Oral-appliance therapy obstructive sleep apnea-hypopnea syndrome

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Chapter 8
Summary/Samenvatting

Chapter 8.1
Summary

The obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common sleep-related breathing disorder characterized by disruptive snoring and repetitive upper airway obstructions. Its neurobehavioral consequences include excessive sleepiness, an increased risk of accidents, and an impaired quality of life. Cardiovascular consequences may include hypertension and an increased risk of ischemic heart disease, congestive heart failure, and stroke. In the management of OSAHS, clinicians may consider various conservative, non-invasive and surgical treatment modalities. Conservative measures and the correction of morphological airway abnormalities should be considered first. If these measures are not effective or not applicable, continuous positive airway pressure (CPAP) is currently regarded as the treatment of choice for, especially, moderate to severe OSAHS. However, due to the obtrusive nature of CPAP, the effectiveness of therapy may be compromised by poor therapeutic acceptance and adherence. Surgical interventions for OSAHS may roughly be classified as ablative soft tissue surgery (*e.g.*, uvulopalato-pharyngoplasty) and surgical interventions that aim at soft tissue repositioning by means of skeletal modifications (*e.g.*, maxillomandibular advancement surgery). Based on the current level of evidence, most surgical interventions for OSAHS should generally be reserved for patients failing CPAP therapy. Pharmacological management of OSAHS is only warranted as supplementary treatment in specific patients. Oral-appliance therapy aims at relieving upper airway obstructions in OSAHS patients by modifying the position of the mandible, the tongue, and pharyngeal structures. Over the past decade, oral appliances have emerged as a popular alternative to CPAP. In clinical practice, however, oral appliances are primarily restricted to patients unwilling or unable to comply with CPAP therapy. The general aim of this thesis is to evaluate the specific role of oral-appliance therapy in the treatment of OSAHS.

Chapter 2.1 provides background information with respect to OSAHS and discusses the various treatment modalities. In Chapter 2.2 the available literature relating to the efficacy and co-morbidity of oral-appliance therapy for OSAHS is systematically reviewed. Sixteen controlled trials related to efficacy of oral-appliance therapy were identified. With respect to improvements in the number of upper airway obstructions (*i.e.*, apnea-hypopnea index [AHI]), oral-appliance therapy was clearly more effective than an "inactive" control device and possibly more effective than uvulopalatopharyngoplasty. Although patients generally preferred oral-appliance therapy, improvements in the AHI were usually better with CPAP therapy. Moreover, specific aspects related to oral-appliance design may influence patient perceived efficacy and preference. Twelve patient-series and one controlled study related to co-morbidity of oral-appliance therapy were identified. Data suggest that oral-appliance therapy may have adverse effects on the craniomandibular and craniofacial complex. We conclude that the available

literature offers an evidence base for the use of oral appliances in the treatment of OSAHS. Because CPAP therapy is apparently more effective and adverse effects of oral appliances have been described, controlled studies addressing the specific indication and co-morbidity of oral-appliance therapy are warranted.

Determination of the effective positive airway pressure in a specific patient is usually a trade-off between the minimization of pressure-related side-effects and the prevention of upper airway obstruction during sleep. This procedure, known as CPAP-titration, is routinely conducted by a technician in a sleep laboratory during polysomnography (manual CPAP-titration). A practical alternative for manual CPAP-titration is titration without polysomnography during an afternoon nap (Nap-titration). In Chapter 3 it is evaluated whether Nap-titration is an appropriate procedure for effective titration of CPAP. Twenty-four eligible OSAHS patients were included in this study. Following Nap-titration all patients started conventional CPAP therapy. Polysomnography and a questionnaire evaluation were performed at baseline and eight weeks after Nap-titration. Nap-titration resulted in successful CPAP titration in 23 of the 24 included patients (96%). In addition, at follow-up review significant improvements were found in OSAHS-symptomatology and quality of life. We conclude that Nap-titration is an appropriate procedure for the effective titration of CPAP.

Chapter 4 focuses on the effects of oral-appliance and CPAP therapy on different neurobehavioral and physiological outcomes. Although oral-appliance therapy is generally effective, this treatment is currently used primarily for patients who do not respond to CPAP. However, many patients prefer an oral appliance to CPAP, and physiological and neurobehavioral outcomes are not substantially different between these therapies. In Chapter 4.1 it is studied whether an oral appliance is not inferior to CPAP in treating OSAHS effectively. We randomly assigned 103 OSAHS patients either to oral-appliance or CPAP therapy. After two to three months, treatment effects were assessed with polysomnography. We determined the proportion of patients for whom oral-appliance or CPAP therapy was effective. For the difference in effectiveness (oral-appliance minus CPAP therapy), a two-sided 95% confidence interval was calculated. Non-inferiority of oral-appliance therapy was considered established when the lower boundary of this interval exceeded -25%. Treatment was effective for 39 of 51 patients using the oral appliance (77%) and for 43 of 52 patients using CPAP (83%). The lower boundary of the confidence interval of the difference in effectiveness was -22%, indicating that oral-appliance therapy was not inferior to CPAP as effective treatment of OSAHS. However, a subgroup analysis revealed that an oral appliance is particularly indicated for patients with mild to moderate disease (AHI ≤30).

Excessive sleepiness in OSAHS patients may adversely affect daytime performance

and consequently, among other sequelae, influence driving performance. It has been shown that performance on driving simulators is impaired in OSAHS patients. Whereas treatment with CPAP generally improves simulated driving performance, the effects of oral-appliance therapy are unknown. In Chapter 4.2 it is studied to what extent OSAHS patients have more difficulty with a monotonous simulated driving test when compared with control subjects, and the effects of oral-appliance therapy are compared with CPAP. Simulated driving performance was evaluated in 20 OSAHS patients and 16 control subjects during a 25-minute driving test. Following randomization ten patients started oral-appliance and CPAP therapy, respectively. After two to three months of treatment patients repeated the driving test. It was demonstrated that OSAHS patients perform worse during a simulated driving test compared with control subjects. Adequate treatment with either oral-appliance or CPAP therapy usually resulted in substantial driving improvements. Our findings also suggest that oral-appliance and CPAP therapy do not differ with regard to improvements in simulated driving performance. However, implications of these findings are mainly constrained by the relatively small patient population in this study.

In patients without cardiovascular disease OSAHS is associated with an increased incidence of both systolic and diastolic cardiac dysfunction and left ventricular hypertrophy. This association is considered an important risk factor for developing cardiovascular disease. CPAP therapy has been shown to improve left ventricular structure and function. In addition, natriuretic peptides, which are believed to reflect the degree of left ventricular wall stress, may improve following successful CPAP therapy. The effects of oral-appliance therapy on cardiac function are largely unknown. In Chapter 4.3 left ventricular structure and function and natriuretic peptides in OSASH patients without cardiovascular disease are studied, and the effects of oral-appliance therapy are compared with CPAP. In 28 moderate to severe OSAHS patients, echocardiography and measurements of concentrations of the amino-terminal fragment of pro-brain natriuretic peptide (NT-pro-BNP) were performed. Fifteen patients were randomized to oral-appliance and 13 to CPAP therapy. After two to three months of treatment echocardiography and NT-pro-BNP measurements were repeated. It was demonstrated that half of the patients had left ventricular hypertrophy, left ventricular dilatation or elevated natriuretic peptides. These patients, therefore, appear to be at increased risk of developing cardiovascular disease. NT-pro-BNP values improved significantly following oral-appliance therapy whereas they did not following CPAP. These findings suggest an improvement in functional cardiac impairment with effective oral-appliance therapy. However, conclusions on specific differences between oral-appliance and CPAP therapy cannot be drawn due to the relatively small patient population in this study.

In addition to various neurobehavioral and cardiovascular sequelae, OSAHS is associated with sexual dysfunction. Although CPAP therapy has been demonstrated to improve sexual dysfunction, the effects of oral-appliance therapy are unknown. In Chapter 4.4 it is determined to what extent male OSAHS patients experience sexual dysfunctions compared with control subjects, and secondly the effects of oral-appliance and CPAP therapy on sexual functioning are evaluated. Sexual functioning was determined in 48 OSAHS patients with the Golombok Rust inventory of sexual satisfaction (GRISS) and compared with 48 age matched male control subjects. Patients were randomized for either oral-appliance or CPAP therapy. After two to three months of treatment the GRISS was repeated. Our results confirm that male OSAHS patients show more sexual dysfunction when compared with aged matched control subjects. Sexual dysfunction in patients primarily related to erectile dysfunction and sexual dissatisfaction. We could not establish significant improvements in sexual functioning in either the oral-appliance or CPAP treated patients. However, a correlation between the extent of erectile dysfunction at baseline and improvements in erectile function following treatment suggested that untreated patients with pronounced erectile dysfunction experience some improvement following OSAHS treatment.

Oral-appliance therapy is generally less effective in relieving upper airway obstructions when compared with CPAP. Conversely, many patients prefer an oral appliance over CPAP therapy. Therefore, predictors of treatment outcome are of importance for selecting suitable candidates that may benefit from either treatment. In Chapter 5 the value of relevant clinical, polysomnographic and cephalometric variables is assessed to separately and jointly predict the outcome of oral-appliance and CPAP therapy. Fifty-one patients treated with oral-appliance therapy and 52 patients treated with CPAP were included in this study. Relevant clinical, polysomnographic and cephalometric variables were determined at baseline. The predictive value of variables for outcomes in both treatments was evaluated in univariate and multivariate analyses. The outcome of CPAP therapy could not be reliably predicted. The outcome of oral-appliance therapy, however, appears favorable especially in patients who are less obese, have milder OSAHS and have certain craniofacial characteristics (in particular mandibular retrognatism). While only requiring information on the patient's maximum mandibular advancement, AHI, and intermaxillary and mandibular relationship, the predictive models obtained from the multivariate analyses classified the outcome of oral-appliance therapy correctly in 80% of the cases. The predictive variables obtained in this study may be valuable for preselecting suitable candidates for oral-appliance therapy.

Chapter 6 focuses on the application of oral appliances in specific cases. Surgical treatment of OSAHS is principally aimed at enlarging airway dimensions and

decreasing airway collapsibility. Maxillomandibular advancement surgery has been suggested to be the most effective and acceptable surgical treatment for OSAHS. Despite a variety in treatment protocols for maxillomandibular advancement surgery, the precise indication for this surgical procedure in the management of OSAHS is currently undefined. In Chapter 6.1 the potential application of oral-appliance therapy preceding maxillomandibular advancement surgery in the treatment of OSAHS patients is evaluated. Forty-three consecutive OSAHS patients treated with an oral appliance that repositioned the mandible (*i.e.*, a mandibular repositioning appliance [MRA]) were considered for inclusion. All patients displaying a substantial reduction in their AHI with MRA therapy (*i.e.*, >50%), who preferred surgical rather than "prosthetic" advancement of the mandible, were offered maxillomandibular advancement surgery. Maxillomandibular advancement surgery was successful (*i.e.*, postoperative AHI <5) in all four patients treated according to this protocol. These results suggest that MRA therapy might be a good predictor for the success of maxillomandibular advancement surgery in OSAHS management. Although confirmation in a larger study sample is indicated, we conclude that patients with a substantial reduction in their AHI with MRA therapy appear candidates for maxillomandibular advancement surgery.

In up to a third of all cases an MRA cannot be inserted because of dental limitations. In the majority of cases there are an insufficient number of teeth to support and retain the appliance. In order to stabilize and retain an MRA in the edentulous patient, osseointegrated implants may be used. In Chapter 6.2 the initial experiences with an implant retained MRA in the treatment of six edentulous OSAHS patients are described. Treatment consisted of the placement of four endosseous dental implants in the mandible and the construction of a new maxillary denture and a mandibular overdenture. Subsequently an MRA was made. After a habituation and adjustment period the effect of treatment was evaluated with polysomnography. Of the five patients completing the follow-up polysomnography, treatment resulted in an AHI <5 in four. These findings suggest that an implant retained MRA in the mandible is a viable treatment modality in edentulous OSAHS patients. Because therapeutic effectiveness may be compromised by excessive pressure of the MRA on the labial mucosa in the maxilla, we suggest that an implant retained MRA in the maxilla is offered as a secondary treatment in selected patients.

In Chapter 7 the main research outcomes of this thesis are discussed in broader context and general conclusions are drawn. Furthermore, this chapter discusses and suggests aspects that may be considered for future research in oral-appliance therapy for OSAHS. After studying the specific role of oral-appliance therapy in the treatment of OSAHS patients we conclude that this therapy may be recommended

as primary treatment in patients with mild to moderate OSAHS besides CPAP therapy. In severe OSAHS and specific patient populations (*e.g.*, edentulous patients), CPAP therapy should always be considered first whereas oral appliances may be used as a secondary intervention. Follow-up studies should be performed to show if these recommendations also hold for the long-term.

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