Journal of
Dental Research

Randomized Trial of Two Self-Titrated Oral Appliances for Airway Management

Journal:	*Journal of Dental Research*
Manuscript ID	Draft
Manuscript Type:	Research Reports
Date Submitted by the Author:	n/a
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Keywords:	Obstructive Sleep Apnea, Clinical studies/trials
Abstract:	Purpose: To evaluate and compare two different oral appliances (OA) in their effectiveness and predictability in reducing the respiratory event index (REI) in moderate and severe obstructive sleep apnea (OSA) patients. Methods: Moderate and severe adult OSA patients, who were previously prescribed continuous positive airway pressure therapy (CPAP), but were dissatisfied with it (n=56) were studied using home-polygraphy. The study design was a randomized cross-over trial using midline traction (MT; with limited mouth opening) and bilateral thrust (BT) design OAs that were titrated by the subjects. OAs were used nightly for 4-weeks (T2) followed by 1-week washout period, then 4-weeks (T4) using the alternate OA. Respiratory event index (REI) and oxygen saturation (SaO2) were primary outcomes, with predictability and efficacy comparison of the two OAs as secondary outcome. Results: Thirty-six participants had used MT and BT-OAs during both 4-week study legs. Twenty MT-OA-using-, (55.6%) and 25(69.4%) BT-OA-using participants and 16(44.4%) participants using both OAs had significant REI reductions. Overall baseline (T0) median REI of 33.7(20.7-54.9) was reduced at T2 to 18.0(8.5-19.4), and at T4, to 12.5(8.2-15.9), ($p < 0.001$). Comparison of the two sequence-groups’

	(MT–BT and BT–MT) REI showed the median differences between T0, and T2 and T4 were highly significant ($p < 0.001$). Regression analysis predicted about half of all users will have REIs between 8 and 16 after 2-months. Baseline overjet measures >2.9mm predicted greater OA advancement at T4. Mean and minimum SaO_2 did not change significantly from T0 to T2 or T4. Conclusion: MT and BT OA designs similarly attenuated REI in moderate and severe OSA individuals who completed the 8-week study protocol with greater REI reduction in those with severe OSA.

Title: Randomized Trial of Two Self-Titrated Oral Appliances for Airway Management

Introduction

Obstructive sleep apnea (OSA) has an estimated prevalence of 5-38% in the general adult population (Punjabi 2008; Appleton et al. 2016; Senaratna 2017). Continuous positive airway pressure (CPAP) is the American Academy of Sleep Medicine (AASM) treatment recommendation for this highly prevalent disorder (Berry et al. 2012). However, approximately 15- 60% of patients with OSA do not adhere to CPAP therapy (Hoekema et al. 2007a). An alternative treatment options for OSA is oral appliance therapy (OAT) which functions to open the airway by bringing the mandible and tongue forward, however, its effectiveness in moderate and severe OSA has been debatable.

The impact of OA varying designs on OSA attenuation has not been previously addressed in the same study population. Comparison of OAs that limit mouth opening versus those that allow mandibular movement and mouth opening which may increase upper airway (UA) collapsibility has not been reported. Particularly in patients with severe OSA, OA "therapeutic success" definitions vary adding to the confusion of OAT effectiveness. The focus of this study addresses these deficiencies in the literature.

Previous reports using a custom-fitted, dentist-titrated midline traction (MT) OA, found large improvements in Epworth Sleepiness Scale (ESS) and Short Form-36 Health Survey (SF-36) scores, oxygen saturation (SaO_2) levels and the apnea hypopnea index (AHI) in patients with severe OSA after about 12-weeks of use (Hoekema et al. 2007b). Three randomized clinical trials (RCT) and two other reports also used the same MT-device in patients with moderate and severe OSA (Hoekema et al. 2008a; Hoekema et al. 2008b; Holley 2011; Ghazal 2009; Deane et al. 2009). AHI improvements ranged from 80-90%. In contrast, several studies in patients with moderate and severe OSA using a bilateral thrust (BT) design OA failed to demonstrate an AHI reduction to <10 events/hour; they did, however show >50% AHI reductions (mean 55.4%; range 53-57%) from baseline conditions (Gotsopoulos et al. 2002; Gotsopoulos et al. 2004; Mehta 2001; Naismith 2005).

Efficacy differences in OAT of moderate and severe OSA could be related to OA design variations although this hypothesis has not been tested. Among the approximately 150 FDA-cleared OAs on the market, the present study is limited to the MT and BT designs because they are widely used, differ in mouth opening range, and have been studied extensively, but not in a single population.

The primary aim of the trial was to determine if MT and BT OA designs differ in effectiveness to reduce the respiratory event index (REI) based on different criteria, within a single test population categorized by OSA severity. Secondary outcomes included efficacy comparison of the OAs in patients with moderate versus severe OSA, self-reported responses to OAT effect on daytime sleepiness and quality of life scores.

Methods

This RCT used a crossover design, was approved by the Institutional Review Board at Texas A&M University College of Dentistry (IRB#2017-0390-CD-FB) and performed at this clinical facility. Adults (≥18 years old) were recruited using radio commercials, flyers and ClinicalTrials.gov. All participants were previously diagnosed by polysomnography (PSG) with moderate or severe OSA, expressed dissatisfaction with their prescribed CPAP therapy and were amenable to trying OAT. Pre-enrollment PSG AHI values ≥15 and ≤ 30, and >30 events/hour were used to categorize participants as having moderate or severe OSA, respectively. Other inclusion criteria included having at least 8 teeth per arch to support an OA. All subjects provided written informed consent,

The team dentists performed the oral examination, recorded key dental parameters, and obtained polyvinyl siloxane impressions (Defend Super Hydrophilic Impression Material, Hauppauge, NY), which were sent to the manufacturers' laboratories for custom fabrication using an occlusal record that was obtained at 60% of the patient's

maximum protrusion. Fabrication was done prior to the participant's second appointment (T1) to insure that problems with fit could be addressed prior to delivery. At T1, each subject was assigned to start with one of the two OAs. The randomization sequence was generated using Online Research Randomizer software, V4 (Urbaniak & Plous 2013). Dentists received the OAs in concealed envelopes with the participants' coded identity numbers prior to fitting. The data analyst and somnologist were blinded to OA sequence. Masking the identities of the OAs from the participants was not possible due to obvious differences in design and color.

The TAP1® (MT design; AMI, Dallas, TX) has an anterior hook that engages the upper with the lower tray, has one anteriorly positioned adjustable screw; the design limits mandibular movement and prevents mouth opening during use. The SomnoDent Flex® (BT design; SomnoMed® Inc. Plano, TX) allows for mouth opening during use, uses side-fins as anchors to move the lower tray forward with left and right-side adjustable screws.

One OA was used nightly for 4-weeks followed by a 1-week washout period, then 4-weeks using the alternate OA. During the washout period the participants were instructed to use their CPAP machines nightly. Participants were instructed to advance their mandibles as follows: for the MT, 1 turn (0.3mm each) per night and for the BT, 2-3 (0.1mm each) turns bilaterally per night during the test period if snoring, observed OSA events or daytime sleepiness persisted and if they did not experience discomfort. Subjects were invited to attend the clinic to have a team dentist assist in this titration process.

Home sleep recordings were collected using the NOX T3 recorder (NOX Medical, Reykjavík, Iceland). SaO_2 was measured with a finger probe pulse-oximeter (Nonin Medical Inc., Plymouth MN). All sleep recordings were collected in the subject's home sleep environment and each subject received instructions on how to self-apply sensors. A minimum of 5 recorded hours without artifact was considered acceptable. All apnea and hypopnea events were visually scored using AASM 2007 scoring criteria (Berry et al. 2012). The Epworth Sleepiness Scale (ESS) and the Short-Form 36 (SF-36) were used to assess daytime sleepiness and health-related quality of life, respectively. Questionnaires were self-administered.

Statistical analysis

SPSS v25 software (IBM Inc., Chicago) was used for data analysis. Most of the sleep studies and survey variables were non-normally distributed, so that frequencies, medians and interquartile ranges (IQR) were used for description. Normally distributed variables were summarized with means and standard deviations. Differences in frequencies were analyzed using Chi-square and McNemar tests. The non-parametric Friedman 2-way analysis of variance (ANOVA) followed by Bonferroni-corrected Wilcoxon Signed Rank Tests were used for testing differences among and between time points respectively; Mann-Whitney tests were used for evaluating differences between-group continuous variables; Spearman correlations were used to evaluate the relationship between certain dental and sleep measures. Linear and robust regression (Hayes et al. 2007) was used to evaluate REI and related variables as a function of treatment time, as well as predictability of response to OAT. An α-error level <0.05 was used throughout.

Power analysis determined that 38 participants were needed to yield a power of 0.90 with $\alpha = 0.05$ and an expected effect size of at least a 10 point difference in the end-of-treatment mean REI scores based on previous work (Lawton et al. 2005).

Subjects

From the screened cohort of 152 adults, 62 (41%) received an interview of which 56 (90.3%) were enrolled (Figure 1). The distribution of baseline-characteristics by group assignment, MT-BT vs BT-MT sequences, is shown in Table 1. There were no significant group differences with regard to age, ancestry, BMI, REI, mean or minimum $Sa0_2$ ($p > 0.41$). Group BT-MT had a greater proportion of male participants (84% vs 71%, p=0.016). Self-reported ancestries were as follows: 43 European/white (76.8%), 4 Hispanic (12.5%), 7 African (7.1%) and 2 Asian (3.6%).

There were no significant baseline-differences between moderate (n=25; 44.6%) and severe OSA (n=31; 55.4%) subjects with regard to age, BMI or mean SaO_2 ($p > 0.45$). Forty-two (75%) of participants completed the first leg of the study. An additional six participants (10.7%) were lost during the wash-out phase due to lack of communication with the study coordinator. Thirty-six participants (64.3%) completed the second leg of the study, consisting of 24 males (BMI: 29.6±3.16) and 12 females (BMI: 29.7±3.89). Those who completed did not differ significantly from dropouts in baseline median REI (32.6[18.8-48.5] versus 36.0[21.7-56.3]; p=0.724), mean or minimum $Sa0_2$ ($p \geq 0.085$). No major adverse events related to the use and titration of OAs were reported.

Dental Assessment and OA Activation

Overall, median overjet (OJ) was 3.0 mm (2.0-4.0). No crowding was observed in 88.7% of participants. Anterior cross-bite was observed in 11.8% and posterior cross-bite in 12.5% of participants. Temporomandibular joints were within normal limits in 88.5% of participants. The overall mean maximum-mouth-opening was 40.7 mm±12.0. None of these values differed significantly between the two OA-sequence groups ($p>0.05$). The median amount of total mandibular advancement (TMA, protrusion) produced by the OAs from baseline (T0) to T2, was 7.5mm (6.5-9.1) and at T4, 7.5mm (4.5-10.4). There were no significant differences between-OA groups ($p >0.14$) or within-participants across each leg of the study ($p>0.05$).

Response to OA Treatment

Respiratory Event Index

Within each OA sequence, Friedman ANOVA omnibus test found significant differences among the time points in REI ($p<0.001$; Figure 2). Follow-up post-hoc Wilcoxon tests showed REI reduced significantly from T0 to T2, and from T0 to T4 ($p<0.001$). No differences were found between T2 and T4 values ($p>0.401$).

The combined study group's REI variability reduced progressively over the 9-weeks from baseline IQR of 34.2 (T0) to 20.9 (T2) to a low of 7.7 events/hour (T4). Friedman ANOVA demonstrated that these distributions differed significantly ($p<0.001$) for the combined and separate groups. Absolute ranges similarly reduced at T4, excluding the three outliers.

"Responders" to a given OA had baseline REI reduced by ≥50% or REI <10 events/hour at 4-weeks. Thirty-six subjects used either MT or BT OAs during both 4-week legs of the study. Twenty (55.6%) participants responded positively to the MT, 25 (69.4%) responded to the BT OAT, and 16 (44.4%) responded to both OATs. McNemar's test showed no significant differences between the two OATs in reducing REI over 4-weeks ($p=0.211$).

Regression analysis of REI as a function of OA treatment over time

Separate linear regressions were performed for the two OA sequence groups, as well as for the two severity groups. There were no significant differences between the OA groups with regard to REI regression coefficients during either leg of the study ($p>0.05$). The two OA groups were then combined to test the effects of severity. The decline in slopes of the regressions for the severe group were significantly steeper versus the moderate group ($p<0.05$) during each leg of the study (Figures 3 & 4). R^2 values during Leg 1 were 0.047 and 0.456 for moderate and severe OSA groups respectively (Figure 3) and R^2 values for Leg 2 were 0.236 and 0.566 for these two groups respectively (Figure 4). All of these regressions except for the moderate OSA group during Leg 1 were highly significant ($p< 0.001$). Robust regression was also performed due to heteroscedasticity. Adjusted standard errors yielded by this procedure did not alter interpretation.

Overjet and Mandibular Advancement

Baseline OJ was highly correlated with TMA at T2 and T4 (rho=0.640, p<0.001; rho=0.448, p=0.009). Overjet was significantly correlated with snore count at T4 (rho =-.593, p=0.007), however, neither OJ nor TMA significantly correlated with any other sleep measures at T2 or T4.

SaO_2

Mean SaO_2 at T2 and T4 did not differ significantly from baseline (p=0.095; p=0.296). The two OA groups did not differ significantly between T2 and T4 (p=0.20). The entire sample's minimum SaO_2 increased from 80% (77.0-85.0) at baseline to 82.5% (79.0-85.0) at T2 and to 84.5% (81.0-87.8) at T4, however neither change achieved statistical significance (p=0.551 and p=0.058). The within-group changes also did not attain significance for the MT-BT and BT-MT groups respectively.

Epworth Sleepiness Scale

Overall the average Epworth Sleepiness Scale score was 10.40±5.40 at baseline that decreased significantly at T2 (7.32±5.38; p=0.022) and T4 (5.96±4.37; p=0.001), but no significant differences between the OA types.

Short Form (SF)-36 Health Survey

The SF-36 Health Survey's physical component summary (PCS) and mental component summary (MCS) were significantly improved at T2 and T4 compared with baseline ($p \leq 0.002$). No statistical differences were found between T2 and T4 SF-36 variables of interest and between gender and OA type (Table 4).

Discussion

The study's key findings in subjects who completed the study protocol after 9-weeks are: 1) MT and BT OAs significantly reduced the REI in adults with moderate and severe OSA; 2) MT and BT OAs demonstrated equivalence in REI attenuation regardless of mechanical differences in jaw-opening limitations; 3) Those with severe OSA showed a more profound REI reduction in terms of both percentage and slope compared to those with moderate OSA; 4) Either REI<10 events/hour or 50% REI reduction criteria identified OA responders and non-responders; 5) Both OAs demonstrated equivalence and predictability in REI attenuation using either of the two criteria; 6) Baseline OJ was significantly correlated with mandibular advancement; 7) ESS and SF-36 QoL scores improved at 4-weeks of OA use.

Dentists play a major role in screening for OSA and using OAT in combination with follow-up monitoring to assess treatment efficacy (ADA-House of Delegates 2019). However, OA design and predictability remained questionable regarding their effectiveness in patients with severe OSA. The OA design question addressed here pertains to whether adjustable OATs with the specific feature of limited mouth opening (i.e. limited mandibular movement) impacts OA efficacy. Meurice et al. (1996) reported that mouth opening increases upper airway collapsibility due to increased critical pressure and could contribute to OSA event increases. We demonstrated that two widely-used OA designs (MT that prevents mouth opening and BT, with more freedom of mandibular movement) were effective in significantly improving the REI in the majority of participants who self-titrated these custom, dentist-fitted OAs for 4-weeks. This unexpected finding could be explained by possible persistent mouth breathing through unsealed lips with both designs which was not assessed and is a limitation of the study. A novel finding was the variability in REI values at the end of the 9-week study that was dramatically less than T2 and especially from baseline. The interquartile range for all participants combined reduced from approximately 32 at T0 to 21 at T2 to 8 at T4 (same pattern in both OA sequence groups). This suggests reasonable predictability with both OA designs: after 2-months of self-titration about half of all users will have an REI between 8 and 16 events/hour; a quarter will do better and a quarter worse. Regression analysis by OSA severity indicates that about 50% of the variability in response can be explained by OA usage in the severe group, but as little as 8% in the moderate participants. These experimental findings support the conclusions of a retrospective study (Haviv et al. 2015) that demonstrated that OAT was

effective at 2-year follow-up in patients with very severe OSA (AHI >40 events/h) who failed CPAP; their finding is augmented by showing predictability of OA responses in those with severe OSA, regardless of OA design. Our data support other reports investigating OA use as treatment options for moderate and severe OSA, their effectiveness and patient preference. (Ghazal et al. 2009; Mehta et al. 2001) This report adds new information to the existing literature showing that in these populations, either MT or BT design, when self-titrated for a month, can effectively halve the REI. This finding has important clinical implications for dentists offering custom-fitted OAT for patients with severe OSA, as our participants with severe OSA showed greater reductions in REI compared to those with moderate OSA.

Overjet at baseline was significantly associated with the amount by which the subjects could advance their mandibles after 4 weeks of OA usage. Not surprising, those with the most pronounced OJs advanced their mandibles the most. The finding of a significant association between snoring reduction and OJ severity over the second leg of the study, requires additional investigation for its clinical utility.

Although we did not find differences in efficacy between the two designs, when self-titrated over a short period of 4 weeks, the results suggest that both designs improve UA function, stability, reduce its collapsibility, and increase oropharyngeal space. Collectively, our data suggest self-titrated OAs can be routinely offered as a treatment option for OSA patients, and clinicians can expect about a 50% response rate and to bring the REI down to about 8-16 events/hour after 8-weeks, including those with severe OSA. The improved ESS and SF-36 QoL scores at T2 and T4 demonstrate that OAT effectiveness can be recognized by patients at 4-weeks. ESS scores at T4 were below the clinical cutoff for excessive daytime sleepiness. SF-36 QoL score increases at T2 and T4 supports OAT use in patients with moderate or severe OSA to also improve their self-reported quality of life at 4-weeks.

The strengths of this study are its randomized cross-over design which eliminated between-subject variability and testing of two mechanically different OAs. Study limitations include use of a 4-week OAT response window. Previous reports involved titration by a single dentist at regular intervals over 9-12 weeks, to attain more than an 80% reduction in AHI or fewer than 5 events/hour (Hoekema et al. 2008a; Hoekema et al. 2008b; Holley et al. 2011). Our findings of 70-73% REI change at 4-weeks in participants with severe OSA is higher than the results of Mehta and co-workers of 50% REI change after 1-week of OAT and the 68% AHI reduction reported for patients with very severe OSA at 2-year follow-up (Mehta et al. 2001; Haviv et al. 2015). The 36% dropout rate was mostly due to participants not communicating with the study coordinator. This, and our failure to monitor mouth breathing with OA use, may have limited our ability to detect OA design differences of interest. Those lost to follow-up did not submit their sleep diaries making it impossible to conclude if intolerance to OAT was the reason for dropping out or to ascertain their OA-use time to compare with those who completed the study. It was our experience that a subset of participants might require a longer time to self-titrate to an optimally protruded mandibular position. Another group needed constant reminders to self-titrate their OAs which was beyond the capacity of the staff and the aims of the study. It is possible that some carry-over effect (increased laxity of TMJ ligaments) of the first OA experience occurred in the second phase of the study but we found no statistical differences between T2 and T4 REI suggesting our washout period was inadequate. A poor understanding of how to self-titrate could have reduced efficacy in some subjects. In future studies, real time feedback on snoring will be used to increase patient self-titration adherence, since about one-quarter of participants did not advance their OAs beyond the initial 60% setting by the study's end. Our use of the most current SomnoMed® OA model and the first generation TAP® might not have provided participants with the most comfortable and state-of-the-art MT TAP® OA experience. The rationale for using the first generation TAP was for comparability with earlier and extensive findings with the exact OA.

In summary, for moderate and severe OSA subjects who completed the study protocol at 8-weeks, MT and BT OA designs similarly attenuate REI with greater and predictable reduction in those with severe OSA and concomitant improvement in ESS and SF-36 scores.

Acknowledgements

This research was supported by the Baylor Oral Health Foundation with in-kind support from Airway Management Inc. and Whip Mix.

Clinical Trials Identifier: NCT03219034
Title: Trial on Oral Appliance Design for Improving Upper Airway Function and Sleep Quality
https://clinicaltrials.gov/ct2/show/NCT03219034

Compliance with Ethical Standards

- This research involved human subjects.
- All participants provided informed consent.
- Funding: This work was supported by a grant from the Baylor Oral Health Foundation to ES. (Ref # 530205)

Conflict of Interest

- All authors declare no conflict of interest.

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Figure Legends

Figure 1. Study flow diagram with attrition

Figure 2. Asterisks are extreme outliers. Differences in medians between baseline (0) and all other time points are highly significant within each OA sequence group ($p < 0.001$); between-group differences are not significant at any time point ($p \geq 0.152$), nor are differences between time points 2 and 4 ($p \geq 0.512$). Similarly, mean REI change values did not differ between OAT groups over the T0 to T2 interval ($p=0.929$) nor from T0 to T4 ($p=0.853$).

Figure 3. After first 4-weeks (T2) of OA use: Respiratory Event Index change in participants with moderate and severe OSA from baseline (T0)

Figure 4. After second 4-weeks (T4) of OA use: Respiratory Event Index change in participants with moderate and severe OSA from baseline (T0)

Table Legends

Table 1. Baseline characteristics of participants by oral appliance sequence group (n=56)

Table 2. Sleep test results by oral appliance sequence group

Table 3. Mean and minimum SaO_2 percent comparison at T2 and T4 with T0 (Baseline) presented as medians (IQR).

Table 4. Short Form – 36 (SF-36) Quality of Life Questionnaire's Physical (PCS) and Mental (MCS) Component Adjusted Scores Compared at T0 – T4

Abbreviations

AASM, American Academy of Sleep Medicine
ADA, American Dental Association
AHI, apnea hypopnea index
ANOVA, analysis of variance
BMI, body mass index
BT, Bilateral thrust
CPAP, continuous positive airway pressure
ESS, Epworth Sleepiness Scale
IQR, interquartile range
MCS, mental component scores of SF-36
MT, midline traction
OA, oral appliance
OJ, overjet
OSA, obstructive sleep apnea
PCS, physical component summary of SF-36
QoL, Quality of Life
RCT, randomized clinical trial
R^2, goodness-of-fit measure for linear regression models
REI, respiratory event index
SaO_2, Oxygen saturation
SF-36, Short Form 36
TAP, Thornton Adjustable Positioner
TMA, total mandibular advancement

Figure 1. Study flow diagram with attrition.

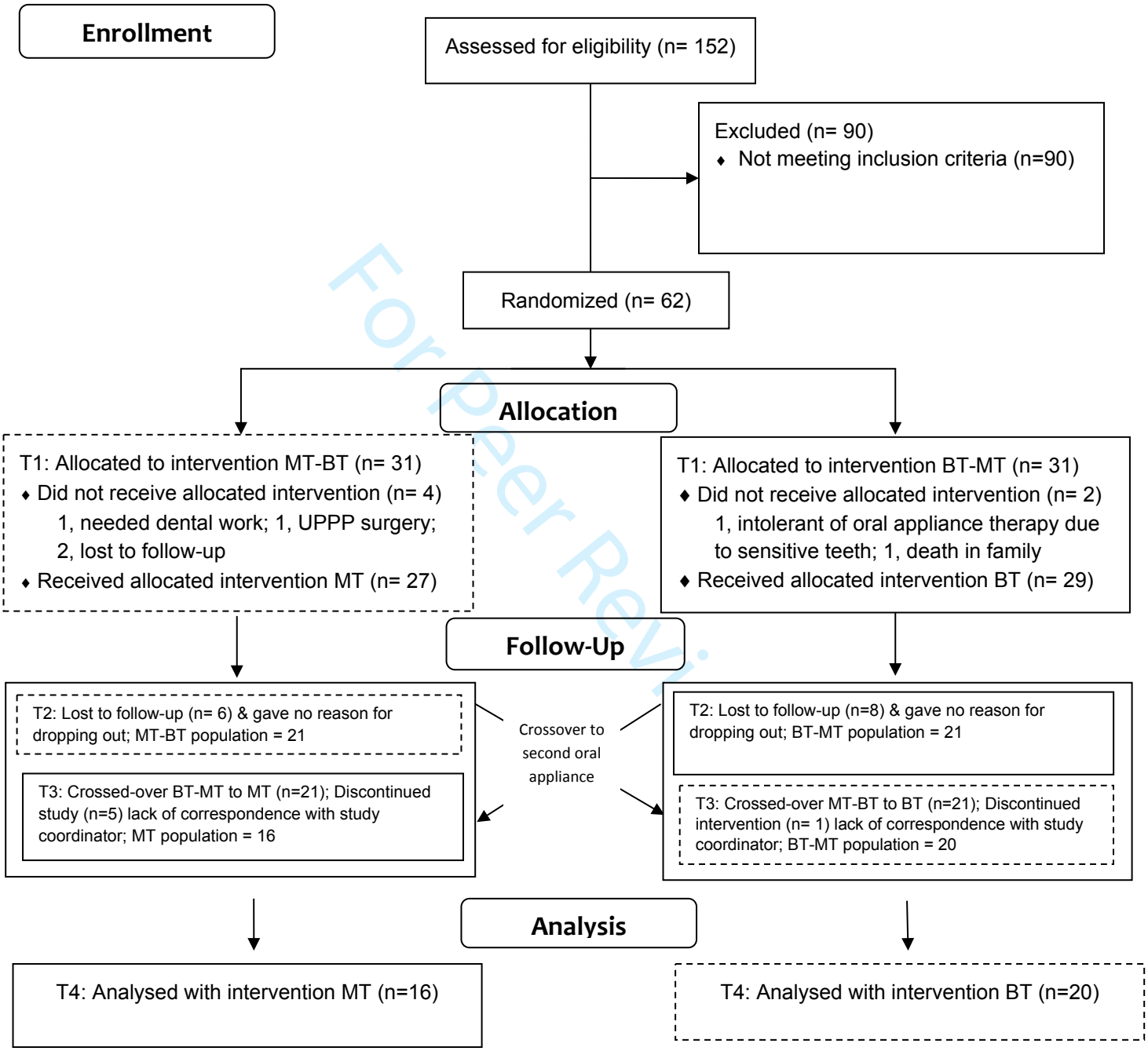

Figure 2. Box plots of medians and interquartile ranges (25th-75th percentiles) for respiratory event index by oral appliance (OA) assignment group.

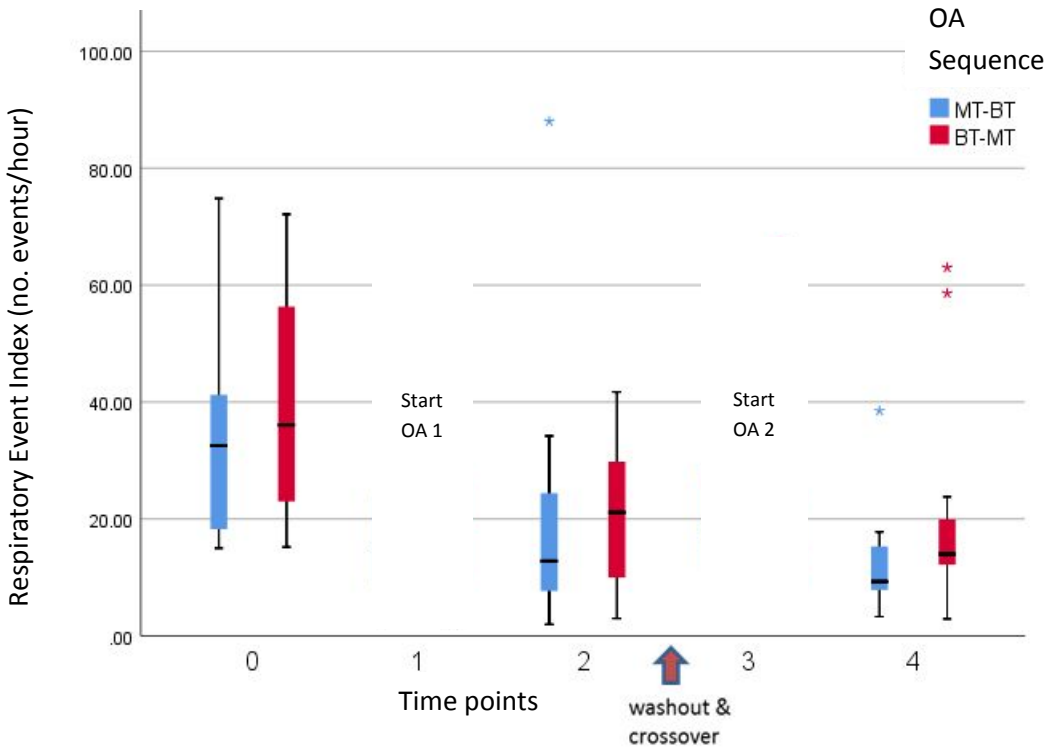

Figure 3. After first 4-weeks of oral appliance use: Respiratory Event Index (REI) change in participants with moderate and severe OSA from baseline (T0) to T2.

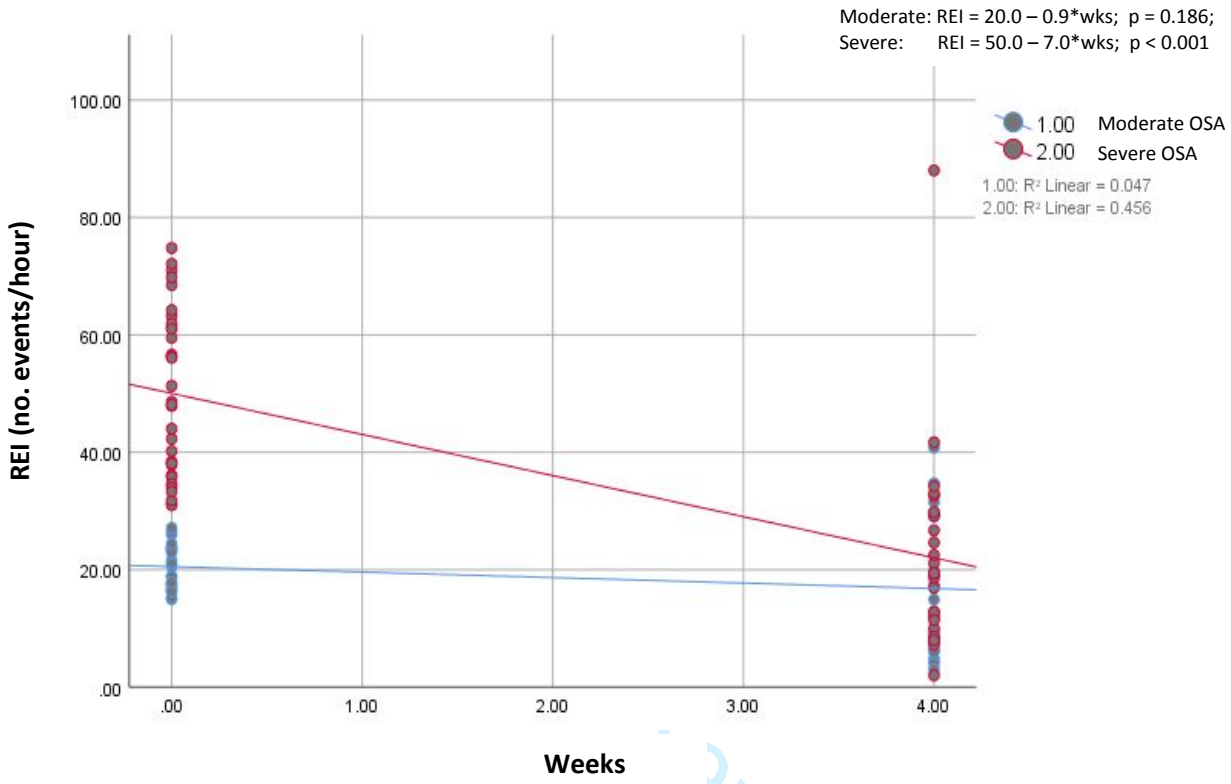

Figure 4. After second 4-weeks of oral appliance use: Respiratory Event index (REI) change in participants with moderate and severe OSA from baseline (T0) to T4.

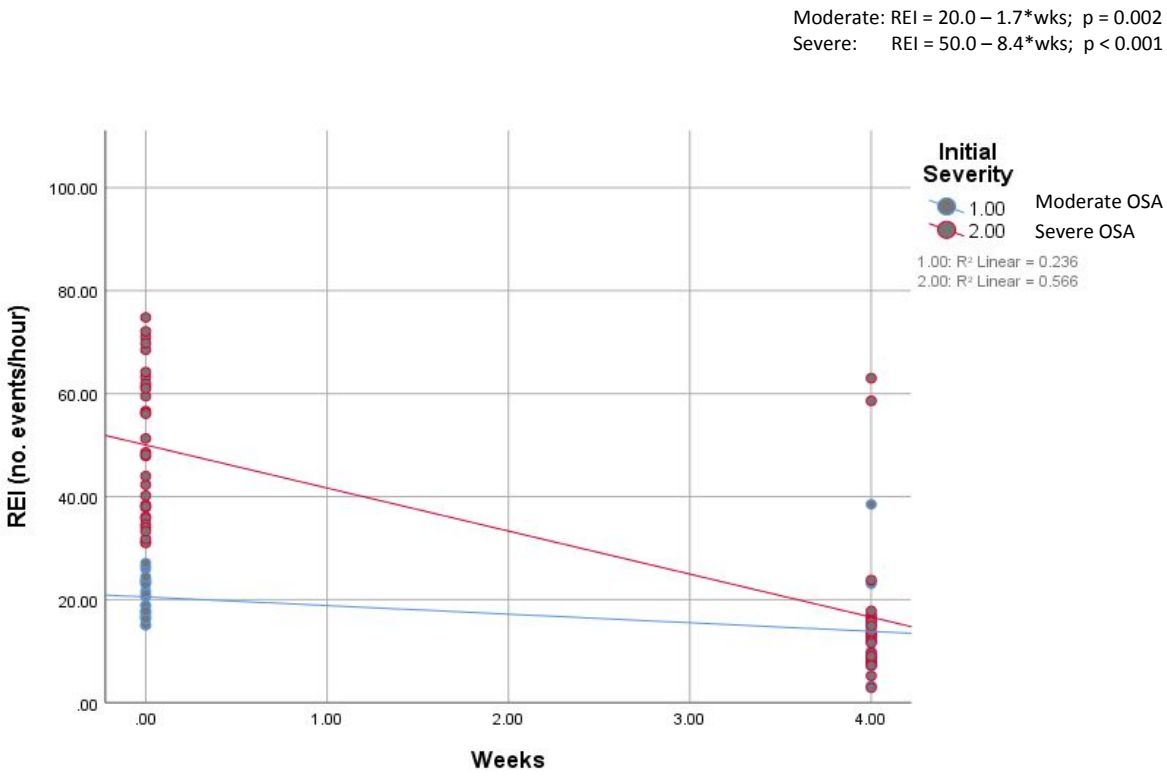

Table 1. Baseline characteristics of participants by oral appliance sequence group (n=56).

	All		MT - BT		BT - MT		
	Median	IQR	Median	IQR	Median	IQR	*P* value
Age (years)	61	51.0-68.0	64.5	46.3-69.0	61.0	52.0-66.0	0.523
Sex (% male)	71.4		56.0		83.9		0.016
Ancestry (% European)	76.8		79.2		77.4		0.491
BMI (kg/m^2)	31.0	27.9-33.8	30.3	27.4-34.0	31.0	28.0-33.6	0.519
REI (no/hr)	33.7	20.7-54.9	32.6	17.9-41.8	36.1	22.3-57.9	0.284
Mean SaO_2	93.0	91.0-95.0	93.0	92.0-94.6	93.1	91.0-95.4	0.441
Minimum SaO_2	80.0	77.0-85.0	80.0	76.0-85.0	82.0	77.0-87.0	0.554

MT, midline traction; BT, bilateral thrust; BMI, body mass index; REI, respiratory event index; SaO_2, oxygen saturation; IQR, interquartile range (25-75%). Between-groups differences in sex and ethnic distribution were tested with chi-square. All others variables analyzed with Mann-Whitney test. Ancestries of the non-European subjects were 12.5% Hispanic, 7.1% African and 3.6% Asian.

Table 2. Sleep test results by oral appliance sequence group

	All		MT-BT		BT-MT		*p* values		
	Median	IQR	Median	IQR	Median	IQR	*Between Groups*	*Within Groups from T2 to T4*	
								MT-BT	*BT-MT*
REI at T2	18.0	8.5-19.4	12.8	7.5-26.7	21.1	9.8-31.2	0.152		
REI at T4	12.5	8.2-15.9	9.3	7.7-15.5	13.1	10.4-16.6	0.232	0.401	0.691
REI Δ T0 to T2	17.3	±22.8	17.0	±25.0	17.6	±20.8	0.929		
REI Δ T0 to T4	22.6	±23.0	25.3	±25.1	19.4	±20.6	0.853	0.152	0.883
Mean SaO_2 at T2	93.0	91.6-93.8	92.3	91.5-93.7	93.1	91.6-93.9	0.505		
Mean SaO_2 at T4	93.4	91.9-94.5	92.6	91.2-94.3	93.8	92.6-94.7	0.258	0.349	0.430
Min. SaO_2 at T2	82.5	79.0-86.0	84.0	80.5-86.5	81.0	78.5-85.0	0.301		
Min. SaO_2 at T4	84.5	81.0-87.8	84.5	81.0-87.3	84.5	81.3-87.8	0.798	0.352	0.073

MT, midline traction; BT, bilateral thrust. Values are presented as median and interquartile range (IQR, 25-75%), except for REI Δ variables which are mean and standard deviation. REI, respiratory event index (no./hr), SaO_2, oxygen saturation. Between- and within group differences were analyzed with the Mann-Whitney and Wilcoxon tests, respectively. Significance level, $p < 0.05$. T2, after 4-weeks of first OA use; T4, after 4-weeks of second OA use.

Table 3. Mean oxygen saturation and minimum oxygen desaturation percent comparison at T2 and T4 with T0 (Baseline) presented as medians (IQR).

	T0	T2	*P* value	T4	*P* value	
			TO vs T2		T0 vs T4	T2 vs T4
Mean O_2 saturation (%)	93.0(91.0-95.0)	93.0(91.6-93.8)	0.095	93.4(91.9-94.5)	0.296	0.200
Minimum O_2 desaturation (%)	80.0(77.0-85.0)	82.5(79.0-85.0)	0.551	84.5(81.0-87.8)	0.058	0.054

IQR, interquartile range; T0, baseline; T2, after 4-weeks of first OA use; T4, after 4-weeks of second OA use.

Table 4. Short Form – 36 (SF-36) Quality of Life Questionnaire's Physical (PCS) and Mental (MCS) Component Adjusted Scores Compared at T0 – T4.

	Baseline – T0	T2	p value Baseline vs. T2	T4	*P* value Baseline vs. T4	*P* value T2 vs. T4
PCS	757.88 ± 140.72	932.30 ± 158.43	<0 .001	927.50 ± 100.06	<0.001	ns
MCS	863.07 ± 177.31	1006.34 ± 198.10	0.002	951.78 ± 245.57	0.013	ns

Means and standard deviations. T0, baseline; T2, after 4-weeks of first OA use; T4, after 4-weeks of second OA use.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1 of 19
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1 of 19
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2 of 19
	2b	Specific objectives or hypotheses	2 of 19
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2-3, 15 of 19
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	**No
Participants	4a	Eligibility criteria for participants	**2 of 19
	4b	Settings and locations where the data were collected	2 of 19
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2-3 of 19
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	2-3, 11-14 of 19
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	3 of 19
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3 of 19
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3 of 19
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	No
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	3 of 19

**Not presented in text due to 3200 word limit-- they are available in ClinicalTrials.gov

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	3 of 19
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	3 of 19
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	3 of 19
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	3,15 of 19
	13b	For each group, losses and exclusions after randomisation, together with reasons	3,15 of 19
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	11
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	15
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	5-6 of 19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	-
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	5-6 of 19
Other information			
Registration	23	Registration number and name of trial registry	7 of 19
Protocol	24	Where the full trial protocol can be accessed, if available	7 of 19
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7 of 19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.