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Efficacy of orthodontic treatment versus adenotonsillectomy in children with moderate obstructive sleep apnoea and mandibular retrognathia: study design and protocol for a non-inferiority randomised controlled trial

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ABSTRACT

Introduction Orthodontic treatment and adenotonsillectomy (AT) are both conventional treatments for paediatric obstructive sleep apnoea (OSA). Each approach has distinct treatment advantages; however, there is currently a lack of solid evidence to support their efficacy comparison. We hypothesise that the objective effect of orthodontic treatment is not inferior to AT in children with moderate OSA and mandibular retrognathia, but orthodontic treatment has the advantage of promoting dentofacial growth.

Methods and analysis This is a randomised, open-label, parallel-group, active controlled trial that will study the efficacy of orthodontic treatment versus AT in children with moderate OSA accompanied by tonsillar adenoid hypertrophy and mandibular retrognathia. A total of 98 patients will be enrolled and randomised in a 2:1 ratio to either orthodontic treatment or AT group. Participants will be recruited at Shanghai Stomatological Hospital, Shanghai Children's Hospital of Shanghai Jiaotong University and Children's Hospital of Fudan University, which are all located in Shanghai, China. The primary endpoint is the per cent change in the obstructive apnoea–hypopnoea index from baseline (month 0) to the primary endpoint (month 7), and the mean reduction in A point, nasion and B point angle on cephalometric measurements by lateral X-ray films. Important secondary efficacy endpoints include sleep duration with oxygen saturation below 90% according to polysomnography and subjective symptoms (assessed by the OSA-20 questionnaire), etc. Safety endpoints will also be evaluated.

Ethics and dissemination The study was approved by the ethics committees of Shanghai Stomatological Hospital (approval no. (2021)002), Shanghai Children's Hospital of Shanghai Jiaotong University (approval no. 2021R046-F01) and Children's Hospital of Fudan University (approval no. (2021)136). Before enrolment, a qualified clinical research assistant will obtain written informed consent from both the participants and their guardians after full explanation of this study. The results will be presented at national or international conferences and published in peer-reviewed journals.

Strengths and limitations of this study

- ► Randomisation will minimise the risk of selection bias.
- ► Both short-term and long-term extended follow-up periods (7, 24 and 48 months) are planned.
- ► A key limitation is the lack of blinding of the participants and researchers.

Trial registration number ChiCTR2000037288.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder in childhood, characterised by recurrent narrowing or collapse of the upper airway (UA), and subsequent sleep fragmentation and multiple episodes of apnoea and/or hypopnoea.[1] If left untreated, it can have detrimental effects on the central nervous system, cardiovascular system and metabolism, leading to growth retardation, poor attention and school performance, and behaviour problems.[1–3]

In contrast to adults, the major risk factor for paediatric OSA is currently adenotonsillar hypertrophy.[4 5] In addition, dentofacial deformities such as maxillary constriction and mandibular retrognathia have a negative effect on the dimension and collapsibility of the UA.[5 6] They may be the primary cause of OSA, or they may be complications caused by chronic oral breathing.[4] Oral breathing is one of the main clinical signs of paediatric OSA.[7] It may change the oropharynx muscle tone, which affects the growth of dentofacial and

presents long faces, maxillary constriction, high arched palates and mandibular retrognathia.[4 8]

Conventional treatments for paediatric OSA include adenotonsillectomy (AT), orthodontic treatment, continuous positive airway pressure, medication and weight loss.[9 10] There is, however, no unanimous opinion on the treatment of OSA.[10] Since the main reason for paediatric OSA is adenotonsillar hypertrophy, the primary method has always been AT, even though many studies have demonstrated that this treatment may not be as effective as expected.[11] The efficacy of AT has been reported to vary from 27.2% to 82.9%.[11–13] Some studies indicated that AT could improve OSA but residual apnea hypopnea index (AHI) may persist in some cases, especially in obese children.[9 14] In fact, the choice of final therapy is predicted primarily on the aetiology, severity and natural history of increased upper airway resistance.

At present, orthodontic techniques have been widely used as alternative or combined treatments of AT in paediatric OSA. The most commonly used orthodontic appliances are rapid maxillary expansion (RME) and mandibular advancement devices (MADs).[15–19] RME benefits children with OSA by enlarging the dimension of the nasal cavity and increasing the maxillary width so that the more nasal respiration and a better tongue position can be induced. MADs can promote the forwards movement of mandible and hyoid bone and enlarge the dimension of UA. Numerous studies have shown that the clinical use of RME and MADs such as Frankel and Twin-block appliances had stable long-term efficacy in paediatric OSA.[9 18 19]

For children with OSA with tonsil–adenoid hypertrophy and mandibular retrognathia, which is a considerable proportion, both orthodontic therapy and AT may have curative effects, but their comparison is still underway to our knowledge. We previously compared the efficacy of orthodontic treatment and AT for children with mild OSA and mandibular retrognathia.[20] We found that the improvement of subjective symptoms, the polysomnography (PSG) data and the dimension of UA were all significant after orthodontic treatment and AT, while the difference of curative effect between these two treatments was undetectable.

On the one hand, the effects of AT on dentofacial growth were found to be limited[11 21–23] and could only be obtained if it was performed before the age of 6 years.[22 24] Orthodontic treatment is still necessary for a large number of children with OSA after AT to eliminate residual AHI while correcting dentofacial deformities. On the other hand, the adenoid–tonsil is considered to be a barrier to pathogens and a warning indicator for diseases. In addition, AT may be associated with routine surgical trauma and risks. There are long debates among clinicians about the indications for AT.

Given those mentioned above, we hypothesise that the objective effect of orthodontic treatment is not inferior to that of AT in children with moderate OSA and mandibular retrognathia, but orthodontic treatment has the advantage of promoting dentofacial growth. To date, there has been a lack of solid evidence to support the efficacy comparison of these two treatment measures. The purpose of this study was to recruit children with moderate OSA with adenotonsillar hypertrophy and mandibular retrusion deformity, and analyse and compare the clinical effect of orthodontic treatment and AT surgery in terms of subjective and objective symptoms such as sleep breathing, general development, neurocognition, UA structure, and dental and maxillofacial development. Here, we present the rationale and methodology for a non-inferiority randomised controlled trial to compare their efficacy in Chinese children with moderate OSA.

OBJECTIVES

This study is designed to compare the efficacy of orthodontic treatment versus AT surgery in children with moderate OSA and dentofacial deformity.

METHODS AND ANALYSIS

The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[25]

Study design

The study (http://www.chictr.org.cn/index.aspx) is a randomised, open-label, parallel-group, active controlled trial that will investigate the efficacy of orthodontic treatment versus AT in Chinese children with moderate OSA accompanied by tonsillar adenoid hypertrophy and malocclusion. The study will be conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/). Three study sites: Shanghai Stomatological Hospital, Shanghai Children's Hospital of Shanghai Jiaotong University and Children's Hospital of Fudan University, which are all located in Shanghai, China, will participate in this study. The recruitment announcements will be published at these hospitals and on their official websites. The participants will undergo a series of medical tests, which will include questionnaires, PSG monitoring, cone beam CT (CBCT) scanning, model analysis and lateral cephalometric radiographs. Once enrolled in the study, subjects will be randomly assigned to one of two treatment groups, either orthodontic treatment or AT surgery in a 2:1 ratio. Tests will be conducted on all subjects before the treatment (month 0), 7 months after the treatment (month 7), 24 months after the treatment (month 24) and 48 months after the treatment (month 48). A brief flow chart of this study is provided in figure 1. Table 1 presents the trial schedule.

Patient and public involvement

There was no patient or public involvement in the design and conduct of this study. The study findings will be conveyed to participants by email.

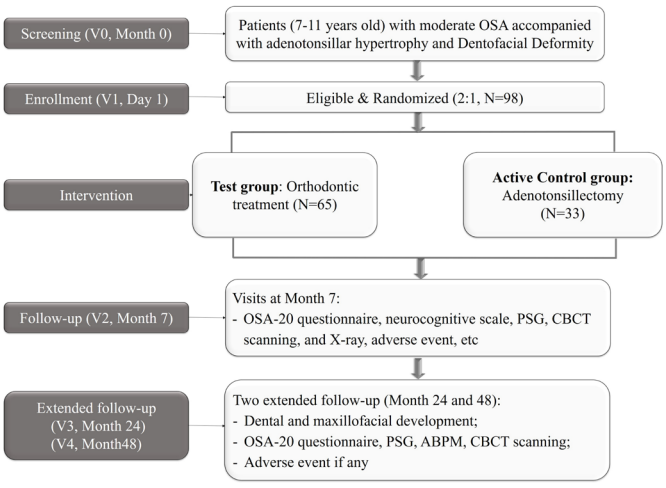

Figure 1 Study flow chart. ABPM, ambulatory blood pressure monitoring; CBCT, cone beam CT; OSA, obstructive sleep apnoea; PSG, polysomnography.

Study patients

A total of 98 eligible patients will be recruited after screening at the study sites. The inclusion criteria are as follows:

1. Patients aged 7~11 years, inclusive.
2. Patients diagnosed with moderate OSA (an obstructive apnoea/hypopnoea index (OAHI) 5~10 events per hour during a period of not less than 7 hours of consecutive sleep according to PSG measurement following the diagnostic criteria recommended by the American Academy of Sleep Medicine).
3. Patients with hypertrophy of tonsil and adenoid.
4. Patients with oral breathing during sleep.
5. Patients with constricted dental arch and mandibular retraction (A point, nasion, B point (ANB) ≥4.5).

The exclusion criteria are as follows:

1. Patients diagnosed with central sleep apnoea.
2. Patients with concurrent systemic diseases.
3. Patients with rhinostegnosis.
4. Candidate patients with the same deformity in the immediate family (genetic predisposition).
5. Abnormal mandible length due to heredity and trauma.
6. Patients with high mandibular plane angle ≥35°.
7. Patients with pathological obesity according to body mass index (BMI) classification criteria for overweight and obesity screening in Chinese school-aged children and adolescents.

Table 1 Schedule of enrolment, interventions and outcome assessment

Action/timepoint	Screening	Enrolment (month 0)	Randomisation	Treatment	Follow-up (month 7)	Follow-up (month 24)	Follow-up (month 48)
Informed consent	○						
Demographic characteristics	○						
Medical history	○						
Physical examination	○						
Questionnaire (OSA-20)	○						
Cephalometric measurements of lateral X-ray		○					
Morphological analysis of UA		○					
Polysomnogram		○					
Confirm suitability for study		○					
Allocation			○				
Orthodontic treatment				○			
Adenotonsillectomy				○			
Assessment							
Questionnaire (OSA-20)					○	○	○
Cephalometric measurements of lateral X-ray					○	○	○
Morphological analysis of UA					○	○	○
Polysomnogram					○	○	○
Adherence of subjects					○	○	○
Cost of time/money					○		
Safety assessment					○	○	○

OSA-20, Obstructive Sleep Apnoea-20; UA, upper airway.

Figure 2 The removable Twin-block appliance combined with rapid maxillary expansion used in the orthodontic treatment.

Recruitment and randomisation process

Before enrolment, there will be one pretreatment screening visit at the study site office, during which a qualified clinical research assistant will obtain written informed consent (online supplemental material) from both the participants and their guardians after full explanation of this study. Then each subject will be assigned a unique serial number by a qualified clinical research assistant.

Once considered eligible for entry, these paediatric patients with moderate OSA will be randomly assigned to one of two treatment groups, for example, either orthodontic treatment or AT surgery in a 2:1 ratio. Stratified block randomisation with randomly varying block size will be performed, stratified by subject gender. Random assignment was generated by an independent statistician and performed through a central randomisation mobile phone app (Shanghai KNOWLANDS MedPharm Consulting Co). To avoid potential selection bias, the randomisation sequence is concealed from both researchers and subjects until final assignment. With these, neither site researchers nor subjects can affect which treatment group the subjects are assigned to.

Description of the interventions

The enrolled subjects will be randomised to undergo orthodontic treatment (figure 2) or AT surgery. Both treatment methods will be implemented by experienced doctors.

Subjects receiving orthodontic treatment according to a consistent comprehensive protocol mainly involve a removable Twin-block appliance combined with RME. Subjects will wear an appliance customised according to their dental models at least 20 hours per day for 7 months.

Subjects in the control group will undergo endoscopic coblation adenoidectomy and tonsillectomy under general anaesthesia. Two weeks after AT surgery, routine follow-up as part of the standard of routine care will be conducted to initially evaluate the surgical effects and prognosis.

Other treatment approaches, such as drugs and acupuncture, are forbidden during the research.

Study visits

Five study visits per subject will be scheduled in the study as follows: pretreatment visit (month 0), treatment visit (day 1), post-treatment month 7 (month 7), extended follow-up visits at years 2 (month 24) and 4 (month 48) post-treatment (table 1). These visits will be made at the study site office. Additional services will be provided through WeChat to arrange the visit time to enhance the adherence of participants. At scheduled visits, data relating to Obstructive Sleep Apnoea-20 (OSA-20) questionnaire, PSG monitoring, CBCT scanning, model analysis and lateral cephalometric radiographs of soft and hard tissues, concomitant medication, adverse events, etc will be recorded and collected.

In case severe adverse events (AEs) occur or the subject/guardian requests to withdraw, the subject can drop out anytime during the study. They will be followed up and receive other treatments defer to experts.

Outcome measures

Primary outcomes

This study was designed with two primary efficacy endpoints. The first is the per cent change in OAHI from baseline (month 0) to the primary endpoint (month 7) compared between the orthodontic treatment and AT groups, given that PSG is still the gold criterion for diagnosing OSA. The OAHI is defined as the number of obstructive events per hour, including mixed events but not central events. Obstructive apnoea or hypopnoea lasting for two respiratory cycles or more is defined as an obstructive event. Obstructive apnoea means a reduction in airflow of more than 90% compared with that preceding sleep breathing while hypopnoea is defined as a reduction in airflow of more than 30%, accompanied by oxygen desaturation of 3% or more and/or arousal.

The second primary outcome is the mean reduction in ANB angle on cephalometric measurements by lateral X-ray films after study treatment. The ANB angle is usually considered the most important index to evaluate the anteroposterior relationship of the upper and lower jaws.

Secondary outcomes

The secondary outcomes are the per cent change in obstructive apnea index (OAI), the sleep duration with oxygen saturation below 90% and the increase in the lowest oxyhaemoglobin saturation according to PSG, subjective symptoms (assessed by the OSA-20 questionnaire), the change in UA dimension by CBCT and the cephalometric measurements by lateral X-ray films.

The OSA-20 questionnaire includes 20 items involving five domains: sleep interference, physical suffering, emotional disorder, diurnal problems and guardian concern. These items are graded on an ordinal Likert scale of 1–7 points (a range of 20–140 points in total). Guardian(s) per subject will complete the study questionnaire without help to ensure reliability and validity. A lower OSA-20 score indicates better quality of life.

The dimension measurements of UA by CBCT and the cephalometric measurements by lateral X-ray films will be performed as described in our previous study.[20]

The adherence of subjects, cost of time and money will be compared between the two groups at month 7.

Safety endpoints

The safety endpoints mainly include AEs, AT surgery-related complications and laboratory tests as appropriate. The AEs of both treatments will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (V.5.0).

Sample size calculation

We used PASS software, V.15.0.5 (NCSS Institute, Utah, USA) to estimate the sample size. The trial is designed to demonstrate non-inferiority of orthodontic treatment as compared with AT in OAHI and its superiority in the ANB angle at month 7 post-treatment. With a sample size of 81 (54 plus 27) patients randomised in a 2:1 ratio, the comparison of orthodontic treatment versus AT will be powered at 80% to establish non-inferiority for the primary endpoint OAHI, at a one-sided alpha level of 0.025, with a non-inferiority margin of 10% and common SD of 15%, assuming an equal true effect between the two treatments. Equally, a sample size of 48 plus 24 subjects will provide a power of 90% to establish superiority for the primary endpoint ANB angle, with a mean difference of 1.47 (2.48 vs 1.01) and SD of 1.6 vs 1.7. Given an expected dropout rate of 20% or less, a total of 98 eligible patients (65 in the orthodontic treatment group and 33 in the AT group) will be required to enrol in the study.

Data collection and statistical analysis

An electronic data capture system designed by researchers and Beijing HUAJING Technology Co will be used for data collection and documentation. Data monitors from Shanghai Shenkang Hospital Development Center will supervise the study process at a fixed period. The participants will be notified that their clinical records may be reviewed by members of the sponsor and/or regulatory authority, but their individual identities will not be revealed in any public report.

The data surveyor will be blinded to the subjects' groups during the measurements. Full analysis set, based on the intent-to-treat principle, will be established as the primary efficacy analysis population. A two-sided p value of 0.05 or less will be considered to indicate significance for any statistical tests. R, V.4.0.4 and SAS software, V.9.4 (SAS Institute) will be used for statistical analysis. Demographics, baseline characteristics and safety data will be summarised based on treatment groups.

The primary efficacy outcome OAHI will be analysed using analysis of covariance (ANCOVA) with treatment group, sex as fixed factors and OAHI values at baseline as covariates. The paired and unpaired t-test will further be used to test OAHI reduction within each group and between groups, respectively. The 95% CIs for the least square mean difference between two groups will also be calculated. To assess the non-inferiority of orthodontic treatment compared with AT, we will assess whether the 95% CI lower limit of the least square mean difference crosses our prespecified non-inferiority boundary (10%).

For the second primary outcome, for example, the mean decrease in ANB angle from baseline, an ANCOVA will also be used. Mixed-model repeated measures analysis including terms for treatment group, sex, time, baseline measurement and time by treatment group interaction will be considered to compare improvement of both outcomes in the study, as appropriate. Subgroup analyses for both outcomes are prespecified according to the following prognostic factors, but are not limited to: sex, age and BMI category at baseline.

Categorical data will be tested using Pearson's X^2 test or Fisher's exact test, as appropriate. Continuous secondary efficacy endpoints will be analysed similarly to the primary endpoint. Missing data will be disposed with the last-observation-carried-forwards method.

ETHICS AND DISSEMINATION

Ethical considerations

The independent ethics committees of Shanghai Stomatological Hospital, Shanghai Children's Hospital of Shanghai Jiaotong University and Children's Hospital of Fudan University all approved the study protocol (protocol version 2.0, issue date: 17 December 2020) for the respective participating sites (approval no. (2021)002; 2021R046-F01; (2021)136). Written informed consent was obtained from both the participants and their guardians after full explanation of this study. They were informed that they could also withdraw from the study as they wished at any time. To reduce the amount of radiation potentially received by the study subjects, the follow-up frequency after 7 months of treatment was set as once every 2 years. In this study, OAI was limited to an interval of 5~10 points as the inclusion criteria of PSG monitoring, which might not only avoid overtreatment, but also minimise the possibility of delayed treatment. Along with these, the ethics committee agreed that this study will not raise patients' risk or cause extra harm to study subjects.

The ethics committee further agreed that the study is in accordance with the Declaration of Helsinki and that the study will be conducted without ethics problems.

Dissemination

The final clinical report will be the basis for the study to be published in a medical journal and presented at national or international conferences. A formal report or publication of the data from the study will be jointly published by a person appointed by principal investigators. A report of the results of this study will be sent to the guardians of participants by mail.

DISCUSSION

Previous studies have reported clinical effects of orthodontic treatment and AT. However, most studies used the

watchful waiting groups as control. Fehrm *et al* conducted a randomised controlled trial to study whether AT is more effective than watchful waiting in children with mild to moderate OSA. They found only small differences between the mild groups regarding changes in OAHI, but large improvements in quality of life (assessed by questionnaires) after AT. Besides, AT was found more effective in children with moderate OSA regarding change in mean OAHI score.[26] Pirelli *et al* found that RME treatment had a positive effect on children with OSA, causing an increase in volume of nasal cavity and nasopharynx.[27] Pavoni *et al* found that after MAD treatment, significant improvements in sagittal airway dimensions, hyoid position and tongue position were induced, and an obvious relief in subjective symptoms was observed in children with sleep-disordered breathing .[28]

Systematic reviews and meta-analyses about OSA treatments have been reported, but the comparison of the different treatments is very limited. Templier *et al* evaluated the evidence for the efficiency of AT and orthodontic treatment in a systematic review, and stated that AT-combined orthodontic treatments (RME and/or MAD) were more effective together than separately to cure OSA in paediatric patients.[29]

In our previous study, the efficacy of AT, orthodontic treatment and AT-combined orthodontic treatments was evaluated in children with mild OSA and mandibular retrognathia, and the drug treatment was used as the control group. A large sample size (352 children) was required and a high dropout rate was observed in that study.[20] Therefore, this study focuses on the comparison of efficacy between orthodontic treatment and AT. To date, there has been a lack of solid evidence to support the efficacy comparison of these two treatment measures. If the outcome of the treatment is not satisfactory at post-treatment month 7, subjects may receive subsequent treatment after assessment of both stomatologists and ear, nose and throat (ENT) specialists. It is expected that this randomised controlled trial will clearly differentiate the potential benefit of orthodontic treatment versus AT surgery. In our subsequent planned analysis by an interdisciplinary team (at least ENT, head and neck surgeons, and orthodontists), the curative effect of both treatment methods will be comprehensively compared with regard to sleep respiratory function, neurocognition, three-dimensional morphology of airway and maxillofacial, and subjective and objective symptoms of patients.

Second, most parents of children with OSA have at present a limited understanding of the adverse consequences of OSA, especially in the long run. Our study subjects were about to make multiple visits for data collection including dental and maxillofacial development until 4 years after treatment.

In addition, for the purpose of better data quality, the study team will employ a dedicated third-party clinical monitoring group for source data verification. To control any possible biases resulting from male and female patients, we will use a gender-stratified randomisation technique as is appropriate for this study. This had better help set up any subsequent statistical modelling for data analysis.

Due to the low acceptance of randomised assignment among guardians, it may take a long time to recruit sufficient subjects for this research. Moreover, we face the challenge of subjects' compliance issues after 7 months. Additional follow-up services by dedicated clinical research coordinator teams will be provided through a mobile phone app to arrange treatment plans and enhance adherence.

The key limitation of this study is the lack of blinding of the participants and researchers. Two researchers will be responsible for cephalometric measurements of lateral X-ray and morphological analysis of UA to avoid the measurement bias.

In summary, orthodontic treatment might be practised more frequently in treating paediatric patients with moderate OSA in the future. The results of the study will be shared with the academic community to facilitate the clinical management of paediatric OSA.

Trial status

The study is ongoing with the first patient on 7 March 2021. The recruitment is expected to be completed by the end of December 2022.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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