Effect of custom made vs thermoplastic heatmolded mandibular advancement devices (MADs) for Obstructive Sleep Apnea (OSA): A randomized non-inferiority trial

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Introduction

Obstructive Sleep Apnea (OSA) is a frequent medical condition, affecting 2% to 8% of adults, which is associated with increased risk of cardiovascular disease and with decreased health-related quality of life (HRQoL) [1,2].

Continuous positive airway pressure (CPAP) therapy is the gold standard treatment of OSA, and for patients refusing or not tolerating CPAP it has been widely demonstrated that **MAD is an acceptable and effective second line treatment** [2].

Today, a wide selection of MADs is available, from ready-made to fully bespoke ones. Equivalence between the different kind of devices remains unclear as some studies reported that custom-made MADs are associated with higher efficacy, compliance and tolerance compared to self-moulded or semi-bespoke MADs[3,4].

Given that thermoplastic titrable MADs are at lower costs and enable to reduce treatment delays, it seems important to bring further data to assess their efficacy, compliance and tolerance in comparison with the reference custom-made MADs .

Objective

To determine if a thermoplastic heat-moulded adjustable MAD (ONIRIS™) is non-inferior to a custom made acrylic MAD (TALI™) in severe OSA patients refusing or not tolerating CPAP.

Materials and Methods

Study design:
Multicenter, single-blind, randomized controlled trial where OSA patients refusing or not tolerating CPAP were randomly assigned to a thermoplastic titrable MAD or to a custom-made acrylic MAD for 2 months, with a stratification by center and OSA severity.

Inclusion / Exclusion criteria:
- *Inclusion criteria*: patients over 18 years old, with severe OSA >15/hour and symptoms, refusing or not tolerating CPAP, without dental, periodontal or joint contra-indications and never treated with MADs.
- *Main exclusion criteria*: > 20% of central sleep apnoea and hypopnea, severe OSA with AHI ≥ 30.h^{-1} associated to other coexistent sleep disorder, BMI > 30kg/m^2, ongoing or scheduled orthodontic treatment, untreatable vomiting reflex, pregnant or breastfeeding women, epileptic patients, inability to give informed consent, patient included in an ongoing clinical study, patient not covered by the French health insurance system.

Devices:
- ONIRIS™ is a 2-units titrable thermoplastic MADs. ONIRIS™ is made of two stiff gutters heat-moulded on dental arches, coupled by two adjustable connecting rods allowing to set the mandibular advancement by steps of 1mm (4 to 15 mm).
- TALI™ is an acrylic custom-made MADs.

Outcomes:
- *Primary outcome*: Rate of success defined by at least 50% decrease from baseline in AHI or an AHI<10.h^{-1}. The non inferiority margin was defined as a difference between groups of 20% for the primary outcome and assessed in per protocol analysis.
- *Secondary outcomes:* AHI per hour, daytime sleepness (Epworth's score), fatigue and depression (Pichot's scores), health-related quality of life (SF12 scale), compliance (self assessment) and treatment acceptability (occurrence of AEs).

Results

1/ Study population.

198 severe OSA patients refusing or not tolerating CPAP have been randomized to the two treatment groups (ITT population). Out of these 198 patients, 42 patients have been excluded from the *per protocol (PP)* analysis population. According to methodological guidelines on non-inferiority trials, the *per-protocol* population, which includes all patients who satisfactorily complied with the assigned treatment and who had no major protocol violations, is more likely to identify any treatment differences and is consequently used to perform analysis. Characteristics of the PP population are detailed in Table 1.

Table 1. Per Protocol population characteristics at inclusion

	Treatment Groups		
	TALI™	ONIRIS™	Whole population
Age (Year; Mean ± SD)	52.92 ± 12.22	49.30 ± 11.20	51.32 ± 11.88
Sex (Men, %)	77%	72.50%	75%
BMI (kg/m2; Mean ± SD)	25.91± 2.85	25.86 ±2.70	25.89 ± 2.78
MADs indications			
• *Refusing CPAP (%)*	*62.10%*	*56.50%*	*59.60%*
• *Not tolerating CPAP (%)*	*37.90%*	*42%*	*37.90%*
AHI.h^{-1} (Mean ± SD)	27.1 ± 9.8	26.1 ± 11.1	26.6 ± 10.4
Hypertension (WHO criteria)			
• *No (%)*	*72.40%*	*72.50%*	*72.40%*
• *Mild (%)*	*20.70%*	*21.70%*	*21.20%*
• *Moderate (%)*	*6.90%*	*5.80%*	*6.40%*
Snoring (VAS, Mean ±SD)	6.42 ± 2.20	6.65 ± 2,46	6.52 ± 2.31
Partially edentulous patients (%)	83.16%	81.16%	82.69%
Number of missing tooth (Mean ±SD)	3.9 ± 3.2	3.4 ± 2.4	3.6 ± 2.8

2/ Primary Outcome.

According to predefined criteria of success, 51.7% and 53.6% were successfully treated for OSA in TALI™ and ONIRIS™ groups respectively. The difference does not exceed the non-inferiority margin (absolute difference 1.9 ; CI90% [-11.40 ; 15.16], p=0.005).

According to physician's subjective evaluation (assessment based on analysis of sleep recordings and clinical criteria), 69.6% of patients were successfully treated in ONIRIS™ group and 63.2% of patients were successfully treated in the TALI™ group.

The non inferiority is observed whatever the study population (ITT or PP). Moreover, results remain the same when patients were stratified by sex, age, BMI, and OSA severity at inclusion.

3/ Secondary Outcomes.

After 2 Months, both treatments enable to significantly improved AHI.h^{-1}, SF12 PCS and MCS, Pichot's fatigue/depression scores, and Epworth's score. No significant differences between the thermoplastic MAD (ONIRIS™) and the custom-made MAD (TALI™) were observed except for the Pichot's fatigue score which is significantly better in the thermoplastic MAD (ONIRIS™) group (Table 2) .

Table 2. Evolution of AHI.h-1, SF12 score, Pichot's score and Epworth's score after 2 Month of treatment in ONIRIS™ and TALI™ groups (PP population)

	Inclusion		After 2 Months		
	TALI™	ONIRIS™	TALI™	ONIRIS™	Difference between groups
AHI.h^{-1} (Mean ± SD)	27.1 ± 9.8	26.1 ± 11.1	-11.2 ± 10.8***	-11.9 ± 9.4***	p= 0.4025(§)
SF12 scores (Mean ± SD)					
• *Physical Component Summary (PCS)*	*54.04 ± 15.82*	*53.40 ± 15.62*	*4.22 ± 14.81**	*7.60 ± 13.10****	p= 0.2867(§)
• *Mental Component Summary (MCS)*	*64.98 ± 18.95*	*60.51 ± 20.25*	*5.27 ± 17.67 **	*9.44 ± 21.23***	p= 0.3600(§)
Pichot's Scores (Mean ± SD)					
• *Fatigue*	*12.5 ± 8.6*	*13.7 ± 8.2*	*-5.1 ± 7.0 ****	*-7.6 ± 7.2 ****	p= 0.0322(§)
• *Depression*	*3.4 ± 3.7*	*3.8 ± 3.7*	*-1.4 ± 3.2 **	*-2.2 ± 3.2****	p= 0.1301(§)
Epworth's score (Mean ± SD)	9.3 ± 4.8	9.2 ± 4.8	-3.4 ± 3.9 ***	-4.4 ± 3.8***	p= 0.0587(§)

Significant evolution from baseline: *p<0.05; **p<0.01; ***p<0.0001 (paired t-test) ; (§)ANCOVA

4/ Compliance and treatment acceptability.

Compliance rates was slightly higher in the custom-made MAD (TALI™) group (90.1% ± 15.7) than in the thermoplastic MAD (ONIRIS™) group (85.8% ± 18.684). In both groups the compliance is over 85% and consequently rated as excellent according to protocol criteria.

After 12 Months of treatment, no impact on temporo-mandibular joints or dental arches have been reported by 85.7% of patients treated with TALI™ and by 85.0% of patient treated with ONIRIS™. No patients treated with ONIRIS™ and only 3.6% of patients treated with TALI™ were affected by a dental impact that could jeopardize the benefits of treatment.

During the 2 first months, 77.6% of patient treated by TALI™ and 87.0% of patient treated by ONIRIS™ have reported discomfort (p=0.091, no significant difference between the two treatment groups). The most frequently reported side effects were dental pain (16.8%), temporo-mandibular joint pain (14.7%), disagreement related to MAD volume in mouth (11.6%), muscular pain (10.5%) and muscular discomfort (10.0%).

Significantly more muscular discomfort were observed in TALI™ group (14.3% vs 5.4%, p=0.0421). Significantly more disagreement due to MAD volume in mouth (19.6% vs 4.1%, p<.001), excessive salivation (14.1% vs 2.0%, p=0.002) and gag reflex (5.4% vs 0%, p=0.0193) were observed in ONIRIS™ group.

Conclusion/Discussion.

In severe OSA patients refusing or not tolerating CPAP, a thermoplastic adjustable MAD (ONIRIS ™) was non-inferior to a custom made acrylic MAD (TALI™). The difference in treatment success rates does not exceed the non-inferiority margin (absolute difference 1.9 ; CI90% [-11.40 ; 15.16], p=0.005), and analysis of secondary outcomes shows that both MADs enable to significantly improve AHI.h-1 as well as Epworth's, Pichot's, and SF12 scores, with a significant inter-group difference reported in favor of the thermoplastic MAD (ONIRIS™) group for the Pichot's fatigue score. Excellent compliance with both MADs was reported, and a slightly better acceptability of the custom-made MAD was noted.

Results are consistent with those reported by Sharples et al. demonstrating that thermoplastic adjustable MAD is the most cost-effective treatment for mild to moderate OSA patients, and also consistent with those reported by Gagnadoux et al. suggesting that some thermoplastic adjustable MADs are as effective as custom-made MADs to treat severe OSA patient refusing or not tolerating CPAP. Our study is the first large randomized controlled trial in the field.

Given adjustable thermoplastic MADs ONIRIS™ are non-inferior to custom-made devices, at lower costs and reduce treatment delays, their interest as screening tool to find good candidates for custom-made MAD therapy should be consider.

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