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Treatment of Obstructive Sleep Apnea and Simple Snoring: Efficacy of a New Mandibular Advancement Device

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Abstract: The following prospective study has the aim of evaluating the efficiency of the F22 MAD (mandibular advancement device), a new oral device for the treatment of OSAS (Obstructive Sleep Apnea Syndrome) and snoring. Methods: AHI (apnea-hypopnea index), ODI (Oxygen Desaturation Index), snoring percentage, time spent in the supine position, and Epworth Sleepiness Scale score were evaluated in 19 patients with snoring, mild to moderate OSAS, or severe OSAS who declined CPAP (Continuous Positive Air Pressure) treatment, before and after the application of the F22 MAD. Results: The median value of AHI varied from 15.6 ± 10.7 to 5.7 ± 5.7; the median value of ODI varied from 13.4 ± 8.8 to 6.2 ± 5.2; the median value of the percentage of snoring varied from 30.7 ± 7 to 7.5 ± 10.8, except for the patient who has severe OSAS who increased their value. The value obtained by the self-completion of the ESS questionnaire (Epworth Sleepiness Scale) underwent a statistically significant variation, while clinically significant for 13\19 patients who obtained a reduction of the value >/= of 2 points. Conclusions: It is possible to conclude that the F22 MAD is effective in the treatment of patients with mild and moderate OSAS or simple snoring, reducing the polysomnographic outcomes with statistically and clinically significant results in terms of reduction of AHI, ODI and percentage of snoring.

Keywords: obstructive sleep apnea; OSAS; mandibular advancement device; apnea–hypopnea index; oral appliance

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1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a chronic respiratory disorder characterized by recurrent partial or complete obstructions of the upper airways during sleep. It is a condition that can affect both pediatric [1] and adult patients [2]. Airway obstructions manifest as a reduction (hypopnea) or complete collapse (apnea) of respiratory airflow, accompanied by persistent chest and abdominal respiratory efforts aimed at overcoming the obstructive phenomenon [3]. Despite such efforts, there is an increase in the partial pressure of carbon dioxide and a decrease in the partial pressure of oxygen in the blood [4].

These respiratory obstruction events are typically associated with cortical arousals, micro-awakenings that occur to restore airway patency and respiratory flow, accompanied by oxygen desaturation events [5]. These events cause alterations in sleep architecture, leading affected patients to experience daytime sleepiness that can significantly impact their quality of life. The most typical clinical manifestations of obstructive sleep apnea syndrome include habitual and persistent snoring, reported respiratory pauses or apneas, sudden awakenings with a choking sensation, and increased risk of cardiovascular diseases [6,7].

Several epidemiological investigations have revealed a correlation between OSA and hypertension, particularly in cases involving nocturnal hypertension [8]. The interest in this condition undoubtedly stems from its impact on patients' daytime functioning.

The severity of OSA is influenced by various factors, including upper airway anatomy, muscle reactivity, arousal threshold, high gain of loop, as well as non-anatomical characteristics such as obesity, gender, aging, and alcohol consumption [9–12]. Polysomnography (PSG) is the gold standard for the diagnosis of OSA, a comprehensive sleep study that provides, among other results, the apnea-hypopnea index (AHI) [10,12,13].

According to the AASM Guidelines [14,15] for the assessment, management, and long-term therapy of the OSAS patient, there are different types of therapeutic approaches based on the characteristics and severity of the pathology. These are divided into Continuous Positive Air Pressure (CPAP) therapy, aimed at patients with moderate to severe OSAS [16], and mandibular advancement device (MAD) therapy, which is the recommended treatment choice in all those who do not tolerate CPAP or wish to adopt other types of therapy. By repositioning the mandible in a protruded position, these devices allow an increase in the posterior airspace at the hypopharyngeal level [17].

The mechanism of the MAD is similar to that of Class II orthodontic devices, which cause a significant increase in the size of the airways in patients with retrognathia, who would benefit from the treatment of OSAS [18].

Despite the availability of various MAD devices on the market, there is no consensus on the optimal design. Customized and titratable devices have shown to be more effective in reducing polysomnographic outcomes [10]. MADs can be monobloc or bimaxillary, with anterior or lateral advancement systems. Titration can be achieved using anterior or lateral screws and connectors, which tend to immobilize the mandible in an advanced or lateral position. This can limit patient movement and cause discomfort, which can affect adherence to therapy [19]. In this context, the idea of developing a new mandibular advancement device, the F22 MAD, emerged at the School of Orthodontics at the University of Ferrara. The F22 MAD aims to overcome the limitations of existing devices on the market. Its simplified design not only allows for a simplified titration procedure, but also enables patients to maintain lateral mandibular excursion freedom, making it suitable for patients with parafunctions.

The aim of this clinical study is to evaluate the effectiveness of the F22 MAD in terms of improving polysomnographic outcomes in the treatment of patients with simple snoring or mild to moderate obstructive sleep apnea syndrome, or severe cases in patients who refuse to use CPAP.

2. Materials and Methods

Participants were selected prospectively from the clinics of the School of Orthodontics at the University of Ferrara and the Otorhinolaryngology and Pneumology departments of the Sant'Anna Hospital in Cona (FE) between January 2020 and March 2022, according to inclusion criteria describe in the Table 1. The diagnosis of OSAS and the selection for intraoral device therapy were made by a specialized Otorhinolaryngology physician based on a comprehensive type III polysomnographic examination [13].

Table 1. Inclusion Criteria.

Inclusion Criteria
Patients with simple snoring
Patients with mild (AHI = 5–15), moderate (AHI = 15–30), or severe OSAS who cannot tolerate or refuse to use CPAP.
Sufficient number of dental elements for good retention of the intraoral device (>6–8 per arch)
Absence of ongoing periodontal disease and/or tooth mobility
No functional limitations in mandibular protrusion movement
>18 years old

The study group consisted of 19 patients, 15 males and 4 females, with ages ranging from 26 to 69 years (mean age 49.6 years, standard deviation 14.6). The patients were treated by the same operator (J.G.) at the same dental clinic. Table 2 describe initial records collected for all patients.

Table 2. Initial Records.

Initial Records
Assessment of daytime sleepiness using the Epworth Sleepiness Scale questionnaire [20]
Dental arch impressions, either analog or digital, to obtain initial study models
Construction bite in an advanced position, recorded using the George Gauge fork, either analog or digital.
Intra- and extra-oral photographs of patients taken before and after application of the F22 MAD device
Polysomnography or full night cardio-respiratory monitoring of type III

Subsequently, the impressions, disinfected with 2% glutaraldehyde solution, were sent to the dental laboratory for the fabrication of the F22 MAD. This is a bi-block device made of thermoplastic polyurethane, DURASOFT® (Scheu-Dental, Iserlohn, Germany) reinforced with low-shrinkage acrylic resin, providing complete occlusal coverage. It consists of an upper block with a titanium pin in a retro-incisal position with a spherical tip, and a lower block with a curvilinear slot extending from canine to canine, featuring a spherical cavity for engaging the metal pin in the upper block (Figure 1). This mechanism allows the mandible to be locked in a protruded position and prevents mouth opening while maintaining lateral mandibular movement through the sliding of the metal pin within the slot. The initial position is determined during the registration of the advancement bite, at approximately 75% of the maximum protrusion achievable by the patient, or identified as the maximum comfortable protrusion that the patient can achieve [21].

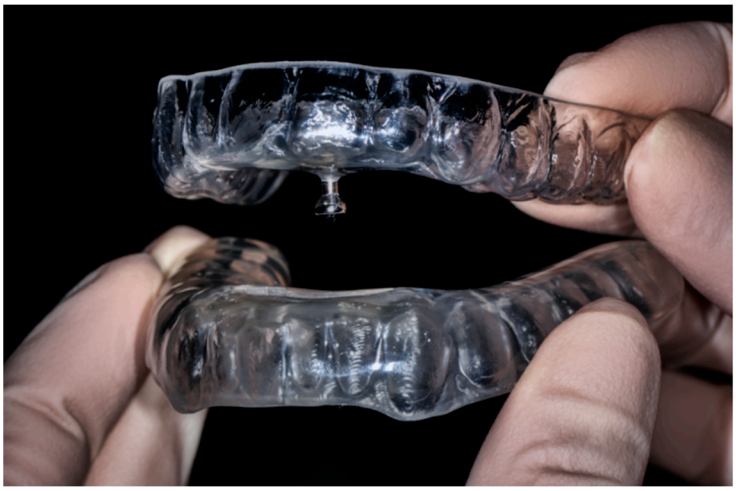

Figure 1. The design of the F22 MAD.

The device is fixed during impression taking by construction bite registration, and can be increased by varying the position of the metal pin at the level of the upper block. Subsequent advancements after the first should be made gradually, increasing by 1 mm at a time, allowing for gradual adaptation of the musculature.

Upon device delivery, the patient receives one lower block and three upper blocks, each with the metal pin positioned 1 mm apart in the anteroposterior direction: STEP 0, STEP −1, STEP +1 (Figure 2).

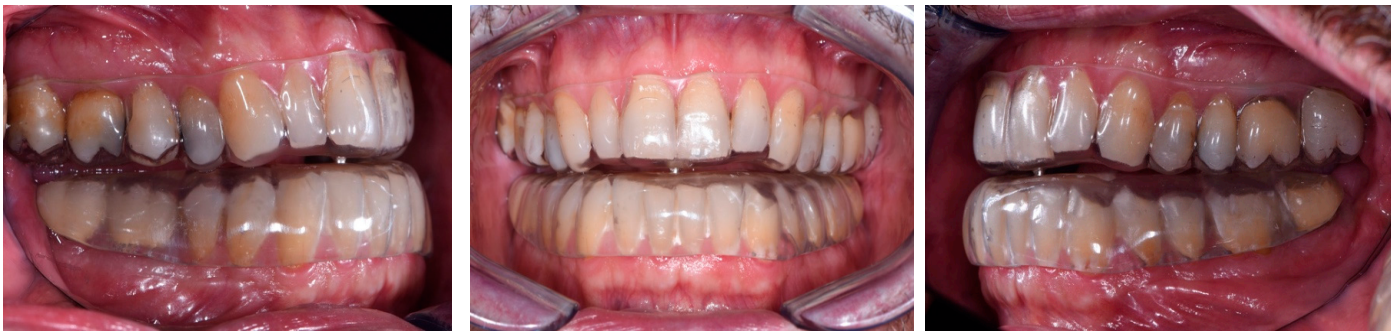

Figure 2. Intraoral photo of the F22 MAD.

STEP 0 corresponds to the initial advancement position, which is the degree of propulsion measured using the Gauge fork (Figure 3) at the time of the fingerprint recording.

Figure 3. George Gauge fork.

If at this stage the advancement were to be excessive, causing pain or a general feeling of discomfort, it will be suggested to the patient to wear STEP −1, which will have a metal pin position 1 mm behind STEP 0, in order to allow for a gradual adaptation to the device. Subsequently, it will be possible to resume the use of STEP 0. Four weeks after the application of the F22 MAD, the polysomnographic outcomes will be reassessed by conducting a new instrumental examination with the MAD in place. If at this point there is insufficient improvement in symptoms or polysomnographic parameters, the treatment would proceed by wearing STEP +1.

The analyzed indices by polysomnography were as follows:

- AHI (Apnea-Hypopnea Index: number of apnea/hypopnea events per hour of sleep) and ODI (Oxygen Desaturation Index: number of oxygen desaturation events $\geq$ 3% per hour of sleep) at T0 and T1 (with MAD in place).
- Snoring, indicated as a percentage, at T0 and T1 (with MAD in place).
- Percentage of time spent in the supine position during sleep compared to the total sleep duration at T0 and T1 (with MAD in place).

Furthermore, the ESS questionnaire score was used to assess self-reported daytime sleepiness [22] (range, 0–24; >10 indicates pathological sleepiness). The questionnaire was completed before the start of therapy and at the attainment of the final titration.

Statistical methods: The data obtained from the study of the 19 included patients were processed to evaluate the variation in polysomnographic outcomes following the application of the F22 MAD mandibular advancement device and to determine if it was statistically significant. To this end, a repeated measures *t*-test was performed using the statistical program R Core Team 2021 (Version 4.5.0 Under development, Vienna, Austria) [23] and its libraries. The significance threshold was assessed using the following type I error thresholds (α): weak (0.10, 10%), standard (0.05, 5%), and strong (0.01, 1% or lower). A descriptive analysis of the sample was also performed for age, sex, and BMI, and a comparison of the mean values of the polysomnographic outcomes were evaluated before and after the placement of the device (Table 3).

Furthermore, analyses were conducted for each individual outcome, using a repeated measures *t*-test to assess whether the mean difference between the values related to the analyzed variable at time T0 and time T1 is statistically significant; significance is evaluated based on the *p*-value, as described previously.

Box plot graphs analyzing the distribution of values for individual outcomes before and after the placement of the mandibular advancement device are shown below (Figures 4–8).

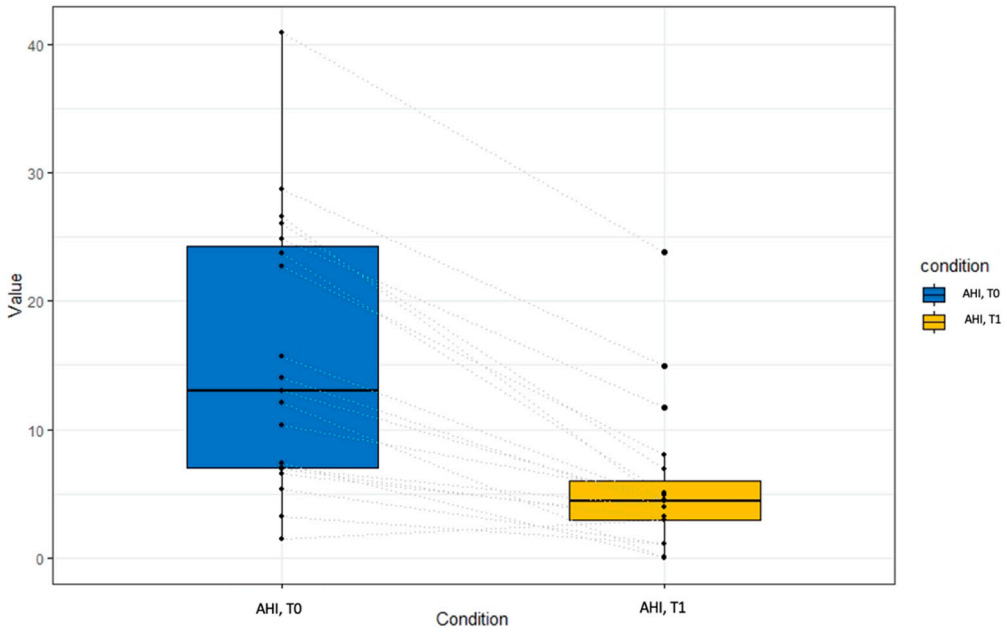

Figure 4. Box-plot type graph showing the values of AHI before and after the application of the F22 MAD.

Table 3. Descriptive analysis of the sample evaluated before and after dispositive placement: BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; AHI: Apnea-Hypopnea Index; ODI: Oxygen Desaturation Index.

	MEAN	STANDARD DEV.	MIN. VALUE	MAX VALUE
AGE	49.6	14.6	26	69
BMI	26.1	3.5	19.6	32.7
T0 ESS	8.75	3.7	4	18
T1 ESS	6.11	2	4	11
T0 AHI	15.6	10.7	1.5	40.9
T1 AHI	5.7	5.7	0	23.8
T0 ODI	13.4	8.8	2.1	36.9
T1 ODI	6.2	5.2	1.2	23.4

Table 3. *Cont.*

	MEAN	STANDARD DEV.	MIN. VALUE	MAX VALUE
% T0 SNORING	30.7	16	1	54
% T1 SNORING	7.5	10.8	0	45.4
% T0 SUPINE POSITION TIME	44.6	18.7	20.5	95.3
% T1 SUPINE POSITION TIME	42.6	21.1	13.7	88.4

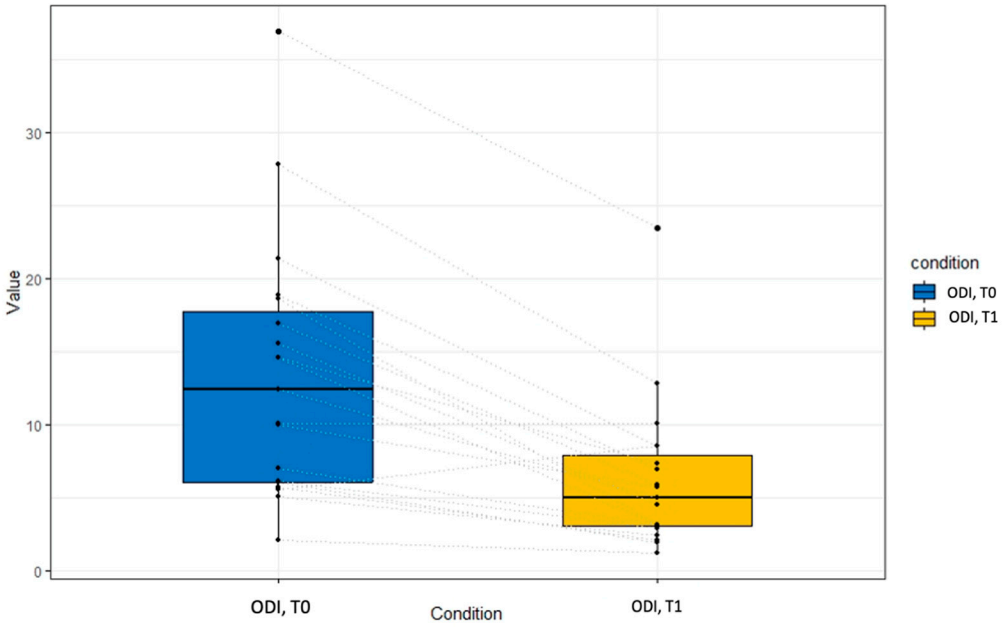

Figure 5. Box-plot type graph showing the values of ODI before and after the application of the F22 MAD.

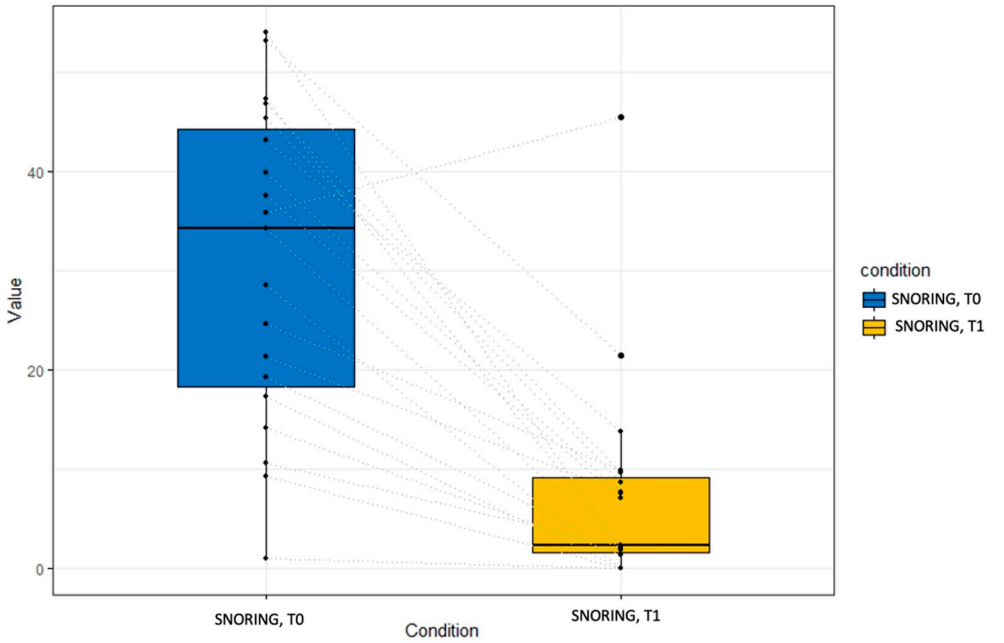

Figure 6. Box-plot type graph showing the values of snoring percentage before and after the application of the F22 MAD.

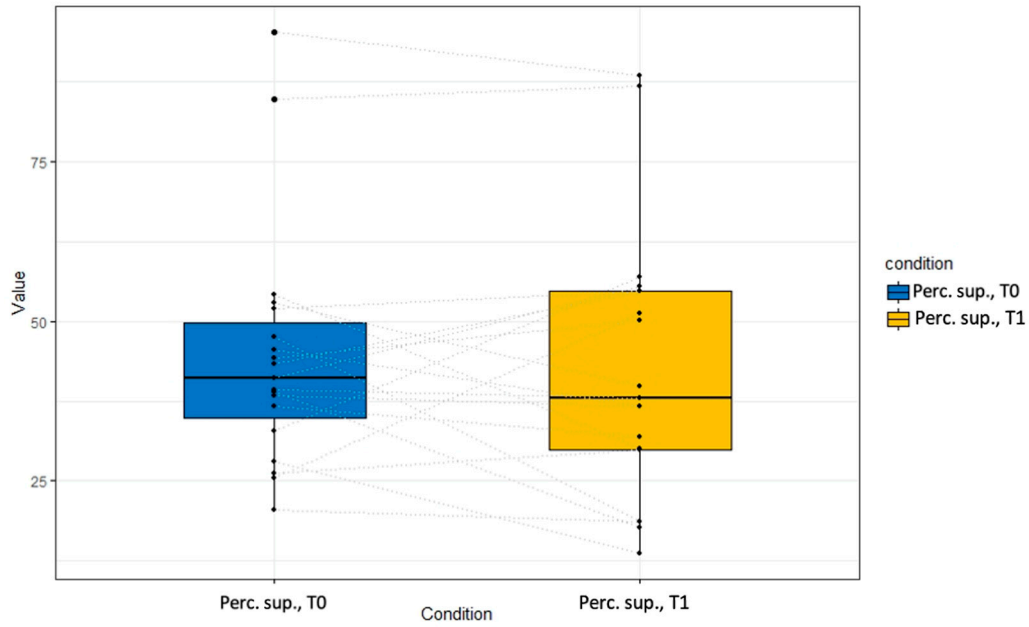

Figure 7. Box-plot type graph showing the values of the percentage of time spent in the supine position before and after the application of the F22 MAD.

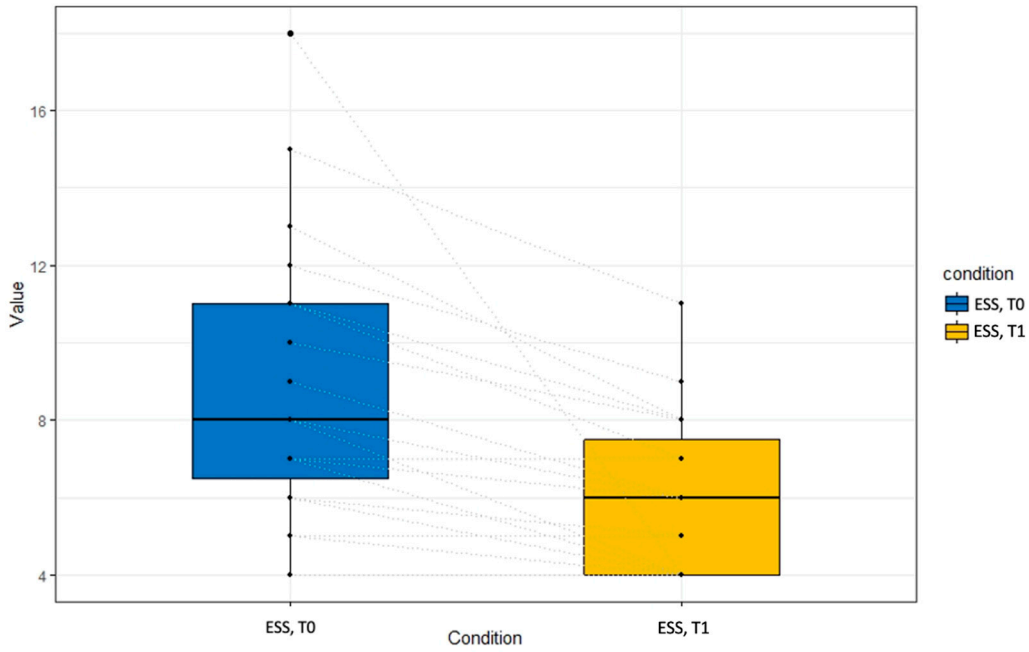

Figure 8. Box-plot type graph showing the values of ESS before and after the application of the F22 MAD.

3. Results

The treatment with the F22 MAD after one month of follow-up, as evidenced by the results obtained from the *t*-test, showed a reduction in AHI, with an average initial value of 15.6 ± 10.7 to a final average value of 5.7 ± 5.7, with a *p*-value = 0.0002. This reduction demonstrated strong statistical significance ($p < 0.01$). There was also a reduction in ODI after the application of the F22 MAD compared to the values obtained before treatment, from 13.4 ± 8.8 to 6.2 ± 5.2, with a *p*-value = 0.02, showing standard statistical significance ($p < 0.05$).

Regarding the snoring percentage, there was a reduction following the application of the F22 MAD from 30.7 ± 7 to 7.5 ± 10.8, with a *p*-value = 0.0001, indicating a strong

statistical significance ($p < 0.01$). Furthermore, no statistically significant differences were found in our sample between the means of the initial supine sleep percentage (44.6 ± 18.7) and the final percentage (42.6 ± 21.1), with a p-value = 0.5738, indicating weak statistical significance ($p > 0.10$).

Finally, the results obtained from the t-test revealed a reduction in the score obtained from completion of the Epworth Sleepiness Scale questionnaire (ESS), indicating daytime sleepiness, following the application of the F22 MAD, from 8.75 ± 3.7 to 6.11 ± 2 with a p-value = 0.0006, indicating a strong statistical significance ($p < 0.01$) (Table 4). A 2-point reduction in the questionnaire score indicates the least clinically significant difference in terms of change in daytime sleepiness [24].

Table 4. T0 and T1 parameters, and the p-values obtained from the t-test.

	T0	T1	p-Value
AHI	15.6 ± 10.7	5.7 ± 5.7	$p < 0.01$
ODI	13.4 ± 8.8	6.2 ± 5.2	$p < 0.05$
Snoring	30.7 ± 7	7.5 ± 10.8	$p < 0.01$
Supine sleep percentage	44.6 ± 18.7	42.6 ± 21.1	$p > 0.10$
ESS	8.75 ± 3.7	6.11 ± 2	$p < 0.01$

4. Discussion

A proper diagnosis of mild and moderate OSAS is essential to initiate adequate management. Symptoms such as frequent snoring, excessive daytime sleepiness, lack of concentration, and irritability, often overlooked or attributed to other causes, must be carefully evaluated to identify this condition. There is a strong correlation between sleep quality and work performance. Insufficient or poor quality sleep can negatively affect attention, memory, creativity, and decision-making ability, thus impairing productivity at work [25].

Overnight polysomnography and sleep studies are fundamental tools for accurate diagnosis and differentiation among various forms of OSAS. For patients presenting with simple snoring, also known as non-apneic snoring, the goal of therapy is to eliminate or significantly reduce the noise and risk of bruxism, as an association between sleep bruxism and simple snoring has been demonstrated, especially in the supine position [26]. Therapeutic options for mild and moderate OSAS include lifestyle changes and the use of Mandibular Advancement Devices (MADs) or Continuous Positive Airway Pressure (CPAP) therapy.

According to a guideline released by the American Academy of Sleep Medicine in 1995, MADs were recommended as the primary treatment for mild OSA and as a secondary option for moderate to severe OSA [27]. In the literature, the effectiveness of CPAP and MAD therapy has been compared, and the results have certainly demonstrated that CPAP has a greater capacity to reduce AHI, improve nighttime oxygen saturation, and decrease the number of arousals. However, the results show overlapping outcomes between the two types of treatments regarding improvement in quality of life, perception of daytime sleepiness, driving performance, and blood pressure control [28,29].

Therefore, we could say that CPAP exhibits high efficacy but low efficiency. On the contrary, thanks to comparative studies between the two types of therapies, it has been understood that MADs are better tolerated and preferred by patients, who show greater compliance with the long-term use of intraoral devices compared to the use of CPAP [30]. In this prospective study, the effects of applying the F22 MAD (Mandibular Advancement Device), an oral appliance designed by the Specialization School of Orthodontics at the University of Ferrara, were analyzed in 18 patients with mild or moderate OSAS and simple snoring, along with one patient with severe OSAS who did not accept CPAP therapy.

From the comparison of polysomnographic outcomes before and after the application of the F22 MAD, the device has proven to be effective in reducing AHI (Apnea-Hypopnea Index), ODI (Oxygen Desaturation Index), and the snoring index. By analyzing each parameter in detail, we can observe that the mean value of the initial AHI compared to the mean value of the final AHI has significantly reduced ($p < 0.01$). In particular, the success of the therapy can be confirmed by adhering to the Kushida criteria: with the MAD in place, there should be a reduction in AHI < 5 or AHI < 10 (in moderate OSAS), or a reduction in AHI > 50% compared to the initial value, with clinically noticeable symptom improvement [31].

In particular, Yoshida et al., in 1994, compared the results of polysomnography before and after the application of MAD and observed a statistically significant reduction in AHI of approximately 50% post-treatment compared to pre-treatment values [32]. Subsequently, Marklund in 1998 reported that in 72% of patients with mild to moderate obstructive sleep apnea (OSA), the post-treatment AHI had decreased to values below 10. In the severe OSAS group, the AHI was significantly reduced from an average of 53 to an average of 14 [33]. Then, Holley et al. in 2011 described the results of their retrospective study conducted on a sample of 497 OSA patients treated with MAD, regardless of the initial severity level of their condition. It was highlighted that the therapy reduced the average AHI from 30.0 to 8.4, with significant improvements also observed in the daytime sleepiness parameter, assessed through the completion of the ESS questionnaire [34]

Regarding the Oxygen Desaturation Index (ODI), the initial mean value has significantly reduced compared to the final mean value ($p < 0.05$). In the examined sample, the initial ODI was 13.4 ± 8.8, and in the final sample it was 6.2 ± 5.2. These results suggest that the MAD therapy has effectively improved the ODI, resulting in a significant reduction in the number of oxygen desaturation events during sleep. Regarding the snoring percentage, it is evident that in the examined sample, the mean value of snoring percentage has significantly decreased from 30.7 ± 7 to 7.5 ± 10.8, with a p-value of 0.0001, indicating strong statistical significance ($p < 0.01$).

This indicates that the MAD therapy has been highly effective in reducing snoring in the patients, resulting in a significant improvement in this aspect of their sleep disorder. A study has shown that 75% of patients treated with MAD for simple snoring reported an improvement in their relationships with their bed partners, who are often the ones urging the individual to seek medical evaluation for the resolution of this condition [35]. In this regard, other studies have considered the evaluation of bed partners as the most relevant outcome to assess the reduction of snoring with MAD, and 86% of them reported an improved quality of sleep for their partner thanks to the application of the intraoral device [36].

Regarding the scores obtained from the self-completion of the Epworth questionnaire, a significant decrease was observed with a p-value of 0.0006, indicating strong statistical significance ($p < 0.01$). However, for clinical relevance, a reduction of at least two points in the questionnaire score is required to confirm a real improvement in clinical symptoms with a reduction in daytime sleepiness [37], with a score of >10/24 indicating pathological daytime sleepiness. Specifically, in the examined sample, the majority of patients (12 out of 19) obtained a score <10 on the initial questionnaire, indicating they were not sleepy, while another 3 out of 19 did not report any difference in the score before and after the questionnaire, and the same number of patients reduced the score by only 1 point before and after treatment.

However, 7 out of 19 patients who initially had a score >10 achieved a reduction of at least 2 points in the score after therapy, indicating an effective improvement in daytime sleepiness. Although a statistically significant improvement is observed in the evaluation of this parameter, given the limited sample size clinical relevance is less evident. We also note that daytime sleepiness may not always be present as a symptom in patients with OSAS [38].

In the data analysis, it was chosen to examine the percentage of time spent in the supine position during sleep. The examined sample consists of patients with OSAS or simple snorers, all of whom are positional, with positional OSAS defined as a patient whose Apnea-Hypopnea Index (AHI) in the supine position is at least double that recorded in the non-supine position. Therefore, the percentage of time spent in the supine position was compared before (without MAD) and after (with MAD in place) to avoid overestimating the therapeutic effects of the F22 MAD. If a positional patient had spent most of the night with the MAD in a non-supine position, the observed reduction in AHI could be attributed to the change in position during sleep and not just to the effect of the MAD. In our sample, no statistically significant differences were found between the means of the percentage of time spent in the supine position initially (44.6 ± 18.7) and finally (42.6 ± 21.1), with a p-value of 0.5738, indicating weak statistical significance ($p > 0.10$).

From the analysis of this parameter, we can conclude that the patients included in the study maintained their positional habits during sleep despite the application of the device, and that the improvement in polysomnographic outcomes is attributable to the effective action of the F22 MAD.

As recommended by the AASM (American Academy of Sleep Medicine), the device was designed to be customized based on the intraoral characteristics of each patient, and titratable, meaning it can be gradually adjusted for advancement [10]. This is achieved through modifications of the position of the metal pin present in the upper plate, tailored to the specific needs of the patient.

The literature affirms that the extent of advancement exhibits a dose-dependent effect on the efficacy of the Mandibular Advancement Device (MAD), although this must be balanced against the potential increase in side effects [39]. It is believed that an approach to titration characterized by minimal and gradual increments over time constitutes the preferred method for identifying the optimal level of advancement, with a view to improving polysomnographic outcomes and related symptoms. The F22 MAD emerges as a suitable option for straightforward and simplified titration, efficiently manageable by both the patient and the practitioner, obviating the need for complex components such as screws and connectors.

The operator can adjust the degree of device advancement by selecting the numbered upper block most appropriate to the patient's specific clinical needs (STEP 0, +1, −1, etc.), with lower production costs compared to other MAD devices available on the market. Concerning design, the current literature does not provide specific indications for the optimal device design. The American Academy of Sleep Medicine (AASM) merely recommends the use of customizable and titratable devices, which can be monoblock or bi-block in nature. The F22 MAD takes the form of a customizable and adjustable bi-block device, equipped with an anterior advancement mechanism that prevents mouth opening and permits lateral movements. A particular study has demonstrated that bi-block MAD devices allow greater lateral mobility compared to monoblock variants [40].

Consequently, bi-block devices appear to have a significantly reduced impact on dental pain, occlusal function, and discomfort related to bulkiness, as they enable the masticatory and facial muscles to maintain their physiological rhythmic activity during sleep, thus promoting proper salivary lubrication. This increased freedom of movement appears to enhance patient comfort, reduce the sensation of confinement, and encourage adherence to therapy. Furthermore, to achieve optimal therapeutic outcomes, it is crucial to counteract vertical mouth opening using the device. While many devices require the patient to use vertical elastics, the F22 MAD, owing to its anterior interlocking mechanism between the upper block pin and the lower block slot, prevents mouth opening and maintains good retention while minimizing posterior elevation.

The device's slim profile, coupled with good retention and mechanical durability, enhances patient comfort and therapy adherence. Additionally, thanks to the lateral movement capabilities offered by the device, the F22 MAD is a suitable choice for patients affected by nocturnal bruxism. From the comparison of polysomnographic outcomes before

and after the application of the F22 MAD, it is possible to notice how the device has proven to be effective in reducing AHI (Apnea-Hypopnea Index), ODI (Oxygen Desaturation Index), and the snoring index.

Despite the encouraging results obtained with the F22 MAD, it is essential to emphasize the numerous limitations of the study. These limitations include the small sample size, potential biases in patient selection (as the study includes only simple snorers or those with mild/moderate OSA, while patients with severe OSA are absent), and the lack of an untreated control group or a group treated with a different MAD model. In the future, it would be interesting to expand the sample size and include a control group to increase the scientific validity of results supporting the F22 MAD. Additionally, extending the follow-up duration over months and years would be beneficial to investigate the mechanical resistance and long-term retention of the device.

5. Conclusions

Considering the limitations of the study, it can be concluded that the F22 MAD has been shown to be an effective device in the treatment of patients with simple snoring and mild to moderate obstructive sleep apnea (OSA), with statistically and clinically significant results in terms of reducing AHI (Apnea-Hypopnea Index), ODI (Oxygen Desaturation Index), and snoring, as detected through polysomnographic investigation.

The clinical significance of the reduction in daytime sleepiness investigated using the ESS (Epworth Sleepiness Scale) needs further exploration by increasing the sample size, ensuring that the criteria outlined in the systematic review by Hensley and Ray in 2009 are met. The design of the F22 MAD has proven to be mechanically robust and reliable, except for one case where device repair was necessary.

Furthermore, its simplified titration system allows clinicians to manage patients and adjust mandibular advancement easily. The slim profile, minimal bulk, and absence of elastic components provide comfort to the patient, enhancing adherence to therapy.

Author Contributions: L.L.: Conception and design of the study; J.G., V.C., F.S.: Acquisition of data; G.P.; Drafting the manuscript; L.L., F.P. and F.C.: Revising the manuscript critically for important intellectual content; F.P., M.P.,G.P., F.C., J.G. and L.L: revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of University of Ferrara (protocol code 10/2022: 2 October 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All authors assured that all data and materials as well as software application or custom code support their published claims and comply with field standards. The raw data supporting the conclusions of this article will be made available by the corresponding author on request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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