The efficacy of different treatment approaches for pediatric OSAHS patients with mandibular rethognathia: a study protocol for a multicenter randomized controlled trial

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Study protocol

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Abstract

Background: Pediatric obstructive sleep apnea/hypopnea syndrome (OSAHS) is a multifactorial syndrome caused by many risk factors, such as craniofacial anomalies, adenotonsillar hypertrophy, obesity and airway inflammation. Although new treatment patterns have been recently proposed, treatment methods for children have continued to be particularly challenging and controversial. This randomized controlled trial was designed to investigate the efficacy of adenotonsillectomy and/or orthodontic treatment for mild OSAHS children with mandibular rethognathia.

Methods: A sample of 352 children with mild OSAHS and mandibular rethognathia, aged between 7 and 10 years, will be enrolled in the study. They will be randomized into four groups – the drug treatment group, or the surgical treatment group, or the orthodontic treatment group, or the surgery and postoperative orthodontic group. After randomization they will receive treatments within 4 weeks. Outcome assessment will take place at points: (1) at baseline, (2) 7 months after the treatment starting point, (3) 12 months after the treatment starting point, (3) 24 months after the treatment starting point. The primary endpoint of the trial is the mean change of obstructive apnea/hypopnea index. Other endpoints will consist of the lowest oxygen saturation, apnea index, and hypopnea index assessed by polysomnogram, subjective symptoms (assessed by questionnaire OSA-20), cephalometric measurements and Morphologic analysis of upper airway.

Discussion: The results of this study will provide valuable evidence for merits and long-term efficacy of different treatment approaches and contribute to facilitate the multidisciplinary treatment of pediatric OSAHS.

Trial registration: Clinicaltrials.gov, ID: NCT03451318. Registered on 2 March 2018 (last update posted 19 April 2018).

Introduction

Background and rationale {6a}

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a sleep disorder characterized by recurrent narrowing or collapse of upper airway (UA), resulting in sleep fragmentation and multiple episodes of apnea and/or hypopnea [1]. Pediatric and adult OSAHS share similar pathophysiology, which is a recurrent reduction or cessation of airflow caused by the narrow anatomic structure and defective function of upper airway. But they are actually different disease categories due to their different pathogenesis [2]. Adenotonsillar hypertrophy is currently major reason of pediatric OSAHS, while in adults, the major risk factor may be obesity [3, 4].

The prevalence of pediatric OSAHS is reported between 2% and 10% in different countries [5]. Children with OSAHS may have a variety of problems, such as cardiovascular disorders, metabolic interferences, cognitive dysfunction, and attention problems [6-9].

Conventional treatments for OSAHS include Adenotonsillectomy (AT), orthodontic treatment, continuous positive airway pressure (CPAP), medication and weight loss [10]. At present, drug therapy was mainly applied in mild OSAHS or as a complementary method for other treatments [11, 12]. For sever OSAHS or obesity, medical management has clear limitations. CPAP, which expands the upper airway but does not regulate the underlying mechanisms of disease, was suggested an effective treatment [13, 14]. CPAP has been used in OSAHS

treatments for many years, but its clinical application is greatly limited by the poor compliance [15]. It is reported that 46%-83% of adult patients cannot adhere to treatment when 4 hours of nightly use was required [16]. As for children, CPAP adherence varies between studies, but the application of CPAP at night is not optimistic due to the long sleep hours [17, 18]. Besides, additional data show that CPAP mask can have an adverse impact on the craniofacial development of a child, which means aggravating maxillofacial deformities and leading to increased collapsibility of UA [19].

As the main reason of pediatric OSAHS is adenotonsillar hypertrophy, the primary treatment in children has always been Adenotonsillectomy, even though lots of studies suggested that the efficacy of this treatment method may not be as favorable as expected [20]. Recent reports have confirmed that the efficacy of AT varied from 27.2% to 82.9% [21-23]. Recent evidence suggested that AT could ameliorate OASHS but residual apnea/hypopnea index (AHI) may persists in some cases especially in obese children [24, 25]. Orthodontic treatment is widely used in recent years as alternative or combination therapy of AT.

Craniofacial deformity has an obvious influence on the collapsibility of the upper airway [26, 27]. It can be a primary pathogenesis of OSAHS as well as a complication caused by long-term abnormal mouth breathing [28]. Mouth breathing is one of the main clinical symptoms of OSAHS in children, and it is common to find the OSAHS among mouth breather [29]. Mouth breathing during growth may alter the oropharynx muscle tone, which affects the development of maxillofacial and presents long faces, maxillary constriction, high arched palates and mandibular rethognathia [28, 30]. The elimination of obstructive factors is the basis for nasal respiration and normal growth of maxillofacial bone and dentition [31]. Some cohort studies has observed that AT had the potential to block the progress of craniofacial malformation [32]. However, the roles of AT on dentofacial growth was found to be limited [15, 16, 33, 34]and could been achieved only if it was operated before 6 years old [34, 35]. It was more unlikely to reverse the dentofacial deformity spontaneously after AT surgery for children in the mixed dentition [36].

Therefore, clinical workers wondered that if it is necessary for all the OSAHS children to go to an orthodontist. Rapid maxillary expansion (RME) and mandibular advancement devices (MADs) are the most commonly used appliances for OSAHS children [37-41]. RME benefit OSAHS children through following mechanisms: 1, enlarge the dimension of nasal cavity and increase the nasal respiration; 2, increased the maxillary width so that a better tongue position can be induced; 3, the normal width of dental arch will stimulate the development of lower jaw. Camacho M et al stated in a systematic review that RME has a stable long-term efficacy for pediatric OSAHS patients with transverse maxillary deficiency or narrow hard palates [39]. Villa MP et al assessed the outcome of AT and RME in a non-randomized controlled trial, and found that both of these treatment methods were effective but further studies were needed to evaluate the long-term efficacy [42].

MADs can promote the advancement movement anterior displacement of the mandible and hyoid bone through oral appliances, leading to an anterior traction of tongue and thus an enlarged upper airway dimension. Pavoni C et al found that after MADs treatment, significant improvements in sagittal airway dimensions, hyoid position and tongue position were induced, and an obvious relief in subjective symptoms was observed in sleep-disordered breathing children [43]. Many studies reported that clinical use of functional therapy of mandibular advancement such as Twin-block and Frankel appliances reduced AHI significantly in OSAHS patients [10, 40, 41]. In recent years, the combination of RME and MADs was illustrated by some clinicians.

For OSAHS children with adenotonsillar hypertrophy and dentoskeletal Class II malocclusions, which is a large proportion of pediatric OSAHS, both orthodontic treatment and AT may be effective, but few evidence-based medical research was found to our knowledge. Actually, there are long debates among clinicians about the indications for AT, especially for mild OSAHS children. More convincing evidence is needed to prove that AT/orthodontic treatment have a therapeutic effect for OSAHS child and improve the craniomaxillofacial deformity caused by mouth-breathing.

Objectives {7}

This clinical trial was designed to investigate the efficacy of AT and/or orthodontic treatment for mild OSAHS children with mandibular rethognathia. The efficacy will be evaluated by the improvement in subjective symptoms, polysomnogram (PSG) data, UA structure and maxillofacial development.

Trial design {8}

This study will be a multicenter and randomized controlled pilot trial. Clinical research coordinators will explain the purpose and the procedure of this study for potential subjects. The participants will go through a series of medical tests, which will include physical examinations, radiography of the maxillofacial, and polysomnography, to verify the diagnosis of OSAHS and malocclusion. Subjects will be randomly divided into four groups – the drug treatment group, or the surgical treatment group, or the orthodontic treatment group, or the surgery and postoperative orthodontic group – at a ratio of 1:1:1:1. Regardless of group assignment, tests will be conducted on each group before the treatment (M 0), 7 months after the treatment (M 7), 12 months after the treatment (M 12), and 24 months after the treatment (M 24). Figure 1 shows the flowchart of the research and Figure 2 shows the clinical trial schedule.

Methods: Participants, Interventions And Outcomes

Study setting {9}

Participants will be recruited at Shanghai Stomatological Hospital, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University and Shanghai Children's Hospital, which are all located in Shanghai, China, from May 2018 to December 2021 (anticipated). These hospitals comprise all diagnostic and treatment departments, including E.N.T. and stomatological departments. Notification of subject recruitment will be published in these three hospitals and their official websites.

Eligibility criteria {10}

All participants will be assessed by a treatment group consisting of more than three experienced pediatric physicians, otolaryngologists and orthodontists.

Inclusion criteria

(1) Patients aged 7~10 years;

(2) Patients diagnosed with mild OSAHS (an apnea index 1~5 events per hour according to PSG);

(3) Patients with hypertrophy of tonsil or adenoid;

(4) Patients with mouth breathing;

(5) Patients with constricted dental arch or mandibular retraction (ANB≥4.5);

(6) Patients whose guardians agreed to enter this trial and signed the relevant informed consent.

Exclusion criteria

1. Patients diagnosed with central sleep apnea/hypopnea syndrome;
2. Patients with concurrent systemic diseases;
3. Patients with rhinostegnosis;
4. Patients with a z score equals to or greater than 3 based on the body-mass index (BMI).

Who will take informed consent? {26a}

A qualified clinical research assistant who is blinded to the patients' group will obtained the written informed consent from guardians of participants after fully explanation of this study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

All subjects will receive different treatments-- drug treatment, surgical treatment, orthodontic treatment and surgery and postoperative orthodontic treatment within 4 weeks after randomization. The practitioners will be doctors who has a minimum of 5 years work experience in their hospital and have gone through a training of trial protocol prior to the study.

Intervention description {11a}

Drug treatment group: Patients in this group will receive mometasone furoate aqueous nasal spray once a day (0.1mg) in the morning for 2 months. The research assistants will interview participants' parents by telephone to remind the patients of treatment stage.

Surgical treatment group: Patients in this group will receive adenotonsillectomy under general anesthesia. Routine follow-up was conducted 2 weeks after surgery to evaluate the security.

Orthodontic treatment group: Patients in this group will receive orthodontic treatments. They will receive orthodontic treatment according to a consistent comprehensive protocol, which mainly contains the use of a removable Twin-block appliance combined with RME (figure 3).

Surgery and postoperative orthodontic group: Patients in this group will receive adenotonsillectomy under general anesthesia and the subsequent orthodontic treatment after surgery. The orthodontic treatment appliance will be also a removable Twin-block combined with RME.

Criteria for discontinuing or modifying allocated interventions {11b}

Participants may quit the study at their guardians' discretion or defer to the supervisory team. Circumstances that suspended participants from study include adverse events and detection of evidence that may influence the outcomes of research. Subjects who leave the study will be followed up until they are in stable status.

Strategies to improve adherence to interventions {11c}

Additional services will be provided for participants through the Wechat or phone to arrange the treatment time to enhance their adherence. The monitor or principle researcher will visit every study site monthly to ascertain that all aspects of the program are being followed and that the trial is being carried out in accordance with the provisions of the drug clinical trial quality management practices (GCP). During monitoring visit, the monitor will check the case report form (CRF) for subjects in the trial to confirm that all items have been completed and the data are obtained according to the protocol. The monitor will also check that the CRF data is consistent with the clinical record or the original data.

Relevant concomitant care permitted or prohibited during the trial {11d}

Other treatments that may affect the outcomes of the study, such as traditional Chinese medicine, acupuncture and massage, are prohibited during the trial.

Provisions for post-trial care {30}

Participants may quit the study at their guardians' discretion or defer to the supervisory team if they are not responding well to treatment. They will be followed up and get corresponding therapy for free after they leave the study.

Outcomes {12}

Endpoint measurements will be performed before the treatment (baseline survey; month 0) and 7 months (M 7) and 12 months (M 12) and 24 months (M 24) after the starting point.

Primary endpoint

The primary endpoint of the trial is the mean change of AHI from the baseline (M 0) to the primary endpoint (M 7), because PSG is still the gold criterion for diagnosing OSAHS. All subjects will undergo attended overnight PSG in hospitalized ward. They will go to bed at their usual sleeping time and sleep for at least 6 hours to ensure PSG monitoring time. A reduction in airflow of more than 90% compared to preceding sleep breathing is considered to be an obstructive apnea. A hypopnea is defined as a reduction in airflow of more than 30%, accompany with an oxygen desaturation of ≥3% and/or an arousal. The duration of obstructive apneas or hypopnea equal to or greater than 2 respiratory cycles is defined as an obstructive event. The definition of AHI is the number of obstructive events per hour. The analysis will include the mixed events but not central events.

Secondary endpoints

The secondary endpoints will consist of the lowest oxyhemoglobin saturation ($LSaO_2$), apnea index, and hypopnea index assessed by PSG, subjective symptoms (assessed by questionnaire OSA-20), Cephalometric

measurements and Morphologic analysis of upper airway.

Subjective symptoms

Subjective symptoms will be assessed according to questionnaire, OSA-20. OSA-20 includes 20 questions divided to five domains, sleep interference, physical suffering, emotional disorder, diurnal problems, and guardian concern. These questions are graded on a scale of 1 to 7 applying an ordinal Likert scoring system. Guardians will complete the questionnaire without help to ensure its reliability and validity. A total of score ranged from 20 to 140 points will be associated with quality of life.

LSaO2

The lowest oxyhemoglobin saturation will be assessed according to PSG.

Cephalometric measurements

Lateral cephalometric radiographs will be taken for all the subjects at intercuspal occlusion, then traced and digitized in the software Dolphin. The cephalometric measurements are presented in Fig. 4. The measurement items are as follows. SNA: angular indicator for assessment of maxillary protrusion; SNB: angular indicator for assessment of mandibular protrusion; ANB: angular indicator for assessment of the sagittal relationship between the jaws; MP-FH: angular between the mandibular plane and Frankfort plane; MP-SN: angular between the mandibular plane and SN plane; UI-SN: angular indicator for assessment of upper anterior teeth protrusion; LI-MP: angular indicator for assessment of upper anterior teeth protrusion; UL-Ep: distance between upper lip and the aesthetic plane; LL-Ep: distance between lower lip and the aesthetic plane.

Morphologic analysis of UA

Cone-bean computed tomography (CBCT) of subjects will be taken at the Radiology Department of Shanghai Stomatological Hospital according to the standard protocol. During the scaning, subjects will be positioned in the orthostatism, with the Frankfort plane parallel to the floor. The images will be digitized in medicine (DICOM) files, and then imported into Dolphin software for anatomic landmark localization and UA measurements. Two orthodontists will be trained as analyst and perform the localization and UA measurements as presented in figure 5. The analyst will be blinded to patients' information during the measurements.

Participant timeline {13}

Schedule of enrollment, interventions and outcome assessment.

Action/Timepoint	Enrolment	Baseline survey (M 0)	Randomization	Treatment	Follow-up (M 7)	Follow-up (M 12)	Follow-up (M 24)
Informed consent	□						
Demographic characteristics	□						
Medical history	□						
Physical examination	□						
Questionnaire（OSA-20）	□						
Lateral cephlometrics		□			□	□	□
Polysomnogram		□			□	□	□
Confirm suitability for study		□					
Allocation			□				
Drug treatment				□			
Surgical treatment				□			
Orthodontic treatment				□			
Surgery and postoperative orthodontic treatment				□			
Assessment							
Symptoms changes					□	□	□
Questionnaire (OSA-20)		□			□	□	□
Cephalometric measurements		□			□	□	□
Morphologic analysis of UA		□			□	□	□
Polysomnogram		□			□	□	□
Safety assessment					□	□	□

Sample size {14}

In this study, our expectation hypothesis is that the intervention may decrease subjects' AHI. In a study reported in 2016, that AHI score decreased by 0.8 in children with mild OSAHS who received adenotonsillectomy, while increased by 2.1 in watchful waiting group(P□0.05)[44]. Another non-randomized study reported that average AHI of children decreased by 2.0, 1.5 and 3.7, respectively, after medical therapy, adenotonsillectomy and orthodontic treatment[45]. If 80 eligible subjects in each group were expected, we were allowed to detect the effect value of 0.4 (the average decreasing of AHI among groups was 2.9) at a power of 80% and a 5% significance level. In consideration of a potential dropout rate of approximately 10%, a total sample size of 352 subjects will be required in this study.

Recruitment {15}

Participants will be recruited at Shanghai Stomatological Hospital, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University and Shanghai Children's Hospital, which are all located in Shanghai, China, from May 2018 to December 2021 (anticipated). These hospitals comprise all diagnostic and treatment departments, including E.N.T. and stomatological departments. Notification of subject recruitment will be published in these three hospitals and their official websites.c

Assignment of interventions: allocation

Sequence generation {16a}

A Central Randomization System was designed with the help of Shanghai KNOWLANDS MedPharm Consulting Co. Ltd, and then installed in researchers' phone in every study site.

Concealment mechanism {16b}

The Central Randomization System can be used for management of participants information and randomization. Before signing an informed consent form, subjects and their guardians will be fully explained about this study by researchers in every study site. The basic information of patients will be registered into the Central Randomization System by research assistants. After the baseline survey, the eligible participants will be divided into four groups at random with a ratio of 1:1:1:1.

Implementation {16c}

Randomization will be implemented by a data analyst from Shanghai KNOWLANDS MedPharm Consulting Co. Ltd using the minimization method with 80% allocation probability according to the following stratification factors: (1) Male/female patient; (2) fat or not based on BMI. Then an email will be submitted automatically to the project coordinator with the ID numbers and groups of participants to be randomized. The project coordinator will then contact participants to inform them about the initiation of treatment.

Assignment of interventions: Blinding

Who will be blinded {17a}

When analyse the outcomes, the analyst will be blinded to patients' information during the measurements.

Procedure for unblinding if needed {17b}

Not applicable, the analysts are not allowed to be unblinded at any circumstances.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Case report form (CRF) specially designed by coordinator investigators and Shanghai KNOWLANDS MedPharm Consulting Co. Ltd are used for documentation. The trainings related with recruitment, screening, randomization, evaluation, instructions for CRF will be organized before the study for researchers in order to conducting a high-quality clinical trial. A CRF must be filled out for every subject by investigators. All data and information in the CRF must be clear. Changes in the CRF must be marked with a line across the incorrect data. Both of incorrect data and corrections must be kept legible and the signature of researcher and time must be marked next to corrected data. A qualified clinical research assistant who is blinded to the patients' group will supervise the study process at fixed period, including the completion of informed consent, the screening process, the intervention treatment, the recording of adverse events, and the filling out of CRF. The original CRFs will be used by the data management center and then return to the sponsor center, Shanghai Stomatological Hospital.

Plans to promote participant retention and complete follow-up {18b}

Clinical research assistants from every study site will contact participants monthly to promote their retention and complete follow-up. Additional services will be provided for participants through the Wechat or phone to arrange the treatment time to enhance their adherence.

Data management {19}

The original CRFs will be used by the data management center and then return to the sponsor center, Shanghai Stomatological Hospital. All the questionnaires, PSG data and image measurement data will be collected, stored into separate folders and regularly checked. The outcomes will be encoded and entered in a timely manner using the EpiData 3.1 double-entry test results

Confidentiality {27}

Subject will be informed that the data will be stored and analysed on the computer, but only the researcher team members can get the information associated with each subject. In addition, subjects will be informed of the possibility that their clinical records will be reviewed by representatives of the sponsor and/or regulatory authority. All unpublished information, including patent applications, production processes, and basic data will be deemed confidential. Any public report of the results of this study will not disclose personal identity of the participants. The trial data will be available for public inquiry and sharing, which will be limited to web-based electronic databases to ensure that no personal privacy information is disclosed.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable, no samples collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statistical analysis will be conducted using IBM SPSS Statistics (version 22.0). Descriptive analysis will be performed for all of our variates. The analysis set will consist of the Intent-to-treat (ITT) set, Per-protocol (PP) set and Safety set. All subjects will be included in the ITT set after randomization regardless of whether they received the treatment or not. Subjects who completed treatment sessions (M0 to M7) without any major violation to the trial procedure will be included in the PP set. Participants who receives treatment will be included in the Safety set for safety analysis. The significance level will be set at $P< 0.05$ will be considered significant.

The primary endpoint of this study is the change of AHI from M0 to M7. Intergroup comparisons will be performed using a covariance analysis (ANCOVA) to adjust for gender, obesity status and baseline AHI. The outcomes will be mainly analyzed using the PP set. Linear regression will be used to evaluate the correlation between observed differences of AHI and the potential prognostic factors, such as gender, BMI, neck size and research site.

Interim analyses {21b}

Not applicable. No interim analysis is planned in the study

Methods for additional analyses (e.g. subgroup analyses) {20b}

The analysis of $LSaO_2$, the volume of upper airway and the total score of OSA-20 in secondary points will use similar statistical methods with AHI. Descriptive statistical analysis will be used for the measurements of lateral cephalometric film and UA.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Missing data will be disposed with the last-observation-carried-forward (LOCF) method.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Not applicable.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The monitor team will visit every study site biannually to ascertain that all aspects of the program are being followed and that the trial is being carried out in accordance with the provisions of the drug clinical trial quality management practices (GCP). There are three research centers in the study. Each research center includes at least three main investigator and one coordinator. Clinical research coordinators will be responsible to register information, get informed consent, keep contact with participants to inform them about treatment procedures. Investigators are experienced doctors who will perform examination and intervention for patients. A supervisory team of three experienced doctor will be established to assess and manage the adverse events. Data processing team includes two orthodontists who will perform the localization and UA measurements and three statistician.

Composition of the data monitoring committee, its role and reporting structure {21a}

Not applicable. Intervention measures in the study are mature and commonly used treatment methods, with almost no safety problems.

Adverse event reporting and harms {22}

Adverse events will be recorded and reported by researchers within 24 hrs. A supervisory team of three experienced doctor from every research site will be established to assess and manage the adverse events. Serious adverse events will be reported to the Ethics Committee. For subjects in drug treatment group and surgical treatment group, the observation time for reporting adverse events will be from M0 to M7. While for subjects who will receive orthodontic treatment, the observation time will be from M0 to the end of orthodontic treatment. Participants may quit the study at their guardians' discretion or defer to the supervisory team. Circumstances that suspended participants from study include adverse events and detection of evidence that may influence the outcomes of research. Furthermore, subjects who leave the study will be followed up until they are in stable status.

Frequency and plans for auditing trial conduct {23}

The monitor team consisting of people from the sponsor Shanghai Hospital Development Center will visit every study site biannually to ascertain that all aspects of the program are being followed and that the trial is being carried out in accordance with the provisions of the drug clinical trial quality management practices (GCP). During monitoring visit, the monitor will check the case report form (CRF) for subjects in the trial to confirm that all items have been completed and the data are obtained according to the protocol. The monitor will also check that the CRF data is consistent with the clinical record or the original data.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

During the study, there may be program modifications that may affect the study or patient safety. Any modifications shall be agreed upon by the sponsor/researcher and the Ethics Committee prior to their implementation. Revisions shall be recorded in written new version and must be signed by the same parties that signed the final draft of the pilot protocol.

Dissemination plans {31a}

The final clinical report will be the basis for the study to be published in a medical journal or reported at meeting. A formal report or publication of the data from the study will be jointly published by a person appointed by principle investigators.

Discussion

Cranial and maxillofacial growth and development in children are influenced by both genetic and environmental factors [46]. The change of respiratory mode in children may alter the oropharynx muscle tone, which affects the development of maxillofacial section. Mouth breathing is one of the main clinical symptoms of OSAHS in children, and it is common to find facial features such as long faces, maxillary constriction, high arched palates

and mandibular rethognathia among mouth breather [28,30]. The contraction of UA is closely related to this kind of maxillofacial deformities, while the maxillofacial deformities can also be the primary or promoting factors of OSAHS. The longer mouth breathing sustains and the more serious skeletal alterations occurs in OSAHS children, the more difficult it will be to get OSAHS cured. Therefore, early diagnosis of the morphologic analysis of upper airway and maxillofacial are crucial for pediatric OSAHS. In this study protocol, CBCT of subjects will be taken for both morphologic analysis of upper airway and cephalometric measurements to assist in diagnosis and efficacy evaluation. Traditional and commonly used efficacy evaluation methods of pediatric OSAHS such as PSG and OSA-20 questionnaire were also included in this study.

Although new treatment patterns have been recently proposed, treatment methods for children have continued to be particularly challenging [26]. Furthermore, there is still a great controversy over the treatment of OSAHS in clinic on account of the lack of randomized controlled studies on the comparison of treatment approaches. In this study, a multi-center RCT was designed to investigate the advantages and disadvantages of AT or/and orthodontic treatment for mild OSAHS children with mandibular rethognathia.

This study protocol still faces several limitations and challenges. The first is the challenge of sample selection of mild OSAHS children with mandibular rethognathia. Due to the limited acceptance of randomization, it may take a long time to collect the sample size required for this study. The second is the challenge of subjects' compliance. Additional services will be provided for participants through the Wechat or phone to arrange the treatment time to enhance their adherence. The third limitation is the consistency of treatment. Before the study begins, all of the surgical and orthodontic treatment teams will get the normalized research procedure through specific trainings to ensure the consistency.

The results of this study will provide valuable evidence for merits and long-term efficacy of different treatment approaches and contribute to facilitate the multidisciplinary treatment of pediatric OSAHS.

Trial Status

The study is ongoing from May 2018. Recruitment is expected to be completed by the end of December 2021. The protocol version is 1.0 (issue date: 17 November 2017).

Abbreviations

OSAHS: obstructive sleep apnea/hypopnea syndrome; AT: adenotonsillectomy; CPAP: continuous positive airway pressure; AHI: apnea/hypopnea index; AI: apnea index; HI: hypopnea index; RME: rapid maxillary expansion; MADs: mandibular advancement devices; BMI: body-mass index; $LSaO_2$：the lowest oxyhemoglobin saturation; CBCT: cone-bean computed tomography; CRF: case report form; CRA: clinical research assistant; ITT set: intent-to-treat set; PP set: per-protocol set.

Declarations

Acknowledgements

Not applicable.

Authors' contributions {31b}

Yy L and Yh L led the conception and design of the study. Jl W, JW, XL, SX, and MZ are site investigators and will lead data collection. JG is the statistician for the study. Yy L and Yh L wrote this manuscript and approved the final version for publication. All authors have reviewed drafts of the manuscript and given final approval.

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Availability of data and materials {29}

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate {24}

This study was approved by the Ethical Committee of the Shanghai stomatological hospital on 17 November 2017 (certificate number 2017–0001). Informed consent will be obtained from all caregivers prior to the intervention, and assent to participate in the study will be obtained from all children. The caregiver's consent will be recorded through a signature. Participants can withdraw from the study for any reason, and this will not affect the normal services received at any of the health facilities. The results of the trial will be published in peer-reviewed journals and presented at national and international conferences.

Consent for publication {32}

Consent for publication will be obtained from each participant prior to participation.

Competing interests {28}

The authors declare that they have no competing interests.

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Figures

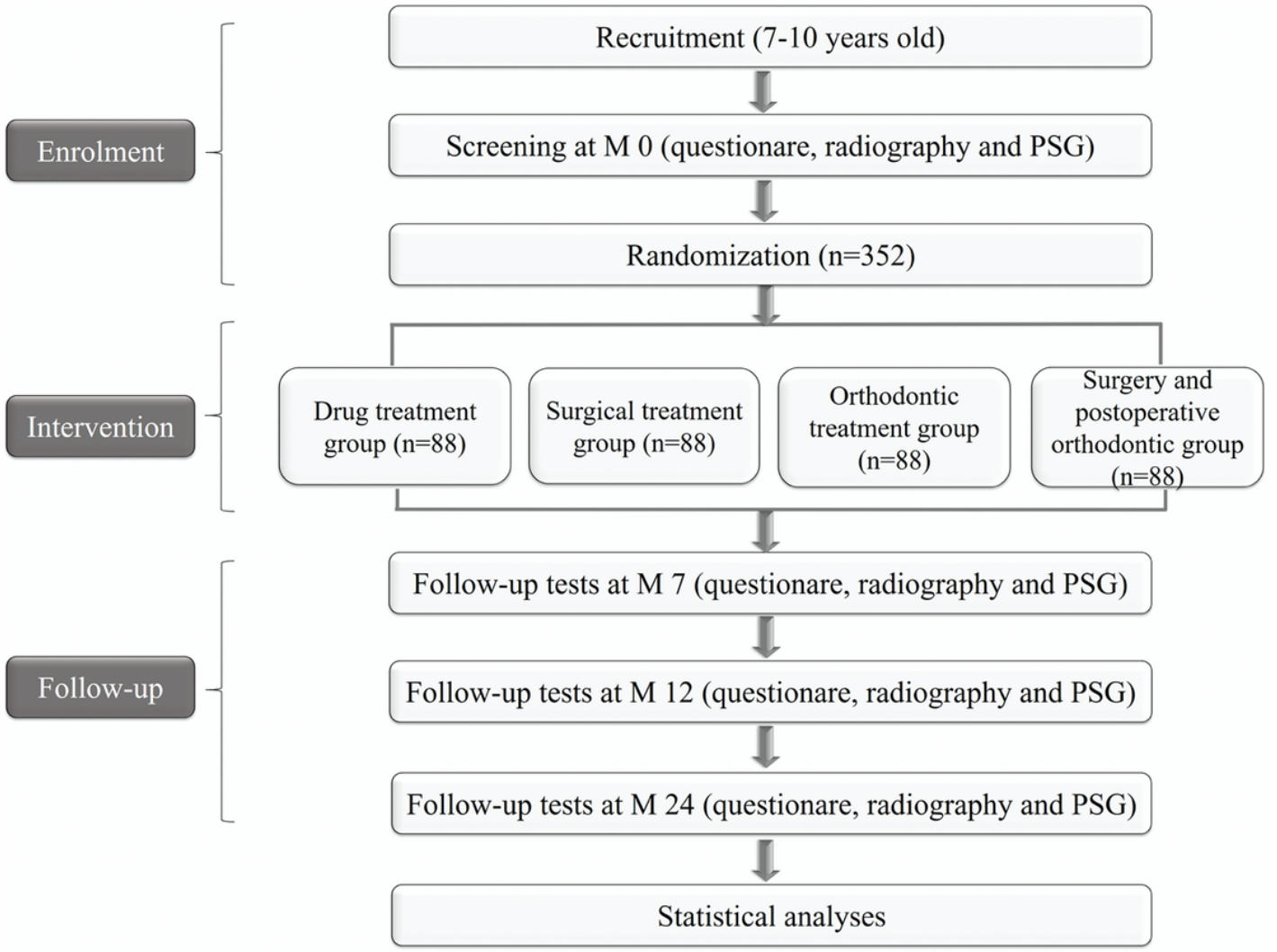

Figure 1

Flow chart of study design.

Action/Timepoint	Enrolment	Baseline survey (M 0)	Randomization	Treatment	Follow-up (M 7)	Follow-up (M 12)	Follow-up (M 24)
Informed consent	●						
Demographic characteristics	●						
Medical history	●						
Physical examination	●						
Questionnaire（OSA-20）	●						
Lateral cephlometrics		●			●	●	●
Polysomnogram		●			●	●	●
Confirm suitability for study		●					
Allocation			●				
Drug treatment				●			
Surgical treatment				●			
Orthodontic treatment				●			
Surgery and postoperative orthodontic treatment				●			
Assessment							
Symptoms changes					●	●	●
Questionnaire (OSA-20)		●			●	●	●
Cephalometric measurements		●			●	●	●
Morphologic analysis of UA		●			●	●	●
Polysomnogram		●			●	●	●
Safety assessment					●	●	●

Figure 2

Schedule of enrollment, interventions and outcome assessment.

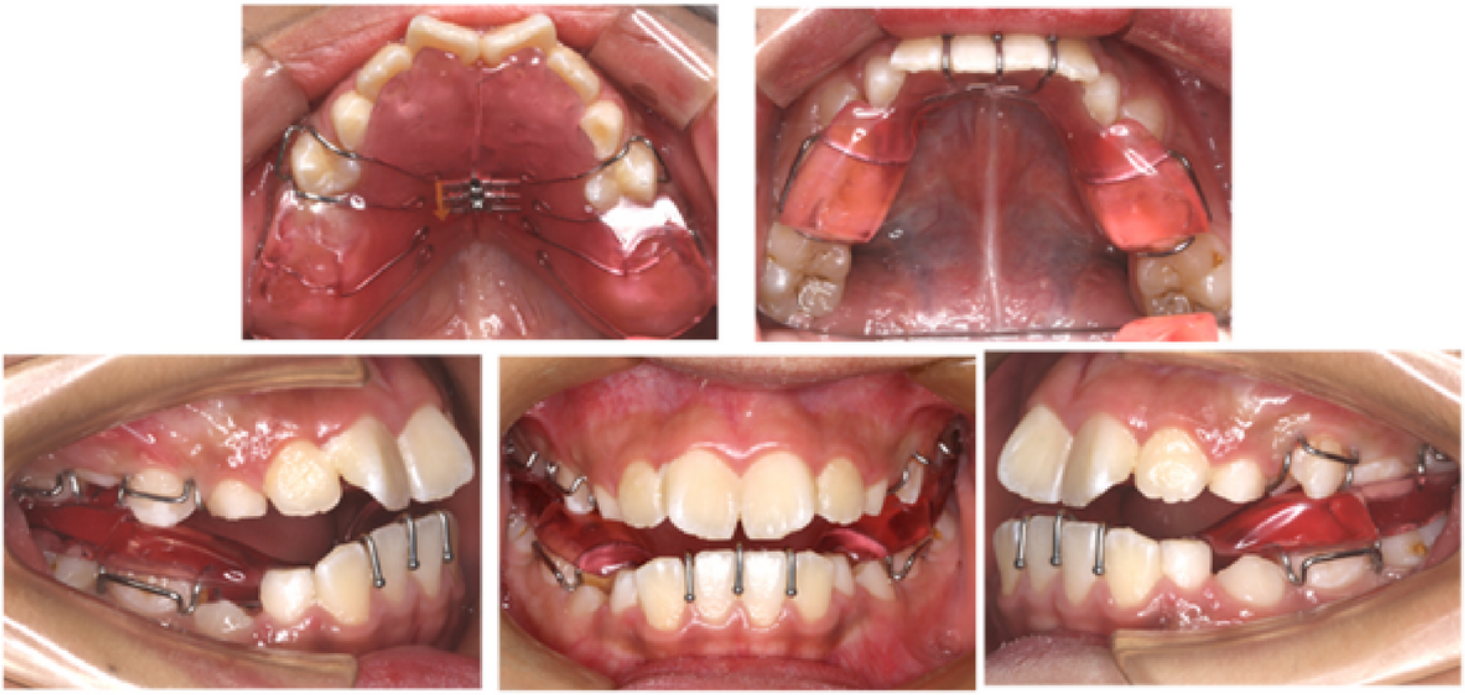

Figure 3

The removable Twin-block appliance combined with RME used in the orthodontic treatment

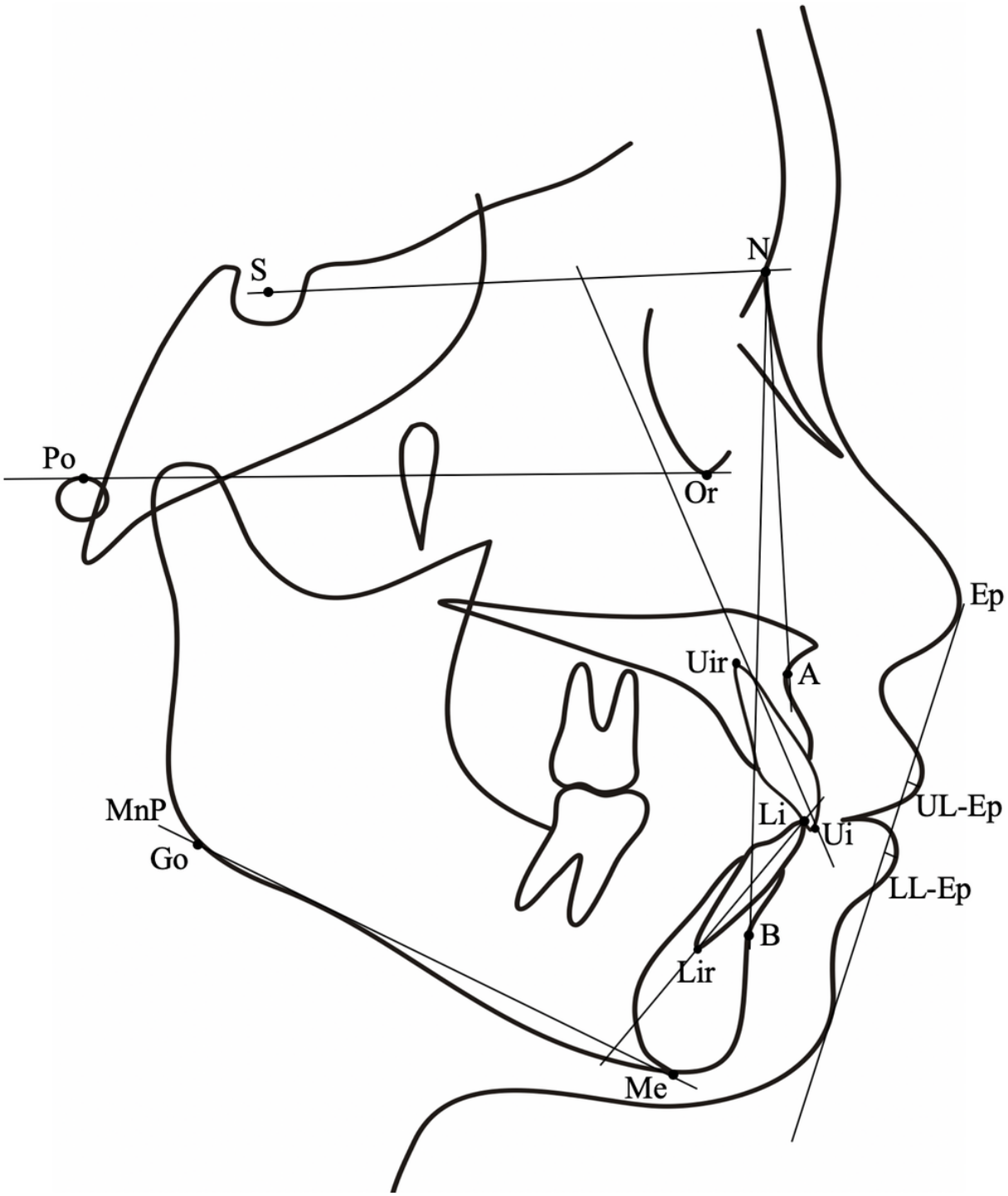

Figure 4

Cephalometric landmarks and indicators. S, sella; N, nasion; Po, porion; Or, orbitale; Ui, upper incisor; Uir, upper incisor root; Li, lower incisor; Lir, lower incisor root; Me, menton; Go, gonion; UL, upper lip anterior; LL, lower lip anterior; FH, the Frankel plane; MnP, the mandibular plane; Ep, the aesthetic plane; UL-Ep, distance between UL and the aesthetic plane; LL-Ep, distance between LL and the aesthetic plane.

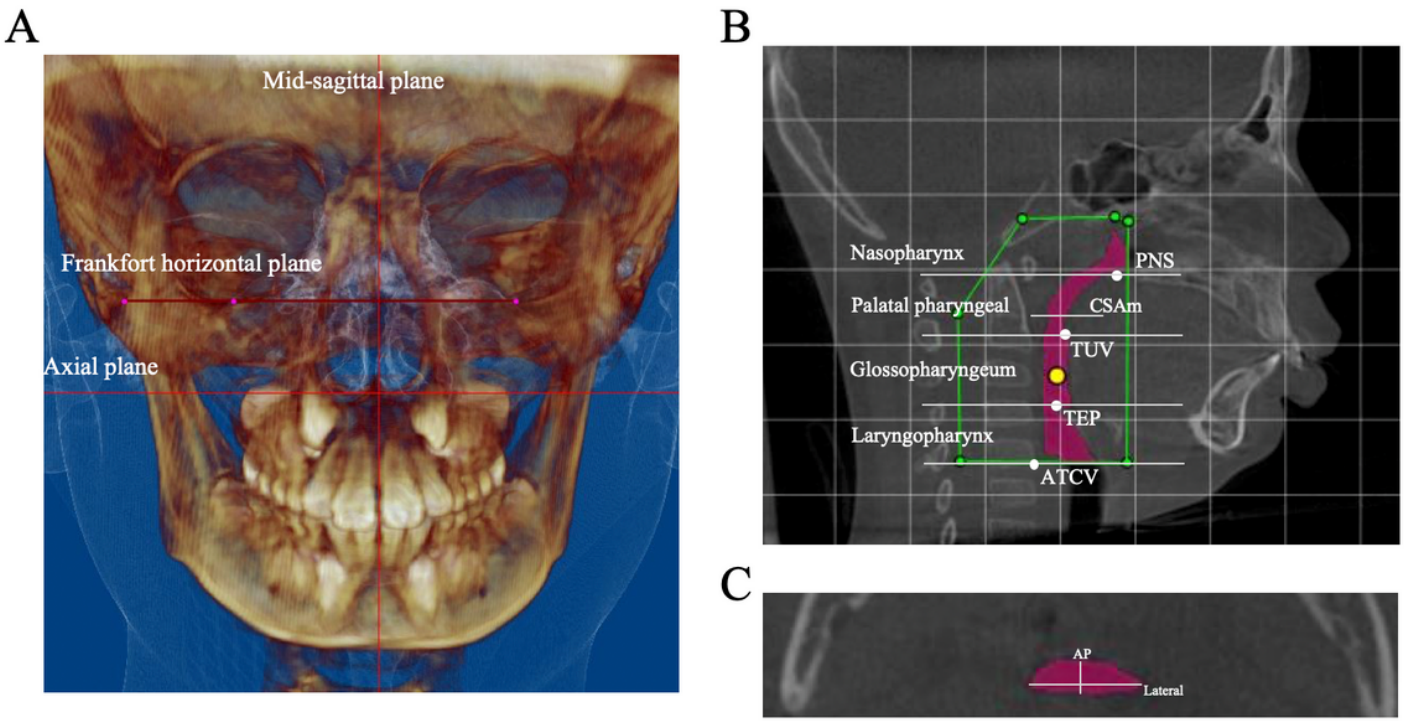

Figure 5

The morphologic analysis of upper airway. A, Localization planes of CBCT images. B, the segmented upper airway. C, the minimum cross-sectional area (CSAm) on the axial slice of the CBCT image. PNS, posterior nasal spine; TUV, tip of the uvula; TEP, tip of the epiglottis; ATCV, anteroinferior aspect of the vertebral body of the third cervical vertebra