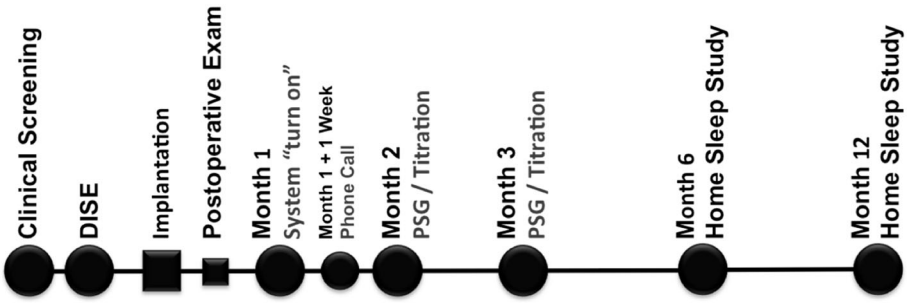

Fig. 1 Timeline of upper airway stimulation implantation and follow-up

stimulation strength gradually from the initially programmed amplitude, and followed by a phone call 1 week later for the acclimatization status of therapy. After 1 month of nocturnal UAS therapy, a titration of the stimulation during an 18-channel inpatient polysomnography (PSG) according to the American Academy of Sleep Medicine (AASM) guidelines from 2012 was performed (month 2) [24]. Furthermore, in every patient, a second titration night was performed during a second inpatient PSG at month 3 to ensure the stability of efficient stimulation. A home sleep polygraphy (PG) was performed at month 6 and 12. The same scoring criteria were used for all sleep studies: Hypopneas were scored based on a 30 % reduction in airflow and 4 % oxygen desaturation. Apneas were scored based on a 90 % reduction in airflow [24]. The outcome measurements and the classification of responders and non-responders were defined in dependence on the criteria postulated by Sher et al. [25]. A response as measured by means of the AHI score was defined as a reduction of at least 50 % and an absolute AHI score at month 6 and month 12 of less than 20 events per hour and as measured by means of the oxygen desaturation index (ODI) as a reduction of at least 25 % from baseline scores. Mean and minimal oxyhemoglobin saturation was recorded. Self-reported sleepiness was assessed during every follow-up visit by the use of the ESS score with a score of less than 10 being considered as threshold for normal subjective sleepiness. Adverse events were recorded during the whole observation interval. Serious adverse events were defined according to the STAR trial as any events that led to death, life-threatening illness, permanent impairment, or new or prolonged hospitalization with serious health impairment.

Statistical analysis

Version 23.0 of the Statistical Package for the Social Sciences software (SPSS, Chicago, IL, USA) was used. Descriptive statistics were calculated for demographic variables. Paired *t* test was used to compare baseline and postimplantation values. Data are given as mean ± standard deviation. *p* values ≤ 0.05 were considered statistically significant.

Results

Patients' characteristics

The study population consisted of 31 participants with a mean age of 59.6 ± 10.9 years. Thirty patients were male (97 %), and one patient was female (3 %). The mean BMI was 28.8 ± 3.1 kg/m^2. The BMI remained stable during the study period. All participants had a history of CPAP incompliance. The mean time between the first diagnosis of OSA to the date of implantation was 33.6 ± 45.1 months. The mean AHI on pre-operative home sleep polygraphy was 26.3 ± 12.9/h, and the mean ODI score was 28.4 ± 13.1/h. The mean AHI score on pre-operative polysomnography was 32.9 ± 11.2/h, and the mean ODI score was 30.7 ± 13.0/h. The mean pre-operative ESS score was 12.6 ± 5.6 (Table 2). No patient was lost to follow-up and all patients completed the follow-up period of 12 months.

Surgical implantation

The UAS device was successfully implanted in all 31 patients. The mean time for surgical implantation was 161 min (median 150 min, ±32). In two patients, a venous vessel was ruptured during the cervical tunneling which required one further cervical incision in one patient. Beyond that no adverse or severe adverse event occurred. Patients were discharged on schedule on the third day after surgery.

Outcome apnea hypopnea index

The mean AHI score at month 2 after surgery decreased 65 % from the baseline value of 32.9 ± 11.2 to 11.5 ± 14.1/h ($p < 0.001$) during the entire night of the titration study. After the optimal stimulation setting was achieved during the titration PSG at month 2 and month 3, the mean AHI was 3.2 ± 3.5 and 3.7 ± 4.9/h, respectively. The AHI reduction was maintained during the home sleep study at month 6 and month 12 after surgery (Table 3; Fig. 2). At 6 months, 30 out of 31 patients (96.8 %) had the

Table 2 Pre-implantation patients' characteristics

Characteristics	
Age (years) ± SD	59.6 ± 10.9
Sex (male/female)	30/1
BMI (kg/m^2) ± SD	28.8 ± 3.1
Range (min–max)	21.4–34.8
Time difference between diagnosis of OSA and implantation (months) ± SD	33.6 ± 45.1
AHI (n/h) ± SD (home sleep polygraphy)	26.3 ± 12.9
ODI (n/h) ± SD (home sleep polygraphy)	28.4 ± 13.1
AHI (n/h) ± SD (inpatient polysomnography)	32.9 ± 11.2
ODI (n/h) ± SD (inpatient polysomnography)	30.7 ± 14.0
ESS ± SD	12.6 ± 5.6

AHI score reduced more than 50 % from the baseline value, with one patient had the AHI score reduced 43 % from the baseline value. At 12 months, 30 out of 31 patients (96.8 %) had the AHI score reduced more than 50 % from the baseline value, with one patient had the AHI score reduced 38 % from the baseline value (Fig. 2).

Outcome oxygen desaturation index

The mean ODI score at month 2 after surgery decreased 55 % from the baseline value of 30.7 ± 14.0 to 13.7 ± 12.2/h ($p < 0.001$) during the entire night of the titration study. After the optimal stimulation setting was achieved during the titration PSG at month 2 and month 3, the mean ODI was 5.1 ± 4.5 and 8.8 ± 10.9/h, respectively. The ODI reduction was maintained during the home sleep study at month 6 and month 12 after surgery (Table 3; Fig. 3). At 6 months, 25 out of 31 patients (80.6 %) had the ODI score reduced more than 25 % from the baseline value, with six patients (19.3 %) had the ODI score reduced less than 25 % from the baseline value. At 12 months, 25 out of 31 patients (80.6 %) had the ODI score reduced more than 25 % from the baseline value (Fig. 3).

Outcome oxygen saturation

The mean oxygen saturation at month 2 after surgery increased from the baseline value of 92.3 % to a value of 93.8 % ($p < 0.001$) and remained stable at month 3, 6, and 12 (Table 3). During the period of optimal stimulation during the titration PSG at month 2 and 3 after surgery, a mean value of 93.7 ± 1.7 and 93.9 ± 2.7 % could be observed.

The minimal oxygen saturation at month 2 after surgery increased from the baseline value of 74.1 % to a value of 83.8 % ($p < 0.001$, Table 3). During the period of optimal stimulation during the titration PSG at month 2 and 3 after surgery, a mean value of 88.1 ± 3.3 and 85.3 ± 16.7 % could be observed.

Table 3 Outcome measures

	Baseline	M2	*p* value	M3	*p* value	M6	*p* value	M12	*p* value
AHI ± SD	32.9/h ± 11.2	11.5/h ± 14.1	<0.001*	10.3/h ± 13.0	<0.001*	7.6/h ± 5.3	<0.001*	7.1/h ± 5.9	<0.001*
					0.995°		0.337°		0.389°
ODI	30.7/h ± 14.0	13.7/h ± 12.2	<0.001*	13.8/h ± 13.8	<0.001*	11.7/h ± 8.8	<0.001*	9.9/h ± 8.0	0.004*
					0.951°		0.770°		0.564°
Mean Sp02	92.3 % ± 2.4	93.8 % ± 2.0	<0.001*	93.7 % ± 2.0	0.001*	92.9 % ± 3.4	0.762*	93.1 % ± 1.9	0.307*
					0.539°		0.062°		0.300°
Min Sp02	74.1 % ± 11.4	83.8 % ± 5.2	<0.001*	84.5 % ± 5.6	<0.001*	79.1 % ± 11.1	0.108*	79.3 % ± 11.6	0.151*
					0.606°		0.017°		0.071°
ESS	12.6 ± 5.6	8.6 ± 5.0	<0.001*	6.8 ± 4.8	<0.001*	5.9 ± 4.8	0.001*	5.9 ± 5.2	0.006*
					0.076°		0.439°		0.427°

* Compared to baseline

° Compared to the previous follow-up

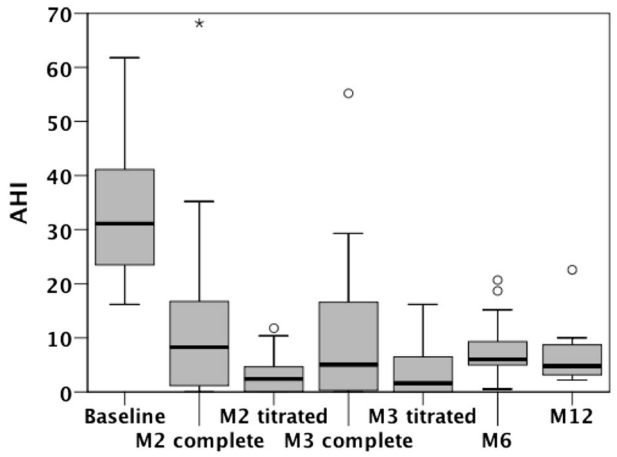

Fig. 2 AHI score at baseline, 2 months after surgery (M2), 3 months after surgery (M3), 6 months after surgery (M6), and 12 months after surgery. "M2 complete" and "M3 complete" represent the AHI score for the complete titration polysomnography (that means including the periods of insufficient stimulation). "M2 titrated" and "M3 titrated" illustrate the AHI score during the period of optimal stimulation during the polysomnography. The baseline AHI was reduced significantly to all postimplantation visits ($p < 0.001$ each). In M6, the two separately shown patients represent AHI scores of 20.7 and 18.7/h. In M12, the separately shown patient represents an AHI score of 22.6/h

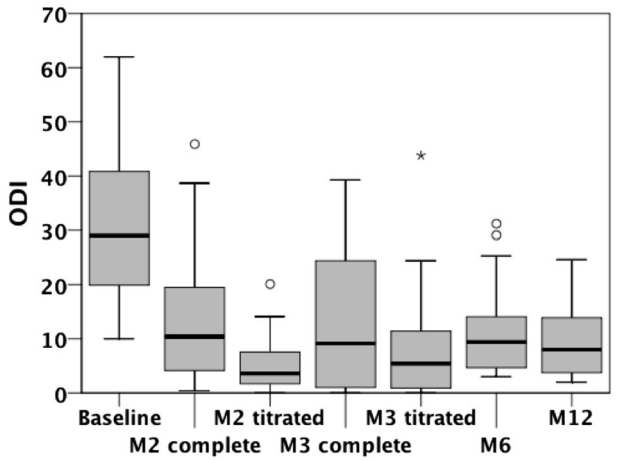

Fig. 3 ODI score at baseline, 2 months after surgery (M2), 3 months after surgery (M3), 6 months after surgery (M6), and 12 months after surgery. "M2 complete" and "M3 complete" represent the ODI score for the complete titration polysomnography (that means including the periods of insufficient stimulation). "M2 titrated" and "M3 titrated" illustrate the ODI score during the period of optimal stimulation during the polysomnography. The baseline ODI was reduced significantly to all postimplantation visits (baseline-M2, baseline-M3, baseline-M6: $p < 0.001$; baseline-M12: $p = 0.004$)

Outcome subjective parameters

The mean ESS score at month 2 after surgery decreased from the baseline value of 12.6 to a value of 8.6 ($p < 0.001$). A further increase at month 12 after surgery to a value of 5.9 could be observed (Table 3; Fig. 4).

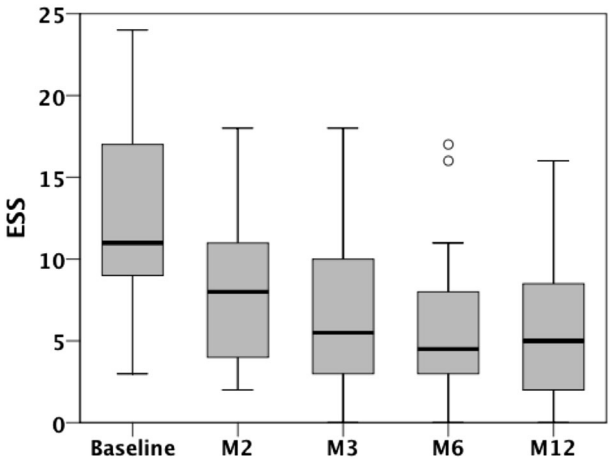

Fig. 4 ESS at baseline, 2 months after surgery (M2), 3 months after surgery (M3), 6 months after surgery (M6), and 12 months after surgery. The baseline ESS was reduced significantly to all postimplantation visits (baseline-M2, baseline-M3: $p < 0.001$; baseline-M6: $p = 0.001$; baseline-M12: $p = 0.006$)

Outcome stimulation settings and therapy adherence

At month 2, the stimulation amplitude was titrated to mean of 2.0 ± 0.5 V. During the second titration PSG at month 3, the stimulation was titrated to a mean of 2.2 ± 0.6 V ($p = 0.054$). During the postoperative follow-ups, the mean nightly device use has been monitored. Throughout the follow-up period, all patients showed high rates of therapy adherence with a mean usage of 7.0 ± 1.5 h/night at month 2, 6.9 ± 2.3 h/night at month 3, 6.0 ± 2.2 h/night at month 6, and 6.6 ± 2.7 h/night at month 12.

Discussion

The effectiveness of the implanted UAS system has been investigated during a prospective multicenter trial followed by a randomized therapy withdrawal trial (STAR trial) and is increasingly applied in patients with moderate to severe OAS and nonadherence to CPAP therapy [18]. The aim of this open prospective study was to evaluate the application and outcome of UAS in the clinical routine of one of the German implantation centers for UAS.

In this study, we demonstrate that the application of unilateral, breath-synchronized selective upper airway stimulation led to a significant reduction of objective parameters and a significant improvement of subjective daytime sleepiness. The effectiveness has been evaluated by the criteria for the evaluation of the efficacy of surgical modifications of the UAW in adults with OSA postulated by Sher et al. [25]. A response of a surgical modification measured by means of the AHI score was defined as a

reduction of at least 50 % and an absolute AHI score of less than 20 events per hour and, as measured by means of the ODI score, as a reduction of at least 25 % from baseline scores [25]. This definition is also used by the previous studies on UAS.

With regard to the relative and absolute reduction of the AHI score, these criteria could be met in 30 patients out of a cohort consisting of 31 patients (96.8 %) after 6 months and in 30 out of 31 patients after 12 months (96.8 %). The relative reduction of the ODI according to the applied criteria could be met in 25 out of 31 patients (80.6 %) after 6 months and 25 out of 31 patients (80.6 %) after 12 months. These results are comparable to previously published findings under controlled clinical trial setting. Van de Heyning et al. published results on the safety and preliminary effectiveness of UAS. Altogether 28 patients were implanted and completed the 6-month observation period. By the adaption of the inclusion criteria, the responder rate—which was defined by the same criteria as in our study—could be increased from 6 out of 20 patients (30 %) during a first part of the study up to 7 out of 8 patients (87.5 %) during a second part. The responders in both the parts of the trial showed significant reductions in AHI and ODI score and a significant improvement in subjective impairment [21].

Strollo et al. conducted a path-breaking prospective multicenter trial on the clinical safety and effectiveness of UAS (STAR trial), during which 126 patients were implanted. Using similar inclusion criteria and the same evaluation criteria, the AHI score decreased 68 % and the ODI score decreased 70 % by median. The criteria for the evaluation of efficacy at month 12 after surgery were met by 66 % with regard to the relative and absolute reduction of the AHI score and by 75 % with regard to the relative reduction of the ODI score. In some patients, a significant increase in the AHI score at month 12 after surgery could be observed. In our study, one patient had an increase in AHI during the titration polysomnography of the UAS at month 2 after surgery. This increase, however, was only related to the whole night; during the period of optimal stimulation, a decrease could be observed. At month 12 after surgery, all patients showed a decrease in their AHI score. A significant improvement of the ESS score could be observed during the STAR trial [18]. Woodson et al. were able to demonstrate the beneficial effect of UAS using a randomized controlled withdrawal study which included the first 46 patients who were successfully treated with UAS during the STAR trial [26].

The population included in the STAR trial has been under long-term observation to describe the stability of improvement of polysomnographic measurements. A durable effect without the necessity of increased stimulation thresholds or negative consequences on tongue mobility was observed 18 months after implantation [27]. Sleep-related quality of life outcome measurements, evaluated using the ESS, the Functional Outcomes of Sleep Questionnaire and self-reported snoring severity, were significantly improved across a 24-month follow-up period [28]. The last results reported of the STAR trial follow-up were published recently and cover a period of 36 months. Improvements of objective and subjective outcomes could be maintained, and the meaning of UAS as a sufficient treatment option for patients with moderate to severe OSA was again highlighted [29].

More recently, Kent et al. published the outcome results of one American implantation center to report on UAS in the clinical practice at a single academic sleep center [30]. During a period of 10 months, 21 patients were implanted with a UAS device. After application of Sher's criteria to evaluate the outcome, only one patient did not meet the cutoff, since the AHI was not reduced at least 50 % (despite improvement below 20/h). Therefore, the definition of therapy success was met in 95 % [30]. These single center experience, including the current study, demonstrated that the improvement of objective and subjective OSA outcome not only can be achieved outside the clinical trial setting, additional enhancement with consistent implementation of patient selection, surgical technique, and postimplantation support in a single center setting could lead to further improvement of therapy success [30].

A well-designed randomized controlled trial on the efficacy and safety of tonsillectomy with uvulopalatopharyngoplasty (TE-UPPP) in OSA has been published recently [31]. Again, using the Sheŕs criteria for the definition of surgical success, 70 % achieved the cutoff regarding the reduction of AHI. According to the authors, these results are situated in the middle range of trials published on the efficacy of TE-UPPP [30, 31]. In addition to exceeding success rate of UAS, a further possible advantage of this functional therapy has to be addressed. In the conventional surgical approaches in OAS, usually, no further adaption is possible, since the surgery has been conducted. Contrarily, UAS enables ongoing titration and, therefore, adapts to possible changes in patienťs characteristics (e.g., BMI) or poly(somno-)graphic measurements. Further trials on this topic need to follow.

Besides the presented Inspire II Upper Airway Stimulation system, one other UAS stimulation systems is already available. The aurora6000^{TM} system (ImThera Medical Inc., San Diego, CA, USA) enables continuous, non-respiration-synchronized stimulation of the hypoglossal nerve. A recently published multicenter study concluded, after reporting an AHI reduction of 34.9 $\pm$ 22.5/h at baseline to 25.4 $\pm$ 23.1/h 6 months after implantation, that UAS therapy with the aurora6000^{TM} system is likely to be safe and effective in selected patients [32]. Just in a

selective subgroup of seven patients, the AHI could be reduced from 32.1 ± 14.5 to 11.3 ± 7.4/h. Further clinical trials are needed to figure out the best candidates for this therapy. Another UAS system is currently part of a safety and performance study (clinicaltrials.gov identifier NCT02312479). The Nyxoah SAT system (Nyxoah SA, Mont-St-Guibert, Belgium) enables non-respiration-synchronized stimulation of the medial branches of the hypoglossal nerve close to the genioglossus muscle after a less invasive procedure in the chin area. The system does not contain a battery, so there is no need to replace it. Furthermore, compared to the other systems, it seems to be compatible with MRI. However, clinical data regarding the efficacy are not available yet.

As limitation of this study, we have to address the study design. The trial was an open prospective study without a randomized control group. This design was chosen, since the aim of this study was to evaluate the application of UAS within the clinical routine of a center for sleep medicine, which is worth knowing for multiple centers interested in the inclusion of UAS in their portfolio of alternative treatments for patients with CPAP incompliance.

Conclusion

In the setting of a tertiary referral center, patients with moderate to severe OSA and incompliance to CPAP therapy reduced OSA severity and improved subjective daytime sleepiness after receiving upper airway stimulation therapy. Patient maintained high adherence of therapy use after 12 months. It is encouraging that the upper airway stimulation has been shown to be successfully implemented in the routine clinical management of OSA outside of a clinical trial setting.

Compliance with ethical standards

Conflict of interest Clemens Heiser is a study investigator and consultant of Inspire Medical System and received personal fees, travel expenses, and research grants. Andreas Knopf, Murat Bas, Constanze Gahleitner, and Benedikt Hofauer have no conflict of interest.

The presented study did not involve animal experiments. Informed consent was obtained from each patient. The study was approved by the local ethics committee (Fakultät für Medizin, Ethikkommission, Technische Universität München, Germany).

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