Side effects of two different mandibular advancement devices (MAD) in the treatment of snoring and obstructive sleep apnea syndrome (OSAS)

Side effects of mandibular advancement devices

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Abstract

Sleep-related breathing disorders (SBAS) are one of the most common causes of non-restorative sleep.
Sleep therapy options include positive pressure ventilation with continuous positive airway pressure (CPAP) masks, mandibular advancement of the mandible with mandibular advancement devices (MAD), back restraining, weight reduction, ear, nose and throat surgical procedures, bimaxillary or mandibular remodeling osteotomies, and neurostimulation procedures N. hypoglossal. In mild to moderate obstructive sleep apnea syndrome (OSAS), MAD, back suppression and weight reduction are potential treatment options. This study aims to identify possible side effects in the temporomandibular system that occur during nocturnal support of a mandibular arch over two years. Two different MADs are compared in terms of construction, height (bite elevation) and protrusion mechanics: the H-MAD with an autumn hinge and the SomnoDent Fusion ™ (called F-MAD) with sliding side wings. In addition, it is to be evaluated whether hinge system according to Herbst as a protrusion-controlling element and the reduction of the splint body for a reduced bite elevation leads to a significant reduction of side effects compared to the F-UPS.

Detailed description

Sleep-related breathing disorders (SBAS), particularly obstructive sleep apnea syndrome (OSAS), are one of the most common causes of non-restorative sleep. Disturbances of sleep disorders include apneas and hypopneas associated with either or not pharyngeal obstruction and hypoventilation. Depending on the type of respiratory disorder present, they are associated with hypoxemia and may cause hypercapnia or acidosis
The consequences of obstructive narrowing of the pharynx are far-reaching. Studies have shown that patients with OSAS have comorbidities such as neurological complaints, heart attacks, dementia, cardiovascular complaints, myocardial infarction, and a higher mortality rate.
Sleep fragmentation caused by respiratory disorders during sleep and wakefulness reactions (arousals) can lead to daytime sleepiness and concentration disorders. In the longer term untreated arousals and apneas are associated with an increased risk for arterial hypertension, stroke, myocardial infarction, diabetes mellitus and libido loss.
OSAS management includes positive pressure ventilation with continuous positive airway pressure (CPAP) masks, mandibular advancement of the mandible with mandibular advancement devices (MAD), weight loss, ear, nose and throat surgical procedures, bimaxillary or mandibular remodeling osteotomies, and neurostimulation procedures of the hypoglossal nerve.
Several studies have shown that the use of MADs is inferior in reducing the severity of OSAS in comparison to CPAP therapy, but its efficacy is comparable and preferred by patients in mild to moderate OSAS.
Due to the forward displacement of the lower jaw for several hours at night, similar symptoms as in temporomandibular dysfunction (TMD) patients may occur. The symptoms may be pain or tiffness on the masticatory muscles or temporomandibular joints.
This study aims to identify possible side effects in the temporomandibular system that occur during the course of two years of nocturnal MAD delivery. Two different

appliance systems are compared in terms of construction height (bite elevation) and protrusion mechanics: the H-MAD ™ with a hinge system according to Herbst and the SomnoDent Fusion ™ (called F-MAD) with sliding side wings.

Hypotheses

1. F-MAD significantly increases pain in the craniofacial aera (primary target variable) compared to H-MAD.
2. The F-MAD leads to a significantly increased number of pressure-pain areas of the masticatory muscles and temporomandibular joints compared to the H-MAD.
3. The F-MAD has a higher loss of posterior contact points than the H-MAD.

Study design

Multicenter, randomized two-arm Phase IV study with active control group, stratified by gender, unblinded with respect to the examiner, blinded to the patient and statisticians in the evaluation.

Primary outcome variable

The primary outcome variable is defined as the change of orofacial pain after applying the MAD as measured by numeric rating scale (NRS; 0-10, 0: no pain, 10: worst imaginable pain) at the time of the follow-up appointments.

Secondary outcome variables:

Dental variables:
- Number of pressure pain points on palpation of the masticatory muscles and in the area of the temporomandibular joints
- Number of posterior contact points
- Clinical occlusion protocol
- digital occlusion protocol determined with occlusal registrations in habitual intercuspidation; Evaluation by software GEDAS (Greifswald Digital Analyzing System) based on transparent contact areas.

Sleep-related variables:
- Sleep quality (Pittsburgh Sleep Quality Index PSQI)
- Epworth Sleepiness Scale (ESS)
- STOP-Bang questionnaire
- Oral Health Impact profile (OHIP-5)
- Apnea Hypopnea Index (AHI)
- Desaturation index (DI)
- Average oxygen saturation during sleep

Methods of data collection

The data collection is paper-based. For each patient, an analog study file is created. The main contents of the study file are the case report forms (CRF) and the questionnaires (PSQI, ESS, STOP-Bang, OHIP-5) and the AHI and EI).

The Pittsburgh Sleep Quality Index (PSQI) retrospectively asks for a four-week period the incidence of sleep disturbing events, sleep quality assessment, sleep habits, sleep latency and sleep duration, sleeping medication use, and daytime sleepiness. A total of 18 items are used for quantitative evaluation and assigned to 7 components, each of which can assume a value range of 0 to 3. The total score is the sum of the component scores and can vary from 0 to 21, with a higher score corresponding to a reduced sleep quality. There is an empirically determined cut-off value (of 5), which allows a classification into "good" and "bad" sleepers.

The Epworth Sleepiness Scale (ESS) is a short questionnaire for the detection of daytime sleepiness, in which the probability of falling asleep or falling asleep in eight typical everyday situations is retrospectively inquired. It can generally be used for sleep disorders, especially for hypersomnia, as a screening instrument for the global detection of daytime sleepiness or as an indication of the presence of hypersomnia. In addition, it is also suitable for measuring progress or success (for example in CPAP patients).

The STOP-BANG questionnaire is a screening for the presence of OSAS in the general population. A low OSAS risk exists if 0-2 answers yes, a medium OSAS risk if yes to 3-4, and high OSAS risk if yes to 5-8 questions.

The Oral Health Impact Profile (OHIP) is a measurement tool for assessing the oral health-related quality of life in adults. It can describe the individual oral health status of patients and measure and compare disease-related burdens in the course.

The Graded Chronic Pain Scale (GCPS) questionnaire records pain intensity and the presence of functional or dysfunctional chronic pain.

The Apnea Hypopnea Index (AHI) is a measure of how many breathing pauses in the form of apneas and hypopneas a patient experiences while sleeping. The AHI is determined in the sleep laboratory via a polysomnographic recording. Depending on the value of AHI, a distinction is made between mild, moderate and severe sleep apnea.

The desaturation index (dI) is the number of oxygen desaturations per hour of sleep.

The questionnaires (PSQI, ESS, OHIP-5, STOP-BANG, GCPS) are completed by the investigators in the form of an interview with the patient. AHI and DI are collected in the sleep laboratory.

Occlusion protocol: The tooth contacts between upper and lower jaw are recorded once with thin (ShimStock) slides for each tooth during the clinical examination. Furthermore, bite registrations in habitual intercuspidation (centric occlusion) are created from thinly flowing, addition-crosslinked silicone and scanned with a document scanner for evaluation in transmitted light. Layer thicknesses ≤ 20 µm are interpreted as occlusal contacts and assigned to the anatomical structures of the chewing surfaces (Greifswald Digital Analyzing System).

Functional Examination is designed to record masticatory jaw joint disorders based on a detailed history and subsequent clinical examination, palpation and orofacial inspection. For this purpose, a current and standardized examination procedure, the Diagnostic Criteria for TMD (DC/TMD) is used. This research toolkit also includes the Questionnaire on Chronic Pain Grading (GCPS), Jaw Functional Limitation Scale (Jaw Functionality), and Oral Behavior Checklist.

Treatment group 1:

Patients with snoring and OSAS, Therapy SomnoDent Fusion ™ Fusion MAD with sliding side wings (F-MAD).

Picking up to reach a 5 mm incisor distance using George Gauge with a lower jaw advancement of 5 mm with insertion of the MAD up to a final titrated mandibular advancement in the therapy phase.

Treatment group 2:

Patients with snoring and OSAS. Therapy with MAD type H-MAD with lateral hinges according to Herbst.
Bite elevation until reaching a min. 2 mm interocclusal distance and the lowest possible incisor distance with a lower jaw advancement of 5 mm with insertion of the MAD up to a final titrated mandibular advancement in the therapy phase.

Group strength: 97 patients per group (194 patients in total)

Description of the recruitment:

Patients are recruited at 7 dental or oral surgery clinics that specialize in the treatment of OSAS patients through MAD and are networked with referring sleep medicine centers.

Inclusion criteria:

- Patients with medical indication for mandibular protrusion (MAD) due to OSAS
- Therapy request for primary ronchopathy
- Age ≥ 18 years and ≤ 75 years
- BMI ≤ 35
- Mandible protrusion of min. 5 mm possible (titration starts at 5 mm)
- At least 8 teeth or 4 implants per jaw
- Fixed dentures and stable, removable partial denture
- at least support up to the area of the 2nd premolars on both sides
- Business ability and the existence of the signed declaration of consent

Exclusion criteria:

- Polyarthritis
- Fibromyalgia, neuralgia
- Central sleep apnea syndrome
- untreated generalized periodontitis PSI> 2
- Chronic dysfunctional pain after GCPS grade 3-4
- Age: <18 years or> 75 years
- long-term use of psychotropic and analgesics (> 4 weeks)
- pregnancy
- Participation in another interventional clinical study (currently up to three months before inclusion)

Experimental procedure

Calibrating the examiner

All Dentists will be trained and calibrated by the study leader prior to the start of the study in the investigation tools and the data collection. Training Center is the practice of Dr. med. med. Dr. med. dent. Jörg Schlieper, Osdorfer Weg 147 in 22607 Hamburg. At a still to be determined weekend, all the doctors are instructed in the course of the investigation and the questionnaire survey explained. Furthermore, the clinical functional examination will be demonstrated and subsequently practiced by the study physicians. All the doctors are calibrated to the palpation pressures to be applied and the overruling determined in a final test.

Sleep Laboratory

All patients received a structured general and somnological anamnesis and examination (height, weight, BMI, ESS, STOP-BANG, PSQI) in a first visit to the sleep laboratory. In addition, a stationary polysomnography or an outpatient polygraphy was performed there. Patients were referred to specialist dental practices for the preparation and integration of a MAD based on the diagnosis of sleep medicine for treatment of sleep apnea syndrome or snoring.

Baseline examination

Patient history and the dental status and periodontal screening index (PSI) are used to check inclusion and exclusion criteria for splint therapy. Subsequently, a functional status, occlusion protocol clinical and digital (GEDAS, Greifswald Digital Analyzing System), the questionnaires for pain chronification (GCSP) and quality of life (oral health impact profile, OHIP-5) are included.

To assess the health of the teeth and to ensure the success of treatment, an X-ray survey (panoramic radiograph) must be available before the treatment, which is not older than 6 months. Such an X-ray photograph can be made by the dentist or the specialized dental practice.

The functional status is determined by means of a standardized functional finding (DC / TMD). The questionnaires are based on validated recommendations.
All examination procedures are part of the routine patient diagnostics, which have been standardized for the individual practices for this project.

Randomization

The randomized grouping into blocks at a ratio of 1: 1 takes place over sealed envelopes containing the allocation key for the respective MAD. The assignment is stratified according to gender because gender is a strong predictor of sleep disorders and also temporomandibular dysfunctions.
Impression taking
Subsequently, the upper and lower jaws are molded to make the respective therapeutic splints and the protrusion registrations are taken. The starting position of the mandibular protrusion is set to 5 mm by default.

Integration of the MAD (start of treatment)

The laboratory-made MAD (F-MAD / H-MAD) is integrated (with a mandibular protrusion of 5 mm) and checked for a comfortable fit. Here, we paid attention to a

surface contact between OK-UK splint, and a tension-free fit of the splint portions on the rows of teeth. If necessary, interfering contacts are ground in. The patient is instructed to always wear the splint during sleep.
All patients receive an extended guide to jaw gymnastics with the instruction to do it in the morning after waking up and in the evening before falling asleep.

First control appointment (4 weeks after incorporation)

Four weeks after incorporation, the titration phase begins, d. H. the slow adjustment of mandibular advancement to optimize sleep medical parameters while minimizing unwanted side effects. The feed rate should be adjusted until clinical and sleep medical parameters are optimal or the patient can no longer tolerate further advancement.
The functional findings, the occlusion protocol, the questionnaires ESS, OHIP-5 and PSQI are collected.

Second control appointment (6 months after start of therapy)

Six months after the start of treatment, another examination is carried out in which the functional findings, the occlusion protocol and the questionnaires ESS, OHIP-5 and PSQI are collected.

Third control appointment (12 months after start of therapy)

A third check is made 12 months after the start of therapy. The functional findings, the questionnaires ESS, OHIP-5 and PSQI, the occlusion protocol, the bite registration for scanning and contact point analysis (GEDAS, Greifswald Digital Analyzing System) are collected.

Fourth control appointment (24 months after start of therapy)

The last examination is 24 months after the start of therapy. The functional findings, the questionnaires ESS, OHIP-5 and PSQI, the occlusion protocol, the bite registration for scanning and contact point analysis (GEDAS, Greifswald Digital Analyzing System) and new models are collected.

Sample size estimation

Determine the required sample size based on the numerical pain scale 0-10 for the primary target variable. Norms are pain scores of 3-5 (myofascial pain) in patients with temporomandibular dysfunction (TMD). To determine a mean difference of 1 level (standard deviation of 2) (1, 2) between the MAD, they must each comprise 78 patients.

Test method:

Wilcoxon-Mann-Whitney test with a two-sided $\alpha = 0.05$, a power = 0.90 assuming the family of logistic distributions (G * Power, version 3.1.)
The net sample consists of 156 persons. The annual dropout is 10% (3), so that for a study period of 2 years a total sample of 194 persons must be calculated (194 - 20 = 174 after 1 year, 174 - 18 = 156 after 2 years).

Statistical evaluation

The evaluation of the primary (and also the secondary) target variable is carried out according to the power analysis using ordinal regression as a generalization of the Wilcoxon-Mann-Whitney test. Adjustments are made according to sex as a stratification variable, age ("restricted cubic splines" with 3 nodes, which requires 2 coefficients), the baseline value of the respective target variable, the centers, the school education and, if appropriate, the blocks of randomization.
The intention-to-treat analysis set includes all patients assigned to one of the two groMAD and the built-up track; the "per protocol" set includes all patients with supported splints, primary target size data at 24 months and no relevant deviations from the study protocol. Sensitivity analyzes are performed with replacement of missing values via multiple imputation.
An interim evaluation is not planned.
Subgroup analyzes are not planned.
The 95% confidence interval is interpreted; the list of primary and secondary target sizes listed above allows $\alpha = 0.05$ to be left uncorrected (Cook & Farewell) (4).
At the University Medicine Greifswald, Center for Dental, Oral and Maxillofacial Surgery (ZZMK) the blinded evaluation of the data takes place.

This study is conducted with particular attention to the contents of the following laws and guidelines:
- Declaration of Helsinki in its current version (Fortaleza, 2013)
- Medical Devices Act - MPG
- Medical Device Operator Ordinance - MPBetreibV
- State Data Protection Act - DSG M-V
- General Data Protection Regulation - EU GDPR
10.1 Independent Ethics Committee
The study will only start after consultation with the responsible ethics committee and only if there are no ethical concerns. Responsible for the application to the ethics committee is the study director (Prof. Dr. Olaf Bernhardt).

Information and consent of patients

A patient may be included in the study only if he / she has given consent, after being informed orally and in writing by a dentist of the study of the nature, significance and implications of the study and having sufficient time to make the decision , He must also have declared with his consent that he agrees with the recording of data in the course of the study and its review by persons appointed by the study leadership (eg Monitor).
It is made clear to the patient that he can withdraw his consent at any time and without stating reasons without incurring disadvantages.
If new information emerges during the course of the study that could influence the willingness of the patient to participate, the patient information will be changed accordingly. The patient is informed by a dentist about the changes. Afterwards (provided sufficient time for reflection) the consent of the enlightening dentist and the patient must be re-signed.
The patient will be given an original of the written patient information and consent. A second original is safely kept in the study center.

Insurance

The study to be carried out is a clinical study of approved medical devices that have passed the conformity assessment procedure successfully, bear a CE mark and are used in accordance with the intended purpose. The study will not perform any additional invasive or stressful examinations. The course of study is based on the clinical routine. It is therefore not expected with study-related risks for the patient. The conclusion of a proband insurance is not provided.

Since the treatment process and the follow-up are based on the clinical routine and the patient has no study-related extra work in the form of additional visits, no path accident insurance is also completed.

Notice

The provisions of the data protection laws (in particular DSG MV and EU-DSGVO) are observed. It will be ensured that all research materials and data are adequately pseudonymised according to the data protection provisions before scientific exploitation. An assignment of personal data to the study data may only be done by the examiners .

Data management

Data collection

For each patient a study file is created, which i.a. contain the respective questionnaires, assessment of adherence, polygraphy and polysomonography measurements. The entries are with documents authentic pens, z. B. make ballpoint pen; Pencil entries are not allowed.

Corrections are made as follows: The wrong entry is crossed out with a simple line, the correct information is entered in the immediate vicinity, initialed with date and, if necessary, given with an indication of the reason for the correction. Data fields that can not be completed due to lack of information must be commented on. The test sheets are promptly filled in by persons who are entitled to the documentation, then checked by the study doctor and signed with a date.

Data Processing

The documentation sheets are checked by the monitor for completeness and plausibility (first plausibility check). Subsequently, data from independent data entry staff are entered and matched twice in the study database. During data entry, the second plausibility check is performed. Any discrepancies and implausibilities will be clarified in writing by the data submitter in writing with the study center concerned. These inquiries (queries) must be answered promptly by the study center.

Quality Assurance and Quality Control

A quality assurance tool is the calibration of the examiner. This ensures that all examiners work according to the same standards and guidelines and that there are no or negligible differences between the examiners.

The Coordinating Center Clinical Trials of the UniversityMedicine Greifswald takes over the monitoring of the study documents and the proper and GCP-compliant study execution according to the study protocol as well as the associated data collection as part of the quality assurance.

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