Novel Approaches on Compliance, Titration and Sleep Position to Optimize the Therapeutic Outcome of Oral Appliance Therapy in Patients with Sleep-Disordered Breathing

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Sleep-disordered breathing (SDB) is a common pathophysiological continuum that ranges from intermittent snoring up to obstructive sleep apnea (OSA)[1-3]. OSA is characterized by repetitive partial or complete collapse of the upper airway[3]. Clinical experience indicates that in the majority of patients with OSA, the frequency and duration of respiratory events are influenced by body position and sleep stage[4]. In approximately 50 to 60% of OSA patients, there are twice as much respiratory events in supine sleeping position when compared to the non-supine sleeping position[5-7]. OSA is often associated with daytime consequences like excessive daytime sleepiness, impaired cognitive performance and reduced quality of life[1]. Even more, there is some evidence that OSA is a strong and independent risk factor for cardiovascular and cerebrovascular diseases[3,8,9].

Therefore, adequate diagnosis and treatment of OSA is important. Oral appliance (OA) therapy is increasingly prescribed as a non-invasive treatment for patients with snoring and OSA[10]. The most common type of OA therapy is worn intraorally at night in order to reduce upper airway collapse by protruding the mandible (OAm)[11-14]. The custom-made OAm are recommended over prefabricated devices[15]. Furthermore OAm with an integrated titratable mechanism allowing for gradual mandibular protrusion are to be preferred. These appliances allow for gradual mandibular protrusion in order to achieve maximum therapeutic effect[16,17]. Due to the progressively applied advancement, the protrusion can be tailored individually in terms of tolerability and positive effects on breathing efficacy. OAm therapy is a treatment that does not eliminate the underlying causes of upper airway collapse and is therefore a lifelong therapy. The appliances used to achieve this goal need to be inserted and removed autonomously by the patients themselves, placing the responsibility to use these appliances adequately, on the patient. Therefore, follow-up of compliance is of primary importance[18,19]. In the past, compliance during OAm therapy was limited to self-reported use and lacked an objective compliance measurement.

Positional therapy is a treatment modality aimed at preventing sleep in the most adverse sleeping position, usually the supine position, and could be applied in patients with supine-dependent OSA (sdOSA)[20]. The most widely used technique to avoid such supine position involves strapping a bulky object, such as tennis balls, to the back of the patient. Several studies have shown that such therapies have a significant positive effect on snoring and OSA severity in patients with sdOSA[6,20-24]. However, the bulky object strapped to the back is often uncomfortable for patients and results in disturbed sleep and low long-term compliance rates[6,21]. Therefore, positional therapy has not found its way into daily OSA treatment routine to date[25]. In order to overcome compliance problems with bulky positional therapies, both a new neck-worn and a chest-worn device correcting the supine sleeping position by activating a vibration alarm have been introduced to the market. This novel concept of positional therapy showed promising results in reducing apnea severity, as well as improved therapy compliance[26,27].

The aim of this doctoral thesis was to calculate and optimize the Mean Disease Alleviation (MDA) as a measure of the therapeutic effectiveness of OAm therapy. The MDA of a given therapy is a combined effect of compliance and efficacy in terms of reduction in OSA severity. To achieve this goal, we focused on three main topics: compliance, titration and combination of OAm with positional therapy. The following research questions were studied:

1. Is it safe and feasible to measure the compliance during OAm therapy in an objective manner at short- and long-term follow-up? This research question is studied in ***chapter 3***.
2. Is there a high agreement between subjective and objective compliance data for OAm therapy? This research question is discussed in ***chapter 4***.
3. Are there some patient-related determinants that predict a poor compliance to OAm therapy? Possible correlations are described in ***chapter 5 and 6***.
4. Will additional titration of the mandibular protrusion lead to a higher therapeutic effectiveness of OAm therapy? The current knowledge on this topic is summarized in ***chapter 7*** and the results of a study on this topic are described in ***chapter 8***.
5. What is the prevalence of sdOSA before and under OAm therapy? See ***chapter 9***.
6. Will patients with a residual sdOSA under OAm therapy benefit from additive positional therapy? The results of a randomized controlled trial are summarized in ***chapter 10***.

Section 'Objective compliance measurement'

Chapter 2 provides an overview of the current knowledge on compliance during OAm therapy. In the past, compliance during OAm therapy was limited to self-reported use and lacked an objective compliance measurement. In ***chapter 3***, we reported in depth on the safety and feasibility of an objective compliance monitor for OAm therapy[28,29]. The objective compliance monitor showed a relatively high compliance with an objective OAm use of 6.7 ± 1.3 h/night at 3-month follow-up. At 1-year follow-up, the discontinuation rate was 9.8%, with a mean use of 6.4 ± 1.7 h/night in continuing users. The regular user rate, defines as patients with an OAm use ≥ 4 h/night on ≥ 70% of all nights[30], was 89% at 1-year follow-up. The availability of an objective compliance monitor allow for the calculation of the MDA. In the reported study, the MDA was calculated as 51.1% at 3-month follow-up (Figure 1), and 54.8% in continuing users at 1-year follow-up. The MDA for OAm therapy was characterized by high compliance and suboptimal efficacy. In addition, in ***chapter 4***, we showed a high agreement between objective and subjective compliance data, with a mean subjective overestimation of 30 minutes.

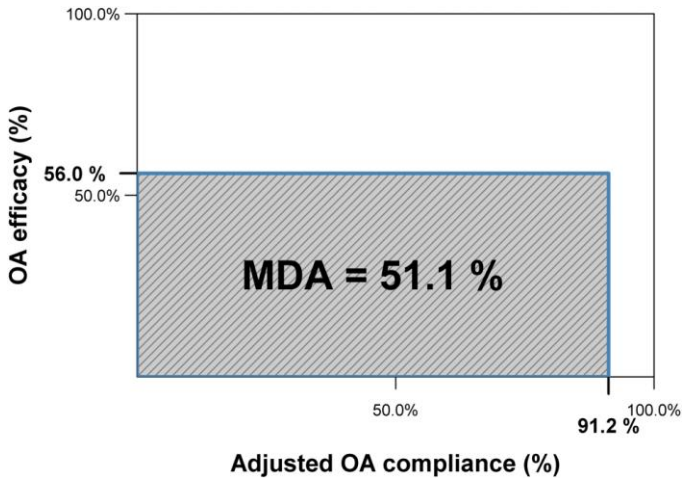

Figure 1. Mean disease alleviation (MDA) at 3 month follow-up. MDA provides a measure of overall therapeutic effectiveness.

In order to maximize the therapeutic effectiveness of OAm therapy, it is important to optimize both compliance and efficacy. In the section 'patient-related determinants of compliance' of this dissertation, we report on patient-related determinants of compliance that could help us to predict a low compliance. Whereas in the sections 'titration' and 'supine-dependent OSA', we describe some interventions that can possible optimize the therapeutic efficacy of OAm therapy.

Section 'Patient-related determinants of compliance'

In ***chapter 5***, the association between compliance and a type D 'distressed' personality, characterized by negative affectivity and social inhibition, was assessed. A higher discontinuation rate and lower compliance was found among type D patients. Furthermore, the association between compliance and some anthropometric and polysomnographic data was studied in ***chapter 6***. In that study, a more pronounced decrease in snoring complaints during OAm therapy was significantly correlated with a better compliance during OAm therapy. In general, screening for patient-related determinants that predict a low compliance could allow for the implementation of structured intervention efforts aimed at improving the patient's compliance.

Section 'Titration'

In literature, it is described that finding the most effective protrusive position within the physical limits of the patient is of utmost important in order to increase the OAm efficacy. Several titration protocols have been described that tried to achieve this effective protrusive position, and are described in ***chapter 7***, each with their own advantages and limitations. In ***chapter 8***, it is studied whether additional titration of the mandibular protrusion leads to a higher efficacy. Additional titration leaded to an increase in success rate, from 32.7% to 44.2% after additional titration.

Section 'Supine-dependent OSA'

It is described in literature that a treatment modality for OSA that is not able to completely eliminate all breathing abnormalities leaves the patient with a residual OSA, which is often less severe than the initial OSA and is therefore probable more supine-dependent[4,31]. The prevalence of supine-dependent OSA (sdOSA) before and under OAm therapy is described in ***chapter 9***. The prevalence of sdOSA in patients starting OAm therapy was 67.5%, using the definition of Cartwright defined as a supine AHI ≥ 2 x non-supine AHI. In addition, 33.9% of patients had a residual sdOSA under OAm therapy. Furthermore, the results of that study showed that one third of patients under OAm therapy shift from non-sdOSA to sdOSA under therapy. It was hypothesized that patients with residual sdOSA under OAm therapy could benefit from additive therapy with positional therapy. ***Chapter 10*** summarizes the results of a randomized controlled trial investigating the feasibility of the additive use of a sleep position trainer (SPT) in patients with sdOSA under OAm therapy. The results showed that both OAm therapy and SPT were individually efficacious. However, combination of SPT + OAm therapy further reduced the sleep apnea severity.

Conclusion

This doctoral thesis shows that is safe and feasible to measure the objective therapy compliance during OAm therapy. This measurement allows for the calculation of the mean disease alleviation (MDA) as a measure of the therapeutic effectiveness of OAm therapy. The MDA of a given therapy is a combined effect of compliance and efficacy in terms of reduction in OSA severity. Therefore, in order to optimize the therapeutic effectiveness of OAm therapy, it is important to optimize both compliance and efficacy. We showed that there are some patient-related determinants of a lower compliance, which allow for the implementation of some structured intervention efforts aimed at improving the compliance in those patients. In addition, the efficacy of OAm therapy could be increased by additive titration of the mandibular protrusion, as well as by additive positional therapy in patients with residual sdOSA under OAm therapy.

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