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Functional therapy and adenotonsillectomy clinical trial for class II malocclusion (FACT-II): protocol for a randomised controlled trial

Feiyang Guo,[1,2] Chenxing Lv,[1,2] Bojun Tang,[1,2] Lizhuo Lin,[1,2] Chen Zhang,[1,2,3] Jie Zheng,[1,2] Tingting Zhao,[1,2,3] Hong He [1,2,3]

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FG and CL contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Hong He; drhehong@whu.edu.cn and Dr Tingting Zhao; zhaott1991@whu.edu.cn

ABSTRACT

Introduction Class II malocclusion with mandibular retrognathia is a common complication of paediatric obstructive sleep apnoea (OSA), often accompanied by transverse maxillary deficiency. In early orthodontic treatment, a twin block (TB) is a regular functional appliance for correcting this malocclusion. For paediatric OSA, the most common risk factor is adenotonsillar hypertrophy (AHT). Untreated AHT may lead to the persistence and worsening of obstructive sleep-disordered breathing traits, including habitual mouth breathing. Additionally, the clockwise mandibular rotation associated with AHT-induced pharyngeal crowding can undermine the effectiveness and stability of TB treatment. Adenotonsillectomy (T&A) is currently the first-line treatment for paediatric OSA. This proposed trial will investigate the impact of T&A surgery timing on the efficacy and stability of TB functional treatment in children with class II mandibular retrognathia and ATH.

Methods and analysis This will be a single-centre, parallel-group, superiority randomised controlled trial with participants randomised to intervention (T&A followed by TB treatment) or control arms (TB treatment followed by T&A) in a 1:1 ratio. A total of 40 patients aged 8–14 years, diagnosed with class II mandibular retrognathia and co-existing ATH-induced OSA, and indicated for both T&A surgery and TB treatment, will be recruited at the School and Hospital of Stomatology, Wuhan University. The primary outcomes will be the changes in the apnoea-hypopnoea index and the point A-nasion-point B angle from baseline to postorthodontic treatment between the two groups. Secondary outcomes will include other dental, skeletal, upper airway and soft tissue changes, as well as subjective sleep-related and oral-related quality of life. Outcome changes within each group and between groups will be analysed.

Ethics and dissemination This study is approved by the Ethics Committee of the School and Hospital of Stomatology, Wuhan University (no. 2022-D07). The research findings will be faithfully disseminated through scientific conferences or published articles.

Trial registration number ChiCTR2200061703 (https://www.chictr.org.cn).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The functional therapy and adenotonsillectomy clinical trial for class II malocclusion is the first randomised controlled trial to provide evidence on the indication and timing of adenotonsillectomy and orthodontic treatment in children with mandibular retrognathia and adenotonsillar hypertrophy.
⇒ With an extended follow-up of 6 months, the study design allows for the investigation of the impact of adenotonsillectomy on the stability of orthodontic treatment in these patients.
⇒ The chosen combination of primary and secondary outcomes contains objective and subjective measurements, which will give a comprehensive reflection of the efficacy of the intervention.
⇒ The lack of blinding of participants and researchers is a limitation of this trial. Data analysts will be blinded to group allocation to mitigate potential information bias.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common clinical condition in childhood, characterised by recurrent collapses of the upper airway that disrupt normal ventilation and sleep patterns during sleep.[1] Adequate and high-quality sleep is imperative for the physical and mental development of children and adolescents. Untreated paediatric OSA can lead to somatic growth retardation, neurocognitive/neurobehavioral impairment, diminished quality of life[2] and other serious general health consequences, as well as cardiovascular diseases,[3] conductive hearing loss[4] and dentofacial deformities.[5]

Children with OSA may exhibit excessive vertical facial growth (adenoid facies or long face syndrome) as a consequence of long-term mouth breathing, which can manifest as an elongated face, a relatively short upper lip, a high arched palate, a narrow upper dental arch and mandibular retrognathia.[6] Class II malocclusion, a common comorbidity of paediatric OSA, can impact the morphology and aesthetics of the lower face. Moreover, it

is one of the risk factors for OSA, in which a constantly retrognathic mandible can cause oropharyngeal airway stenosis correspondingly.[7] The twin block (TB) appliance is a regular functional appliance in early (ie, prior to age 14) orthodontic/dentofacial orthopaedic (O/DO) treatment of class II malocclusion with mandibular retrognathia.

Along with the effects of forward movement of the mandible and enhancement in the growth of the condyles, TB can improve sagittal dentofacial relationships, facial profile and upper airway pharyngeal size.[8 9] Nevertheless, its treatment effect and stability are affected by many factors, such as growth potential, jaw growth type and patient compliance.[10] Furthermore, our previous research revealed that TB treatment benefited children with OSA by significantly increasing the superior posterior airway space.[9] Patients with mandibular retrognathia often exhibit maxillary transverse constriction, especially in mouth breathers[11]; achieving mandibular advancement can be challenging without first addressing the commonly associated maxillary transverse deficiency. Therefore, one of the initial steps will involve the accurate diagnosis of maxillary transverse deficiency and the determination of the need for dentofacial orthopaedic expansion of the maxilla.[12] Rapid maxillary expansion (RME) is commonly used in combination with TB appliances to increase the transverse maxillary width, which will also benefit OSA-affected children by enlarging the transverse dimension of the nasal cavity and sagittal depth of the bony nasopharynx.[13 14]

Adenotonsillar hypertrophy (ATH) is the most commonly recognised risk factor for paediatric OSA. Both adenoids and palatine tonsils belong to Waldeyer's ring.[15] In normal physiological conditions, these structures gradually atrophy and disappear by the age of 10 for the majority of people. However, in cases of pathological hypertrophy, adenoids and tonsils are unable to involute at a normal rate. Failure to address these primary pharyngeal-crowding issues may result in the persistence and worsening of obstructive sleep-disordered breathing (OSDB) traits, including habitual mouth breathing, snoring, low resting tongue posture and other nasorespiratory problems known to be associated with increasing nasal disuse.[16 17] Consequently, children will often tend to maintain the habit of mouth breathing, which can cause the elongation of the lower face via a clockwise rotation of the mandible. Such oral habits, often associated with ATH-induced pharyngeal crowding, can exacerbate dentofacial development, resulting in more severe class II malocclusion and subsequently affect the effectiveness and stability of TB functional O/DO treatment. This potential risk is often overlooked by orthodontists, who proceed with functional therapy directly without addressing the underlying issues.

Adenotonsillectomy (T&A) is currently recommended as the first-line treatment for paediatric OSA.[3] In a randomised controlled trial (RCT) conducted by Marcus *et al*,[18] it was observed that early T&A for paediatric OSA could improve polysomnographic findings and the quality of life. Relevant systematic reviews have indicated potential beneficial effects of T&A on dentofacial deformity, including tendencies of normalisation towards labial inclination of incisors and a more horizontal mandibular growth pattern after surgery.[19–21]

As of now, there is a paucity of studies exploring the impact of T&A on the efficacy of functional treatment in children. Moreover, a continuous debate surrounds the necessity of T&A performed prior to O/DO treatment intervention. Previous evidence has indicated that addressing upper airway obstruction as a primary step in children with malocclusion and OSA is conducive to the normalisation of dentofacial growth[19] and may enhance the stability and efficacy of O/DO treatment. However, these studies yielded an indirect and low-to-moderate level of evidence.

Therefore, we intend to conduct an RCT to provide evidence on the indication and timing of O/DO treatment in children with class II mandibular retrognathia and AHT comorbidity. This is of great significance to help establish a standardised clinical treatment pathway of multidisciplinary sequence therapy for children with OSA and craniofacial alterations.

Objectives

This study is designed to investigate the impact of T&A performed prior to or after indicated O/DO treatment on (1) the effectiveness and stability of TB functional treatment and (2) the sleep quality, quality of life and oral health in children with class II mandibular retrognathia and ATH comorbidity.

METHODS AND ANALYSIS

The study protocol is written in accordance with the Standard Protocol Items: Recommendation for Interventional Trials reporting guidelines.[22]

Study design and setting

This will be a single-centre, parallel-group, superiority RCT with participants randomised to intervention and control arms in a 1:1 ratio (figure 1). Participants will be recruited at the Department of Orthodontics, School and Hospital of Stomatology, Wuhan University, Wuhan, China.

Eligibility criteria

Eligible patients will be enrolled after screening at the study site. The inclusion criteria are as follows.

1. Patients aged 8–14 years, at prepubertal or pubertal stage according to the cervical vertebral maturation method (cervical vertebrae stage (CVS) 1–3).[23]
2. Dental class II division 1 malocclusion, skeletal class II malocclusion and mandibular retrognathia (A point, nasion and B point angle (ANB) ≥4° and overbite ≥5 mm).

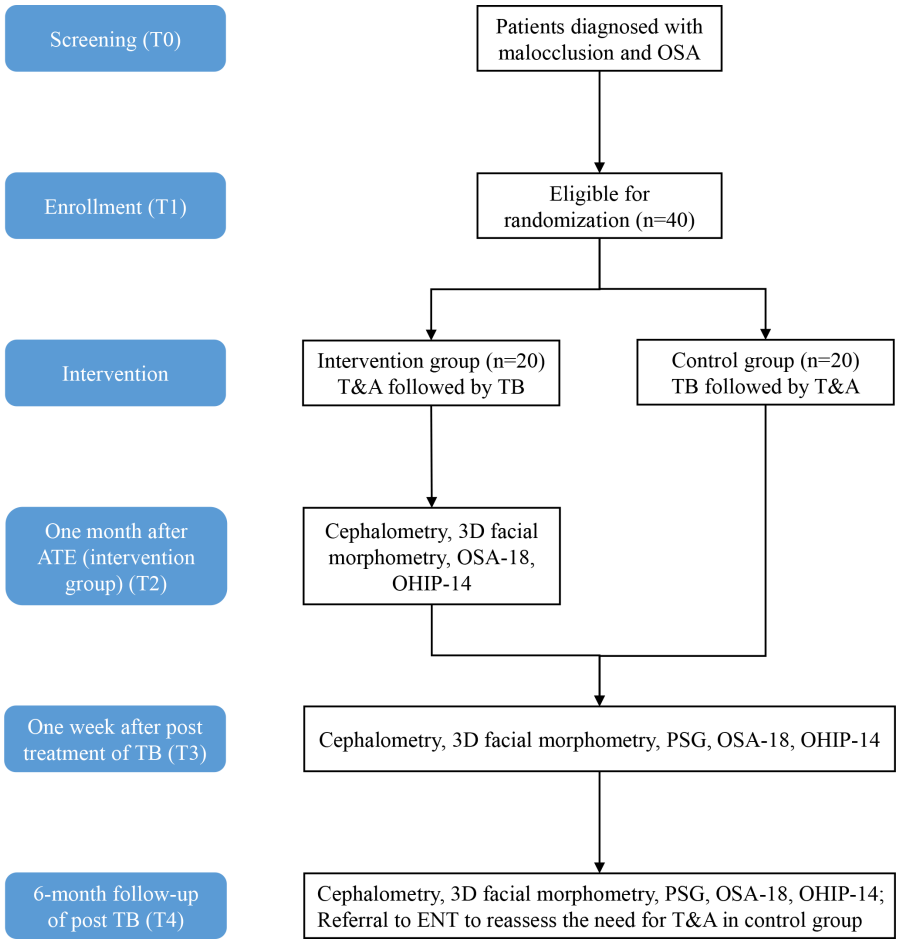

Figure 1 Flow diagram of this study. ENT, ear-nose-throat; OHIP, oral health impact profile; OSA, obstructive sleep apnoea; PSG, polysomnography; T&A, adenotonsillectomy and TB, twin block.

3. No obvious symptoms of temporomandibular joint disorders in the clinical examination.
4. Patients exhibiting symptoms of mouth breathing or snoring during sleep, along with a diagnosis of mild to moderate OSA (apnoea-hypopnoea index (AHI) 1–10 times/hour).
5. Patients diagnosed with adenoid and/or tonsil hypertrophy by an otolaryngologist and eligible for T&A.
6. Good oral hygiene, agreeing to participate in the study and good compliance during treatment.
7. Obtaining written informed consent from their guardians.

The exclusion criteria include:

1. Patients diagnosed with acute upper respiratory infection;
2. Overweight (age-standardised scores for body mass index (BMI z-score) >1 using the WHO AnthroPlus software)[24];
3. Severe OSA (AHI >10 times/hour);
4. History of orthodontic treatment, adenoidectomy and/or tonsillectomy and
5. Diagnosed with congenital craniofacial malformation, neuromuscular or cardiopulmonary diseases.

Recruitment and allocation

A recruitment announcement will be disseminated through posters at the hospital and on the official website. Before enrolment, potential participants will undergo a series of clinical and radiographic examinations, including intraoral and extraoral evaluation, an orofacial myofunctional assessment for the presence of orofacial myofunctional disorders,[25] lateral cephalometric and panoramic radiographs, polysomnography (PSG) examination and an ear-nose-throat (ENT) examination. The PSG and ENT examinations will be conducted at Zhongnan Hospital of Wuhan University, which is a district general hospital equipped with an ENT clinic and sleep centre. Once considered eligible for entry, written informed consent (online supplemental additional file for informed consent) from both participants and their guardians will be obtained following a detailed explanation of the study by the principal investigator. Subsequently, each participant will be assigned a unique identification number.

Consecutive participants will be randomised in a 1:1 ratio to either the intervention or control group. Simple randomisation will be performed using a computer-generated randomisation sequence. To minimise

potential selection bias, an independent staff who is not involved in the subsequent study procedures will generate and keep the allocation sequence. Opaque and sealed envelopes with identical size, colour and material will be prepared to contain identification numbers and corresponding group information. The allocation sequence will remain concealed from both researchers and participants until the final assignment.

Blinding

Given the nature of the intervention (T&A surgery), blinding the participants to their assigned group is not feasible. Participants will be informed of their group assignment after enrollment. Additionally, researchers conducting the intervention and data collectors will be aware of the group allocations due to the visual identification of adenoids and/or tonsils in lateral cephalometric radiographs or intraoral examinations. To minimise potential bias, data analysts will be blinded throughout the analysis process.

Interventions

Upon enrollment, participants will be randomly assigned to either the intervention group (T&A followed by TB treatment) or the control group (TB treatment followed by T&A) using computerised randomisation. Subjects in the intervention group will undergo adenoidectomy and/or tonsillectomy at the initial step of the treatment process. Endoscopic coblation adenoidectomy and/or tonsillectomy (if tonsils satisfy indications for surgery) under general anaesthesia will be performed by one senior otolaryngologist at the Department of Otorhinolaryngology-Head and Neck Surgery at Zhongnan Hospital of Wuhan University. O/DO treatment using the TB appliance will commence 1 month after the surgery. Subjects in the control group will receive O/DO treatment with the TB appliance at the initial step. Following 6 months of post-TB treatment, they will be referred to the otolaryngologist for reevaluation to determine if adenoidectomy and/or tonsillectomy are necessary.

To mitigate bias, standardised instructions for TB treatment will be applied to both groups. The O/DO treatment will be performed by a team of five experienced orthodontists, each possessing a minimum of 5 years of clinical expertise and undergoing training in the trial protocol prior to the commencement of the study. For patients with maxillary transverse deficiency, an additional RME procedure will be conducted at a rate of 0.5 mm per day for a period of 1–2 weeks, until the mesiolingual cusp of the maxillary first molar is located at the tip of the buccal cusp of the mandibular first molar. Maxillary transverse deficiency will be diagnosed at baseline using either dental cast measurement (Andrews 6-elements)[26] or cone-beam CT (CBCT) with the transverse analysis developed by Miner *et al*[27]). The RME procedure will be administered before the TB treatment, specifically 1 month after T&A and before TB treatment for patients assigned to the intervention group. Thereafter, the job model and occlusal wax record will be obtained to make a customised TB appliance. The working bite is adjusted with the incisors in an edge-to-edge relationship and at 2–4 mm beyond the freeway space.[28] The posterior bite blocks are ground for 0.5–1 mm every 4–6 weeks until the posterior teeth establish occlusion. Then the TB appliance will be left in the mouth to maintain stabilisation. Patients will be instructed to wear TB appliances for at least 22 hours per day for approximately 12 months. Outcome measurements will be performed 1 week after TB removal.

Timeline

The schedule of assessments performed at each study visit is shown in table 1. Outcome measurements are performed at screening (T0), enrollment (T1), 1 month after T&A (intervention group) (T2), 1 week after post-treatment of TB (T3) and 6-month follow-up of post-TB (T4). During the study period, patients will be prohibited from using other types of orthodontic appliances or participating in other clinical trials that involve orthodontic treatment.

Data related to questionnaires (OSA-18, Oral Health Impact Profile-14 (OHIP-14)), intraoral and extraoral photos, study models, 3-dimensional (3D) digital facial photographs, lateral cephalometric radiographs, adverse events, etc, will be recorded and collected at baseline, 1 month after T&A (only intervention group) (T2), post-treatment of TB (T3) and 6-month follow-up of post-TB (T4). PSG and panoramic radiographs will be conducted at baseline, post-treatment of TB (T3) and 6-month follow-up of post-TB (T4). The 6-month follow-up assessment aims to evaluate the stability of the orthodontic treatment following T&A.

Outcomes

Primary outcomes

The primary outcomes of this study consist of the changes in AHI and ANB angle from baseline to the primary timepoint (T3) between the two groups. AHI is defined as the number of obstructive events per hour, which serves as an important and objective index reflecting the severity of sleep apnoea. It will be measured using PSG. The other primary outcome is the ANB angle on lateral cephalometric radiographs, which is widely regarded as the most crucial cephalometric index for evaluating the anteroposterior intermaxillary relationships.

Secondary outcomes

Cephalometry

All lateral cephalometric radiographs will be taken in the natural head position by the same X-ray machine (Soredex, Tuusula, Finland). The images will be imported into Dolphin Imaging software (Dolphin Imaging & Management Solutions, Chatsworth, USA) and traced by the same investigator. Cephalometric analyses include 10 angular (except for ANB angle) and 15

Table 1 Schedule of enrollment, interventions and outcome assessments.

Data collection	Screening (T0)	Enrollment (T1)	One month after T&A (intervention group) (T2)	One week after treatment of TB (T3)	6 month follow-up of post-TB treatment (T4)
Baseline information					
Basic characteristics	×				
Medical history	×				
History of T&A or orthodontic treatment	×				
Orofacial myofunctional disorder	×				
Informed consent		×			
Clinical examinations					
PSG	×			×	×
Intraoral and extraoral photos	×		×	×	×
Study model	×		×	×	×
3dMD		×	×	×	×
ENT-related examinations	×				×
Radiological examinations					
Lateral cephalometric radiographs	×		×	×	×
Panoramic radiographs	×			×	×
Survey on the quality of life					
OSA-18		×	×	×	×
OHIP-14		×	×	×	×

3DMD, 3dMDface system; ENT, ear-nose-throat; OHIP, oral health impact profile; OSA, obstructive sleep apnoea; PSG, polysomnography; T&A, adenotonsillectomy; TB, twin block.

linear measurements to reflect dental, skeletal and upper airway changes[29 30] (figure 2):

- Angular measurements reflecting dental and skeletal changes: (1) SNA (sella-nasion-point A angle); (2) SNB (sella-nasion-point B angle); (3) FMA (angle between MP and FH); (4) U1-SN (angle between UiUir and SN); (5) L1-MP (angle between LiLir and MP); (6) U1-L1 (angle between UiUir and LiLir); (7) SArGo (articular angle); (8) ArGoMe (gonial angle); (9) NGoAr (upper gonial angle) and (10) NGoMe (lower gonial angle).
- Linear measurements reflecting dental and skeletal changes: (1) overbite (distance between Ui and Li, perpendicular to OP); (2) overjet (distance between Ui and Li, parallel to OP); (3) N-Me (anterior face height); (4) S-Go (posterior face height); (5) Co-Gn (distance between Co and Gn); (6) Wits appraisal (distance between perpendiculars dropped from points A and B onto the occlusal plane); (7) PV-A (linear distance from A point to porion vertical) and (8) NV-A (linear distance from A-point to nasion vertical).[31]
- Linear measurements reflecting upper airway changes: (1) PNS-U (soft palatal length, distance between U and PNS); (2) PNS-UPW (distance between PNS and UPW); (3) U-MPW (distance between U and MPW); (4) PAS (airway thickness along the Go-B line); (5) V-LPW (distance between V and LPW); (6) ad_1-Ptm (sagittal depth of the airway through the nasopharynx, distance between ad_1 and Ptm) and (7) ad_2-Ptm (sagittal depth of the airway through the nasopharynx, distance between ad_2 and Ptm).[32]

3D facial morphometry

3D digital facial photographs will be captured by the 3dMDface system software (3dMD, Atlanta, USA) with the subject's head in the natural head position, the teeth in centric occlusion and the lips in a relaxed state. Thereafter, the 3D facial images will be processed and exported using 3dMD software. Changes in facial soft tissue will be measured using Geomagic Qualify software (3D Systems, Rock Hill, USA). The 3D facial morphometry method, as established in previous studies, will be employed to collect the x, y and z coordinates of 22 facial regions.[33 34] The obtained facial data at T2, T3 and T4 will be matched with the baseline images to calculate facial changes through qualitative and quantitative analyses.

Polysomnography

PSG is recommended for a definitive diagnosis of OSA.[35] PSG will be performed in a sleep laboratory for all subjects before (T0) and after treatment (T3 and T4). A

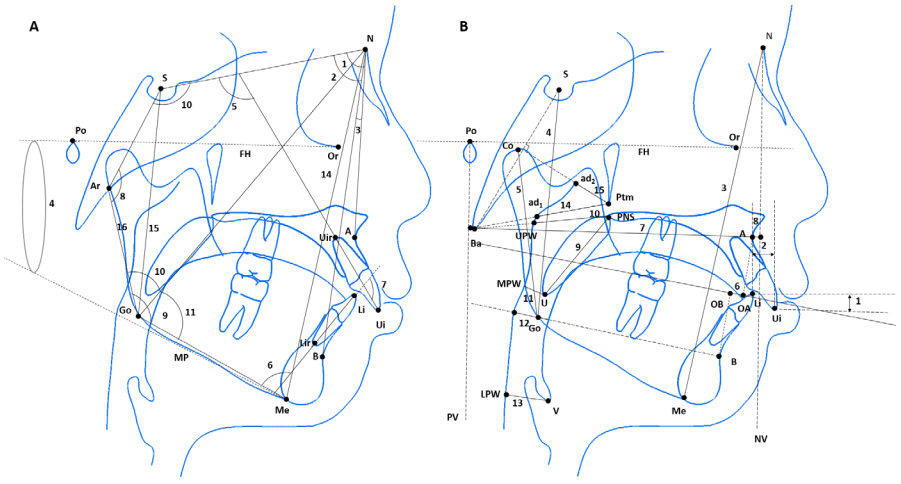

Figure 2 Cephalometric measurements. (A) Angular measurement reflecting dental and skeletal changes. (1) SNA (sella-nasion-point A angle); (2) SNB (sella-nasion-point B angle); (3) ANB (point A-nasion-point B angle); (4) FMA (angle between MP and FH); (5) U1-SN (angle between UiUir and SN); (6) L1-MP (angle between LiLir and MP); (7) U1-L1 (angle between UiUir and LiLir); (8) SArGo (articular angle); (9) ArGoMe (gonial angle); (10) NGoAr (upper gonial angle) and (11) NGoMe (lower gonial angle). (B) Linear measurements reflecting dental, skeletal and upper airway changes. (1) Overbite (distance between Ui and Li, perpendicular to OP); (2) overjet (distance between Ui and Li, parallel to OP); (3) N-Me (anterior face height); (4) S-Go (posterior face height); (5) Co-Gn (distance between Co and Gn); (6) Wits appraisal (distance between perpendiculars dropped from points A and B onto the occlusal plane); (7) PV-A (linear distance from A point to porion vertical); (8) NV-A (linear distance from A-point to nasion vertical); (9) PNS-U (soft palatal length, distance between U and PNS); (10) PNS-UPW (distance between PNS and UPW); (11) U-MPW (distance between U and MPW); (12) PAS (airway thickness along the Go-B line); (13) V-LPW (distance between V and LPW); (14) ad_1-Ptm (sagittal depth of the airway through the nasopharynx, distance between ad_1 and Ptm) and (15) ad_2-Ptm (sagittal depth of the airway through the nasopharynx, distance between ad_2 and Ptm).

technologist will monitor sleep stages, limb movements, airflow, respiratory effort, heart rate and rhythm, oxygen saturation (SaO_2) and body position during the night. SaO_2, referring to the amount of oxygen in the blood during respiratory events and normal sleep stages, will be obtained by pulse oximetry. Two SaO_2 variables (mean SaO_2 and lowest SpO_2), the respiratory distress index and the oxygen desaturation index (using the ≥3% desaturation criterion) will be recorded during sleep to assess the objective improvement of nocturnal breathing and oxygen supply.

OSA-18 questionnaire

The OSA-18 questionnaire will be completed by guardians with the assistance of the researcher to evaluate subjective changes in sleep quality. The questionnaire contains 18 items divided into five areas: sleep disturbance, physical suffering, emotional distress, daytime problems and caregiver concerns. Each question is scored on a Likert scale of 1–7 points. Scores are summed to a total score ranging from 18 to 126, with a higher score indicating a worse quality of life.

OHIP-14 questionnaire

The OHIP-14 questionnaire will be completed by the participants and their guardians with the assistance of the investigator. The OHIP-14 scale is currently widely used in investigating oral health-related quality of life. It includes seven areas of functional limitations: physical pain, physiological disability, psychological discomfort, physical disability, social disability and handicap. Each question is scored on a Likert scale of 0–4 points and a total OHIP-14 score can range from 0 to 56. The higher score indicates a worse oral-related quality of life.

Sample size calculation

The sample size calculation is performed based on two primary outcomes (AHI and ANB angle), showing a difference between the two treatment groups using two-sided tests at an α of 0.05 and 80% power. Based on the primary outcome of AHI, the minimal clinically important difference (MCID) between the control and intervention arms is 1.5, with a standard difference (SD) of 2.1.[36 37] This generates the minimum sample size of 16 patients in each arm. For the primary outcome of the ANB angle, an MCID of 1° is considered with an SD of 0.97°.[29] A minimum sample size of eight patients in each group is necessary. Therefore, a sample size of 32 patients in total (16 per group) is required. To account for a potential attrition rate of 20%, a total of 40 participants will be recruited, with 20 participants in each group.

Data collection

Baseline demographics (age, sex, BMI z-score and ethnicity), medical history, allergic history, concomitant medication and history of T&A and orthodontic treatment will be obtained through a chart review. At each time point, the researchers will contact participants via text message or telephone and request their presence at the study site for the completion of relevant outcome measures. All data will be collected by investigators with Good Clinical Practice) certificates. The collected data

will be accurately recorded on the case report form (CRF) for each participant in time. A detailed overview of the specific data that should be collected at each time point is provided in table 1.

Data management

A qualified clinical research assistant will supervise the study process and verify the integrity of the data. This study uses printed case report forms specially designed by investigators for documentation. A CRF must be completed by investigators with original data. Any necessary changes made to the CRFs must be clearly indicated with a line across the incorrect data. Both the incorrect data and the corrections should remain legible, and the researcher's signature and the time of correction must be recorded alongside the corrected data. All data files will be stored in a secure environment and managed by a dedicated person. Access to the data will be restricted to the study team and authorised personnel. All staff involved in the study will receive training on data management and the importance of maintaining participant confidentiality.

Statistical analysis

SPSS software (IBM SPSS, V.26.0, IBM Corp., Armonk, NY, USA) will be employed in statistical analysis. Intent-to-treat approach and per-protocol analysis will be used in data analysis. Demographics, baseline characteristics and outcome data will be summarised based on the treatment group. Continuous data consistent with the normal distribution will be described as mean±SD (x±SD). Otherwise, the median and IQR will be used.

Multivariable regression analyses will be used to identify potential factors that may influence treatment outcomes (primary outcomes, ANB and AHI).[38 39] Tested covariates include age, sex, BMI z-score, time, pre-O/DO measurements (such as overjet, skeletal vertical patterns and AHI values), necessity of RME and time by treatment interaction. The vertical skeletal patterns were classified into hypodivergent (FMA ≤23°), normodivergent (23°<FMA<30°) and hyperdivergent (FMA ≥30°) groups.[40]

The Shapiro-Wilk test will be employed to check for normality. If data are normally distributed, the paired sample t-test and independent sample t-test will be used to analyse within-group and between-group effects on primary and secondary outcomes. Non-parametric analyses, including the Wilcoxon signed-rank test and Mann-Whitney U test, will be used to compare non-normally distributed data within and between groups. All statistical tests will be performed on a two-sided test, and $p \leq 0.05$ will be considered statistically significant.

Patient and public involvement

Patients and the public will not be involved in the design, recruitment and conduct of this study. All participants will be informed by a summary of the study results at the end of the trial.

Ethics and dissemination

The study will be conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO). The study protocol (V.3.0, issue date: 10 August 2023) has been approved by the Ethics Committee of the School and Hospital of Stomatology, Wuhan University (no. 2022-D07). Written informed consent must be formally obtained from all patients and their guardians after a full explanation of this trial. All participants will be informed that they have the right to withdraw from this study at any time for no reason. To avoid the potential harm caused by adenotonsillar hypertrophy in the control group, participants will be referred to the otolaryngologist to reassess the need for T&A 6 months after TB treatment.

All related research data will be securely stored and will not be released externally without the permission of participants. Regardless of the magnitude and trend of the final results, we will report them faithfully through scientific conferences or published articles.

DISCUSSION

The use of functional appliances to correct the retrognathic mandible is widely practiced in orthodontics. The benefits of improving upper airway dimensions make TB an alternative to T&A for managing paediatric OSA. Orthodontists are becoming increasingly aware of the issue of OSA, as it may impact dentofacial development and orthodontic treatment outcomes in growing patients. A retrospective study indicated that OSA has a deleterious effect on the treatment efficacy of patients receiving fixed orthodontic appliances.[41] However, there is a lack of convincing evidence on the advantages of receiving T&A over non-T&A approaches in OSA-affected children undergoing functional therapy. The understanding of the specific role played by the T&A during functional therapy is rather limited, which provides the rationale for this RCT.

To our knowledge, our study is the first RCT aiming to investigate the impact of T&A on the effectiveness and stability of functional therapy rather than comparing the efficacy of two treatment approaches.[42 43] The functional therapy and adenotonsillectomy clinical trial for class II malocclusion study will provide evidence regarding the potential benefits of preorthodontic T&A in children with mild to moderate OSA undergoing functional therapy. The findings may have key implications for clinical treatment in children with OSA and malocclusion, including the potential to increase the effectiveness and stability of functional therapy, the necessity of surgical removal of obstructive adenoids and tonsils before O/DO treatment intervention and more rational use of appropriate interventions to manage paediatric ATH-induced OSA.

A study with a duration of over 1 year and multiple visits may pose potential challenges regarding participant dropout due to failure to obtain treatment records at key stages. To minimise the dropout rate in this study, a

research nurse will remind patients of the appointment time in advance of the visits through text messages or telephone. When a patient fails to return on time, we will contact them through a telephone call. Besides, we found attitudes about the surgical intervention of OSA vary greatly among families in China. Many parents feel strongly that their children need a timely T&A, while others have concerns about the general anaesthesia procedures and the convenience of scheduling surgery. Therefore, it may take a long time to recruit enough subjects for this study.

TB is known as a traditional and frequently used appliance in the treatment of class II malocclusion with mandibular retrognathia. Our study focuses on investigating the impact of T&A on the effectiveness and stability of TB treatment in relation to dentofacial development and sleep quality. Similar to previous studies on TB effectiveness,[38 39 44] RME is needed if necessary; however, resolving maxillary constriction is not the primary objective. Besides, not all patients with mandibular retrognathia necessitate maxillary expansion. Previous research has provided evidence of the beneficial effects of RME in children with paediatric OSA and maxillary constriction.[13] Comparative studies between RME and T&A have been conducted.[16 45] Given the potential influence of maxillary expansion on study outcomes, we have included the necessity of RME as a covariance in regression analyses. Future prospective research is still needed to explore the impact of T&A on the effectiveness of TB in children with mandibular retrognathia, maxillary constriction and paediatric OSA.

In order to diagnose maxillary transverse deficiency, we have employed a combination of traditional model analysis and, if necessary, CBCT imaging. This approach has been chosen for two reasons. First, considering the young age of the patients involved in the study, it is ethically important to minimise their exposure to radiation,[46 47] and CBCT is not necessary for all patients unless there are specific indications such as joint problems or impacted teeth. Second, given the absence of a standardised diagnostic method for evaluating maxillary transverse deficiency,[48] we have decided against imposing additional financial burdens on the patients and subjecting them to unnecessary radiation.

In this study, the necessity of RME and different types of sagittal skeletal patterns are not considered as stratified factors for randomisation. Patients in this study are consecutively enrolled, which means that the sample size for each stratified factor needs to be determined at the stage of trial design for allocation concealment. Due to the absence of empirical data or pilot studies, the composition of these stratified factors in advance remains unknown. Therefore, the sample sizes for each blocking unit are unable to be predetermined.[49] Considering the potential importance of these variables as predictors of outcomes, an alternative approach is chosen, in which a multivariate model is used to adjust the analysis for treatment effectiveness for covariates (poststratification).[50]

There are some limitations to this study design. First, this trial is single-centre research; therefore, the sample recruited in this study may confer some selection bias. Second, we may have limited power regarding the secondary outcomes because the sample size estimation was only based on the main outcomes. Third, we only analyse the 6-month stability of class II correction using the TB appliance. Long-term follow-up will not be required, as children may receive comprehensive orthodontic treatment after functional therapy.

In summary, this study will serve as evidence to guide clinicians in deciding whether to perform the T&A on patients prior to functional therapy based on a wide range of objectively and subjectively measured outcomes and provide a reference for multidisciplinary management of OSA with craniofacial alterations in growing children.

Trial status

At the time of manuscript submission, ethics (no. 2022-D07) and contract approvals have been given. The investigator team is awaiting recruiting patients.

Author affiliations
[1]State Key Laboratory of Oral and Maxillofacial Reconstruction and Regeneration, Key Laboratory of Oral Biomedicine Ministry of Education, Hubei Key Laboratory of Stomatology, School and Hospital of Stomatology, Wuhan University, Wuhan, China
[2]Department of Orthodontics, School and Hospital of Stomatology, Wuhan University, Wuhan, China
[3]Center for Dentofacial Development and Sleep Medicine, School and Hospital of Stomatology, Wuhan University, Wuhan, China

Contributors TZ and HH conceived this study idea. FG, CL and TZ designed the study. CZ and JZ were involved in the refinement of the protocol with clinical expertise. BT and LL advised on the statistical plan and data analysis. FG and CL drafted the manuscript. All authors read or revised and approved the final version.

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ORCID iD
Hong He http://orcid.org/0000-0002-9234-0015

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