Sleep Care – Greenslopes Private Hospital

Research Proposal

Can mandibular advancement improve CPAP effectiveness in patients sub-optimally treated with CPAP using an oronasal mask?

Principle Investigator – Dr Robyn O'Sullivan
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GREENSLOPES PRIVATE HOSPITAL

Contents

1 STUDY DESCRIPTION

1.1 Formal title

Can mandibular advancement improve CPAP effectiveness in patients sub-optimally treated with CPAP using an oronasal mask?

1.2 Short title

Combination therapy for OSA.

1.3 Study description

Obstructive sleep apnoea (OSA) is common[1] and an important contributor to cardiovascular disease,[2-6] stroke,[3, 7, 8] and depression.[9] The first line treatment for OSA is continuous positive airway pressure (CPAP) which is highly effective in treating OSA. However, up to 50% of patients are unable or unwilling to tolerate CPAP[10, 11]. Nasal masks are most frequently used, however oronasal masks covering the nose and mouth, may be chosen due to patient preference, nasal obstruction or air leak through the mouth. There is growing evidence suggesting that oronasal masks are less effective in controlling OSA. Patients using oronasal masks are a clinically difficult group of patients to treat, often requiring higher CPAP pressures, with significant mask leaks, a higher residual AHI and lower adherence to treatment[12-14].

Mandibular Advancement Devices (MAD) are emerging as an alternative treatment particularly in patients with mild to moderate OSA, CPAP intolerant OSA and primary snorers [15, 16]. The O_2Vent T is a custom-made MAD with an enclosed airway that allows airflow through the device. Like all MADs, the lower jaw is brought forward to stabilize the upper airway, however unlike other devices, patients can also breathe through the device while the jaw position stabilized. This may be of benefit to those with nasal obstruction and a tendency to mouth breathe i.e. patients using oronasal masks.

Our aim is to assess whether treatment effectiveness can be improved with combination CPAP and MAD, in a group of patients with OSA who are sub-optimally treated with CPAP using an oronasal mask. Treatment effectiveness is a clinical decision based on factors including compliance, residual Apnoea-Hypopnea Index (AHI), pressure requirements and leak.

We hypothesize that compared to CPAP with oronasal mask, combination therapy will result in:

a) Lower pressure requirements

b) Lower AHI

c) Lower leak

d) Better compliance

Participants will be monitored for CPAP efficacy and compliance using their oronasal mask for 1 month whilst using an auto-titrating CPAP (APAP). They will be fitted with a customized MAD (O2Vent T) at 60% max protrusion and continue to use APAP. APAP will be downloaded after 1 week of combined treatment. Further advancement of MAD will occur if clinically indicated over a 3-8week period with downloads and reviews as clinically indicated. CPAP effectiveness will be compared using download data with CPAP alone, CPAP and MAD at 60% protrusion, and CPAP and MAD at final advancement.

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2 RESEARCHER'S DETAILS

2.1 Principle Investigator

Full name of Principal Investigator: Dr Robyn O'Sullivan
Full mailing address: Suite 3a Admin Bdg, Greenstones Private Hospital
Newdegate St, Greenslopes QLD 4120
Business Hours Phone Number: 07 3397 1488
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Email Address: robynosullivanatgph@bigpond.com

2.2 Co-investigators

Full name of Co-Investigator: Dr Tim Baird
Full mailing address: Sleep Care Sleep Investigation Unit, Greenslopes Private Hospital
Newdegate St, Greenslopes QLD 4120
Business Hours Phone Number: 07 3394 7036
After Hours Phone Number (optional)
Email Address: tmbaird@gmail.com

3 LIST OF PLACES WHERE RESEARCH IS BEING UNDERTAKEN

This research is being conducted at:

Sleep Care - Greenslopes Sleep Investigation Centre

Greenslopes Private Hospital

Newdegate Street

Greenslopes QLD 4120

PHONE: 3397 3036

PHONE: 1300 753 375

FAX: 3397 3013

Patients prescribed MAD will be assessed for MAD suitability, fitted with MAD and followed from the Dental aspect at:

Breathing Assist Solutions*

1 Swann Road

Indooroopilly QLD 4068

PHONE: 1300 416 743

* whilst MAD treatment and dental follow up will occur at Breathing Assist Solutions, all the research is being conducted at Sleep Care, Greenslopes Sleep Investigation Centre.

4 PROJECT RATIONALE AND OBJECTIVES

Our aim is to assess whether treatment effectiveness can be improved with combination CPAP and MAD, in a group of patients with OSA who are sub-optimally treated with CPAP using an oronasal mask. Treatment effectiveness is a clinical decision based on factors including compliance, residual Apnoea-Hypopnea Index (AHI), pressure requirements and leak.

We hypothesize that compared to CPAP with oronasal mask, combination therapy will result in:

a) Lower pressure requirements
b) Lower AHI
c) Lower leak
d) Better compliance

5 PROPOSED METHODS

5.1 Design of study

Prospective case series to determine whether treatment effectiveness can be improved with combination CPAP and MAD, in a group of patients with OSA who are sub-optimally treated with CPAP using an oronasal mask.

Participants will be monitored for CPAP efficacy and compliance using their oronasal mask for 4 weeks whilst using an auto-titrating CPAP (APAP). They will be fitted with a customized MAD (O2Vent T) at 60% max protrusion and continue to use APAP. APAP will be downloaded after 1 week of combined treatment. Further advancement of MAD will occur if clinically indicated over a 3-12week period with downloads and reviews as clinically indicated.

CPAP effectiveness will be compared using download data with CPAP alone (4 weeks), CPAP and MAD at 60% protrusion (1 week), and CPAP and MAD at optimal advancement (1 week).

Whilst this is a prospective case series, previous CPAP downloads and sleep study results will be used to evaluate current treatment effect and assess the meeting of inclusion criteria as sub-optimally treated with CPAP. Data from previous sleep studies and downloads may also be collected as part of this research.

5.2 Duration of the study

The total time for this research study is approximately 12 months.

From enrolment, it is anticipated that trial participation will be approximately 2-3 months depending on the amount of mandibular advancement that will be indicated and depending on the time to reach optimal advancement. This is an approximation only as there is individual variability in the level of advancement required as well as the time taken to reach optimal advancement.

5.3 Selection of patients

Participants will be selected based on the following inclusion criteria:

1. Age ≥ 18 years old
2. Obstructive sleep apnoea as diagnosed by polysomnography in the last 5 years with AHI>5
3. Current treatment with CPAP and oronasal mask deemed as suboptimal
4. Assessed as dentally suitable for oral appliance
5. Able to provide written informed consent to all study procedures, investigators to access clinical records from treating physician and agrees to adhere to all protocol requirements
6. Geographically suitable and able to travel across town

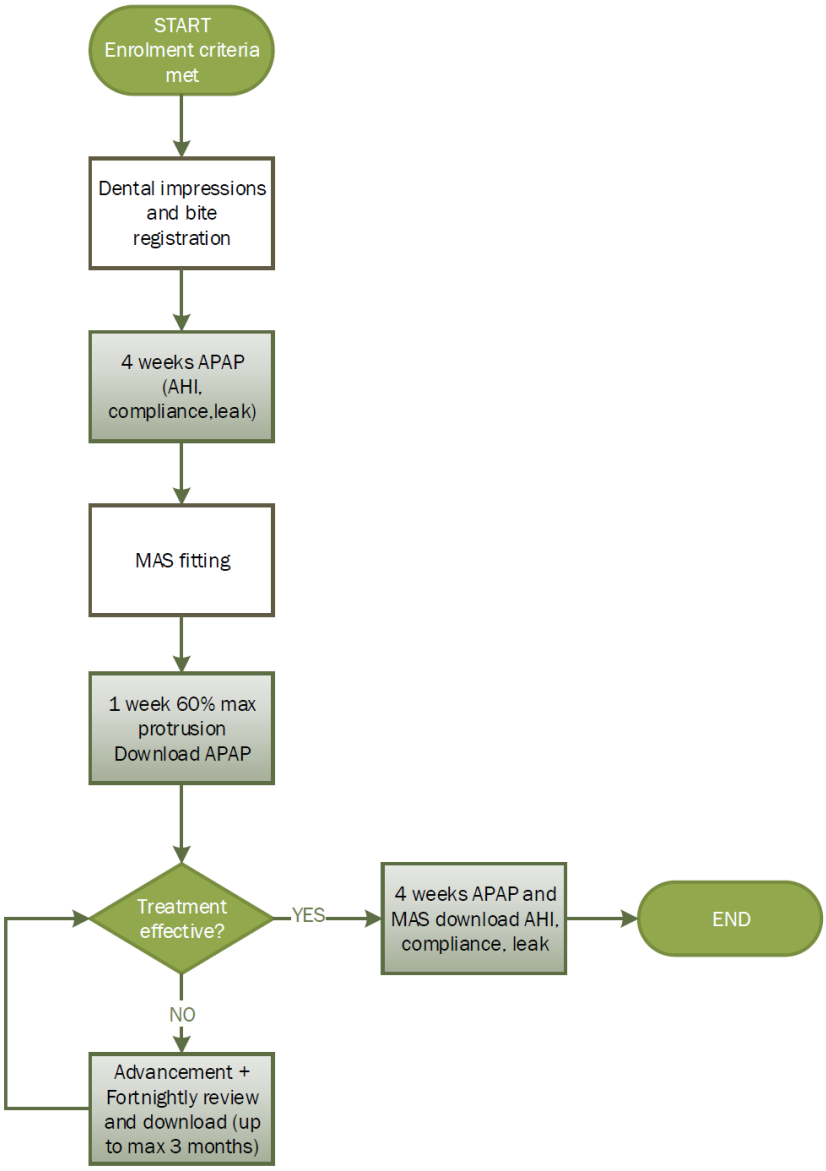
5.4 Exclusion and withdrawal criteria

1. Pregnant or lactating females
2. Participating in another interventional clinical trial

3. Uncontrolled or untreated cardiovascular disease
4. Central Sleep Apnoea events (≥5/hr)
5. Previous Uvulopalatopharyngoplasty (UPPP)
6. Severe somatic or psychiatric disorders
7. Periodontal disease, temporomandibular disorder or dental pain that would prevent ongoing suitability for an oral appliance

Participants have the right to withdraw from the study at any time without prejudice. The date and the reason of the individual study termination must be documented. Subjects may be replaced if for any reason combination therapy data is not available for primary endpoint analysis. Available data for all withdrawn subjects will be included in the final report including the reason for withdrawal.

5.5 Study Flow Chart



5.6 Statistical considerations

The primary outcome will be to compare CPAP pressures required with and without MAD.

Prior data indicate that the difference in the response of matched pairs is normally distributed with standard deviation 2.3 [17]. If the true difference in the mean response of matched pairs is 2, we will need to study 16 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05.

Whilst this study is not powered to detect differences in compliance, compliance with and without MAD will be tested for significance using paired t-tests.

6 DRUG/DEVICE PROFILE

Participants will already be using CPAP as their primary treatment for OSA. If a fixed pressure device is being used, an auto-titrating device will be provided for the duration of the study. Participants will use their own oronasal mask where appropriate, but may be provided with an alternative mask for the duration of the study if required.

Participants will be fitted with an O_2Vent T Mandibular Advancement Device. The O_2Vent T is a customized duo-block titratable oral appliance similar in appearance to a mouth guard. It is designed to treat snoring and OSA and is made up of two materials. The main structure which forms the breathing port at the front leading to the airways on each side to the rear of the appliance, is made from polished medical grade titanium customized to the patient's maxillary arch formation. The "landing" area or inserts for the top and lower teeth is customized to the patient's dentition and are made from dual laminate material. The upper insert is fixed to the titanium arch whilst the lower insert is positioned in an advanced position to bring the jaw forward. Further titration is possible with a screw mechanism.

The O_2Vent T is registered with the Therapeutic Goods Administration (TGA) as a Class I therapeutic product. The Instructions For Use is attached.

7 PROCEDURES INCLUDING DRUG TREATMENT INVOLVING THE SUBJECT:

7.1 Dosage and mode of administration

CPAP will be applied via participants own oronasal mask in an auto-titrating mode (APAP).

The O_2Vent T will be fitted by a dentist with experience in oral appliance therapy. The initial position will be set at 60% of maximum protrusion. If further advancement is clinically indicated, this will occur over a 1-3 month period with incremental advancement until maximum limit of comfort or optimal position is reached.

7.2 Concurrent treatment

The O_2Vent T will be used in combination with CPAP throughout the study, following the first 4 weeks of CPAP used alone.

7.3 Invasive procedures

Nil

7.4 Procedures involving X-rays or ionising radiation

Nil

7.5 Facilities for dealing with contingencies

N/A

8 ASSESSMENT OF PATIENTS

8.1 Clinical

All participants will be assessed by their treating sleep physician. Clinical assessment of treatment effectiveness will be based on a number of factors including data from CPAP downloads – AHI, leak, pressure, compliance, as well as participants' subjective symptoms

8.2 Laboratory

Baseline OSA severity will be obtained from laboratory records of sleep studies performed. There will be no laboratory assessment of patients as part of this research protocol. All information will be acquired as part of routine care and obtained from medical records by the investigators.

8.3 Other (eg radiological)

Nil

8.4 Monitoring adverse effects

Device related adverse effects will be monitored by the dentist as part of usual care.

The potential risks associated with MAD treatment including the O2Vent T include excessive salivation, temporomandibular joint pain, gum irritation, mouth dryness, jaw discomfort, tooth loosening, tooth wear and jaw set (protrusion of the lower jaw) for a period post removal of the device. Most of these potential risks are minor and transient in nature and addressed in the acclimatization period to achieve maximal comfort and treatment effect whilst minimizing side effects. Risks are managed by regular follow up during the acclimatization period by dentists fitting the device and ongoing follow up to monitor longer term dental changes that may occur.

The Principle Investigator or the Advanced Trainee in Sleep Medicine will have regular routine clinical follow up of the participants to evaluate treatment effectiveness as well as monitor adverse events. In the unlikely event if injury, medical treatment will be provided under the guidance of the Principle Investigator. Any serious adverse events will be reported to the Ethics Committee.

9 ADMINISTRATIVE ASPECTS

9.1 Source of funding

This clinical research study will collect information during routine care of patients already under the care of the investigators. The collation of data will be performed by the Advanced Trainee in Sleep Medicine as part of their research training. No additional funding is required.

9.2 Source of drug/device supply

MAD will be supplied by Oventus Medical Limited, the manufacturer of the O_2Vent T. There will be no charge to patients for the supply or fitting of these devices. Oventus has also agreed to provide the costs associated with hiring auto PAP as required for the duration of the study.

9.3 Formulation of placebo

N/A

9.4 Special facilities required, (approval of other areas involved)

N/A

9.5 Notification of other areas that may be involved

Other sleep/respiratory physicians working within the practice will be informed of the study and may identify potential participants meeting the inclusion criteria.

9.6 Use of hospital facilities

N/A

10 PARTICIPANT INFORMATION SHEET AND CONSENT FORM

10.1 Who will obtain consent?

Consent will be obtained from participants by one of the investigators named in this proposal.

11 ETHICAL CONSIDERATIONS

11.1 Benefit anticipated from the study

There may be no benefit in participation in this study. However, participation may result in better treatment of OSA with combination therapy.

11.2 Risks

The potential risks associated with MAD treatment including the O_2Vent T include excessive salivation, temporomandibular joint pain, gum irritation, mouth dryness, jaw discomfort, tooth loosening, tooth wear and jaw set (protrusion of the lower jaw) for a period post removal of the device. Most of these potential risks are minor and transient in nature and addressed in the acclimatization period to achieve maximal comfort and treatment effect whilst minimizing side effects. Risks are managed by regular follow up during the acclimatization period by dentists fitting the device and ongoing follow up to monitor longer term dental changes that may occur.

11.3 Research on people in dependent relationships – mentally ill.

N/A

11.4 Separation of research and clinical responsibilities.

Potential participants will be identified by their treating sleep physician. All participants will receive a Participant Information Statement and Consent Form and given time to consider participation. They will be assured that participation is voluntary and they are permitted to withdraw consent from the project at any time and discontinue without affecting their right to treatment and appropriate care.

11.5 Normal volunteers (source, honoraria).

N/A

11.6 Method and nature of advertising (enclose advertisement).

N/A

11.7 Protection of privacy and preservation of confidence.

The study will be conducted in accordance with the Declaration of Helsinki as well as the National Statement on Ethical Conduct in Human Research (2007) - Updated May 2015, published by the NHMRC.

Prior to commencing the trial, approval must be obtained from a Human Research Ethics Committee (HREC) registered with the NHMRC and the study will be registered with Australia and New Zealand Clinical Trials Registry.

12 PRIVACY CONSIDERATIONS

12.1 Use of information

Data from medical records including CPAP downloads and sleep studies performed as part of usual care will be collected and used to assess treatment effectiveness. This data will also be analysed and compiled into a report and may be presented at scientific conferences. The results may also be published, however without any information which could identify subjects.

12.2 Privacy and confidentiality

Study records obtained from medical records will only be collected in a deidentified manner. The investigators will retain the code to reidentify participants if required. Data will be retained in accordance with good scientific practice. Paper records will be kept in a locked filing cabinet accessible only by the investigators. Electronic records will be password protected on a secure network and accessible only to the investigators. No personal information that can identify participants will be made available to other researchers or third parties.

12.3 Retention of study records

De-identified study records will be retained for at least fifteen (15) years and will be readily accessible to the investigators. The Principle Investigator will be responsible for retaining the codes to reidentify participants if required.

13 LEGAL MATTERS

13.1 Form of Indemnity for clinical trials.

N/A. This is an investigator initiated study obtaining records from usual care.

14 REFERENCES

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