**EFFICACY OF A MANDIBULAR ADVANCEMENT APPLIANCE ON SLEEP DISORDERED BREATHING IN CHILDREN**

Lay Summary

Sleep-Disordered Breathing (SDB) varies from habitual snoring to completely stopped breathing and can be found in up to 10% of New Zealand children. SDB can cause breathlessness and frequent waking during sleep due to partial or complete obstruction of the upper airway. It can also cause growth disorders, daytime sleepiness, educational concerns, and behavioral problems.

In the most severe cases, SDB can also lead to life-threatening events like heart failure. Therefore, SDB may have a significant impact on the well-being of children, and a considerable financial burden on the national health system. Thus, early diagnosis and treatment of SDB in children is vital to prevent health issues later.

Continuous positive air pressure and surgery (adenotonsillectomy) represent the primary treatment modalities for SDB in children. Mandibular Advancement Splints (MAS) represent an alternative treatment that is less invasive, cheaper, more comfortable and acceptable than other treatment modalities. While the efficacy of these appliances has been clearly demonstrated in adults, there is little information about their usefulness in children.

This project aims to determine the efficacy of mandibular advancement appliances for the management of SDB and related health problems in children. This project will utilise skills from multiple research groups, thus establishing a multidisciplinary research team for the study of SDB in children in New Zealand.

Children with SDB will be recruited and randomly assigned to two groups; both groups will receive the same treatment with active MAS and non-active MAS but in different sequences; the first group will receive three weeks treatment with active MAS, two weeks break, and three weeks treatment with non-active MAS, the second group will receive the appliances in a reversed order. Potential improvement in SDB symptoms and some other accompanied health related problems will be assessed using a portable breathing monitoring instrument, questionnaires, and collecting blood samples.

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**Background**

Sleep-disordered breathing (SDB) varies in a continuum spectrum from habitual snoring and upper airway resistance syndrome (UARS) to obstructive sleep apnea (OSA), due to either partial or complete airway obstruction, respectively.[1](#_ENREF_1),[2](#_ENREF_2)

Obstructive Sleep Apnea (OSA) is characterized by recurring episodes of complete and/or partial obstruction of the upper airway during sleep, resulting in intermittent hypoxemia and hypercapnia, frequent arousals and sleep fragmentation.[3-5](#_ENREF_3) Snoring is the cardinal clinical symptom of OSA and the hallmark of all SDB syndromes. Those patients who snore but do not fulfil the criteria for OSA are considered to have habitual snoring.[6](#_ENREF_6),[7](#_ENREF_7)

The health impact of OSA has been increasingly recognized[2](#_ENREF_2) in both adults and children.[8](#_ENREF_8) Pediatric and adult OSA differ in prevalence, physiology, clinical presentation, polysomnographic characteristics and outcomes.[2](#_ENREF_2),[5](#_ENREF_5),[9](#_ENREF_9),[10](#_ENREF_10" \o "Li, 2009 #117) The prevalence of OSA varies from 3 to 7%[11-13](#_ENREF_11) in adults. Epidemiological studies in New Zealand have shown that OSA affects over 15% of the adult males, and its prevalence is twice as high in Māori men than non-Māori men.[14](#_ENREF_14),[15](#_ENREF_15)In children, the prevalence of OSA varies from 1 to 4%,[8](#_ENREF_8),[16-20](#_ENREF_16) while that of habitual snoring varies from 0.7 to 10.3%; most authors have reported a 10% prevalence of habitual snoring in children.[21-24](#_ENREF_21) Habitual snoring is more common in Māori than non-Māori children[19](#_ENREF_19),[25](#_ENREF_25),[26](#_ENREF_26), but the exact prevalence of OSA in New Zealand children is still unknown.

SDB have been associated with growth disorders, daytime sleepiness,[10](#_ENREF_10) educational and behavioral problems,[27-29](#_ENREF_27) and nocturnal enuresis.[30](#_ENREF_30),[31](#_ENREF_31) In the most severe cases, OSA may have life-threatening consequences like cardiorespiratory failure, which can lead to death.[2](#_ENREF_2),[10](#_ENREF_10),[32](#_ENREF_32)

Adenotonsilar hypertrophy or recurrent infection is the primary cause of pediatric OSA.[10](#_ENREF_10),[33](#_ENREF_33),[34](#_ENREF_34) Jaw anomalies and malposition also are associated with changes in airway morphology and respiratory problems,[35](#_ENREF_35),[36](#_ENREF_36) and an obstructed airways may affect craniofacial development.[37-39](#_ENREF_37) Orthodontic and craniofacial anomalies have often been reported in pediatric sleep-disordered breathing. A triad of narrow upper airway, maxillary constriction and mandibular retrusion is a common phenotype of pediatric OSA syndrome.[33](#_ENREF_33),[34](#_ENREF_34),[40-43](#_ENREF_40)

There is an abnormal secretion of growth hormone (GH) during sleep and somatic growth impairment in children with OSA,[44](#_ENREF_44) which affects the craniofacial traits, especially the height of mandibular ramus.[45-47](#_ENREF_45)Studies have reported an accelerated ramus growth, and improved facial morphology after adenotonsillectomy in pediatric OSA patients.[48](#_ENREF_48) This improvement may be due to normalization in GH status, balance between tongue and cheeks, and nasal breathing after adenotonsillectomy.[39](#_ENREF_39),[49](#_ENREF_49) However, this growth acceleration is not sufficient to correct the malocclusion and the underlying skeletal discrepancy often requires dentofacial growth modification treatment.[50](#_ENREF_50)

Polysomnography (PSG) is considered the gold standard in diagnosis of SDB, particularly OSA.[2](#_ENREF_2),[9](#_ENREF_9)Other diagnostic tools include portable monitoring devices,[51](#_ENREF_51) physical examination to detect anatomic risk factors, upper airway imaging using magnetic resonance imaging (MRI),[52](#_ENREF_52),[53](#_ENREF_53) endoscopy and cephalometry.[43](#_ENREF_43),[54](#_ENREF_54) Continuous positive air pressure (CPAP) and adenotonsillectomy are the primary treatment options for the adult and pediatric OSA patients, respectively.[2](#_ENREF_2),[10](#_ENREF_10) Surgery to increase the upper airway cross-sectional area, remove obstructive tissues, or ultimately bypass the upper airway[10](#_ENREF_10),[55](#_ENREF_55) is indicated in severe adult cases,or where CPAP is not tolerated.[2](#_ENREF_2),[56](#_ENREF_56) Oral appliances (OA) have also been widely used for the treatment of OSA, especially in adults.[2](#_ENREF_2),[57-62](#_ENREF_57) These appliances increase the posterior oropharyngeal airway by reducing upper airway collapsibility during sleep. They may also trigger stretch receptors, which in turn activate the airway supporting muscles.[2](#_ENREF_2) Previous studies have shown that use of OA are better tolerated than CPAP treatment,[58](#_ENREF_58) because of improved comfort, quietness, and portability.[63](#_ENREF_63),[64](#_ENREF_64)Mandibular advancement appliances are the most common type of oral appliances used in the treatment of SDB in adults, but their use in children is less common.

There is a significant relationship between pediatric OSA and craniofacial traits.[34](#_ENREF_34),[43](#_ENREF_43),[65](#_ENREF_65),[66](#_ENREF_66) It is generally accepted that advancing the mandible will increase the nasopharyngeal dimensions,[67](#_ENREF_67),[68](#_ENREF_68) thereby improving the symptoms of OSA.[57](#_ENREF_57),[61](#_ENREF_61),[63](#_ENREF_63) Mandibular Advancement Splints (MAS) can be used to advance the mandible in adults, and also for growth modification in children.[69](#_ENREF_69) MAS are suitable for both mixed and permanent dentition,[70](#_ENREF_70) relatively well tolerated by patients, with low failure rates,[71](#_ENREF_71) and may potentially be used for treatment of pediatric OSA[64](#_ENREF_64) by incremental advancement of the lower jaw[71](#_ENREF_71) and upper arch expansion,[70](#_ENREF_70) Although there is increasing evidence regarding the efficacy of MAS in adults with OSA,[58](#_ENREF_58),[72](#_ENREF_72)there is little information about their efficacy in children.[73](#_ENREF_73)The few studies on the subject suffer from important methodological flaws like heterogeneous samples; lack of randomization; limited power to detect a clinically relevant effect; and lack of an adequate control conditions such as the use of a placebo-like appliance.[57](#_ENREF_57),[61](#_ENREF_61),[64](#_ENREF_64),[73](#_ENREF_73) Therefore it is difficult to draw a conclusion regarding the efficacy of MAS appliances in treating children with SDB.

**Study design**

This study will be designed as a randomized clinical trial with crossover administration of two appliances (active MAS and non-active/sham MAS). Each appliance will be worn for three weeks, followed by two-week washout period.

**Objectives:**

The aims of the study are: (1) to test the efficacy of MAS in the treatment of children with SDB; and (2) to assess the effect of MAS treatment on quality of life, behavior, growth hormone levels, and nocturnal enuresis in SDB children.

**Research hypothesis**

The mandibular advancement splints are effective in reducing SDB symptoms in children.

**Experimental Approach**

**Participants**

***Sample size estimation***

A reduction of 50% in Apnea/Hypopnea Index AHI (number of apnea and hypopnea events recorded per hour of sleep) is generally considered clinically relevant.[58](#_ENREF_58) This change corresponds to a large effect size (Cohen’s d= 1.5). To detect this effect size, and setting α error to 0.05 and β error to 0.80 (one-tail test), we have estimated that at least 13 participants are needed. We will recruit 16 children to avoid problems occur from possible dropouts.

***Recruitment***

We will advertise in newspapers to invite children to participate in the study according to the following eligibility criteria: age 8-12 years; snore three times or more per week; no previous orthodontic treatment.

Eligible patients should meet the following inclusion/ extrusion criteria.

*Inclusion criteria*: SDB diagnosis.

*Exclusion criteria*: severe OSA AHI more than ten events per hour;[74](#_ENREF_74) craniofacial syndromes and genetic syndromes; neuromuscular diseases; body mass index at or above 95th percentile of normative values.

**Methods**

*Portable unit for SDB monitoring*

Home-based abbreviated polysomnography (PSG)[51](#_ENREF_51) will be performed using a portable monitoring unit (Visi Black Shadow, Stowood Scientific Instruments Ltd, Oxford, UK). This unit records nasal airflow, respiratory efforts, oximetry, pulse profile, snoring sounds, body movement, body position, and electrocardiographic signals.

### *Oral appliances*

The oral appliance that will be used in the study is a Twin-block design consisting of two removable plates; one is worn on the upper arch, the other on the lower. Each plate has matching pieces which encourage the lower jaw to posture or slide forward as the teeth come together(active MAS).[70](#_ENREF_70) To ensure keeping the mandible in an advanced position during sleep a fastener (MDSA Ltd., Victoria, Australia), will be imbedded in the splints.[75](#_ENREF_75) The new sagittal and vertical position of the mandible will be determined by taking the bite records and the construction bite using George Gauge™,[76](#_ENREF_76),[77](#_ENREF_77) which provides an aid in determining the amount of protrusion needed in construction of the mandibular protruding devices.

The non-active appliance (sham MAS) will consist of an upper and lower acrylic plate resembling the design of the active MAS, but without any component to protrude the mandible.

Participant in the study will be asked to wear the appliances at night and for two to three hours during the daytime. Wearing time will be recorded by parents using diaries.

**Outcome measurements *Apnea/Hypopnea Index (AHI – primary outcome)***

This isdefined as number of apnea and hypopnea events recorded per hour of sleep.[78](#_ENREF_78) An apnea episode is defined as cessation of breathing for 10 seconds or longer.[78](#_ENREF_78) A hypopnea episode is defined as reduced respiratory airflow by 30% with a 4% decrease in oxygen saturation.[78](#_ENREF_78)

AHI will be assessed using the portable monitoring device.[51](#_ENREF_51) This monitoring will be carried out four times. (Figure 1)

***Sleep Questionnaires***

SDB associated symptoms will be assessed using the Pediatric Sleep Questionnaire. Daytime sleepiness and related behavioral disturbances will be assessed using the Epworth Sleepiness Scale (ESS).[79-81](#_ENREF_79) A questionnaire of sleep related breathing disorder scale (PSQ-SRBD scale) will also be completed by parents to ascertain the quality of the child’s sleep including difficulties in getting to sleep, frequency of waking during the night, and alertness in the morning and daytime signs of sleepiness. It will also include questions about the history of the breathing difficulties during sleep, snoring, family history of SDB, and levels of household smoking.[82](#_ENREF_82) These questionnaires will be administered before and after each treatment period.

***Snoring frequency and intensity***

Snoring sounds will be assessed using the portable PSG equipment at the beginning and the end of each treatment period. Reports of snoring frequency and intensity will also be collected by parents using daily diaries.

***Growth hormone levels***

Blood samples will be taken from SDB children twice in the middle of each treatment period. A specialist in venipuncture will collect the samples to minimize discomfort and potential complications of venipuncture. Growth hormone will be assessed indirectly by determination of insulin-like growth factor-1 (IGF-1) levels.

***Parent-report of nocturnal enuresis***

A child will be diagnosed as having urine incontinence when it occurs at least one night per week.[31](#_ENREF_31)This will be assessed during both treatment periods using diaries.

***Neurobehavioral assessment***

Behavioral changes will be assessed using the BASC-2 rating scale, which has been widely used in studying behavioral differences in pediatric SDB patients.[83](#_ENREF_83)’[84](#_ENREF_84)

***Quality of life***

Quality of life in SDB children will be assessed using the OSA-18 and the Pediatric Quality of Life Inventory™ (PQoL).[85](#_ENREF_85) Parents or caregivers will rate the frequency of symptoms before treatment and at the end of each treatment period.

***Clinical procedure***

Assessments will be taken at baseline (T0) and four times (T1, T2, T3, T4) during the study period. Details about assessments are described in Figure 1.

**Significance of the research**

Early treatment of SDB in children is vital to prevent significant health issues that may develop later, including behavioral and learning concerns. In the most severe cases, OSA may have life-threatening consequences like cardio-respiratory failure, which can ultimately lead to death. SDB may therefore have a significant impact on the wellbeing of many New Zealand children, as well as direct and indirect cost the health system.

The use of MAS in selected children may represent an effective treatment that is less invasive and better tolerated than other treatment modalities such as CPAP or surgery.

This project will utilise skills from multiple research groups, thus establishing a multidisciplinary team for treatment of SDB in children in New Zealand. The expertise of orthodontists, pulmonologists, pediatricians will be combined to conduct much-needed clinical research into a condition that may affect up to 4% of New Zealand children.[19](#_ENREF_19)

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| D:\PhD OTAGO\Figures and Shapes\protocol to ANZCTR\protocol to ANZCTR جديد1.jpg  Figure 1 The study is designed as a crossover randomized controlled trial. Sixteen patients will be randomly assigned to two treatment sequences, each including the use of an active or non-active (sham) mandibular advancement appliance in a reverse order. Active and non-active treatment periods will be separated by a two-week washout period. Assessments will be taken at baseline (T0) and four times (T1, T2, T3, T4) during the study period. PSG data will be collected during home-based recordings, whereas all the other data will be collected in a clinic environment.  List of abbreviations: Abbreviated polysomnography (PSG), Cephalograms (Ceph), Behavior assessment system for children, second edition (BASC-2) the quality of life questionnaire (OSA-18), pediatric quality of life inventory (PQoL), and the Epworth sleepiness scale (ESS). |

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