Oral-appliance therapy obstructive sleep apnea-hypopnea syndrome

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Appendices

Appendix 1

Supplement to chapter 4.1 & 5

Recruitment of patients

The University Medical Center Groningen has a catchment area that includes most of the north eastern part of The Netherlands. Patients suspected of having obstructive sleep apnea-hypopnea syndrome (OSAHS) are referred to this medical centre by general practitioners in the region and physicians at departments of pulmonary medicine, neurology, and ear, nose, & throat surgery in several regional hospitals. We used the recommendations of the American Academy of Sleep Medicine to diagnose OSAHS.[1] Each patient diagnosed as having OSAHS consulted our Department of Home Mechanical Ventilation for treatment.

Selection of patients and informed consent

To screen for any underlying disease, all eligible patients underwent a comprehensive physical evaluation, spirometry, thoracic radiography, electrocardiography, and blood tests.

General criteria for inclusion in the study

- age >20.
- polysomnography showing an apnea-hypopnea index (AHI) ≥5; *i.e.*, the mean number of apneas and hypopneas per hour of sleep.

Medical and psychological criteria for exclusion from the study

- previous treatment of OSAHS (continuous positive airway pressure [CPAP], oral-appliance therapy, or uvulopalatopharyngoplasty).
- clearly reversible morphological airway abnormalities (*e.g.*, a compromised nasal passage, enlarged tonsils or adenoids, or upper airway soft-tissue or craniofacial abnormality).
- endocrine dysfunction (hypothyroidism, acromegaly, or pituitary adenoma).
- a reported or documented history of severe cardiac or pulmonary disease (daytime respiratory insufficiency, severe chronic obstructive pulmonary disease [Tiffeneau-index <40%],[2] heart failure, coronary disease, or severe cardiac arrhythmias).
- moderate or severe periodic limb movement disorder (periodic limb movement index >25).
- a psychological condition precluding informed consent (mental retardation or psychiatric disorder; *e.g.*, depression or schizophrenia).

Dental criteria for exclusion from the study

- extensive periodontal disease or tooth decay.
- active temporomandibular joint disease (including severe bruxism).
- restrictions in mouth opening (<25 mm) or advancement of the mandible (<5 mm).

- partial or complete edentulism (less than eight teeth in upper or lower jaw).

Patients who qualified for inclusion were informed about the study and their questions were answered by the pulmologist (A.F. Meinesz) and dentist (A. Hoekema) who evaluated the patients. Each patient was given a brochure with details about the study and had one week to decide whether or not he or she wanted to participate. Patients who decided to participate signed and returned an informed consent form before enrollment. The trial was approved by the Groningen University Medical Center's ethics committee (METc 2002/032).

Randomization procedure

The cooperating clinical epidemiologist (B. Stegenga) made computer-generated randomization sequences, balancing for disease severity. The randomization sequences were used for selecting randomly permuted blocks with lengths of two, four, and six.[3] The clinicians supervising oral-appliance and CPAP therapy were not informed about how the randomization was performed. The randomization sequences were concealed and administered by Department of Oral and Maxillofacial Surgery staff. After each patient's serial number and diagnosis of disease severity was provided, the treatment was disclosed. Each serial number could be provided only once. It was not possible to blind patients or clinicians to treatment assignment.

Interventions, conservative measures and treatment adjustments

Oral-appliance therapy was initiated in the Department of Oral and Maxillofacial Surgery and was supervised by one dentist (A. Hoekema). CPAP therapy was initiated in the Department of Home Mechanical Ventilation and was supervised by one pulmologist (A.F. Meinesz). Oral-appliance therapy was initiated within a four-week period and CPAP therapy within a two-week period after a patient was enrolled in the study. Before treatment was initiated, all patients were instructed to adopt conservative measures; specifically, to avoid using depressants (*e.g.*, alcohol, sleep medication) and to have at least seven to eight hours of sleep each night. When indicated, patients were encouraged to give up smoking and lose weight.

The oral appliance used in this study (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) consisted of two separate parts.[4] The upper part was supported by the dentition of the maxilla and the lower part by the dentition of the mandible. By turning a propulsion screw incorporated anteriorly in the appliance, the patient could adjust the amount of mandibular advancement in 0.2-mm increments. The maximum advancement of the mandible was determined with a George-Gauge™ (H-Orthodontics, Michigan City, IN, USA) before oral-

appliance therapy began. Initially, the mandible was set at 50% of the patient's maximum advancement. After patients became accustomed to the oral appliance during a two-week period, they returned for a check-up visit. They were instructed to adjust the oral appliance over the following six weeks. To do so, patients were instructed to advance the mandible each night with one to two increments (*i.e.*, 0.2 to 0.4 mm) whenever OSAHS-symptomatology persisted (*e.g.*, snoring, apneas, hypopneas, or excessive sleepiness). This titration of the appliance was continued until symptoms abated or until further advancement caused discomfort.

CPAP-titration was performed during an afternoon nap. This titration regime has been shown to be an appropriate procedure for the initiation of optimal CPAP therapy.[5] All patients using CPAP received detailed instructions about the titration regime and use of CPAP from a skilled nursing consultant. Patients were fitted with a comfortable CPAP mask before titration. For CPAP-titration, patients were instructed to adopt their own typical sleeping habits. After CPAP-titration, all patients received a similar CPAP device (Breas® PV10, Mölnlycke, Sweden). Patients were permitted to become accustomed to CPAP during a two-week period, after which they returned for a check-up visit. Patients were offered a change in the CPAP mask and the use of chin straps or a humidifier to supplement therapy if required. Following the check-up visit a six-week follow-up period was arranged that allowed for further habituation and, if necessary, adjustments of CPAP therapy.

After patients had been using an oral appliance or CPAP for approximately eight weeks, the treatment effect was assessed with a second polysomnographic study. For patients whose AHI was still ≥5, treatment was adjusted, if possible, to improve effectiveness. For this purpose patients treated with an oral appliance were instructed to maximally protrude their mandible with the appliance. In CPAP treated patients the pressure was raised with 1 or 2 cm H_2O (depending on the severity of residual OSAHS with CPAP). In these patients the follow-up period was extended with another four weeks. Then the effect was assessed with a third polysomnographic study. This adjustment sequence was continued until the AHI was <5 or until the adjustments became uncomfortable for the patient. Follow-up review ended with a patient's final polysomnographic evaluation or when a patient discontinued treatment because of poor tolerance or another reason.

Patients for whom oral-appliance or CPAP therapy was effective continued the treatment. Patients for whom treatment was not effective were offered the alternative CPAP or oral-appliance therapy.

Polysomnography

Surface electroencephalography, submental electromyography, and left and right electrooculography were used to stage sleep. A pulsoximeter (Oximeter Flex Sensor – 8000J-3, Medcare, Reykjavik, Iceland) was used to record oxyhemoglobin

saturation. Electrocardiography was used to monitor cardiac function. Oronasal airflow was recorded with a pressure cannula. Respiratory effort was monitored with thoracic and abdominal strain gauges. An anterior tibial electromyogram was recorded to screen for periodic limb movements. Each polysomnographic study started at 11 AM and ended at 9 AM the next morning. Standardized criteria were used to score apneas and hypopneas,[1] arousals,[6] sleep stages,[7] and periodic limb movements.[8] Polysomnographic outcomes were assessed during the night while the patient was asleep. Outcomes included total sleep time, sleep efficiency, AHI, lowest oxyhemoglobin saturation during sleep ($minSaO_2$), the percentage of non-rapid-eye-movement (non-REM) sleep during stages 1 & 2 and 3 & 4, and the percentage of REM-sleep. Baseline polysomnographic outcomes were those obtained at the time of diagnosis.

Neurobehavioral examination

Patients completed the Epworth sleepiness scale questionnaire to asses their propensity to fall asleep in eight different situations.[9] Patients completed the functional outcomes of sleep questionnaire to assess the impact of excessive sleepiness on a number of activities of everyday living.[10] This questionnaire consists of 30 different questions that yield a score for five different subscales and a total score. Patients completed the medical outcomes study 36-item short-form health survey (SF-36), to assess their perception of their health status.[11] This questionnaire consists of 11 questions that yield a score for eight different dimensions and one item regarding changes in the patient's health. Patients completed the hospital anxiety and depression scale to assess the presence of anxiety and depression states.[12] This questionnaire consists of two seven-question scales that yield a score for anxiety and depression.

Patients' satisfaction and treatment usage were evaluated with a questionnaire. Patients graded their satisfaction with treatment as "very satisfied," "satisfied," "dissatisfied," or "very dissatisfied." In addition, patients were asked to grade satisfaction with treatment on a ten-point scale (range 1–10), the higher scores indicating greater satisfaction. Patients' usage of their therapy was evaluated by asking patients how many nights each week and how many hours each night they used their treatment. Whereas CPAP usage can be monitored covertly with a mechanism built into the device, oral-appliance usage cannot be assessed covertly in any reliable way. To eliminate bias, we ensured that treatment usage was assessed in the same manner by basing the assessments on self-reports in both groups. Some patients did not use treatment during the entire week—for example, on weekends when they did not anticipate a strenuous day. Patients were considered nonadherent to therapy only if they voluntarily discontinued use of the therapy due to poor tolerance or any other reason.

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Appendix 2

Supplement to chapter 4.1

APPENDIX 2. Proportions of effective treatments with an oral appliance or CPAP according to three different criteria.

Criterion	Oral appliance*	CPAP*	Difference (95% CI)†
Effective treatment‡			
Total population (n = 103)	39 / 51 (76.5%)	43 / 52 (82.7%)	-6.2% (-21.7 to 9.4)
Non-severe OSAHS (n = 50)	21 / 25 (84.0%)	20 / 25 (80.0%)	4.0% (-17.7 to 25.4)
Severe OSAHS (n = 53)	18 / 26 (69.2%)	23 / 27 (85.2%)	-16.0% (-37.1 to 6.8)
AHI <5			
Total population (n = 103)	29 / 51 (56.9%)	40 / 52 (76.9%)	-20.0% (-36.6 to -1.9)
Non-severe OSAHS (n = 50)	21 / 25 (84.0%)	20 / 25 (80.0%)	4.0% (-17.7 to 25.4)
Severe OSAHS (n = 53)	8 / 26 (30.8%)	20 / 27 (74.1%)	-43.3% (-62.4 to -16.5)
AHI <10§			
Total population (n = 88)	31 / 44 (70.5%)	33 / 44 (75.0%)	-4.5% (-22.6 to 13.9)
Non-severe OSAHS (n = 35)	16 / 18 (88.9%)	12 / 17 (70.6%)	18.3% (-8.7 to 43.3)
Severe OSAHS (n = 53)	15 / 26 (57.7%)	21 / 27 (77.8%)	-20.1% (-42.1 to 4.9)

* Values are the number of effective treatments divided by the total number of patients in the treatment groups. Values in parentheses are the percentages of effective treatments.
† Differences in effectiveness between oral-appliance and CPAP therapy (oral-appliance therapy minus CPAP therapy) are reported as percentages with two-sided 95% confidence intervals in parentheses.
‡ Treatment was considered effective when the AHI either was <5 or showed "substantial reduction," defined as reduction in the index of at least 50% from the baseline value to a value of <20 in a patient who had no symptoms while using therapy.
§ Seven patients in the oral-appliance group and eight patients in the CPAP group who had an AHI between five and ten were excluded from this analysis.
Abbreviations: AHI = apnea-hypopnea index, CI = confidence interval, CPAP = continuous positive airway pressure, OSAHS = obstructive sleep apnea-hypopnea syndrome.