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Oral appliance for the treatment of obstructive sleep apnoea :

A randomized controlled blinded multicentre study comparing the effect of two devices

Abbreviated title: Oral appliance sleep apnoea

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Abstract

The use of an oral appliance (OA) is an established treatment for Obstructive Sleep Apnoea (OSA). It pulls the tongue forward and prevents the pharynx from collapsing and breathing becoming interrupted.

Two types of OA are used, a so-called monobloc OA and a two-piece so-called bibloc OA; the latter can be adjusted without the support of technicians. The cost of a bibloc OA is 50% higher, but the risk of side effects are considered to be less in the case of nightly bruxism. Evidence is, however, lacking for such a statement.

Our hypothesis is that a bibloc OA has the same effect on breathing as a monobloc OA and that treatment costs are comparable. Objective: to primarily compare the change in the Apnoea -Hypopnea Index (AHI) value after six weeks and secondary treatment costs during one year.

This RCT (two-centre) study has two parallel groups (monobloc OA and bibloc OA), each of 158 subjects. The subjects visits the participating clinics on five planned occasions: the enrolment visit (baseline), after three weeks for delivery of the appliance (start of treatment), a five-week control visit, a nine-week evaluation visit, and at the end of the study after one year. Registrations are made at clinical examination, from questionnaires, and from examination with polygraphiy i.e. the registration of respiration, oxygenation, body position, snoring, bruxism noise and electromyography (EMG) of a jaw muscle.

The recruitment base for the study is the patients with a diagnosis of OSA referred to the respective specialist dental care clinic.

The primary outcome variable is the difference in AHI, from baseline without OA vs. with OA at the evaluation visit.

Planned study period: the study will commence February 2014, the final evaluation visit in June 2015, and the study end in June 2016.

Study significance: the study data will help to fill several knowledge gaps, i.e. is the expensive bibloc OA as effective as the monobloc OA? Are treatment costs comparable? What impact has bruxism on treatment outcomes and side effects? The study will be a valuable contribution to increasing quality and design choice in treating individuals diagnosed with OSA. The benefit-risk balance in the trial is therefore considered to be positive.

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Abbreviations and definitions of terms

OA	Oral Appliance
AHI	Apnoea Hypopnea Index, i.e. number of apnoea e and hypopneae events per sleep hour
AI	Apnoea Index, i.e., number of apnoea e events per sleep hour
Apnoea	Total reduction (> 80%) of airflow through nose and mouth $\geq$ 10 seconds
CRF	Case Report Form
CPAP	Continuous Positive Airway Pressure
ESS	Epworth Sleepiness Scale. Scale from 0-24 describing daytime sleepiness
FOSQ	The Functional Outcomes of Sleep Questionnaire
Hypopnea	Airflow reduced by $\geq$ 50% for at least 10 seconds while SaO_2 is reduced by $\geq$ 4% or simultaneous arousal
ITT	Intention To Treat
ODI	Oxygen Desaturation Index, i.e. number of episodes with SaO_2 saturation reductions of $\geq$4% per sleep hour
OSA	Obstructive Sleep Apnoea
Polygraphy	Registration of sleep apnoea parameters and concurrent jaw muscle activity
PTR	Protrusion, the protrusion of the lower jaw is measured from the buccal surface of the upper jaw incisive to the lower jaw incisive + horizontal overbite
PP	Per Protocol
SaO_2	Oxygen saturation as a percentage of arterial blood haemoglobin
SaO_2 nadir	The lowest oxygen saturation as a percentage of arterial blood haemoglobin during the registration time

Introduction

A diagnosis of obstructive sleep apnoea (OSA) is caused by the pharyngeal obstruction that prevents or decreases airflow during sleep and is associated with snoring and, often, daytime sleepiness. The severity of respiratory distress is graded with the Apnoea Hypopnea Index (AHI), which measures the number of apnoea and hypopnoea events per hour during sleep. The OSA rating is mild (AHI 5-14), moderate (AHI 15-29) and severe (AHI $\geq$ 30). AHI values <5 are considered normal (1). There is a co-variation between OSA and cardiovascular disease including stroke and premature death in men (2).

The treatment of OSA usually includes various treatment options such as general lifestyle advice (weight loss), surgery, an Oral Appliance (OA), and Continuous Positive Airway Pressure (CPAP), i.e. an airway pressure ventilator which applies mild air pressure on a continuous basis. The recommendation is to treat moderate/severe

OSA with CPAP and mild/moderate OSA with an OA (3). Those who do not tolerate CPAP are usually offered an OA (3).

Treatment of OSA with an OA aims to pull the tongue/tongue base forward to prevent pharyngeal collapse during sleep. An effective OA not only prevents snoring and respiratory arrest but also decreases daytime sleepiness and reduces swelling of the pharyngeal mucosa (4). Pharyngeal lumen increases with the degree of mandibular advancement (4) concomitant with increased risk of dental/occlusal changes (5). The risk of adverse effects in terms of pain from the jaw muscles and jaw joints, which results in opening and chewing difficulties, also increases with the degree of advancement.

The traditional type of OA is a so-called monobloc OA. i.e., a one-piece device that grips around the teeth in both the upper and lower jaw, and the jaw is thus locked in a protruded position. In recent years, two-piece OAs, called bibloc OAs, have begun to be marketed. In this case, one appliance is made for each jaw and the two appliances are connected with replaceable connectors in such a way that the lower jaw is forced into a protruded position. A bibloc OA can be adjusted by the dentist at chairside while the monobloc OA must be sent to a dental technician to be changed, which results in an additional treatment visit. A bibloc OA could therefore save chair time and, thus, costs, but this assertion lacks evidence today. The risk of damage to the OA construction is considered to be less with a bibloc OA in case of nightly bruxism, but the evidence is lacking for such an assertion. On the other hand, it has been confirmed that bruxism activity is reduced when using an OA (6, 7). There are also indications that bruxism activity is reduced more with an OA compared with a traditional occlusal bite appliance (7).

A bibloc OA costs about 50% more than a monobloc OA. There are also indications that, in some cases, a bibloc OA increases respiratory arrest (unpublished data from the researcher’s clinic).

During year 2010-2011, Swedish patients began receiving treatment with a bibloc OA from the "Narval" brand (8) (hereinafter called bibloc OA) at the Department of Orofacial pain and jaw function at Västmanland County Hospital in Västerås, as well as at the Department of Dental Sleep Medicine, Postgraduate Dental Education Center, Örebro. The treatment costs and outcomes of the bibloc OA compared with the monobloc OA are not known.

Hypothesis and objectives

The hypothesis is that a bibloc OA has the same effect on respiration as a monobloc OA when treating OSA after six weeks of treatment and that treatment costs over one year are comparable.

The primary objective of this study is therefore to compare one type of bibloc OA with one type of monobloc OA after six weeks of use with respect to the reduction of the AHI value.

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The secondary objective is to evaluate the difference in the total treatment costs, including the purchase price of the appliances plus dental office costs over one year. Over the same period, compliance will be evaluated in the use of the respective appliance as well as in daytime sleepiness.

The secondary objective after 6-weeks of treatment includes changes in daytime sleepiness, the respiratory parameters ODI, SaO_2 nadir, time with $SaO_2 < 90\%$, SaO_2 average, the subjects´ experience of the OA, and the subjects´ and the relatives´ assessment of snoring and respiratory arrests as well as adverse events. In addition, the degree of bruxism is evaluated as a confounder for treatment outcomes and side effects.

Material and methods

Study design and flowchart

This study of patients with OSA is designed as a randomized single-blind, controlled multi-centre (two-centre) trial with two parallel groups of 158 subjects each, in which one group is treated with a monobloc OA and one with a bibloc OA. The subjects are consecutively refereed patients to the respective clinic with a diagnosis of OSA. The study team at each centre consist of two dentists and one nurse. To the study an independent person will analyze the polygraphic data based solely on a subject's enrolment number and who will be completely blinded to the choice of treatment.

The subjects visited the clinic on five planned occasions.

Visit 1: Selection and informing the subject, informed consent obtained, assignment of enrolment number. Dentist # 1 check the inclusion and exclusion criteria and register the clinical variables. The subject completes questionnaires. Dentist # 1 assisted by the study nurse, make impressions of the upper and lower jaws in alginate and takes an index for production of the OA. The material is then transferred to another room where the study nurse opens a randomization envelope with its randomization number, pack the material and sent it to the technical laboratory that would manufacture the type of appliance specified by the randomization. Dentist # 1 is blinded to the choice of OA. Polygraphic equipment is handed out after instruct the subject how to apply the equipment for a night's sleep. The data collected on this day and the following night will be referred to as the baseline registrations.

The polygraphic equipment will be returned to the study nurse on the following day.

Visit 2: The start of treatment visit three weeks ± 7 days after visit 1 - repeated check of the inclusion criteria. Dentist # 2 hands out the OA. The subject is instructed in how the device is to be used and maintained. At the end of the visit, the subject is asked if she/he experience any health concerns during the visit.

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Visit 3: The control visit two weeks (±3 days) after the start of treatment. Dentist # 2 checks the appliance and make adjustments if needed.

If the subject indicates that the OA had not intended effect on respiration / snoring / daytime sleepiness or if symptoms of the jaws occurred, then the degree of protrusion of the lower jaw is adjusted. Adjustment of the bibloc OA will be carried out at the clinic during the visit. Adjustment of the monobloc OA requires a new index and the appliance with models and the new index will then be sent to the technician. The subject then returns within one week (± 2 days) to have the adjusted appliance fitted.

The subject will be asked if they had experienced any health problems since the start of the treatment.

Extra visit: A monobloc ABS that requires the technician's adjustment or a bibloc-ABS that required additional technical adjustment. Dentist # 2 will always be responsible. The number of extra visits are recorded.

Visit 4: The evaluation visit six weeks ± 7 days after visit 3. Dentist # 1 solely, performs a clinical examination, asks for any health problems and collects questionnaires without knowing what kind of appliance had been used. Polygraphic equipment will be handed out for return the following day.

The subject will be notified by telephone or by post the data recorded at baseline and at the evaluation visit. Those subjects who, according to the clinic's routine, not achieving the desired treatment effect of their OA will be forwarded to the lung or otorhinolaryngology clinic for assessment of alternative treatments, but then outside the study protocol.

Visit 5: The one-year evaluation. Dentist # 1 performs a clinical examination of the subject and collects questionnaires

Table 1. Schedule of study events from the baseline visit to the end of study

	Visit 1 Baseline visit	Visit 2 Start of treatment	Visit 3 Control visit	Visit 4 Evaluation visit	Visit 5 1-year study end
	0w	3w	5w	9w	1 yr
Inclusion-exclusion criteria	x	x			
Informed consent *	x				
Randomization **	x				
Clinical examination	x			x	x
Questionnaire	x			x	x
Impressions of teeth	x				
Appliance hand out		x			
Polygraphy	x			x	
Observed adverse events		x	x	x	x
Observed adverse events		x	x	x	x

* Allocation of enrolment number
** Allocation of randomization number

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Study subjects

The recruitment base for the study will be patients referred to the specialist dental care clinic from the otorhinolaryngology or lung clinic at Västmanland Hospital Västerås and from the lung clinic at Örebro University Hospital, with the following inclusion and exclusion criteria:

Inclusion criteria

- A diagnosis of obstructive sleep apnoea with respiratory data AHI $\geq$ 15 without respiratory aid according to the referral
- Odontological status allowing retention of an OA construction in the mouth and with at least one molar in each jaw quadrant
- Maximum protrusion $\geq$ 6 mm
- Willing to be included in the study and written informed consent
- Understand and able to communicate in Swedish
- Expected to understand instructions and put on/take off the polygraphic equipment at home
- Valid respiratory data at baseline polygraphy

Exclusion criteria

- Age <18 years
- BMI >35
- Jaw function complaints that required treatment during the previous year
- Pain or locking of the jaw during the baseline visit
- Assessed by investigative dentists as unable to follow the study instructions
- Hypersensitivity to the materials included in the oral appliances
- Ongoing CPAP or OA treatment or end of such treatment in the previous month

Intervention with Oral appliances

Bibloc OA

All the bibloc OAs are manufactured by the company ResMed according to a model called "Narval", a CAD/CAM produced polyamide device with an appliance in each jaw that is connected by connectors keeping the lower jaw in a protruded position. With the device in place, the trial subject could open the mouth to a certain degree whilst keeping the lower jaw in the protruded position. The appliance could be easily adjusted during the treatment visit and the grip around the teeth can be adjusted with a heat gun and the degree of mandibular

protraction could be changed by changing to a shorter or longer linking arm. Prior to the evaluation visit, no additional arrangements are allowed to connect the upper and lower part of the device.

Monobloc OA

Produced by two companies, Boxholm Tandteknik and Public Dental Service, Örebro, after individual primary models in wax, which then is transferred to heat-polymerized methyl methacrylate. The construction fixate the mandible in the dentist's predetermined position. If the position of the lower jaw needs to be adjusted to create better treatment results, it is necessary to create a new index for the position of the mandible. This requires the involvement of a technician for the adjustment of the appliance with the consequence of an additional treatment visit.

OA handling

The treatment of the two groups follows the same care routine. Impression of both the lower and upper jaws is made in alginate. Using an instrument (George Gauge™), the overall jaw protrusion (PTR) is measured, i.e., the distance from a maximum retracted to a maximum protruded position of the lower jaw. The instrument's bite fork (2 mm thickness) is fixed in a position that is 75% of the maximum PTR or at least 5 mm and an index in Tenax vax is produced. The laboratory produce plaster models from the alginate impressions and the index defines how the lower jaw relates with the upper jaw in the construction.

The subjects are encouraged to use their OA every night and throughout the entire night for the duration of the study period. If the subject during the course of the control visit two weeks after the start of treatment reports an incomplete effect, an adjustment of the appliance should be made. This is aimed at further advancing the lower jaw which for monobloc OA-treated subject cause an extra visit. The subjects reporting jaw / jaw muscle complaints are handled individually depending on the nature of the problem.

Those subjects who, regardless of the design, needs according to their own judgment to have their appliance adjusted or who has symptoms from jaws or teeth, should be offered extra visits.

Treatment compliance

The subject note in the questionnaire how much the device has been used. A use with the appliance in the mouth $\geq$ 75% of sleep time is considered valid for a "per protocol" analysis. Each subject also filled in a “sleep diary” when going to bed, when falling asleep and awakening all days from the enrolment visit to the evaluation visit.

Treatment costs

The treatment costs during the one-year treatment period is calculated as follows:

- construction price from the laboratory (+ possible additional costs for adjustments)
  plus
- dental office time calculated on a flat-rate basis as one hour for the first visit and 30 minutes for all other visits.

Dental costs are calculated according to the Swedish *Dental and Pharmaceutical Benefits Agency* price list, correct as of July 1, 2014.

Treatment in case of no effect

During the course of the study, the subject underwents treatment with only one of the two OA appliances. At evaluation visit and if polygraphy data indicate an incomplete effect of the oral appliance, the subject is offered CPAP or other appropriate treatment according to the established routine at the respective clinic. This treatment will be done outside the study protocol. At the end of the study after one year, the subject will then be registered as having "discontinued treatment due to incomplete effect".

Previous treatment and other treatment during the study period

OA naive subjects will be included. Subjects previously treated with CPAP are allowed to be included provided that such treatment is terminated at least one month prior to inclusion in the study. No treatment in addition to the randomized apnoea appliance is allowed during the study period.

Polygraphy

Respiratory examination as a basis for primary inclusion in the study is done by the respective hospital physiology clinic using a 3-channel polygraphy equipment (Embletta™, ResMed) for one night.

Within the study, registration of respiration parameters is made using portable equipment, NOX-T3™[1], for use at home. All study participants will be subjected to one night's polygraphic examination at baseline and one night in conjunction with the evaluation visit.

NOX-T3™ is a device with a nasal pressure cannula that records airflow and pulse oximeter for the measurement of arterial oxygen saturation and pulse. Posture as well as chest and abdominal movements are also registered. Snoring is recorded with an integrated microphone. Electrodes for electromyography, EMG, measure m. masseter activity.

[1] http://www.noxmedical.com/products/

Outcome variables are analyzed using Noxturnal™ software[2] for individual interpretation of the polygraphic data. A trained biomedical analyst linked to the Department of Physiology at Västmanland County Hospital Västerås makes all the analysis blinded to the choice of treatment.

Data are considered valid at a total recording time ≥ 4 hours. If the registration time is shorter, the examination will be repeated within the next few days and treatment will commence when the valid baseline values are obtained. Those subjects who did not deliver valid NOX-T3™ data after two attempts are excluded from the study.

EMG and bruxism

Concomitant with the study subject being instructed in the use of the polygraphic equipment, EMG electrodes are applied to the m. masseter on one side and an earth electrode over the collarbone on the same side. In a regular bite position, the person is prompted to bite as hard as possible and the maximum amplitude of the EMG signal is recorded.

From the survey night, all masseter EMG potentials associated with bruxism activity are identified on the audio records. The signals that have an amplitude of at least 20% of the maximum voluntary contraction are marked as a burst of bruxism (7). Episodes of bruxism are separated by intervals of at least 3 seconds.

According to Lavigne et al (9) the definition of a noxturnal bruxer is when the following three criteria are met

- > 4 episodes of bruxism per hour
- > 6 bursts of bruxism per episode and / or 25 bruxism bursts per hour of sleep
- ≥ 2 episodes of bruxism noise as measured by the microphone on the NOX-T3 equipment

Study variables

Primary efficacy variable

The primary efficacy variable is the difference in AHI from baseline without appliances vs. with appliances during the evaluation visit nine weeks after baseline.

Secondary efficacy variables

- Polygraphic data
    - ODI
    - AI
    - SaO_2 nadir
    - Time with SaO_2 <90%
    - Mean SaO_2

[2] http://support.noxmedical.com/entries/20804878-Noxturnal-Software-Manuals

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- Bruxism
- Snoring
- Sleep efficiency

- Subject-reported variables

Sleepiness during the day	Numerical grading scale 0-10, 0 = no sleepiness and 10 = worst imaginable sleepiness
ESS	Epworth Sleepiness Scale. Verbal scale for assessing daytime sleepiness with eight questions, each graded: never, slight, moderate, high. The grading is transcribed to numerical values, 0-3, for each question and the scale then received a range from 0 to 24 (10)
FOSQ	Psychometric instrument on the consequences of sleep disorders. Validated in Swedish OSA patients (11)
Awakening at night	Yes/No. events per night. An average for the previous week
Apnoea events	Yes/No. Disturbed / wakes up, bed partner worried
Snoring	Yes/No. Disturbed by own snoring, Snoring disturbes others
Own problems with snoring	Free text
Rating of how important the appliance is for the subject / partner	Numerical grading scale, 0 = no importance and 10 = greatest possible importance
The effect of the OA treatment	Verbal predefined scale (0-7): very much worse, much worse, slightly worse, unchanged, slightly improved, much improved, very much improved
Problems when using the appliance	Free text

Treatment compliance

Number of nights per week with the OA	Number: 0 to 7
Percentage of sleep time with the OA	0 to 100%
If the OA is not used	Reason why the OA is not used all night, free text

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Clinical registrations for the assessment of inclusion and adverse events

Occlusal contacts	Yes/No. Normal occlusion contacts on one or both sides. The operator holds a pair of Miller tweezers with an occlusion foil between the teeth while the subject bites together gently.
Palpation tenderness of jaw muscles	Yes/No. Unilateral or bilateral tenderness on palpation of m. masseter and/or m. temporalis.
Painful jaw movement at jaw muscles	Yes/No. Trial subject reports painful jaw movement from unilateral or bilateral m. masseter and/or m. temporalis when opening the mouth
Restricted condyle translation	Yes/No. Unilateral or bilateral restriction of condylar translation assessed by the operator by placing fingers on the skin over the jaw joints whilst maximally opens the mouth.
Jaw joint noise	Yes/No. Unilateral or bilateral TMJ noise. The operator assess the occurrence of noise by listening without aids while gently touching the skin anterior to the jaw joints whilst the subject opens the mouth.
Painful jaw movement at jaw joint	Yes/No. Unilateral or bilateral painful jaw movement. The subject reports pain and points to the actual joint whilst fully opening the mouth.
Palpation tenderness of jaw joints	Yes/No. Unilateral or bilateral tenderness of over and around the condylar pole.

Jaw function measurements

Maximum PTR (mm) in the premolar area	The distance between the retruded to maximum protruded jaw position. The operator maks a vertical mark on the upper jaw's second premolar. With a slight pressure against the chin, the lower jaw is guided to a retroded position and a mark made that is congruent to the vertical line upper jaw premolar mark. Thereafter, the subject is asked to push the lower jaw to a maximum protruding position and with a steel ruler in the occlusal plane the protrusion is measured.
Maximum mouth opening capacity (mm).	The distance between the incisors at maximum mouth opening without assistance + vertical overbite

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Other clinical registrations

Protrusion of the lower jaw with the OA in place (mm)	Will be measured in the premolar area. The markings listed above will be used for assessment of the lower jaw protrusion with a monobloc OA which is made of transparent plastic. Bibloc OA: the same type of measurement as for the monobloc ABS but markings are made on the appliance in the upper jaw and the lower jaw with and without the connection rod attached.

Safety registration

Incident (adverse event) definition: an incident is an accidental and unfavourable sign or symptom of illness associated with the use of an OA, regardless of whether it has a causal link with the design. The severity is judged to be "serious" or "non-serious".

A serious incident is defined as:

- resulting in death
- is life threatening
- requiring hospitalization or extends ongoing hospitalization
- resulting in permanent or significant disability
- a congenital anomaly / birth defect

The investigator assess the causal link between the treatment and the serious incident according to the following classification:

1. Probably related. There is a time causal link. No other causal factors exist.

2. Possibly related. There is a time causal link. Other causal factors may exist.

3. Not Related. No temporal causal relationship or doubtful and / or other confirmed or probable factors exist.

Procedures for incident registration: information regarding incidents is recorded from the time of OA delivery to the end of the study one month after treatment.

At the end of the treatment visit, during the evaluation visit, and at the one-year evaluation, the subjects are asked if they had experienced any incidents via the following standardized questions:

"Have you had any health problems since you started treatment?"

"Have you had any health problems with your jaw / mouth since you started treatment?"

"Have you had any health problems since leaving the clinic?"

"Have you had any health problems with your jaw / mouth since leaving the clinic?"

In addition, incidents will be recorded that are spontaneously reported by the subject or that are observed by the study staff from the time of OA delivery to the end of the study. All incidents are recorded on the CRF.

Intensity of the incident is graded as either mild, moderate or pronounced:

Mild: aware of signs or symptoms but that are easily tolerated.

Moderate: discomfort to such an extent that it affects normal activities.

Pronounced: performance impaired to such an extent that normal activities could not be done.

Symptoms reported during the study: local reactions are reported as an incident if there is a significant change compared with baseline. Unfavourable changes in respiratory data from the time of OA delivery to the end of the study are recorded as an effect parameter and not as an incident.

Report of incidents and side effects: the coordinating investigator / sponsor is responsible for informing the Ethics Committee of any serious side effects.

Statistical methods

Calculation of sample size (power)

The primary variable, AHI, is a continuous response variable. The magnitude of the difference in AHI value with and without OA treatment and estimation of expected standard deviation (SD) is based on data from an open-label prestudy of 113 patients treated with a monobloc OA and 58 patients with a bibloc OA at the Department of Orofacial pain and jaw function at Västmanland County Hospital.

When the size of the sample in each group is 144, based on an unpaired t-test with a one-sided significance level of 0.025 (the same as double-sided 0.05), the study has 80% power to reject the zero hypothesis that test and standard are not equivalent (mean difference, $\mu_T - \mu_{S)}$, is 5.0 or more from zero in the same direction in favour of the alternative hypothesis that the mean difference is 0.0 and the expected SD 15.0, and is the same in both groups. The power calculation is made with Nquery Advisor software[3]. The assessment is that there could be a loss of 10% to the evaluation visit nine weeks after baseline and, therefore, 158 subjects are included in each group.

Analysis methods

The bibloc OA group is compared with the monobloc OA using an unpaired t-test where the mean difference of AHI between the groups will be reported with 95% confidence intervals on a subject's absolute change of AHI without an OA at baseline and with an OA during evaluation visit.

[3] Statistical Solutions Ltd, Cork, Ireland

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Polygraphic registration of m. masseter activity at baseline constitutes the basis for classification of the subject as "bruxist" or "non-bruxist". A Wilcoxon rank sum test is used to test the effect of bruxism on both effect parameters and side effects. Secondary variables are analyzed with descriptive statistics.

Randomized, but untreated subjects are considered invalid for analysis. Subjects with invalid respiratory data at baseline are also considered invalid for analysis. The exclusion and its cause are reported.

The main analysis of the study is done on an Intention-To-Treat (ITT) population in which all randomized and treatment initiated subjects are included. All missing observations are extrapolated by applying a "last observation carried forward" procedure.

Randomized subjects excluded for reasons not related to side effects are replaced by the same number.

When all the subjects had passed their evaluation visit, an independent statistician makes an interim analysis for the first part of the study, i.e. the main topic and primary variable associated data, which are data from baseline to the evaluation visit nine weeks after baseline. The second part of the study that includes the one-year follow-up is evaluated when all the subjects passed the one-year evaluation and the code is broken.

Randomization

Randomization is generated via the website http://randomization.com. Sealed envelopes labelled with the randomized treatment method and randomization number are prepared by a person who is not linked to the trial.

Records management, monitoring and data management

Two independent monitors from the Centre for Clinical Research (CKF), Västmanland County Council, and the Odontological Research Unit, Örebro County Council, will check the source data of the study against the data specified for the study's variables as well as for the safety records, all according to a monitoring plan (not included). The CRFs from the various centres are collected by the monitor, and associated staff enters data into the study database and establish "clean file" when all the study data are entered and checked.

The patient's record had to state the name of the study, the randomization number, the date when the subject signed the informed consent form, an indication that all the inclusion / exclusion criteria had been met, as well as the date when the investigator terminated or interrupted the study. The record must also indicate how the code could be broken in the case of emergency.

The investigator and the sponsor establish and store the documents with the recorded data from the study. The data will be made available in legible condition throughout the filing period which is 10 years after completion of the study. The CKF in Västerås is responsible for the archiving of all the study data and the data files are protected by privacy rules, archives ordinance and the patient data act. The respective clinics also archiv the data from their subjects under the same regulatory system.

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ETHICS

Ethical application will be submitted to the Ethics Committee in Uppsala according to the study schedule. The study will be conducted in accordance with the principles of the Helsinki Declaration.

The final study protocol, including trial subject information and the informed consent form, must be approved by the Ethics Committee before any subject is enrolled in the study.

The investigator is responsible for ensuring that each subject receives complete and adequate oral and written information about the study and its implementation, purpose, risks and benefits. Time also had to be given so that the subject could ask questions and, if possible, be allowed a period of reflection regarding participation in the study. The investigator is responsible for ensuring that all the subjects provided written consent before their enrolment.

The subjects are also informed that at any time, they could interrupt their participation in the study without affecting their care at the respective clinic.

STUDY PERIOD

- The ethics review to be submitted in January 2014
- Calibration of centres / personnel and logistics planning from December 2013 to January 2014
- The study will begin in February 2014 to be completed in June 2015 for all evaluation visits, and the study will end in June 2016
- Data processing, analysis and reporting of results June to November 2016

THE CONSEQUENCE OF THE STUDY

The results of this study will help to fill several knowledge gaps in the treatment of apnoea patients. Is the expensive bibloc OA as effective as the affordable monobloc OA? Do the two constructions have comparable healthcare costs, and what impact has bruxism on treatment outcomes and side effects? The study will be a valuable addition to increasing quality and design choice in treating individuals diagnosed with OSA. The benefit-risk balance in the trial is therefore considered to be positive.

This is a direct translation of the study original protocol made November 2017

References

1. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667-89. Epub 1999/08/18.

2. SBU. Obstructive Sleep Apnoea Syndrome. A Systematic Literature Review. Swedish Council on Technology Assessment in Health Care (SBU). 2007;SBU-report # 184E. ISBN 978-91-85413-16-4.

3. Kushida CA, Morgenthaler TI, Littner MR, Alessi CA, Bailey D, Coleman J, Jr., et al. Practice parameters for the treatment of snoring and Obstructive Sleep Apnoea with oral appliances: an update for 2005. Sleep. 2006;29(2):240-3. Epub 2006/02/24.

4. Fransson AM, Svenson BA, Isacsson G. The effect of posture and a mandibular protruding device on pharyngeal dimensions: a cephalometric study. Sleep & breathing = Schlaf & Atmung. 2002;6(2):55-68. Epub 2002/06/21.

5. Fransson AM, Tegelberg A, Svenson BA, Lennartsson B, Isacsson G. Influence of mandibular protruding device on airway passages and dentofacial characteristics in obstructive sleep apnoea and snoring. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 2002;122(4):371-9. Epub 2002/11/02.

6. Landry ML, Rompre PH, Manzini C, Guitard F, de Grandmont P, Lavigne GJ. Reduction of sleep bruxism using a mandibular advancement device: an experimental controlled study. The International journal of prosthodontics. 2006;19(6):549-56. Epub 2006/12/15.

7. Landry-Schonbeck A, de Grandmont P, Rompre PH, Lavigne GJ. Effect of an adjustable mandibular advancement appliance on sleep bruxism: a crossover sleep laboratory study. The International journal of prosthodontics. 2009;22(3):251-9. Epub 2009/06/25.

8. Vecchierini MF, Leger D, Laaban JP, Putterman G, Figueredo M, Levy J, et al. Efficacy and compliance of mandibular repositioning device in obstructive sleep apnoea syndrome under a patient-driven protocol of care. Sleep medicine. 2008;9(7):762-9. Epub 2007/11/06.

9. Lavigne GJ, Rompre PH, Montplaisir JY. Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study. Journal of dental research. 1996;75(1):546-52. Epub 1996/01/01.

10.Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5. Epub 1991/12/01.

11.Korpe L, Lundgren J, Dahlstrom L. Psychometric evaluation of a Swedish version of the Functional Outcomes of Sleep Questionnaire, FOSQ. Acta odontologica Scandinavica. 2013;71(5):1077-84. Epub 2012/11/21.