New developments in the treatment of obstructive sleep apnoea

Anita K Simonds
Sleep & Ventilation Unit, Royal Brompton & Harefield NHS Trust, London SW3 6NP, UK

Introductory articles

Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial

C Jenkinson, RJO Davies, R Mullins, JR Stradling

Background. Nasal continuous positive airway pressure (NCPAP) is widely used as treatment for obstructive sleep apnoea. However, to date there are no randomised controlled trials of this therapy against a well matched control. We undertook a randomised prospective parallel trial of therapeutic NCPAP for obstructive sleep apnoea compared with a control group on subtherapeutic NCPAP.

Methods. Men with obstructive sleep apnoea, defined as an Epworth sleepiness score of 10 or more and ten or more dips per h of more than 4% Sao2 caused by obstructive sleep apnoea on overnight sleep study, were randomly assigned therapeutic or subtherapeutic NCPAP (about 1 cm H2O) for 1 month. Primary outcomes were subjective sleepiness (Epworth sleepiness score), objective sleepiness (maintenance of wakefulness test), and SF-36 questionnaire measurements of self-reported functioning and well-being.

Findings. 107 men entered the study: 53 received subtherapeutic NCPAP and 54 therapeutic NCPAP. Use of NCPAP by the two treatment groups was similar: 5.4 h (therapeutic) and 4.6 h (subtherapeutic) per night. Subtherapeutic CPAP did not alter the overnight number of Sao2 dips per h compared with baseline, and thus acted as a control. Therapeutic NCPAP was superior to subtherapeutic NCPAP in all primary outcome measures. The Epworth score decreased from a median of 15.5 to 7.0 on therapeutic NCPAP and from 15.0 to 13.0 on subtherapeutic NCPAP (between treatments, p<0.0001). Mean maintenance of wakefulness time increased from 22.5 to 32.9 min on therapeutic NCPAP and, not significantly, from 20.0 to 23.5 min on subtherapeutic NCPAP (between treatments, p<0.005). Effect sizes for SF-36 measures of energy and vitality were 1.68 (therapeutic) and 0.97 (subtherapeutic) NCPAP (between treatments, p<0.0001). For mental summary score the corresponding values were 1.02 and 0.4 (between treatments, p=0.002).

Interpretation. Therapeutic NCPAP reduces excessive daytime sleepiness and improves self-reported health status compared with a subtherapeutic control. Compared with controls, the effects of therapeutic NCPAP are large and confirm previous uncontrolled clinical observations and the results of controlled trials that used an oral placebo. (Lancet 1999;353:2100–5)

Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake calibre of the velopharynx

CF Ryan, LL Love, D Peat, JA Fleetham, AA Lowe

Background. The mechanisms of action of oral appliance therapy in obstructive sleep apnoea are poorly understood. Videendoscopy of the upper airway was used during wakefulness to examine whether the changes in pharyngeal dimensions produced by a mandibular advancement oral appliance are related to the improvement in the severity of obstructive sleep apnoea.

Methods. Fifteen patients with mild to moderate obstructive sleep apnoea (median (range) apnoea index (AI) 4 (0–38)/h, apnoea-hypopnoea index (AHI) 28 (9–45)/h) underwent overnight polysomnography and imaging of the upper airway before and after insertion of the oral appliance. Images were obtained in the hypopharynx, oropharynx, and velopharynx at end tidal expiration during quiet nasal breathing in the supine position. The cross sectional area and diameters of the upper airway were measured using image processing software with an intraluminal catheter as a linear calibration.

Results. AI decreased to a median (range)
Nasal continuous positive airway pressure

“The effectiveness of continuous positive airway pressure in improving health outcomes has been poorly evaluated”. So concluded a systematic review of the health effects of obstructive sleep apnoea (OSA) in 1997 which stimulated fierce debate and raised concerns that the provision of treatment for OSA in the UK would be undermined. The review questioned the link between OSA and vascular disease and criticised previous randomised trials of the efficacy of continuous positive airway pressure (CPAP) therapy on the grounds that an oral placebo was an inadequate control. While it is accepted that the impact of OSA on vascular morbidity and mortality remains to be determined, unresolved questions about the effectiveness of CPAP in controlling daytime somnolence are now addressed by the randomised comparison of therapeutic versus sham (subtherapeutic) CPAP in obstructive sleep apnoea (OSA) by Jenkinson et al. Sham CPAP was provided using an identical device to the therapeutic system, set to deliver the lowest possible positive pressure (about 1 cm H2O) and incorporating a deliberate leak to minimise rebreathing. Although use of an oral placebo has been defended, the employment of a subtherapeutic control circumvents criticisms of previous studies, and a pilot study confirmed the safety of the sham approach. Contrary to a previous study of sham respiratory support using negative pressure ventilation, patients were able to use the subtherapeutic CPAP for most of the night but duration of use was lower than in patients receiving therapeutic CPAP (4.6 versus 5.4 hours). All recruits were naive to CPAP therapy and were informed that the purpose of the study was to compare different levels of CPAP. OSA was diagnosed by the presence of 10 or more dips in SaO2 of >4% per hour. The therapeutic CPAP level for each patient was determined using an autotitration device. Primary outcome measures were the Epworth sleepiness score (ESS), modified maintenance of wakefulness test (MWT – in which response times are measured while individuals are requested to resist sleep for 40 minutes in a darkened room on four occasions throughout the day), and two components of the SF-36 health status questionnaire (energy and vitality, and mental domain total score). The number of overnight hypoaxemic dips fell significantly in patients receiving therapeutic CPAP but was unchanged in those on sham CPAP, confirming the validity of the technique as control therapy. Both subjective (ESS) and objective measures of sleepiness improved in those using therapeutic CPAP. There were gains in energy and vitality, general health perception and the mental component summary of the SF-36 questionnaire compared with the sham limb. Small improvements occurred in the subtherapeutic group, confirming a placebo effect, but these were dwarfed by increases in the therapeutic category.

Positional treatment vs continuous positive airway pressure in patients with positional obstructive sleep apnoea syndrome

R Jokic, A Klimaszewski, M Crossley, G Sridhar, MF Fitzpatrick

Objectives. The aim of this study was to compare the relative efficacy of continuous positive airway pressure (CPAP) and positional treatment in the management of positional obstructive sleep apnoea (OSA), using objective outcome measures. Design. A prospective, randomized, single blind crossover comparison of CPAP and positional treatment for 2 weeks each. Setting. A university teaching hospital.

Patients. Thirteen patients with positional OSA, aged (mean ± SD) 51 ± 9 years, with an apnoea-hypopnea index (AHI) 17 ± 8. Measurements. (1) Daily Epworth Sleepiness Scale scores; (2) overnight polysomnography, an objective assessment of sleep quality and AHI; (3) maintenance of wakefulness testing; (4) psychometric test battery; (5) mood scales; (6) quality of life questionnaires; and (7) individual patient’s treatment preference. Results. Positional treatment was highly effective in reducing time spent supine (median, 0; range, 0 to 32 min). The AHI was lower (mean difference, 6.1; 95% confidence interval [CI] 2 to 10.2; p = 0.007), and the minimum oxygen saturation was higher (4%; 95% CI, 1% to 8%; p = 0.02) on CPAP compared with positional treatment. There was no significant difference, however, in sleep architecture, Epworth Sleepiness Scale scores, maintenance of wakefulness testing, sleep latency, psychometric test performance, mood scales, or quality of life measures. Conclusion. Positional treatment and CPAP have similar efficacy in the treatment of patients with positional OSA.
As usual there are several caveats when interpreting such data. Firstly, the patients recruited had around 30 hypoxaemic dips/h – that is, moderate obstructive sleep apnoea. They were also middle aged and markedly sleepy (median ESS 16) before treatment was initiated. The results cannot therefore be extrapolated to younger, less symptomatic patients with mild OSA, although a proportion with mild OSA do seem to benefit symptomatically from CPAP. Secondly, the study was short term and specifically looked at measures of sleepiness so that the long term impact on mortality and cardiovascular and cerebrovascular health remains unclear and cannot be used to justify prescription. Important evidence on morbidity is likely to emerge from the Sleep Heart Health Study funded by the US National Heart, Lung and Blood Institute in the next few years. Finally, for reasons which were not discussed, only men were recruited to the study. There is no reason to suspect that women with OSA respond differently to CPAP physically, although presenting symptoms of OSA may vary slightly in women.

Taking into account the results of this trial, the oral placebo controlled study and a recent Spanish randomised study which showed that the combination of moderate weight loss plus CPAP offers greater symptomatic benefit than weight loss alone, it is now difficult to resist the conclusion that CPAP has a proven role in controlling sleepiness and improving quality of life in subjects with moderate OSA. This is of great clinical and public health importance, not least because OSA is associated with an increased risk of road traffic accidents. The Wisconsin Sleep Cohort study showed that patients with an AHl of >15 were more than seven times likely to have had multiple accidents. It is necessary for individuals in the UK with sleepiness as a result of OSA to notify the Driver and Vehicle Licensing Agency (DVLA) of their condition and these patients should not drive until their sleepiness has been adequately controlled. Available evidence suggests that impairment in simulated driving performance is successfully reversed by CPAP therapy.

LIMITATIONS OF CPAP

There are still a number of dilemmas concerning effective use of CPAP. These concern its role in mild OSA, frequent side effects, and compliance issues. In one study of patients with mild OSA (AHl 5–15) an improvement in symptom scores, subjective sleepiness, and quality of life was seen with CPAP therapy, but objective measures of sleepiness were unchanged and nightly use (average 2.8 hours) was significantly lower than in patients with more severe OSA.

While daytime hypersomnolence, quality of life, and functional performance all improve with CPAP therapy, measures of sleepiness and cognitive impairment rarely return to normal. Numerous factors may contribute to persistent cognitive dysfunction including sleep fragmentation and reversible and irreversible cerebral damage due to hypoxaemia. It is not clear whether this failure to correct functional disturbance and alertness is due to the fact that CPAP therapy is inadequate or that its application is suboptimal, as many patients use it for only part of the night. In another sham CPAP controlled study both CPAP and sham CPAP had similar effects on sleep architecture, which was contrary to the expectation that sleep pattern and efficiency would be better with therapeutic CPAP. This study lasted only seven days, however, and it is possible that sleep architecture improves over a longer period of time as a result of better acclimatisation to the mask and machine.

Compliance with CPAP has long been regarded as imperfect, although it is difficult to know what is the “optimal dose” of CPAP. In the study by Jenkinson et al’ two of the 54 patients (4%) did not take up CPAP. Long term use was not examined but discontinuation rates in other studies have been shown to be around 30–40%. McCreadie et al found that 68% of patients with OSA were still using CPAP at three years. This percentage increased to 86% in those with an ESS of >10 and AHl of >30. Early comprehensive technical support tends to improve compliance, and this is better in those patients who initiate referral themselves rather than those who are persuaded to seek treatment by their partners, which shows that there are limits to altruism. Frequently reported problems associated with CPAP include inconvenience, nasal stuffiness, mask discomfort, claustrophobia, noise, and social/psychological difficulties.

For all these reasons, alternatives to CPAP therapy have been actively sought. The mandibular advancement splint and positional management usefully extend treatment options. Interesting new information emerges from the studies by Ryan et al and Jokic et al which shed light on their mechanism of action and effectiveness relative to CPAP.

Mandibular advancement splint (MAS)

Oral devices, constructed with the aim of maintaining airway patency during sleep, have existed for almost a century. An early version for correcting retrognathia was described by Pierre Robin in 1934. The exploration of oral positioning devices gained pace in the early 1980s but was overshadowed by the rapid development of CPAP. There have now been several randomised cross-over studies comparing the mandibular advancement splint with CPAP in patients with OSA (table 1). Nearly all devices fit over the upper and lower teeth with the goal of positioning the mandible more anteriorly by gradual adjustment. Cumulative evidence suggests that both the MAS and CPAP reduce the AHl in patients with mild to moderate OSA, but the decrease achieved with CPAP is usually superior. Sleepiness scores also fall, but here again CPAP may be more effective than the MAS. A proportion of patients prefer the MAS because of its greater convenience, and in some studies this applied to most subjects. On the other hand, there were individuals who could not tolerate the MAS and preferred CPAP.

As the MAS lifts the mandible forward it has been assumed that the device works by increasing the cross sectional area of the oropharynx and is therefore most likely to be successful in patients with airway obstruction at the oropharyngeal level. Such subjects comprise the minority of those with OSA, as by far the most common level of obstruction is at the velopharynx (soft palate), although a substantial proportion of patients with OSA have multi-segment collapse, particularly if they are obese. The article by Ryan et al is important as it challenges the preconception that the MAS improves oropharyngeal dimensions. In the group of patients studied, use of the MAS during wakefulness increased the cross sectional area of the velopharynx but not that of the oropharynx. Moreover, the reduction in AHl recorded during polysomnography was correlated with the increase in cross sectional area of the velopharynx. A greater increase was seen in the lateral than in the anteroposterior dimension, hence normalising the con-
position of <15 during a minimum duration of one hour
Figure 2, but the effect was greater. The effects were
duced upper airway muscle activity. Mechanisms which
affect the upper airway during sleep are poorly un-
derstood, but it seems plausible that gravity dependent
backward movement of the tongue is less likely to occur
in the lateral position. As a result, some patients have
a clear positional variation in AHI in the supine and
lateral position. This differential effect is lost in those
with severe OSA and in markedly obese patients.
Positional OSA is characterised by a 50% reduction in
AHI from, say, 100 to 50. A more rigorous clinical
treatment success criterion may be desirable. In our
study, we compared CPAP and the mandibular ad-
Vanced Splint (MAS). Of the 13 patients who started
CPAP (13.8) 4.2 (2.2) 10.3 4.7 5.1
6 months, 6 preferred MAS, 1 CPAP

Table 1 Review of crossover studies of CPAP therapy versus the mandibular advancement splint and positional management in OSA

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Duration each limb</th>
<th>Mean AHI</th>
<th>ESS</th>
<th>Pt preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark21</td>
<td>21</td>
<td>MAS v CPAP</td>
<td>2 weeks</td>
<td>33.9 (14.3)</td>
<td>19.9 (12.7)</td>
<td>17/21</td>
</tr>
<tr>
<td>Ferguson21</td>
<td>21</td>
<td>MAS v CPAP</td>
<td>4 months</td>
<td>26.8 (11.9)</td>
<td>13.3 (14.5)</td>
<td>11/21</td>
</tr>
<tr>
<td>Ferguson22</td>
<td>24</td>
<td>MAS v CPAP</td>
<td>4 months</td>
<td>13.6 (14.5)</td>
<td>4.2 (2.2)</td>
<td>12/21</td>
</tr>
<tr>
<td>Jokic18</td>
<td>13</td>
<td>Positional v CPAP</td>
<td>2 weeks</td>
<td>17 (8)</td>
<td>13.3 (13.1)</td>
<td>4 positional, 7 CPAP, 2 no preference</td>
</tr>
</tbody>
</table>

AHI = apnoea hypopnoea index; MAS = mandibular advancement splint; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnoea; ESS = Epworth sleepiness score.

Positional management of OSA

It should be recognised that, despite offering symp-
tomatic benefit, CPAP and, to a lesser extent, the MAS are hardly unobtrusive. Patients and their medical
attendants have been keen to seek simpler long term
solutions which do not involve a major change in lifestyle or dependence on cumbersome equipment. Clearly,
weight loss, cessation of smoking, and sleep hygiene advice will always have a role wherever appropriate, but
positional management during sleep is an attractive complementary proposition.

There is a sound underlying logic to the strategy of
persuading a snorer or patient with OSA to sleep in the lateral body position because snoring and obstructive events are increased when lying supine. Even during wakefulness, supraglottic airway resistance is higher when supine than erect. During sleep this effect is compounded by a further fall in lung volume and re-

Figuration of the pharynx which tends to be elliptical in
normal subjects but more spherical in patients with OSA. These findings fit well with the clinical observation
that the MAS tends to produce beneficial results in a
wide range of patients with mild to moderate OSA,
including those who do not have primary obstruction
at the oropharyngeal level.

As the authors discuss, a major limiting factor is that
the imaging with and without the MAS was carried out
while the patients were awake. It is well known that loss of pharyngeal muscle activity during sleep is a key
determinant of airway collapse, and therefore it is pos-
sible that imaging studies during sleep might give differ-
ent results. However, preliminary work23 elsewhere has
confirmed that the MAS increases the cross sectional
area of the upper airway during sleep and decreases pharyngeal compliance. It is hypothesised that anterior
displacement of the mandible by the MAS pulls the
tongue forward, thereby tensing the palatopharyngeus and palatoglossal muscles. Their combined action in-
creases the lateral diameter of the pharynx which de-
creases upper airway compliance, thereby reducing
collapsibility during sleep. Ryan et al used a two piece
adjustable appliance (Klearway®); and one of the
difficulties in comparing data on oral devices is that a huge variety of designs is employed. However, since the
overall aim is to advance the mandible, generalisation
is possible and it seems that the greater the degree of
advancement (achieved by gradual adjustment), the better the outcome.24
of life, and psychometric measures. However, contrary to the underlying hypothesis, there was no difference in sleep architecture or arousals during positional management or when using CPAP. An unusual feature of the study was that maintenance of wakeful time was within the normal reference range after positional and CPAP therapy, but unfortunately no baseline pre-treatment measurement of MWT was carried out for comparison. Interestingly, at the start of the trial most patients expressed the hope that the positional management would be more effective, but by the end of the study seven preferred CPAP, four the positional device, and two had no preference. The authors conclude that simple positional management offers similar clinical efficacy to CPAP (at least short term) in patients with pOSA. It should be noted, however, that only a relatively small number of patients was studied, increasing the possibility of a type II statistical error—their inadequate power to exclude a small difference between treatments.

The study raises the question of whether positional management works long term, and also whether a training effect develops, as proposed by Cartwright,28 the pioneer of positional management of OSA. Using a similar backpack, Freebeck and Stewart29 showed that the time spent sleeping supine was reduced to less than 5% of total sleep time and 80% of patients achieved an AHI of less than 5. In a subsequent study26 they reported that 17 of 18 patients complied with positional therapy and, even after reducing use of the backpack to one night per week, supine sleep time was less than 10% of total sleep time on nights without the pack which suggests that modification of sleep position without the positional device can be maintained, at least in the short term.

Which treatment for what patient?
These studies are helpful in deciding which option is most suitable for individual patients. Unequivocally, CPAP therapy is the treatment of choice for patients with moderate or severe OSA. In symptomatic patients with mild to moderate OSA, CPAP or the MAS can be considered. It is not possible to use the MAS in edentulous patients, those with severe periodontal disease, temporomandibular joint problems, or in children with growing dentition. Crossover studies have consistently shown that CPAP is slightly more effective than the MAS and therefore, for individuals with incomplete symptom relief with the MAS, CPAP should be explored. The MAS is also an option in patients with severe OSA who cannot tolerate CPAP, although long-term outcome studies are lacking. In a recent prospective uncontrolled study of 21 patients with severe OSA (AHI 50–115),31 use of a MAS reduced the AHI to <10 in six patients, in 13 the AHI was reduced by more than 50%, and only two patients showed no improvement. Compliance with the MAS is much more difficult to quantify than CPAP use, and it is possible that long-term discontinuation rates are high. Pancer et al.32 found that, after an average follow up of about one year, 86% of patients reported continued nightly use, 60% were satisfied with the MAS, 13% were dissatisfied, and 10% were lost to follow up. The most common side effects were teeth discomfort in 32% and jaw discomfort in 26% of patients. Over long periods of time it is possible that the MAS may cause occlusal changes or even mandibular remodelling,25 and therefore it is critical that adequate follow up is carried out with attention to these issues as well as control of sleep disordered breathing.

Positional management clearly requires further assessment and is only curative in those with true positional OSA. To identify such individuals it is necessary for multichannel diagnostic screening methods to incorporate a reliable body position monitor—this is not possible using simple oximetry alone to establish the diagnosis of OSA. Positional management is less likely to be successful in obese patients who may not sense the backpack, or if used with a soft mattress. It is conceivable that different positional devices have different success rates, and individual variation in tolerance is also probable. Oksenberg and Silverberg26 have described an individual who managed to sleep on his back with two tennis balls and a baseball in place! pOSA should be seen as a dynamic situation in which the use of alcohol, sedation, or weight gain may convert a positional OSA patient to a non-positional type.

To complicate matters, although the above treatments serve many patients well, there is an increasing trend to combine modes—for example, positional management with the MAS or positional management with CPAP—allowing use of a lower therapeutic level of CPAP.32 Some patients prefer to use CPAP for most of the week and the MAS for short trips away from home. The combination of MAS and CPAP has been used in some units in patients who are unable to tolerate high CPAP levels. The cost of dental construction of a mandibular advancement splint is broadly similar to a CPAP machine, but positional management is obviously cheaper. At present we have little knowledge about the “equivalence” of the techniques—for example, is eight hours of sleep using the MAS preferable to four hours of CPAP, despite the fact that the MAS is less effective than CPAP in controlling AHI? Studies looking at the effects of combination approaches on AHI and sub-

**LEARNING POINTS**

* CPAP therapy reduces sleepiness and improves health status in patients with moderate OSA.

* The mandibular advancement oral device increases the cross sectional area of the upper airway and the increase in size of the velopharynx is correlated with the reduction in the apnoea/hypopnoea index during sleep.

* The mandibular advancement splint gives similar results to CPAP in patients with mild OSA

* Positional management may be useful in patients with positional OSA.
jective and objective sleepiness will be relatively easy to perform, but longer term evaluation of the impact on cardiovascular and cerebrovascular end points will be extremely difficult, especially as treatment permutations may change over time, overall risk varies between individuals, and we cannot be sure that simple indices such as AHI, arousals, or autonomic variables are the best indicators of vascular stress.

Over the last few years much has been learned about the effectiveness of CPAP, which is now confirmed as evidence-based medicine for the management of sleepiness in patients with moderate OSA. Similar questions are now being addressed with alternative treatments which hold out hope for patients with mild sleep disordered breathing and those who fail with CPAP. Clearly, any treatment is ineffective and wasteful of resources if it is not used, and a pragmatic approach demonstrating that AHI and symptoms are controlled and patient preference is taken into account seems reasonable, pending the results of further long term studies.


New developments in the treatment of obstructive sleep apnoea

AK Simonds

Thorax 2000 55: S45-S50
doi: 10.1136/thorax.55.suppl_1.S45

Updated information and services can be found at:
http://thorax.bmj.com/content/55/suppl_1/S45.citation

These include:
References
This article cites 6 articles, 2 of which you can access for free at:
http://thorax.bmj.com/content/55/suppl_1/S45.citation#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/