MAXILLOFACIAL TREATMENT PLANNING IN OBSTRUCTIVE SLEEP APNEA

M.H.T. (Maurits) de Ruiter

Part of the research described in this thesis was financially supported by Nuts Ohra Fund.

Financial support for printing and distribution of this thesis was kindly supported by:

ACTA, NVTS, NVMKA, KNMT, NWVT, SomnoMed, Prosomnus, ResMed, Vivisol, KLS Martin, Straumann, Dentsply Sirona

Academic thesis, University of Amsterdam, The Netherlands

Provided by thesis specialist Ridderprint, ridderprint.nl

Printing:	Ridderprint
Layout and design:	Wiebke Keck, persoonlijkproefschrift.nl
Schilderij omslag:	Wolter Jagt
ISBN:	978-94-6483-228-0

Maxillofacial treatment planning in Obstructive Sleep Apnea

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op woensdag 20 september 2023, te 14.00 uur

door Maurits Hendrik Théodore de Ruiter
geboren te Nieuwerkerk aan den IJssel

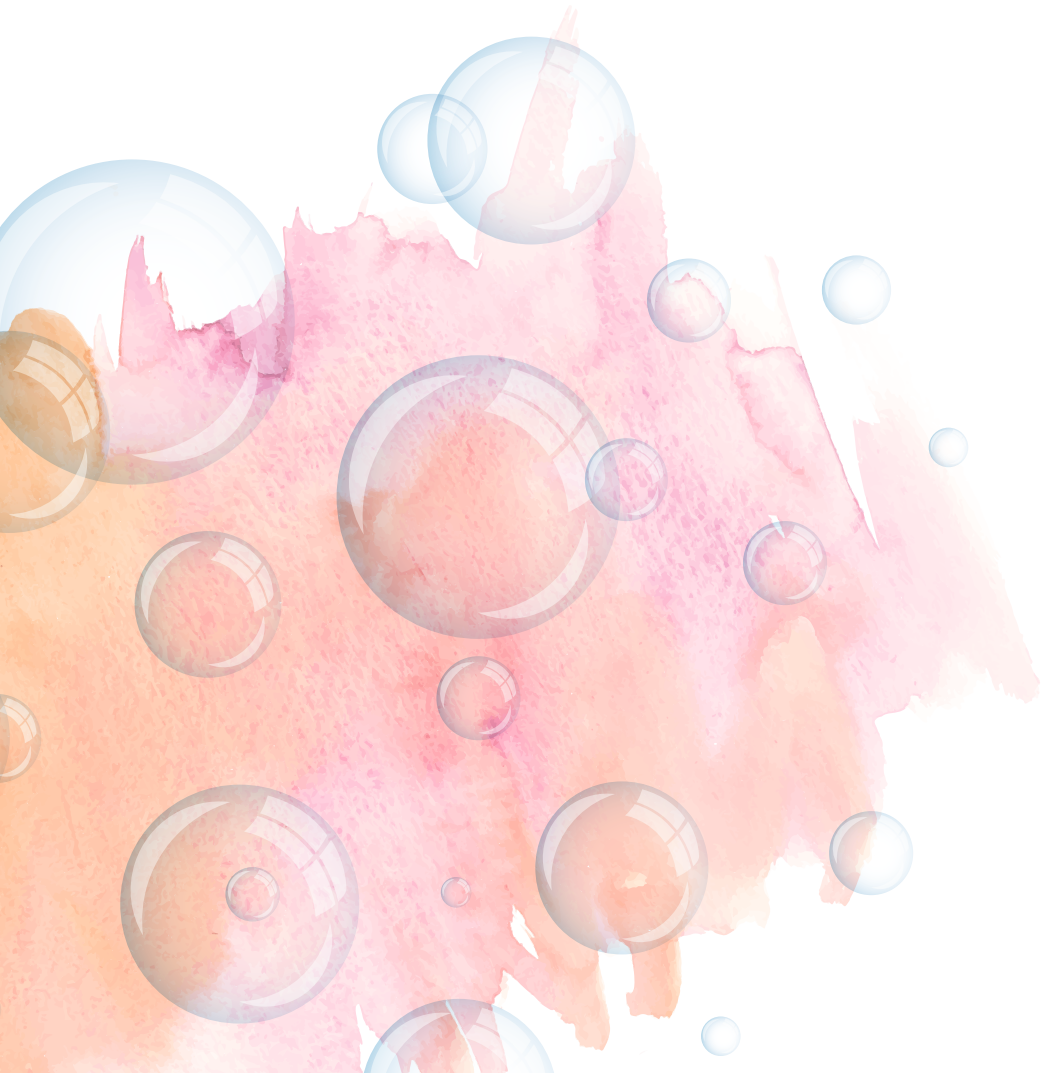
Promotiecommissie

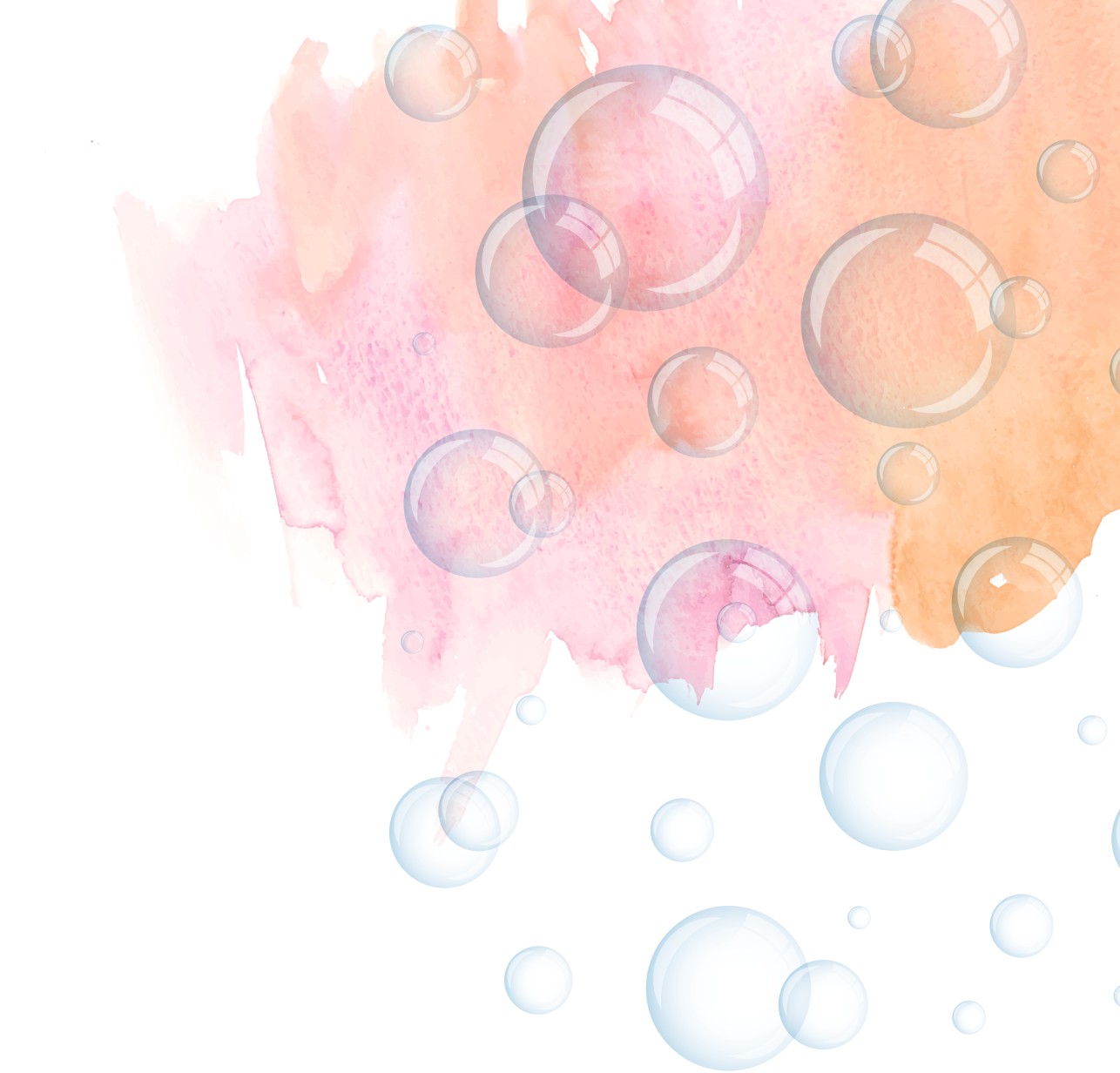
Promotores:	prof. dr. J. de Lange	Universiteit van Amsterdam
	prof. dr. N. de Vries	Universiteit van Amsterdam
Copromotores:	dr. D.M.J. Milstein	Universiteit van Amsterdam
	dr. H.C.M. Donders	Isala Klinieken Zwolle
Overige leden:	prof. dr. F. Lobbezoo	Universiteit van Amsterdam
	prof. dr. A.G. Becking	Universiteit van Amsterdam
	prof. dr. F.R. Rozema	Universiteit van Amsterdam
	prof. dr. G. Aarab	Universiteit van Amsterdam
	dr. A. Hoekema	Ziekenhuis Tjongerschans
	prof. dr. A.J.W.P. Rosenberg	Universiteit Utrecht
	prof. dr. O.M. Vanderveken	Universiteit Antwerpen

Faculteit der Tandheelkunde

CONTENTS

CHAPTER 1





General introduction and outline of the thesis

GENERAL INTRODUCTION

BRIEF HISTORY

Symptoms such as snoring and excessive daytime sleepiness have been observed for centuries and due to the effort of technology and physicians the understanding of sleep and sleep apnea-like symptoms has been improved significantly. First records indicate that these symptoms were noticed and remarked upon nearly 2.000 years ago, and in the nineteenth century, doctors began to summarize sleep apnea symptoms together using the name “Pickwickian syndrome”. The name is derived from the Charles Dickens’ *The Pickwick Papers*, in which an overweight boy exhibited symptoms of what would later become known as sleep apnea. From the 1950s and 1960s research focused more on exploring the pathophysiology of this chronic disease and physiological consequences were described. An exponential growth of high-quality research papers emerged since and in recent literature the focus of these studies moved from pathophysiology to treatment planning.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is characterized by recurring collapse of the pharyngeal airway during sleep leading to partial (hypopnea) or complete (apnea) obstruction in breathing. This temporary stop in breathing results in disturbances (e.g., intermittent hypoxia (low oxygenation), sleep fragmentation, intrathoracic pressure abnormalities) that are related to a range of neurobehavioral and cardiometabolic effects. Common symptoms of OSA include (loud) snoring, apneas and excessive daytime sleepiness; daytime fatigue, cognitive impairment, personality and mood changes.[1-3]

The severity of OSA is as a rule expressed in the apnea-hypopnea-index (AHI): it is defined as the mean number of apneas and hypopneas per hour of sleep and is assessed through a sleep registration test (e.g., polysomnography). During polysomnography, oronasal airflow, respiratory effort, oxyhemoglobin saturation, snoring level, sleeping position, limb movements, cardiac function (electrocardiography) and brain activity (electroencephalography) are registered. Based on the outcome of this polysomnographic study, OSA is classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI >30).[1] The majority of patients with OSA tend to show more apneic events in a supine sleeping position. Moreover, approximately 56% have an AHI that is at least twice as high in supine position as compared to the AHI in non-supine position, which is defined as position-dependent OSA (POSA).[4-6] POSA correlates negatively with OSA severity; thus while the majority of patients with mild OSA are positional, positional OSA is less common in severe OSA.[7]

The overall prevalence of OSA is 9-38% in the general adult population and is higher in men and rises with increasing age.[8] The HypnoLaus study claims higher prevalence rates compared to earlier findings: 84% of men versus 61% of women had OSA, defined as an

AHI >5, recorded by polysomnography (PSG).[8, 9] Specifically, the prevalence of moderate and severe OSA (AHI >15) was estimated at 50% in men and 24% in women.[10] Recent appraisals suggest over one billion people are affected worldwide and extrapolating the data provides a prevalence in the Netherlands estimated at around 300,000 to 600,000 patients. People with OSA are often asymptomatic and therefore OSA remains largely an underrecognized or undiagnosed medical condition. The presence of symptoms in patients with OSA, results in the diagnosis obstructive sleep apnea *syndrome* and in daily practice symptoms are of increasing importance. It is estimated that approximately 80-90% of them are expected to remain undiagnosed.[11]

Obesity has been recognized as a significant risk factor associated with OSA and the prevalence of OSA in the obese population is approximately 40%.[12, 13] Other risk factors related to OSA in adult patients include age, male sex, anatomic variations associated with pharyngeal airway and maxillomandibular skeleton, menopause, alcohol, medication and smoking.[14-16] The other way around, OSA is an independent risk factor for hypertension, cardiac disease, stroke, diabetes mellitus type 2 and involvement in motor vehicle accidents, industrial accidents, risk and death.[2, 10]

TREATMENT OF OSA

CONSERVATIVE THERAPY AND CONTINUOUS POSITIVE AIRWAY PRESSURE

Treatment of OSA is usually initiated with conservative therapies consisting of lifestyle changes, improved sleep hygiene, weight reduction and avoidance of alcohol.[17] Next to these conservative measures treatment options include positional therapy, oral appliance therapy (OAT), continuous positive airway pressure (CPAP) and surgery.[18-22] The golden standard of OSA therapy is CPAP, which is highly effective in preventing pharyngeal collapse but is dependent on the number of hours of nightly usage.[23, 24] Many patients are suboptimal CPAP users because of side effects related to the interface (e.g., skin abrasion), pressure (e.g., nasal congestion, gastric, bowel distension, recurrent ear and sinus infections) and negative social factors.[25] Due to the mediocre adherence of OSA patients to CPAP treatment other options are often explored.[26]

ORAL APPLIANCE THERAPY

Oral appliances (OA) are extensively used in patients with OSA and often decrease AHI with clinically relevant improvements. There are generally two types of oral appliances: mandibular repositioning apparatus/device (MRA) and tongue retaining devices. The most commonly used type of oral appliance is the MRA, which positions the mandible and its supportive soft tissue structures (e.g., hyoid bone and muscles) in a slightly prognathic (forward) position during sleep.[27] Concepts regarding custom-made OAs have evolved from a monobloc OA (single occlusal surface splint) towards a duobloc OA consisting of an upper and lower splint that can be dynamically positioned on both occlusal surfaces. During a titration procedure the mandible is gradually positioned in a more anterior position to achieve a maximum therapeutic effect on opening the upper

respiratory airway.[28] Equally important is to achieve a well-tolerated position in order to ensure optimal compliance by the patient. This full procedure is called Oral Appliance Therapy (OAT). Extensive evidence-based data is available concerning the side effects associated with OAT, especially on teeth and the temporomandibular joints.[29, 30] In the initial acclimatization to OAT, adverse effects are commonly experienced. Adverse effects include excessive salivation, mouth dryness, tooth pain, gum irritation, headaches and discomfort of the temporomandibular joint. Adverse symptoms are often transient, lasting approximately two months.[29-31] Ideal titration occurs when the final positioning of the mandible is most effective on subjective (complaints) and objective (polysomnographic) metrics, and also results in acceptable side effects in the short and long term and providing the highest possible adherence or compliance rate concerning the desired OAT *(this thesis*).[32]

When compared to CPAP, OAT has a non-inferior efficacy based on symptomatic response; in other words, CPAP is more effective in reducing AHI.[33] However, while CPAP and OAT have different efficacy and compliance profiles, their overall therapeutic efficacy is similar: OAT has better adherence rates while CPAP therapy is more efficacious.[34]

SLEEP POSITION TRAINER

The supine sleeping position is an important risk factor in OSA. The severity of OSA can be reduced by avoidance of this sleeping position.[5, 6, 35-37] From a historical point of view, the supine sleeping position is a well-known predisposing factor for snoring and apneas, given which physicians developed several different methods for avoidance of this position during sleep. In the army different methods were used to avoid supine sleeping, with different objects, e.g. cannonballs or a more evolved metal spiky-ball-construction, strapped onto the sleeper's back. Since the 1980s studies have been conducted to assess positional therapy, which are now referred to the so-called "tennis-ball-technique".[36] This technique uses straps, belts or a specifically designed shirt to hold the tennis ball onto the back of the sleeper, however this technique failed to reduce the supine sleeping position because of patient discomfort, disrupted sleep and poor long-term adherence.[38] Several new generation devices, now called "sleep position trainers" (SPT), have been introduced over the past 10 years and focuses more on comprehensible and comfort.[39-42] Prospective cohort studies on the SPT claim a reduction of the average supine sleeping time from 46% to 5% and AHI level reductions of less than 5 in 48% of patients with mild and moderate POSA.[42] Using sleep position trainers, adherence among OSA patients was measured at 64% after 6 months of treatment with improvement in sleep-related quality of life outcomes. Long-term efficacy and compliance when treating OSA using sleep position trainers are promising.[22]

SURGICAL INTERVENTIONS

For patients who are non-responsive to therapy, non-compliant, or who desire a permanent solution, various forms of surgery can be considered.[18, 43] A variety of upper

airway surgical modalities are available, either as single or multilevel procedures. Most pharyngeal surgeries such as modern palatal reconstructive techniques and various forms of tongue base intervention; radiofrequent ablation of the tongue base, hyoid suspension or a combination of these, show mediocre consistency and adverse effects.[18] One of the most promising surgical approaches known as the maxillomandibular advancement surgery (MMA) yields very good results for treating severe OSA.

MMA is a procedure in which a Le Fort I osteotomy and a bilateral sagittal-split osteotomy (BSSO) is performed to advance the maxillary and mandibular facial skeletons, respectively. The maxilla is regularly advanced to a preoperatively planned position (8-10 mm anteriorly, and an intermediate splint is inserted to immobilize the advanced maxilla. After fixation of the maxilla with osteosynthesis, the mandible is repositioned in the planned position using a final splint and fixated with osteosynthesis. Elastics are commonly used postoperatively for guiding maxillomandibular occlusion. MMA has demonstrated high therapeutic efficacy in management of severe OSA with results comparable to the golden standard therapy of CPAP in patients with severe OSA.[44] Therapeutic efficacy in surgical procedures for OSA is defined using criteria described by Sher et al., which proposes therapeutic successes if AHI drops of more than 50% and below 20 events/h postoperatively and defines surgical cure as an AHI of <5 after surgical intervention.[45] According to these definitions MMA results in good surgical outcome with surgical success rates reported as 86% and a cure rate of 43%.[43, 46, 47] MMA can provide an effective and lifelong solution for patients with severe OSA. However, one downside associated with MMA is that since it is regarded as highly invasive is can alter facial appearance dramatically.[43, 46]

Another surgical procedure that has demonstrated interesting clinical benefit in treating severe OSA is neurostimulation of the hypoglossal nerve (9th cranial nerve). Upper airway stimulation is a recent development with high expectations. Neurostimulation of the hypoglossal nerve is activated during inspiration with consequent activation of the genioglossus muscle. Short and relatively long-term results (12, 24, 36, 48 and 60 months, respectively 60 months) showed this intervention is safe and the effect was durable. According to the definition of Sher et al. the effect on AHI showed a success rate of 74%.[45, 48, 49, 50]

GENERAL AIMS AND OUTLINE OF THE THESIS

The overall aim of the research described in this thesis was twofold. The first part was aimed at assessing the clinical outcomes of a sleep position trainer in comparison with oral appliance therapy on efficacy (polysomnographic parameters) and specific patient outcomes (adherence, subjective impairment and side-effects) concerning severe OSA. The second part was aimed at determining and creating an overview associated with the efficacy of the MMA procedure in treating severe OSA by measuring surgical invasiveness in regard to treatment success or failure. And also to evaluate the side effects associated with MMA, in particular the change in facial esthetics.

Part I focuses on the evaluation of the sleep position trainer in clinical use prospectively and is compared with oral appliance therapy in a randomized controlled trial. First the efficacy of the oral appliance, mandibular repositioning apparatus (type duobloc), was validated in a standardized way using a newly formulated titration protocol for the most efficacious forward positioning of the oral appliance **(Chapter 2)**. The sleep position trainer is evaluated on efficacy (polysomnographic parameters) and specific patient outcome (i.e., adherence, subjective impairment and side-effects) for short term results in a randomized controlled trial as compared to the oral appliance **(Chapter 3)**. Following on from this, the long-term results between 3 and 12 months were examined regarding the previously mentioned outcome parameters described in this thesis **(Chapter 4)**.

Part II addresses the efficacy concerning MMA procedures as one of the treatment options for patients with moderate and severe OSA. MMA therapy is currently not common practice nor broadly applied, due to it being an invasive treatment with severe side-effects. This research project identified different variables that could play a role in the selection of the ideal patient and procedure for surgical success and/or failure associated with MMA surgery **(Chapter 5)**. Next to this the invasiveness and the effect on facial esthetics after the MMA surgery were assessed **(Chapter 6).** Comments on the potential influences of the newly gained insights in clinical use of the sleep position trainer, the oral appliance and MMA procedure were appraised in **Chapter 7**, described in general as “summarizing discussion and future perspectives”. Finally, Dutch translation of chapter 7 is presented in **Chapter 8.**

REFERENCES

1. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667-689.
2. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122:352-360.
3. El-Ad B, Lavie P. Effect of sleep apnea on cognition and mood. *Int Rev Psychiatry* 2005;17:277-282.
4. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep* 1984;7:110-114.
5. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997;112:629-639.
6. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol* 2006;263:946-950.
7. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest* 2005;128:2130-2137.
8. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev* 2017;34:70-81.
9. Heinzer R, Petitpierre NJ, Marti-Soler H, Haba-Rubio J. Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. *Sleep Med* 2018;48:157-162.
10. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310-318.
11. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997;20:705-706.
12. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165:1217-1239.
13. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol (1985)* 2005;99:1592-1599.
14. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA* 2004;291:2013-2016.
15. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a risk factor for sleep-disordered breathing. *Arch Intern Med* 1994;154:2219-2224.
16. Peppard PE, Austin D, Brown RL. Association of alcohol consumption and sleep disordered breathing in men and women. *J Clin Sleep Med* 2007;3:265-270.
17. Shneerson J, Wright J. Lifestyle modification for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2001:CD002875.
18. Caples SM, Rowley JA, Prinsell JR, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. *Sleep* 2010;33:1396-1407.
19. Hoekema A, Stegenga B, De Bont LG. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. *Crit Rev Oral Biol Med* 2004;15:137-155.
20. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2004:CD004435.

21. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011;15:343-356.

22. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep* 2014;37:1209-1215.

23. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *JAMA* 2015;314:2280-2293.

24. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835-843.

25. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006:CD001106.

26. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173-178.

27. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep* 2006;29:244-262.

28. Dieltjens M, Vanderveken OM, Heyning PH, Braem MJ. Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. *Sleep Med Rev* 2012;16:177-185.

29. Doff MH, Veldhuis SK, Hoekema A, et al. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. *Clin Oral Investig* 2012;16:689-697.

30. Doff MH, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. *Clin Oral Investig* 2013;17:475-482.

31. Giannasi LC, Almeida FR, Magini M, et al. Systematic assessment of the impact of oral appliance therapy on the temporomandibular joint during treatment of obstructive sleep apnea: long-term evaluation. *Sleep Breath* 2009;13:375-381.

32. Dieltjens M, Vanderveken OM, Hamans E, et al. Treatment of obstructive sleep apnea using a custom-made titratable duobloc oral appliance: a prospective clinical study. *Sleep Breath* 2013;17:565-572.

33. Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2013;187:879-887.

34. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. *J Clin Sleep Med* 2014;10:215-227.

35. Oksenberg A, Silverberg DS. The effect of body posture on sleep-related breathing disorders: facts and therapeutic implications. *Sleep Med Rev* 1998;2:139-162.

36. Cartwright RD, Diaz F, Lloyd S. The effects of sleep posture and sleep stage on apnea frequency. *Sleep* 1991;14:351-353.

37. Ravesloot MJL, White D, Heinzer R, Oksenberg A, Pepin JL. Efficacy of the New Generation of Devices for Positional Therapy for Patients With Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *J Clin Sleep Med* 2017;13:813-824.

38. Bignold JJ, Deans-Costi G, Goldsworthy MR, et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. *J Clin Sleep Med* 2009;5:428-430.

39. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *J Clin Sleep Med* 2011;7:376-383.

40. Eijsvogel MM, Ubbink R, Dekker J, et al. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. *J Clin Sleep Med* 2015;11:139-147.

41. van Maanen JP, Richard W, Van Kesteren ER, et al. Evaluation of a new simple treatment for positional sleep apnoea patients. *J Sleep Res* 2012;21:322-329.

42. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep Breath* 2013;17:771-779.

43. Zaghi S, Holty JE, Certal V, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2016;142:58-66.

44. Vicini C, Dallan I, Campanini A, et al. Surgery vs ventilation in adult severe obstructive sleep apnea syndrome. *Am J Otolaryngol* 2010;31:14-20.

45. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996;19:156-177.

46. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev* 2010;14:287-297.

47. Li KK, Riley RW, Powell NB, Guilleminault C. Patient's perception of the facial appearance after maxillomandibular advancement for obstructive sleep apnea syndrome. *J Oral Maxillofac Surg* 2001;59:377-380; discussion 380-371.

48. Strollo PJ, Jr., Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139-149.

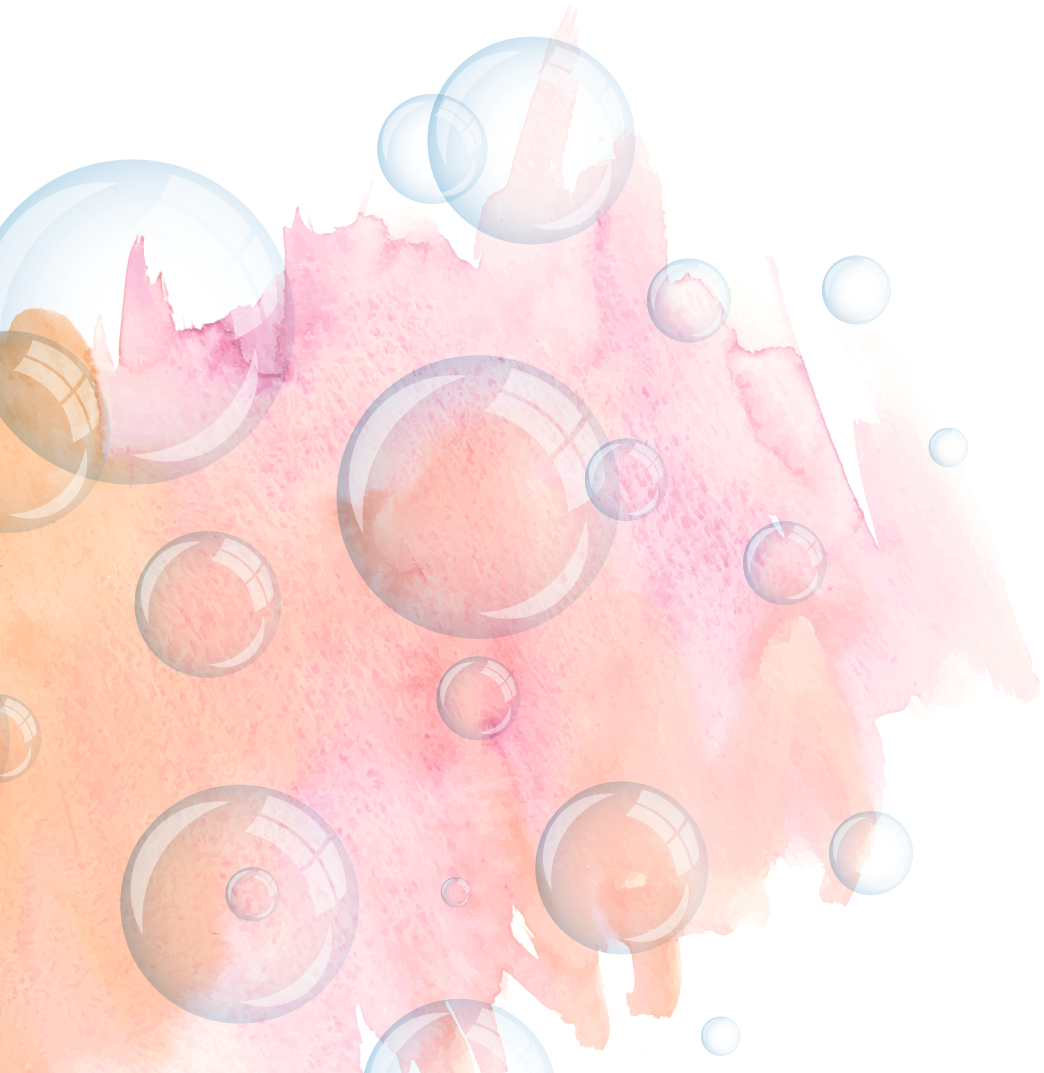
49. Woodson BT, Soose RJ, Gillespie MB, et al. Three-Year Outcomes of Cranial Nerve Stimulation for Obstructive Sleep Apnea: The STAR Trial. *Otolaryngol Head Neck Surg* 2016;154:181-188.

50. Bosschieter PFN, de Vries N, Mehra R, et al. Similar effect of hypoglossal nerve stimulation for obstructive sleep apnea in 5 disease severity categories. *J Clin Sleep Med* 2022;18:1657-1665.

PART I

Evaluation of the Sleep Position Trainer with the Oral Appliance

CHAPTER 2



A stepwise titration protocol for oral appliance therapy in positional obstructive sleep apnea patients: proof of concept.

M.H.T. de Ruiter
G. Aarab
N. de Vries
F. Lobbezoo
J. de Lange

This chapter is based on the publication in: Sleep and Breathing 2020

Abstract

Purpose In patients with positional obstructive sleep apnea (POSA), oral appliance therapy (OAT) is among the first-line treatments. The aim of this study was to evaluate the effects of a new standardized stepwise titration protocol for OAT in a group of patients with POSA.

Methods This was an observational intervention trial. Patients who were previously randomized to the OAT intervention arm of a comparison study comprised the subjects for this study. These patients, who had mild to moderate POSA, were assessed after 3 and 12 months for treatment efficacy, objective adherence by temperature microsensor, and side effects. The titration of OAT was performed using a standardized stepwise titration protocol including advancement levels of 60%, 75%, and 90% of the maximum mandibular protrusion. The optimal advancement level per individual was based on a weighted compromise between efficacy and side effects.

Results In total, 36 patients were included and all completed the titration protocol after 3 months. At baseline, the OAT was set at 60% of the maximal mandibular protrusion position. At a 3-month evaluation, the advancement remained at 60% in 16 patients (44%) and reached 75% advancement in 20 patients (56%). Mean apnea-hypopnea index decreased from 12.9 events per hour (9.1–16.7) to 6.9 (3.7–10.3) ($P < 0.001$), and median objective adherence was 97.4 (61.4–100.00) after 3 months. The 12-month analysis showed consistent results and good OAT tolerance. Six patients (16.7%) terminated OAT and one patient (2.8%) was lost to follow-up.

Conclusions This standardized stepwise titration protocol for OAT showed good efficacy, good OAT tolerance, and good objective adherence in patients with mild to moderate POSA. Therefore, the protocol is recommended in research projects to improve standardization of methods between studies and in clinical practice for its practical feasibility.

Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. Overall prevalence is estimated 9 to 38% in the general adult population, is higher in men, and rises with increasing age.[1,2] Adequate treatment for OSA is indicated, as to counter problems in daily functioning, reduce cardiovascular and cerebrovascular risk, and sometimes even reduce mortality-risk in severe OSA patients.[3-5] In patients with moderate to severe OSA, continuous positive airway pressure (CPAP) is the gold standard therapy.[6] Unfortunately, CPAP is not always well tolerated, which results in a suboptimal level of adherence.[7] Other treatment options are upper airway surgery, maxillomandibular advancement surgery, hypoglossal nerve stimulation, and oral appliances (OAs).[8,9]

Positional OSA (POSA) is defined as an apnea-hypopnea index (AHI) that is at least twice as high in the supine position as compared to the non-supine positions.[10] Prevalence is estimated around 56% in mild OSA. In an additional 30% of the patients, the apneic events are higher in supine than in non-supine position, not reaching 50% difference. [11] For patients with mild to moderate POSA, oral appliance therapy (OAT) is among the first-line treatments, while positional therapy and surgery can be considered as well.[12,13] OAs are widely used and often result in decreased AHI and oxygen desaturations (ODI) with clinical improvement in excessive daytime sleepiness and snoring.[14] When OAs are compared to CPAP, the latter is in general more effective in reducing AHI.[15] However, OAs often have better adherence, which makes that CPAP and OAs have similar overall therapeutic effectiveness. [16,17]

Concepts about custom-made OAs have evolved from the monobloc OA towards a duobloc OA that consists of an upper and lower splint, which can be dynamically positioned against each other. During the titration-procedure, the mandible is gradually positioned in a more anterior position to achieve maximum therapeutic effect on opening the upper airway.[18] Equally important is to achieve a well-tolerated position, in order to ensure optimal compliance. Extensive evidence is available for the side effects of OAT, especially on teeth and the temporomandibular joints.[19,20] It is therefore of utmost importance that the “target” protrusion of the mandible: 1. is most effective on subjective (complaints) and objective (polysomnographic) metrics (AHI and ODI); 2. results in acceptable side effects in the short and long term; and 3. gives the highest possible adherence rate.[21] Currently, there is no consensus on the titration procedure, which makes it difficult to compare the outcomes of studies on OA and thus there is need for standardization. Therefore, the aim of this study was to determine the effects of a standardized titration protocol on the efficacy (i.e., decrease in AHI and ODI), self-reported side effects, and objective adherence in mild to moderate POSA patients in a 1-year follow-up.

Methods

Participants

This study is part of a randomized controlled trial in which OAT was compared with a Position Trainer in patients with POSA.[13,22] Participants were eligible for enrollment if they had mild or moderate POSA, were 18 years or above, and were able to provide informed consent. Exclusion criteria were inadequate dentition for wearing an OA, subjective snoring in lateral position, diagnosed with central sleep apnea, night or rotating shift work, severe chronic heart disease, active psychiatric disease, seizure disorder, medication usage for sleeping disorders, muscular or joint injuries in head/neck, or back area, previous OAT usage, simultaneous other treatment for OSA, reversible morphological upper airway abnormalities (e.g., enlarged tonsils), pregnancy, and coexisting non-respiratory sleep disorders (e.g., insomnia, periodic limb movement disorder, narcolepsy) that would compromise functional sleep assessment.

Study design and oversight

This study is a sub-assessment of the OAT therapy group in POSA trial, [13,22] focusing on the standardized *step-wise* titration-protocol used. The POSA trial is a multicenter, prospective randomized controlled trial. The randomization sequence was generated by an independent clinical research unit. Allocation of treatment of 1:1 was performed with random block sizes of maximum 6 and stratified for smoking and body mass-index (BMI). The protocol of this study was approved by the medical ethics committee (Amsterdam UMC: METC2012_208) and was registered before start in clinicaltrials.gov (NCT02045576). All participants provided written informed consent before enrollment. Independent monitors performed verification of the source data and documentation. The study investigators had full access to the data and had the right to submit the manuscript for publication without input from the sponsor.

Treatment

The OA was a custom-made duobloc (SomnoDent flex, SomnoMed, Sidney, Australia). The OA was adjusted individually, and advancement was titrated using a standardized *step-wise* titration-protocol, developed by one of the authors (GA). After adequate assessment of the central relation and maximum protrusion using the George Gauge system with a standard 5 mm vertical dimension (Great Lakes Orthodontics, Tonawanda, NY), the OA was set at 60% advancement of maximum protrusion at baseline. During the first 3 months, at each consecutive visit, the OA was evaluated and advanced to 75% or 90% if subjective improvement (e.g., perceived reduction of snoring or apneic events) of OSA was not reached. On the other hand, if side effects were not acceptable for the patient (e.g., tooth pain or signs of temporomandibular disorders), the advancement was adjusted backwards to 75%, 60%, or 45%. No adjustments were made when the patient reported a sufficient efficacy without side effects. The patient returned to clinical practice at 6, 10, and 14 weeks after placement of the OA for this standardized titration protocol. After the titration

procedure was completed for each patient, they only returned when further adjustments were necessary, based on subjective impairments, viz., recurrent snoring or increasing excessive daytime sleepiness. The vertical dimension was not controlled in our patients using frontal elastics. Objective compliance was measured using a temperature-sensitive microsensor with on-chip integrated read-out electronics (Theramon, Handels- und Entwicklungsgeselschaft, Handelsagentur Gschladt, Hargelsberg, Austria). Temperature was recorded at a sampling rate of 1 measurement per 15 min, allowing data acquisition on usage for a consecutive 100-day period. A recorded temperature of >30°C indicated that the OA was worn. This microsensor was embedded in the OA at the lower right side. Data was extracted at 3 months (±2 weeks) using a dedicated reading station. Missing results in the adherence data is due to problems with the reading station of the microsensors. Our titration protocol is enclosed as supplementary material 1.

Outcome measures

The titration protocol was analyzed using different outcome measures. Polysomnographic response is presented by the AHI and ODI, and these parameters were used for assessment of therapy failure/success for OAT. Other measures were defined as patient's adherence to OA-treatment and self-reported side effects or discomfort resulting in termination of treatment. Adherence was defined as the percentage of daily use of ^{3}4h per night, during ^{3}5 nights per week. Adherence failure was defined as an inability of the patient to continue treatment for any reason mentioned by the patient. These outcomes were recorded during the adaptation period for each new position of the mandible. Adverse events were reported in accordance with the International Conference of Harmonization ICH E2A guidelines (Good Clinical Practices) by the principal investigators and evaluated by clinical data monitors.

Statistical analysis

Data were assessed on normality, both graphically using histogram-plots and by the Shapiro-Wilk test, and were analyzed and expressed as median (interquartile range) or mean ± SD for descriptive purposes. The presented variables were tested for differences using the Fisher Exact Test for categorical variables and the Wilcoxon Signed Rank test for continuous variables with a non-normal distribution. When comparing groups between specific titration positions, the Kruskal Wallis test was used in case of a non-normal distribution as an alternative for the ANOVA for normally distributed variables. Associations between continuous variables were described using Spearman's Rho correlation. A *P*-value <0.05 was considered statistically significant. The test used for the statistical analysis is mentioned in the manuscript when a *P*- value is provided (*T = t-test, W = Wilcoxon Signed Rank test, and H = Kruskal Wallis test).*

Results

A total of 36 patients were included and all completed the titration-protocol after three months. Six patients (16.7%) terminated OAT between 3 and 12 because of treatment-related reasons, and one patient (2.8%) was lost to follow-up (fig. 1). This study cohort showed a mean ± SD age of 50.0 ± 9.4 years, 25 patients were male (69%), and mean BMI was 27.5 ± 3.8 kg/m^2. At baseline, the AHI was 12.9 (9.1 – 16.7) events/hour of sleep and ODI was 10.0 (6.0 – 13.8) events/hour of sleep (table 1). BMI of the patients increased slightly after 3 and 12 months from 27.5 to resp. 27.9 (*T: -2.41; P* = .021) and 28.9 (*T: -2.790*; *P*= .009). After three months, 16 patients (44%) had their OA set at a 60% advancement level, while 20 of the OAs (56%) were set on an advancement level of 75%. The first evaluation of efficacy after three months by polysomnography with the OA *in situ* showed a statistically significant improvement in AHI; baseline AHI of 12.9 (9.1 – 16.7) events/h decreased after three months to 6.9 (3.7 – 10.3) events/h (*W: 5.388; P*< .001). When the protrusion level was evaluated after three months, the largest decrease in AHI and ODI was seen in patients set at an advancement level of 75%, which tended towards significance (*H: 3.778; P* = .052). None of the patients were titrated to 90% at the 3 months evaluation (Table 2). At long-term evaluation (twelve months), only 3 patients (8.3%) were still on 60% advancement, 41.7% (15 patients) were in 75% protrusion, and 30.6% (11 patients) of the OAs were set in a 90% advancement position. The AHI after twelve months decreased significantly to 5.0 (3.9 – 8.9) events/h compared to baseline AHI (*W: 5.073; P*<.001). Between 3 and 12 months, there was no significant difference in AHI (*W: .492; P* = .531). At 12 months, patients showed a trend towards the highest efficacy in the 75% advancement group compared to the 60% and 90% groups (*H: 5.928 P* = .052).

The different success definitions with their respective percentages are summarized in table 3. Treatment success defined as an AHI below 5 events per hour was achieved in 41.7% of the patients after 3 months, and in 51.7% after 12 months. Treatment success defined as an AHI decrease of more than 50% was seen in 55.2% of the patients after 12 months. If treatment success was defined by an AHI below 10, the population showed 75% treatment success after 3 months and almost 80% success after 12 months. A correlation analysis showed no significant correlation between AHI decrease after 3 and 12 months in comparison with the mandibular protrusion levels increased in this specific period, viz., .07 (*P* = .687) and .14 (*P* = .476), respectively.

Side effects of treatment

All patients completed the titration-protocol in the first three months. None of the patients ended treatment in the first 3 months because of discomfort or side effects due to OAT. Two patients encountered severe problems with OAT, for which titration was set back to 45% in the beginning, but at the evaluation period at three months with PSG, the titration was set again at 60%, after symptoms improved. One of these two patients had no decrease of AHI together with severe discomfort while wearing OA, and terminated the

study directly after the three months evaluation. The other patient could be motivated to continue therapy and eventually ended the study at 12 months successfully on a titration of 75% with good efficacy. After the three months evaluation with PSG, two patients terminated OAT because of severe discomfort in wearing the appliance, and three patients ended the study preliminary because of lack in efficacy with no desire to continue the protocol (no decrease AHI and persistent excessive daytime sleepiness). These patients did not report any discomfort. In total, six patients (17%) terminated OAT because of treatment-related reasons. One patient was lost to follow-up at nine months because of emigration.

Adherence

Median adherence (>4hrs, 5 nights a week) was 97.4% (61.4 – 100.00) after three months of OAT (N=33) and 100.0% (90.0 – 100.0) after twelve months (N=23). No differences were seen after three months between the different advancement levels (*H: 2.567; P*= .109). After 9 and 12 months of OA use, the median adherence was excellent (100%) in the 75% and the 90% titration groups. The few patients (n=2 and n=3) in the 60% titration group after 9 and 12 months showed lower adherence when compared to the 75% and the 90% groups (*H: 1.122; P*= .571) (fig. 2 and table 4).

Discussion

This is the first prospective study that evaluated a standardized step-wise titration-protocol for OAT in patients with mild and moderate POSA. It showed that this titration-protocol is effective in treating patients by significantly reducing AHI and ODI in short- and long-term analysis. The rate of adherence was high for the different advancement levels. After three months of treatment, no patients terminated the study, while after twelve months six patients (17%) stopped treatment because of adverse effects.

The treatment success of this protocol is in accordance with results available in the literature. Our treatment success (AHI decrease of ≥50%) is 50-55%, while in the literature 40-65% is reported.[23,16,24-26] It is as yet unknown whether OAT is more or less effective in supine-positioned OSA. Marklund et al. showed in a cohort of 26 patients that an OA would be more effective in supine-positioned OSA in comparison with non-positional OSA.[25] Chung et al. confirmed this hypothesis and concluded that the OAT is better in lowering AHI in position-dependant OSA compared to non-positional OSA.[24] However, more recently, a large retrospective cohort study of Sutherland et al. showed better results of OAT in non-positional OSA compared to patients with positional OSA, 36% vs. 59% for an AHI below 10.[26] When applying the definition of treatment success according to Sutherland et al. (AHI below 10), our success percentage was 75% after 3 months and almost 80% after 12 months. Another large cohort in non-positional patients showed a mean outcome of 52%.[23] For treatment cure (success defined as an

AHI decrease below 5 events per hour), our protocol achieved success in 41.7% after 3 months and in 51.7% after 12 months. Ferguson et al. found an average of 42% applying the same definition of success.[23] The different treatment outcomes between the above-cited studies and our study could be explained by patient selection or different titration protocols. Phenotyping can identify specific patient characteristics, e.g., BMI, neck circumference, age, and baseline AHI values. In addition, most of the above-cited studies do not report the specific titration protocol that was used. More recent study of Milano et al. showed the importance of controlling the vertical dimension of the OAT, especially in patients with POSA.[27] The OA with elastic fixation is significantly better in treating patients with POSA. In our study none of the patients received elastic retention.

The relatively good outcome of our study can be contributed to the fact that in this protocol the treating dentist was adjusting the OA to its most optimal protrusive position in several visits based on a combination of efficacy, subjective parameters, and objective adherence. In our population, the group of patients with an advancement of 75% had the most favourable outcome after three and twelve months compared to the other groups (60% and 90% advancement), yet this result showed no significance, possible due to the small sample size with a post-hoc power of 47.5%. Power calculation using our data shows a preferred group sample-size of n=39 per group to yield a power of 90. It can be reasoned that most patients will receive optimal treatment in 75% advancement, while in case of insufficient improvement, advancement to 90% can be considered. Available studies show an effective response on AHI already at a protrusion of 25%, but more response is achieved when the advancement is increased to 50% or 75%.[28,29] Thereby, our results show that 90% advancement is not always yielding the most effect on AHI. Our cohort showed an optimal position of 75% advancement in most patients. It could be advocated that further protrusion to 90% should only be considered in case of insufficient improvement with 75% protrusion and in case further protrusion is not contraindicated because of side effects.[16] No correlation was found in our cohort between the decrease in AHI and amount of mandibular protrusion. Therefore, every titration is based probably on other (yet unknown) individual characteristics and not mandibular protrusion.

This is the first study wherein objective adherence was assessed in relation to mandibular protrusion levels as dictated by efficacy and side effects. A limited number of studies report objective adherence data unrelated to a specific titration protocol; overall mean outcome of adherence in OAT was around 80%.[30] Our study shows similar outcome data of adherence at our different advancement levels. At twelve months, the adherence is better in the patients of the 75% and 90% groups compared to the 60% group; in other words, a better adherence is realised with more protrusion of the mandible. A possible explanation for this phenomenon could be that these patients are ambivalent to negative outcomes of the OAT (e.g., side effects) and are more motivated to reach an optimal treatment. On the other hand, patients who declined more advancement in their OA were less adherent.

Our study has some notable limitations. Although this study is part of an RCT, the proposed titration-protocol was not part of the initial research question. Therefore, this study lacks a control group and so this article demonstrates the *proof of concept* of our titration protocol rather than an analysis on possible superiority or non-inferiority. The review of Dieltjens et al. describes several titration protocols based on subjective, objective, or a combination of both outcomes and concludes that at present no gold standard titration protocol is available, and the titration of the OAT is based on "trial and error" procedure in daily clinical practice.[18] For future research, we propose using our standard *step-wise* titration protocol, so that different outcomes in subjective and objective improvement with the OAT can be evaluated using standardized outcome measures. Possible negative effects of OAT might be attributed to a suboptimal adjustment of the OA. This will also enhance comparability of research projects on OAT and provide insight in other variables that might influence the efficacy of OAT, like e.g. specific jaw dysmorphology or the vertical dimension of the OA.[28]

Conclusion

This standardized step-wise titration-protocol for OAT showed good efficacy, good OAT tolerance, and good objective adherence in mild to moderate POSA. Therefore, the protocol is recommended in research projects to improve the comparability between studies, and in clinical practice for its practical feasibility.

References

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC (2017) Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev 34:70-81. doi:10.1016/j.smrv.2016.07.002
2. Heinzer R, Petitpierre NJ, Marti-Soler H, Haba-Rubio J (2018) Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. Sleep Med 48:157-162. doi:10.1016/j.sleep.2018.02.011
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG (2005) Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 365 (9464):1046-1053. doi:10.1016/S0140-6736(05)71141-7
4. Bradley TD, Floras JS (2009) Obstructive sleep apnoea and its cardiovascular consequences. Lancet 373 (9657):82-93. doi:10.1016/S0140-6736(08)61622-0
5. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J (1999) The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med 340 (11):847-851. doi:10.1056/NEJM199903183401104
6. Marklund M, Franklin KA, Sahlin C, Lundgren R (1998) The effect of a mandibular advancement device on apneas and sleep in patients with obstructive sleep apnea. Chest 113 (3):707-713
7. Weaver TE, Grunstein RR (2008) Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 5 (2):173-178. doi:10.1513/pats.200708-119MG
8. de Ruiter MHT, Apperloo RC, Milstein DMJ, de Lange J (2017) Assessment of obstructive sleep apnoea treatment success or failure after maxillomandibular advancement. Int J Oral Maxillofac Surg. doi:10.1016/j.ijom.2017.06.006
9. Strollo PJ, Jr., Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP, Group ST (2014) Upper-airway stimulation for obstructive sleep apnea. N Engl J Med 370 (2):139-149. doi:10.1056/NEJMoa1308659
10. Cartwright RD (1984) Effect of sleep position on sleep apnea severity. Sleep 7 (2):110-114
11. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N (2006) The role of sleep position in obstructive sleep apnea syndrome. Eur Arch Otorhinolaryngol 263 (10):946-950. doi:10.1007/s00405-006-0090-2
12. Benoist L, de Ruiter M, de Lange J, de Vries N (2017) A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. Sleep Medicine 34:109-117
13. de Ruiter MHT, Benoist LBL, de Vries N, de Lange J (2018) Durability of treatment effects of the Sleep Position Trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial. Sleep Breath 22 (2):441-450. doi:10.1007/s11325-017-1568-4
14. Hoekema A, Stegenga B, De Bont LG (2004) Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. Crit Rev Oral Biol Med 15 (3):137-155
15. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, Marks GB, Cistulli PA (2013) Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 187 (8):879-887. doi:10.1164/rccm.201212-2223OC

16. Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, Cistulli PA (2014) Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med 10 (2):215-227. doi:10.5664/jcsm.3460

17. Aarab G, Lobbezoo F, Hamburger HL, Naeije M (2011) Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration 81 (5):411-419. doi:10.1159/000319595

18. Dieltjens M, Vanderveken OM, Heyning PH, Braem MJ (2012) Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. Sleep Med Rev 16 (2):177-185. doi:10.1016/j.smrv.2011.06.002

19. Doff MH, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LG, Stegenga B (2013) Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. Clin Oral Investig 17 (2):475-482. doi:10.1007/s00784-012-0737-x

20. Doff MH, Veldhuis SK, Hoekema A, Slater JJ, Wijkstra PJ, de Bont LG, Stegenga B (2012) Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. Clin Oral Investig 16 (3):689-697. doi:10.1007/s00784-011-0555-6

21. Dieltjens M, Vanderveken OM, Hamans E, Verbraecken JA, Wouters K, Willemen M, De Backer WA, Van de Heyning PH, Braem MJ (2013) Treatment of obstructive sleep apnea using a custom-made titratable duobloc oral appliance: a prospective clinical study. Sleep Breath 17 (2):565-572. doi:10.1007/s11325-012-0721-3

22. Benoist L, de Ruiter M, de Lange J, de Vries N (2017) A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. Sleep Med 34:109-117. doi:10.1016/j.sleep.2017.01.024

23. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W (2006) Oral appliances for snoring and obstructive sleep apnea: a review. Sleep 29 (2):244-262

24. Chung JW, Enciso R, Levendowski DJ, Morgan TD, Westbrook PR, Clark GT (2010) Treatment outcomes of mandibular advancement devices in positional and nonpositional OSA patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109 (5):724-731. doi:10.1016/j.tripleo.2009.11.031

25. Marklund M, Persson M, Franklin KA (1998) Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. Chest 114 (6):1630-1635. doi:10.1378/chest.114.6.1630

26. Sutherland K, Takaya H, Qian J, Petocz P, Ng AT, Cistulli PA (2015) Oral Appliance Treatment Response and Polysomnographic Phenotypes of Obstructive Sleep Apnea. J Clin Sleep Med 11 (8):861-868. doi:10.5664/jcsm.4934

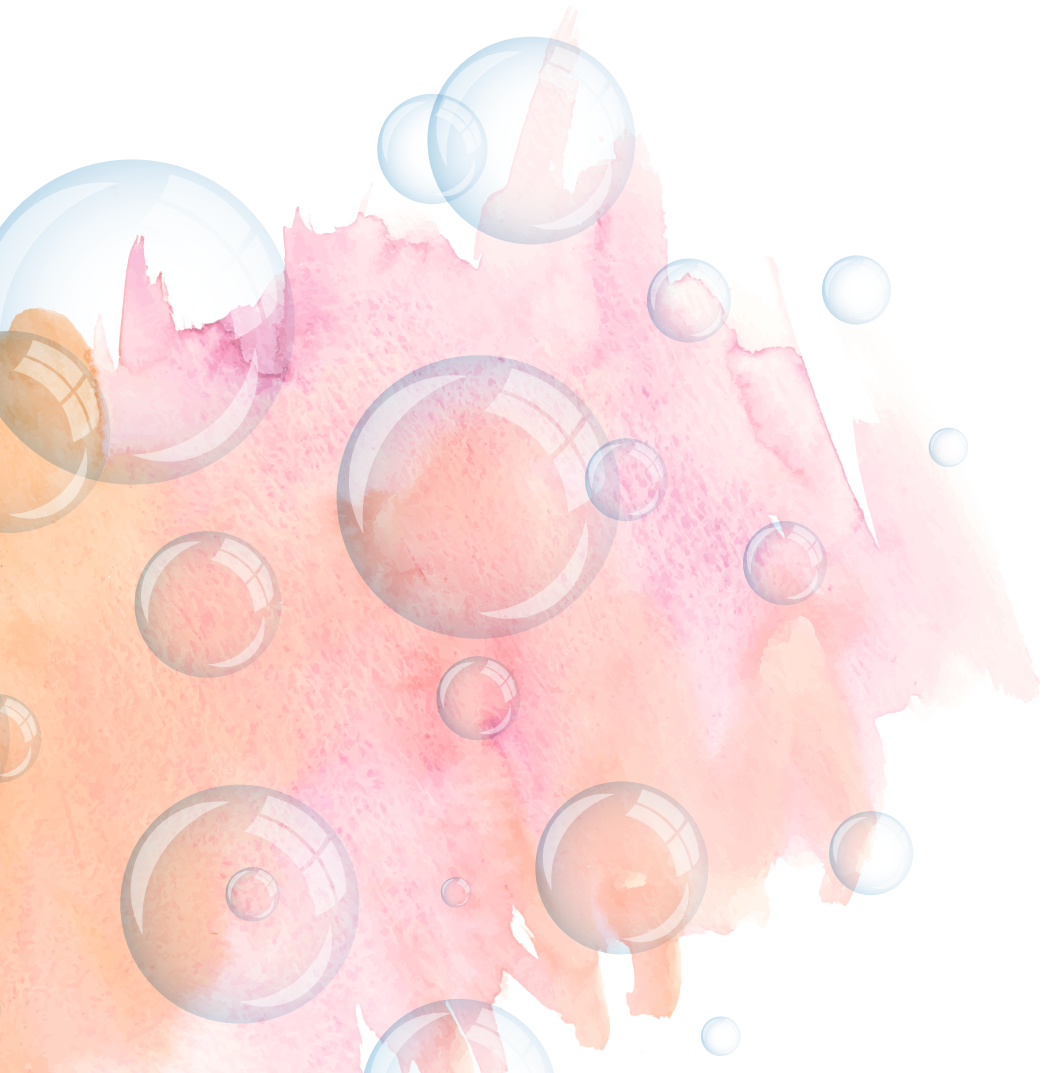
27. Milano F, Mutinelli S, Sutherland K, Milioli G, Scaramuzzino G, Cortesi A, Siciliani G, Lombardo L, Cistulli P (2018) Influence of vertical mouth opening on oral appliance treatment outcome in positional obstructive sleep apnea. J Dent Sleep Med 5 (1):17-23

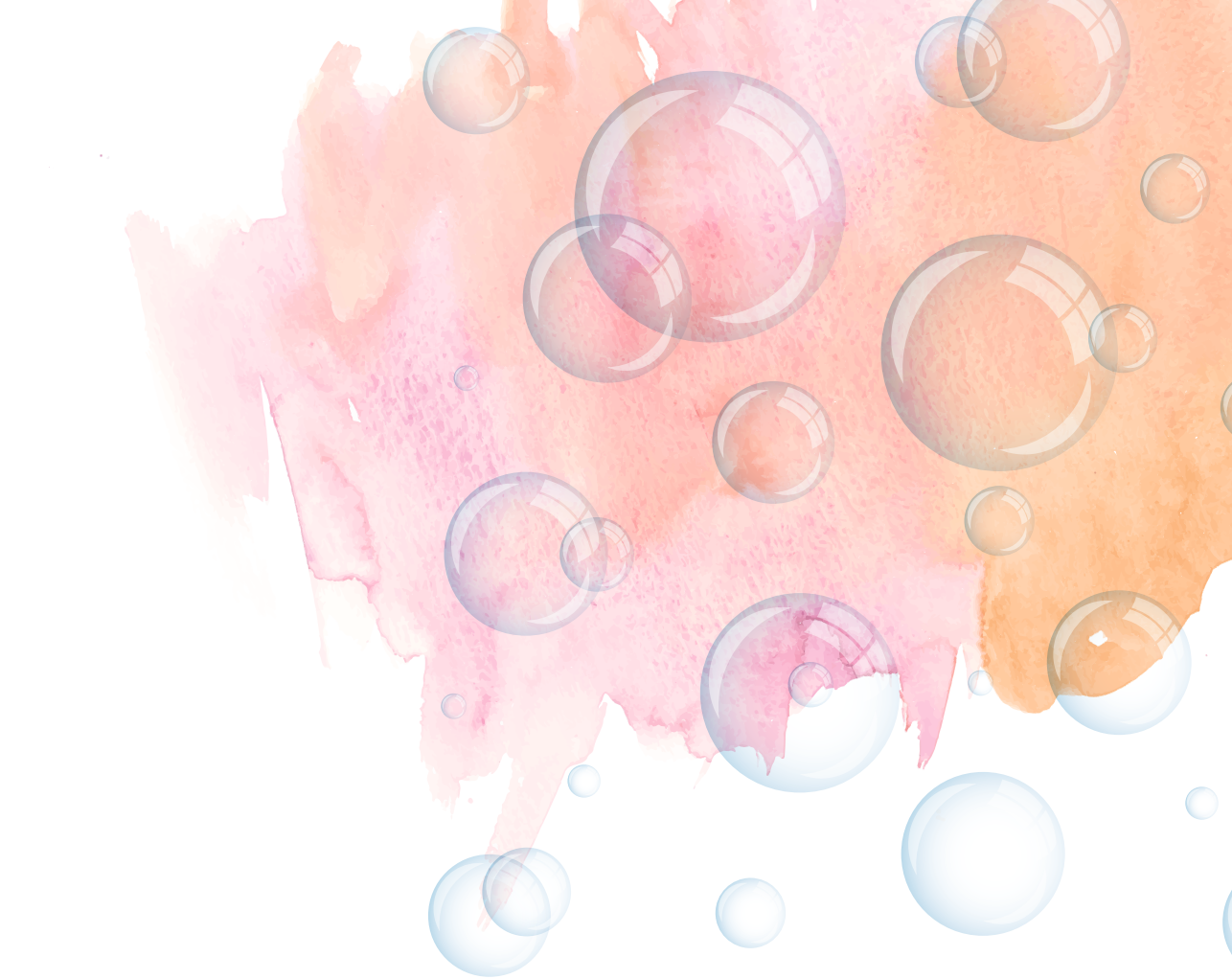
28. Aarab G, Lobbezoo F, Hamburger HL, Naeije M (2010) Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnea. Clin Oral Investig 14 (3):339-345. doi:10.1007/s00784-009-0298-9

29. Kato J, Isono S, Tanaka A, Watanabe T, Araki D, Tanzawa H, Nishino T (2000) Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. Chest 117 (4):1065-1072

30. Dieltjens M, Braem MJ, Vroegop A, Wouters K, Verbraecken JA, De Backer WA, Van de Heyning PH, Vanderveken OM (2013) Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. Chest 144 (5):1495-1502. doi:10.1378/chest.13-0613

CHAPTER 3





A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea

L.B.L. Benoist
M.H.T. de Ruiter
J. de Lange
N. de Vries

This chapter is based on the publication in: Sleep Medicine, 2017

Abstract

Objective

To compare the effectiveness of positional therapy (PT) with the sleep position trainer (SPT) to oral appliance therapy (OAT) in patients with mild-to-moderate positional obstructive sleep apnea
(POSA).

Methods

Multicenter, prospective, randomized, controlled trial. Patients with mild-to-moderate POSA (apnea-hypopnea index (AHI) 5 - 30/hour sleep) were randomized for PT or OAT. Polysomnography was repeated after 3 months. Efficacy, adherence, mean disease alleviation (MDA), quality of life, dropouts and adverse events were evaluated.

Results

A total of 177 patients were screened for the study; 99 underwent randomization and 81 completed the study. Intention-to-treat (ITT) analysis of median [IQR] AHI showed a reduction in the PT group from 13.0 [9.7e18.5] to 7.0 [3.8e12.8], $p < 0.001$ and in the OAT group from 11.7 [9.0e16.2] to 9.1 [4.9e11.7], $p < 0.001$. Mean adherence (4 h/night, 5 days/week) was 89.3 ± 22.4% for SPT versus 81.3 ± 30.0% in OAT patients, $p = 0.208$.

Conclusions

Oral appliance therapy and positional therapy were equally effective in reducing the median AHI in patients with mild-to-moderate POSA. The results of this study have important implications for future OSA treatment guidelines and daily clinical practice.

Introduction

Obstructive sleep apnea (OSA) has an overall prevalence of 9-38% in the general adult population, which is higher in men and rises with increasing age [1]. Obstructive sleep apnea is associated with daytime sleepiness, snoring, poor sleep quality, increased risk of cardiovascular disease, and motor vehicle accidents [2-5]. Conservative treatment starts with lifestyle alterations, such as weight reduction and avoidance of alcohol near bedtime, if applicable. In the case of position dependency, avoidance of the supine sleeping position is recommended. More aggressive treatment options include continuous positive airway pressure (CPAP) [6], oral appliance therapy (OAT) [7], and surgery, including upper airway stimulation [8]. All treatment modalities have their own specific indications, contraindications and side effects. Oral appliance therapy (OAT) is an established treatment for patients with mild-to-moderate OSA, both as a primary therapy and secondary treatment after CPAP failure. Oral appliance therapy often decreases the apnea-hypopnea index (AHI), with clinically relevant improvement [9]. When compared to CPAP, OAT has a non-inferior efficacy based on symptomatic response, although CPAP is more effective in reducing the AHI [10,11]. Although CPAP and OAT have different efficacy and compliance profiles, the overall therapeutic effectiveness is similar. Oral appliance therapy has better usage rates, while CPAP therapy is more efficacious [12]. The use of mean disease alleviation (MDA) enables calculation of overall therapeutic effectiveness; MDA is the product of the percentages for sleep time adjusted adherence and therapeutic efficacy measured by AHI reduction. Since MDA provides data that are a more comprehensive metric of clinical effectiveness, MDA has been preferred above reporting AHI alone for treatment evaluation in recent studies [13,14]. However, OAT might have various downsides. Petit et al. demonstrated that approximately one-third of patients screened for OAT had a contraindication that was mainly associated with insufficient tooth number and periodontopathy coupled with tooth mobility [15]. In addition, OAT may induce dry mouth, jaw discomfort and changes in teeth position and occlusion [9,16]. Selfreported compliance is high (75-100%), although compliance decreases over time [17]. In one previous study, estimated OAT use was 32% after four years [18]. Non-compliance is due to complications, side effects, or absence of beneficial effects [19]. The majority of patients with mild-to-moderate OSA have more apneic events in the supine position, as compared to non-supine positions [20e23].

Positional OSA (POSA) is defined as an apneahypopnea index (AHI) that is at least twice as high in the supine position as compared to non-supine positions [20]. The prevalence of POSA is 56%, with an additional 30% having more apneic events in the supine position, although not twice as much [24]. Promising results have recently been reported for active positional therapy (PT) with new smart and adaptive devices [14,25-27]. The sleep position trainer (SPT) is a device that is worn around the chest with a strap that gives vibro-tactile feedback on supine positions at minimum intensity. The SPT aims to eliminate sleep time in the supine position without disturbing sleep quality [25]. Positional therapy

with the SPT has improved sleep-related quality of life outcomes with an objectively measured adherence of 64.4% after six months of treatment [25,28]. It is well known that various patient factors have been associated with therapeutic outcome. For example, OAT has proven to be more effective in POSA patients compared to non-positional OSA patients [7,29,30]. It is believed that active PT has not directly been compared to OAT in the treatment of OSA. This multicenter, prospective, randomized study assessed the effectiveness of PT compared with OAT in mild-to-moderate POSA patients. The efficacy, adherence, MDA, quality of life and the side effects were evaluated after three months of therapy.

Materials and methods

Patients

Patients were recruited at the departments of Otolaryngology and Clinical Neurophysiology at OLVG West Hospital, Amsterdam. Patients were eligible for inclusion if they met the following criteria: mild-to-moderate positional OSA, defined as an AHI in supine position at least twice as high as compared with the AHI in non-supine position, with 10e90% of total sleep time (TST) in the supine position, and aged 18 years. Exclusion criteria were: inadequate dental status for wearing oral appliances, central sleep apnea, night or rotating shift work, severe chronic heart disease, active psychiatric disease, seizure disorder, medication usage for sleeping disorders, muscular or joint problems in head, neck or back area, previous treatment with OAT or SPT, simultaneous other OSA treatments, reversible morphological upper airway abnormalities (e.g., enlarged tonsils), pregnancy, self-reported severe snoring in the lateral position as a primary complaint, and coexisting non-respiratory sleep disorders (e.g., insomnia, periodic limb movement disorder, narcolepsy) that would influence functional sleep assessment.

Study design

In a multicenter, randomized, controlled trial, randomization was carried out centrally using a specialized computer system maintaining allocation concealment, stratified for BMI and, to a lesser extent, smoking. These two parameters were chosen as both factors could potentially contribute to sleep apnea. It was hypothesized that participants treated with PT would show equivalence in AHI compared with those treated with OAT. The physician and participant were not blinded to treatment arms. Primary outcome measures were assessed by overnight polysomnography (PSG) and scored manually by scorers blinded to therapy arm. The institutional Medical Ethics Committee of the OLVG West Hospital, Amsterdam and the Academic Medical Center Amsterdam approved the protocol. Written informed consent was obtained before enrollment. Independent monitors performed verification of documentation and source data.

Polysomnography

A digital PSG system (Embla A10, Broomfield, CO, USA) was used and recorded electroencephalogram (EEG) (FP2-C4/C4-O2), electro-oculogram (EOG), electrocardiogram (ECG) and submental and anterior tibial electromyogram (EMG). Nasal airflow was measured by a nasal pressure cannula, and blood oxygen saturation was measured by finger pulse oximetry. Straps containing piezoelectric transducers recorded thoracoabdominal motion, and a position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions. The recorded data were analyzed using special software (Somnologica ™ studio, OLVG West Hospital, Amsterdam) and manually edited. Apnea was defined as the cessation of nasal airflow of more than 90% for a period of 10 s in the presence of respiratory efforts. In accordance with the prevailing definition from the American Academy of Sleep Medicine (AASM) at that time, a hypopnea was scored whenever there was a >30% reduced oronasal airflow for at least 10 s, accompanied by 4% oxygen desaturation from prevent baseline.

Study treatment

Participants were assigned either to the SPT or OAT after stratified randomization. The SPT (SPT-DEV-PX-11.08) of Night-Balance™ (NightBalance B.V., The Hague, The Netherlands) is a small lightweight device (72 35 10 mm; 25 g) worn across the chest using a neoprene strap (Fig. 1). The sensor contains a lithium polymer battery cell of 3.7 V and 180 mAh, a 3.2 G vibration motor and a protection circuit integrated in the printed circuit board. A three-dimensional digital accelerometer is used to determine body position. The SPT gives a soft vibration when supine position is detected, in order to urge a patient to change body position. Treatment is divided into three phases. During the first two nights, the SPT analyzes body position without giving active feedback. During the following seven nights, the SPT trains the patient by vibrating in an increasing percentage of episodes while in the supine sleeping position. If the patient does not change position, the SPT will vibrate again after 2 min. At day 10, the full therapy phase begins, in which the SPT will vibrate every time the patient is in the supine sleeping position. The SPT has a USB port to recharge the internal battery and to upload data to an online self-monitoring system that can also be accessed by the patient and physician.

Figure 1 Sleep position trainer (SPT) SPT-DEV-PX-11.08 of NightBalance™

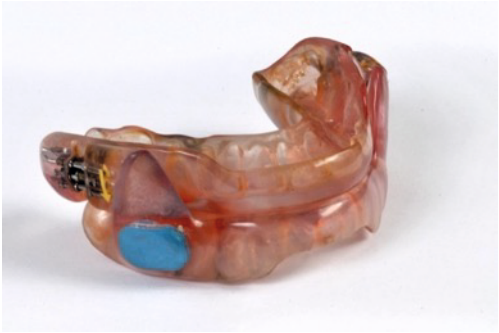


Figure 2 Oral appliance, type SomnoDent flex, SomnoMed, with Orthosmart, TheraMon chip (blue).

In the present study, OAT was carried out using a custom-made titratable device (SomnoDent flex, SomnoMed™, Sydney, Australia) (Fig. 2). The device was worn intraorally and had a soft inner liner that supported comfort and maintained retention. The OAT was adjusted individually and advancement was titrated using a standard titration protocol [31]. After adequate assessment of the central relation and maximum protrusion using a construction bite with the George Gauche instrument, the OAT was set at 60% advancement at baseline. At each consecutive visit, the OAT was evaluated and advanced to 75%, or 90% if necessary. On the other hand, if side effects were not acceptable for the participant (e.g., tooth pain or signs of temporomandibular dysfunction) the advancement was adjusted backwards to 75, 60 or 45%. Objective compliance was measured using a temperature-sensitive microsensor with on-chip integrated read-out electronics (Theramon®, Handels-und Entwicklungsgeselschaft, Handelsagentur Gschladt,Hargelsberg, Austria). Temperature was recorded by the microsensor at a sampling rate of one measurement per 15 min, allowing data acquisition on usage for a consecutive 100-day period. A recorded temperature of 30 C indicated that the OAT was worn [32]. This microsensor was embedded in the OAT at the lower right side. Data were extracted at three months (±2 weeks) using a dedicated reading station.

Study end points

The primary outcome measure was AHI. Secondary outcomes were other respiratory indices, including oxygen desaturation index (ODI) (4% decrease in oxygen saturation), and percentage of supine sleep time. Other outcome measures were subjective improvement in daytime sleepiness, measured with the Epworth Sleepiness Scale (ESS) (overall score between 0 and 24, a score <10.0 is regarded as normal) [33], and the Functional Outcomes of Sleep Questionnaire (FOSQ) (global score ranging from 5 to 20, the lower the score the more dysfunctional the individual secondary to sleepiness) [34]. Furthermore, adherence and mean disease alleviation (MDA) were addressed. Adherence was defined as the percentage of daily use of 4 h per night, during 5 days per week [35]. The MDA (%) was calculated by the product of the percentages for adjusted compliance and therapeutic efficacy, divided by 100. Within this definition, adjusted compliance was defined as the

percentage of daily use (4 h/night, 5 days/week) adjusted for sleep time (recorded by PSG) and limited to 100%. Therapeutic efficacy is defined as the AHI baseline minus AHI with therapy, expressed as a percentage [13].

Adverse events

Adverse events were reported in accordance with the International Conference of Harmonization ICH E2A guidelines (Good Clinical Practices) by the principal investigators and evaluated by clinical data monitors [36].

Statistical analysis

Descriptive statistics and inferential statistics were used. A Kolmogorov-Smirnov test, Q-Q plot and Levene's test first tested all data for normality. Categorical and dichotomous variables were expressed as n (%). Normally distributed continuous variables were expressed by their mean and standard deviation (SD) and tested with the independent samples Student's t-test. Skewed distributed data were expressed by their median and interquartile range [IQR] and tested with the independent samples Mann-Whitney U test or Wilcoxon signed-rank test. Significance level was set at $p < 0.05$. Statistical analysis was performed using SPSS Statistical software (version 21.0, SPSS Inc., Chicago, IL). Both intention-to-treat (ITT) (n=99) and per-protocol (PP) (n=81) analyses were executed for the main outcome parameters. For ITT analyses, none of the patients could be excluded, and patients were analyzed according to the original randomization. Therefore, missing data, in case of dropout, were imputed from baseline to the 3-month values.

Results

Characteristics

A total of 177 patients were screened (70.7% men, age 48.3 ± 10.1 years; BMI 27.6 ± 3.8 kg/m2), of whom 99 underwent randomization (Fig. 3). Participant characteristics are shown in Table 1. Both groups were similar in the baseline characteristics of age, gender, BMI, AHI, percentage supine time and TST. A total of 81 participants (81.8%) completed the 3-month follow-up. Most dropouts, including withdrawal, were seen in the OAT group (15 versus 3) (Fig. 3).

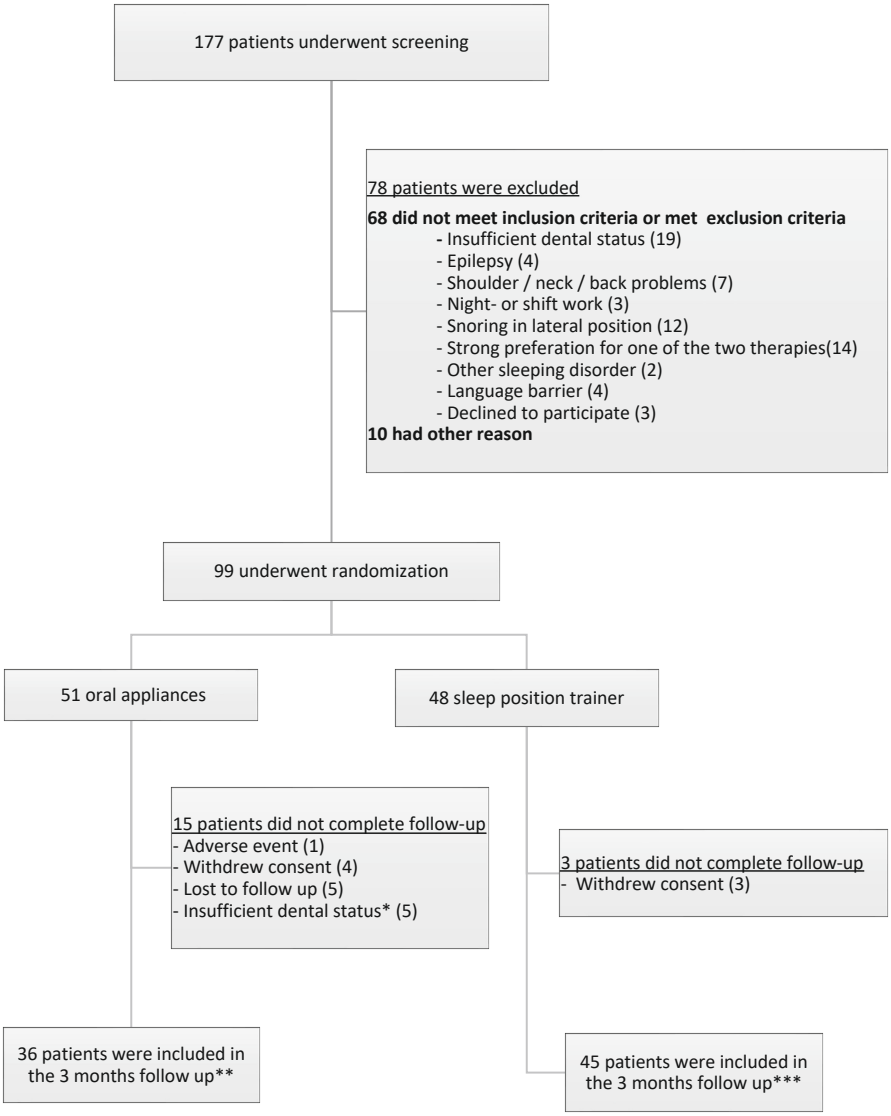


Figure 3 Study enrollment

Overview of screening (enrollment), randomization and 3-month follow up
*Although insufficient dental status was an exclusion criteria, a dentist checked this through regular physical examination. Some dental problems were only visualized after the orthopantomography was made.
** Adherence data for the OAT was retrieved in 32 patients since there was a technical error with the chip in four patients.
*** Adherence data for the SPT was retrieved in 43 patients since one patient did not show at his follow up visit after his 3-month PSG, for exporting the data. The other patient did not use the SPT during the 3-month PSG.

Table 1 Characteristics of the study population at baseline (n=99)

	SPT N=48	MRA N=51	**P-value**[a,b]
Male sex, no. (%)	34 (70.8)	36 (70.6)	**0.979**
Age, yr.	47.3 ± 10.1	49.2 ± 10.2	**0.347**
BMI, kg/m²	27.5 ± 2.9	27.7 ± 4.5	**0.797**
Neck circumference, cm	38.0 ± 3.6	37.7 ± 3.2	**0.624**
Smoking, no. (%)	11 (22.9)	12 (23.5)	**0.943**
Alcohol			
≤2 EH/day, no. (%)	45 (93.7)	48 (94.1)	**0.499**
>2 EH/day, no. (%)	3 (6.3)	3 (5.9)	
Blood pressure, mmHg			***0.032***
Systolic	135.0 [125.0-150.0]	130.0 [120.0-140.0]	***0.033***
Diastolic	90.0 [80.0-97.5]	85.0 [80.0-90.0]	**0.530**
Pulse, bpm	69.0 [64.0-78.0]	72.0 [66.0-80.0]	**0.318**
AHI, events/h	13.0 [9.7-18.5]	11.7 [9.0-16.2]	**0.687**
AHI supine, events/h	27.0 [18.7-43.1]	25.8 [17.4-35.0]	**0.575**
percentage supine sleep	44.5 [30.0-55.5]	39.0 [26.0-54.0]	

Mean ± SD standard deviation. Median [Q1eQ3]. AHI, apnea hypopnea index; BMI, body mass index; OAT, oral appliance therapy; SPT, sleep position trainer.
a Independent t-test.
b Mann Whitney U test.

Primary outcome

Intention-to-treat

In an ITT analysis, including dropouts, the median AHI in OAT decreased from 11.7 [9.0-16.2] to 9.1 [4.9-11.7], $p < 0.001$, and in SPT patients from 13.0 [9.7-18.5] to 7.0 [3.8-12.8], $p < 0.001$. These results are graphically illustrated in Fig. 3. No significant between-group difference was seen at 3 months, $p = 0.535$ (Table 2).

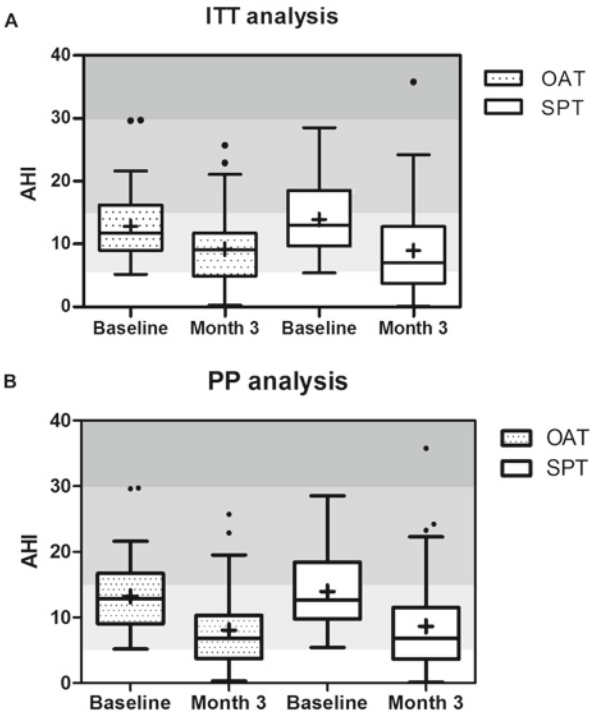


Fig. 3. a and b). Intention-to-treat and per-protocol analysis for primary outcome AHI reduction. Overall apnea-hypopnea index (AHI) for OAT and SPT. The different gray scales represent the levels of sleep apnea severity, ranging from normal nocturnal breathing (AHI <5/hour sleep), mild OSA (AHI 5e15/hour), moderate OSA (AHI 15e30/hour), to severe OSA (AHI >30/hour). Box plots are displayed for the two different study nights subdivided for OAT (spotted fill) and SPT (blanc fill). The 25th and 75th percentiles are represented by the upper and lower margins, the mean values by the cross, and the median values by the horizontal line. Whiskers represent the maximum value (top) and the minimum value (bottom) of the dataset. Outliers are represented by a closed dot.

Table 2 primary and secondary outcome measures, per-protocol analysis (n=81)

	Sleep position trainer n=45				Oral appliance therapy n=36				
Outcome	**Baseline**	**3 months**	**Change**	**p Value[a]**	**Baseline**	**3 months**	**Change**	***p* Value[a]**	***p* Value[b]**
Primary outcomes									
Total AHI, events/h	13.9 ± 5.9 12.7 [9.8-18.4]	8.7 ± 7.4 6.8 [3.7-11.5]	-5.3 ± 6.4 -5.4 [-9.8 - -1.5]	***0.000***	13.2 ± 6.0 12.9 [9.1-16.7]	8.1 ± 5.9 6.9 [3.7-10.3]	-5.2 ± 5.8 -5.1 [-7.9 - -2.4]	***0.000***	0.875
AHI supine, events/h	31.0 ± 17.2 26.0 [18.8-42.1]	19.6 ± 22.5 12.3 [0.1-32.8]	-11.4 ± 18.2 -14.3 [-23.4- -2.3]	***0.000***	32.3 ± 19.3 27.7 [16.5-42.4]	17.7 ± 13.4 15.0 [6.0-27.0]	-14.5 ± 18.1 -10.6 [-23.7 - -4.4]	***0.000***	0.394
AHI *non*-supine, events/h	4.0 ± 3.3 3.4 [1.7-5.6]	6.2 ± 6.0 4.3 [1.9-9.2]	2.2 ± 6.2 1.3 [-1.3 - 4.1]	***0.016***	3.7 ± 3.0 3.2 [0.9-5.3]	4.0 ± 5.7 1.9 [0.8-4.7]	0.2 ± 5.6 -0.5 [-3.1- 1.8]	0.402	***0.005***
ODI, oxygen desaturation Index	11.6 ± 5.8 10.0 [7.0-15.5]	7.5 ± 6.6 5.0 [3.0-10.0]	-4.3 ± 6.0 -3.0 [-7.0 - -1.0]	***0.000***	10.4 ± 6.0 10.0 [6.0-13.8]	7.3 ± 5.4 6.5 [4.0-9.0]	-3.1 ± 5.4 -3.0 [-6.0 - -1.0]	***0.001***	0.689
Percentage supine sleep	42.4 ± 17.4 43.0 [30.0-54.0]	14.4 ± 14.7 11.0 [1.0-22.5]	- 28.0 ± 20.0 -31.0 [-41.0 - -16.0]	***0.000***	39.9 ± 20.3 34.0 [25.0-56.3]	38.9 ± 25.7 32.0 [16.8-57.8]	-0.9 ± 19.6 -1.0 [-9.8 - 8.0]	0.922	***0.000***
Sleep efficiency	89.6 ± 8.2 92.0 [85.0-95.5]	89.8 ± 7.1 91.0 [86.0-95.0]	0.36 ± 9.2 0.5 [-0.5 - 6.0]	0.617	88.9 ± 7.7 90.5 [86.0-95.0]	87.3 ± 11.0 91.0 [84.0-95.5]	-1.6 ± 9.3 0.0 [-5.0 - 2.0]	**0.448**	0.526
Secondary outcomes									
Epworth Sleepiness Scale score (/24)	8.5 ± 5.3 8.0 [5.0-12.0]	8.1 ± 4.8 7.0 [5.0-10.0]	-0.4 ± 3.9 0.0 [-2.0 - 2.0]	0.836	8.1 ± 5.4 7.0 [4.0-11.0]	6.0 ± 4.6 5.0 [3.0-8.0]	-1.2 ± 3.6 -2.0 [-3.0 - 1.0]	0.112	***0.035***
FOSQ score	15.2 ± 3.8 16.4 [12.9-18.1]	15.3 ± 4.2 16.2 [13.1-18.6]	0.3 ± 2.9 1.0 [-1.8 - 2.0]	0.590	15.5 ± 3.5 15.8 [12.4-18.3]	15.2 ± 3.7 15.8 [12.5-18.8]	-0.5 ± 2.3 -0.2 [-2.0 - 1.0]	0.332	0.814

Mean ± SD.Median [Q1, Q3].
AHI, apnea hypopnea index; FOSQ, Functional Outcomes of Sleep Questionnaire; ITT, intention-to-treat; ODI, oxygen desaturation index; PP, per-protocol.
a Wilcoxon signed rank test.
b Mann Whitney U Test at 3 months.
Per-protocol analysis
The PP analysis showed that the AHI dropped from 12.4 [9.1-17.2] to 6.8/hour sleep [3.7-10.8], p < 0.001. No significant between-group differences were seen in AHI reduction, p = 0.875. The median AHI in the SPT group dropped from 12.7 [9.8-18.4] to 6.8/hour sleep [3.7-11.5] (46.5%, p < 0.001) and in the OAT group from 12.9 [9.1-16.7] to 6.9/hour sleep [3.7-10.3] (46.5%, p < 0.001). For the 3-month PSG, 13 participants were titrated at 60% and 23 at 75%. Objective outcome measures for PP analysis, as well as other sleep parameters, are shown in Table 2.

Secondary outcomes

Respiratory indices

The ODI was lower in both groups at three months than at baseline, p=0.689, with an equal improvement. Both percentage of supine sleep and the AHI in supine position dropped in the total sample from 41.0 [26.0-54.0] to 19.0% [8.0-35.5] (p < 0.001) and 26.0 [17.8-40.1] to 13.0/hour sleep [4.6-27.5] (p < 0.001), respectively. Sleep efficiency did not change: 92.0 [86.0-95.0] to 91.0% [85.3-95.0], p = 0.928. Median percentage of supine sleep time, as recorded by PSG, decreased significantly in the SPT group from 43.0 [30.0-54.0] to 11.0% [1.0-22.5], p < 0.001. For OAT, median percentage supine sleep time remained unchanged from 34.0 [25.0-56.3] to 32.0% [16.8-57.8], p=0.922. The median percentage of supine sleep time per night over the three-month period, as recorded by the SPT, is depicted in Fig. 4.

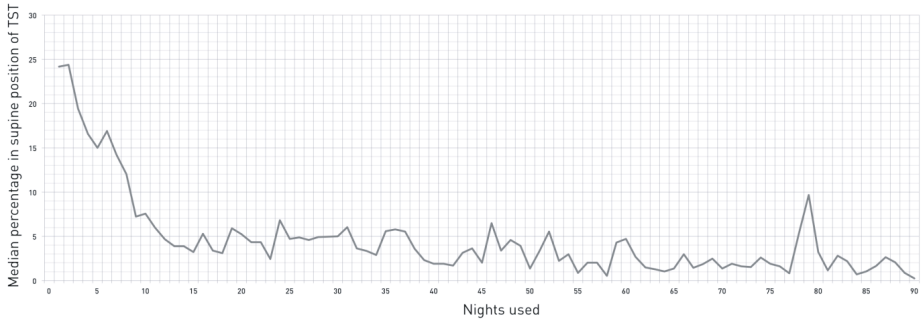


Figure 4

Median percentage of sleep time in the supine position per night. The first 9 days of the SPT therapy are part of the training program in which the SPT gradually decreases the number of times in which patients can sleep on their backs.

Adherence and mean disease alleviation

Mean adherence (4 h/night, 5 days/week) for PP analysis over three months was similar in both groups, 89.3 ± 22.4% for SPT versus 81.3 ± 30.0% in OAT patients, p = 0.208 (Table 3). Mean adjusted compliance for ITT analysis was 88.4% and 60.5% for SPT and OAT, respectively, with an efficacy of 36.3% vs 28.0%. Combining these numbers gives a calculated MDA of 33.2% for SPT and 23.6% for OAT, p = 0.215. For the PP analysis, mean adjusted compliance for SPT was 96.0% and for OAT 88.8%, the efficacy 38.7% (SPT) vs 39.6% (OAT) and, hence, MDA 36.1% for SPT and 34.7% for OAT in the continuing users. This difference in MDA was not significant, p = 0.879.

Table 3

Mean disease alleviation (n = 81).	SPT N = 45	OAT N = 36	p[a]
Adherence (4 h/night, 5 days/week), %	89.3 ± 22.4	81.3 ± 30.0	0.208
Adjusted compliance[b], %	96.0 ± 10.1	88.8 ± 29.5	0.199
Therapeutic efficacy, %	38.7 ± 41.9	39.6 ± 35.9	0.912
Mean disease alleviation, %	36.1 ± 37.7	34.7 ± 35.4	0.879

Mean ± SD standard deviation.
OAT, oral appliance therapy; SPT, sleep position trainer; TST, total sleep time.
a Independent t-test.
b Used nightly hours as percentage of polysomnography-derived TST.

Questionnaires

Questionnaires were collected at baseline and three months. In the OAT group, fully completed questionnaires at three months were collected in 80.6% (n = 21/36) for the ESS and in 58.3% (n = 29/36) for the FOSQ. For SPT these percentages were 88.9 (n = 40/45) and 64.4 (n = 29/45) for the ESS and FOSQ, respectively. In both treatment groups, no clinically relevant change in quality of life, as measured with the FOSQ, was found. A minimal increase in mean FOSQ score was seen in the SPT arm (15.2 ± 3.8 to 15.3 ± 4.2). For OAT the mean FOSQ score dropped minimally from 15.5 ± 3.50 to 15.2 ± 3.7. A significant between-group difference was observed in mean ESS score at three months (8.1 ± 4.8 vs 6.0 ± 4.6, p = 0.035) for SPT and OAT, respectively.

Adverse events

In total, 97 adverse events (AEs) were reported; 40.2% were device-related. In OAT, AEs (eg, pain/sensitive teeth, dry mouth, occlusion problems) occurred in 26.8% (n = 26). In the SPT group, 13.4% (n = 13) reported AEs (e.g., vibro-tactile feedback disturbs sleep quality or wakes up partner, discomfort). Other AEs were: persistent snoring (22.7%; 12 SPT, 10 OAT); persistent tiredness (21.6%; 10 SPT, 11 OAT), other sleeping disorder (5.2%; 3 SPT, 2 OAT), and shoulder/joint complaints (3.1%; 3 SPT).

Discussion

It is believed that this is the first article on three-month results of an effectiveness and efficacy comparison of SPT with OAT in patients with mild-to-moderate positional OSA. The SPT and OAT were equally effective in reducing the AHI and ODI. In the samples, higher adherence and MDA (efficacy, adherence) values were observed for the ITT analysis in the SPT group compared to OAT. Earlier studies on short-term results (one month) of the SPT showed a reduction in AHI from 39% to 68% [14,25,27]. The SPT results in the present study were in agreement with this, although the follow-up period in the present study (three months) was longer. OAT has been extensively investigated, being effective in improving respiratory indices [11]. In the current study, the AHI in OAT dropped 46.5%; this is in line with the earlier literature [7]. In reporting treatment outcomes in OSA, there is an essential difference in efficacy and effectiveness [12,37,38]. Efficacy reflects the reduction in apneic events when a device is actually used. Effectiveness also takes adherence into account and is a better reflection of the real success of the treatment. Suboptimal adherence results in less effectiveness. Continuous positive airway pressure, for example, is highly efficacious when used, but the majority of patients have adherence problems that result in poor usage [35,39,40]. In fact, 29e83% of patients using CPAP are nonadherent [2,41-43]. In general, OAT has higher usage rates than CPAP treatment, but is less effective [12,13]. Objective adherence monitoring of OAT is possible by using microsensors thermometers embedded in the OA [7]. In a prospective trial, an objective adherence (4 h/night, 5 days/week) of 84% was measured in 51 patients with OSA using OAT over a three-month period [13]. These results are in line with the findings in the present study, where the mean adherence (4 h/night, 5 days/week) was 81.3 ± 30% for OAT participants.

New-generation PT, with chest-worn devices providing vibrotactile feedback if the supine position is adopted, is gaining renewed interest. Short-term [14,25] and long-term [28] objective adherence with SPT have been previously described. Van Maanen et al. reported a median adherence (4 h/night, 7 days/week) after one month and six months of 92.7% and 64.4%, respectively. Another study looked at adherence of SPT in comparison with the tennis ball technique and demonstrated that after 1 month, the reduction in AHI was similar, but adherence (4 h/night, 5 days/ week) was significantly better in the SPT group, 75.9% vs 42.3%, p . 0.01 [14]. The present study observed higher mean objective adherence (4 h/night, 5/week) over the study period of three months in SPT participants as compared with the OAT group (89.3% vs 81.3%, p . 0.208).

Objective measurement of therapy adherence is becoming standard clinical practice. A combination of adherence with efficacy results in the calculation of MDA as a measure of effectiveness. An MDA for OAT of 51.1% and 54.9%, respectively, were reported in two studies [13,44]. Another study reported an MDA for the SPT of 70.5% [14]; MDA has also been reported for OAT and CPAP. Although in general OAT is inferior to CPAP in reducing

respiratory indices, adherence on the other hand is higher, resulting in similar overall MDA [10,12]. Recently, Dieltjens et al. identified that a more pronounced decrease in reports of snoring and the presence of dry mouth were the two parameters that were correlated with higher objective compliance during OAT [45]. In the present study, ITT analysis showed higher MDA at three months in the PT group (37.2% for SPT vs 28.9% for OAT), while per-protocol analysis numbers were similar (40.3% for SPT and 42.5% OAT). Both results, however, were not significantly different between the groups. When comparing SPT with OAT, SPT seems to have several advantages: it is well tolerated and reversible [28], and a daily readout of number of corrections and remaining percentage of supine position is available online for patients. A disadvantage may sometimes be continued snoring in the lateral position. Advantages of OAT are its efficacy and preference. Disadvantages of OAT are more reported side effects [7] and also limited inclusion because of dental status. In the case of insufficient effect, the custom-made OAT cannot be returned and used by someone else. The devices can be combined with each other or with other treatments, if needed.

For POSA patients with a partial response to OAT, combination therapy (adding PT to OAT) has already been shown to further decrease OSA severity in an earlier study; OAT and SPT were equally effective in reducing the AHI. The combination of OAT and PT gave an additional statistically significant AHI reduction [27]. In the present study population, adding PT to the OAT group could have potentially improved the AHI by eliminating the non-supine AHI. For patients using SPT, the AHI will likely decrease in all sleeping positions when OAT is added. Follow-up studies are needed to evaluate the effect of combination therapy. Vanderveken also recently highlighted the importance of combining different treatment options for OSA [46]. Additional effects of PT after partial effective surgery have also been recently reported [47].

The results of this study have important implications for future OSA treatment guidelines and daily clinical practice, where the potential of PT is still undervalued [23]. According to the findings, mild and moderate POSA patients with similar characteristics could benefit from both PT and OAT.

Limitations

Several limitations for this study should be considered. Eighteen of the 99 participants dropped out. Nonetheless, power analysis suggested a minimum sample size of 36 participants per study arm (to reach a power of 80%), which was achieved despite the dropouts. Orthopantomography was not routinely performed before randomization to identify unsuitable patients for OAT. One third of the OAT dropouts were lost to follow-up, perhaps due to the fact that the custom-made titratable device had to be fitted and manufactured at the next visit, and titrated afterwards elsewhere, which might have caused a delay in patient intake and diminished patient commitment.

While the study participants, on average, had mild POSA with limited self-reported sleepiness, it is believed that the results of this study could be generalized to patients with mild-to-moderate POSA in Western populations. Future studies will need to investigate whether a stepped-care approach is feasible and will result in higher quality of life of patients and increased cost-effectiveness of treatment.

Conclusion

Results of this first RCT comparing respiratory indices and MDA between OAT and SPT indicate that after three months, OAT and PT are equally effective in reducing the AHI in mild-to-moderate POSA patients. It is believed that the results of this study have important implications for future OSA treatment guidelines and daily clinical practice. Additionally, long-term results still have to be determined.

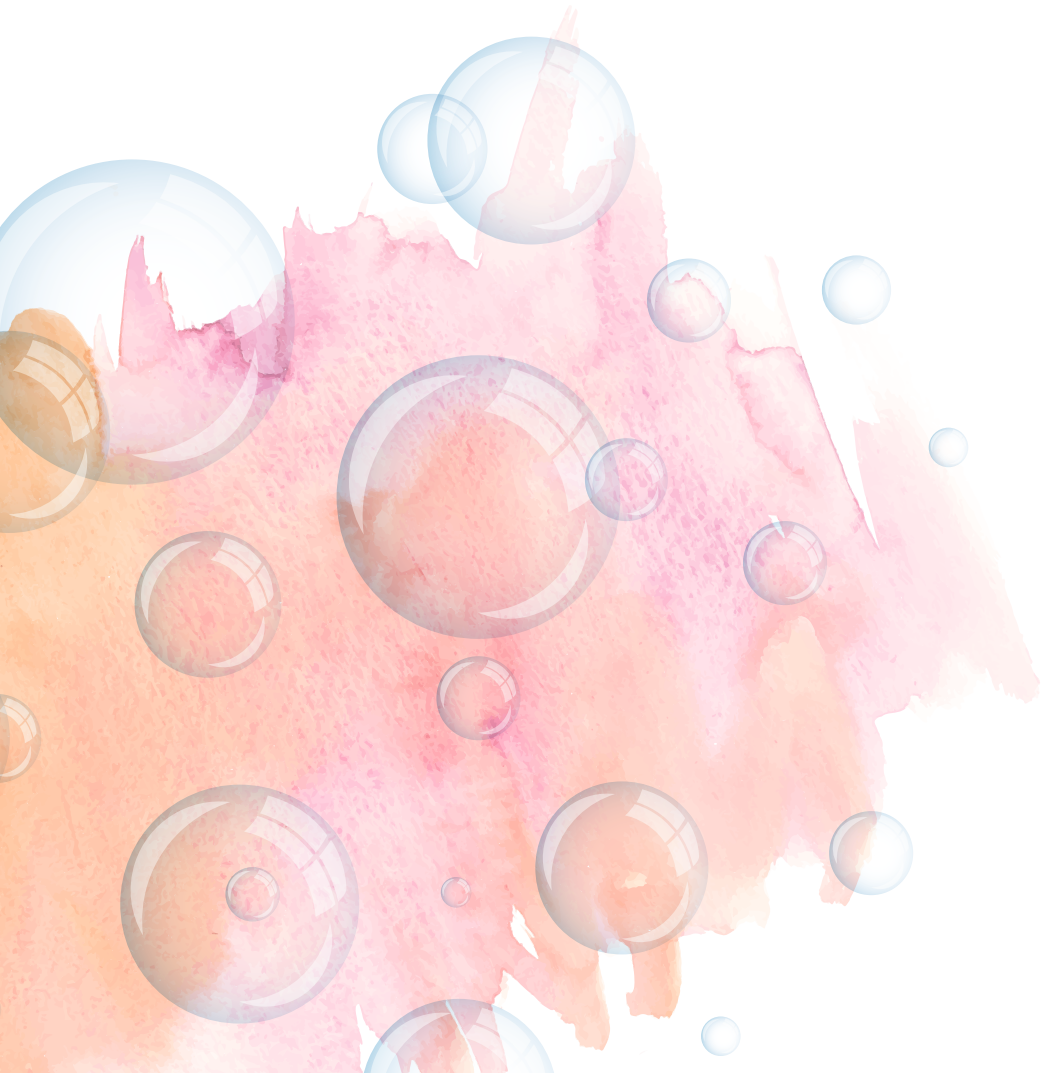
References

1. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 2016. http:// dx.doi.org/10.1016/j.smrv.2016.07.002 [Epub ahead of print].
2. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016;375:919e31.
3. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046e53.
4. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010;182:269e77.
5. Kendzerska T, Mollayeva T, Gershon AS, et al. Untreated obstructive sleep apnea and the risk for serious long-term adverse outcomes: a systematic review. Sleep Med Rev 2014;18:49e59.
6. Sullivan CE, Issa FG, Berthon-Jones M, et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981;1:862e5.
7. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med 2014;10:215e27.
8. Strollo PJJ, Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med 2014;370:139-49.
9. Hoekema A. Efficacy and comorbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review and preliminary results of a randomized trial. Sleep Breath 2006;10:102-3.
10. Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2013;187:879-87.
11. Lim J, Lasserson TJ, Fleetham J, et al. Oral appliances for obstructive sleep apnoea. Cochrane Database Syst Rev 2004:CD004435.
12. Sutherland K, Phillips CL, Cistulli P. Efficacy versus effectiveness in the treatment of obstructive sleep apnea: CPAP and oral appliances. JDSM 2016;3: 175e81.
13. Vanderveken OM, Dieltjens M, Wouters K, et al. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. Thorax 2013;68:91-6.
14. Eijsvogel MM, Ubbink R, Dekker J, et al. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. J Clin Sleep Med 2015;11:139-47.
15. Petit FX, Pepin JL, Bettega G, et al. Mandibular advancement devices: rate of contraindications in 100 consecutive obstructive sleep apnea patients. Am J Respir Crit Care Med 2002;166:274-8.
16. Chung JW, Enciso R, Levendowski DJ, et al. Treatment outcomes of mandibular advancement devices in positional and nonpositional OSA patients. Oral Surg Oral Med Oral Pathol Oral Radiol 2010;109:724-31.
17. Lindman R, Bondemark L. A review of oral devices in the treatment of habitual snoring and obstructive sleep apnoea. Swed Dent J 2001;25:39-51.
18. Rose E, Staats R, Schulte-Monting J, et al. [Long term compliance with an oral protrusive appliance in patients with obstructive sleep apnoea]. Dtsch Med Wochenschr 2002;127:1245-9.
19. McGown AD, Makker HK, Battagel JM, et al. Long-term use of mandibular advancement splints for snoring and obstructive sleep apnoea: a questionnaire survey. Eur Respir J 2001;17:462-6.

20. Cartwright RD. Effect of sleep position on sleep apnea severity. Sleep 1984;7: 110-4.
21. Cartwright RD, Diaz F, Lloyd S. The effects of sleep posture and sleep stage on apnea frequency. Sleep 1991;14: 351-3.
22. Oksenberg A, Silverberg DS, Arons E, et al. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. Chest 1997;112:629e39.
23. Ravesloot MJ, van Maanen JP, Dun LN, et al. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea-a review of the literature. Sleep Breath 2013;17:39e49.
24. Richard W, Kox D, den Herder C, et al. The role of sleep position in obstructive sleep apnea syndrome. Eur Arch Otorhinolaryngol 2006;263:946e50.
25. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. Sleep Breath 2013;17: 771e9.
26. Bignold JJ, Mercer JD, Antic NA, et al. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. J Clin Sleep Med 2011;7:376e83.
27. Dieltjens M, Vroegop AV, Verbruggen AE, et al. A promising concept of combination therapy for positional obstructive sleep apnea. Sleep Breath 2014;19:637e44.
28. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. Sleep 2014;37: 1209-15.
29. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. Chest 2004;125:1270-8.
30. Marklund M, Persson M, Franklin KA. Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. Chest 1998;114: 1630-5.
31. George PT. Selecting sleep-disordered-breathing appliances. Biomechanical considerations. J Am Dent Assoc 2001;132:339-47.
32. Schott TC, Goz G. Applicative characteristics of new microelectronic sensors Smart Retainer® and TheraMon® for measuring wear time. J Orofac Orthop 2010;71:339-47.
33. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14: 540-5.
34. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 1997;20: 835-43.
35. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993;147: 887-95.
36. ICH harmonized tripartite guideline. Guideline for good clinical practice. J Postgrad Med 2001;47: 45-50.
37. Ravesloot MJ, de Vries N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. Sleep 2011;34: 105-10.
38. Ravesloot MJ, de Vries N, Stuck BA. Treatment adherence should be taken into account when reporting treatment outcomes in obstructive sleep apnea. Laryngoscope 2014;124: 344-5.
39. 39. Pepin JL, Krieger J, Rodenstein D, et al. Effective compliance during the first 3 months of continuous positive airway pressure. A European prospective study of 121 patients. Am J Respir Crit Care Med 1999;160: 1124-9.

40. Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). Sleep Med Rev 2003;7: 81-99.
41. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008;5: 173-8.
42. Richard W, Venker J, den Herder C, et al. Acceptance and long-term compliance of nCPAP in obstructive sleep apnea. Eur Arch Otorhinolaryngol 2007;264: 1081-6.
43. Stuck BA, Leitzbach S, Maurer JT. Effects of continuous positive airway pressure on apnea-hypopnea index in obstructive sleep apnea based on long-term compliance. Sleep Breath 2012;16: 467-71.
44. Dieltjens M, Braem MJ, Vroegop AV, et al. Objectively measured vs selfreported compliance during oral appliance therapy for sleep-disordered breathing. Chest 2013;144: 1495-502.
45. Dieltjens M, Verbruggen AE, Braem MJ, et al. Determinants of objective compliance during oral appliance therapy in patients with sleep-disordered breathing: a prospective clinical trial. JAMA Otolaryngol Head Neck Surg 2015;141: 894-900.
46. Vanderveken OM. Combination therapy for obstructive sleep apnea in order to achieve complete disease alleviation: from taboo to new standard of care. JDSM 2015;2: 7-8.
47. Benoist LB, Verhagen M, Torensma B, et al. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. Sleep Breath 2016. http://dx.doi.org/10.1007/s11325-016-1397-x [Epub ahead of print].

CHAPTER 4



Durability of treatment effects of the sleep position trainer versus Oral Appliance Therapy in positional OSA: 12-month follow-up of a randomized controlled trial

M.H.T. de Ruiter#
L.B.L. Benoist#
N. de Vries
J. de Lange
Shared first authorship

This chapter is based on the publication in: Sleep and Breathing, 2017

Abstract

Purpose

The Sleep Position Trainer (SPT) is a new option for treating patients with positional obstructive sleep apnea (POSA). This study investigated long-term efficacy, adherence, and quality of life during use of the SPT device compared with oral appliance therapy (OAT) in patients with POSA.

Methods

This prospective, multicenter trial randomized patients with mild to moderate POSA (apnea-hypopnea index [AHI] 5–30/h) to SPT or OAT. Polysomnography was performed at baseline and after 3- and 12-months' follow-up. The primary endpoint was OSA severity; adherence, quality of life, and adverse events were also assessed.

Results

Ninety-nine patients were randomized and 58 completed the study (29 in each group). Median AHI in the SPT group decreased from 13.2/h at baseline to 7.1/h after 12 months ($P < 0.001$); corresponding values in the OAT group were 13.4/h and 5.0/h ($P < 0.001$), with no significant between-group difference ($P = 1.000$). Improvements throughout the study were maintained at 12 months. Longterm median adherence was also similar in the two treatment groups; the proportion of patients who used their device for ≥ 4 h for 5 days in a week was 100% in the SPT group and 97.0% in the OAT group ($P = 0.598$).

Conclusions

The efficacy of SPT therapy was maintained over 12 months and was comparable to that of OAT in patients with mild to moderate POSA. Adherence was relatively high, and similar in the two groups.

Trial registration: www.clinicaltrials.gov (NCT02045576).

Introduction

Obstructive sleep apnea (OSA) is the most common sleep related breathing disorder. With an overall prevalence of 9–38% in the general adult population, OSA is more common in men and increases with age [1]. Recent data from Switzerland showed that OSA was more prevalent than previously reported. The proportion of men and women with an apnea hypopnea index (AHI) of > 5/h on polysomnography (PSG) was 84 and 61%, respectively [2]. An AHI of ≥ 5/h is required for a diagnosis of OSA, with disease severity rated as mild if the AHI is 5–15/h, moderate if the AHI is 15–30/h, and severe if the AHI is > 30/h [3].

OSA is characterized by recurrent (partial) obstruction of the upper airway, accompanied by oxygen desaturation, sleep disturbance, and sympathetic activation [4]. Consequences of OSA include excessive daytime sleepiness, reduced quality of life, and increased risk of developing cardiovascular disease. More than half of the OSA population (56%), and predominantly those with mild and moderate OSA, have position dependent OSA (POSA) with more apneic and hypopneic events in supine position. POSA is commonly defined as more than twice as many respiratory events in the supine sleep position compared to non-supine sleep position [5–8].

Therapy for OSA generally starts with conservative treatment, consisting of lifestyle changes such as weight reduction and avoidance of alcohol, sedatives, and the supine sleeping position, when applicable. Thereafter, current options include continuous positive airway pressure (CPAP), oral appliance therapy (OAT) and pharyngeal surgery [9–11]. CPAP is the gold standard therapy for moderate to severe OSA, but adherence to CPAP is often suboptimal, necessitating exploration of other options [12]. Oral appliances (OA) are widely used in mild to moderate OSA, and are associated with clinically relevant decreases in the AHI [13], making them an increasingly attractive first-line therapy option in these patients. Vecchierini et al. reported OAT success rates of 40–70 and 78–81% in mild to moderate patients for an AHI to < 5/h

and for an AHI reduction of at least 50%, respectively [13]. However, adverse events such as tooth pain, changes in tooth position resulting in a different occlusion and articulation, or temporomandibular dysfunction can limit adherence to this therapy [14, 15]. Surgery can be an option for patients who are unresponsive, noncompliant, or desire a permanent treatment for their OSA [16–18].

For POSA, alternatives include the use of specific treatments designed to avoid the supine sleeping position. However, the effectiveness of therapy with first generation devices has been limited. For example, the “tennis ball-technique” is uncomfortable for patients to use and disrupts sleep, leading to poor long-term adherence [19]. Next-generation treatment options with active feedback and autoadapted treatment intensity to decrease discomfort and improve compliance were introduced. These include active

positional therapies like supine alarm devices and neck or chest worn vibrating devices [20, 21]. The Sleep Position Trainer (SPT) is such a chest-worn device and it showed to significantly reduce the average supine sleeping time (from 46 to 5%), the AHI to < 5/h in 48%, and an AHI reduction of at least 50% in 71% of patients with mild or moderate POSA [22]. Effectiveness and adherence were good, with an objective adherence rate (> 4 h of nightly use) of 64.4% after 6 months of treatment and improved sleep-related quality of life [23]. Additionally, short-term results have recently been published on the effectiveness of the SPT versus OAT, showing equal efficacy in reducing the median AHI in patients with mild to moderate POSA [24]. However, there are no data on the use and effect of the SPT beyond 6 months. Therefore, we aimed to study the longer-term efficacy and adherence of the SPT (the intervention) in comparison to OAT (active comparator). Hence, we hypothesized that the SPT would be more efficacious in reducing the AHI compared to OAT in patients with mild to moderate POSA. This paper investigated the durability of the previously reported short-term effects of the SPT with respect to efficacy, adherence, and quality of life, after 12 months of follow-up.

Methods

Participants

Participants were eligible for enrollment if they had a diagnosis of mild-to-moderate POSA (AHI of 5–30) and spent 10–90% of their total sleep time in the supine position during baseline PSG. Exclusion criteria included inadequate dentition for wearing an oral appliance, subjective snoring in the lateral position, central sleep apnea, night or rotating shift work, severe chronic heart disease, active psychiatric disease, seizure disorders, medication usage for sleeping disorders, muscular or joint injuries in the head, neck, or back area, previous OAT or SPT usage, simultaneous use of other treatment for OSA, reversible morphological upper airway abnormalities (e.g., enlarged tonsils), pregnancy, and coexisting non-respiratory sleep disorders (e.g., insomnia, periodic limb movement disorder, narcolepsy) that would compromise functional sleep assessment. All participants underwent medical and dental consultations, and a baseline PSG prior to the start of the study.

Study design and oversight

The study was designed as a multicenter, prospective randomized controlled trial. Patients were recruited and followed at the departments of Otolaryngology and Clinical Neurophysiology at OLVG West Hospital, Amsterdam, and at the department of oral and maxillofacial surgery at the Academic Medical Center, Amsterdam. The institutional Medical Ethics Committee of the OLVG West Hospital, Amsterdam, and the Academic Medical Center Amsterdam approved the protocol. The randomization sequence was generated by an independent clinical research unit using ALEA software with a 1:1

allocation using maximum random block sizes of 6 and stratification for smoking and body mass index (BMI). Independent monitors verified the source data and documentation.

Study treatments

The sleep position trainer (SPT-DEV-PX-11.08; NightBalance) consists of a small lightweight device (72 Å˜ 35 Å˜ 10 mm; 25 g) worn across the chest using a neoprene strap (Fig. 1) [22]. The SPT vibrates when a supine position is detected to prompt a change in body position. Data storage on the device allows for objective measurement of adherence to the therapy. Further details on functionality of the SPT are described elsewhere [24]. As active comparator, the OA was a custom-made duo-bloc device (SomnoDent flex; SomnoMed) (Fig. 2). After adequate assessment of the central relation and maximum protrusion, the OA was set at 60% of maximum protrusion at baseline. The OA was adjusted individually and advancement was titrated using a standard protocol by the dentist, which was described in greater detail elsewhere [24]. Objective adherence was measured using a temperature-sensitive microsensor with on-chip integrated read-out electronics (Theramon, Handels- und Entwicklungsgeselschaft, Handelsagentur Gschladt, Hargelsberg, Austria) with a sampling rate of one measurement every 15 min. A recorded temperature of > 30 °C indicated that the OA was worn.

Figure 1. Sleep Position Trainer

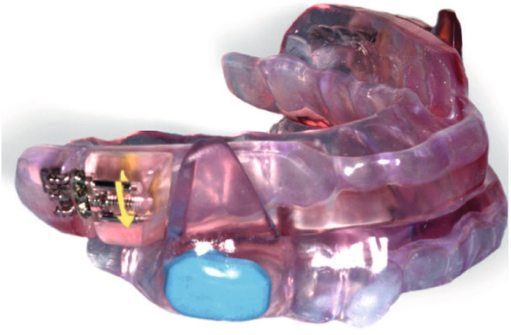


Figure 2. Oral appliance therapy

Outcome measures

The primary outcome was the change in OSA severity after 12 months compared with baseline. OSA severity was determined based on the AHI and the oxygen desaturation index (ODI; the number of times per hour of sleep that the blood oxygen level drops by ≥ 4% from baseline, according to the prevailing definition at that time). These parameters were determined from overnight PSG (Embla A10, Broomfield, CO, USA) which records electroencephalogram (EEG) (FP2-C4/C4-O2), electro-oculogram (EOG), electrocardiogram (ECG), and submental and anterior tibial electromyogram (EMG). Nasal airflow was measured by a nasal pressure cannula and blood oxygen saturation by finger pulse oximetry. Straps containing piezoelectric transducers recorded thoracoabdominal motion, and a position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions. Recordings were manually scored by an independent core laboratory using American Academy of Sleep Medicine (AASM) 2012 scoring criteria [25]. Secondary outcomes included additional polysomnographic variables, percentage of time spent sleeping in the supine position, AHI in the supine and non-supine positions, and sleep efficiency. Self reported daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS; score range 0–24, score ≥ 10 indicates excessive daytime sleepiness). Disease-specific quality of life was assessed with the Functional Outcomes of Sleep Questionnaire (FOSQ-30; score range 5–20, higher scores indicate better functioning). Adherence was defined as device (SPT or OAT) usage for ≥ 4 h/night at least 5 days per week.

Follow-up

This paper aimed at testing the durability of treatment effect after 12-month follow-up. Throughout the follow-up, patients underwent repeat PSG at 3 and 12 months, while using the SPT or OAT. Patients completed the ESS and FOSQ-30 at baseline and after 3 and 12 months of therapy. Objective adherence and medical evaluation (including heart rate and blood pressure measured twice seated by two independent physicians with an interval of 3 min) were also assessed at 3 and 12 months.

Adverse event

Adverse events were reported in accordance with the International Conference of Harmonization ICH E2A guidelines (Good Clinical Practice) by the principal investigators and evaluated by independent data monitors [26].

Statistical analysis

Power analysis resulted in a minimum sample size of 36 participants per study arm (to reach a power of 80%). In order to allow for dropout, the recruitment target was inflated to 49 per group. The level for statistical significance was set at $\alpha = 0.05$. The statistical programming and analysis were performed using IBM SPSS statistics version 24 (IBM Corp., Armonk. NY, USA). Due to the proportion of missing data at 12 months, analyses were primarily conducted on a per-protocol (PP) basis. Additionally, illustrative worst-case and best-case intention-to-treat (ITT) analyses were performed through imputing missing data through the Last-Observation-Carried- Forward method. Variables were summarized using descriptive statistics: mean value with standard deviation for continuous symmetric variables, median and interquartile range for continuous skewed variables, and frequency with percentage for categorical variables. For the primary outcome, repeated measures ANOVA was performed to test for differences over time. Thereafter, within-subject comparisons (patient progression over time; paired) between continuous variables at baseline and follow-up (3 and 12 months) and between the 3- and 12-month follow-ups were made using the paired t test (non skewed data) or the Wilcoxon signed rank test (skewed data). Between-group difference tests (deltas baseline vs. follow-up) were performed using an independent t test (non-skewed data) or Mann-Whitney U test (skewed data). Both the between-group and within-subject analyses were adjusted for multiple comparisons using the Bonferroni correction.

Results

A total of 177 patients with mild to moderate POSA were screened for eligibility (70.7% male, age 48.3 ± 10.1 years; BMI 27.6 ± 3.8 kg/m2). Of these, 99 patients met all eligibility criteria and were randomized to OAT (n = 51) or SPT (n = 48) (Fig. 3). Baseline characteristics for these patients are shown in Table 1 with comparison of the characteristics between “completers” and “dropouts”. There was only a statistically significant difference in blood pressure between the OAT and SPT groups at baseline (Table 1). The total number of patients receiving allocated treatment with OAT and SPT, and completing 3 months’ follow-up was 36 and 45, respectively. Over the remaining 9 months of follow-up, an additional seven patients withdrew in the OAT group (one lost to follow-up and six discontinued treatment due to adverse events [n = 2], lack of efficacy [n = 3], or both adverse event and efficacy [n = 1]) (Fig. 3). In the SPT group, 2 patients were lost to follow-up and 14 discontinued treatment (lack of efficacy [n = 3], persistent snoring [n = 4], adverse events [n = 3; 2 not related to SPT], or other non-related reasons [n = 4]) (Fig. 3). A total of 58 patients were eligible for per-protocol analysis after 12months (Fig. 3).

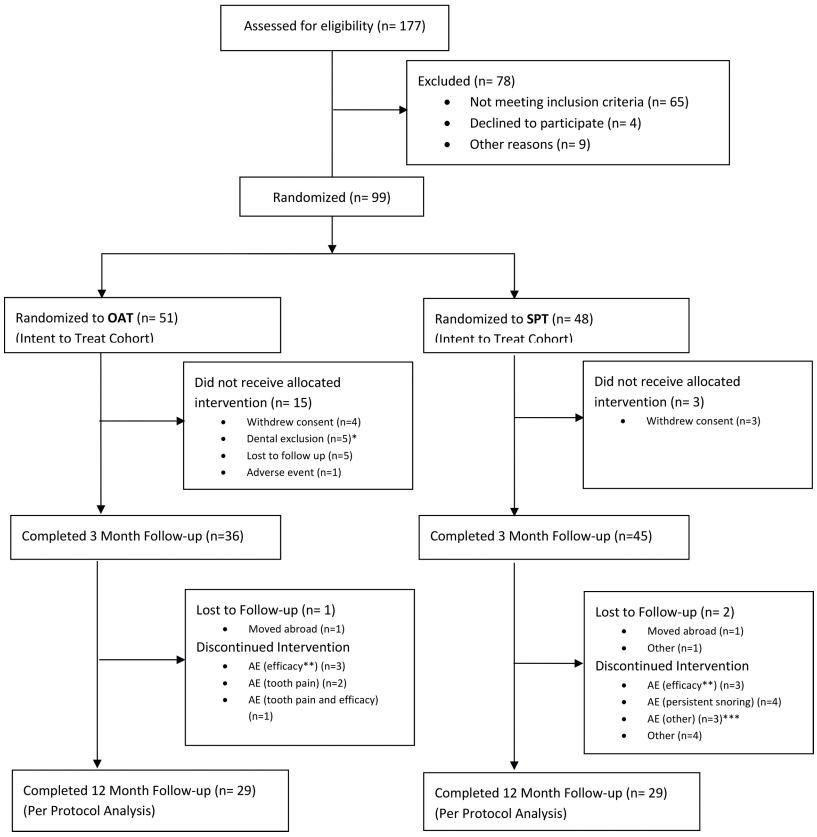


Fig. 3 Flow Diagram of the study POSA

Fig. 3 Flow of patients through the study. AE, adverse event; OAT, oral appliance therapy; SPT, Sleep Position Trainer. *Although insufficient dental status was an exclusion criterion, a dentist checked this through regular physical examination. Some dental problems were only visualized after the orthopantomography was made.
** Efficacy: persistent apneas/ AHI. *** Adverse events; one related events (joint problems due to wearing SPT), two non-related events (one patient had nasal problems and was not motivated to continue and one patient had broken ribs due to an accident and did not want to continue)

Primary outcome

PP analysis showed that the AHI and ODI were significantly reduced compared with baseline at both the 3- and 12-month follow-up visits for both treatment groups, with no significant between-group differences (Table 2). The absolute reductions in AHI and ODI at 3 months were maintained at 12 months in both groups (Table 2). ITT analysis for the primary outcome is provided in Table S1. The AHI reduced for more than 50% in 48.3 and 51.7% of SPT patients after 3 and 12 months, respectively. For the OAT group, this

reduction was found in 48.3% patients after 3 months and 55.2% patients after 12 months of follow-up. The outcomes were not statistically different between the two treatment groups (P = 1.000 at 3 months and P = 0.792 at 12 months). Alternatively, a reduction of the AHI under 5/h for the 3- and 12-month follow-up was found in 34.5 and 41.4% of SPT patients and 41.4 and 51.7% of OAT patients, respectively. These outcomes were also not significantly different between the groups (P = 0.5888 at 3 months and P = 0.430 at 12 months). Durability of the treatment effect of both the SPT and OAT groups was good (Fig. 4). There was a statistically significant effect of time on the AHI under treatment ($F(2, 56) = 65.97$, $P < 0.001$), with no significant between-group difference (P = 0.592). For the reduction in AHI, stratification by OSA severity at baseline (mild [n = 34) vs. moderate [n = 24]) was performed ($F(2, 54) = 102.39$, $P < 0.001$). However, no severity-related difference in reduction of AHI was observed between the treatment arms (P = 0.200).

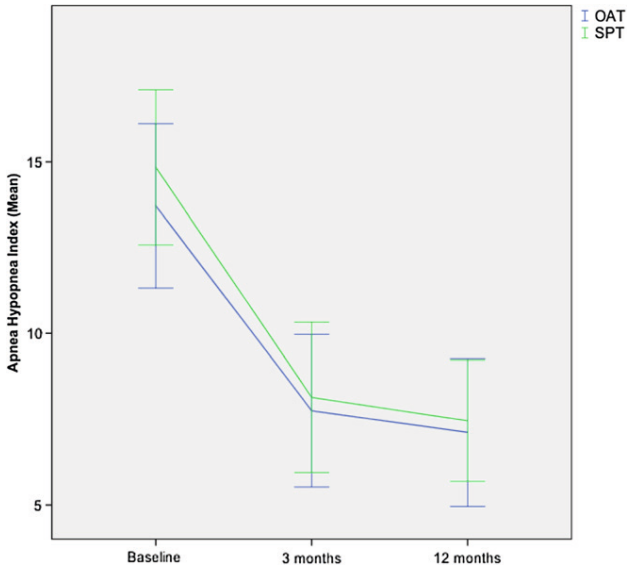


Figure 4. Durability of effects on the apnea-hypopnea index (AHI) over time in the Sleep Position Trainer (SPT) and oral appliance therapy (OAT) groups (ANOVA repeated measures)

Secondary outcomes

Polysomnographic indices

Treatment with SPT was associated with a significant decrease in supine sleeping time ($P < 0.001$ vs. baseline after 3 and 12 months), but supine sleeping time was unchanged from baseline in the OAT group (between-group difference, $P < 0.001$) (Table 2). Supine AHI decreased to a similar extent in the two groups (Table 2). Sleep efficiency remained stable over the 12-month follow-up, and no significant changes in cardiovascular parameters were observed between the two treatment groups (Table 2).

Table 1 Baseline characteristics in all randomized patients (n = 99) and comparison between "completers" and "dropouts"

	SPT			OAT				
	Total (n = 48)	Completers (n = 29)	Dropouts (n = 19)	Total (n = 51)	Completers (n = 29)	Dropouts (n = 22)	P value[a]	P value[b]
Male, n (%)	34 (70.8)	19 (65.5)	18 (62.1)	36 (70.6)	15 (78.9)	18 (81.8)	0.979c	0.340c
Age, years	47.3 ± 10.1	49.5 ± 9.4	49.5 ± 8.5	49.2 ± 10.2	43.8 ± 10.3	48.9 ± 12.3	0.347d	0.209f
Body Mass Index, kg/m2	27.5 ± 2.9	27.7 ± 2.8	28.3 ± 3.6	27.7 ± 4.5	27.1 ± 2.9	26.8 ± 5.5	0.797d	0.501f
Height, cm	177.0 ± 10.2	176.7 ± 11.2	172.7 ± 12.1	174.4 ± 11.9	177.4 ± 8.8	176.5 ± 11.6	0.247d	0.422f
Weight, kg	86.2 ± 13.2	86.9 ± 14.9	84.2 ± 11.4	83.9 ± 14.2	85.1 ± 10.3	83.5 ± 17.4	0.401d	0.820f
Neck circumference, cm	38.0 ± 3.6	37.9 ± 3.8	37.2 ± 3.1	37.7 ± 3.2	38.3 ± 3.4	38.3 ± 3.2	0.624d	0.655f
Smokers, n (%)	11 (22.9)	5 (17.2)	7 (24.1)	12 (23.5)	6 (31.6)	5 (22.7)	0.942c	0.719c
Alcohol intake, n (%)								
≤ 2 drinks/day	45 (93.7)	26 (89.7)	27 (93.1)	48 (94.1)	19 (100.0)	21 (95.5)	0.446c	0.688c
> 2 drinks/day	3 (6.3)	3 (10.3)	2 (6.9)	3 (5.9)	0 (0.0)	1 (4.5)		
Blood pressure, mmHg								
Systolic	135.0 (125.0–150.0)	130.0 (125.0–150.0)	130.0 (120.0–141.0)	130.0 (120.0–140.0)	140.0 (122.0–155.0)	129.0 (120.0–136.3)	0.032e	0.162f
Diastolic	90.0 (80.0–97.5)	80.0 (90.0–95.0)	85.0 (80.0–90.0)	85.0 (80.0–90.0)	90.0 (80.0–100.0)	82.5 (79.5–90.0)	0.033e	0.141f
Heart rate, beats/min	69.0 (64.0–78.0)	68.0 (63.0–78.0)	72.0 (62.0–78.0)	72.0 (66.0–80.0)	74.0 (64.0–80.0)	71.0 (67.0–82.3)	0.530e	0.292f
AHI, /h	13.0 (9.7–18.5)	13.2 (10.2–19.0)	13.4 (8.7–16.9)	11.7 (9.0–16.2)	12.1 (7.0–17.2)	10.3 (9.0–13.3)	0.318e	0.222f
Supine AHI, /h	27.0 (18.7–43.1)	28.5 (18.9–46.2)	25.8 (15.8–45.1)	25.8 (17.4–35.0)	26.0 (11.6–36.8)	26.1 (18.8–34.2)	0.687e	0.491f
Non-supine AHI, /h	3.5 (1.6–5.7)	4.1 (2.4–5.8)	3.8 (0.8–5.7)	3.1 (1.0–5.0)	2.4 (0.9–5.7)	2.6 (1.2–3.7)	0.361e	0.057f
Supine sleep time, %	44.5 (30.0–55.5)	41.0 (30.0–54.0)	35.0 (25.0–61.0)	39.0 (26.0–54.0)	47.0 (25.0–57.0)	42.5 (27.5–47.5)	0.575e	0.901f

Table 1 Baseline characteristics in all randomized patients (n = 99) and comparison between "completers" and "dropouts" *(continued)*

	SPT			OAT				
	Total (n = 48)	Completers (n = 29)	Dropouts (n = 19)	Total (n = 51)	Completers (n = 29)	Dropouts (n = 22)	P value[a]	P value[b]
ODI, /h	10.5 (7.0–15.8)	9.0 (7.0–15.5)	10.0 (6.5–14.0)	9.0 (6.0–14.0)	13.0 (7.0–16.0)	8.0 (5.5–11.8)	0.137e	0.218f
AI, /h	9.0 (5.0–15.0)	11.0 (5.5–15.5)	8.0 (3.5–12.5)	8.0 (4.0–12.0)	7.0 (3.0–11.0)	7.0 (3.8–11.3)	0.183e	0.310f
Sleep efficiency, %	92.0 (84.5–95.0)	92.0 (84.0–95.5)	91.0 (85.5–95.0)	92.0 (86.0–95.0)	92.0 (89.0–94.0)	93.0 (87.8–96.3)	0.820e	0.811f
Mean oxygen saturation, %	95.0 (94.0–96.8)	95.0 (94.5–96.0)	95.0 (94.0–96.0)	95.0 (94.0–96.0)	95.0 (94.0–97.0)	95.5 (94.0–96.3)	0.451e	0.575f
ESS score	8.1 ± 5.2 (n = 42)	8.9 ± 5.7	6.9 ± 4.4	8.7 ± 5.6 (n = 45)	7.1 ± 4.3	10.7 ± 6.3	0.625e	0.073f
FOSQ score	19.0 (17.3–19.7) (n = 33)	18.9 (16.8–19.5)	19.3 (16.9–19.8)	18.4 (16.2–19.7 (n = 40)	19.4 (18.8–19.7)	18.3 (16.2–19.4)	0.646e	0.864f

Values are mean ± standard deviation, median (interquartile range), or number of patients (%)
AHI apnea-hypopnea index, AI apnea index, ESS Epworth Sleepiness Scale score, FOSQ Functional Outcomes of Sleep Questionnaire, OAT oral appliance therapy, ODI oxygen desaturation index, SPT
Sleep Position Trainer
a Comparing total group scores between SPT and MAD (two groups)
b Comparing completers' and dropouts' scores between SPT and MAD (four groups)
c Pearson chi-square test
d Independent T test
e Mann-Whitney test
f One-way ANOVA

Adherence

Device usage and adherence were similar in the SPT and OAT groups throughout the 12-month follow-up (Table 3 and S2). The average usage per night was 5.2/h for SPT and 5.0/h for OAT (P = 0.743). Median adherence per patient (≥ 4 h for 5 days/week) was 100% in the SPT group and 97.0% in the OAT group (P = 0.598).

Subjective daytime sleepiness and sleep-related quality of life

Complete 12-month data from the ESS questionnaire were available for 21/29 (72%) and 25/29 (86%) patients in the SPT and OAT groups, respectively; corresponding values for completion of the FOSQ were 12/29 (41%) and 13/29 (45%). No significant changes in the ESS score and FOSQ score were identified in either treatment group (Table 2).

Table 2 Primary and secondary outcome variables (per-protocol analysis)

	SPT (n = 29)			OAT (n = 29)		
	Baseline	3 months	12 months	Baseline	3 months	12 months
Primary outcome						
Total AHI, /h	13.2 (10.2, 19.0)	6.8 (4.1, 11.5)[a]	7.1 (4.0, 10.0)[a]	13.4 (8.7, 16.9)	5.9 (3.8, 9.6)[a]	5.0 (3.9, 8.9)[a]
ODI, /h	9.0 (7.0, 15.5)	5.0 (4.0, 8.0)[a]	6.0 (3.0, 8.0)[a]	10.0 (6.5, 14.0)	7.0 (4.0, 9.0)[b]	7.0 (3.0, 10.5)
Secondary outcomes						
Supine AHI, /h	28.5 (18.9, 46.2)	12.4 (0.0, 34.3)[c]	10.0 (0.0, 20.2)[a]	25.8 (15.8, 45.1)	14.3 (5.6, 26.8)	10.3 (5.5, 18.3)[a]
Non-supine AHI, /h	4.1 (2.4, 5.8)	4.3 (2.0, 7.2)	4.5 (2.6, 7.8)	3.8 (0.8, 5.7)	1.6 (0.6, 4.0)	1.8 (0.5, 4.5)
Supine sleep, %	41.6 ± 17.0	13.3 ± 12.9[a, d]	12.7 ± 13.6[a, d]	42.3 ± 21.4	41.4 ± 26.4	43.9 ± 23.7
AI, /h	11.0 (5.5, 15.5)	4.0 (1.0, 8.5)[a]	3.0 (2.0, 6.0)[a]	8.0 (3.5, 12.5)	3.0 (1.0, 6.5)[a]	2.0 (1.0, 5.0)[a]
Sleep efficiency, %	92.0 (84.0, 95.5)	92.0 (89.5, 96.0)	91.0 (84.5, 95.5)	91.0 (85.5, 95.0)	91.0 (84.5, 94.0)	93.0 (86.0, 95.0)
Average SpO2, %	95.0 (94.5, 96.0)	96.0 (95.0, 97.0)	96.0 (94.5, 97.0)	95.0 (94.0, 96.0)	95.0 (93.5, 96.0)	94.0 (94.0, 96.5)
SBP, mmHg	130.0 (125.0, 150.0)	125.0 (120.0, 135.0)[b, e]	130.0 (120.0, 142.5)	130.0 (120.0, 141.0)	125.0 (122.5, 137.5)	125.0 (120.0, 139.0)
DBP, mmHg	90.0 (80.0, 95.0)	80.0 (75.0, 90.0)[a, f]	80.0 (80.0, 90.0)[b]	85.0 (80.0, 90.0)	85.0 (80.0, 90.0)	80.0 (80.0, 85.0)
Heart rate, bpm	68.0 (63.0, 78.0)	70.0 (66.5, 80.0)	72.0 (69.0, 80.0)	72.0 (62.0, 78.0)	70.0 (63.0, 80.0)	74.0 (67.0, 80.0)
ESS scoreg	9.0 (3.5, 12.8)	7.0 (5.0, 10.0)	7.0 (3.5, 10.0)	6.0 (4.0, 10.8)	4.5 (3.0, 7.0)	4.0 (2.0, 8.0)
FOSQ scoreh	18.9 (16.8, 19.5)	18.9 (17.0, 19.9)	19.0 (18.2, 19.7)	19.3 (16.9, 19.8)	18.5 (16.1, 19.6)	17.7 (16.9, 19.9)

Values are mean ± standard deviation or median (interquartile range). P values are adjusted for multiple comparisons by a Bonferroni correction*AHI* apnea-hypopnea index, AI apnea index, bpm beats/min, DBP diastolic blood pressure, ESS Epworth Sleepiness Scale, FOSQ Functional Outcomes of Sleep Questionnaire, OAToral appliance therapy,
ODI oxygen desaturation index, SBP systolic blood pressure, SpO2 oxygen saturation, SPT Sleep Position Trainer
a P < 0.001 vs baseline (Wilcoxin signed rank test)
b P < 0.01 vs. baseline (Wilcoxin signed rank test)
c P < 0.05 vs. baseline (Wilcoxin signed rank test)
d P < 0.001 vs. OAT (Mann-Whitney U test)
e P < 0.05 vs. OAT (Mann-Whitney U test)
f P < 0.01 vs. OAT (Mann-Whitney U test)
g Data available in 24, 27, 21 patients in the SPT group and 24, 24, 25 patients in the OAT group for baseline, 3 months, and 12 months, respectively
h Data available in 19, 19, 12 patients in the SPT group and 20, 18, 18 patients in the OAT group for baseline, 3 months, and 12 months, respectively

Table 3. Objective adherence and device usage (Per Protocol analysis)

	SPT (n=29)	**OAT (n=28)**	**P-value**
Total nights	365.0 (362.5-365.0)	356.5 (165.0-326.5)	0.805[a]
Total nights with adherence >4h	237.6±96.3	239.9±96.1	0.930[b]
Average hours of use per night	5.2±2.2	5.0±2.0	0.743[b]
Adherence >4h on 7 days in a week, % patients	82.0 (47.0-90.5)	79.8 (59.7-97.4)	0.314a
Adherence >4h on 5 days in a week, % patients	100.0 (65.5-100.0)	97.0 (79.9-100.0)	0.598a

Values are mean ± standard deviation or median (interquartile range). One patient missing data in OAT group
OAT oral appliance therapy, SPT Sleep Position Trainer
a Mann-Whitney test
b Independent T test

Table 4 Adverse events

	Total	SPT	OAT
Number of subjects (%)	58 (100)	29 (100)	29 (100)
Reporting at least 1 AE (%)	48 (82.8)	20 (69.0)	28 (96.6)
Frequency of events (%)	114 (100)	37 (100)	77 (100)
Persistent snoring (%)	29 (25.4)	14 (37.8)	15 (19.5)
Persistent tiredness (%)	21 (18.4)	7 (18.9)	14 (18.2)
Persistent apneas (%)	1 (0.9)	1 (2.7)	0 (0.0)
Comfort problems (%)	7 (6.1)	5 (13.5)	2 (2.6)
Other (%)	4 (3.5)	2 (5.4)	2 (2.6)

Table 4 Adverse events *(continued)*

	Total	SPT	OAT
OAT			
Tooth pain (%)	21 (18.4)		21 (27.3)
TMD (%)	9 (7.9)		9 (11.7)
Open bite (%)	7 (6.1)		7 (9.1)
Dry mouth (%)	4 (3.5)		4 (5.2)
Hypersalivation (%)	1 (0.9)		1 (1.3)
Dental fracture (%)	1 (0.9)		1 (1.3)
Oral lesions (%)	1 (1.3)		1 (1.3)
SPT			
Woken up by vibration (%)	4 (3.5)	4 (10.8)	
No reaction to vibration (%)	4 (3.5)	4 (10.8)	

AE adverse event, OAT oral appliance therapy, SPT Sleep Position Trainer, TMD temporomandibular dysfunction

Adverse events

A total of 114 device-related adverse events (AE) were reported by 48 patients (82.8%) overall, 20 (69.0%) in the SPT group, and 28 (96.6%) in the OAT group (Table 4). Overall, the most common adverse events in both groups were persistent snoring and persistent tiredness. A similar degree of persistent snoring was reported for SPT and OAT; by 14 and 15 patients, respectively. However, for an additional four SPT patients, persistent snoring was a reason for dropping out of the study (Fig. 3). The most common SPT-specific adverse events were being woken by the vibration and no reaction to the vibration. In the OAT group, the most common device-specific events were tooth pain, temporomandibular dysfunction, and open bite. In patients treated with the SPT, no events necessitated a temporary discontinuation of device use. For the OAT group, study treatment was temporarily discontinued as a result of six events in a total of five patients (17.2%of patients). The number of device-specific adverse events (vs. non-specific events) was higher in the OAT group (44 vs. 8 in the SPT group; $P < 0.001$). No statistical difference was found in the duration (in days) of adverse events ($P = 0.830$) between the groups.

Discussion

The results of this study in patients with POSA showed that the beneficial effects of both the SPT and OAT observed at 3 months persisted through 12 months of device use. The SPT improved sleep apnea to a similar extent as OAT and was associated with high adherence rates. This is the first long-term, randomized controlled trial comparing positional therapy using the SPT with OAT for the treatment of POSA. These findings are consistent with previous short-term data on the SPT [22, 27] and confirm that benefits are maintained over a longer-term follow-up. It is important to assess OSA therapies over longer periods of time because many, including CPAP, show reduced adherence over time. When adherence is defined as device usage for > 4 h/night, 46–83% of CPAP users are non adherent [12]. Objective data on use of OAT have shown that 83% of patients used the device regularly [28]. Adherence rates for OAT in our study were similar, and SPT device usage was also of a similar magnitude. In this study, SPT had similar long-term efficacy to OAT and was associated with consistently high levels of adherence over 12 months' follow-up, highlighting the potential clinical utility of the SPT in everyday practice.

Analysis of patients not allocated to treatment and those withdrawn from the study provides some insight into optimal patient selection and the challenges faced with each therapy. No significant difference between completers and dropouts was found in baseline characteristics (Table 1). Most dropouts in the OAT group were seen before the start of treatment. Dentition played an important role in the initiation to treatment, and prevented device use in 33% of OAT patients who did not start the allocated treatment. It has been reported that dental limitation might preclude the use of OAT in up to 34% of all OSA cases [29]. In our study, the rate of adverse events over the first year of therapy was higher in the OAT group than in the SPT group. However, more subjects discontinued use of the SPT due to AEs between the 3- and 12-month assessments (14 vs. 6 for OAT), although the number of completers was the same in both groups (n = 29). Within the non-completers, the rate of persistent AHI was similar between groups as reason for dropout. Tooth pain was mentioned in the OAT group, while in the SPT group persistent snoring, joint problems, nasal problems, and broken ribs were reported as reason for dropout. Due to the mechanism of action of the SPT device, AHI and continuous snoring in the lateral position are not decreased. Just as dentition may play a role in patient selection for OAT, high lateral AHI and/or lateral snoring may be factors that identify patients less suitable for the SPT. Knowledge of the advantages, disadvantages, and adverse effects with each therapy can help guide clinicians to proper individual therapy selection and follow-up regimes that maximize adherence and long-term outcomes.

Study limitations

The main limitation of this study was the slightly higher than expected observed dropout rate at 3 months. We mitigated this by performing additional ITT analyses on the primary outcome, using the Last-Observation-Carried-Forward method. The relatively low number of patients at 12 months could also be raised as a concern; however, the 20% dropout rate was predicted for the 3-month assessment as the primary outcome, and therefore more dropout would have been expected at 12 months. Regardless, we have included a sensitivity analysis to demonstrate the robustness of our results to the high dropout rate at 3 and 12 months. The best- and worst-case scenarios demonstrate the maximum and minimum bounds for the treatment effects (respectively) under different missing mechanisms for the treatment and control groups. The best-case scenario assumed a 50% decrease in AHI from baseline for patients with missing data in the SPT group compared to a 0% change in AHI from baseline for patients with missing data in the OAT group. The worst-case scenario assumed a 0% change in AHI from baseline for patients with missing data in the SPT group compared to a 50% decrease in AHI

from baseline for patients with missing data in the OAT group. The results from these analyses demonstrate the extremes that would be expected if the missingness in the SPT and OAT groups occurred for contrasting reasons (Table S3).

Conclusion

The results of this study show that the efficacy of SPT was maintained over 12 months of therapy, and was comparable to that of OAT in patients with mild to moderate POSA. Adherence to both treatment modalities was high, and similar in the two groups. Good long-term adherence can make an important contribution to the ongoing effectiveness of treatment in clinical practice.

References

1. Senaratna CV, Perret JL, Lodge C et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Medicine Reviews* 2016:18 Jul [Epub ahead of print].
2. Heinzer R, Vat S, Marques-Vidal P et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310-8.
3. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667-89.
4. Strollo PJ, Jr., Rogers RM. Obstructive sleep apnea. *N Engl J Med* 1996;334:99-104.
5. Cartwright RD Effect of sleep position on sleep apnea severity. *Sleep* 1984;7:110-4.
6. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997;112:629-39.
7. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol* 2006;263:946-50.
8. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest* 2005;128:2130-7.
9. Hoekema A, Stegenga B, De Bont LG. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. *Crit Rev Oral Biol Med* 2004;15:137-55.
10. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2004:CD004435.
11. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011;15:343-56.
12. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173-8.
13. Vecchierini M, Attali V, Collet J et al. A custom-made mandibular repositioning device for obstructive sleep apnoea–hypopnoea syndrome: the ORCADES study. *Sleep Med* 2016;19:131-40.
14. Doff MH, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. *Clin Oral Investig* 2013;17:475-82.
15. Doff MH, Veldhuis SK, Hoekema A et al. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. *Clin Oral Investig* 2012;16:689-97.
16. Caples SM, Rowley JA, Prinsell JR et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. *Sleep* 2010;33:1396-407.
17. Strollo PJ, Jr., Soose RJ, Maurer JT et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139-49.
18. Zaghi S, Holty JE, Certal V et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2016;142:58-66.

19. Bignold JJ, Deans-Costi G, Goldsworthy MR et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. *J Clin Sleep Med* 2009;5:428-30.

20. van Maanen JP, Richard W, Van Kesteren ER, Ravesloot MJ, Laman DM, Hilgevoord AA, de Vries N (2012) Evaluation of a new simple treatment for positional sleep apnoea patients. J Sleep Res 21(3):322–329.

21. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *J Clin Sleep Med* 2011;7:376-83.

22. van Maanen JP, Meester KA, Dun LN et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep Breath* 2013;17:771-9.

23. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep* 2014;37:1209-15.

24. Benoist LB, de Ruiter M, de Lange J, de Vries N. A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. *Sleep Medicine* 2017;34:109-17.

25. Berry RB, Brooks R, Gamaldo CE, Harding SM, Marcus C, Vaughn B. The AASM manual for the scoring of sleep and associated events. *Rules, Terminology and Technical Specifications, Darien, Illinois, American Academy of Sleep Medicine* 2012.

26. Bhuiyan P, Rege N ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice. 2001.

27. Eijsvogel MM, Ubbink R, Dekker J, Oppersma E, de Jongh FH, van der Palen J, Brusse-Keizer MG (2015) Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. J Clin Sleep Med 11(2):139–147.

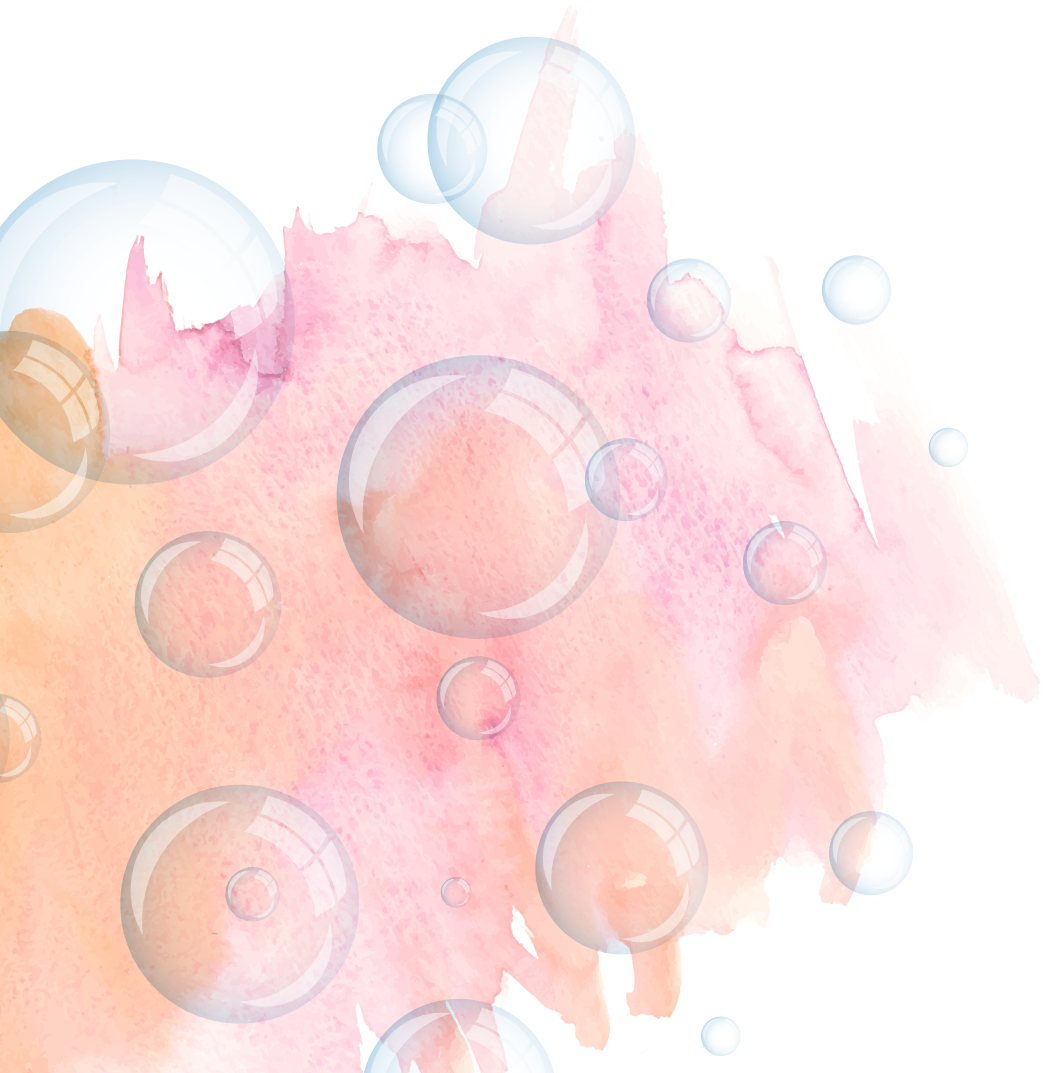
28. Dieltjens M, Braem MJ, Vroegop AV et al. Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. *Chest* 2013;144:1495-502.

29. Petit FX, Pepin JL, Bettega G, Sadek H, Raphael B, Levy P. Mandibular advancement devices: rate of contraindications in 100 consecutive obstructive sleep apnea patients. *Am J Respir Crit Care Med* 2002;166:274-8.

PART II

Appraisal of the maxillomandibular advancement surgery in a broader context

CHAPTER 5



Assessment of obstructive sleep apnea treatment success or failure after maxillomandibular advancement

M.H.T. de Ruiter
R.C. Apperloo
D.M.J. Milstein
J. de Lange

This chapter is based on the publication in: International Journal of Oral and Maxillofacial Surgery, 2017

Abstract

Maxillomandibular advancement (MMA) is an alternative therapeutic option that is highly effective for treating obstructive sleep apnoea (OSA). MMA provides a solution for OSA patients that have difficulty accepting lifelong treatments with continuous positive airway pressure or mandibular advancement devices. The goal of this study was to investigate the different characteristics that determine OSA treatment success/failure after MMA. The apnea-hypopnea-index (AHI) was used to determine success/failure of OSA treatment after MMA. Sixty-two patients underwent MMA for moderate and severe OSA. A 71% success rate was observed with a mean AHI reduction of 69%. A statistically significant larger neck circumference was measured in patients with failed OSA treatments following MMA (P=0.008) and older patients had failed OSA treatments with MMA: 58 vs. 53 years respectively (P=0.037). Cephalometric analysis revealed no differences between successful and failed OSA treatment outcomes. There was no difference in maxillary and mandibular advancements between success and failed MMA treated OSA patients. The complications most frequently reported following MMA were sensory disturbances in the inferior alveolar nerve (60%) and malocclusion (24%). The results suggest that age and neck girth may be important factors that could predict susceptibility to OSA treatment failures by MMA.

Introduction

Obstructive sleep apnoea (OSA) is a chronic sleep breathing disorder that is becoming a major problem in national and international healthcare. For example in the US the prevalence of OSA in general population is estimated between 9-38% and is higher in men, in older patients, and in patients with high body mass index (BMI).[1] OSA severity is classified using the apnoea-hypopnoea-index (AHI; events/h), which is assessed using a polysomnography (mild OSA: AHI >5-15; moderate OSA: AHI >15-30; severe OSA: AHI >30). Present treatment guidelines may include mandibular advancement device (MAD) and continuous positive airway pressure (CPAP) for treating patients with OSA.[2] Maxillomandibular advancement (MMA) is an alternate therapeutic option that is highly effective for treating patients with OSA and is currently performed on a relatively small scale. Our first 10 patients were described in a report in 2013.[3] MMA provides a solution for OSA patients that have difficulty accepting lifelong treatments with CPAP or MAD. The combination of a Le Fort I osteotomy with a bilateral sagittal split osteotomy (BSSO) creates significant enlargement of the pharyngeal airway-space.[4] Therapeutic success is defined according to Sher et al. as postoperative AHI changes that decreased beyond 50% and <20 events/h.[5] MMA has demonstrated satisfactory reductions in mean AHI from 63.9 to 9.5 events/h with a pooled surgical success rate of 86% and an OSA cure rate of 43%.[6] However, whether MMA is a success depends on more than just a decrease in AHI. For physicians working in the field of OSA MMA is regarded as a very invasive procedure and is therefore only indicated as a last resort.

Detailed information regarding the advantages of MMA procedures is available but not on the disadvantages and complications, it is therefore unknown, which variables are of influence in patient selection and what complications and side effects should be considered for predicting success or predisposition to failure in relation to OSA therapy. This investigation aims to identify which variables could influence the rate of OSA treatment failure after MMA procedures. It seems that in approximately 10-20% of OSA cases treated with MMA that AHI was not successfully decreased after surgery.[7] It is currently unknown which pre-operative patient-related factors could be of importance in the selection of adequate patients for achieving OSA treatment success. Recently Zaghi et al. showed that the pre-operative severity of OSA was the most reliable predictor of outcome.[7] More specific the most severe cases of OSA tend to benefit most after MMA in decreasing AHI, but the cure rate was only 20% among patients with a preoperative AHI of >90 events/h. Patients with a preoperative AHI of <30 events/h showed cure in 56% and thus showed a higher chance for success.

MMA is a routine procedure performed in many centres in patients without OSA. In those patients the most common complications and side effects are well known (e.g., sensory disturbances from the IAN) and the risk for developing complications are discussed in detail with these patients to ensure adequate patient information briefing.

Studies that present large cohorts of patients treated with MMA for OSA show detailed polysomnographic results and symptom relief measured by the Epworth Sleeping Scale (ESS) or the Functional Outcome Sleep Questionnaire (FOSQ), but are inadequate in providing data on side effects and complications after MMA.[8-10] This lack of information makes evidence-based decision-making difficult in patients with OSA and it is relatively unclear what role MMA has in the guideline for OSA treatment.

The aims of this study were to identify factors that could pre-dispose MMA failure in OSA patients and to present the findings of our centre's experience regarding complications and assessments of factors that could elicit surgical failures in relation to MMA surgery. In order to identify factors that determine the success or failure of OSA patient treatment by MMA a detailed preoperative work-up including AHI, cephalometric analysis, physical examination including neck girth measurements, as well as post-operative information on AHI, complications and side effects were analysed.

Material and Methods

The data for this single-centre observational study was obtained from patients admitted between 2011 and 2015 for elective MMA therapy for moderate and severe OSA. The institutional medical ethics review board of the Academic Medical Center of the University of Amsterdam reviewed the research proposal and study procedures and granted permission to collect data and questionnaires (Project Nr. W16_006). All participants registered in this investigation's database received a detailed explanation of the study guidelines and procedures and written informed consent was obtained. This investigation was conducted in accordance with the principles established in the Declaration of Helsinki (Fortaleza, October 2013).

Study participants

Patients with moderate or severe OSA referred to the Department of Oral & Maxillofacial Surgery of the Academic Medical Center of the University of Amsterdam for elective MMA reconstruction procedures were eligible for participation in this study. Pre-operative (baseline) patient data included gender, age, BMI (kg/m^2), neck circumference (cm), AHI, and co-morbidities (e.g. diabetes mellitus, smoking) represented through ASA-score.

Cephalometric workup

Pre-operative (baseline) and post-operative cephalometric analysis was performed using skeletal landmarks that include the sella (S), nasion (N), A-point (A), B-point (B) and

posterior airway space (PAS; distance between the base of the tongue and the posterior pharyngeal wall, derived from a line connecting B-point to gonion in millimetres). The following reference lines were placed on all cephalometric tracings to create descriptive linear measurements of interest, a constructed horizontal plane (S-N line, 7°) and x-axis (vertical at S, perpendicular to constructed horizontal plane). Using points S, N, A and B the maxilla, mandible and the skeletal relationship between maxilla and mandible was computed. SNA indicates whether or not the maxilla is normal, prognathic or retrognathic. SNB assesses the mandible in a similar way (normal, prognathic and retrognathic) and ANB defines the skeletal relationship as a class I (+2 degrees), class II (+4 degrees or more) or class III (0 or negative). The distance between points A and B was measured with respect to the x-axis (Ax and Bx) to assess the horizontal movement of the maxilla and the mandible. Similarly, the distance of points A and B to the constructed horizontal plane was measured (Ax') to assess the vertical movement of the maxilla (see Fig. 1).

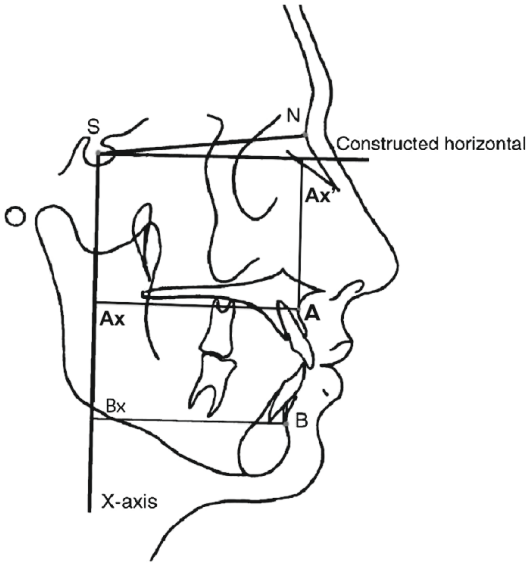


Fig. 1. Skeletal landmarks and measurements.

Polysomnography

Standard polysomnographic evaluation at pre- (baseline) and post-operative was based on electroencephalography, electrooculography, chin and leg electromyography and electrocardiography. Respiration was assessed through oronasal airflow, thoracic and abdominal movements (inductive plethysmography) and peripheral capillary oxygen saturation measurements (pulse oximetry). Polysomnographic variables were integrated into the AHI, because the scope of this article is on the technical considerations of the MMA.

Maxillomandibular advancement (MMA) procedure

A Le Fort I osteotomy and a BSSO was performed to advance the maxillary and mandibular facial skeleton. The maxilla was advanced to the pre-operatively planned position (~8-10 mm anteriorly) and an intermediate splint was installed to immobilize the advanced maxilla. After fixation of the maxilla with osteosynthesis, the mandible was repositioned using a final splint and fixated with osteosynthesis. Post-operatively, elastics were used for guiding the occlusion. Intra-operative information such as surgical time, admission time and blood loss were recorded. Potential complications associated with the MMA procedure were assessed for each patient and included malocclusion, sensory disturbances of the IAN, symptomatic ostheosynthesis requiring hardware removal and malunion of the maxilla or mandible.

Primary outcome was defined as surgical success or failure according to the criteria by Sher et al. for surgical treatment of OSA (AHI <20 and >50% reduction).(5) Secondary outcomes were specific patient characteristics like age, gender, ASA-score, BMI, neck circumference and pre- and post-operative AHI and cephalometric variables.

Statistical analysis

All datasets were analysed with SPSS® (IBM® SPSS® Statistics version 21, IBM Corp. Armonk, NY, USA). Descriptive statistics were assessed on normality and were analysed and expressed as median (interquartile range) or mean ± standard deviation. All presented variables were tested for their influence on post-operative surgical success or failure using the Fisher Exact Test for categorical variables and the Mann-Whitney U Test for continuous variables. We describe associations between continuous variables using Spearman's Rho correlation. Strength of correlation was categorized as either being absent (<0.20), poor (0.20-0.34), moderate (0.35-0.50) or strong (>0.50).(11) A *P*-value <0.05 was considered statistically significant.

Results

Sixty-two consecutive patients (87% male) were treated with MMA for OSA. Baseline characteristics showed a median age of 54 (47-61) years, BMI was 29 (27-33) and median neck circumference was 43 (40-45). Polysomnographic parameters showed a median AHI pre-operative of 52 (36-67). Only 19 patients (31%) had a medical history coinciding with ASA I, 35 patients (57%) with ASA II and 8 patients (13%) with ASA III. The primary outcome formulated as surgical success or failure showed a 71% success rate in our population after MMA when applying the success formula according to Sher.

Secondary outcome defined as a reduction of the AHI after MMA showed a 69% decrease in AHI in our patient population. A statistically significant difference between patient age and neck circumference was found when comparing success vs. failed therapeutic outcomes (P=0.037 and P=0.008, respectively). There were no significant differences observed between gender, BMI and ASA scores. A comparison of BMI separations of obesity (BMI >30) vs. non-obesity (BMI <30), showed no significant difference between the MMA success and failed outcomes. A reduction of AHI was higher in the obese patients 82% (49-90) in comparison to the non-obese patients 73% (53-87). A summary of each parameter separated as successful and failed outcomes is presented in Table 1.

Table 1. Variables assessed for therapeutic success and failure after MMA. Datasets presented as median (IQR; interquartile range). Bolded *P*-value indicates significant differences.

	Success	**Failure**	*P*-value
ASA [I/II/III]	16 / 23 / 5	3 / 12 / 3	0.325
Gender [M/F]	37 / 7	17 / 1	0.418
Age [years]	53 (43-60)	58 (52-62)	**0.037**
BMI	29 (27-33)	30 (28-33)	0.609
Neck circ.[a] [cm]	42 (40-44)	44 (43-48)	**0.008**
AHI pre-op	51 (35-67)	56 (37-74)	0.515
ODI pre-op	38 (26-52)	49 (26-65)	0.223
PAS pre-op [mm]	7 (5-10)	8 (6-10)	0.365
SNA pre-op [degrs]	81 (79-83)	80 (78-85)	0.739
SNB pre-op [degrs]	76 (73-78)	77 (73-82)	0.299
ANB pre-op [degrs]	5 (3-7)	4 (-1-7)	0.480

[a] data is based on 45 patients because of missing data.

Table 2. Cephalometric analysis.

	SNA[a] (°)	**SNB[a] (°)**	**PAS[a] [mm]**
Pre-operative	81 (78-84)	76 (73-79)	7 (5-10)
Post-operative	87 (85-92)	80 (77-84)	14 (11-17)

Datasets are presented as median (IQR; interquartile range).
[a] SNA (S-N line and A-point), SNB (S-N line and B-point), PAS (pharyngeal airway space)

Cephalomatric parameters

Pre-operative skeletal profile (ANB) showed a class I in 21 patients (34%), a class II (retrognathism) in 34 patients (56%) and a class III (prognathism) in 6 patients (10%). Baseline and post-operative differences in skeletal relationships represented by SNA, SNB and ANB are shown in Table 2. The advancement of the maxillomandibular complex sets the maxilla in a prognathic position, the mandible is within normal range and the skeletal relationship between maxilla and mandible was retrognathic in most cases. The PAS showed a

significant increase from median pre-operative of 7 (5-10) to 14 (11-17) post-operatively (P<0.001). In this population the median advancement of the maxilla was 7 mm (5-8) in the success cases and 8 mm (7-10) in the patients with failure in decrease of OSA. The mandible also had an advancement of median 7 mm (5-10) in patients with success OSA decrease, the failure cases showed an advancement of 6 mm (4-6). The advancement of the maxilla and mandible and the enlargement in PAS were not different when comparing therapeutic success cases with failures. Table 3 summarizes baseline and post-operative maxillary and mandibular skeletal dimensional relationships. Maxillary and mandibular advancement were not correlated with the decrease in AHI, -0.147 (P=0.265) and 0.117 (P=0.378) respectively. Only the enlargement of the PAS and the advancement of the mandible (B) were positively correlated 0.439 (*P*<0.001).

Reported complications

Thirty-seven patients (60%) reported sensory disturbances from the IAN that persisted for >1 year. In 13 patient's additional treatment for severe malocclusion was required. A second procedure in general anaesthesia was necessary in 25 patients (40%); 5 patients were treated with a second Le Fort I osteotomy and 3 patients with a second MMA because of a combination of malocclusion and malunion. The remaining 17 patients were treated for symptoms that required hardware removal. A bad split occurred in only one patient and could be corrected during the procedure. No systemic complications were reported (i.e. cardiac events, respiratory, or neurologic adverse events) or associated with the MMA surgery. One patient had a pharyngeal rupture as a result of extubation by the anaesthesiologist and required re-intubation with reconstruction of the posterior pharyngeal wall with prolonged ICU admission. Overall no tracheotomies were performed. Perioperative variables showed a mean operating time of 20270± min and mean blood loss of 366±218 ml. Mean post-operative admission for patients treated with MMA was 3±1 days.

Table 3. Cephalometric analysis.

	Success	**Failure**	*P*-value
Maxillary adv. Hor. [mm]	7 (5 - 8)	8 (7 – 10)	0.164
Maxillary impaction Vert. [mm]	1 (-2 – 2)	1 (0 - 2)	0.820
Mandibular adv. Hor. [mm]	7 (5 – 10)	6 (4 – 10)	0.248
PAS adv. [mm]	5 (2 – 8)	6 (4 – 12)	0.302

Datasets are presented as median (IQR; interquartile range).
[α] SNA (S-N line and A-point), SNB (S-N line and B-point), PAS (pharyngeal airway space)

Discussion

The aim of this study was to identify factors that could be of influence on the success or failure in terms of OSA treatment following MMA surgery. This patient cohort presented two variables that were related with the outcome of success and failure; the first was age, which was higher in the patients that did not have a decrease in AHI successfully, the second was neck circumference that was higher in patients with OSA treatment failure. With regard to age, possible explanation for this might be because of degeneration of the muscle fibers in the pharyngeal airway, that gives a more relaxation and softening. The mechanism behind MMA is to widen the pharyngeal airway by stretching soft tissues, but because of the increasing age of tissues, this mechanistic effect might be more susceptible to failure. In limited pharyngeal airway, gravity plays another important role and neck circumference can make gravitational forces even more important. The amount of tissue in the neck is possibly due to increased fat deposition. This report shows that both physiological characteristics could be of potential interest for preoperative screening for indicating MMA procedure. Previous research showed that age was already recognized as a predictor of success in decrease of AHI.[6] But neck circumference was not described in previously performed patient cohort studies and systematic reviews by Holty et al.[6], Pirklbauer et al.[12] and more recently Zaghi and colleagues.[7] This suggests that neck circumference may be a relatively new parameter that was not previously recognized and requires further exploration. It is well known that neck circumference plays a significant role in the diagnosis of OSA,[13] for example this variable is included in the broadly used screening-instrument STOP-Bang.[14] Therefore it could also be of great importance in selecting patients for different treatment modalities.

Other possible factors that were assessed in this study like BMI or advancement of the maxilla and a lower pre-operative AHI were not recognized as possible influential factors for success. BMI is a physiological characteristic comparable to neck circumference, but apparently there may be a difference in influence on OSA. When assessing the advancement of the maxilla and the mandible in relation to the decrease in AHI, no relation could be found. It seems more likely that there is a threshold system for decreasing AHI instead of a linear relation. The only significant correlation that exists was the correlation between the advancement of the mandible and the enlargement of PAS. Whether PAS is a good indicator for the degree of the OSA is debatable. PAS is measured on a lateral cephalometric radiograph that is taken in an upright position in a fully awake state as opposed to a sleeping state.

MMA in OSA patients consists of greater advancements than manoeuvres indicated for orthodontics and is regarded as a more aggressive therapeutic manoeuvre in comparison with MMA for orthodontic purposes. Literature on MMA shows great insight in the efficacy of the treatment, but less extensively on the morbidity, adverse effects and complications. New studies aim to address these factors, for example Passeri et

al.[15] showed a comparison between MMA procedure for OSA patients and non-OSA patients and found a high level of reoperation, this was mostly due to hardware failure (32%). The indication for reoperation was comparable in our patients' group, in which 40% was re-operated. The reasoning for this high rate of reoperation is not fully understood yet and needs further evaluation. A possible explanation may be the greater amount of repositioning, surgical technique, and the experience of the surgeon but also patient depended factors like age and comorbidity may influence regeneration abilities.

The most frequently described complication associated with MMA procedures (not specific for OSA) is the loss of neurosensory function in the IAN, with a reported incidence of 0-85% in non-OSA patients.[16] Retrospective analysis revealed an increased age was an important factor in manifestations of complications, 33% of the patients with an age >30 years had neurosensory disturbances after 6 months and 15% after one year.[17] Literature suggests that peripheral nerve regeneration and re-innervation is decreased in older patients.[18] The results from our study showed a subjective impairment of the IAN in almost 60% of our patients after a mean period of more than one year. Few publications have reported the loss of function of the IAN in OSA patients; 40% of the patients reported by Boyd et al. subjectively perceived a decreased sensation.[19] Another study showed 52% of subjectively perceived loss of IAN-function.[20] Earlier research reported similar results for IAN loss of function, around 40%.[21]

In patients with a relatively healthy dentition and good occlusion, adjunct orthodontic treatment is mandatory. Maybe even just for a short period of time to maintain a stable occlusion. Most common complication after MMA without orthodontics is iatrogenic malocclusion despite the usage of arch bars or skeletal screws for an adequate maxillomandibular fixation. In our cohort 13 patients (i.e. not treated with orthodontics (n=29) and edentulous patients excluded) reported malocclusion after MMA, which represents 45%. This is comparable to present literature with reports of malocclusion of up to 44%.[6, 21] A possible explanation this high rate of malocclusions is that large distances of the maxilla and mandible can cause stronger traction of the muscles on these bony structures. Eventually this may result in an unstable occlusion despite a good occlusion immediately postoperatively and guidance with elastics. Besides one extubation trauma (which was not attributed to MMA) no other life-threatening or severely disabling complications occurred caused by MMA surgery.

In conclusion, this study reveals new parameters for identifying potential non-responding patients treated with MMA for moderate and severe OSA. Neck circumference and age were parameters in this study that were different comparing failures patients with success; in other words, the greater the neck circumference or higher a patient's age, the more likely the MMA procedure could fail to adequately decrease AHI. MMA is an effective procedure for reducing AHI, with a moderate risk for major complications or side effects. The most reported complications are (subjectively perceived) loss of neurosensory

function of the IAN and malocclusion. More research is needed to explore especially the role of neck circumference and possible other factors in relation to possible failures regarding MMA for treating and selecting OSA patients.

References

1. Senaratna CV, Perret JL, Lodge C, et al. Prevalence of Obstructive Sleep Apnea in the general population: A systematic review. *Sleep Medicine Reviews*.
2. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5:263-276.
3. de Ruiter MH, Apperloo RC, de Lange J. [Maxillomandibular advancement surgery as an optional therapy for patiens with severe obstructive sleep apnoea]. *Ned Tijdschr Tandheelkd* 2013;120:470-474.
4. Butterfield KJ, Marks PL, McLean L, Newton J. Linear and volumetric airway changes after maxillomandibular advancement for obstructive sleep apnea. *J Oral Maxillofac Surg* 2015;73:1133-1142.
5. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996;19:156-177.
6. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev* 2010;14:287-297.
7. Zaghi S, Holty JE, Certal V, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2016;142:58-66.
8. Li KK, Riley RW, Powell NB, Troell R, Guilleminault C. Overview of phase II surgery for obstructive sleep apnea syndrome. *Ear Nose Throat J* 1999;78:851, 854-857.
9. Prinsell JR. Maxillomandibular advancement surgery in a site-specific treatment approach for obstructive sleep apnea in 50 consecutive patients. *Chest* 1999;116:1519-1529.
10. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a surgical protocol for dynamic upper airway reconstruction. *J Oral Maxillofac Surg* 1993;51:742-747; discussion 748-749.
11. Juniper EFaG, Gordon H and Jaeschke, Roman. How to develop and validate a new health-related quality of life instrument. *Quality of life and pharmacoeconomics in clinical trials* 1996;2:49-56.
12. Pirklbauer K, Russmueller G, Stiebellehner L, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea syndrome: a systematic review. *J Oral Maxillofac Surg* 2011;69:e165-176.
13. Davies RJ, Ali NJ, Stradling JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. *Thorax* 1992;47:101-105.
14. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008;108:812-821.
15. Passeri LA, Choi JG, Kaban LB, Lahey ET, 3rd. Morbidity and Mortality Rates After Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea. *J Oral Maxillofac Surg* 2016.
16. Agbaje JO, Salem AS, Lambrichts I, Jacobs R, Politis C. Systematic review of the incidence of inferior alveolar nerve injury in bilateral sagittal split osteotomy and the assessment of neurosensory disturbances. *Int J Oral Maxillofac Surg* 2015;44:447-451.
17. Verweij JP, Mensink G, Fiocco M, van Merkesteyn JP. Incidence and recovery of neurosensory disturbances after bilateral sagittal split osteotomy in different age groups: a retrospective study of 263 patients. *Int J Oral Maxillofac Surg* 2016;45:898-903.

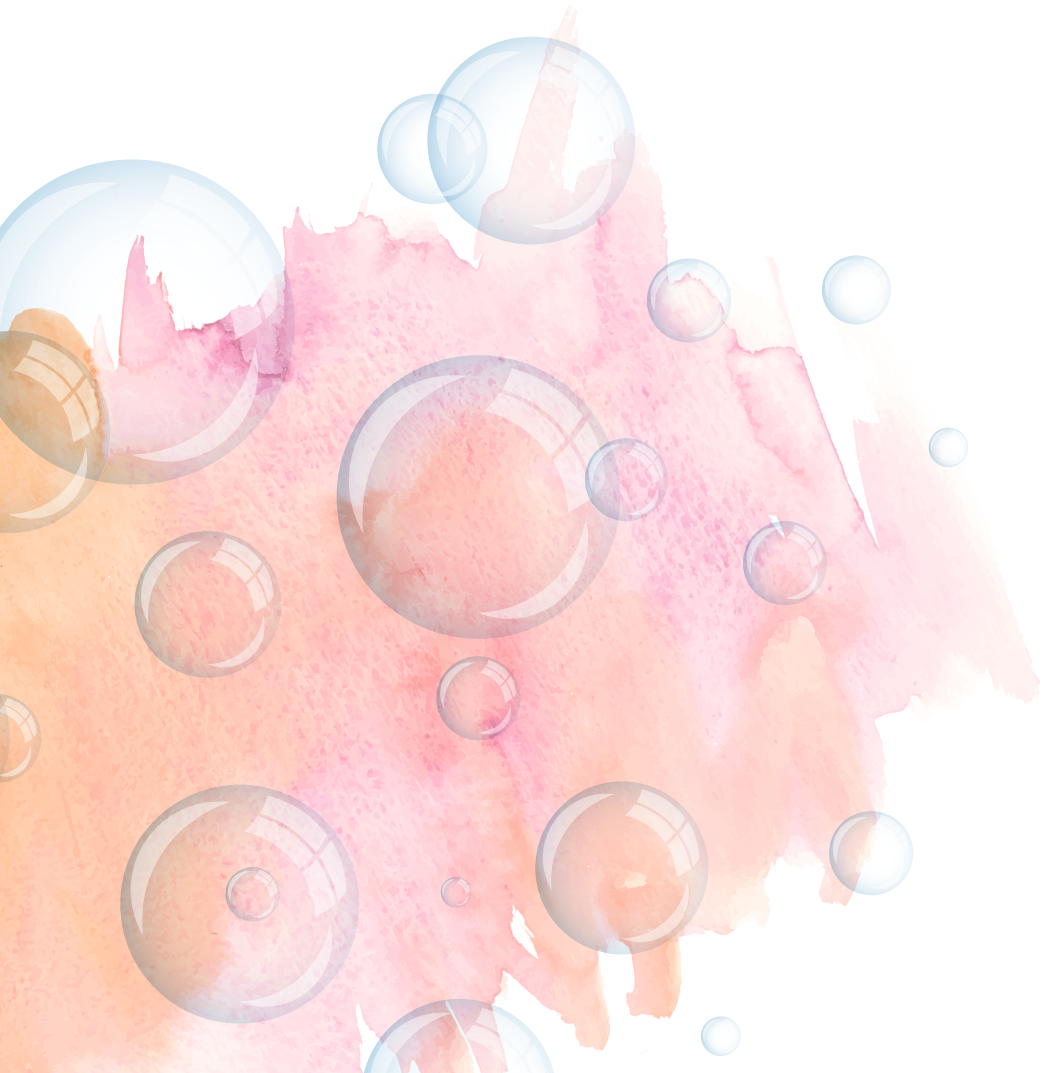
18. Verdu E, Ceballos D, Vilches JJ, Navarro X. Influence of aging on peripheral nerve function and regeneration. *J Peripher Nerv Syst* 2000;5:191-208.

19. Boyd SB, Walters AS, Waite P, Harding SM, Song Y. Long-Term Effectiveness and Safety of Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea. *J Clin Sleep Med* 2015;11:699-708.

20. Blumen MB, Buchet I, Meulien P, Hausser Hauw C, Neveu H, Chabolle F. Complications/ adverse effects of maxillomandibular advancement for the treatment of OSA in regard to outcome. *Otolaryngol Head Neck Surg* 2009;141:591-597.

21. Waite PD, Wooten V, Lachner J, Guyette RF. Maxillomandibular advancement surgery in 23 patients with obstructive sleep apnea syndrome. *J Oral Maxillofac Surg* 1989;47:1256-1261; discussion 1262.

CHAPTER 6



Facial esthetics and subjective impairment assessed after maxillomandibular advancement surgery for patients with obstructive sleep apnea

M.H.T. de Ruiter
R.C. Apperloo
D.M.J. Milstein
J. de Lange

This chapter is based on the publication in: CRANIO, The Journal of Craniomandibular & Sleep Practice 2020

Abstract

Objective

To assess facial esthetics and quality of life (QoL) as a measure of success or failure after maxillomandibular advancement (MMA) surgery for obstructive sleep apnea (OSA).

Methods

Visual analogue scales (VAS) on facial esthetics and QoL survey, including EQ-5D-3L, Epworth Sleepiness Scale (ESS) and Functional Outcome of Sleep Questionnaire (FOSQ) were collected. Outcomes were analyzed for surgical-success/failure after MMA.

Results

Forty-one OSA patients returned completed surveys (response-rate 66%). Mean VAS on facial esthetics was 57±22 mm preoperative and 51±24 mm postoperative (P=0.217). When MMA was considered a surgical-failure VAS was significantly more negative (40±22 mm; P=0.026). EQ-5D-3L showed an overall mean score of 73.2 ± 15.7, ESS was 6.3 ± 5.4 and FOSQ was 16.0 ± 3.3.

Conclusion

No significant alteration of facial esthetics were reported after MMA; however, lower QoL was associated with surgical-failure whereas in surgical-success QoL were higher.

Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. The overall prevalence of OSA is 9-38% in the general adult population and is higher in men and rises with increasing age [1]. Recently higher prevalence rates were reported compared to earlier findings: 84% of men vs. 61% of women had OSA, defined as an apnea-hypopnea-index (AHI) >5, recorded by polysomnography (PSG). Specifically, the prevalence of moderate and severe OSA (AHI >15) was estimated at 50% in men and 24% in women [2]. OSA is a chronic disorder characterized by recurrent (partial) closure of the upper airway accompanied by intermittent oxygen desaturation and sympathetic activation [3]. OSA causes neurocognitive problems resulting in impaired quality of life and excessive daytime sleepiness. It has also been described as an independent risk factor of cardiovascular sequelae [4, 5].

Treatment of OSA is usually initiated with conservative therapies consisting of lifestyle changes, improved sleep hygiene, weight reduction, avoidance of alcohol and supine sleeping position[6]. After these conservative measures, treatment options include oral appliance therapy (OAT), continuous positive airway pressure (CPAP) and surgery[7-9]. The golden standard of OSA therapy is CPAP, but because of disappointing adherence to this treatment other options are often explored [10]. In the case of CPAP intolerance, oral appliance therapy is often considered and provides satisfactory outcomes on treatment success, especially in patients with mild and moderate OSA (AHI <30) [7]. In patients with severe OSA (AHI >30) treatment by OAT is considered but often proves insufficient. Next to OAT and CPAP, different types of surgery for a patient with OSA are available [11]. One promising surgical approach, the maxillomandibular advancement surgery (MMA), shows very good results for treating severe OSA [12]. Therapeutic efficacy in surgical procedures for OSA is defined using criteria described by Sher et al., which proposes achieved therapeutic *success* when AHI drops more than 50%, there are less than 20 events/h postoperatively and defines surgical *cure* as an AHI <5 after intervention [13]. Based on the aforementioned definitions above MMA results in good surgical outcome with surgical success rates reported as 86% and a cure rate of 43% [11, 12, 14, 15]. MMA can provide an effective and lifelong solution for patients with severe OSA; however, it has as downside because it is highly invasive and can alter facial appearance dramatically.

The aim of this study was to assess facial esthetics and quality of life as a measure of success or failure associated with MMA surgery for severe OSA. It was hypothesized that higher quality of life outcomes is associated with successful MMA. Perceived changes in facial esthetics were also assessed since MMA may also yield an undesired effect on facial esthetics despite MMA surgery's main goal, which is the curative treatment of severe OSA.

Methods

The data for this single-center observational study was obtained from patients admitted between 2011 and 2015 for elective MMA therapy for moderate and severe OSA. The institutional medical ethics review board of the Amsterdam University Medical Centre (location AMC) reviewed the study guidelines and procedures and granted permission to collect data and questionnaires (Project No. W16_006). All participants registered in this investigation's database received a detailed explanation of the study guidelines and procedures and written informed consent was obtained. This investigation was conducted in accordance with the principles established in the Declaration of Helsinki (Fortaleza, October 2013).

Study participants

Patients with moderate or severe OSA referred to the Department of Oral & Maxillofacial Surgery of the Academic Medical Center of the University of Amsterdam for elective MMA procedure were eligible for participation in this study. This study is a second part of a large cohort of data derived from patients that participated in a previously reported investigation concerning technical considerations associated with surgical success and failure after the MMA procedure [12].

Questionnaires

All patients were asked to complete three questionnaires after MMA surgery: EQ-5D-3L (for general health quality of life), Epworth Sleepiness Scale (ESS) and the Functional Outcome of Sleep Questionnaire (FOSQ). Specific data of the EQ-5D-3L, ESS and FOSQ questionnaires before MMA surgery was not available for analysis. The change in facial esthetics was assessed using a visual analogue scale (VAS) and data was collected before and after MMA surgery.

EQ-5D-3L

The EQ-5D-3L, developed by the EuroQol Group (EuroQol Research Foundation, Rotterdam, The Netherlands), is a standardized self-administrated questionnaire for general health in 5 dimensions: mobility, self-care, daily activities, pain/discomfort, and mood consisting of both anxiety and depression. It uses a 3-point rating scale in which 1 stands for "no problems", 2 for "moderate problems" and 3 for "extreme problems". The questionnaire also contains a EuroQol-Visual Analogue Scale (EQ-VAS) from 0 (worst imaginable overall health) to 100 (best imaginable overall health) that generates a self-rating general health score. The EuroQol instruments have been extensively validated [16, 17].

Epworth Sleepiness Scale (ESS)

The ESS was designed as a subjective method of estimating excessive daytime sleepiness [18]. It consists of 8 questions about subjective daytime sleepiness in 8 every-day situations

(each question scores 0-3, max. of 24). The cut-off to determine excessive sleepiness was set at a score of 10 [19].

Functional Outcomes of Sleep Questionnaire (FOSQ)
To determine the impact of disorder of excessive sleepiness on daily living and quality of life in adults, the FOSQ was used [20]. The FOSQ consists of 30 questions with a 5-point rating scale (0=always and 4=never). Factor analysis of the FOSQ yielded 5 factors: activity level (9 items), vigilance (7 items), intimacy and sexual relationships (4 items), general productivity (8 items) and social outcome (2 items). Subscale scores were summed up to get a total score with a maximum of 20 points. A low score represents dysfunction of the respondent, due to excessive daytime sleepiness.

Visual Analogue Scale (VAS)
Facial appearance was assessed retrospectively by VAS before and at least 6 months after surgery subjectively by the patients. Overall satisfaction and treatment recommendation for the MMA procedure was also assessed using VAS. Subjective snoring assessment was evaluated by using VAS pre- and postoperatively as reported by the study subject. The VAS is a psychometric response scale from 0 to 100 on a 100 mm horizontal line, in which 0 is the worst outcome possible and 100 is the best achievable result. For example, the VAS on facial esthetics was described as a range from 0 (not pretty/beautiful) to 10 (very pretty/beautiful).

Maxillomandibular advancement (MMA) procedure
A Le Fort I osteotomy and a bilateral sagittal-split osteotomy were performed to advance the maxillary and mandibular facial skeletons respectively. The maxilla was advanced to the preoperatively planned position (~8-10 mm anteriorly) and an intermediate splint was installed to immobilize the advanced maxilla. After fixation of the maxilla with osteosynthesis the mandible was repositioned in the planned position using a final splint and fixated with osteosynthesis. Elastics were used postoperatively for guiding maxillomandibular occlusion.

Statistical analysis
All datasets were analyzed with SPSS® (IBM® SPSS® Statistics version 25, IBM Corp. Armonk, NY, USA). Descriptive statistics were assessed on normality and were analyzed and expressed as median (interquartile range) or mean ± standard deviation. Presented variables were tested for differences between postoperative surgical success or failure using the Fisher Exact Test for categorical variables and the Mann-Whitney U Test for continuous variables. Associations were described between continuous variables using Spearman's Rho correlation. Strength of correlation was categorized as either being absent (<0.20), poor (0.20-0.34), moderate (0.35-0.50) or strong (>0.50) [21]. A *P*-value <.05 was considered statistically significant.

Results

Overall outcomes measures

A total of 62 patients had MMA surgery for severe OSA of which eventually 41 patients were included into the study population (i.e. response rate of 66%). The study population had a mean age of 55±10 years, and 35 patients were male (85%). All demographic parameters of the study population are presented in Table 1 (including details regarding non-responders). No differences between responders and non-responders were noticed, indicating that the current cohort sample may be a good representation of MMA treated severe OSA patients.

Table 1. Characteristics of the study population. Data is presented as mean (±SD).

	Patients (N=41)	%	Missing patients (N=21)	%	P-value
Gender [M:F]	35:6	85:15	19:2	90:10	.577
Age [years]	55 (±10)		50 (±10)		.056
BMI [m^2/kg]	30 (±4)		31 (±5)		.243
Neck circumference [cm][a]	42 (±4)		44 (±3)		.135
AHI preoperative	54 (±22)		50 (±18)		.550
AHI postoperative	18 (±17)		13 (±14)		.274
MMA success [yes/no][b]	27/14	66/34	17/4	81/19	.222
ASA score [I / II / III]	11/25/5	27/61/12	8/10/3		.598

[a] Data is based on 31 patients, because of missing data.
[b] Success/failure based on the Sher criteria: postoperative AHI changes >50% and <20 events/h.
ASA: American Society of Anesthesiologists, BMI: body mass index, AHI: Apnea-hypopnea-index, MMA: maxillomandibular advancement, SD: standard deviation

The EQ-5D-3L showed a lower overall score in overall health that was also reflected by the EQ-VAS and in every other domain of the questionnaire compared to the normal scores of the general population in the Netherlands (Table 2). Postoperatively the ESS had a mean of 6.3±5.4 and the FOSQ a mean of 3.3±16.0. When patients were selected for MMA success or failure (criteria defined by AHI decrease of >%50 and AHI <20) the FOSQ and EQ-VAS showed significantly better result in favor of the success-group (*P*=.003 and *P*=.028 respectively). However, the ESS remained <10 for both groups and showed no significant difference (Table 3).

Table 2. OSA patient health-related quality of life using EQ-5D-3L compared with the general reference population in the Netherlands. This table presents an overview of the mean EQ-VAS ratings and the proportions of reported problems on each of the five EQ-5D dimensions.

	Patients (N=41)	MMA success (N=27)	MMA failure (N=14)	Standardized EQ-5D-3L results NL
Mobility	0.22	0.11	0.43	0.04
Self-care	0.00	0.00	0.00	0.03
Daily activity	0.19	0.15	0.29	0.15
Pain	0.58	0.52	0.71	0.31
Mood	0.29	0.22	0.43	0.17
EQ-VAS (0-100) Mean ratings	73.2	77.6	65.4	81.4

MMA: Maxillomandibular advancement, NL: the Netherlands

Table 3. Disease-specific quality of life (ESS, FOSQ, EQ-VAS).

	Total population (N=41)		MMA success (N=27)		MMA failure (N=14)		
	Mean	SD	Mean	SD	Mean	SD	*P*-value
ESS	6.3	5.4	5.1	4.1	8.6	7.0	.102
FOSQ	16.9	3.3	18.2	2.2	14.5	3.8	**.003**
EQ-VAS	73.2	15.7	77.6	12.0	65.4	18.7	**.028**

Bold P-value (<.05) indicates significant difference.
EQ-VAS of the EQ-5D-3L questionnaire, ESS: Epworth Sleepiness Scale, FOSQ: Functional outcome of Sleep Questionnaire, MMA: maxillomandibular advancement, SD: standard deviation

The mean VAS outcome for subjective assessment regarding facial esthetics was 58±22 mm at preoperative and 51±23 mm at postoperative and showed no significant difference (*P*=0.217). Nineteen patients (51%) perceived their postoperative facial esthetics as negative, 14 patients (38%) rated their change as positive after surgery and 8 patients (11%) were indifferent. When comparing the differences in VAS on facial esthetics after MMA, the success-group (57±21) reported a significantly better result in comparison to the MMA failure-group (40±22) (*P*=0.026).

The outcome on snoring using VAS showed a significant decrease in snoring postoperatively, from 83±21 to 20±21 (*P*<0.001). The snoring outcome after MMA didn't show significant differences when comparing patients with success and failed MMA on polysomnographic parameters (AHI) (Table 4). Overall satisfaction was good after MMA (65±29 mm) but in patients with MMA failure satisfaction was negatively experienced (55±34 mm) (Table 4).

Table 4. VAS snoring and assessment of facial change. Data is presented as mean (±SD). Differences between MMA success and failure are presented including P-values.

	Patients (N=37)	MMA success (N=24)	MMA failure (N=13)	P-value
VAS esthetics preop (0-100 mm)	58 (±22)	62 (±19)	51 (±27)	.200
VAS esthetics postop (0-100 mm)	51 (±23)	57 (±21)	40 (±22)	**.026**
VAS snoring preop (0-100 mm)	83 (±21)	84 (±18)	80 (±26)	.998
VAS snoring postop (0-100 mm)	20 (±21)	19 (±19)	20 (±24)	.868
VAS satisfaction (0-100 mm)	65 (±29)	71 (±25)	55 (±34)	.107
VAS recommendation (0-100 mm)	66 (±33)	68 (±31)	63 (±37)	.649

Bold P-value (<.05) indicates significant difference.
VAS: Visual Analogue Scale, MMA: maxillomandibular advancement, SD: standard deviation

Correlations between questionnaires

In this OSA patient population the satisfaction after MMA surgery was correlated with the outcome of the ESS, the FOSQ and the EQ-VAS, -0.368 (P=0.027), 0.620 (P<0.001) and 0.537 (P<0.001) respectively. The EQ-VAS showed a correlation with the ESS and FOSQ, -0.326 (P=0.043) and 0.599 (P<0.001) respectively.

Discussion

The main research objectives were to evaluate the subjective outcomes after MMA surgery based by using the EQ-5D-3L, ESS, FOSQ and subjective assessment of perceived facial esthetics using VAS. The results on general health, expressed by the overall quality of life (EQ-VAS) and daily function related to sleep problems (FOSQ), demonstrate good outcome yields associated with MMA. The overall outcome measurements based on sleepiness (ESS), snoring and facial esthetics (VAS) indicated that OSA patients were less sleepy and experienced reductions in snoring with no differences in perceived facial esthetics pre- and postoperatively following MMA.

The results of the EQ-5D-3L showed higher scores in all domains in OSA patients that were successfully treated by MMA surgery. In comparison to the healthy reference population in the Netherlands, OSA patients after MMA surgery reported a lower EQ-VAS[17]. This could be explained by other possible confounding factors such as gender, age, BMI and existing medical co-morbidities. At present, this is the first report concerning MMA surgery that illustrates the level of general quality of life after the MMA procedure and that compares OSA patient satisfaction as either success or failure of MMA on the basis of perceived facial esthetics. EQ-VAS scores were higher in patients that were

successfully treated by MMA surgery compared to those with an inadequate response in AHI. Patients with moderate-severe OSA that were treated with CPAP had already shown good response using EQ-5D [22]. Unfortunately, CPAP is a medical device with poor patient adherence, which is necessary for achieving desired therapeutic results [9, 10]. In treating patients using MMA surgery, it is recommended to use questionnaires assessing general quality of life next to specific sleep quality of life questionnaires because of the influence of OSA on daily function, mental state and overall wellbeing. The impact of OSA is not limited to excessive daytime sleepiness, but significantly contributes to the impairment of all domains of general health quality of life, e.g. mobility, mood and pain.

Excessive daytime sleepiness was evaluated using the ESS and showed an overall score of <10 for both MMA success and failure groups. No difference was observed between both success and failure groups which suggests that patients were not reporting excessive daytime sleepiness after MMA regardless of the outcome on AHI. Patients who were treated successfully by the MMA procedure had a significantly better daily functioning represented by the FOSQ. Previous studies addressed disease-specific quality of life by using ESS, FOSQ and OSA-Q and showed good beneficial effects after MMA [23-27]. Our OSA patient data also showed similar results on ESS and FOSQ postoperative assessments, supporting the conclusion that MMA is a procedure that results in improved quality of life outcomes. In patients with inadequate AHI-reduction the ESS still showed a positive response (<10), however, other results (FOSQ) indicated that these patients had problems with daytime functioning and sleepiness because of persistent sleep impairment.

On snoring and esthetics

OSA patients reported no significant alteration regarding perceived facial esthetics after MMA in pre- and postoperative assessments. Although our OSA patients were less positive about the facial esthetic changes (38%) compared to the studies by Li et al. (55%) and Islam et al (54%) [26, 28]. A possible explanation for this difference could be patient selection and the inherent subjectivity associated with questionnaires. It is noteworthy to mention that MMA procedures were not refused to severe OSA patients in whom it was thought that the procedure could potentially alter their face intensely, yet these severe OSA patients persisted with the notion of getting an effective treatment for OSA and accepted facial alterations. OSA patients perceived their facial esthetics as being more negative when MMA failed to strongly reduce AHI in comparison to the patients that were operated successfully (strong reduction in AHI) for their OSA. OSA patients treated by MMA report less snoring after MMA (i.e., in both success and failure cases).

Recommendations for future research

This investigation only reported the postoperative subjective response from OSA patients and the differences associated with success and failed MMA procedures. Future research on MMA should explore the variables that were used in this study to evaluate longitudinal outcomes over time, but for assessing causal effect on quality of life, pre- and postoperative measurements are necessary. Overall our OSA study population was relatively small and a larger patient sample would place the current observations into a more robust clinical perspective. MMA is not the first treatment of choice for OSA and because of its highly invasive nature it remains a less popular therapeutic option in general.

The use of the EQ-5D-3L in moderate to severe OSA patients remains interesting with regards to its utility and because of the absence of validity in OSA patients. Jenkinson et al. showed that the EQ-5D-3L had limited responsiveness in OSA patients [29], yet the EQ-5D-3L is a clear and easy to use short questionnaire. When using the EQ-5D-3L in combination with the ESS or FOSQ, a greater perspective is gained from each individual OSA patient and a study population.

Conclusion

In this study, patients generally reported no significant alteration in their perceived facial esthetics before or after the MMA procedure. If postoperative esthetics were negatively perceived by the patient then MMA was considered a surgical-failure. Interestingly, EQ-5D-3L assessments showed a negative overall score postoperatively across all domains when compared to the scores of the general reference population in the Netherlands. When patients achieve surgical-success after MMA the results on quality of life are close to outcomes of the healthy reference population in the Netherlands.

References

1. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev* 2017;34:70-81.
2. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310-318.
3. Strollo PJ, Jr., Rogers RM. Obstructive sleep apnea. *N Engl J Med* 1996;334:99-104.
4. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122:352-360.
5. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 2010;182:269-277.
6. Benoist L, de Ruiter M, de Lange J, de Vries N. A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. *Sleep Medicine* 2017;34:109-117.
7. Hoekema A, Stegenga B, De Bont LG. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. *Crit Rev Oral Biol Med* 2004;15:137-155.
8. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2004:CD004435.
9. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011;15:343-356.
10. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173-178.
11. Caples SM, Rowley JA, Prinsell JR, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. *Sleep* 2010;33:1396-1407.
12. de Ruiter MHT, Apperloo RC, Milstein DMJ, de Lange J. Assessment of obstructive sleep apnoea treatment success or failure after maxillomandibular advancement. *Int J Oral Maxillofac Surg* 2017;46:1357-1362.
13. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996;19:156-177.
14. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev* 2010;14:287-297.
15. Zaghi S, Holty JE, Certal V, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2016;142:58-66.
16. Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQolc-questionnaire. *Health Econ* 1993;2:237-246.
17. Szende A, Williams A. *Measuring self-reported population health: an international perspective based on EQ-5D*: SpringMed publishing; 2004.
18. Rosenthal LD, Dolan DC. The Epworth sleepiness scale in the identification of obstructive sleep apnea. *J Nerv Ment Dis* 2008;196:429-431.
19. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. *J Sleep Res* 2000;9:5-11.

20. Weaver TE, Chasens ER. Continuous positive airway pressure treatment for sleep apnea in older adults. *Sleep Med Rev* 2007;11:99-111.

21. Juniper EFaG, Gordon H and Jaeschke, Roman. How to develop and validate a new health-related quality of life instrument. *Quality of life and pharmacoeconomics in clinical trials* 1996;2:49-56.

22. Moyer CA, Sonnad SS, Garetz SL, Helman JI, Chervin RD. Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Med* 2001;2:477-491.

23. Boyd SB, Walters AS, Waite P, Harding SM, Song Y. Long-Term Effectiveness and Safety of Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea. *J Clin Sleep Med* 2015;11:699-708.

24. Butterfield KJ, Marks PL, McLean L, Newton J. Linear and volumetric airway changes after maxillomandibular advancement for obstructive sleep apnea. *J Oral Maxillofac Surg* 2015;73:1133-1142.

25. Goodday R, Bourque S. Subjective outcomes of maxillomandibular advancement surgery for treatment of obstructive sleep apnea syndrome. *J Oral Maxillofac Surg* 2012;70:417-420.

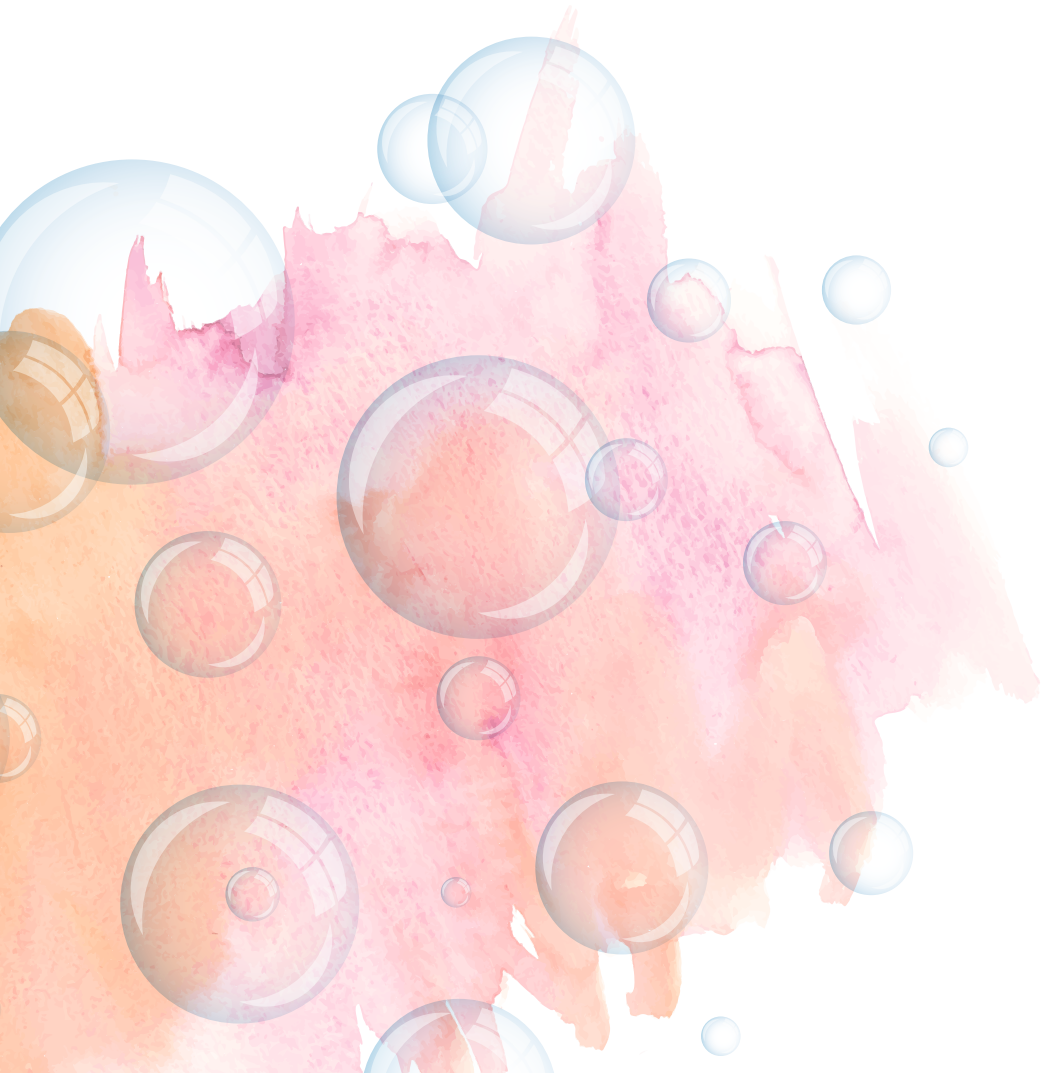
26. Islam S, Aleem F, Ormiston IW. Subjective assessment of facial aesthetics after maxillofacial orthognathic surgery for obstructive sleep apnoea. *Br J Oral Maxillofac Surg* 2015;53:235-238.

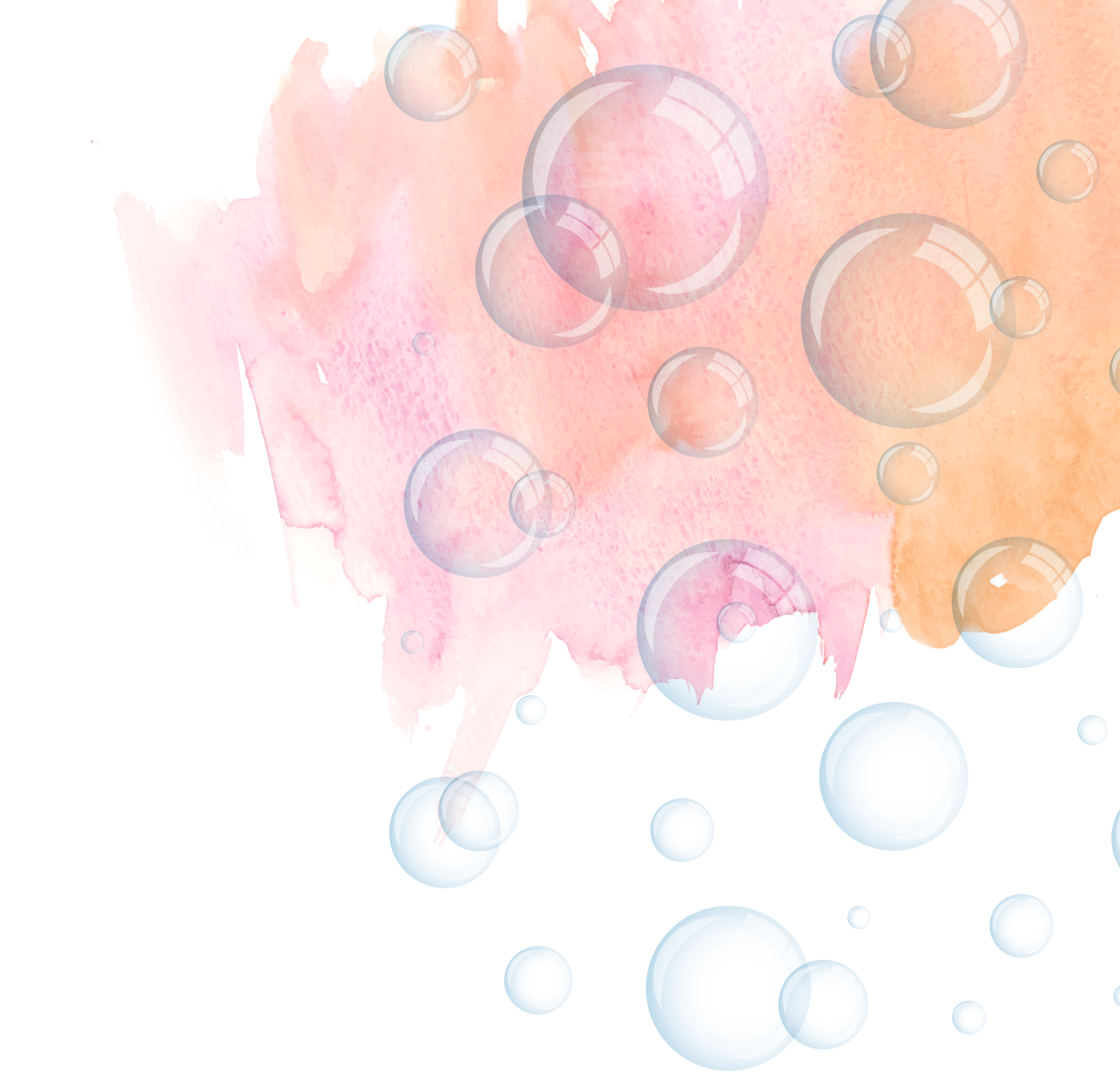
27. Lye KW, Waite PD, Meara D, Wang D. Quality of life evaluation of maxillomandibular advancement surgery for treatment of obstructive sleep apnea. *J Oral Maxillofac Surg* 2008;66:968-972.

28. Li KK, Riley RW, Powell NB, Guilleminault C. Patient's perception of the facial appearance after maxillomandibular advancement for obstructive sleep apnea syndrome. *J Oral Maxillofac Surg* 2001;59:377-380; discussion 380-371.

29. Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. *J Sleep Res* 1997;6:199-204.

CHAPTER 7





Summarizing discussion, clinical implications and future perspectives

Summarizing discussion and clinical implications

A substantial increase in Obstructive Sleep Apnea (OSA) prevalence has been identified in The Netherlands (and worldwide), which results in great impact on (inter)national healthcare systems.[1, 2] Clinicians and healthcare providers are struggling with this new cohort of patients and the need for improved insights in different treatment strategies for these patients is mandatory. To achieve a consensus on treatment strategy between different clinicians (e.g., pneumonologists, ENT-doctors, neurologists, dental sleep medicine specialists), not only the efficacy of the available therapies is desired but also more clarity on (long-term) treatment adherence, quality of life and patient specific parameters is necessary. The fore mentioned hiatus in treatment planning for OSA patients was explored in this thesis, specifically in oral appliance therapy (OAT), sleep position trainer (SPT) in part I and the maxillomandibular advancement surgery (MMA) in part II.

PART I

Oral appliance therapy is one of the most applied therapies for OSA, in particular in mild to moderate disease. However, a method to determine the optimal forward position of the mandible, compromise between comfort and maximal effectiveness in each individual patient is lacking.[3] In **chapter 2** a new standardized *stepwise* titration protocol for an OAT is assessed for its clinical usefulness in positional dependent OSA (POSA) patients. This chapter is the first article that proposed a standardized manner for titration in OAT to 1) achieve a maximum therapeutic effect on subjective and objective metrics; 2) results in acceptable side-effects in the short and long term; and 3) gives the highest possible adherence rate.[3] This study is a sub-assessment of a randomized controlled trial in which OAT was compared to the SPT in patients who had mild or moderate POSA (**chapters 3 and 4)**. The oral appliance (OA) was adjusted individually, and advancement was titrated using a standardized *stepwise* titration protocol. This titration protocol showed good efficacy on objective polysomnographic metrics, e.g. apneu hyponea index (AHI) and oxygen-desaturation index (ODI). Although all patients completed the first three months of treatment, 6 patients (17%) terminated OAT because of adverse effects (severe discomfort) and/or unsatisfactory results, and these results are corresponding with evidence available in recent literature.[4] Adherence to OAT in this protocol showed excellent outcomes. The titration protocol was not part of the initial research question of this PhD and therefore this study lacks a control group in the initial protocol. This article thus demonstrates the *proof of concept* of our titration protocol rather than an analysis on possible superiority or non-inferiority. The titration protocol for OAT is recommended in future research projects to improve the comparability between studies and in clinical practice for its practical feasibility.

The search for an adequate way to avoid supine sleeping position is since longtime topic of interest in the field of position dependent OSA (POSA).[5] Only recently a new device was developed to correct the sleep posture by giving a stimulus to avoid the supine sleeping position.[6] The SPT vibrates when a supine position is detected to prompt a change in body position. The device records objectively the adherence to the therapy. Cohort studies showed good effect in reducing the AHI and percentage of supine sleeping time, and the adherence was high after 6 months.[7] When comparing the new SPT with the old tennis ball technique, the SPT showed superior effect of efficacy and adherence.[8] In **chapter 3** the SPT was assessed in a prospective randomized controlled trial with the OAT over a period of three months. This study showed both therapies were equally effective in reducing AHI and adherence was excellent in both groups. The side-effects in both therapies did not resulted in a termination of therapy at three months and were equally distributed. The only significant finding between both therapies was the difference in outcome on the Epworth Sleepiness Scale (ESS). The ESS outcome showed a better decrease in the OAT group compared to the SPT group. However, this significant difference is of no value because all values below 10 display a lack of clinically relevant sleepiness in OSA patients.[9]

The durability of the SPT with the OAT was explored in the next chapter; long-term results of this prospective trial (after 12 months) are described in **chapter 4**. Both treatment modalities showed good persistent results on objective (polysomnographic) metrics and adherence data remained excellent after 12 months. One of the preferred areas of interests are the drop-outs in this analysis. While the number of patients that did not start treatment was higher in OAT, mostly because of lacking sufficient dental status, the number of patients who terminated therapy was higher in the SPT because of persistent snoring and apneas in the lateral position. This study shows the importance of increased knowledge of the advantages, disadvantages and adverse effects of each therapy. This could help guide the clinicians to proper individual therapy selection and follow-up regimes that maximize adherence and long-term outcomes. Due to the publications of this study, reimbursement of the SPT is granted in the Dutch Healthcare System.

PART II

Maxillomandibular advancement surgery (MMA) is regarded as one of the most effective treatment options for patients with OSA.[10] Because of the high invasiveness of this procedure most studies are cohort studies and there is only one randomized controlled trial. The overall outcome of these cohort studies represents excellent treatment outcomes on polysomnographic metrics and subjective parameters.[10, 11] One randomized controlled trial, which compared the MMA with continuous positive airway pressure (CPAP; regarded as the golden standard) showed both treatments were equally effective in reducing AHI.[12]

However, CPAP has only limited adherence in nightly usage and overall dedication to treatment, while the MMA has a long lasting effect on OSA.[13, 14] To identify the different aspects of the surgery and to give more insight in patient selection, **chapter 5** illustrates a broad exploration on the different variables that might influence surgical outcome after MMA. To distinguish the variables that could have an effect on the surgical outcome after MMA, a difference is made between patients with surgical success or surgical failure according to the criteria used by Sher et al; AHI decrease of more than 50% and below 20.[15] This study showed a higher age (>53 years) and greater neck circumference (> 43cm) as possible indicators for patients who are more susceptible for surgical failure after MMA surgery. Secondly, patients are more likely to undergo a second operating procedure after MMA surgery, mostly for hardware removal that appear to be symptomatic in these patients.[16] The adverse effects of orthognathic surgery are consistent with MMA surgery, e.g., neurosensory disturbances, but are prone to occur in a greater percentage of patients.[13] This is to be expected because of the different patients' characteristics; e.g., higher age, more comorbidities. And due to the differences in surgical features; e.g., larger displacement of the jaws compared to regular movements in orthognathic surgery. MMA surgery is regarded to be more complex than standard orthognathic surgical procedures and perhaps complications after MMA are more likely to be depended on the experience of the surgeon.

Next to the high efficacy of the MMA, more insight is needed in the subjective outcomes after MMA surgery. Especially the changes in the facial esthetics because of significant alterations in the facial skeleton are of interest of clinicians and patients.[17, 18] Also, other subjective outcomes measures like disease specific questionnaires are discussed in **chapter 6**. To analyze the outcomes of the different subjective parameters, difference is made between surgical success and failure according to the criteria of Sher et al; AHI decrease of more than 50% and below 20.[15] Overall outcome measurements based on sleepiness (ESS), snoring and facial esthetics (using visual analogue scales (VAS)) indicated that OSA patients were less sleepy (ESS) and experienced reductions in snoring with no differences in perceived facial esthetics pre- and postoperatively following MMA. Yet patients perceived their facial alterations as being more negative when MMA failed to reduce AHI in comparison to the patients who were treated successfully.

FUTURE PERSPECTIVES

Based on previously discussed outcomes on efficacy and side-effects, adverse effects and patients' subjective outcomes, clinicians should be able to create a more patient-tailored approach for treatment of OSA patients. The pathophysiology of OSA is multifactorial therefore the causes and consequences can vary substantially on an individual level.[19] This thesis emphasizes on the anatomical factors that cause pharyngeal airway obstructions, but also non-anatomical factors are crucial determinants of OSA in many people. These

include impairment of the pharyngeal dilator muscle control and function during sleep, increased propensity for awakening during airway narrowing (low respiratory arousal threshold) and respiratory control instability (high loop gain).[20] Different phenotypes are possible targets for ultimate OSA treatment.

Understanding all different treatment modalities for OSA is regarded extremely complicated for a single physician, because of the variety of specific pro's and contra's that needs to be addressed before the correct specific therapy can be assigned to the correct individual patient. Because of this, a multidisciplinary approach is mandatory and a framework on treatment planning is still lacking in (inter)national guidelines. Future research should focus to elucidate the different types of OSA patients on the one hand (phenotyping).[20-22] And on the other hand, more focus is needed to compare the different therapies with each other not only in efficacy, but also in side-effects, adherence and adverse effects; e.g. randomized controlled trial with MMA surgery and alternatives like pharyngeal airway surgery or hypoglossal nerve stimulation.

OSA represents a chronic multifactorial disease, which needs extensive knowledge and experience of the clinician, but also needs intense collaboration between the different clinicians. In the end this will all attributes to the improved wellbeing of the individual patient and the healthcare system as a whole entity.

REFERENCES

1. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev* 2017;34:70-81.
2. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015;3:310-318.
3. Dieltjens M, Vanderveken OM, Heyning PH, Braem MJ. Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. *Sleep Med Rev* 2012;16:177-185.
4. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. *J Clin Sleep Med* 2014;10:215-227.
5. Ravesloot MJ, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea-a review of the literature. *Sleep Breath* 2013;17:39-49.
6. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep Breath* 2013;17:771-779.
7. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep* 2014;37:1209-1215.
8. Eijsvogel MM, Ubbink R, Dekker J, et al. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. *J Clin Sleep Med* 2015;11:139-147.
9. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-545.
10. Zaghi S, Holty JE, Certal V, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2016;142:58-66.
11. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev* 2010;14:287-297.
12. Vicini C, Dallan I, Campanini A, et al. Surgery vs ventilation in adult severe obstructive sleep apnea syndrome. *Am J Otolaryngol* 2010;31:14-20.
13. Boyd SB, Walters AS, Waite P, Harding SM, Song Y. Long-Term Effectiveness and Safety of Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea. *J Clin Sleep Med* 2015;11:699-708.
14. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008;5:173-178.
15. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996;19:156-177.
16. Passeri LA, Choi JG, Kaban LB, Lahey ET, 3rd. Morbidity and Mortality Rates After Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea. *J Oral Maxillofac Surg* 2016.
17. Islam S, Aleem F, Ormiston IW. Subjective assessment of facial aesthetics after maxillofacial orthognathic surgery for obstructive sleep apnoea. *Br J Oral Maxillofac Surg* 2015;53:235-238.
18. Li KK, Riley RW, Powell NB, Guilleminault C. Patient's perception of the facial appearance after maxillomandibular advancement for obstructive sleep apnea syndrome. *J Oral Maxillofac Surg* 2001;59:377-380; discussion 380-371.

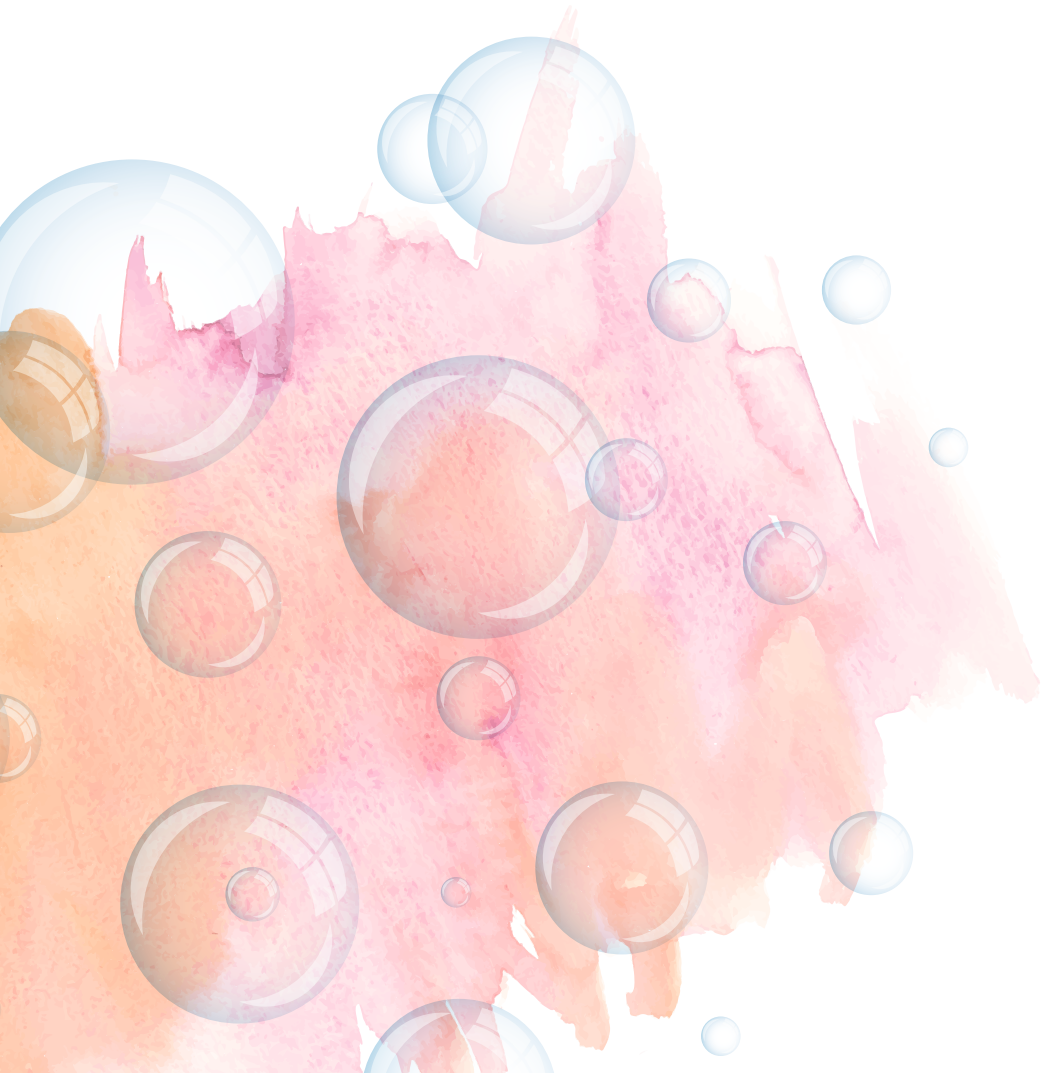
19. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47-112.

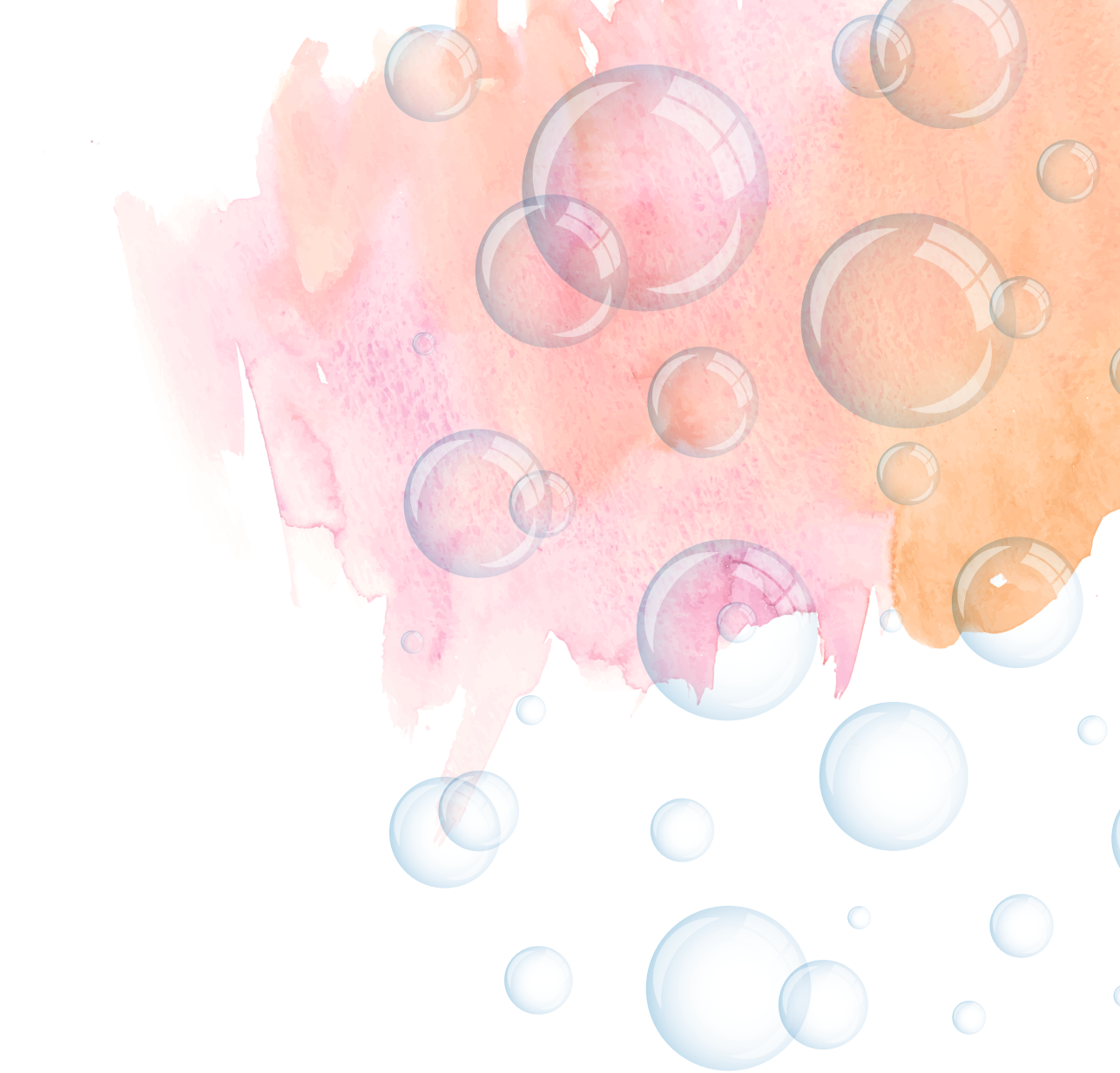
20. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - New pathways for targeted therapy. *Sleep Med Rev* 2018;37:45-59.

21. Bosi M, De Vito A, Eckert D, et al. Qualitative Phenotyping of Obstructive Sleep Apnea and Its Clinical Usefulness for the Sleep Specialist. *Int J Environ Res Public Health* 2020;17.

22. Lavigne GJ, Herrero Babiloni A, Beetz G, et al. Critical Issues in Dental and Medical Management of Obstructive Sleep Apnea. *J Dent Res* 2020;99:26-35.

CHAPTER 8





Summary in Dutch (Nederlandse samenvatting)

SAMENVATTING (Nederlands)

In Nederland (en ook wereldwijd) is een forse toename in de prevalentie van obstructief slaapapneu (OSA) waarneembaar, wat een grote impact heeft op nationale én internationale zorgstelsels. Zorginstanties en zorgverleners zoeken naar de adequate wijze om met deze relatief nieuwe patiëntenstroom te verwerken en er is een hoge noodzaak voor vernieuwde inzichten in de verschillende (behandel)strategieën voor deze patiënten. Om tot een consensus te komen over een juiste behandelindicatie tussen de verschillende zorgverleners, zoals longartsen, KNO-artsen, neurologen en tandheelkundige slaapspecialisten, kan men niet alleen de effectiviteit van de verschillende behandelmodaliteiten beschouwen, maar is ook meer duidelijkheid noodzakelijk over de (lange termijn) therapietrouw, kwaliteit van leven en patiëntspecifieke factoren die hierop van invloed zijn. Het ontbreken van een goede behandelplanning voor patiënten met OSA is de focus van dit proefschrift, waarbij specifiek wordt gekeken naar het mandibulair repositie apparaat (MRA), de slaap positie trainer (SPT) in deel I en de bimaxillaire osteotomie (MMA) in deel II.

Deel I

Gestandaardiseerd stapsgewijs titratieprotocol

De behandeling met een mandibulair repositie apparaat (MRA) is een van de meest toegepaste behandelmodaliteiten voor OSA, in het bijzonder bij lichte to matige OSA. Echter een gestandaardiseerde methode (titratie) voor het instellen van de MRA in de optimale voorwaartse positie van de onderkaak bij een specifieke patiënt is op dit moment niet beschikbaar. In **hoofdstuk 2** wordt een nieuw gestandaardiseerd en stapsgewijs titratieprotocol beschouwd op verschillende klinische aspecten bij patiënten met positieafhankelijke obstructieve slaapapneu (POSA; de apneu hypopneu index (AHI) is in rugligging minstens tweemaal zo hoog als in niet-rugligging). Het wetenschappelijk artikel wat de basis vormt voor dit hoofdstuk, is het eerste artikel dat een gestandaardiseerde manier voor MRA-titratie presenteert met als doel 1) maximaal therapeutisch effect op subjectieve en objectieve parameters; 2) resulteert in maximaal comfort en effect op eventuele bijwerkingen op de korte- en lange termijn; en 3) leidt tot de hoogst haalbare therapietrouw. Deze studie is een subonderdeel van een gerandomiseerd gecontroleerd onderzoek waarin de MRA werd vergeleken met de SPT voor patiënten met lichte en matige OSA (**hoofdstuk 3 en 4**). De MRA werd individueel ingesteld en de voorwaartse verplaatsing werd bepaald met behulp van een gestandaardiseerd *stapsgewijs* titratieprotocol. Er wordt aangetoond in deze studie dat dit titratieprotocol een goed effect heeft op de objectieve polysomnografische parameters, zoals de AHI en de desaturatie-index (ODI). Alhoewel alle patiënten die gestart waren met MRA-therapie de eerste drie maanden voltooiden, beëindigden zes patiënten (17%) de MRA-therapie vanwege de bijwerkingen (ernstig ongemak in het dragen van

de MRA) en/of onvoldoende resultaten op de hoofdklacht. Deze uitkomsten zijn in lijn met de in de literatuur beschikbare resultaten. De therapietrouw van de patiënten op deze behandelmethode was zeer goed. Het titratieprotocol was geen onderdeel van de opzet en de initiële onderzoeksvragen van deze gerandomiseerde studie en derhalve ontbreekt een controlegroep voor deze methode. Het artikel is toont derhalve eerder het idee van een *proof of concept* dan dat het een analyse is van de graad van effectiviteit afgezet tegen de "standaardbehandeling". Dit titratieprotocol voor de MRA-therapie wordt aanbevolen in toekomstige onderzoeksprojecten, zodat deze beter met elkaar te vergelijken zijn en ook wordt aanbevolen om dit protocol te gebruiken in de dagelijkse praktijk vanwege zijn praktische toepasbaarheid.

Slaap positie trainer versus mandibulair repositie apparaat

Hoofdstuk 3 en 4 vormen samen een beschrijving van een prospectief gerandomiseerd gecontroleerde studie naar de effecten van een nieuw ontwikkelde behandelmodaliteit, namelijk de SPT in vergelijking met de MRA op effectiviteit, bijwerkingen en therapietrouw op korte en lange termijn. Reeds zeer lange tijd wordt gezocht naar een adequate wijze om rugligging in de slaap te voorkomen. Recent is een apparaat ontwikkeld om de rugligging in slaap te corrigeren met behulp van een stimulus. Het apparaat vibreert zodra deze een rugligging detecteert om zodanig direct de lichaamspositie te doen veranderen en het meet tevens objectief de therapietrouw. Eerdere cohortstudies tonen een goed effect in het verminderen van de AHI en het percentage rugligging in de totale slaap, daarbij blijkt de therapietrouw hoog ook na 6 maanden. Deze nieuwe generatie van positietherapie is beduidend superieur in effectiviteit en therapietrouw in vergelijking met de ouderwetse methode, samengevat onder de parapluterm "tennisbal-techniek". **Hoofdstuk 3** toont de eerste drie maanden resultaten van deze studie: beide behandelingen zijn even effectief in het verlagen van de AHI en de therapietrouw blijkt excellent in beide groepen. De bijwerkingen van beide behandelingen resulteren niet in een vroegtijdig staken van de therapie en blijken gelijk verdeeld. Het enige verschil werd gevonden in de uitkomst van de ziekte-specifieke kwaliteit van leven vragenlijst, de Epworth Sleepiness Scale (ESS). Het resultaat van de ESS toonde dat de patiënten met MRA een grotere daling in de ESS-score rapporteerden dan de patiënten met een SPT. Het is echter de vraag of dit significante verschil van klinische waarde is, aangezien in beide groepen bij start van de studie sprake was van een score van minder dan 10. Een ESS-score is afwijkend als sprake is van een score hoger dan 10, waarbij in dat geval wordt gesproken over een klinisch relevante overmatige slaperigheid overdag.

De stabiliteit van de behandeling op langere termijn van de SPT in vergelijking met de MRA wordt verkend in het volgende hoofdstuk; de resultaten van de eerdergenoemde prospectieve studie worden beschreven in **hoofdstuk 4**. Beide behandelmodaliteiten tonen goede stabiele uitkomsten op objectieve parameters (polysomnografie) en de therapietrouw blijft excellent ook na 12 maanden. Het aantal patiënten dat vroegtijdig staakt met de behandeling blijkt van belang in dit onderzoek. Bij de start van de studie

blijkt het aantal drop-outs (vroegtijdig staken van behandeling) het grootste te zijn in de MRA-groep (zijn dus nooit gestart met therapie) vanwege onvoldoende sanering van het gebit. Daarnaast was het aantal drop-outs in de SPT-groep groter omdat zij nog persisterend snurken in zijligging ervaarden, en snurken is vaak de hoofdklacht van de patiënt. Het resultaat van deze studie toont derhalve niet alleen de waarde van effectiviteit van behandeling, maar ook van voor- en nadelen van therapie en de bijwerkingen van de therapie. Deze kennis is essentieel voor zorgverleners voor het bepalen van patiëntenselectie, de juiste individuele therapie en het begeleiden van het beloop na start behandeling zodat een maximale therapie-uitkomst en therapietrouw kan worden behaald. De klinische relevantie van deze studie blijkt uit het feit dat de SPT als behandeling is opgenomen in het basispakket van de verzekerde zorg in Nederland, mede op basis van onze uitkomsten.

Deel II

Maxillomandibular advancement chirurgie

De bimaxillaire osteotomie wordt reeds gedurende vele jaren verricht bij patiënten met faciale dysgnathie. Meer recent is echter de ontwikkeling dat de bimaxillaire osteotomie kan worden toegepast bij patiënten met OSA, waarbij de dezelfde chirurgische ingreep dan een maxillomandibular advancement (MMA) wordt genoemd. De chirurgische ingreep is technisch hetzelfde als bij patiënten met dysgnathie, echter de verplaatsingen van de kaken zijn niet gebaseerd op het corrigeren van de dysgnathie, maar het openen van de bovenste luchtweg geldt als belangrijkste onderdeel van de planning. De MMA wordt beschouwd als een van de meest effectieve (en permanente) methodes voor het behandelen van patiënten met OSA, zowel op objectieve uitkomstmaten (polysomnografie) als subjectieve parameters. Echter, vermoedelijk vanwege het ingrijpende karakter van de behandeling zijn relatief weinig prospectief gerandomiseerde studies (n=1) beschikbaar over dit onderwerp, echter wel cohortstudies. De enige prospectieve studie vergelijkt de MMA met patiënten die behandeld worden met Continuous Positive Airway Pressure (CPAP), wat wordt beschouwd als de gouden standaard voor behandeling. De studie toonde dat een MMA gelijk is aan de CPAP in effectiviteit, het verlagen van de AHI. Echter CPAP heeft een matige lange termijn therapietrouw, terwijl de MMA een permanent continu effect heeft. In **Hoofdstuk 5** wordt de MMA-procedure onderzocht 1) op de verschillende variabelen die van invloed kunnen zijn op een succesvolle chirurgische ingreep en 2) om het ingrijpende karakter van de chirurgische ingreep beter in kaart te brengen. Er is onderscheid gemaakt in de mate van chirurgisch succes of falen met behulp van de meet gebruikte criteria in de literatuur (de criteria volgens Sher et al 1996), namelijk een daling in AHI van meer dan 50% én onder de 20. De resultaten tonen aan dat een hogere leeftijd (>53 jaar) en grotere nekomtrek (>43 cm) as mogelijk bepalende factoren kunnen worden gezien voor een chirurgisch falen van de MMA. Daarnaast blijkt dat patiënten na MMA regelmatig een tweede chirurgische ingreep ondergaan, meestal om

osteosynthesemateriaal (platen en schroeven) te verwijderen vanwege klachten hieraan. Het belangrijkste neveneffect van de MMA ingreep is neurosensorische verstoringen van de nervus alveolaris inferior, consistent in vergelijking met de bimaxillaire osteotomie (voor dysgnathie). Echter dit neveneffect lijkt bij MMA vaker voor te komen, waarschijnlijk vanwege de specifieke karakteristieken, zoals hogere leeftijd, meer co-morbiditeit en grotere verplaatsingen van de boven- en onderkaak. De MMA ingreep wordt beschouwd als meer complex dan standaard orthognathische chirurgie en de neveneffecten en complicaties lijken in grotere mate afhankelijk van de ervaring en kunde van de chirurg.

Naast de hoge effectiviteit en de eventuele complicaties, is meer inzicht gewenst in de subjectieve uitkomsten na de MMA. Zorgverleners en patiënten hebben begrijpelijkerwijze grote interesse in de verandering van de esthetiek van het gezicht, vanwege de grote verplaatsingen in de aangezichtsbeenderen. Dit en andere subjectieve uitkomsten zoals ziekte-specifieke vragenlijsten worden besproken in **Hoofdstuk 6**, waarbij wederom onderscheid wordt gemaakt in patiënten met een chirurgisch succes of falen (AHI-daling van meer dan 50% én onder de 20). Uitkomsten tonen aan dat de patiënten behandeld met MMA minder klachten ervaren van overmatige slaperigheid overdag (Epworth Sleepiness Scale; ESS), en een significante daling in snurken. Tevens was er geen significant verschil in hoe de patiënten de verandering van hun gezicht waardeerden voor en na de ingreep. Echter, als de patiënt een onvoldoende daling van de AHI had (= chirurgisch falen), werden de veranderingen van het gezicht als meer negatief ervaren in vergelijking met de patiënten die wel succesvol werden geopereerd.

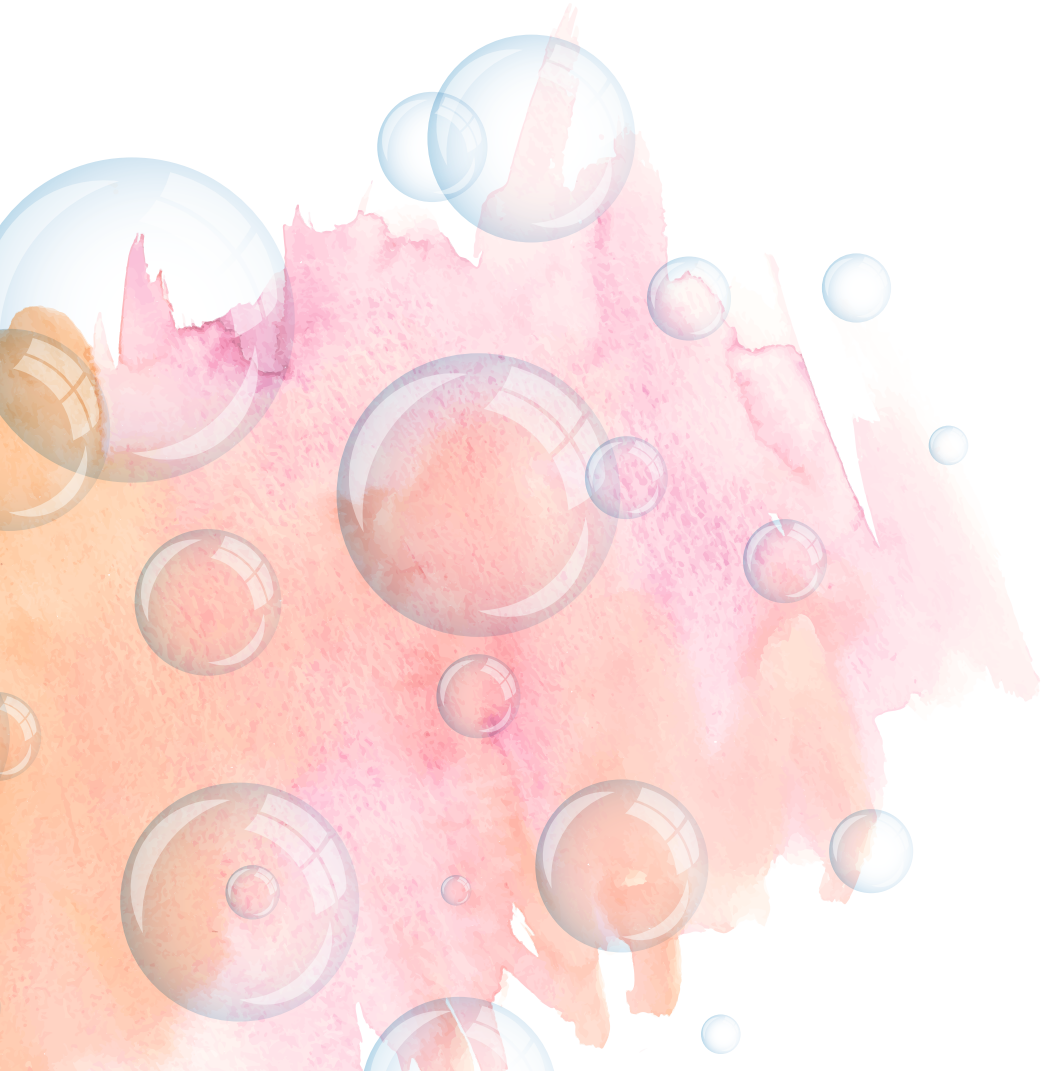
Klinische aanbevelingen en toekomstperspectieven

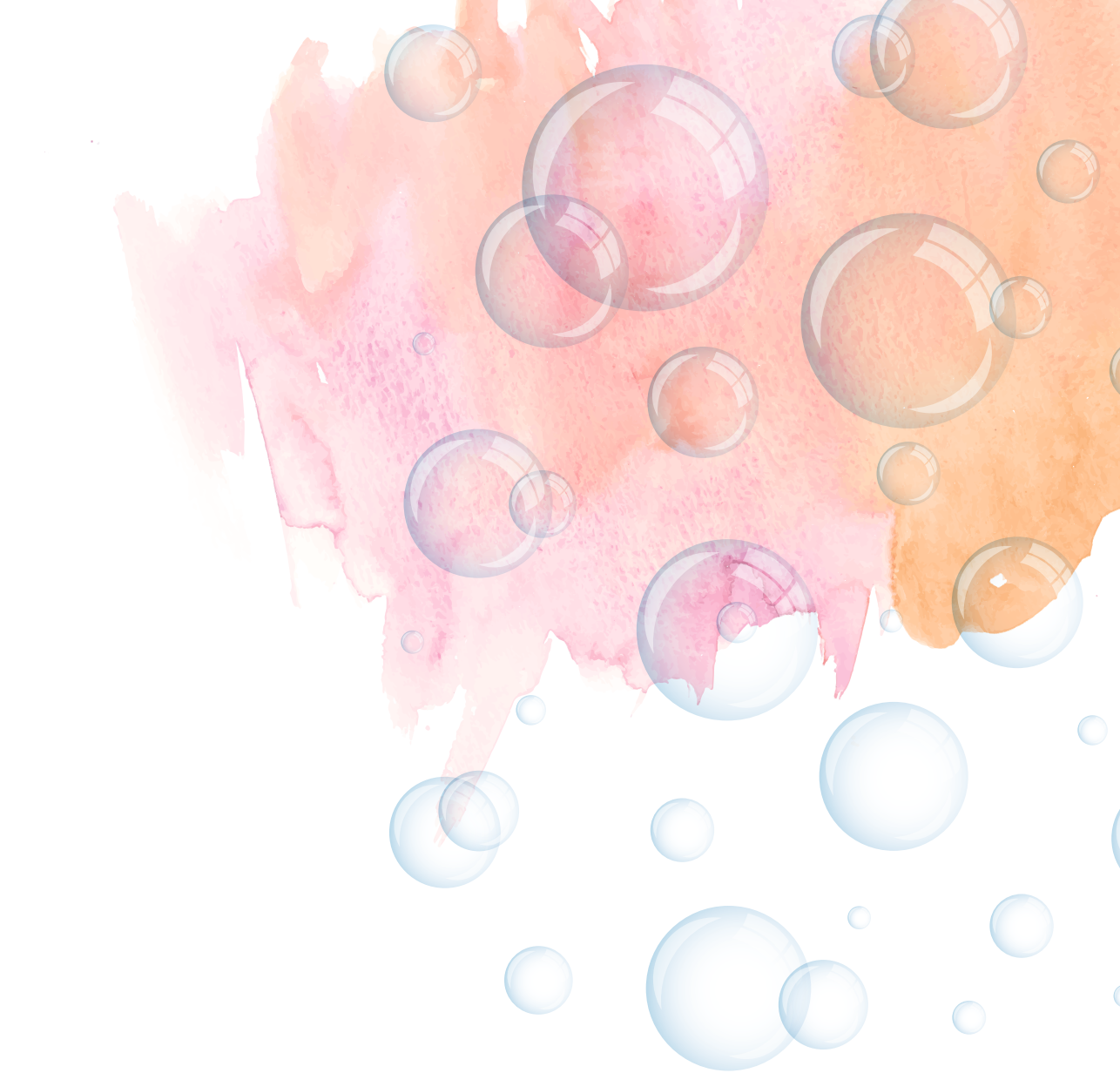
Zorgverleners kunnen op basis van de uitkomsten van dit proefschrift; zowel op effectiviteit, neveneffecten, bijwerkingen en subjectieve ervaringen van de patiënten, een meer patiënt-specifieke behandeling kiezen voor de patiënten met OSA. De pathofysiologie van OSA is multifactorieel en derhalve kunnen de oorzaken en de gevolgen op individueel niveau zeer verschillend zijn. Dit proefschrift richt zich specifiek op de anatomische factoren die bovenste luchtwegobstructies kunnen veroorzaken, maar niet-anatomische oorzaken kunnen wel degelijk ook van invloed zijn en vallen buiten de beschouwing van dit proefschrift. Voorbeelden hiervan zijn beperking in de aansturing van de faryngeale dilatatoren tijdens de slaap, verhoogde neiging van luchtwegvernauwing (lage drempelwaarde voor een respiratoire *arousal*) en instabiliteit in de ademhalingscontrole (*high loop gain*). Meer onderscheid zou gemaakt moeten worden in de verschillende fenotypes (anatomische en niet-anatomische factoren) van een patiënt voor een ultieme patiënt-specifieke behandeling.

Vanwege de grote mate van patiënt-specifieke factoren, en vervolgens ook de grote verscheidenheid in behandeltechnieken voor patiënten met OSA, lijkt het vaak lastig

(of onmogelijk) om dit voor een zorgverlener alleen te analyseren en toe te passen bij elke individuele patiënt. Dit onderstreept het belang van een multidisciplinaire strategie in de diagnostiek en behandeling van OSA, waarbij het op dit moment (nog steeds) ontbreekt aan een goed raamwerk voor behandeling in nationale en internationale richtlijnen. Toekomstig onderzoek zou bij voorkeur enerzijds meer inzicht moeten geven in fenotypering van de OSA-patiënt aan de ene kant. Aan de andere kant is ook meer inzicht nodig niet enkel in de effectiviteit van de verschillende behandelingen, maar vooral ook de neveneffecten, bijwerkingen en therapietrouw, bijvoorbeeld een prospectief gerandomiseerde studie naar de MMA ingreep in vergelijking met de faryngeale (multilevel) chirurgie of nervus hypoglossus stimulatie.

Intensieve samenwerking tussen de verschillende zorgverleners is cruciaal voor een succesvolle, strategische aanpak van de patiënten met OSA in de zorginstellingen. Uiteindelijk zal deze samenwerking leiden tot een verbetering van het welbevinden van de individuele patiënt en de gezondheidszorg in zijn geheel.





APPENDICES

CONTRIBUTING AUTHORS

G. Aarab (GA)
Department of Orofacial Pain and Dysfunction, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam, Amsterdam, the Netherlands.

R.C. Apperloo (RA)
Department of Oral & Maxillofacial Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands.

L.B.L. Benoist (LB)
Department of Otorhinolaryngology Head and Neck Surgery Amsterdam University Medical Centre (UMC), University of Amsterdam, Amsterdam, the Netherlands.

J. de Lange (JL)
Department of Oral & Maxillofacial Surgery, Amsterdam University Medical Centre (UMC), Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam, Amsterdam, the Netherlands.
Department of Oral and Maxillofacial Surgery, Isala Hospital, Zwolle, the Netherlands.

F. Lobbezoo (FL)
Department of Orofacial Pain and Dysfunction, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam, Amsterdam, the Netherlands.

D.M.J. Milstein (DM)
Department of Oral & Maxillofacial Surgery, Amsterdam University Medical Centre (UMC), Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam, Amsterdam, the Netherlands.

M.H.T. de Ruiter (MR)
Department of Oral & Maxillofacial Surgery, Amsterdam University Medical Centre (UMC), Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam, Amsterdam, the Netherlands.
Department of Oral and Maxillofacial Surgery, Diakonessenhuis Utrecht, Zeist, the Netherlands.

N. de Vries (NV)
Department of Otorhinolaryngology Head and Neck Surgery, OLVG west, Amsterdam, The Netherlands.
Department of Orofacial Pain and Dysfunction, Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam, Amsterdam, the Netherlands.
Department of Otolaryngology and Head and Neck Surgery, Antwerp University Hospital, Antwerp, Belgium.

CHAPTER INFORMATION Chapter 2

Published as:
A stepwise titration protocol for oral appliance therapy in positional obstructive sleep apnea patients: proof of concept

Published in:
Sleep and Breating, 2020

Authors:
M.H.T. de Ruiter, G. Aarab, N. de Vries, F. Lobbezoo, J. de Lange

Author contributions:

Study concepts and design	MR, GA, NV, FL, JL
Data collection	MR, GA
Data analysis	MR
Manuscript preparation	MR
Manuscript review	MR, GA, NV, FL, JL

Funding sources:
This study is supported by the Foundation Nuts Ohra for the execution of the POSA study.

Conflicts of interest:
M.H.T. de Ruiter declares no conflict of interest.

G. Aarab receives OSA-related research grants from SomnoMed and sleep bruxism-related research grants from Sunstar Suisse S.A.

N. de Vries is a member of the Medical Advisory Board of NightBalance, consultant of Philips Healthcare and Olympus, researcher for Inspire Medical Systems, and has shares in NightBalance.

F. Lobbezoo receives OSA-related research grants from SomnoMed and Airway Management, and sleep bruxismrelated research grants from Sunstar Suisse S.A.

J. de Lange declares no conflict of interest.

CHAPTER INFORMATION Chapter 3

Published as:
A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea

Published in:
Sleep Medicine, 2017

Authors:
L.B.L. Benoist, M.H.T. de Ruiter, J. de Lange, N. de Vries

Author contributions:

Study concepts and design	LB, MR, JL, NV
Data collection	LB, MR
Data analysis	LB, MR
Manuscript preparation	LB, MR
Manuscript review	LB, MR, JL, NV

Funding sources:
This study is supported by the Foundation Nuts Ohra for the execution of the POSA study. NightBalance for supplying SPT devices in the POSA study.

Conflicts of interest:
L.B.L. Benoist declares no conflict of interest.

M.H.T. de Ruiter declares no conflict of interest.

J. de Lange declares no conflict of interest.

N. de Vries is a member of the Medical Advisory Board of NightBalance, consultant of Philips Healthcare and Olympus, researcher for Inspire Medical Systems, and has shares in NightBalance.

CHAPTER INFORMATION Chapter 4

Published as:
Durability of treatment effects of the Sleep Position Trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial

Published in:
Sleep and Breathing, 2018

Authors:
M.H.T. de Ruiter, L.B.L. Benoist, N. de Vries, J. de Lange

Author contributions:

Study concepts and design	MR, LB, NV, JL
Data collection	MR, LB
Data analysis	MR, LB
Manuscript preparation	MR, LB
Manuscript review	MR, LB, NV, JL

Funding sources:
This study is supported by the Foundation Nuts Ohra for the execution of the POSA study. NightBalance for supplying SPT devices in the POSA study.

Conflicts of interest:
M.H.T. de Ruiter declares no conflict of interest.

L.B.L. Benoist declares no conflict of interest.

N. de Vries is a member of the Medical Advisory Board of NightBalance, consultant of Philips Healthcare and Olympus, researcher for Inspire Medical Systems, and has shares in NightBalance.

J. de Lange declares no conflict of interest.

CHAPTER INFORMATION Chapter 5

Will be published as:
Assessment of obstructive sleep apnoea treatment success or failure after maxillomandibular advancement

Accepted for publication in:
International Journal of Oral and Maxillofacial Surgery, 2017

Authors:
M.H.T. de Ruiter, R.C. Apperloo, D.M.J. Milstein, J. de Lange

Author contributions:

Study concepts and design	MR, JL
Data collection	MR
Data analysis	MR
Manuscript preparation	MR, DM
Manuscript review	MR, RA, DM, JL

Funding sources:
None

Conflicts of interest:
None

CHAPTER INFORMATION Chapter 6

Published as:
Facial esthetics and subjective impairment assessed after maxillomandibular advancement surgery for patients with obstructive sleep apnea

Published in:
Cranio, The Journal of Craniomandibular & Sleep Practice, 2020

Authors:
M.H.T. de Ruiter, R.C. Apperloo, D.M.J. Milstein, J. de Lange

Author contributions:

Study concepts and design	MR, JL
Data collection	MR
Data analysis	MR
Manuscript preparation	MR, DM
Manuscript review	MR, RA, DM, JL

Funding sources:
None

Conflicts of interest:
None

Dankwoord

Dankwoord

Allereerst mijn immense waardering voor alle patiënten die mee hebben gewerkt aan deze studies. Het getuigt mijns inziens van een groot moreel besef om speciaal voor de medische wetenschap, extra langs een ziekenhuis te komen, extra onderzoeken te ondergaan en extra kostbare tijd te investeren in niet alleen je eigen gezondheid, maar ook in die van anderen. Mijn oprechte dank hiervoor.

Prof. dr. J. de Lange, hooggeleerde promotor, beste Jan. Hartelijk dank voor alle hulp en begeleiding die je hebt gegeven aan mij in dit project. "*Vooruitzien, is regeren";* is een van jouw beste kwaliteiten en het "lezen" van mensen en hun handelen is iets wat ik echt van jou heb geleerd. Het is bijzonder om te zien, hoe iemand met rust en ogenschijnlijk weinig moeite, juist zoveel weet te bereiken. Meer dan verdiend, ben jij dan ook het eerste Hoofd van de gezamenlijke afdeling MKA-chirurgie van het Amsterdam UMC. Ook in mijn promotietraject, was jij aanwezig op de sleutelmomenten en heb je mij te allen tijde gesteund in mijn handelen. Veel dank voor je vertrouwen dat je in mij hebt gehad en ik hoop nog vele jaren in de toekomst met je te blijven samenwerken.

Prof. dr. N. de Vries, hooggeleerde promotor, beste Nico. Heel veel dank voor alle hulp en begeleiding tijdens de onderzoeken die wij samen hebben mogen uitvoeren. Je bent een ongelofelijk goede wetenschapper en de oprechte "snurk-koning" van Nederland. Jij hebt een echt verschil gemaakt voor patiënten met obstructief slaapapneu (OSA) in Nederland en internationaal met de introductie van de slaappositietrainer en de hypoglossusstimulatie. Ik kan me moeilijk voorstellen dat jij achter de geraniums gaat zitten, nu als pensionado. Ik weet zeker dat dit niet het geval zal zijn.

Dr. D.M.J. Milstein, weledelzeergeleerde copromotor, beste Dan. Je bent een geweldige inspirator en wetenschapper, en gelukkig heb je mij geholpen in het tweede deel van mijn promotietraject. Dankzij jouw hulp zijn er prachtige artikelen gekomen, omdat je mijn wervelende geest om kan zetten in duidelijk en leesbaar wetenschappelijk Engels. Het was een ongelofelijke eer om met jou samen te werken.

Dr. H.C.M. Donders, weledelzeergeleerde copromotor, beste Marie-Chris. Gelukkig wilde jij mij helpen met het laatste zetje van dit boekje. Veel dank voor alle begeleiding die ik heb mogen ontvangen in deze laatste fase. Onder het motto "*beter goed gejat, dan slecht bedacht*", gun ik elke toekomstige promovendus jou als copromotor.

Geachte leden van de **promotiecommissie**: Prof. dr. G. Aarab, prof. dr. A.G. Becking, dr. A. Hoekema, prof. dr. F. Lobbezoo, prof. dr. A.J.W.P. Rosenberg, prof. dr. F.R. Rozema en prof.

dr. O.M. Vanderveken. Hartelijk dank voor het kritisch beschouwen van mijn proefschrift en het is een grote eer om dit proefschrift tegenover u te mogen verdedigen.

Heel veel dank aan de **mede-auteurs**, dr. Linda Benoist en Ruben Apperloo voor hun samenwerking. Zal de vele vrijdagochtenden op het "SLAZ" met Linda herinneren, daar is de basis voor de prachtige artikelen gelegd. En het is een groot feest om samen met Ruben te opereren. We hebben veel MMA's samen gepland en geopereerd, geweldig om dit van jou te leren en samen te doen, *Guitar Heroes!*

Lieve weledelgeleerde **paranimfen**, Egbert en Rik. Het is een geruststellende gedachte dat ik jullie aan mijn zijde heb tijdens de verdediging van dit proefschrift. Lieve Rik, al sinds de allereerste stapjes in onze studententijd zijn wij beste vrienden en met ongelofelijk veel plezier kijk ik terug naar die tijd in het Vensterhuis bij het Kroegdispuut de Tempeliers! Jij hebt al je motorrijbewijs gehaald en ik hoop snel na mijn verdediging, dit ook te voltooien. Dan kunnen we samen mooie tochten maken op de motor en onze vriendschap tot in lengte van dagen voortzetten. Lieve Egbert, niemand (en wij zeker niet) had kunnen vermoeden dat wij zo'n ongelofelijk goed team zouden zijn. Ik geniet dagelijks van onze samenwerking en ik hoop dat wij nog vele, vele jaren samen verder kunnen bouwen aan onze eigen "tent". The sky is the limit!

Beste dames en heren van de **afdeling Mondziekten, Kaak- en Aangezichtschirurgie van het Amsterdam UMC**, locatie ("het oude") AMC! Alle medewerkers veel dank voor al jullie hulp in mijn assistententijd. Alle (oud-)stafleden, oa Frans Kroon, Jacco Tuk, Jitske Nolte, dank voor al jullie geduld om mij het vak als MKA-chirurg te leren. Daarnaast uiteraard alle oud-mede-AIOS; Willem, Ewoud, Roel, Michael, Leander, Matthijs, Pim, Robert, Bram, JP, Tom, Renée, MC, Sophie (en ga zo nog maar even door!). Heel veel dank voor alle gezellige en leerzame momenten die wij samen hebben gehad op het AMC. Van jullie allemaal heb ik ongelofelijk veel geleerd en nog altijd staat het AMC-adagium in mijn geheugen gegrift: "*See one, do one, teach one*".

Beste medewerkers van de **afdeling KNO van het "oude" Sint Lucas Andreas Ziekenhuis** (SLAZ) en met name Miranda de Wekker. Veel dank voor de organisatie en het plannen van al onze patiënten.

Beste mensen van de **afdeling MKA-chirurgie van het Diakonessenhuis Utrecht/Zeist**; mijn lieve maten Ellen, Robert, Egbert en Laurens. Het is ongelofelijk fijn om deel uit te mogen maken van deze maatschap. Ik denk dat wij een unieke combinatie hebben, waardoor we zover komen met elkaar. Ik kijk uit naar nog vele gezellige jaren werken met elkaar in ons Diak! En uiteraard alle dames: lieve Marjolein, Ellemiek, Marloes, Latifa, Joyce, Fadoua, Amina, Angelique, Ans, Ravenna, Jane, Denise, Sabine, Hafida, Margit, Kitty, Corina en Ietje. Het is ongelofelijk gezellig en fijn om met jullie allemaal samen te werken. Ik hoop nog vele jaren dit samen met jullie te kunnen doen!

Mede-enthousiastelingen van de **Tandheelkundige Slaapgeneeskunde**, en met name alle (oud)-bestuursleden van de Nederlandse Vereniging voor Tandheelkundige Slaapgeneeskunde (NVTS). Veel dank voor de samenwerking de afgelopen jaren en ik wens de Tandheelkundige Slaapgeneeskunde in Nederland een sterke toekomst. Met deze mensen in het bestuur van de NVTS, zal dat vast en zeker gaan lukken.

Lieve **Daily Champagne**, Pim en Jantine, Harrie en Anne, Marleen en Gerben, Robean en Marieke, Nina en Thierry. Het is altijd genieten om samen met elkaar te borrelen, te dansen en te feesten! Dit jaar wederom een Cadzand-editie en ik hoop nog vele jaren te genieten van jullie vriendschap! *"ik heb er zinin!"*

Lieve **CGB**-ers, Anneke, Sjoukje, Manuela, Johan-Paul en Jelle. Mede vanwege dit boekje heb ik jullie de afgelopen jaren veel te weinig gezien. Ik kijk weer uit naar de onvergetelijke avondjes eten/stappen met elkaar.

Lieve **Klassenvaders**, Eric en Simon. Het tempo van gezellige avondjes kan na dit boekje nog verder omhoog. ☺ Wellicht toch nog een nieuwe uitdaging in de Leeuwenklas volgend jaar. Wij gaan er in ieder geval een feest van maken. *Hakuna Matata*!

Lieve **Wolter** en **Joke** en lieve **Coby**. Zoveel dank voor alle liefde die wij "zomaar" van jullie mogen ontvangen. Ik hou van jullie.

Mijn allerliefste dochters **Neeltje** en **Yfke** en mijn allerliefste zoon **Willem**; met veel plezier en bewondering mag ik toeschouwer zijn van jullie leven. Ik hou zielsveel van jullie!

Mijn allerliefste **Marleen**, de vrouw van mijn leven! Je bent de liefste en mooiste vrouw die ik me maar kan wensen. Zonder jouw hulp was dit boekje afkrijgen zeker niet gelukt en jouw kritische blik en nuchtere kijk op zaken (en het leven), werkt bij mij altijd zeer verhelderend. Ik hoop nog tot in lengte van dagen te genieten van ons leven samen en met onze lieve kinderen. *"Love you forever and ever!"*

ABOUT THE AUTHOR

Maurits was born in Nieuwerkerk aan den IJssel on December 8th, 1982. He grew up in a little town (NWK IJSSEL) nearby Rotterdam and graduated from the Marnix Gymnasium in July 2001.

He moved to Nijmegen to study Dentistry at the Radboud University Nijmegen, which he finished on November 15th 2007. During his study, in 2007, he worked as a student-dentist for 4 months in the Gemelli International Hospital in Rome, Italy (Odontoiatria Generale e Ortodonzia, Policlinico Gemelli).

He worked in dental practices in Rotterdam, Utrecht and The Hague, while in the meantime, he finished his bachelor's in medicine in 2012. Directly after this he started his training program in Oral and Maxillofacial (OMF) surgery on October 1st 2012 under supervision of prof. dr. J. de Lange. It was during this residency time, professor De Lange introduced him to the fascinating field of Obstructive Sleep Apnea (OSA), more specific the Mandibular Advancement Devices and the Maxillomandibular Advancement surgery. Next to this, the project around the Sleep Position Trainer (SPT) started together with Prof. dr. N. de Vries from the Onze Lieve Vrouwe Gasthuis (OLVG), location West.

As a part of the OMFS training program, he was seconded as a resident to the Netherlands Cancer Institute (NKI) Antoni van Leeuwenhoek (supervised by prof. dr. L.E. Smeele) and the Isala Clinics in Zwolle (supervised by dr. E.M. Baas). After four years, he successfully finished his OMFS training program and worked his way through the Master degree of Medicine School. At the end of 2018 he was registered as an Oral and Maxillofacial surgeon, and he directly started as a consultant in the Diakonessenhuis Utrecht and Zeist.

Maurits recently married his wonderful partner in life, Marleen Vos. They are proud parents of Neeltje (2015), Yfke (2018) and "little" Willem (2021).

Correspondence:
Diakonessenhuis Utrecht
Department of Oral and Maxillofacial Surgery
Bosboomstraat 1
3582 KE Utrecht
The Netherlands

mdruiter@diakhuis.nl