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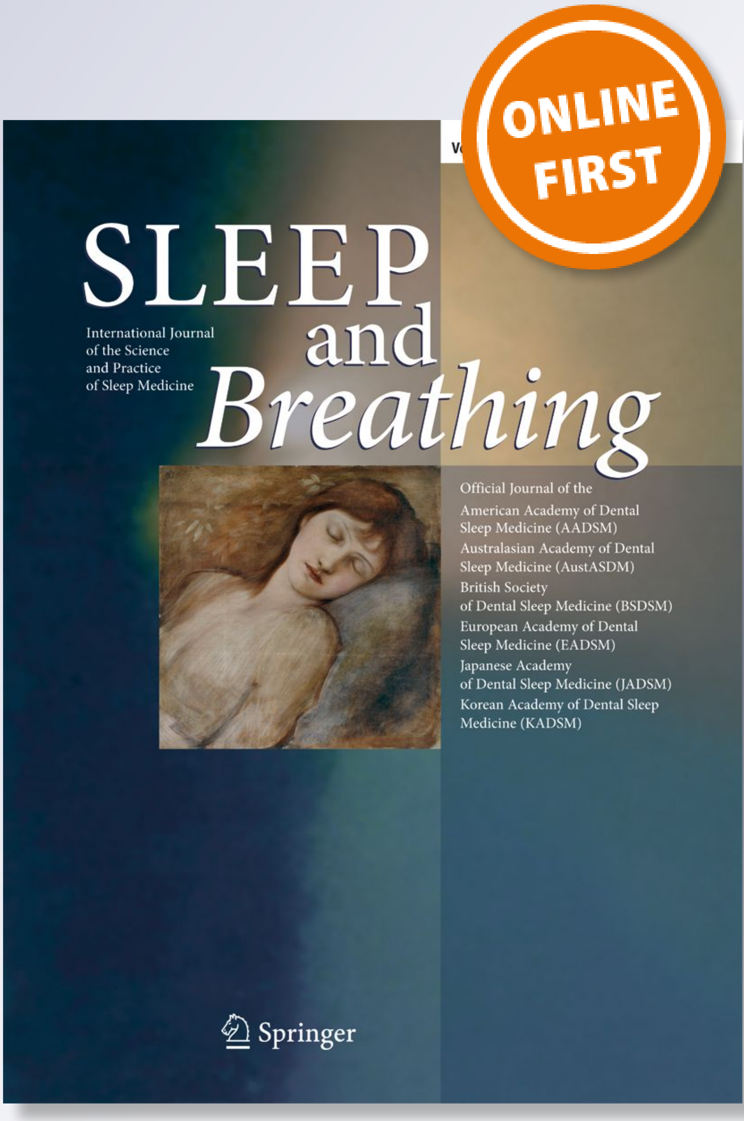

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DENTISTRY • ORIGINAL ARTICLE

The long-term effects of mandibular advancement splint on cardiovascular fitness and psychomotor performance in patients with mild to moderate obstructive sleep apnea: a prospective study

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Abstract
Background Obstructive sleep apnea (OSA) manifests as a reduction or complete cessation of airflow despite an ongoing inspiratory effort, leading to hypoxemia and hypercapnia. The inability to maintain normal breathing reduces the oxygen saturation in blood leading to a cycle of various systemic implications. Hence, a prospective single arm study was planned to evaluate the long-term (2 years) effect of oral appliance on cardiovascular fitness and psychomotor performance in patients with mild to moderate obstructive sleep apnea.
Methods Thirty dentulous OSA patients (25 males; 5 females; age 41 ± 4 years; BMI 22 ± 5; AHI 5–30) were included in the study. All the patients were assessed for systolic blood pressure (SBP), diastolic blood pressure (DBP), apnea/hypopnea index (AHI), lipid peroxidation, and psychomotor vigilance test at baseline, 6 months, 1 year, and 2 years after wearing mandibular advancement splint (MAS).
Results A significant reduction in AHI, blood pressure, and lipid peroxidation was observed following MAS use. Psychomotor vigilance test showed marked improvement in response time with almost 0 count of lapses after 2 years of MAS use.
Conclusions The present study suggested that MAS can be helpful in improving cardiovascular fitness and cognitive response in patients with mild to moderate OSA.

Keywords Apnea/hypopnea index (AHI) · Oxidative stress · Psychomotor vigilance test · Mandibular advancement splint · Obstructive sleep apnea

Introduction

Obstructive sleep apnea is a silently progressive affliction with rising severity. While the worldwide prevalence range is 3.5–27%, it is 3–28% in males and 2.2–16% in females in India [1–5]. Hypertension is a frequent co-morbidity with a 28–57% presence in OSA patients and it is directly related to the severity of apnea [6–8]. Treatment of OSA with oral appliances has served to reduce hypertension too [9–12]. Comprehensive investigations have shown reductions in systolic, diastolic, as well as nocturnal systolic blood pressure following oral appliance use [13]. While oral appliances had shown positive effect on blood pressure, constant positive air pressure (CPAP) therapy produced confounding results with some studies reporting a positive, while others reporting a negative, outcome [14–17]. Intermittent hypoxia increases sympathetic activity, suppresses vagal tone, and ushers the production of reactive oxygen species and free radicals which, in turn, induce inflammation and degrade endothelial function to produce oxidative stress. Consequently, the nocturnal sleep time blood pressure and heart rate are deregulated and daytime tachycardia, hypertension, and eventually, congestive heart failure (CHF) follow [18–20]. Intermittent hypoxia can lead to cognitive impairment in form of deficient intelligence, thought, memory etc. Thus, OSA patients are highly prone to automobile and industry related mishaps [21, 22].

Oral appliances which essentially serve to reposition the tongue and/or mandible and thus serve to expand the upper airway have elicited interest in the recent times. Few data suggests the effectiveness of OA on cardiovascular fitness but its long-

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Table 1 Demographic characteristics of the patients

	Baseline	2 years	*P* value
Age (years)	41 ± 4	41 ± 4	
Gender (male/female)	25/5	25/5	
BMI	22 ± 5	22.3 ± 2.2	Not significant
AHI	22	3.53	<0.001
Mean O2/range of O2 saturation	93.34 ± 1.01 Range (92.0–96.2)	94.71 ± 1.44 Range (92.5–96.8)	0.004

term effect is still controversial [23–27]. Hence, the present study was planned to evaluate the long-term (2 years) effect of oral appliance on cardiovascular fitness and psychomotor performance in patients with mild to moderate obstructive sleep apnea.

Materials and methods

The present study was conducted in the Department of Prosthodontics, Dental College & Hospital, Azamgarh. Prior approval of the institutional ethical committee had been obtained (committee for ethics in human research, Azamgarh).

The inclusion criteria were the following: apnea/hypopnea index (5 < (AHI) < 15 per h) and at least two of the following symptoms—daytime sleepiness, snoring, witnessed apneas, and fragmented sleep; patients that had inconvenience using CPAP.

The exclusion criteria were the following: at least five teeth per quadrant (excluding the third molar) for better retention for the mandibular advancement splint; TMJ disorders including pain, significant joint crepitation, restricted mouth opening, or masticatory muscle tenderness; grossly carious and/or periodontal weakened tooth; systolic blood pressure of greater than 140 mm of Hg; and diastolic blood pressure of greater than 90 mm of Hg.

Thirty dentulous OSA patients (25 males; 5 females; age 41 ± 4 years; BMI 22 ± 5; AHI 5–30) (Table 1), who volunteered and provided written informed consent were included in the study. A mandibular advancement splint (MAS) was fabricated (Figs. 1 and 2). MAS was fixed at 70% of the maximum mandibular protrusion recorded, to avoid any possible anterior impingement of the glenoid fossae by the condyles as done by Keyf et al. [28]. Recall appointments were scheduled every week till 1 month. Patients that were comfortable with MAS after 1 month were assessed for systolic blood pressure (SBP), diastolic blood pressure (DBP), apnea/hypopnea index (AHI), lipid peroxidation, and psychomotor vigilance test at baseline, 6 months, 1 year, and 2 years after wearing mandibular advancement splint (MAS).

Fig. 1 MAS used for the study

Fig. 2 Intraoral view of MAS

Blood pressure

The blood pressure (BP) was measured between 9 and 11 a.m. BP readings were taken with patients in supine position and the arm at heart level. Blood pressure was measured baseline, at 6 months, 1 year, and 2 years using a BP monitor on the left upper arm.

Polysomnography [29]

A full night polysomnography was performed (S-7000, Cogent technologies, EMBLA System Inc.) that included electroencephalograms (EEG), electrooculogram, chin and leg electromyogram (EMG), nasal airflow (nasal pressure cannula), oxygen saturation (pulse oximetry), movements of thorax and abdomen, electrocardiogram (ECG), and body position. Somnologica Studio software was used to calculate AHI. AHI was determined by the frequency of these events per hour during sleep time based on the results of the overnight polysomnography. Recordings were cross-checked manually for scoring of sleep stages, apneas, and hypopnea events.

Lipid peroxidation

Thiobarbituric acid reactive substance (TBARS) assay test was done according to the methods described by Lavie et al.

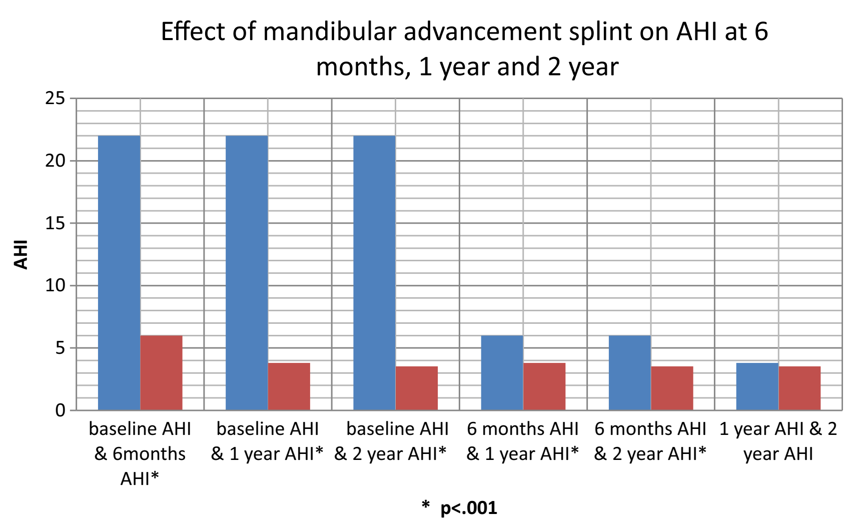

Fig. 3 Effect of mandibular advancement splint on AHI at 6 months, 1 year, and 2 years

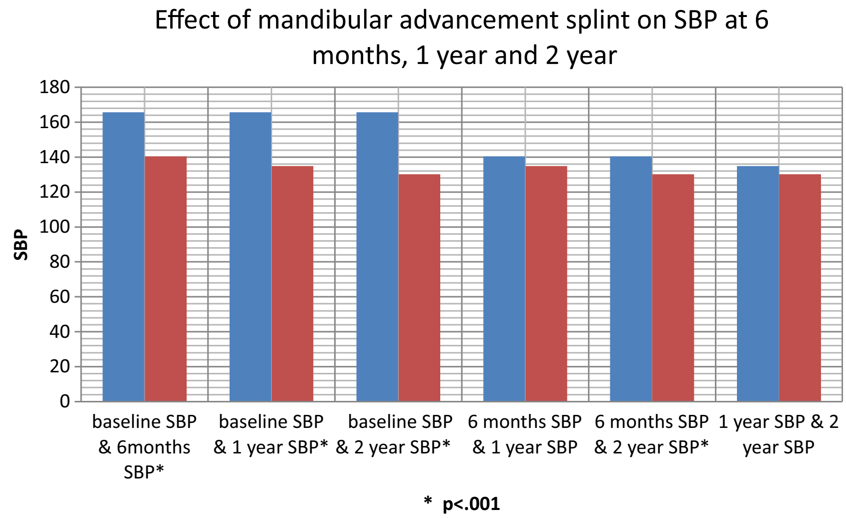

Fig. 4 Effect of mandibular advancement splint on systolic blood pressure (SBP) at 6 months, 1 year, and 2 years

[30]. TBARS, a byproduct of lipid peroxidation, was detected by the TBARS assay using thiobarbituric acid as reagent. This test involved condensation of two molecules of TBA with one molecule of malondialdehyde (MDA). Plasma samples were added to TBA dissolved in tetramethoxy propane to form TBARS working solution. The solution was then heated at 100 °C for 20 min and then centrifuged at 1000×g for 10 min. Data was expressed in terms of nanomoles of malondialdehyde (MDA) per milliliter of plasma.

Psychomotor vigilance test

The psychomotor vigilance test was performed using PC-PVT software [31]. The PC-PVT software involved two separate applications, the “Manager” and the “Tester”. The Manager was used to enter testing protocol (visual stimuli), patient information, and interpretation of the results at the end of PVT session. The Tester was used by the subject to perform a 5- or 10-min PVT session. During each session, visual stimuli appeared at variable intervals of 2 to 10 s, and the patients were instructed to click on that stimulus using mouse as quickly as possible. A response time > 500 ms was considered as count of lapse. Average response time and count of lapses were generated at the end of the session.

Data was analyzed using Statistical Package for Social Sciences Version 15.0. Paired *t* test was used to evaluate before-after changes. A “*P*” value less than 0.05 indicated statistically significant difference. Pearson correlation analysis was used to correlate between AHI and other parameters.

Results

AHI

The baseline (0 month) and postoperative (6 month, 1 year and 2 years) AHI scores of OSA patients are shown in Fig. 3.

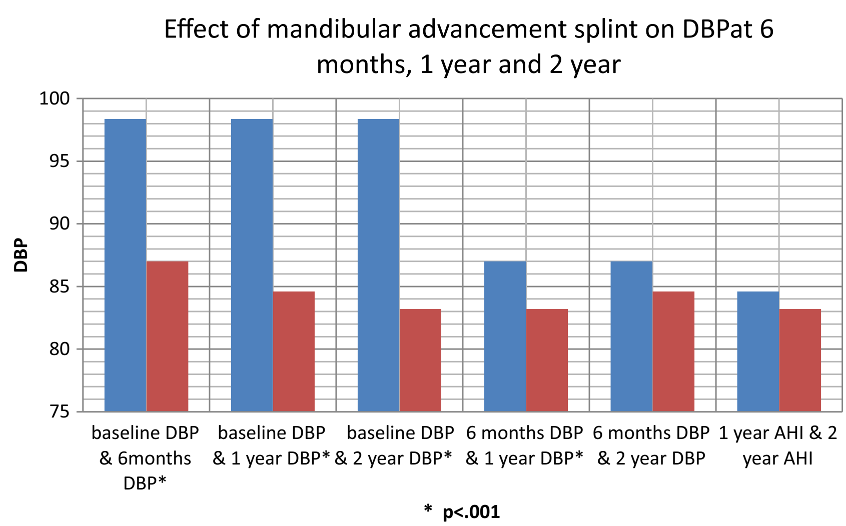

Fig. 5 Effect of mandibular advancement splint on diastolic blood pressure (DBP) at 6 months, 1 year, and 2 years

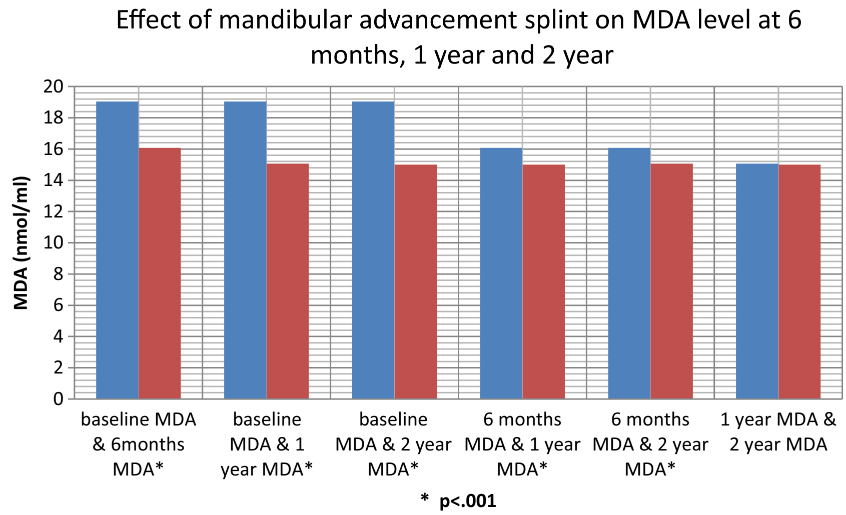

Fig. 6 Effect of mandibular advancement splint on MDA level at 6 months, 1 year, and 2 years

The mean (± SD) AHI at 0, 6, 1 year, and 2 years were 22.00 ± 3.98, 6.00 ± 2.24, 3.8 ± 1.54, and 3.53 ± 1.36, respectively. The mean AHI at posttreatment periods decreased (improved) as compared to baseline. On comparing the mean AHI between the periods, paired *t* test revealed significant difference ($P < 0.001$) and lower AHI at 6 months (difference of 16), 1 year (difference of 18.2), and 2 years (difference 0f 18.46) as compared to 0 month. However, mean AHI was the same ($P = 0.058$) at 1 year and 2 years.

Blood pressure

A significant reduction in systolic and diastolic blood pressure was observed at 6 months, 1 year, and 2 years (Figs. 4 and 5). On comparison of the mean values of systolic blood pressure at baseline, 6 months, 1 year, and 2 years, the maximum change was observed at 6 (difference of 25.33); thereafter, the change was almost constant (Fig. 4). Diastolic blood pressure followed the same trend. However, diastolic blood pressure continued to decrease even after 2 years following use of MAD.

TBARS level (nanomoles of malondialdehyde (MDA) per milliliter of plasma)

The baseline (0 month) and postoperative MDA levels of OSA patients are shown in Fig. 6. The mean (± SD) MDA levels (nmol/ml) at 0, 6, 1 year, and 2 years were 19.04 ± 1.76, 16.07 ± 1.04, 15.06 ± 0.53, and 15.06 ± 0.56, respectively. The mean MDA levels at all posttreatment periods decreased (improved) as compared to baseline. Comparing the mean MDA levels of four periods (Fig. 6), paired *t* test revealed significant ($P < 0.001$) difference and lower MDA levels at 6 months (difference of 2.96), 1 year (difference of 3.97), and 2 years (difference of 4.03) as compared to 0 month. The maximum reduction was observed till 1 year; thereafter, the change was almost constant.

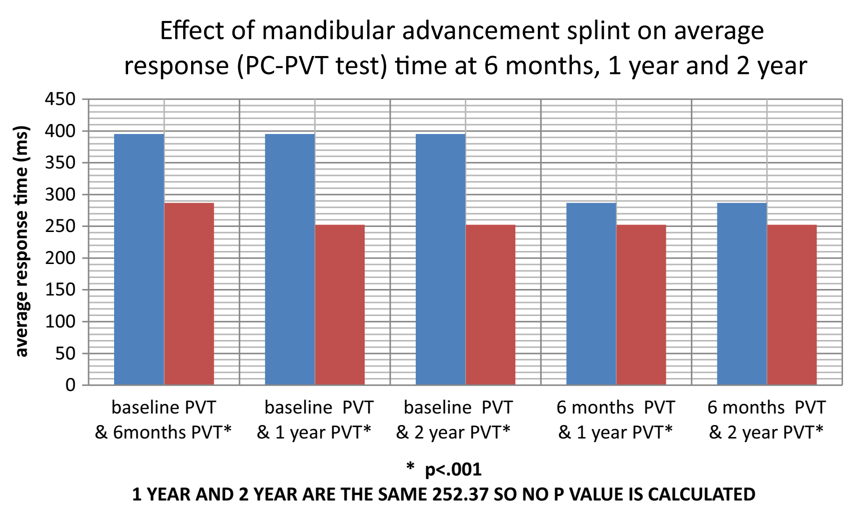

Fig. 7 Effect of mandibular advancement splint on average response time (PC-PVT test) at 6 months, 1 year, and 2 years

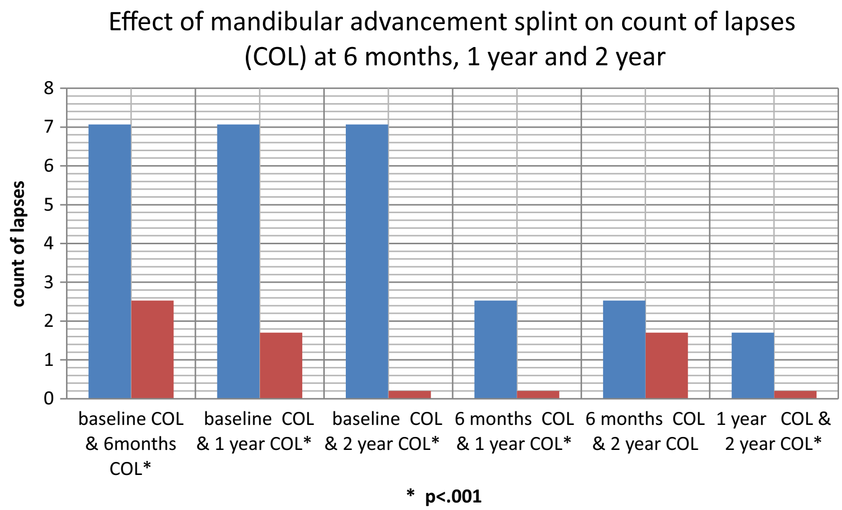

Fig. 8 Effect of mandibular advancement splint on count of lapses at 6 months, 1 year, and 2 years

Psychomotor vigilance test

The baseline (0 month) and postoperative average response time and count of lapses of OSA patients are shown in Figs. 7 and 8. There was a marked improvement in average response time at 6 months following use of MAD. Failure to response (count of lapses) almost reached to 0 at 2 years of MAD use.

On seeking the correlation between AHI, C-reactive protein level, MDA level, and average response time at 6 months, only average response time showed a mild positive correlation with AHI (r = 0.382) (Table 2). At 1 year, MDA showed a moderate positive correlation with AHI (r = 0.4) (Table 3), and at 2 years (Table 4), both MAD and C-reactive protein showed a moderate positive correlation with AHI (r = 0.466 and 0.483, respectively).

Discussion

The basic pathophysiological factor in OSA is compromised upper airway. Oral appliances serve to advance the mandible within a range of physiological limits along the path of condylar guidance and bring about an increase in the volume of the hypopharynx. Although MAS is less effective than nCPAP, but MAS reduces AHI and improves sleep efficiency [7, 32, 33]. The AHI in present study reduced from 22 to 3.53.

Another interesting finding was TBARS levels and blood pressure. Oxidative stress and subsequent lipid peroxidation is important in the initiation and development of atherosclerosis. TBARS levels in the present study were significantly reduced following MAS use. In long term, there was no improvement in TBARS level after 1 year. Both systolic and diastolic blood pressure almost followed the similar trend with improvement till 1 year and constant thereafter.

Table 2 Correlation between AHI, C-reactive protein, MDA level, and average response time at 6 months

Correlations

		6 months AHI	6 months C-reactive protein level (mg/dl)	6 months MDA level (nmol/ml)	6 months average response time (ms)
6 months AHI	Pearson correlation	1			
	Sig. (2-tailed)				
	N	30			
6 months C-reactive protein level (mg/dl)	Pearson correlation	.081	1		
	Sig. (2-tailed)	.672			
	N	30	30		
6 months MDA level (nmol/ml)	Pearson correlation	.089	.124	1	
	Sig. (2-tailed)	.639	.515		
	N	30	30	30	
6 months average response time (ms)	Pearson correlation	.382[a]	−.025	.111	1
	Sig. (2-tailed)	*.037*	.895	.558	
	N	30	30	30	30

[a] Correlation is significant at the 0.05 level (2-tailed)

Table 3 Correlation between AHI, C-reactive protein, MDA level, and average response time at 1 year

Correlations

		1-year AHI	1-year C-reactive protein level (mg/dl)	1-year MDA (nmol/ml)	1-year average response time (ms)
1-year AHI	Pearson correlation	1			
	Sig. (2-tailed)				
	N	30			
1-year C-reactive protein level (mg/dl)	Pearson correlation	.189	1		
	Sig. (2-tailed)	.317			
	N	30	30		
1-year MDA (nmol/ml)	Pearson correlation	.405[a]	.057	1	
	Sig. (2-tailed)	*.026*	.765		
	N	30	30	30	30
1-year average response time (ms)	Pearson correlation	−.007	−.055	−.374[a]	1
	Sig. (2-tailed)	.970	.774	*.042*	
	N	30	30	30	30

[a] Correlation is significant at the 0.05 level (2-tailed)

Only few studies [6] so far have reported the long-term effect of MAS on cardiovascular system, exhibiting a marked reduction in diastolic blood pressure. Since cardiovascular morbidity is an invariable sequel to OSA even in stable patients, we believe MAS is a viable treatment alternative for patients non-responsive to CPAP therapy and may serve to retard and reduce cardiovascular complications.

The improvement in task time as a descriptor of speed, accuracy, and mental endurance might be of clinical significance because the reaction time and psychomotor speed are crucial in driving performance and may reduce the risk for motor vehicle accidents [18]. Psychomotor vigilance test showed marked improvement in response time with almost 0 count of lapses after 2 years of MAS use. Our results agree with the results reported by Galic et al. [11] who evaluated oral appliance effect on long-term cognitive and psychomotor performance. Treatment with MAS could also be important in an effort to reduce workplace accidents that are associated with suboptimal speed of thinking and responding.

A negligible change in BMI was observed at 2 years following MAS use. BMI was not evaluated at 6 months and 1 year; however, it would be interesting to observe MAS effect on BMI of the patients. Another limitation in the present study was no reference group was included that would have

Table 4 Correlation between AHI, C-reactive protein, MDA level, and average response time at 2 years

Correlations

		2-year AHI	2-year C-reactive protein level (mg/dl)	2-year MDA (nmol/ml)	2-year average response time (ms)
2-year AHI	Pearson correlation	1			
	Sig. (2-tailed)				
	N	30			
2-year C-reactive protein level (mg/dl)	Pearson correlation	.466[a]	1		
	Sig. (2-tailed)	*.047*			
	N	30	30		
2-year MDA (nmol/ml)	Pearson correlation	.483[b]	.186	1	
	Sig. (2-tailed)	*.007*	.325		
	N	30	30	30	
2-year average response time (ms)	Pearson correlation	−.133	.186	−.273	1
	Sig. (2-tailed)	.484	.324	.145	
	N	30	30	30	30

[a] Correlation is significant at the 0.05 level (2-tailed)

[b] Correlation is significant at the 0.01 level (2-tailed)

correlated between normal OSA patients and patients with hypertension.

Conclusion

The present study suggested that MAS can be helpful in improving cardiovascular fitness and cognitive response in patients with mild to moderate OSA.

Compliance with ethical standards

Funding No funding was received for this research.

Conflict of interest None.

Ethical approval Prior approval of the institutional ethical committee had been obtained.

Informed consent Written informed consent was obtained from all the subjects.

References

1. Young TM, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. New Engl J Med 328:1230–1235
2. Garcia-Rio F, Racionero MA, Pino JM, Martinez I, Ortuno F, Villasante C et al (2000) Sleep apnea and hypertension. Chest 117:1417–1425
3. Sharma SK, Ahluwalia G (2010) Epidemiology of adult obstructive sleep apnoea syndrome in India. Indian J Med Res 131:171–175
4. Lam JCM, Sharma SK, Lam B (2010) Obstructive sleep apnoea: definitions, epidemiology & natural history. Indian J Med Res 131: 171–175
5. Reddy EV, Kadhiravan T, Mishra HK, Sreenivas V, Handa KK, Sinha S, Sharma SK (2009) Prevalence and risk factors of OSA in middle aged urban Indians: a community based study. Sleep Med 10:913–918
6. Lavie P, Herer P, Hoffstein V (2000) Obstructive sleep apnea syndrome as a risk factor for hypertension: population study. BMJ 320: 479–482
7. Clark GT, Blumenfeld I, Yoffe N et al (1996) A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. Chest 109:1477–1483
8. Peppard PE, Young T, Palta M, Skatrud J (2000) Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 342:1378–1384
9. Andren A, Hedbeg P, Walker-Engstrom ML, Wahlen P, Tegelberg A (2013) Effects of treatments with oral appliance on 24 hr blood pressure in patients with obstructive sleep apnea and hypertension: a randomized clinical trial. Sleep Breath 17:705–712
10. Andren A, Sjoquist M, Tegelberg A (2009) Effects on blood pressure after treatment of obstructive sleep apnoea with a mandibular advancement appliance: a three-year follow-up. J Oral Rehabil 36: 719–725
11. Otsuka R, Ribeiro de Almeida F, Lowe AA, Linden W, Ryan F (2006) The effect of oral appliance therapy on blood pressure in patients with obstructive sleep apnea. Sleep Breath 10:29–36
12. Zhang LQ, Zheng X, Wang JL, Wang YZ, Ren B, He B (2009) Effects of oral appliance treatment upon blood pressure in mild to moderate obstructive sleep apnea-hypopnea syndrome. Zhonghua Yi Xue Za Zhi 89:1807–1810
13. Iftikhar IH, Hays ER, Iverson MA, Magalang UJ, Maas AK (2013) Effect of oral appliances on blood pressure in obstructive sleep apnea: a systematic review and meta-analysis. J Clin Sleep Med 9:165–174
14. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA (2013) Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 187:879–887
15. Faccenda JF, Mackay TW, Boon NA, Douglas NJ (2001) Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 163:344–348
16. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N et al (2002) Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 359:204–210
17. Barbe F, Mayoralas LR, Duran J et al (2001) Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. Ann Intern Med 134:1015–1023
18. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK (1998) Altered cardiovascular variability in obstructive sleep apnea. Circulation 98:1071–1077
19. Vanderveken OM, Boudewyns A, Ni Q et al (2011) Cardiovascular implications in the treatment of obstructive sleep apnea. J Cardiovasc Transl Res 4:53–60
20. Somers VK, Dyken ME, Clary MP et al (1995) Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96:1897–1904
21. Findley L, Unverzadt M, Suratt P et al (1988) Automobile accidents in patients with obstructive sleep apnea. Am Rev Respir Dis 138: 337–340
22. Tregear S, Reston J, Schoelles K, Phillips B (2009) Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. J Clin Sleep Med 5:573–581
23. Galic T, Bozic J, Pecotic R, Ivkovic N, Valic M, Dogas Z (2016) Improvement of cognitive and psychomotor performance in patients with mild to moderate obstructive sleep apnea treated with mandibular advancement device: a prospective 1-year study. J Clinc Sleep Med 12:177–186
24. Peker Y, Hedner J, Norum J et al (2002) Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med 166:159–165
25. Akshay B, Arvind T, Ashutosh G, Suryakant T (2015) The effect of an oral appliance in obstructive sleep apnea patients with prehypertension. J Dent Sleep Med 2:37–43
26. Yamauchi M, Nakano H, Maekawa J et al (2005) Oxidative stress in obstructive sleep apnea. Chest 127:1674–1679
27. Itzhaki S, Dorchin H, Clark G, Lavie L, Lavie P, Pillar G (2007) The effect of 1 year treatment with Herbst mandibular advancement splint on obstructive sleep apnea, oxidative stress and endothelial function. Chest 131:740–749
28. Keyf Filiz, Ciftci Bulent, Guven Firat Selma. Management of obstructive sleep apnea in an edentulous lower jaw patient with a mandibular advancement device. Case Report Dent. 2014; 2014 : 436904 (published online)
29. Ashutosh G, Arvind T, Chhavi T, Piyush S, Avinash M (2016) A study to evaluate the effect of different mandibular horizontal and vertical jaw positions on sleep parameters in patient with obstructive sleep apnea. Quintessence Int 47:661–666

30. Lavie L, Vishnevsky A, Lavie P (2004) Evidence for lipid peroxidation in obstructive sleep apnea. Sleep 27:123–128
31. Khitrov MY, Laxminarayan S, Thorsley D, Ramakrishnan S, Rajaraman S, Wesensten NJ, Reifman J (2014) PC-PVT: a platform for psychomotor vigilance task testing, analysis, and prediction. Behav Res Methods 46:140–147
32. Randerath WJ, Heise M, Hinz R et al (2002) An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. Chest 122: 569–575
33. Hoekema A, Stegenga B, de Bont LGM (2004) Efficacy and comorbidity of oral appliances in the treatment of obstructive sleep apnea hypopnea: a systemic review. Crit Rev Oral Biol Med 15: 137–155