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MISCELLANEOUS

Palatal implants in the treatment of obstructive sleep apnea: a randomised, placebo-controlled single-centre trial

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Abstract Palatal implants have been used to treat snoring and mild to moderate obstructive sleep apnea (OSA). Two previous controlled trials have published conflicting results regarding the effects of palatal implants on objective outcome measures, although they both could demonstrate superiority over placebo. The aim of the present study was to assess the effects of palatal implants in patients with mild to moderate sleep apnea in a randomised, placebo-controlled trial. Twenty-two patients with mild to moderate OSA (AHI 18 ± 5, BMI 28 ± 3, age 51 ± 13 years) due to palatal obstruction were enrolled in this randomised, double-blind, placebo-controlled trial. Respiratory parameters and sleep efficiency (evaluated by polysomnography), snoring (evaluated by the bed partner), and daytime sleepiness (evaluated by ESS) were assessed before and 90 days after surgery. One patient in each group did not show up for follow-up. The AHI, HI and LSAT showed statistically significant improvement in the treatment group ($p < 0.05$). Snoring as rated by bed partners also showed statistically significant improvement within the treatment group ($p = 0.025$). There was no statistical difference when comparing the means of the treatment group with the placebo group. There were no peri- or post-operative complications and no extrusions during the follow-up period. The study supports the idea that palatal implants lead to a reduction in respiratory events in patients with mild to moderate OSA, although a statistically significant superiority of palatal implants over placebo could not be demonstrated in this trial.

Keywords Obstructive sleep apnea · Implants · Snoring · Soft palate

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Introduction

Obstructive sleep apnea (OSA) is a common disorder affecting 2–4% of the middle-aged population [15]. It is characterised by intermittent complete or partial closure of the pharyngeal airway during sleep; resulting in episodes of hypoxemia, cardiovascular stress, and sleep disruption. During the last decade, it has been proven that untreated OSA independent from other factors results in excessive daytime sleepiness, causing an increased risk for accidents, and that it results in systemic arterial hypertension with an increased likelihood for fatal and non-fatal cerebro- and cardiovascular incidents [7]. If OSA is treated effectively, daytime symptoms as well as cardiovascular morbidity improve significantly or may even disappear completely [1, 5]. Treatment with nasal continuous positive airway pressure (CPAP) completely eliminates pharyngeal obstruction and is therefore considered the standard treatment for OSA. However, only 50–80% of patients initially accept nasal ventilation and only 17–71% sufficiently adhere to long-term treatment [2]. This reduces the overall efficacy of nasal CPAP treatment [12, 14], and as a result, many patients seek alternative treatment.

With mild sleep apnea, palatal flutter often plays a major role in increased airway resistance and hypopneas and contributes to airway collapse. Surgical treatment options are various and often bear a relevant morbidity like uvulopalatopharyngoplasty (UPPP), which still is the standard operation for palatal collapse. Apart from its known morbidity, such as nasopharyngeal stenosis and insufficiency, there is evidence that the success rates of surgical treatments decrease if tonsils are small or absent [11]. During the last decade, minimally invasive techniques for the treatment of OSA have gained increasing interest, such as radiofrequency surgery and related procedures. Palatal implants made of polyethylene terephthalate that were intended for permanent implantation were introduced as a treatment for simple snoring [8]. Recently, there have been several studies investigating the efficacy of palatal implants in OSA patients. Apart from prospective case series with longer follow-up periods [9, 10], there have been two placebo-controlled trials undertaken in the United States [4, 13]. In those trials, the results regarding the effects on objective outcome measures are conflicting, although they both demonstrated a superiority of palatal implants over placebo. The aim of the present study was to determine the results of palatal implants in comparison to placebo in a randomised, double-blind, placebo-controlled, European single-centre trial.

Methods

This was a prospective, randomised, double-blind, placebo-controlled study in a single centre (Department of Otorhinolaryngology, Head and Neck Surgery, Mannheim, Germany). It was reviewed and approved by the local ethics board of the Medical Faculty Mannheim, Germany. Written informed consent was obtained from all participants. Patients were recruited from the outpatient clinic as well as from the Sleep Disorders Centre of the Department of Otorhinolaryngology, Head and Neck Surgery at the University Hospital Mannheim, Germany. Patients who met the inclusion criteria as given in Table 1 were enrolled in the study. Patients were excluded if they were mentally incapable of signing an informed consent form, following the instructions, or returning for regular follow-up visits.

Objective and subjective parameters were measured at baseline and 90 days post-intervention in both groups. Objective parameters were obtained by fully attended polysomnography and comprised the apnea-hypopnea index (AHI) as primary outcome and the apnea index (AI), hypopnea index (HI), mean (MSAT) and lowest (LSAT) oxygen saturation, and sleep efficiency index (SEI) as secondary outcomes. Obstructive apneas were defined as a >90% drop in respiratory flow, and hypopneas were defined as a >50% drop combined with a 4% drop in O_2 saturation. The SEI was defined as the percentage of total sleep time in relation to total bed time. Subjective data in terms of daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS). Snoring intensity was rated by the bed partner with a 10 cm visual analogue scale (VAS).

Table 1 Inclusion criteria

Age >18 years
Apnea-hypopnea index (AHI) 10–40 episodes/h
Body mass index (BMI) ≤32 kg/m^2
Soft palate length >25 mm
Tonsil size <50% of the airway
No signs of retrolingual obstruction
No significant nasal obstruction
No previous history of upper airway surgery other than nasal, adenoid, or tonsil
No other relevant disorders affecting sleep or daytime performance

Twenty-two male patients with a mean age of 51 ± 12.7 years (range of 33–69), a body mass index (BMI) of 28.3 ± 2.6 kg/m^2 (range of 22–32), and mild to moderate OSA with an AHI of 18.2 ± 5.2 (range 10.5–26.8) were included in the trial. One patient in each group was not willing to return for follow-up without reason, leaving 20 patients for evaluation.

The manufacturer (Restore Medical Inc., St. Paul, MN, USA) prepared the delivery tools so that the placebo devices looked identical but did not contain an implant. Three delivery tools were assigned to each specific study participant. Patients and bed partners as well as study personnel were blinded. The procedure consisted of three palatal implants at the soft palate under local anaesthesia and was performed in the same way as described previously [6].

Statistics

All statistical analyses were performed by the Centre for Medicine and Society, Mannheim Institute of Public Health, Social and Preventive Medicine (MIPH), University of Heidelberg, Mannheim Medical Faculty with the IBM SPSS Statistic 19.0 software package and G*Power 3.1. Results of data analysis were displayed as mean ± standard deviation and were considered statistically significant when $p < 0.05$. All continuous variables were assessed for normal distribution by the Kolmogorov–Smirnov test. Patients were analysed according to their randomised groups by an intervention-to-treat analysis. Independent t tests (two-tailed) or Mann–Whitney U tests

were used to compare between the groups. Paired sample *t* tests (two-tailed) or Wilcoxon signed-rank tests were used to compare preoperative versus postoperative values within each group. Additionally, the effect-size index *d* (Cohen 1977 [3]) and two-tailed post hoc power analysis (alpha = 0.05) for dependent and independent means (both: *t* test or Wilcoxon signed-rank test) were calculated.

Results

The treatment groups did not differ significantly according to age, BMI, or other pretreatment values (Table 2).

All implantations were done in an outpatient setting under local anaesthesia. There were no peri- or postoperative complications and no palatal penetrations into the nasopharynx. During the follow-up period, there were no extrusions or other reasons leading to unforeseen unblinding.

The HI and the AHI were reduced statistically significantly in the actively treated group from 18.3 ± 5.1 to 7.8 ± 5.5 and 19.1 ± 5.0 to 8.2 ± 6.1, respectively (both $p < 0.05$), but they remained unchanged in the placebo group (Table 3). The AI showed a slight but not statistically significant improvement in both groups; however, the significance of the changes in AI is limited due to low baseline numbers. The differences between the two groups missed statistical significance and are demonstrated in Fig. 1.

The LSAT increased from 82.8 ± 8.1 to 88.3 ± 3.7 (treatment) and from 83.7 ± 5.1 to 84.1 ± 5.3% (placebo). The improvement in LSAT was statistically significant for the treatment group only, but there was no statistically significant difference between the means of the two groups. The MSAT improved slightly in the treatment group and remained unchanged in the placebo group, but neither the changes in MSAT nor the group difference was statistically significant. The SEI decreased comparably in both groups.

The ESS improved from 7.4 ± 4.0 to 6.2 ± 3.6 in the placebo group and from 7.1 ± 3.3 to 6.9 ± 2.0 in the treatment group (both $p > 0.05$). The bed partners rated snoring on the visual analogue scale with 7.7 ± 1.8 before and 5.1 ± 2.8 after placebo compared to 7.1 ± 1.3 before versus 5.5 ± 2.3 after treatment. Only the latter improvement reached statistical significance. The change of subjective parameters did not differ statistically significantly between the two groups.

Detailed results and the results of the statistical analysis are given in Table 3.

Table 2 Baseline parameters of both groups

	Placebo	Verum	*p* value
Age	53.3 ± 14.0 (11)	48.9 ± 11.4 (11)	0.434
BMI	28.1 ± 3.0 (10)	28.6 ± 2.4 (11)	0.675
ESS	7.4 ± 4.0 (10)	7.1 ± 3.3 (9)	0.868
Snore	7.7 ± 1.8 (10)	7.1 ± 1.3 (8)	0.484
AI	2.5 ± 3.3 (11)	0.8 ± 0.9 (11)	0.316[a]
HI	14.9 ± 7.3 (11)	18.3 ± 5.1 (11)	0.218
AHI	17.4 ± 5.5 (11)	19.1 ± 5.0 (11)	0.462
LSAT	83.7 ± 5.1 (10)	82.8 ± 8.1 (10)	0.909[a]
MSAT	93.4 ± 2.2 (11)	90.1 ± 9.4 (11)	0.277
SEI	81.7 ± 12.9 (11)	82.1 ± 18.7 (10)	0.955

Values are given as mean ± standard deviation (counts)

BMI body mass index (kg/m^2), *ESS* Epworth Sleepiness Scale, *AI* apnea index, *HI* hypopnea index, *AHI* apnea-hypopnea index, *LSAT* lowest oxygen saturation (%), *MSAT* mean oxygen saturation (%), *SEI* sleep efficiency index

[a] Mann–Whitney *U* test

Discussion

The present study investigated the effects of the Pillar®[1] Palatal Implant System in the treatment of OSA using a randomised, placebo-controlled, single-centre trial. Controlled trials are of particular importance in the field of OSA, keeping the high night-to-night variability of the major objective outcome measures in mind. The study demonstrated that palatal implants lead to a statistically significant reduction in HI and AHI as well as LSAT in the actively treated group, although the differences between the implant and placebo groups were not statistically significant.

Currently two placebo-controlled trials are available regarding palatal implants, both using the same implant system from the same manufacturer that was used in the present trial [4, 13]. Friedman et al. investigated a group of 62 patients with OSA, 55 of them returning for postinterventional polysomnography. The authors demonstrated a statistically significant superiority of the implants compared to placebo for AHI, quality of life, snoring and daytime sleepiness (ESS) in their single-centre trial. Steward et al. presented the data of a multi-centre trial including 100 patients with mild to moderate sleep apnea. According to their data, a clinically significant reduction in AHI (as defined by a reduction of at least 50% below a level of 20) was statistically significantly more common in the actively treated group compared to placebo. In addition, statistically significant differences between the two groups were found for LSAT and the Functional Outcome of Sleep Questionnaire. A statistically significant difference in

[1] Pillar® was acquired by Medtronic Inc., Minneapolis, Minnesota, USA.

Table 3 Pre- and postoperative data for both groups and the results of statistical testing

	N	Mean ± SD	*p* value	Effect size (*d*)	Power
ESS					
Placebo					
Preoperative	10	7.4 ± 4.0			
Postoperative	10	6.2 ± 3.6			
Mean change	9	−1.8 ± 2.9	0.104	−0.621	0.418
Verum					
Preoperative	9	7.1 ± 3.3			
Postoperative	7	6.9 ± 2.0			
Mean change	7	−1.0 ± 3.3	0.449	−0.303	0.105
Diff in means		0.8 ± 3.4	0.622	0.258	0.076
Snore					
Placebo					
Preoperative	10	7.7 ± 1.8			
Postoperative	9	5.1 ± 2.8			
Mean change	8	−2.1 ± 3.1	0.098	−0.677	0.381
Verum					
Preoperative	8	7.1 ± 1.3			
Postoperative	6	5.5 ± 2.3			
Mean change	5	−2.7 ± 1.7	0.025	−1.588	0.756
Diff in means		−0.6 ± 3.0	0.711	0.240	0.067
AI					
Placebo					
Preoperative	11	2.5 ± 3.3			
Postoperative	10	1.7 ± 3.0			
Mean change	10	−1.1 ± 4.8	0.496[b]	−0.229	0.097[b]
Verum					
Preoperative	11	0.8 ± 0.9			
Postoperative	10	0.4 ± 0.9			
Mean change	10	−0.4 ± 1.1	0.313[b]	−0.363	0.170[b]
Diff in means		0.6 ± 4.5	0.517[a]	0.201	0.070[a]
HI					
Placebo					
Preoperative	11	14.9 ± 7.3			
Postoperative	10	15.3 ± 12.4			
Mean change	10	0.0 ± 14.1	0.997	0.001	0.050
Verum					
Preoperative	11	18.3 ± 5.1			
Postoperative	10	7.8 ± 5.5			
Mean change	10	−10.0 ± 7.2	0.002	−1.389	0.973
Diff in means		−10.0 ± 16.2	0.060	0.893	0.472
AHI					
Placebo					
Preoperative	11	17.4 ± 5.5			
Postoperative	10	17.0 ± 14.8			
Mean change	10	−1.1 ± 14.5	0.822	−0.076	0.055
Verum					
Preoperative	11	19.1 ± 5.0			
Postoperative	10	8.2 ± 6.1			
Mean change	10	−10.5 ± 7.0	0.001	−1.491	0.987
Diff in means		−9.4 ± 15.8	0.081	0.826	0.416
LSAT					
Placebo					
Preoperative	10	83.7 ± 5.1			
Postoperative	10	84.1 ± 5.3			
Mean change	9	0.8 ± 5.8	0.867[b]	0.138	0.065[b]
Verum					
Preoperative	10	82.8 ± 8.1			
Postoperative	9	88.3 ± 3.7			
Mean change	8	3.1 ± 4.4	0.047[b]	0.705	0.385[b]
Diff in means		2.3 ± 7.1	0.367	0.447	0.138
MSAT					
Placebo					
Preoperative	11	93.4 ± 2.2			
Postoperative	10	93.1 ± 2.8			
Mean change	10	0.0 ± 1.2	1.00	0.000	0.050
Verum					
Preoperative	11	90.1 ± 9.4			
Postoperative	10	93.3 ± 2.7			
Mean change	10	3.1 ± 10.2	0.360	0.304	0.139
Diff in means		3.1 ± 9.9	0.350	0.427	0.148
SEI					
Placebo					
Preoperative	11	81.7 ± 12.9			
Postoperative	10	77.6 ± 13.2			
Mean change	10	−3.1 ± 15.7	0.545	−0.197	0.087
Verum					
Preoperative	10	82.1 ± 18.7			
Postoperative	10	78.1 ± 19.4			
Mean change	9	−6.2 ± 28.3	0.527	−0.220	0.090
Diff in means		−3.1 ± 30.5	0.767	0.135	0.059

ESS Epworth Sleepiness Scale, *AI* apnea index, *HI* hypopnea index, *AHI* apnea-hypopnea index, *LSAT* lowest oxygen saturation (%), *MSAT* mean oxygen saturation (%), *SEI* sleep efficiency index

[a] Mann–Whitney *U* test

[b] Wilcoxon signed-rank test

daytime sleepiness (ESS) could not be detected. In contrast to those two publications, statistically significant differences between the two groups could not be detected in the present trial.

The following aspects need to be considered in the interpretation of the present results and the results of the two previous placebo-controlled trials: (1) severity of the disease, (2) group size, and (3) degree of reduction of respiratory events.

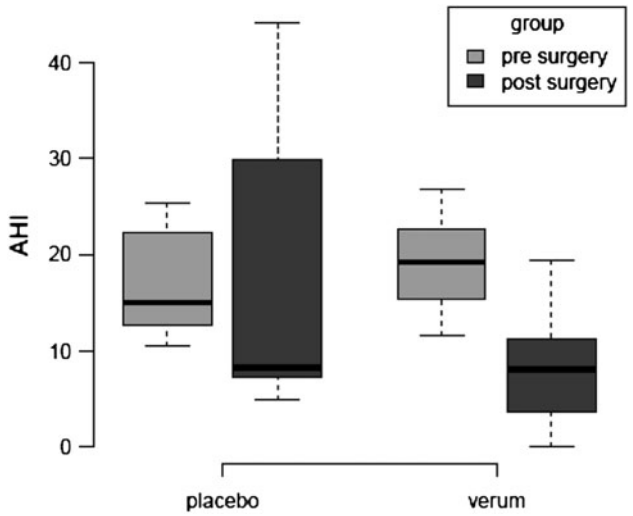

Fig. 1 Pre- and postoperative AHI for both study groups. Box-whisker plot of the AHI for both groups before and after surgery. The *boxes* represent the interquartile range (IQR) with the whiskers extending up to 1.5 times the IQR, the median is marked as a *solid line*

The severity of the disease based on baseline AHI and daytime sleepiness was mild to moderate in all trials. Especially with regard to daytime sleepiness, the average ESS was close to normal in the group of Steward et al. and within normal ranges in the present study (7.4/7.1). Under these circumstances, a relevant reduction of the ESS could not be expected in the present group. This may explain why only Friedman et al. could demonstrate a statistically significant superiority of palatal implants over placebo in their publication, starting from a higher baseline ESS (12.7 in the treatment and 11.7 in the placebo group).

The group size in the present study was significantly smaller ($n = 22$) compared to the previous trials ($n = 62$ and $n = 100$). Because of the ethical concerns associated with placebo-controlled surgical trials, we decided to use the smallest possible group size that was calculated before the beginning of the trial based on the expected treatment effect and the variation of the expected data. The fact that the present results could not verify a superiority of palatal implants over placebo therefore may be explained by the small sample size and an overexpected treatment effect. Given the significant reduction of AHI that occurred only in the treatment group and given the results of the two previous trials conducted by Friedman et al. and Steward et al., a superiority of palatal implants over placebo seems to exist although it could not be verified in the present trial.

The studies report conflicting results regarding the degree of reduction of respiratory events. Friedman reported a reduction in mean AHI of 7.9, whereas Steward et al. demonstrated an *in*crease in AHI in both groups, although the effect was less pronounced in the treatment group which lead to the statistically significant difference between the two groups. In the present study, the effect on mean AHI was most pronounced with a reduction in the treatment group from 19.1 to 8.2.

Conclusion

The present results support the idea that palatal implants lead to a reduction in respiratory events in patients with mild to moderate OSA, although a statistically significant superiority over placebo could not be demonstrated in this trial, in contrast to two previous studies with a larger sample size.

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Conflict of interest The department of Otorhinolaryngology, Head and Neck Surgery Mannheim, has received research grants and financial support for clinical trials from Restore Medical.

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