Maria Cecília Monteiro Marques Magalhães

Impacto da adenotonsilectomia e da expansão rápida da maxila nas vias aéreas superiores em crianças com Síndrome da Apneia Obstrutiva do Sono (SAOS) – estudo clínico randomizado

Impact of adenotonsillectomy and rapid maxillary expansion on the upper airways in children with obstructive sleep apnea syndrome (OSA) – a randomized controlled clinical

.

Dissertação apresentada à Faculdade de Odontologia da Universidade Federal de Uberlândia, para a obtenção do Título de Mestre em Odontologia, Área de Clínica Odontológica Integrada.

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Iniciando os trabalhos o(a) presidente da mesa, Dr(a). Guilherme Araújo Almeida, apresentou a Comissão Examinadora e o candidato(a), agradeceu a presença do público, e concedeu ao Discente a palavra para a exposição do seu trabalho. A duração da apresentação do Discente e o tempo de arguição e resposta foram conforme as normas do Programa.

A seguir o senhor(a) presidente concedeu a palavra, pela ordem sucessivamente, aos(às) examinadores(as), que passaram a arguir o(a) candidato(a). Ultimada a arguição, que se desenvolveu dentro dos termos regimentais, a Banca, em sessão secreta, atribuiu o resultado final, considerando o(a) candidato(a):

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A fé e a força de vocês me inspiram.

A minha irmã, *Anna Klycia* sempre tão perto mesmo estando tão longe.

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SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

AT: Adenotonsilectomia

CPAP: Pressão Positiva Contínua na Via Aérea

ECG: Eletrocardiograma

EEG: Eletroencefalograma

EMG: Eletromiografia

EOG: Eletrooculograma

ERM: Expansão Rápida da Maxila

HC-UFU: Hospital de Clínicas da Universidade Federal de Uberlândia

IAH: Índice de Apneia e Hipopneia

PSG: Polissonografia

SAOS: Síndrome da Apneia Obstrutiva do Sono

SUS: Sistema Único de Saúde

VAS: Vias Aéreas Superiores

RESUMO

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Introdução: O objetivo deste estudo clínico randomizado foi avaliar a alteração volumétrica nas vias aéreas de crianças diagnosticadas com Síndrome da Apneia Obstrutiva do Sono (SAOS) após receberem os dois tipos de tratamentos, adenotonsilectomia e expansão rápida da maxila. **Métodos:** Amostra de trinta crianças diagnosticadas com Síndrome da Apneia Obstrutiva do Sono. Os critérios de elegibilidade incluíram os participantes com sintomas clínicos de distúrbio respiratório, como ronco noturno e respiração bucal, hipertrofia de amígdalas e adenóides, atresia maxilar, palato profundo, mordida cruzada posterior unilateral ou bilateral e / ou algum grau de retrusão mandibular. Os participantes foram divididos em 2 grupos. O primeiro grupo recebeu adenotonsilectomia como primeiro tratamento e, posteriormente, expansão rápida da maxila; o segundo grupo recebeu a expansão rápida da maxila como primeiro tratamento e posteriormente a adenostonsilectomia. Os exames de tomografia computadorizada de feixe cônico foram obtidos antes do primeiro tratamento, 5-6 meses após o primeiro tratamento e 5-6 meses após o segundo tratamento. As imagens foram importadas e exibidas no *software* de imagem: *Mimics Research* 21.0 para análise volumétrica das vias aéreas superiores. A análise intragrupo foi realizada pelo teste de Friedman, a análise intergrupo foi realizada pelo teste de Mann Whitney ($\alpha = 0,05$). **Resultados:** Houve diferença estatisticamente significante nos dois grupos ao comparar o volume inicial e final dos tratamentos. A análise intergrupos mostrou diferença estatisticamente significante no volume total das vias aéreas superiores e na orofaringe. **Conclusão:** Adenotonsilectomia e expansão rápida da maxila promoveram um aumento volumétrico nas vias aéreas superiores; e com o uso combinado dos dois tipos de tratamentos foi encontrado maior ganho volumétrico das vias aéreas superiores quando a adenotonsilectomia foi realizada como a primeira opção de tratamento.

Palavras chaves: síndrome da apneia obstrutiva do sono, vias aéreas superiores, crianças.

ABSTRACT

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Introduction: The purpose of this 2-arm parallel study was to evaluate the volume upper airway change in children diagnosed with Obstructive Sleep Apnea after receiving both types of treatments, adenotonsillectomy and rapid maxillary expansion. **Methods:** A sample of thirty children with Obstructive Sleep Apnea. Eligibility criteria included participants in the clinical symptoms of breathing disorder, such as snoring, and mouth breathing, palatine tonsil hypertrophy, adenoid hypertrophy, constricted maxillary arch, high palate, unilateral or bilateral posterior crossbite, and/or some degree of mandibular retrusion. The participants were consecutively divided into 2 study groups. The first group received adenotonsillectomy as the first treatment and later the rapid maxillary expansion; the second group received the rapid maxillary expansion as the first treatment and later the adenostonsillectomy. Cone-beam computed tomography examinations were obtained before of first treatment, 5-6 months post first treatment, and 5-6 months post second treatment. The images were imported and displayed in the imaging software: Mimics Research 21.0 for analysis the volumetric upper airways. Intragroup analysis was performed using Friedman test, intergroup analysis was performed using the Mann Whitney test ($\alpha = 0.05$). **Results:** There was a statistically significant difference in the both groups when comparing the total volume between initial and final. Intergroup analysis was statistically significant differences in the volume total upper airway and oropharyngx. **Conclusion:** Adenotonsillectomy and rapid maxillary expansion contributed to the increase of airway volume; and that the combined use of two types treatments greatest volumetric upper airway gain occurs when adenotonsillectomy was made as the first treatment option.

Keywords: obstructive sleep apnea, upper airway, children

INTRODUÇÃO E REFERENCIAL TEÓRICO

1. INTRODUÇÃO E REFERENCIAL TEÓRICO

A Síndrome da Apneia Obstrutiva do Sono (SAOS) é um distúrbio respiratório relacionado ao sono que acomete indivíduos de todas as idades, desde neonatos até idosos (Lumeng *et al*., 2008; Jean-Louis *et al*., 2009). É caracterizada por episódios de obstrução parcial (hipopneia) ou total (apneia) das vias aéreas superiores (VAS), simultaneamente ao esforço respiratório durante o sono desencadeando um quadro de hipóxia intermitente e despertares (AASM 1999; Udwadia *et al*., 2004). Trata-se de uma doença crônica, progressiva e incapacitante, apresentando altas taxas de mortalidade e morbidade cardiovascular (Young *et al*., 2008) sendo portanto, considerada um problema de saúde pública (Lavie *et al*., 2005).

Segundo a Classificação Internacional dos Distúrbios do Sono, o diagnóstico da SAOS envolve a aplicação de questionários específicos, história clínica detalhada, exame físico, polissonografia (PSG) clássica (AASM 2005) e poligrafia ambulatorial (AASM 2014). O padrão ouro para o diagnóstico da SAOS é a PSG (Marcus *et al*., 2012). O uso da PSG de noite completa, realizada em laboratório especializado, com acompanhamento de profissionais treinados, permite avaliar o registro do eletroencefalograma (EEG), eletrooculograma (EOG), eletromiografia (EMG), não invasiva do mento e dos membros inferiores, das medidas do fluxo oronasal, do movimento torácico-abdominal; do eletrocardiograma (ECG), da oximetria de pulso e da posição corporal. Com esses registros, pode-se calcular o Índice de Apneia e Hipopneia (IAH) por hora de sono, a dessaturação da oxi-hemoglobina, as porcentagens dos estágios do sono, a eficiência e a fragmentação do sono; que podem ser atribuídas aos eventos respiratórios.

A gravidade da SAOS é baseada em seus índices polissonográficos, intensidade dos sintomas, o impacto nas funções sociais e profissionais, considerando gênero, idade e profissão; e presença de doenças cardiovasculares (AASM 1999). Em crianças, a SAOS se classifica como leve quando o paciente apresenta de 1 a 5 eventos respiratórios por hora de sono; apneia moderada para crianças com 5 a 10 eventos; e grave quando for registrado em polissonografia, mais de 10 eventos por hora de sono (AASM 1999).

Estima-se que a SAOS atinja cerca de 1-4% de crianças em idade pré-escolar (Lumeng *et al*., 2008; Marcus *et al*., 2012). O mecanismo exato dessa síndrome em crianças não está completamente esclarecido na literatura, embora importantes fatores anatômicos de risco tenham sido identificados, como a hipertrofia adenotonsilar. Nas faixas etárias de 3 a 6 anos, amígdalas e adenoides se encontram com grau de hipertrofia maior quando comparadas ao tamanho da VAS, representando o pico de incidência da SAOS na infância (Jeans *et al*., 1981). Técnicas como radiografia lateral do pescoço, telerradiografia lateral de cabeça, e ressonância magnética têm demonstrado que a VAS de crianças com apneia é menor quando comparadas a crianças saudáveis (Arens *et al*., 2004; Gozal *et al*., 2004).

Os principais fatores de risco para o desenvolvimento da SAOS em crianças: são obesidade, hipertrofia adenotonsilar, distúrbios neuromusculares, e alterações craniofaciais (AAP 2002; Kholer *et al*., 2008; Shintani *et al*., 1998). Os distúrbios oclusais encontrados são: retrognatismo mandibular, mordida cruzada uni ou bilateral, e mordida aberta anterior (Carvalho *et al*., 2014; Defabjanis *et al*., 2014).

Estudos apontam que crianças com SAOS apresentam elevação da pressão arterial noturna, hipertensão arterial sistêmica diurna, mudanças na geometria e função ventricular esquerda (Amin *et al*., 2005), assim como alterações endoteliais (Capdevila *et al*., 2008). Além disso, apresentam ativação mantida do sistema nervoso simpático, inflamação sistêmica, e alteração no metabolismo da glicose e dos lipídeos, levando ao início e propagação de processos de aterogênese (Capdevila *et al*., 2008).

Garetz & Arbor (2008) avaliaram estudos que analisaram aspectos do comportamento, cognição e qualidade de vida em crianças com SAOS antes e após adenotonsilectomia. Os autores encontraram 25 artigos relevantes em crianças e adolescentes: 10 artigos avaliaram qualidade de vida; 4 estudos examinaram mudanças comportamentais; 5 avaliaram ambos, comportamento e cognição; 2 avaliaram qualidade de vida e comportamento; e 1 artigo avaliou os 3 domínios. Apesar de diferentes metodologias de diagnósticos e de avaliação desses 3 domínios, além da amostra ter uma grande variabilidade (de 19 a 297 sujeitos), todos os estudos demonstraram aumento em uma ou mais das medidas avaliadas, ou seja,

mudanças na qualidade de vida; melhora no comportamento, principalmente nos índices de hiperatividade e problemas de agressão; melhoras de escores em tarefas de memória, atenção e desempenho acadêmico.

O tratamento da SAOS depende dos sintomas e da gravidade da doença. A perda de peso deve ser incentivada em todos os pacientes com sobrepeso ou obesidade (Tuomilehto *et al*., 2009). Aparelhos de avanço mandibular representam uma opção de tratamento para SAOS leve a moderada (Gagnadoux *et al*., 2009; Lim *et al*., 2006). O tratamento com exercícios orofaríngeos se mostrou eficaz na redução do IAH em pacientes com SAOS moderada (Guimaraes *et al*., 2009) e na redução da frequência e intensidade do ronco em roncadores primários (Ieto *et al*., 2015). Mais recentemente, o tratamento com estimulação do nervo hipoglosso foi proposto como alternativa para pacientes com SAOS (Certal *et al*., 2015; Friedman et al., 2016). A terapia com pressão positiva contínua na via aérea (CPAP) é o tratamento mais usado em adultos, sendo considerado como padrão ouro para SAOS moderada-grave (Kushida *et al*., 2006). A sua utilização diminui a mortalidade cardiovascular (Marin *et al*., 2005), no entanto, o tratamento com CPAP é pouco tolerado e tem baixa adesão, aproximadamente 50% dos pacientes diagnosticados com SAOS não continuam o tratamento após 3 meses (Engleman *et al*., 2003; Sawyer *et al*., 2011). Nas crianças portadoras da doença, a adenotonsilectomia (AT) é o principal tratamento. Estudos de intervenção demonstraram que após adenotonsilectomia, houve uma melhora em curto prazo das variáveis respiratórias na polissonografia em 83% dos pacientes (Brietzke *et al*., 2006). Além disso, há uma melhora no metabolismo dos lipídeos e variáveis inflamatórias (Gozal *et al*., 2008).

Apesar da adenotonsilectomia ser o tratamento mais efetivo para a SAOS em crianças, a cirurgia não melhora as alterações morfológicas da criança respiradora bucal (McColley *et al*., 1992). Além do custo elevado, a cirurgia para remoção das amígdalas e adenoides é pouco acessível pelo Sistema Único de Saúde (SUS). No ambulatório de otorrinopediatria do Hospital de Clínicas da Universidade Federal de Uberlândia (HC-UFU) a fila de espera para sua realização chega a 3000 crianças, sendo que aproximadamente 90 destas estão hoje em caráter de urgência por apresentarem sinais e sintomas de apneia do sono, levando a

outras comorbidades clínicas. O tempo de espera mínimo é de 3 a 4 anos, sendo considerado longo demais devido a evolução dos efeitos negativos da SAOS em crianças. Ainda que esta cirurgia melhore a permeabilidade nasal e faríngea, ela não corrige a hipotonia de mandíbula, palato duro elevado, alterações posturais e mastigatórias.

A expansão rápida da maxila promove uma distração osteogênica na base óssea superior. Essa distração óssea ao nível da sutura palatina expande a maxila, aumentando sua dimensão transversal, assim como, o espaço volumétrico da cavidade nasal, proporcionando uma melhora nos índices de distúrbio respiratório em crianças (Villa *et al*., 2002; Pirelli *et al*., 2004; Pirelli *et al*., 2005; Principato *et al*., 1991).

Villa e colaboradores (2007) avaliaram de maneira isolada a expansão rápida da maxila em tratamento de crianças com sinais e sintomas de SAOS. Após 12 meses de acompanhamento, 92.8% desses pacientes deixaram de ser respiradores bucais, sugerindo que a cavidade nasal foi aumentada. Outros autores também verificaram uma redução na resistência nasal após o tratamento de crianças e adolescentes com ERM (Bicakci *et al*., 2005). Reduzir a resistência nasal é um dos principais objetivos da ERM e foi documentada por Timms (1990) por meio da rinonanometria.

Apesar de não estar estabelecido na literatura, as evidências apontam que tanto a expansão maxilar quanto a adenotonsilectomia, podem levar a uma melhora no quadro clínico da apneia do sono infantil, sugerindo que uma abordagem multidisciplinar seria a melhor forma de tratamento.

A avaliação da anatomia da via aérea superior por meio de exames de imagem permite estudar de maneira objetiva sua contribuição na fisiopatologia da SAOS. Recentemente, a análise volumétrica das vias aéreas superiores tem despertado o interesse de médicos e cirurgiões-dentistas para os pacientes diagnosticados com SAOS. No entanto, a validação da correlação entre as alterações morfológicas tridimensionais (3D) das vias aéreas com os parâmetros polissonográficos ainda não está bem esclarecida na literatura. O uso da imagem 3D permite criar um novo horizonte de possibilidades de diagnóstico. Portanto, o objetivo deste estudo foi avaliar o ganho volumétrico nas vias aéreas superiores de crianças

diagnosticadas com SAOS, que receberam dois tipos de tratamentos, adenotonsilectomia e expansão rápida da maxila, com intuito de verificar o impacto de cada uma destas modalidades de tratamento sobre o volume das vias aéreas superiores, nas regiões de nasofaringe e orofaringe, e verificar se há uma ordenação de intervenção mais eficiente entre ambas (adenotonsilectomia – expansão rápida, ou expansão rápida – adenotonsilectomia).

CAPÍTULO

2. CAPÍTULO ÚNICO

ARTIGO 1 - Impact of adenotonsillectomy and rapid maxillary expansion on the upper airways in children with obstructive sleep apnea syndrome (OSA) – a randomized controlled trial

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Maria Cecília Monteiro Marques Magalhães; Gabriella Lopes de Rezende Barbosa; Carlos José Soares; Guilherme de Almeida Araújo.

Impact of adenotonsillectomy and rapid maxillary expansion on the upper airways in children with obstructive sleep apnea syndrome (OSA) – a randomized controlled trial

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Impact of adenotonsillectomy and rapid maxillary expansion on the upper airways in children with obstructive sleep apnea syndrome (OSA) – a randomized controlled trial

Abstract

Introduction: The purpose of this 2-arm parallel study was to evaluate the volume change in children diagnosed with Obstructive Sleep Apnea after receiving both types of treatments, adenotonsillectomy and rapid maxillary expansion. **Methods:** A sample of thirty children with Obstructive Sleep Apnea. Eligibility criteria included participants in the clinical symptoms of breathing disorder, such as snoring, and mouth breathing, palatine tonsil hypertrophy, adenoid hypertrophy, constricted maxillary arch, high palate, unilateral or bilateral posterior crossbite, and/or some degree of mandibular retrusion. The participants were consecutively divided into 2 study groups. The first group received adenotonsillectomy as the first treatment and later the rapid maxillary expansion; the second group received the rapid maxillary expansion as the first treatment and later the adenostonsillectomy. Cone-beam computed tomography examinations were obtained before of first treatment, 5-6 months post first treatment, and 5-6 months post second treatment. The images were imported and displayed in the imaging software: Mimics Research 21.0 for analysis the volumetric upper airways. Intragroup analysis was performed using Friedman test, intergroup analysis was performed using the Mann Whitney test ($\alpha = 0.05$). **Results:** There was a statistically significant difference in the both groups when comparing the total volume between initial and final. Intergroup analysis was statistically significant differences in the volume total upper airway and oropharyngx. **Conclusion:** Adenotonsillectomy and rapid maxillary expansion contributed to the increase of airway volume; and that the combined use of two types treatments greatest volumetric upper airway gain occurs when adenotonsillectomy was made as the first treatment option.

Keywords: obstructive sleep apnea, upper airway, children

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a sleep-related breathing disorder characterized by partial and complete upper airway obstruction that disrupts the normal sleep pattern and ventilation inducing intermittent hypoxia and frequent arousals during sleep.[1,2] OSAS is a major public health problem affecting significant portion of the population.[3] It is estimated that approximately 80-90% of the population meet the criteria at least moderate OSAS remain undiagnosed.[4] The prevalence of OSA in childhood is 1-4%.[5,6] The "gold standard" method for diagnosis the OSA is polysomnography (PSG).[7] However, it is expensive, time-consuming, labor-intensive and not universally available.[8,9]

In growing individuals, OSA is primarily caused by naso and/or oropharynx obstruction due to hypertrophic adenoids and tonsils[10] which are most prominent during childhood, when the size of the pharyngeal space is not yet fully developed.[11] The involution of the lymphoid tissue begins around puberty, and in old age there is very little lymphoid tissue remaining.[12] But despite the physiologic regression of the size of the lymphatic tissue along the aging process, in cases of recurrent throat infections and OSA, the American Academy of Otolaryngology – Head and Neck Surgery clinical practice guideline[13] recommends adenotonsillectomy. Thus, is considered to be a common procedure during childhood[14,15] and represents one of the most frequent indications for surgery in children,[16] with more than a half-million procedures performed annually.[17]

Another treatment option is Rapid Maxillary Expansion (RME) is an effective and valid orthodontic treatment approach for managing OSA in children with maxillary constriction.[18,19] RME can be used as an alternative orthopedic treatment method to expand the maxilla until providing appropriate and stable maxillary width increase, maxillary and mandibular dental arch coordination, nasal respiratory function, opening the mid-palatal suture, preventing posterior uni- or bilateral cross-bite, and dental crowding among children with OSA.[18, 20-22]

The use of imaging exams such as cone-beam computed tomography (CBCT) and magnetic resonance imaging (MRI), allows three-dimensional (3D) reconstruction of

airway structures.[23] Three-dimensional imaging is more accurate than 2-dimensional imaging for assessment of airway volume and area of maximum constriction.[23] Airway imaging with the use of a cephalogram does not portray medio-lateral changes in the oropharyngeal airway and may give misleading information as to the volume and minimal cross-sectional. Studies of the upper airway on CBCT scans are considered to be reliable in defining the border between soft and void space thus providing important information about the morphology of the pharyngeal airway.[24,25] Due the treatment of OSA in children is mainly focused on the surgical removal of the tonsils and adenoids, the visualization of the airways is an intuitive method to quantify the morphologic changes provided by adenotonsilectomy and thus to infer that corresponding improvements of the breathing parameters are likely to happen.

The aim of study was to evaluate the upper airway volume change in children diagnosed with OSA after receiving both types of treatments, adenotonsillectomy and rapid maxillary expansion, in order to verify the impact of these treatments on upper airway volume in the naso- and oropharynx regions; determine what intervention is more efficient to increase the airway volume in children diagnosed with OSA. The null hypotheses were: 1) the upper airway volume would not change after adenotonsillectomy and rapid maxillary expansion; and 2) the adenotonsillectomy and rapid maxillary expansion would produce similar airway volume change in children diagnosed with OSA.

MATERIAL AND METHODS

Trial design and any changes after trial commencement

The study was conducted as a prospective, parallel groups, randomized 2-arm, single-blinded, clinical trial with a 1:1 allocation ratio. No changes to the study design were made after commencement.

This study followed the Consolidated Standards of Reporting Trials guidelines[26] and was revised and approved by the Research Ethics Committee of Universidade Federal de Uberlândia (58609816.0000.5152). At the beginning of the study, the parents signed

informed free consents at the beginning of the children's treatment authorizing the use of the examinations for research purposes.

Participants, eligibility criteria, and settings

Thirty children (15 boys, 15 girls) with a mean age of 8.8 years old were recruited from the Clinical Hospital, Federal University of Uberlândia, in Uberlândia, Brazil, from March 2016 to April 2019.

The inclusion criteria included: (1) clinical symptoms of breathing disorder, such as snoring, and mouth breathing; (2) palatine tonsil hypertrophy classified by means of mouth examination according to the grading criteria of Brodsky;[27] (3) adenoid hypertrophy assessed by means of flexible nasoendoscopy; (4) diagnosis of OSA with the aid of PSG examination revealing an obstructive AHI $\geq$ 1 event/hour, according to the criteria of the American Academy of Sleep Medicine (AASM);[28] (5) constricted maxillary arch, high palate, unilateral or bilateral posterior crossbite, and/or some degree of mandibular retrusion; (6) children between 5 and 12 years old incomplete. Exclusion criteria included: (1) obese children (BMI > 95 kg/m^2); (2) genetic syndrome; (3) craniofacial anomalies; (4) systemic diseases.

The children were randomly and blindly allocated into two groups. Randomization was performed by a researcher who did not participate in the study, taking into consideration population size and sample size for each groups as well as the treatment used. The randomization was done by the program available on line www.randomizer.org. The blocked randomization (4 patients) was chosen to ensure an equal distribution of the number of patients in the study groups.

Interventions

All subjects underwent polysomnography (PSG) using the same equipment (Alice Night One – Philips Respironics, Twain). To analyze both sleep structure and microstructure at three different times: (1) basal PSG; (2) post-final PSG of the first proposed treatment; (3) PSG after second proposed treatment. The examination was performed according to the

usual sleep schedule of each patient, and was accompanied by the adult responsible. All polysomnographic record was obtained at the same place. OSA was defined if obstructive apnea index was ≥ 1 event/hour. Subsequently, the patients were referred to a private radiology clinic, for CBCT (T_0) examination for diagnoses purpose, such as evaluation of upper airway geometry.

The first group, ADRM, (n = 15; 7 males and 8 females) initially received adenotonsillectomy (AT) as their first treatment. After 5-6 months the first treatment, the patients were submitted to a new polysomnography (PSG_1) and CBCT (T_1). The patients with IAH ≥ 1 event/hour proceeded to the next treatment. The rapid maxillary expansion (ERM) was second treatment. At the end of the last treatment the patients were submitted again to polysomnography (PSG_2) and CBCT (T_2) exams.

The second group, RMAD, (n = 15; 6 males and 10 females) initially received rapid maxillary expansion as their first treatment. After 5-6 months the first treatment, the patients were submitted to a new polysomnography (PSG_1) and CBCT (T_{1*}). The patients with IAH ≥ 1 event/hour proceeded to the next treatment. The adenotonsillectomy (AT) was second treatment. At the end of the last treatment the patients were submitted again to polysomnography (PSG_2) and CBCT (T_{2*}) exams.

Adenotonsillectomy was performed at Public Health Hospital at Federal University of Uberlândia. All procedures were included in the Health Unified System in Brazil – SUS. Standard clinical protocol was followed for all patients: (1) preoperative clinical medical evaluation; (2) surgery procedure; (3) postoperative control 7 days after surgery; (4) return of 5-6 months after surgery for reevaluation.

For rapid maxillary expansion, all patients were treated with a hyrax type of maxillary expander (Morelli, Sorocaba – São Paulo, Brazil). Due the participants were in mixed dentition, appliance anchorage was provided by bands (Orthometric, Marília – São Paulo, Brazil) adapted on either the maxillary permanent first molars or the deciduous second molars, and circumferential clamps (Wire Morest Standard, Sorocaba – São Paulo, Brazil) were bonded to the maxillary deciduous or permanent canines. The prescribed expansion

regime was a quarter turn (approximately 0.25 mm), twice a day until an overcorrection of approximately 2 to 3 mm was obtained. Clinically corresponding the palatal cusps of upper molars occluded with the buccal cusp tips of lower molars. The initial ¼ activation were performed by the professional, and the rest by parents or guardians. The steps of bandage, cementation, initial activation and removal of the expander were performed by a single trained operator (G.A.A.). The breaker was held in position for 5 or 6 months until bone formation occurred in the palatal fissure region, after this time, the expander was removed.

CBCT scans were acquired using the same Planmeca Promax 3D Max unti (Helsinki, Finland) under an extended field of view mode (14.5 cm x 13.0 cm). The overall effective radiation dose was 125,Sv, with a 0.35-mm isotropic voxel size, a total scanning time of 20 seconds, and scanning time of 4.5 seconds. Patients sat upright with a natural head position. Mandible position was stabilized with use of a chin holder, keeping the Frankfort plane parallel to the ground. The patients were asked to breathe normally and to nor swallow. All CBCT scans were acquired without sedation of the subjects. These images were imported as a DICOM (Digital Imaging and Communications in Medicine) formatted file and displayed using in imaging software: Mimics Research 21.0 (Materialize, Leuven, Belgium) by a well-calibrated and trained evaluator. The nasal airway volume (NV) and oropharynx airway (OV) were assessed separately excluding the sinus areas. The threshold was defined manually in an attempt to include the airway spaces and to remove any visible extraneous scatter, artifacts, and background. The volumetric region of interest (VOI) was cropped and narrowed to comprise only the structure that would be segmented.

The OV was defined as the volume of the pharynx between the palatal plane and the parallel plane that intersects the most anteroinferior point of the third cervical vertebra (C3), extending posteriorly to the wall of pharynx (Figure 1A). For this OV volume, the superior and inferior limits were slightly modified from the ones used by Ogawa et al.[29] The NV was characterized as the nasal airway without sinuses, with an inferior limit demarcated as the superior boundary of the OV airway. The NV volume was rendered as a whole structure, including the nasopharynx and turbinates (Figure 1A and 1B).

After the threshold selection and definition of the boundaries, the mask was created, with a threshold value of -1024 to -500, consistent with the density of air. This tool allows the filling of the nasal airway volume (NV) and oropharynx volume (OV), distinguishing them from other structures, such as soft and hard tissues. The semiautomatic segmentation was performed, by removing noninterest structures for analysis, and adding areas which, in turn, could not be selected by the threshold, in coronal, sagittal and axial slice. To assess the different regions of the upper airway (UAW), the segmentation was divided into 3 different parts:

1. Total Upper Airway (tUAW): anterior boundary (external nostrils); inferior boundary (most inferior point of C3);
2. Nasal airway volume (NV): anterior boundary (anterior limit of tUWA); posterior boundary (most inferior posterior point at the inferior choanae and nasopharynx);
3. Oropharynx volume (OV): superior boundary (inferior boundary of the NV); inferior boundary (most inferior point of third cervical vertebra).

After the threshold selection and definition of the boundaries, a combination of manual slice editing and 3D editing was used to obtain refined surfaces of the segmentation of the airway. The resulting set of masks of the VOI was rendered into a shaded surface mesh in the same software; and according to the manufacturer's recommendations, each segmented volume (cm^3) was calculated (Figure 2).

Outcomes

Three cone-beam computed tomography and three polysomnography were taken of each patient regardless of the group they belonged to. The CBCT and PSG were taken at the beginning of treatment of the first group, ADRM, (T_0, mean age = 9.8, SD = 2.18), at the end first treatment (T_1, mean age = 10.10, SD = 2.20), and post second treatment (T2, mean age = 10.7, SD = 2.26). In the second group, RMAD, cone-beam computed tomography and polysmnography were taken (T_0, mean age = 7.4, SD = 1.78), at the end first treatment (T_1, mean age = 7.9, SD = 2.09), and post second treatment (T2, mean age = 8.3, SD = 2.04).

For the methodological error, 12 tomography selected at random were traced and measured twice with an interval of 2 weeks to assess measurement repeatability.

Sample size calculation

Sample size was based on the results of the analysis of the different types of apnea treatments in children from the Guilleminault et al., 2008 study.[30] The minimum sample was estimated to include 30 individuals (fifteen per group), with an alpha error of 5% and a test power of 95%.

Blinding

Blinding of treatment was not possible. However, all data were blindly assessed, thereby endorsing the single-blind design of the study.

Statistical analyses

Data analysis was performed using GraphPad Prism Software version 8.0.1 for Windows (GraphPad Software, La Jolla California USA). Descriptive statistical analysis for each of the studied variables was performed. Normality (Shapiro-Wilk) and homogeneity (Levene test) tests were performed. Mann-Whitney test was used to evaluate comparison between two groups; and the Friedman test was performed to analyze comparisons of different moments within the same groups.

RESULTS

Participant flow

The flow of the subjects through the study is shown in Figure 3. Children with palatine tonsil hypertrophy degree III or IV and adenoid hypertrophy were screened for eligibility, a total of 43 subjects: Thirteen children were excluded; (n = 8) not meeting inclusion criteria, (n = 3) declining to participate, (n = 2) including another protocol. Thirty children were randomized in a 1:1 ratio to treatment groups. In the first group, ADRM (n = 15) all patients received both types of treatments, with adenotonsillectomy being the first treatment option. In the second group, RMAD (n = 15) all patients received both types of treatment,

with rapid maxillary expansion the first treatment option. No harms were encountered during the follow-up of the two groups. The follow-up study of the patients is still in progress.

Number analyzed for each outcome, estimation, and precision

Considering that a high intraexaminer agreement was obtained for all variables (0.97 to 0.99), results are presented as the mean values of both measurements. 3D reconstruction can be seen in Figure 2 showing the three times of both treatments. The mean volumes of nasal airway, oropharynx airways and total upper airway are shown in Table I.

Intragroup analysis was performed using Friedman test. There was a statistically significant difference in both groups when comparing the total volume between phases T_0 and T_2. Comparing the phases – T_0, T_1 and T_2 – a statistically significant difference was found in the Nasal airway (NV) volume at pre and posttreatment, both for group ADRM ($T_0 - T_1$) and for group RMAD ($T_{1*} - T_{2*}$). No significant difference was found for Oropharynx (OV) volume in any of the group studied. Intergroup analysis was performed using the Mann Whitney test. According to the results, the phases T_0 and T_2 showed no significant differences. However, between the T_1 phases of each group, the results showed statistically significant differences for both tUAW and OV (Figure 4).

DISCUSSION

As with adults OSA, impaired neuromuscular tone underlines upper airway collapsibility in children. In addition to etiologic factors similar to those in adults, exacerbating factors for pediatric OSA often include lymphoid hyperplasia and growth-related changes in the size of the upper airway.[31] The main forms of treatment for childhood OSA are adenotonsillectomy and rapid maxillary expansion.[32] Assessing the volumetric gain of the upper airway of our patients who received these two types of treatments, we concluded that there was a volumetric increase in all patients. However, those who received adenotonsillectomy as the first treatment option presented a more significant volumetric increase in the upper airway. Therefore, our two hypotheses were rejected.

The diagnostic measurement of the nasal cavity and airway changes is performed by acoustic rhinometry, a well-established and noninvasive technique.[33] However, the introduction of CBCT allows to a more accessible 3D evaluation of UAW of the patient, and as consequence, a large number and variety of software is emerging for different clinical purpose.[34] Regarding the segmentation of the airway, the programs may have manual and/or automatic segmentation. In our study, Mimics software was chosen due to its accuracy and possibility of a detailed individualization of the VOI after the selection of the density values in the threshold. Additionally, the software is simple to work with and allows quick and easy airway segmentation.[35]

Comparing the effectiveness of both tested groups and the phases of treatment, the ADRM group revealed a statistically significant volume gain in the time T_0, T_1 and T_2 in the total airway and in the nasopharynx. In the RMAD group, no statistical difference was found at time T_{0*} and T_{1*} in the total volume and in the nasopharynx, and only in T_{2*} the volume had a statistically significant volumetric change. No statistical difference was found in the volumetric gain in the oropharynx in the two groups.

The oropharynx airway can be subdivided into the retropalatal (from the level of the hard palate to the caudal margin of the soft palate) and retroglossal (from the caudal margin of the soft palate to the base of the epiglottis) regions.[36] Most traditional CBCT studies that have evaluated airway caliber in patients with sleep apnea during wakefulness have found narrowing in the retropalatal region.[37-39] Few studies have evaluated the effects of maxillary expansion in the oropharynx, and none of them found significant changes in the dimensions of this region after maxillary expansion.[40,41] It is important to mention that several studies in the literature correlate head posture with dimension changes of the upper airways, especially in the oropharynx.[41] Ingman et al.[42] suggested that the change in the oropharynx may be associated with the change in head position. Other factors that could influence the dimensions of the oropharynx are tongue position at the time of acquisition of the examination and repositioning of the tongue and the mandible due to the clinical procedure (ie, after RME and anterior mandibular repositioning as a direct consequence of the jaw expansion). Although our results demonstrate a volumetric increase in the oropharynx by

the surgery, the quantitative difference between the two types of treatment did not allow for statistical significance.

The immediate and long-term effects of RME over the upper airway have been show in previous studies.[43-47] The literature shows that patients presenting with maxillary constriction tend to have a higher nasal airway resistance.[48] The maxilla forms most of the lateral walls of the nasal cavity; therefore, an increase in volume in the nasal cavity would be an expected RME effect. The series of events that cause this phenomenon is mainly the triangular[49] or parallel[46] opening of the median palatal suture, which increases the width of the nasal floor and results in an increased volume of the nasal cavity. In our study, the first reference point of nasopharynx delimitation was located in the choana, including the area of the pharyngeal tonsil, and continued to the inferior portion of the soft palate. In our sample, we observed that there was a mean increase in the absolute numbers of the nasophrynx volume, especially when adenotonsillectomy was proposed as the first treatment option, while the patients who received rapid maxillary expansion as the first treatment, no statistically significant difference was found in volumetric gain in the nasopharynx ($P > 0.9$). Zhao et al.[46] who analyzed the same area with CBCT before and 15 months after RME, found no significant differences in the volume of the oropharynx and nasopharynx. They reported that hypothesis that there is a chance in the upper airways after the procedure is not supported. Results of the present study were similar to other findings[40,47] in which no significant changes in the dimensions of the nasopharynx after REM were observed. Charoenworaluck[40] evaluated the effects of RME on the nasopharynx after 1 year of the active phase of treatment an noted an increase in the airway. However, this increase is not statistically significant, and it is possible that growth changed the immediate effects of maxillary expansion. Usymez et al.[47] evaluated lateral cephalograms of 8 patients after 8 months of the RME procedure and observed mean values in nasopharynx, but they attributed the lack of statistical significance of this variable to the small sample size.

In the comparative analysis inter-groups, ADRM and RMAD, at different moments of the study, no statistical difference was found in the initial and final volumes in tUAW, NV and OV, indicating an initial and final homogeneity between the groups. However, the

volume assessed after the first treatment in both groups, did not indicate a statistical difference in the nasopharynx, only in the tUAW and OV. In other words, adenotonsillectomy followed by rapid maxillary expansion generated a significant volumetric increase in the total volume of the upper airway and in the oropharynx. Bertoz et al.[48] evaluated the airway volume changes of 30 children who underwent adenotonsillecomy. They used CBCT scans made before and 12 months after the surgery, concluded AT contributed to the increase of airway volume, accompanied by an improvement in the breathing pattern of all the children, which was expected and has been previously described.[49]

In the present sample, following adenotonsillectomy and rapida maxillary expansion a significant improvement in the breathing pattern of the children and in quality of life was reported by parents. Early treatment in most children reduced the symptoms of OSA.[31] The joint action of doctors and orthodontists is fundamental in the choice of treatment for each patient. All orthodontists should consider incorporating OSA screening into their history-taking and examination of patients. It is strongly recommended that orthodontists be familiar with the signs and symptoms of OSA.

Limitations of this study include the absence of a control group without symptoms of OSA, a limited number of patients who met all the inclusion criteria, and dependence on medical staff for adenotonsillectomy. The use CBCT in study involving children is a controversy issue, due the radiation to be performed. However, the radiation dose may be reduced minimizing the children exposition. It was used a conventional CBCT equipment used where patients were awake in a seated position, which did not reflect the actual dimension that are likely to occur during snoring in a sleeping child. In future studies, the use of new measurements from CBCT scans, or the use of new methodologies using computational fluid dynamics could provide different views about the efficacy of using 3D assessment of airways to quantify improvements.

CONCLUSION

Adenotonsillectomy and rapid maxillary expansion contributed to the increase of airway volume; and that the combined use of two types treatments greatest volumetric upper airway gain occurs when adenotonsillectomy was made as the first treatment option.

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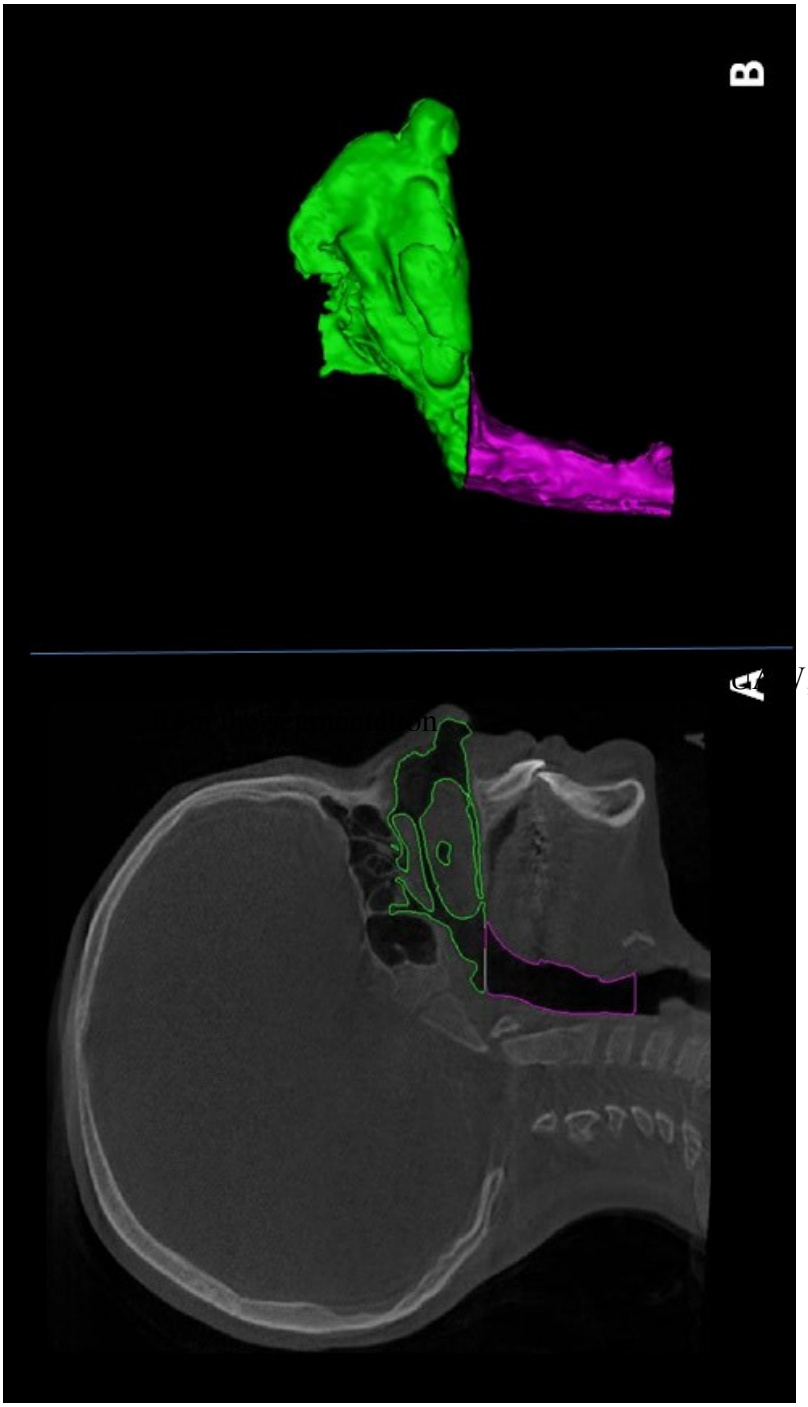
FIGURES



; **Figure 1B:** The three-dimensio

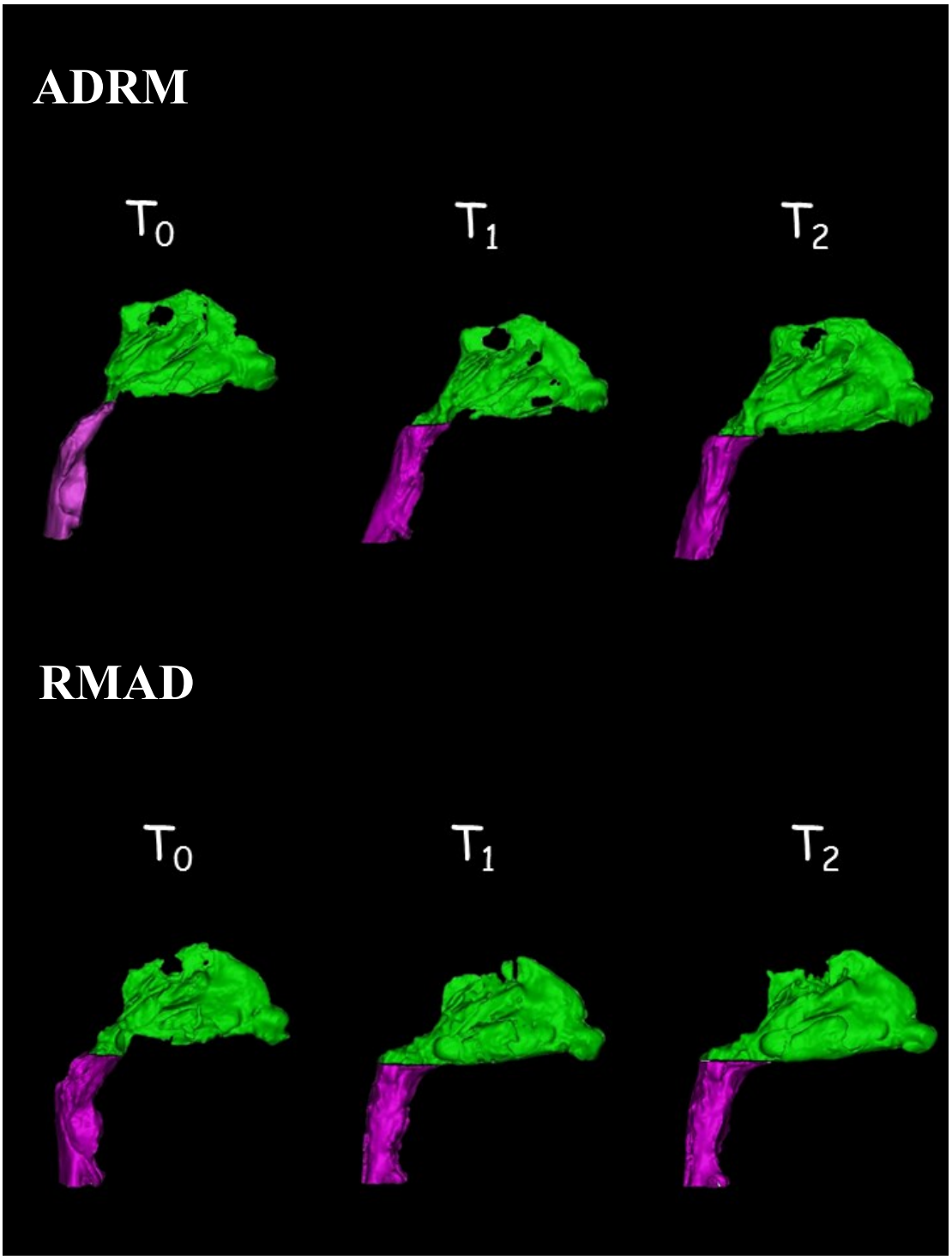


Figure 2: Three-dimensional models generated by the upper airway reconstruction of ADRM and RMAD. Different colors represent different anatomical division, as follow: Light green: nasal airway. Pink: oropharynx.

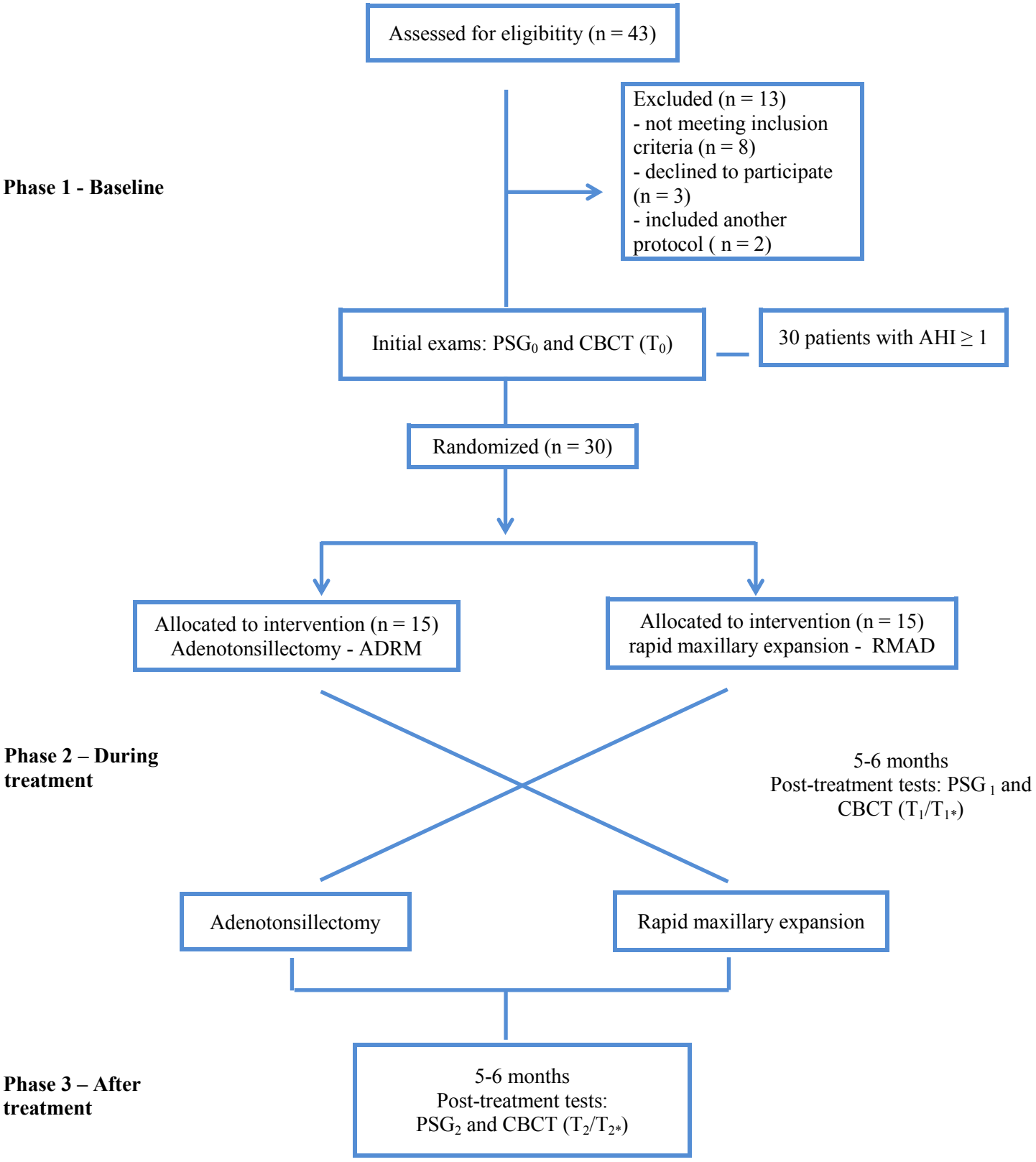


Figure 3: Diagram showing the study design.

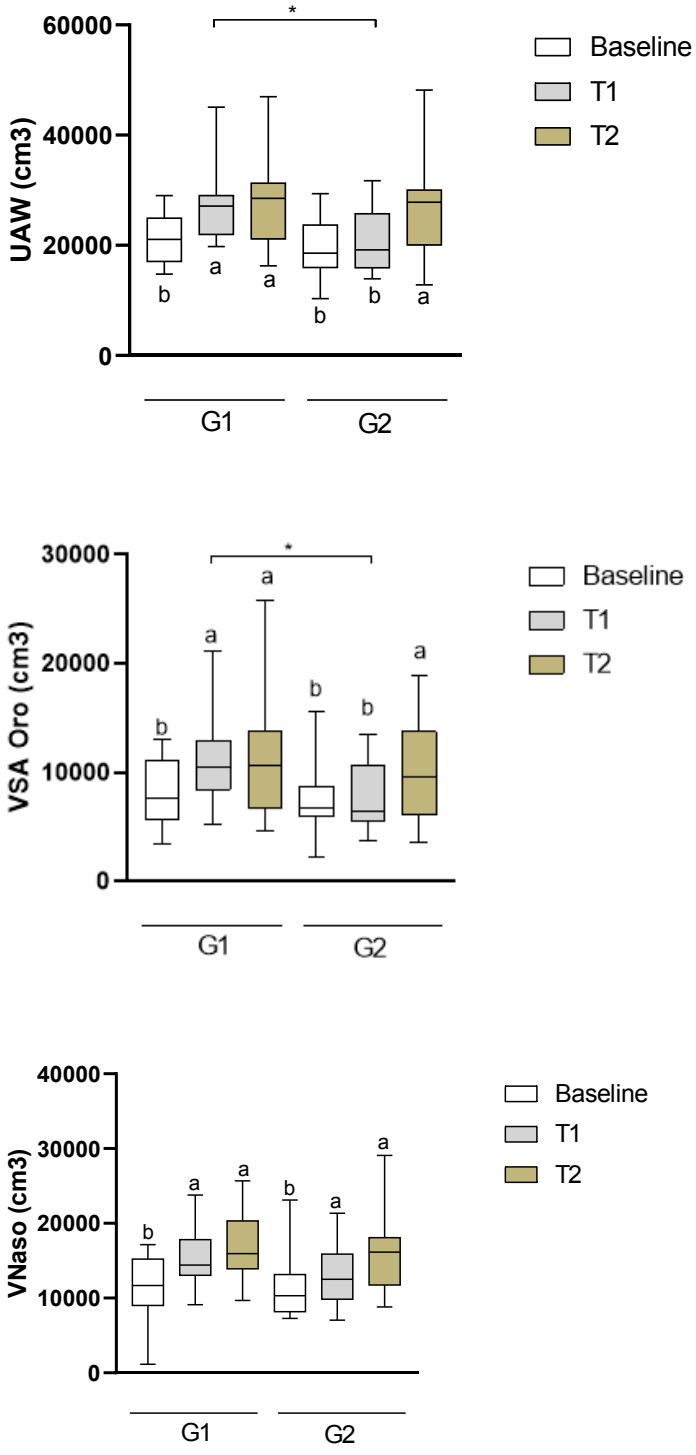


Figure 4: [a,b] Values with the same letters are not statistically different (P > 0.05) according to Mann-Whitney test.

TABLE

Table I. Mean of Nasal Cavity, Oropharynx and Total Upper Airway (cm^3)

	ADRM (n = 15)			*RMAD (n = 15)*		
		Mean			Mean	
Variable	T0	T1	T2	T0	T1*	T2*
Nasal Cavity	10876	15611	16597	11783	13024	16263
Oropharynx	8274	11111	11223	7735	7745	9687
Total Upper Airway	21086	26881	28069	19829	21258	26333

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