


BMJ Open 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

Yuanyuan Li,^{1,2} Yun Lu,^{2,3} Xuan Li,⁴ Limin Zhao,⁵ Jinghan Guo,^{2,3} Liming Yu,^{2,3} Jinqiu Feng,^{1,2} Bing Li,⁴ Xiaoyan Li,⁵ Yuehua Liu ^{2,3}

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For numbered affiliations see end of article.

Correspondence to

Dr Yuehua Liu;
liyuehua@fudan.edu.cn and
Professor Xiaoyan Li;
chshent@163.com

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.⁴⁸

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.

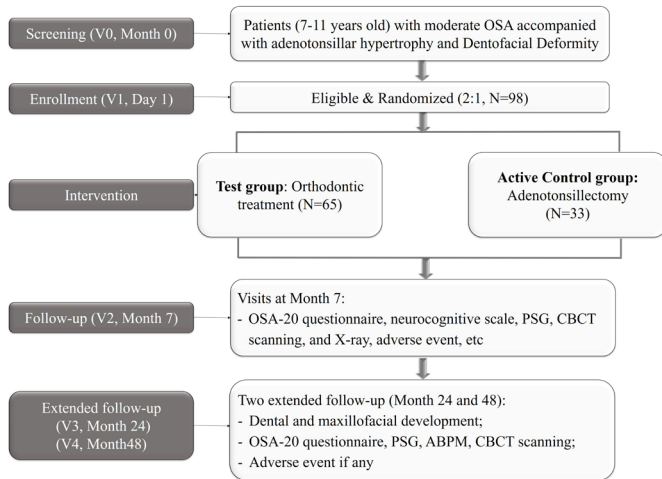


Figure 1 Study flow chart. ABPM, ambulatory blood pressure monitoring; CBCT, cone beam CT; OSA, obstructive sleep apnoea; PSG, polysomnography.

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 (OAH) 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 $\geq 35^\circ$.

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 OAH1 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 OAH1 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 OAHl 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 OAHl, 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 Shengkang 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 OAHl will be analysed using analysis of covariance (ANCOVA) with treatment group, sex as fixed factors and OAHl values at baseline as covariates. The paired and unpaired t-test will further be used to test OAHl 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 χ^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 OAH1, 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 OAH1 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.

Author affiliations

¹Shanghai Stomatological Hospital, Department of Pediatric Dentistry, Fudan University Affiliated Stomatological Hospital, Shanghai, China

²Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases, Fudan University, Shanghai, China

³Shanghai Stomatological Hospital, Department of Orthodontics, Fudan University Affiliated Stomatological Hospital, Shanghai, China

⁴Children's National Medical Center, Department of Stomatology, Children's Hospital of Fudan University, Shanghai, China

⁵Shanghai Children's Hospital, Department of Otolaryngology and Head and Neck Surgery, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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Contributors YLi assisted with the design of the study protocol, drafted the first version of the manuscript and prepared subsequent revisions. YLiu and XiaoyanL conceived, designed and supervised the study protocol, read and reviewed the manuscript and approved the final version of the manuscript. YLi, YLu, XuanL, LZ, JF and BL were involved in the initial study design and implementation of the protocol. JG and LY were involved in the statistical analysis for the study. All authors were involved in the protocol discussion and approved this submission.

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ORCID iD

Yuehua Liu <http://orcid.org/0000-0003-3033-8873>

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Notification page of Informed Consent

知情同意书·知情告知页 *for guardians*

(法定监护人版)

亲爱的家长或法定监护人

医生已经确诊您的孩子患有儿童睡眠呼吸暂停低通气综合征伴错颌畸形。您的孩子将被邀请参加一项“中度 OSAHS 患儿口腔正畸治疗与扁桃体腺样体切除术疗效比较的前瞻性随机对照研究”,本研究为上海申康医院发展中心促进市级医院临床技能与临床创新能力三年行动计划项目,课题编号为:SHDC2020CR2043B。本研究方案已经得到上海市口腔病防治院医学伦理委员会审核,同意进行临床研究。

在您和孩子决定是否参加这项研究之前,请尽可能仔细阅读以下内容。它可以帮助您了解该项研究以及为何要进行这项研究,研究的程序和期限,参加研究后可能带来的益处、风险和不适。如果您愿意,您也可以和您的亲属、朋友一起讨论,或者请医生给予解释,帮助您做出决定。

一、为什么进行这项研究?

1.1 疾病负担和治疗现状

儿童在生长发育过程中常遇到睡眠呼吸异常(如口呼吸、打鼾)等问题,患儿因睡眠呼吸障碍影响智力发育、颜面美观及咀嚼功能、社会行为心理等,严重影响身心健康。

多数患儿的病因是扁桃体、腺样体肥大,手术切除扁桃体腺样体是目前治疗儿童睡眠呼吸异常主要手段之一,但是部分患儿手术后,仍存在颜面不协调:马脸、下巴后缩等,需要通过口腔正畸的手段矫正颌面部畸形。而口腔正畸治疗能扩大上气道,改善睡眠呼吸障碍的症状,同时又可以纠正颌面部畸形。

1.2 本研究目的

本研究拟分析比较口腔正畸治疗和扁桃体腺样体切除术对睡眠呼吸暂停低通气综合征(OSAHS)伴错颌畸形的治疗效果,并从全身发育状况、上气道结构和

牙颌面部发育等角度分析正畸治疗的优势,探索对疗效产生影响的可能因素,为儿童 OSAHS 伴扁桃体腺样体肥大及错颌畸形的多学科诊疗提供精准化的诊治方案和临床决策依据。

1.3 研究参加单位和预计纳入参试者例数

本研究涉及多个研究中心的合作招募,研究单位为上海市口腔医院和上海市儿童医院,预计纳入例数 98 例以上,其中我院将招募 60 名受试者。

二、哪些人被邀请参加这项研究?

本研究受试人群为 7-11 岁中度 OSAHS 患儿 (PSG 监测示: $5 \leq \text{OAI} < 10$ 次/小时), 合并有扁桃体/腺样体肥大、口呼吸习惯, 且已经形成牙弓狭窄或/和下颌后缩畸形者。而具有以下特点者不适合纳入本研究: 并发全身性疾病、鼻阻塞疾病或病理性肥胖患者, 遗传、外伤等致下颌骨长度异常或下颌平面角高 ($\text{FMA} \geq 38^\circ$) 的患者。

三、该研究是怎样进行的?

本研究将收集 98 例符合条件的 7-11 岁中度 OSAHS 患者, 受试者纳入后将采用分层随机法按 2: 1 比例随机分配至口腔正畸治疗组和外科治疗组 (即进入正畸治疗组和外科治疗组的概率为 2: 1)。分组后一个月内分别接受口腔正畸治疗和扁桃体腺样体切除术, 治疗开始后 7 个月来院随访, 评价治疗效果, 随访时的检查项目主要包括 X 线片拍摄, CBCT 扫描和 PSG 监测以及调查问卷的填写等内容。治疗结束后 2 年和 4 年各有一次随访 (扩展随访期)。

四、参加该研究对受试者日常生活的影响?

当您和您的孩子决定是否参加本研究时, 请仔细考虑如上所列的检查和随访对您和孩子的日常工作、家庭生活等可能的影响。考虑每次回访的时间与交通问题。若您和孩子对试验涉及的检查和步骤有任何疑问, 可以向我们咨询。在服用任何新的处方药物前请咨询您的研究医生。考虑到受试者的安全以及为确保研究结果的有效性, 在研究期间若想再参加其他任何有关药物和医疗器械的临床研究, 请告知研究医生。

五、参加研究可能的不良反应、风险和不适、不方便

口腔正畸治疗和扁桃体腺样体切除术都是儿童睡眠呼吸异常的常规治疗手段。本研究中扁桃体腺样体切除手术相关的风险为全麻常规风险、术后出血等,

口腔活动矫治器治疗相关的不良反应主要有：因佩戴矫治器口腔卫生不易清洁导致牙龈炎等。研究中心均有专业的医疗团队负责治疗相关风险或不良反应。如果因参与试验而发生任何与试验相关的损害，受试者将得到及时的治疗和相应的补偿。如果在研究中受试者出现任何不适，或病情发生新的变化，或任何意外情况，不管是否与药物/检查有关，均应及时联系受试者的主诊医生，医生将对此做出判断和医疗处理。

病史采集可能带来风险的描述：研究需要进行问卷调查，对于您和您的孩子来说，与我们进行沟通、交谈可能会有些心理不适。若问卷中的某些问题让您感到不舒服，您可以拒绝回答。

六、参加研究可能的受益

尽管已经有证据提示正畸治疗或扁桃体腺样体切除术有满意的疗效，但这并不能保证对您的孩子肯定有效，儿童睡眠呼吸疾病病因复杂，若本研究种所采取的正畸治疗或扁桃体腺样体切除术对您孩子的病情无效，您可以向医生询问有可能获得的替代治疗或补充治疗方法。

参加本研究可能的受益：

1. 免费口腔初步检查、咨询；
2. 详尽的治疗方案，有利于早期预防阻断患儿牙颌面部异常或畸形；
3. 实施全程治疗效果评价；
4. 更快的多院区诊治绿色通道。

七、个人信息的保密

您孩子的医疗记录（研究病历/CRF、化验单等）将完整地保存在就诊的医院。医生会将化验和其它检查结果记录在病历上。研究者、伦理委员会和药品监督管理部门将被允许查阅您孩子的医疗记录。任何有关本项研究结果的公开报告将不会披露受试者的个人身份。我们将在法律允许的范围内，尽一切努力保护您孩子的个人医疗资料隐私。

按照医学研究伦理，除了个人隐私信息外，试验数据将可供公众查询和共享，查询和共享将只限于基于网络的电子数据库，保证不会泄漏任何个人隐私信息。

八、有关费用

参与研究的受试者诊断和治疗过程不涉及额外的检查费用，故挂号费、诊治

费等由受试者承担。完成研究项目后，本研究中心将发放 2000 元交通等补贴。

患者治疗中戴用矫治器而出现牙龈炎等，研究者将免费提供治疗。如果在临床试验中出现不良事件，医学专家委员会将会鉴定其是否与本研究有关。申办者将按照我国《药物临床试验质量管理规范》的规定对与试验相关的损害提供治疗的费用及相应的经济补偿。

九、是否一定要参加并完成本项研究？

是否参加研究完全取决于您和您孩子的意愿。您可以选择不参加本项研究，这对您的孩子获得常规治疗不会带来任何不良影响。即使您同意参加之后，您和您的孩子也可以在任何时间无需任何理由退出本研究，而且这同样不会影响您的孩子获得正常的医疗服务。当您和您的孩子决定不再参加本研究时，希望您及时告知研究医生，研究医生可就您孩子的健康状况提供建议和指导。

出于对您孩子的最大利益考虑，医生或研究者可能会在研究过程中随时中止您的孩子继续参加本项研究。

如果您的孩子因为某种原因从研究中退出，您可能被询问有关您的孩子治疗的情况。对于中途退出的受试者，出于安全性考虑，我们有末次随访计划，您和您的孩子有权拒绝。如果医生认为需要，受试者也可能被要求进行实验室检查和体格检查。

十、现在该做什么？

是否参加本项研究由您和您的孩子决定。

在您做出参加研究的决定前，请尽可能向医生询问有关问题。工作时间请拨打 021-63601149，下班时间、周末和节假日拨打 13472883404。

医院伦理委员会监督电话：021-54668034

感谢您阅读以上材料。如果您和您的孩子决定参加本项研究，请告诉研究医生，他/她会为您安排一切有关研究的事务。请您保留这份资料。

Notification Page of Informed Consent

知情同意书 • 知情告知页

(未成年人版)

亲爱的小朋友：

医生已经确诊你患有 儿童睡眠呼吸暂停低通气综合征伴错颌畸形，被邀请参加一项“中度 OSAHS 患儿口腔正畸治疗与扁桃体腺样体切除术疗效比较的前瞻性随机对照研究”，本研究为“中度 OSAHS 患儿口腔正畸治疗与扁桃体腺样体切除术疗效比较的前瞻性随机对照研究项目”，课题编号：SHDC2020CR2043B。本研究方案已经得到上海市口腔病防治院医学伦理委员会审核，同意进行临床研究。

一、 为什么进行这项研究？

儿童在生长发育过程中常遇到如口呼吸、打鼾等睡眠呼吸异常问题， 这些问题可能影响智力发育、颜面美观及咀嚼功能等。手术切除扁桃体腺样体是目前的主要治疗方法之一，但是部分患儿手术后疗效不确定，正畸治疗也是睡眠呼吸障碍的重要治疗手段。

本研究的目的是比较外科手术和正畸治疗对儿童睡眠呼吸暂停低通气综合征伴错颌畸形的治疗效果。

二、 你们会对我做什么

我们要收集 98 名符合条件的 7-11 岁跟你类似的小朋友，随机分配至不同的两个组，一个组接受口腔正畸治疗，另一组接受外科手术，分组后一个月内分别接受相应治疗，治疗开始后 7 个月来院做一些检查，评价治疗效果，检查项目主要包括 X 线片拍摄，CBCT 扫描和 PSG 监测以及调查问卷的填写等内容。治疗结束后 2 年和 4 年各有来一次医院进行随访。

三、 参加此研究会会有什么风险和不良反应

外科手术和口腔正畸矫治器治疗均为儿童 OSAHS 的常规治疗手段。本研究中扁桃体腺样体切除手术相关手术的风险为常规手术或麻醉风险，口腔正畸治疗相关的不良反应主要有：因佩戴矫治器口腔卫生不易清洁导致牙龈炎等。我们有专业的医生来负责治疗相关风险或不良反应。如果在研究中你有任何不舒服，均应及时联系你的主诊医生，医生将对此做出判断和医疗处理。我们填写调查问卷时会与你进行交谈，若问卷中的某些问题可让你感到不舒服，你可以拒绝回答。

四、 这项研究对我有什么好处

参加本研究，你可能获得以下好处：

1. 免费口腔检查、咨询；
2. 详尽的治疗方案，有利于早期预防或矫正颜面畸形；
3. 实施全程治疗效果评价；
4. 更快的多院区诊治绿色通道。

五、 我必须参加此研究吗

是否参加研究完全取决于你的自愿。你可以拒绝参加此项研究，或在研究过程中的任何时间退出本研究，这都不会影响你和医生间的关系，都不会影响对你的医疗或有其他方面利益的损失。

如果你需要其他治疗，或者你没有遵守研究计划，或者发生了与试验相关的损伤或者有任何其他原因，研究医师可以终止你继续参与本项研究。

六、 我现在应该做什么？

和你的父母一起阅读这份资料，和他们讨论资料的内容并提出你的问题。同时也和你的医生或护士进行讨论，确认你愿意参加研究并清楚接下来你需要做什么。如果你决定参加本项研究，请告诉研究医生，他/她会为您安排一切有关事务。

Signature page of Informed consent

知情同意书. 同意签字页

研究者声明

“我已告知该受试者和受试者的监护人“中度 OSAHS 患儿口腔正畸治疗与扁桃体腺样体切除术疗效比较的前瞻性随机对照研究”的研究背景、目的、步骤、风险及获益情况，给予他/她足够的时间阅读知情同意书、与他人讨论，并解答了其有关研究的问题；我已告知该受试者当遇到与研究相关的问题时可随时与项目负责人刘月华教授联系，遇到与自身权利/权益相关问题时随时与医院医学伦理委员会联系，并提供了准确的联系方式；我已告知该受试者监护人在研究期间的任何时候无需任何理由可以要求其被监护人退出本研究；我已告知该受试者和受试者的监护人他/她们将得到这份知情同意书的副本，上面包含我和他/她们的签名。我确认已向患者解释了本试验的详细情况，包括其权力以及可能的受益和 risk，并给其一份签署过的知情同意书副本。

Signature of Researcher

医生签名: _____

Date: _____年____月____日

医生的工作电话: _____

受试者声明 ~~Phone of Researcher~~

我和我的孩子已被告知“儿童 OSAHS 患者口腔正畸治疗与扁桃体腺样体切除术疗效比较的前瞻性随机对照研究”的研究的背景、目的、步骤、风险及获益情况。我们有足够的时间和机会进行提问，并对问题的答复很满意。我们也被告知，当我们有问题、想反映困难、顾虑、对研究有建议，或想进一步获得信息，或为研究提供帮助时，应当与谁联系。我已经阅读这份知情同意书，同意我的孩子参加这项研究，我知道在研究期间任何时刻无需任何理由我都可以要求让我的孩子退出本研究。此外，我已经和孩子讨论过这个研究项目，我的孩子同意参加本研究，知道在研究期间任何时刻无需任何理由我都可以要求让他/她退出本研究。我被告知我将得到这份知情同意书的副本，上面包含我和研究者的签名。”

Signature of Subject 受试者签名: _____

Date: _____年____月____日

Signature of guardians 监护人签名: _____

Date: _____年____月____日

与受试者关系: _____ 联系电话: _____

Relationship to Subject

phone number.