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Randomized Controlled Trial

Use of bibloc and monobloc oral appliances in obstructive sleep apnoea: a multicentre, randomized, blinded, parallel-group equivalence trial

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Summary

Background: The clinical benefit of bibloc over monobloc appliances in treating obstructive sleep apnoea (OSA) has not been evaluated in randomized trials. We hypothesized that the two types of appliances are equally effective in treating OSA.

Objective: To compare the efficacy of monobloc versus bibloc appliances in a short-term perspective.

Patients and methods: In this multicentre, randomized, blinded, controlled, parallel-group equivalence trial, patients with OSA were randomly assigned to use either a bibloc or a monobloc appliance. One-night respiratory polygraphy without respiratory support was performed at baseline, and participants were re-examined with the appliance in place at short-term follow-up. The primary outcome was the change in the apnoea–hypopnea index (AHI). An independent person prepared a randomization list and sealed envelopes. Evaluating dentist and the biomedical analysts who evaluated the polygraphy were blinded to the choice of therapy.

Results: Of 302 patients, 146 were randomly assigned to use the bibloc and 156 the monobloc device; 123 and 139 patients, respectively, were analysed as per protocol. The mean changes in AHI were –13.8 (95% confidence interval –16.1 to –11.5) in the bibloc group and –12.5 (–14.8 to –10.3) in the monobloc group. The difference of –1.3 (–4.5 to 1.9) was significant within the equivalence interval (P = 0.011; the greater of the two P values) and was confirmed by the intention-to-treat analysis (P = 0.001). The adverse events were of mild character and were experienced by similar percentages of patients in both groups (39 and 40 per cent for the bibloc and monobloc group, respectively).

Limitations: The study shows short-term results with a median time from commencing treatment to the evaluation visit of 56 days and long-term data on efficacy and harm are needed to be fully conclusive.

Conclusion: In a short-term perspective, both appliances were equivalent in terms of their positive effects for treating OSA and caused adverse events of similar magnitude.
Trial registration: Registered with ClinicalTrials.gov (#NCT02148510).

Introduction

The American College of Physicians (ACP) recommends that patients with obstructive sleep apnoea (OSA) concomitant with overweight and obesity are encouraged primarily to lose weight and secondarily to be treated with continuous positive airway pressure (CPAP) therapy. The ACP recommends mandibular advancement appliances as an alternative therapy for those who prefer to use an appliance or for those experiencing adverse effects with CPAP (1). The European Respiratory Society task force on non-CPAP therapies also concluded that evidence supports the use of appliances in mild-to-moderate OSA (2).

A number of different designs of appliances are available, but there are two main types: the bibloc and the monobloc appliance. The bibloc has separate constructions for the upper and lower jaws and is equipped with connectors that advance the mandible. The monobloc is a one-piece acrylic retainer with clasps on the teeth that keeps the jaws in a fixed closed mandibular advanced position.

Lettieri *et al.* (3) reported significant advantages in reducing the apnoea–hypopnea index (AHI) with adjustable compared with fixed appliances. In a systematic review, Serra-Torres *et al.* (4) also concluded that adjustable and custom-made mandibular advancement appliances give better results than fixed and prefabricated appliances and that monobloc appliances are associated with more adverse events. However, in a retrospective study that compared 55 bibloc- and 110 monobloc-treated patients, Isacsson *et al.* (5) found similar efficacy and incidence of adverse events. Thus, there are conflicting data about whether either of the construction types provides better efficacy and fewer adverse events.

Using as the background the data of Isacsson *et al.* (5), we tested the hypothesis that bibloc mandibular advancement appliances are equally effective as monobloc appliances in treating OSA from the short-term perspective.

Methods

Study design

We performed a multicentre, randomized, single-blind equivalence study on verified OSA patients in two parallel groups: one treated with a bibloc and one with a monobloc appliance. The study was performed in accordance with the principles of the Declaration of Helsinki and good clinical practice principles. The Regional Ethical Review Board approved the study on February 2014 (#2014/021). This trial is registered with ClinicalTrials.gov (NCT02148510).

The patients visited the clinic on four scheduled occasions: 1. baseline, 2. start of treatment when the appliance was fitted, 3. check-up, and 4. evaluation. At the baseline, each subject provided written informed consent and completed a set of questionnaires. Impressions of the jaws and a mandibular advancement index were taken, and one-night polygraphy (NOX-T3, ResMed) without respiratory support was performed. The treatment started 2–3 weeks after the baseline visit. The control visit was made 2 weeks after the start of treatment and, if needed based on the subjective symptoms, the appliance was adjusted. The evaluation visit was planned for 6 weeks after the baseline visit. The clinical examination was repeated, and the participants completed the same questionnaires and a follow-up home polygraphy while wearing the appliance. If needed, additional visits were allowed. The full study protocol is available at http://www.medfarm.uu.se/ckfvasteras/forskning/studieprotokoll.

Study population

The patients had been referred to the participating dental specialist clinics by a physician with request for treatment with an oral appliance. The inclusion criteria were a verified diagnosis of OSA with a minimum AHI of 15 according to the referral, an oral status that allowed retention of an appliance, at least one molar in each quadrant, mandibular maximal advancement capacity of ≥6 mm, provision of informed consent, capacity to understand and communicate in Swedish, capacity to understand the instructions about applying the portable polygraph equipment, and valid baseline polygraphy results. The exclusion criteria were age <18 years, body mass index (BMI) >35 kg/m^2, jaw functional problems treated within the past year, pain or locking of the jaw at the baseline visit, inability to follow the study instructions as judged by the investigator, hypersensitivity to the components of the appliances, and CPAP or appliance treatment in the past month.

Appliances and mandibular advancement

The Narval™ bibloc appliance (hereafter, the bibloc appliance) manufactured by ResMed (Kista, Sweden) allows the dentist to adjust the mandibular advancement chairside without involvement of a technician.

The monobloc appliance, fabricated by Boxholm Tandteknik (Boxholm, Sweden) and the Public Dental Service Örebro (Örebro, Sweden), is a one-piece, heat-cured acrylic retainer with clasps on the teeth (Figure 1). Adjustments of the mandibular advancement required a new construction bite and support by a technician. Additional details on study material are described in the Supplementary Materials.

A construction bite was made using the George Gauge® (6) instrument to make an appliance that advanced the mandible to 75 per cent of the maximal capacity and with ≥5 mm advancement. At the start of treatment, participants were encouraged to use the appliance during the full night and for all nights.

Outcomes

The primary outcome was the absolute change in the AHI from baseline without any respiratory support to the follow-up with concomitant use of the oral appliance obtained from one-night at-home respiratory polygraphy. Secondary polygraph outcomes were oxygen desaturation index (ODI), apnoea index (AI), arterial oxygen saturation (SpO_2), snore index, and estimated sleep efficiency. Details on the polygraphic methods are described in the Supplementary Materials section online.

Sleepiness as a secondary outcome was evaluated using the Epworth Sleepiness Scale (ESS) (7) and an 11-point Likert scale (0 = no sleepiness; 10 = worst imaginable sleepiness) with the statement 'Grade your inconvenience of sleepiness in the morning and

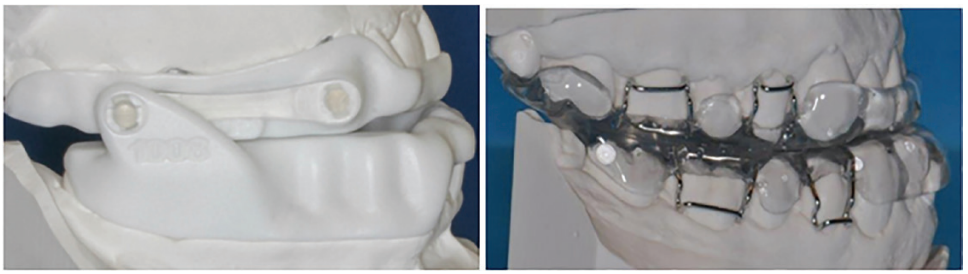

Figure 1. The bibloc (left) and monobloc (right) appliances.

during the day'. The effect of sleepiness on activities of daily living was obtained from the Functional Outcomes of Sleep Questionnaire (FOSQ) validated in Swedish (8). We also assessed, as exploratory outcomes at the evaluation visit, the patients' rating of the change in their overall status since the beginning of the study on the 7-point Patient Global Impression of Change (PGIC) scale, which ranges from very much improved to very much worse (9).

Compliance was evaluated by asking the patients to record in a questionnaire how many nights and the proportion of the sleeping time the appliance was used in the past week.

Adverse events

Spontaneously reported adverse experiences as well as adverse events registered by the investigator were recorded throughout the study period. Each adverse experience was evaluated by the investigator, and its relationship to the study treatment (probably, possibly, or unlikely) was recorded.

Statistical analysis

The primary objective was the respiratory efficacy after a 6-week treatment with the bibloc versus the monobloc appliance, which was measured as the difference in AHI within each group.

The size of the study sample was calculated on the basis of data from a retrospective comparative study of the bibloc and monobloc (5). For a two-sided confidence interval (CI) approach, the sample size per group required to demonstrate the equivalence of two means in a 1:1 randomized design based on anticipated common mean, with standard deviation (SD) 15 and level of equivalence set as ±5, was 155 at the 0.05 significance level and 80 per cent power. The chosen margin of equivalence was based on a reasonable size on the night-to-night variation in polygraph recording. We planned to recruit about 320 patients to the study.

This equivalence trial was analysed using intention-to-treat (ITT) and per-protocol (PP) approaches, and the trial was considered positive only if both approaches supported equivalence. The results from the PP analysis were expected to be more reliable because the ITT results are not conservative for equivalence trials.

The result of the equivalence test was accepted as significant if the two P values from testing if the lower limit of the 95% CI was greater than −5 and the upper limit less than 5 were both <0.025.

Likert scale data were analysed using ordinal logistic regression and are presented with median, first and third quartiles, and odds ratios with 95% CIs for the bibloc versus monobloc appliance for a greater reduction in sleepiness.

The paired t-test (verified using the Wilcoxon signed-rank test) was used for additional analysis. The P values should be interpreted descriptively. Additional information on the statistical methods is described in Supplementary Material online.

Randomization and masking

An independent person prepared a computer-generated randomization list (Nquery Advisor, Statistical Solutions Ltd, Cork, Ireland) with blocks of 12, arranged sealed envelopes with randomization number and treatment choice and kept the randomization list until 'clean file' status was declared.

At the baseline visit and after the first dentist had taken the index and impressions of the jaws, the study nurse brought the material to another locality where the randomization envelope was opened and the material distributed to the technician. The first dentist and patient were blinded to the choice of treatment. Fitting of the appliance as well as the control and extra visits were made by a second dentist. At the follow-up visit, the first dentist made the evaluation while blinded to the used appliance. The biomedical analysts who evaluated the polygraphy results were blinded to the choice of therapy.

Monitoring and data management

Two independent persons based at the Centre for Clinical Research and the Dental Research Unit monitored the three study sites.

Results

Enrolment of patients started in March 2014 and ended in April 2016; the last patient out was in August 2016. From a total of 313 enrolled patients, 11 of whom were excluded because of invalid baseline polygraphy. The ITT analysis included 146 bibloc- and 156 monobloc-treated patients. The trial profile and reasons for withdrawal are presented in Figure 2. The median time from starting treatment to the evaluation visit was 56 days (interquartile range, 45 to 79).

The two groups were well matched for baseline characteristics except for the percentage of patients with mild OSA, which was higher in the monobloc group, and with moderate OSA, which was higher in the bibloc group (Table 1).

For the PP analysis, the mean of the paired differences in AHI was −13.8 (95% CI −16.0 to −11.4) in the bibloc group and −12.5 (−14.8 to −10.3) in the monobloc group (Table 2). The effect of reducing AHI was significantly equivalent between the two appliances in both the PP and ITT analysis. For PP, the difference was −1.3 (−4.5 to 1.9) and the greater of the two P values was 0.011; for ITT, the respective values were −0.5 (−3.4 to 2.5; P = 0.001) (Table 2). The significant equivalence of the two appliances was supported by the sensitivity analysis in the PP population (P = 0.010). Supplementary Figure 1 on the statistics is accessible online. Responders classified according to different cut-offs are included in Table 3.

The subgroup of patients with severe OSA at the baseline showed the greatest improvements in both AHI and ODI for both treatment

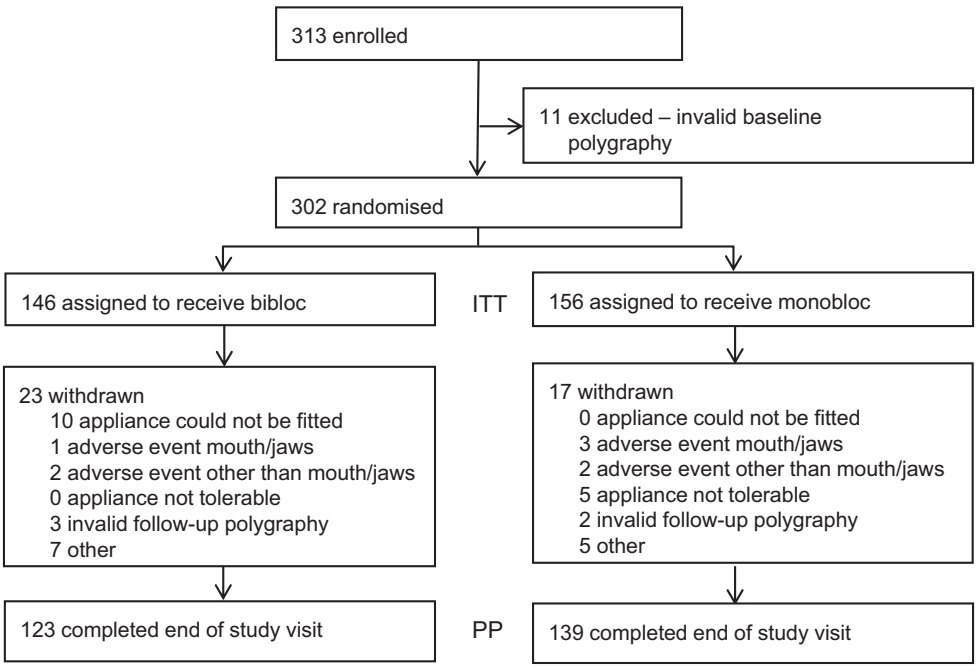

Figure 2. Trial profile. Population: ITT = intention-to-treat, PP = per protocol.

Table 1. Patient demographics and baseline characteristics of the intention-to-treat (ITT) and per-protocol (PP) populations. Data are number of patients (%) or mean (SD). ITT population: numbers in monobloc analysis of smoking 151, of snuff use 153, of mandibular advancement with index 155, and of per cent of appliance-guided mandibular advancement 154. PP population: numbers in monobloc analysis of smoking 134, of snuff use 136, of mandibular advancement with index 138, and of per cent of appliance-guided mandibular advancement 137. BMI, body mass index; AHI, apnoea–hypopnea index; OSA, obstructive sleep apnoea; ODI, oxygen desaturation index; AI, Apnoea index; SpO_2, oxygen saturation; ESS, Epworth sleepiness scale.

	Bibloc		Monobloc	
	ITT population (n = 146)	PP population (n = 123)	ITT population (n = 156)	PP population (n = 139)
Male	115 (79%)	95 (77%)	115 (74%)	103 (74%)
Age	54 (12.2)	55 (11.5)	55 (11.4)	56 (10.9)
BMI	28 (3.6)	28 (3.5)	28 (3.8)	28 (3.8)
Smoking	17 (12 %)	14 (11%)	11 (7%)	9 (7%)
Using snuff	31 (21%)	29 (24%)	26 (17%)	23 (17%)
AHI	27 (14.2)	26 (14.3)	25 (14.1)	25 (14.5)
OSA severity, categorized by AHI				
Mild (AHI < 15)	25 (17%)	21 (17%)	43 (28%)	41 (29%)
Moderate (AHI 15–29)	70 (48%)	63 (51%)	59 (38%)	51 (37%)
Severe (AHI ≥ 30)	51 (35%)	39 (32%)	54 (35%)	47 (34%)
ODI	25 (14.0)	25 (14.0)	24 (13.5)	23 (13.8)
AI	14 (11.6)	13 (11.6)	13 (11.6)	12 (11.8)
Longest apnoea, s	44 (22.2)	43 (20.5)	44 (26.3)	44 (26.5)
Lowest SpO_2	81 (5.8)	81 (5.5)	82 (5.1)	82 (5.1)
Average SpO_2	93 (1.7)	93 (1.7)	93 (1.5)	93 (1.6)
SpO_2 time <90% (% of sleep time)	10 (16.1)	10 (17.2)	8 (13.7)	9 (14.3)
Snore index (% of sleep time)	51 (26.0)	51 (26.5)	48 (23.9)	47 (24.4)
Estimated sleep efficiency (%)	89 (13.3)	89 (13.7)	90 (11.1)	90 (9.9)
Mandibular mobility				
Maximal mandibular advancement,* mm	12 (2.3)	12 (2.4)	12 (2.3)	12 (2.3)
Mandibular advancement with index, mm	9 (1.9)	9 (1.9)	9 (1.9)	9 (1.9)
Proportion of appliance-guided mandibular advancement in relation to maximal advancement, %	80 (9.4)	80 (9.8)	79 (9.6)	79 (9.1)
ESS	10 (5.0)	10 (4.8)	10 (5.1)	9 (5.1)

*Mandibular advancement, measured by the George Gauge instrument.

Table 2. Primary outcomes of the apnoea–hypopnea index (AHI) in the intention-to-treat (ITT) and per-protocol (PP) populations. The greater of the two *P* values (one for each tail of the equivalence test) is presented. AHI, apnoea–hypopnea index; CI, confidence interval.

	Bibloc				Monobloc				Equivalence test	
	n	Mean AHI at baseline	Mean AHI after 6-week treatment	Mean of paired differences (95% CI)	*n*	Mean AHI at baseline	Mean AHI after 6-week treatment	Mean of paired differences (95% CI)	Difference (95% CI)	*P* value
ITT	146	26.8	12.3*	−11.6** (−13.7 to −9.5)	156	25.2	12.5*	−11.2** (−13.2 to −9.1)	−0.5 (−3.4 to 2.5)	0.001
PP	123	26.1	12.3	−13.8 (−16.1 to −11.5)	139	25.0	12.5	−12.5 (−14.8 to −10.3)	−1.3 (−4.5 to 1.9)	0.011

*Excluding missing observations (23 for bibloc, 17 for monobloc).
**Baseline observation carried forward.

Table 3. Treatment outcome expressed as the percentages of responders following the 6-week treatment—ancillary analysis of the per-protocol population. Data are *n* (%). AHI, apnoea–hypopnea index; CI, confidence interval.

Responder definition	Bibloc (*n* = 123)	Monobloc (*n* = 139)	Percentage unit difference between groups (95% CI)
Evaluation visit AHI <5	36 (29%)	32 (23%)	6.2 (−4.4 to 16.9)
Evaluation visit AHI <10	61 (50%)	74 (53%)	−3.6 (−15.8 to 8.5)
50% reduction of baseline AHI	71 (58%)	73 (53%)	5.2 (−6.8 to 17.3)
Evaluation visit AHI <10 and ≥50% reduction of baseline AHI	52 (42%)	56 (40%)	2.0 (−10.0 to 13.9)
Evaluation visit AHI <10 and/or ≥50% reduction of baseline AHI	80 (65%)	91 (65%)	−0.4 (−12.0 to 11.1)

modalities. The improvements in the AI longest apnoea, SpO_2, and snore index were similar in the two groups (Table 4).

A series of ancillary analyses were performed. Daytime sleepiness, measured by the ESS and Likert scale, was reduced with both types of appliances, and the CIs for the differences between the appliances showed no differences (Table 5). The FOSQ score also improved similarly in both groups (Table 5). Sixty-five per cent of the patients in both the bibloc and monobloc groups reported that their symptoms were much or very much improved on the PGIC scale. None in the bibloc group, and two patients (1.4 per cent) in the monobloc group, scored worse.

The mean numbers of nights the patients used the appliance in the past week were 6.2 (SD 1.3) and 6.3 (SD 1.2) for the bibloc and monobloc groups, respectively. The mean percentages of sleep time using the appliance per night in the past week were 89 (SD 19) and 88 per cent (SD 17) for the two groups, respectively.

Adverse events were similar between the groups—39 and 40 per cent for the bibloc and monobloc groups, respectively. Unspecified complaints about the mouth, jaw, or teeth were the most commonly reported treatment-emergent adverse events, which were modest in intensity (Table 6).

Discussion

To our knowledge, this is the largest randomized, controlled, blinded trial to compare a bibloc appliance with a monobloc construction in the treatment of OSA. According to our definition of equivalence of the primary outcome AHI, the efficacy was statistically equivalent for the bibloc and monobloc appliances. The limit of the 95% CI for the difference between the two groups was −3.4 to 2.5 (ITT) and −4.5 to 1.9 (PP), which were well within the predefined boundaries of AHI ± 5.

Efficacy

The AHI for both the bibloc and monobloc appliances in our study decreased significantly by a mean of 12–14 events per hour, and the changes were greatest for severe OSA, which is consistent with the results of individual studies and systematic reviews (10–13). In contrast, in a retrospective study of 805 patients, Lettieri *et al.* (3) found a higher treatment success rate with adjustable compared with fixed appliances. Serra-Torres *et al.* (4) concluded in a systematic review that adjustable mandibular advancement appliances (i.e. biblocs) produced better results than fixed appliances (i.e. monoblocs). We found equivalent outcomes for the two devices, and our results support the findings of the retrospective study by Isacsson *et al.* (5), the cross-over study by Bloch *et al.* (14), and the systematic review by Ahrens *et al.* (10). Open labelling, lack of randomization, and selection of appliance according to resource availability in the Lettieri study explain the different results. The novelty of our study is the equivalence design with predefined boundaries, its blinding, randomization to intervention groups, and with power to fulfil the requirements to test the study hypothesis.

The various brands of appliances may elicit different treatment outcomes. Previous studies on the Narval® appliance reported a successful treatment response (>50 per cent reduction in the baseline AHI) in about 60 per cent of patients (5, 15, 16), which is higher than the 50 per cent found in the present study. Using the criterion to identify responders as a reduction in AHI to <10, Bloch *et al.* (14) reported that 67 per cent of bibloc users and 75 per cent of monobloc users were responders; these rates are substantially higher than those in our study. The reason for the differences in results may depend on factors such as the severity of OSA, the degree of mandibular advancement, insufficient statistical power, lack of descriptions of the treatment of study dropouts, and the use of the 3 or 4 per cent cut-off for the definition of hypopnea at the polygraph evaluation.

Table 4. Changes in polygraph variables from the baseline following the 6-week treatment—ancillary analysis of the per-protocol population. For the equivalence test, the greater of the two *P* values (one for each tail of the test) is presented. AHI, apnoea–hypopnea index; ODI, oxygen desaturation index; AI, apnoea index; CI, confidence interval; SpO_2, oxygen saturation; $\bar{d}$, mean difference.

	Bibloc			Monobloc			Bibloc versus monobloc	
	n	$\bar{d}$ (95% CI)	*P* value*	*n*	$\bar{d}$ (95% CI)	*P* value*	Difference between groups (95% CI)	Equivalence test *P* value
AHI severity								
Mild group (baseline AHI <15)	21	−4.0 (−5.8 to −2.3)	<0.001	41	−1.9 (−3.8 to −0.02)	0.048	−2.1 (−5.0 to 0.8)	0.013
Moderate group (baseline AHI 15–29)	63	−9.7 (−12.2 to −7.2)	<0.001	51	−10.6 (−13.0 to −8.2)	<0.001	0.9 (−2.5 to 4.4)	0.010
Severe group (baseline AHI ≥30)	39	−25.7 (−29.5 to −21.8)	<0.001	47	−23.8 (−27.9 to −19.8)	<0.001	−1.8 (−7.4 to 3.8)	0.127
ODI								
Total sample	123	−12.9 (−15.1 to −10.7)	<0.001	139	−11.2 (−13.2 to −9.1)	<0.001	−1.7 (−4.7 to 1.2)	
Mild group (baseline AHI <15)	21	−3.4 (−5.2 to −1.7)	<0.001	41	−1.6 (−3.4 to 0.3)	0.090	−1.9 (−4.7 to 0.9)	
Moderate group (baseline AHI 15–29)	63	−9.2 (−11.6 to −6.8)	<0.001	51	−9.6 (−11.9 to −7.3)	<0.001	0.4 (−3.0 to 3.7)	
Severe group (baseline AHI ≥30)	38	−24.2 (−28.0 to −20.4)	<0.001	47	−21.3 (−25.0 to −17.7)	<0.001	−2.9 (−8.1 to 2.4)	
AI	123	−9.0 (−10.7 to −7.3)	<0.001	139	−8.3 (−10.2 to −6.4)	<0.001	−0.7 (−3.2 to 1.9)	
Longest apnoea (s)	123	−14.8 (−18.1 to −11.5)	<0.001	139	−15.8 (−20.3 to −11.3)	<0.001	1.0 (−4.6 to 6.7)	
Lowest SpO_2 (%)	123	2.9 (2.1 to 3.8)	<0.001	139	3.6 (2.8 to 4.3)	<0.001	−0.6 (−1.8 to 0.5)	
Average SpO_2 (%)	123	−0.1 (−0.3 to 0.1)	0.352	139	−0.1 (−0.3 to 0.1)	0.496	−0.0 (−0.3 to 0.3)	
SpO_2 time <90% (% of sleep time)	123	−1.6 (−3.3 to 0.1)	0.073	139	−0.9 (−3.0 to 1.2)	0.396	−0.7 (−3.4 to 2.1)	
Snore index (% of sleep time)	123	−27.4 (−32.2 to −22.5)	<0.001	139	−22.5 (−26.8 to −18.3)	<0.001	−4.8 (−11.2 to 1.6)	
Estimated sleep efficiency, (%)	123	4.2 (2.5 to 5.9)	<0.001	139	2.8 (0.7 to 5.0)	0.010	1.4 (−1.4 to 4.1)	

*The hypothesis of an effect following the 6-week treatment was tested by paired *t*-test.

Table 5. Changes in sleepiness and quality of life variables from the baseline following the 6-week treatment—ancillary analysis of the per-protocol population. $\bar{d}$ mean difference; ESS, Epworth sleepiness scale; FOSQ, Functional Outcomes of Sleep Questionnaire; CI, confidence interval; Md, median (first to third quartile); OR, odds ratio (95% CI) for a greater reduction in sleepiness in the ordinal logistic regression.

	Bibloc		Monobloc		Bibloc versus monobloc
	n	$\bar{d}$ (95% CI)	*n*	$\bar{d}$ (95% CI)	Difference between groups (95% CI)
ESS	123	−3.3 (−3.9 to −2.6)	139	−2.9 (−3.5 to −2.3)	−0.3 (−1.2 to 0.5)
Sleepiness in the morning (0–10 Likert scale)*	122	Md −1 (−4 to 0)	139	Md −2 (−3 to 0)	OR 1.01 (0.66 to 1.54)
Sleepiness during the day (0–10 Likert scale)*	122	Md −2 (−3.25 to 0)	139	Md −2 (−3 to 0)	OR 1.19 (0.78 to 1.82)
FOSQ					
Total	75	1.1 (0.7 to 1.4)	86	0.8 (0.6 to 1.1)	0.3 (−0.1 to 0.7)
General productivity	109	0.3 (0.2 to 0.3)	123	0.2 (0.1 to 0.2)	0.0 (0.0 to 0.2)
Social outcome	123	0.2 (0.1 to 0.3)	139	0.2 (0.1 to 0.3)	0.0 (−0.1 to 0.1)
Activity level	104	0.3 (0.3 to 0.4)	126	0.2 (0.2 to 0.3)	0.1 (0.0 to 0.2)
Vigilance	89	0.4 (0.3 to 0.5)	97	0.2 (0.2 to 0.3)	0.1 (−0.0 to 0.3)

*In response to the statement, 'Grade your inconvenience of sleepiness in the morning respectively during the day by circling the number (Likert scale 0 = no sleepiness; 10 = worst sleepiness imaginable) that best describes the mean for the past week'.

Table 6. Incidence of reported and observed adverse experiences from the baseline to the evaluation visit—intention-to-treat population. Data are number (%) of patients reporting the event.

	Bibloc (*n* = 146)	Monobloc (*n* = 156)
Any adverse event	57 (39%)	63 (40%)
Upper airway infection	21 (14%)	22 (14%)
Complaints/diseases outside head, jaw, and mouth	17 (12%)	29 (19%)
Unspecified complaints about the mouth or jaws	24 (16%)	11 (7%)
Complaints about the teeth	13 (9%)	10 (6%)
Treatment-related adverse events*	41 (28%)	30 (19%)
Unspecified complaints about the mouth or jaws	23 (16%)	11 (7%)
Complaints about the teeth	12 (8%)	6 (4%)
Complaints about the temporomandibular joint	6 (4%)	9 (6%)
Complaints about the jaw muscles	3 (2%)	7 (4%)
Psychological complaints associated with the use of the appliance	0 (0%)	1 (1%)
Headache or clenching	2 (1%)	2 (1%)

*Rated by investigator as probably or possibly related to the intervention.

Compliance

Compliance with treatment is crucial to the efficacy of an intervention. One weakness of our study was the lack of objective measures because one of the appliance providers could not establish the retention of microsensors. However, Vanderveken *et al.* (17) used microsensor chips embedded in the appliances and found non-significant differences between the objective measurements and the self-reported use of the appliance. By extrapolating this to our study, we believe that the compliance with the treatment was probably good considering the subjective report of a mean use of six or more days per week and 87 to 89 per cent of sleep time. We acknowledge that subjective reports may be overestimated by 30 minutes (18).

Sleepiness

Exploratory analysis of daytime sleepiness was performed with the ESS scale and the 11-graded Likert sleepiness scale. The improvement in the morning and daytime sleepiness scores showed that the bibloc and monobloc appliances were equally effective. The ESS score improved by about three units, which is greater than that reported in studies comparing oral appliances with control appliances reported in a Cochrane review by Lim *et al.* (19) (−1.81; 95% CI −2.72 to −0.90), and in a meta-analysis by Qaseem *et al.* (1) (−1.95; 95% CI −2.93 to 0.97). The greater improvement in daytime sleepiness registered in our study may be explained by the high compliance with the treatment.

Harm

Adverse events commonly occur with the use of oral appliances in the treatment of OSA but are usually mild, and the devices are well tolerated by most patients. Our study does not confirm the previous assumption that the monobloc has a higher incidence of events than the bibloc appliance (4). The overall reporting was similar between groups, but the number of treatment-related events was higher in the bibloc group. The most frequent complaints were localized to the mouth, jaws, teeth, temporomandibular joint, and jaw muscles. Our findings are thus consistent with those of previous reports (16, 20).

Study limitations and comments

One limitation of our study is the relatively short observation time, which was a median of 56 days. Vibration of the pharyngeal tissues associated with the sound of snoring is caused by narrowing of the pharyngeal lumen and obstructive breathing, which have effects

on the mucosa in terms of impaired function of the nerve endings (21) and associated oedematous mucosa (22). The time required for improved nerve function and reduced oedema may exceed 2 months, and long-term follow-up studies are needed.

The justification to use the inclusion criteria of the maximal protrusion, 'at least 6 mm', and to use a 'predefined advancement of 75% of the maximal protrusion' (gives at least 5 mm advancement) in the present study were based on published data. In a meta-regression analysis concluding 13 randomized controlled studies with advancements of 50 to 89 per cent of maximal protrusion, Bartolucci *et al.* (23) found that amounts higher than 50 per cent do not significantly influence the success rate. In terms of the length of minimum effective mandibular advancement, Anitua *et al.* (24) concluded that the majority of patients achieved 'success' in terms of at least 50 per cent reduction of the AHI with an advancement of 5 mm or less. In our study, we choose a predefined start-up advancement of 75 per cent of the maximal protrusion in order to ensure sufficient effect also for those with a lesser degree of protrusion ability.

In the report of the Swedish agency for health technology assessment and assessment of social services (http://www.sbu.se/sv/publikationer/vetenskap--praxis/vetenskap-och-praxis/somnapne/), they conclude that a registration of AHI using polysomnography shows moderately strong evidence of agreement between measurements. The agency also concludes that manual interpretation of a one-night polygraphic registration shows high sensitivity and specificity to identify pathological AHI compared with polysomnography, i.e. to identify pathology from non-pathology. However, in our study, the absolute change of the AHI was the primary outcome measure, and the night-to-night variability was not controlled. With the high number of randomized patients in both our groups, we can assume that the variability was of the same level in both groups, and thereby, the study hypothesis then could be tested with reasonable accuracy.

Generalizability

Our short-term study results may be generalized because of the novelty in the trial design using a randomized and blinded protocol and inclusion of patients representing a typical apnoea population prescribed appliance therapy. Our findings suggest that the substantial improvements in OSA signs and symptoms outweighed the modest treatment-related adverse reactions in both the bibloc and monobloc groups.

Conclusions

In conclusion, in a short-term perspective, both appliances were equivalent in terms of their positive effects for treating OSA and caused adverse events of similar magnitude.

Supplementary Material

Supplementary data are available at *European Journal of Orthodontics* online.

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Conflict of Interest

GI participated in and received remuneration from one advisory board organized by ResMed, France, in February 2016. The other authors declare that they have no conflict of interest.

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