GUIDELINES OF HELLENIC SOCIETY OF SLEEP DISORDERS (HSSD)

Guidelines for Diagnosing and Treating Sleep related Breathing Disorders in Adults and Children (Part 2: Treatment)

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Obstructive Sleep Apnea Syndrome (OSAS) should be approached as a chronic disease requiring long-term multidisciplinary management. The patient should be an active participant in the decision on treatment type and taught to contribute to the management of his or her own disease.

I. Positive Airway Pressure (PAP)

PAP is the preferred treatment for patients with OSAS[1,2] providing pneumatic splinting of the upper airway and may be delivered in continuous (CPAP), bilevel (BPAP), or autotitrating (APAP) modes. A PAP delivery system consists of three main components: a PAP device; a nasal, oral, or oronasal interface (i.e., nasal mask, nasal pillows, full face mask) held snug to the face by headgear; and a flexible hose that connects the device to the interface. A PAP device is basically an air pump (fan-driven or turbine system) that draws in external, filtered air and delivers pressurised airflow, which is adjustable by varying the pressure valve diameter or fan/turbine speed.

A. Continuous Positive Airway Pressure (CPAP)

The delivered pressure is fixed and does not vary during the application. The inspiratory PAP (IPAP) is equal to the expiratory PAP (EPAP).

1. Effects of CPAP use

a. Reduction of Apnea Hypopnea Index (AHI)

Evidence derived from current literature supports that CPAP reduces sleep related breathing disorders by reducing AHI.

According to previous clinical trials CPAP use has given better results in comparison to sham CPAP[3-8,9,11,12], placebo administration[13], conservative therapy[14,15] and positional treatment[16]. This effect was demonstrated by follow-up sleeping studies 16 days[9] 65 days[3] 2 weeks[16] 10 weeks[15] or 24 weeks[14] or 3 months[13] after the initiation of treatment.

b. Sleep architecture

It has not been confirmed in controlled clinical studies that CPAP has any effect on the total duration of sleep, compared to sham CPAP[4,6], placebo[10,13] or positional treatment[16]. The findings of placebo-controlled studies were ambiguous, as some supported association of CPAP with duration and percentage of stages 1 or 2 of sleep[10,13,17], whereas others did not[4,6]. Two placebo-controlled studies found differences in the duration of REM sleep[4,17]. Three out[10,13,17] of 5 placebo-controlled studies[4,6,10,13,17] reported improvement in stages 3 and 4. On the other hand, several randomized clinical trials demonstrated that CPAP treatment is not superior to placebo administration[4,10,13] or to positional treatment[16] in term of sleep adequacy. Evidence on the effect of CPAP in arousal index is also conflicting. However, several level I (randomised trials with low beta error) and II (randomised trials with high alpha and beta error) studies reported a reduction in the arousal index with CPAP than with placebo[10,13,17] and only one study announced opposing results[6].

c. Daytime sleepiness

The effect of CPAP on objective and subjective daytime sleepiness, especially in underlying mild-to-moderate OSAS, has been extensively studied. The majority of these studies evaluated subjective sleepiness using the Epworth Sleepiness Scale (ESS). Most of the placebo-controlled trials using ESS[3,5,6,13,17-19,20-24] demonstrated that CPAP reduced subjective daytime sleepiness[6,13,17-19,21-24].

Level I and II evidence on objective sleepiness is less indistinct. Two[23,24] out of three[3,23,24] studies in the literature on sham CPAP and use of the Maintenance of Wakefulness Test (MWT) in patients with ESS > 10 found a greater effect of CPAP than the effect of sham CPAP. In the third study however, with the opposite results, patients included in the study did not report sleepiness prior to the therapeutic intervention. Severity of sleepiness was also evaluated with Multiple Sleep Latency Test (MSLT). Two[22,25] out of 6[5,13,19,20,21,26] studies found CPAP treatment more effective in reducing sleepiness compared to placebo.

In a meta-analysis[27] of mild-to-moderate OSAS patients with ESS> 10, CPAP reduced subjective daytime sleepiness by 1.2 grades, increased objective maintenance of wakefulness by 2.1 minutes (MWT), but had no effect

on objective daytime sleepiness assessed by MSLT.

d. Neurobehavioral function and psychological outcomes

Ten out of 29 placebo-controlled trials[3-5,9, 13,19-21,23,26] revealed an effect of CPAP on neurobehavioral function. The parameters studied were conception and sensitivity, maintenance of attention, advanced functional status, memory and mood. Only 2 placebo-controlled studies[19,28] out of 9 that evaluated conception and sensitivity[3-5,9,13,19-21,28] found CPAP superior to placebo. However, the results concerning improvement in attention with CPAP[3-5,13,19-21,28] have been inconclusive. The two studies that compared conservative therapy to CPAP were ambiguous in terms of conception and sensitivity[18,29]. Studies comparing maintenance of attention with CPAP or conservative therapy were few and unable to reach safe conclusions. Although CPAP treatment was not associated with improved outcome compared to placebo[3,5,13], it was more efficient compared to conservative therapy in the terms of sleep hygiene and weight loss[14,29]. Among level I and II studies that evaluated superior cognitive functions[3,4,13,19-21,28,30] few were able to demonstrate a more favourable effect of CPAP compared to placebo[3,4,13,19,21] and only one level I study found better efficiency of CPAP compared to conservative therapy[14]. The results of placebo-controlled studies were indecisive to the effect of CPAP on mood[5, 11,12,13,19-21,28].

These variations in the results of CPAP on neurobehavioral function are probably attributed to the variety of methods used for estimating these outcomes, as well as the possibility of beta error.

e. Quality of life

Many studies have evaluated the effect of CPAP therapy on quality of life compared to placebo[3,5,18-22,24,25,28,31] or conservative therapy[14,15,32]. These studies have used various questionnaires, both general (SF36, Nottingham Health Profile) and disease-specific (Functional Outcomes of Sleep Questionnaire). The results of level I and II placebo-controlled studies were equally positive[13,19,20,24,28] or negative[3,5,18,21,31] in terms of the effect of CPAP use. In the three randomized trials, existing in literature, that compared CPAP to conservative therapy, one found improvement in 2 of 6 subscales (social isolation and energy) of Nottingham Health Profile[2], whereas the second trial that used a general and a disease-specific questionnaire[31] and the third one that used only a general questionnaire [15] found no significant improvement. One study evaluated quality of life in patients randomized in CPAP treatment or positional therapy failed to demonstrate any advantage with CPAP use[33].

f. Cardiovascular morbidity

The effect of CPAP on cardiovascular morbidity[34] and especially on arterial hypertension has been the object of many studies[3,5-8,12-14,22,35]. The majority of placebo-controlled trials that recorded blood pressure for a minimum of 19 hours were unable to find any improvement in mean blood pressure with CPAP application[3,5-8,13,22]. However, many level I and II studies demonstrated that CPAP use had greater effect on nocturnal arterial hypertension compared to placebo[7,21,35] and 2 of them found lower mean diastolic pressure with CPAP compared to control group[22,35]. One level I study noted significant reduction in mean arterial pressure comparable to the effect of antihypertensive medication therapy[35], whereas one level II trial found greater reduction in 24-hour systolic, diastolic and mean arterial pressure with use of CPAP compared to placebo in patients whose Respiratory Disturbance Index (RDI) is greater than 20[31]. One study that compared CPAP to conservative therapy in terms of weight loss, nutrition and sleep hygiene reported that blood pressure that was measured by sphygmomanometer in patients on CPAP use did not differ from that of patients on conservative therapy[18]. Yet, another study failed to demonstrate any differences on blood pressure between CPAP use or administration of a placebo pill[3]. Two level II trials evaluated the effect of CPAP on heart rate compared to placebo with ambiguous results[12,22].

Evidence on the correlation between OSAS and stroke is also limited. One large-scale follow-up study[36] found that patients with severe OSAS are at 3-fold greater risk of having a stroke, even if they are being treated for OSAS. However, no randomized trials were able to determine the efficacy of CPAP in these patients.

Additionally, in a 10-year observational study, Marin et al[37] demonstrated that patients with severe OSAS who did not receive treatment with CPAP were at increased risk of fatal or non-fatal cardiovascular events, compared to patients who were under CPAP treatment.

Recent studies in the literature have also demonstrated the beneficial effect of CPAP application on cardiovascular risk factors such as hs-CRP homocysteine[38], total cholesterol[39] and glycated haemoglobinlevels[40], especially after adherent use.

g. CPAP effects according to OSAS severity

The majority of level I and II studies, that assessed the effect of CPAP, have included patients with moderate (AHI 15-30) and severe (AHI > 30) OSAS, as defined by the American Society of Sleep Medicine[40]. Three level I[13-15] and 3 level II studies[5,19,20] in patients with mild-to-moderate OSAS found that CPAP use reduced AHI[13-15] but failed to improve subjective sleepiness[5,13-15,19,20] or blood pressure[5,13,14]. Conflicting results were also reported when objective assessment of sleepiness[5,14,15,19,20], neurobehavioral function[5,13,14,19,20], mood and quality of life were evaluated[5,13-15,19,20,32]. Further studies are required in order to confirm whether CPAP has an outcome advantage in mild-to-moderate severity.

Other level I and II studies that used more strict severity criteria (AHI > 30) demonstrated that, compared to placebo CPAP reduced the number of apneas and hypopneas[4,7,9-12], increased the duration of REM sleep[4,10-12], and improved the oxygen saturation during sleep[4-12]. Evidence on the effects of CPAP on other parameters such as sleep architecture, subjective and objective sleepiness, neurobehavioral function, mood, quality of life and blood pressure remains inconclusive.

No level I and II trials have studied the effect of CPAP on treatment of OSAS in patients with AHI < 5. Many re-

cently reviewed level III studies[41] assessed use of CPAP in UARS (with AHI < 5) and in patients with AHI < 10. Evidence is insufficient to extract any conclusions on the efficacy of CPAP treatment in this population group.

2. Titration of CPAP pressure[1,42]

a. Application/ titration study

An attended full polysomnography at a sleep centre is the validated method of titrating the ideal CPAP pressure.

CPAP pressure application/ titration study is essential in patients with OSAS in order to:

1. Confirm airway patency and restoration of hypoxemia with the use of CPAP during sleep.

2. Confirm elimination of snoring and paradox thoracic and abdominal wall movements in all sleeping positions.

3. Employ titration, addition or modification of a therapeutic method if hypoventilation or hypoxemia persists, provided that there is always appropriate attendance during sleep study in order to achieve maximal therapeutic outcome.

b. Split night study. Titration of ideal CPAP pressure during split night study (diagnostic and therapeutic) can be another validated method, provided that the following criteria are met:

1. The patient has been informed of the procedure and has selected the appropriate ventilation mask in case a therapeutic appliance is used.

2. During the 2 hours of diagnostic split night study, the patient reaches RDI > 40/h or 30-40/h, associated with long episodes of obstructive apnea or severe desaturations.

3. Pressure titration is considered sufficient after at least 3 hours of sleep study.

4. After CPAP application, respiratory events during REM and NREM sleep should be reduced to a great extend, if not completely eliminated, including events in REM sleep and supine position.

In the case of an established diagnosis where these criteria are not met, a second full polysomnographic study is required.

c. Daytime attended full polysomnography

Current evidence does not support the routine use of this study for CPAP titration. However, it can be performed under certain circumstances to patients who work in night shifts or who are unable to complete a nocturnal study due to other causes.

d. Attended limited study

This study can be used under certain circumstances, as is extensively discussed in the relevant chapter.

e. Unattended limited study in sleep center

There are no available studies evaluating this method and it is currently not recommended for CPAP titration.

f. Attended and unattended full polysomnographic study at home

There are no available studies evaluating this method and it is currently not recommended for OSAS diagnosis or CPAP titration. Nevertheless, it can be performed under compelling indications and inability to move the patient.

g. Attended limited study at home

This study is currently contraindicated for CPAP titration.

h. Unattended limited study at home

According to current data, this study is not recommended for CPAP application and titration.

3. Adherence/ compliance with CPAP

OSAS patients should apply CPAP appliance every night during their sleep. The duration of treatment should be at least 4 hours/ night, although a 6-hour/ night application has been associated with better outcomes in terms of daytime sleepiness and functionality.

The appliance should not be turned off while operating and should be used every night, as missing one session may reconvert the patient to the state prior to treatment. The duration of CPAP treatment must be monitored objectively.

Each sleep laboratory is responsible for the evaluation of patient compliance with the treatment and for making appropriate adjustments during follow-up. The following parameters can be useful in predicting compliance with CPAP use and should be included in the initial evaluation and reevaluation of the patient:

a. Pressure titration based on the aforementioned parameters.

b. Selection of the appropriate mask and option of replacement with another mask when necessary.

c. Reduction of nasal resistance and addition of a heated humidifier.

d. Pressure re-titration when significant parameters have altered, e.g. dramatic weight reduction or persistence of daytime sleepiness (ESS > 10) or when other symptoms develop.

CPAP application must be evaluated after one week of treatment. Close monitoring and frequent evaluations are suggested. Provision must be made for technical repair as well as replacement of any expendables (mask, tube) that could increase duration of therapy and life-expectancy of the appliance. Especially for patients with respiratory failure, plenty of time to familiarize themselves with the appliance and its operation should be given.

4. Follow-up studies in OSAS patients under treatment

Follow-up studies in OSAS patients under treatment are:

a) indicated in case of recurrence of symptoms such as snoring, hypersomnolence or weight gain, for reevaluation of diagnosis or treatment selection

b) indicated in persistence of symptoms like daytime sleepiness, despite appropriate CPAP titration and satisfactory patient compliance

c) indicated in patients with mild OSAS but deteriorating their clinical presentation

d) unnecessary when symptoms have receded and the patient is asymptomatic or has improved substantially

B. Automatic Positive Airway Pressure (APAP)[43]

PAP increased as needed in order to maintain airway patency and then decreased if no abnormal events are detected within a set period of time.

1. APAP application is currently contraindicated in the management or treatment of:

a) Patients with congestive heart failure

b) Patients with severe lung disease, e.g. COPD

c) Patients at high risk of developing respiratory disorders secondary to other causes (e.g. obese patients with hypoventilation syndrome)

d) Patients who do not snore either normally or after surgical treatment

e) Patients with central sleep apneas

2. APAP application is currently not recommended for split night study.

3. APAP application can be performed during attended full polysomnography and pressure titration study for the treatment of moderate-to-severe OSAS.

4. The efficacy and safety should be evaluated in all patients whose CPAP was titrated with APAP or who are using APAP. This is particularly important during the first weeks of treatment.

5. If symptoms fail to subside or in case of limited efficiency, reevaluation with new study is required.

C. Bilevel Positive Airway Pressure (BPAP)[44]

The pressure during inspiration (IPAP) is higher than the pressure during expiration (EPAP).

Long-term BPAP application is indicated for disorders that cause hypoventilation and sometimes OSAS:

1. Disorders that cause hypoventilation: primary hypoventilation syndrome, central apnea, obesity-hypoventilation, thoracic wall abnormalities (kyphoscoliosis, ankylosing spondylitis, post-polio seq, thoracoplasty), disorders of the diaphragm

2. Lung parenchymal diseases that cause respiratory failure (COPD, cystic fibrosis)

3. Neuromuscular diseases (muscular dystrophy, Guillain- Barrè syndrome, spinal injuries, polymyositis, systemic sclerosis)

4. Application of BPAP can also be tried in OSAS patients with intolerance to CPAP or whose respiratory disorder did not improve with CPAP due to its severity or the presence of comorbidities such as COPD (overlap syndrome)

Inspiratory and expiratory pressure must be titrated appropriately to every patient and blood gas analysis along with overnight monitoring with pulse oximetry or capnography must be assessed.

In cases of respiratory failure, other functional parameters in addition to inspiratory and expiratory pressure must be determined, such as respiratory rate, time of pressure initiation, maximum inhalation time, delivered volume, etc. The selection and titration of the appropriate appliance must follow a thorough assessment of patient's needs by specialized health care providers.

Oxygen can be administered with a mask or T- system via patient- appliance circuit and the flow is determined after evaluation of SpO_2 and blood gases.

II. Oral Appliances

The use of oral appliances should always be considered, especially in patients with mild-to-moderate obstructive sleep apnea, in order to eliminate or limit the number of breathing events during sleep[45,46]. OSAS diagnosis should be established according to previously mentioned requirements.

Mechanism of action

Oral appliances are portable dental devices used by the patient during his sleep. Depending on their design, they are used as:

1. soft palate lifters
2. tongue position trainers
3. tongue retaining devices
4. mandibular repositioning advancement appliances.

The first three types have been practically abandoned mostly due to their ineffectiveness in treating breathing disorders but also due to patient intolerance.

The fourth type of appliance has been broadly accepted and used in routine clinical practice. These devices are either prefabricated and fit to individual dentition or custom-made based on clinical data and dental impressions. They can be made in one piece that is fitted to both mandibles or in two pieces connected together with a fixed screw.

Mandibular repositioning/ advancement appliances are attached to interdental regions and teeth crowns with globular flanges and retained by the front teeth with wire braces. Moreover, they are made of acrylic or thermolabile material that can be molded to the patient's oral mucosa.

Dental appliances hold the lower jaw forward and downward and reposition the tongue in the same direction. This frontal repositioning causes suprahyoid, geniohyoidal, mylohyoid and genioglossus muscles to reshape and retain the tongue preventing its collapse to posterior pharyngeal walls due to gravity. Mandibular repositioning also causes remodeling of muscular and skeletal structures and hyoid bone advancement, resulting in pharyngeal widening at the anatomical level of soft palate and tongue base.

Application criteria

Clinical application of Mandibular Replacements (MARs)/ Mandibular Advancement (MADs) is recommended for patients with sleep related breathing disorders[46,47] as an initial treatment option in patients with: primary snoring, upper airway resistance syndrome, mild-to-moderate OSAS.

1. as an alternative treatment option in patients with sleep disorders and mild- to-moderate OSA and sufficient number of teeth

2. requires performing a complete dental diagnostic evaluation including:

a. detailed medical and dental history

b. intraoral and extraoral clinical examination, functional evaluation of mouth and jaw

c. laboratory diagnostic tests, such as dental casts, cephalometric radiation and computed imaging of temporomandibular joints. These methods are used for estimation of hyoid bone position, angle of mandible, frontal-low facial height, frontal cranial base, upper jaw length, soft palate length, pharyngeal airway diameter, mandibular movement capacity, body mass index, neck circumference, age and AHI.

3. Clinical application of MARs/ MADs is considered successful when reduced AHI and respiratory events are recorded in sleep study.

4. Remission of clinical symptoms related to underlying breathing disorder is not considered an objective measure of MARs/ MADs efficiency.

5. Clinical application of MARs/ MADs should be reevaluated at frequent intervals in order to prevent possible dental or skeletal side effects.

6. Clinical application of MARs/ MADs should be performed by specialized orthodontists who are fully aware of their capacities and limitations as well as up-to-date with current knowledge on sleep related breathing disorders.

Side effects

Most common side effects are dental, mucous and mandibular sensitivity, increased salivation and dry mouth. Intense vomit reflex, periodontal and dental injuries are less common. Most of these symptoms appear on application and usually subside after a short period of time.

At times, use of certain types of appliances can have an unfavorable effect on temporomandibular joint physiology and cause subsequent transient or permanent dental movements. These complications can be limited by minimizing neuromuscular derangement in the oral cavity, whereas undesirable dental movements can be prevented with stabilization by the appliance. Mandibular repositioning should not supervene 70% of its moving capacity, should be less than 15 mm at all circumstances and maximal downward movement should be 5 mm.

III. Surgical Treatment

PAP is the standard treatment for OSAS. However, there are few selected patients in whom surgical management indicated after careful evaluation by sleep experts and patient informed consent[46]

A. Indications of surgical management

Surgical management is indicated in patients with mild- to-moderate OSAS who failed to improve with or were intolerant of medical treatment with CPAP or BPAP.

B. Criteria of success

Surgical management is considered successful when postoperative AHI is equal to AHI recorded with CPAP application.

If the patient was not subjected to polysomnography with CPAP, surgery is considered successful under the following conditions:

1. Postoperative AHI must be reduced by at least 50% compared to preoperative AHI.

2. Postoperative AHI must be lower than 20 events per hour slept.

3. Postoperative SpO_2 must be within normal range.

4. Satisfactory sleep architecture.

5. Improvement of daytime sleepiness.

Preoperatively all patients must be evaluated both physically (including nasopharyngeal endoscopy with Móller maneuver) and with imaging techniques (lateral radiographic cephalometry, computed or magnetic tomography) in order to recognize and restore upper airway narrowing at the exact locus. Patients who developed OSAS due to evident skeletal disfigure, such as retrognathia, micrognathia or their combination, should be assessed for surgical management.

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