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Review Article

Debates in pediatric obstructive sleep apnea treatment

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Abstract Pediatric obstructive sleep apnea (OSA) is among the most common sleep-disordered breathing (SDB) diseases in children. Its high prevalence and multiple systemic complications lead to increasing numbers of children and families affected by OSA. Timely diagnosis and effective intervention in children with this condition is extremely important in improving their prognosis. The major approaches in the treatment of OSA in children are to eliminate the causes of upper airway obstruction and prevent and treat complications. Considering the specific individual differences in children's growth and development, as well as the diversity of etiologies in children's OSA, pediatric treatment strategies need to be precise, multidisciplinary, and individualized. First-line clinical treatment consists of surgical (adenotonsillectomy) and non-surgical therapies [including anti-inflammatory medications and non-invasive ventilation (NIV)]. However, a considerable controversy exists concerning the indications, treatment standards, and the evaluation of the efficacy of the aforementioned treatment methods. In this review, reviews and assessment of literature studies and multidisciplinary clinical experience were performed to analyze the application of each treatment and discuss controversial issues and future research directions. We suggest that the above interventions should be tailored to each child's needs, comorbidities, and the availability and expertise of the practitioner. The ideal case is when a multidisciplinary team of doctors together with the patients and their parents, or guardians, have a thorough discussion regarding the benefits and risks of all available treatment options and all agree on an effective treatment plan.

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Introduction

Pediatric obstructive sleep apnea (OSA) is a disorder of breathing during sleep, characterized by prolonged partial upper airway or intermittent complete obstruction, or both, which disrupts normal sleep patterns and ventilation during sleep.[1] Without timely diagnosis and effective intervention, pediatric OSA can lead to serious complications, including behavioral abnormalities, neurocognitive impairment, learning disabilities, systemic hypertension and pulmonary hypertension, endocrine metabolic disorders, maxillofacial dysplasia (adenoid faces), delayed growth and development, and an increase in the risk of cardiovascular events in adulthood.[2–5] Therefore, early intervention in children with OSA is extremely important for improving their long-term prognosis. The major approaches of the treatment of OSA in children are to eliminate the causes of upper airway obstruction and prevent and treat complications. First-line clinical treatment includes surgical (adenotonsillectomy) and non-surgical therapies such as anti-inflammatory medications and non-invasive ventilation (NIV). However, a considerable controversy exists concerning the indications, treatment standards, and evaluation of efficacy of the aforementioned treatment methods.

Adenotonsillectomy

Adenotonsillectomy (AT) is currently one of the first-line treatments for pediatric OSA.[1] Its clinical effect is particularly significant in children with moderate or severe OSA [obstructive apnea hypopnea index (OAHI) $>$ 5 events/h]. AT can achieve improvements in the quality of life, the symptoms of sleep-related breathing disorders, and OSA-associated morbidities (i.e., growth delay, frequency of enuresis, pulmonary hypertension, corpulmonale, increased heart rate, and central nervous system-associated morbidity). Adenoidectomy or tonsillectomy surgery (or both), is the suggested treatment of choice for moderate to severe pediatric OSA when the findings of the endoscopic examination or the evaluation of the upper airway (including nose, nasopharynx, oropharynx, laryngopharynx, and larynx) are consistent with adenoid and/or tonsil hypertrophy, and there is no serious contraindication to surgery (based on the 2012 American Academy of Pediatrics guidelines).[1] Of course, a child's symptoms and parents' expectations are also to be considered in the assessment of the indications for surgery.[2] Children and parents need to fully understand the risks and benefits of the surgery. Thus, realistic expectations of surgical outcomes should be fully communicated to them.

It is also necessary to prepare for the possibility of perioperative complications, including anesthesia complications, postoperative respiratory failure, bleeding, velopharyngeal insufficiency, nasopharyngeal stenosis, pain, and dehydration.[1]

To the best of our knowledge, the youngest child reported to have undergone adenoidectomy was three months old, and the youngest one to have undergone AT was six months old.[4] Few published reports of original research and systematic assessments of the optimal age range for AT in children are currently available. The European Respiratory Society's 2017 statement on children aged 1–23 months with sleep-disordered breathing (SDB) recommended that children under three years old be hospitalized for monitoring after undergoing AT. ENT surgeons should balance the age and severity, and base their decisions on the results of comprehensive assessment, experience, and the degree of airway obstruction.[4]

It is important that attention be given to residual OSA after AT in children, particularly obese ones. Obesity deserves special consideration because it is both an independent risk factor for pediatric OSA and a risk factor for residual OSA. Postoperative polysomnography (PSG) or monitoring with a portable instrument is suggested for evaluation of residual sleep apnea. If necessary, supplementary treatment by noninvasive positive pressure ventilation or an oral appliance can be considered. In 2015, a systematic review (51 studies, $n = 3413$) found that, after AT, the AHI of children was lower by an average of 12.4 events/h than the pre-operative values. Additionally, the obstructive apnea, hypopnea, and central apnea indexes decreased, and the level of the lowest oxygen saturation increased significantly.[6] The overall percentage of the apnea hypopnea index (AHI) $<$ 1 events/h post-AT was 51%, whereas the overall percentage of AHI$<$5 events/h was 81%. A meta-regression analysis showed positive correlations between the rate of persistence of OSA and pre-AT AHI, age and sex-standardized BMI scores. Thus, surgical intervention can significantly improve OSA-associated sleep breathing variables in children, especially in non-obese children, who benefit more from such treatment. Consistently with the previous remarks, residual OSA is more likely to occur in children with severe OSA and obesity. Additionally, according to previous guidelines and recommendations,[1,2,6] risk factors for postoperative residual OSA include age$<$3 years, comorbidities such as asthma and allergic rhinitis, severe OSA (baseline OAHI$>$10 events/h), family history of SDB, retro-position of the mandible, syndromic craniosynostosis, Down syndrome, achondroplasia, cerebral palsy, and Prader–Willi syndrome.

More detailed and comprehensive evaluation of the upper airway by PSG is indicated in children whose disease severity does not correlate with their clinical exam of adenoid or tonsil hypertrophy (or both). Examples are children with obvious hypertrophy of the adenoids and tonsils who do not have frequent sleep apnea events, and more importantly, children with frequent sleep apnea events, who do not have adenotonsillar hypertrophy. Additionally, other systemic diseases that may contribute

to OSA should be considered. Drug-induced sleep endoscopy (DISE) and airway reconstruction via imaging is indicated for children with OSA who have small tonsils, as well as for those with persistent OSA.[7] Such patients may also benefit considerably from multidisciplinary consultation.

Natural history of treatment options for mild pediatric OSA

Appropriate clinical interventions should be chosen for children with mild OSA (1<OAHI≤5 events/h) only after the cause has been fully assessed. Limited evidence currently exists about the benefit of medications or surgery for children with mild OSA.

In determining whether AT or watchful waiting is more appropriate in children with mild OSA, one study suggested that watchful waiting is a reasonable option in children with few symptoms (in particular, with little snoring), who also have low AHIs and do not have centripetal obesity. Volsky et al[8] conducted a long-term follow-up of children with mild OSA (1 < AHI<5 events/h) and concluded that surgery was indicated in children with moderately impaired quality of life (OSA-18 score of 60—80), whereas close observation without surgery is appropriate for children with OSA-18 score<60, at least in the short term. Athanasios et al[9] concluded that treatment may be beneficial in children with 1—5 events/h associated with the following conditions: cardiovascular or central nervous system-associated morbidity, enuresis, somatic growth delay or growth failure, decreased quality of life, and persistent risk factors for SDB. Due to the heterogeneity of the children in these studies, more randomized controlled trials or high-quality data from evidence-based medicine (across multiple age groups), are needed to better understand which subsets of children benefit from surgical and nonsurgical strategies.

Although many studies have shown that surgical treatment of OSA is effective, few have evaluated the outcomes in children with mild OSA who have not undergone surgical treatment. The requirements of such children for therapeutic interventions and the consequences of not receiving treatment remain unknown. A systematic review showed that mild OSA is relieved in approximately two-thirds of the children as they grow older.[10] However, Li et al[11] reported that mild OSA aggravated in 29% of the untreated children after two years of follow-up.

The Childhood Adenotonsillectomy Trial (CHAT) was a randomized control trial that investigated treatment of pediatric OSA with adenotonsillectomy. Eligible for inclusion were children with mild to moderate OSA. This study provided evidence for the beneficial effects of early adenotonsillectomy, including improvements in symptoms, parent-reported behavior, quality of life, and polysomnographic findings in the treatment group.[12] Of note, polysomnographic abnormalities were also resolved in 46% of the children in the watchful waiting group. The primary outcomes of attention and executive function ability did not differ significantly between the treated and control children. These findings indicate that medical management and reassessment after a period of observation may be a valid therapeutic option. Thus, the results of this trial supported the overall safety and efficacy of both early adenotonsillectomy and watchful waiting, provided that the children were treated conservatively and monitored clinically.[12]

Non-surgical treatment of pediatric OSA

Non-surgical therapies are feasible when surgery is contraindicated by co-morbid medical conditions, or the child has residual post-AT OSA. These treatment options primarily include anti-inflammatory medications, non-invasive ventilation (NIV), orthodontic treatment, orofacial myofunctional therapy, high-flow nasal cannula, nasal expiratory positive airway pressure valve, and weight loss.

Anti-inflammatory medications

Anti-inflammatory medications are widely recognized and used in clinical practice, particularly in children with mild to moderate OSA.

Studies have shown that repeated hypoxia and fragmentation of sleep in children with OSA can lead to local and systemic inflammation,[13,14] which can in turn contribute to airway lymphoid tissue hyperplasia and endothelial cell dysfunction, imbalance of blood pressure regulation, and impaired cognitive function. Anti-inflammatory medications are, therefore, an option for treating OSA and preventing complications.

Many studies have provided strong evidence for the efficacy of the treatment of pediatric OSA with anti-inflammatory medications. A 2017 meta-analysis showed that in the groups treated with drugs, including mometasone furoate, budesonide, and fluticasone, AHI was lower by 1.4, 3.5, and 5.3 events/h than that in the placebo group, respectively. These data suggest that intranasal corticosteroids can alleviate AHI, among which fluticasone appears to be the most effective. This study also found that a leukotriene receptor antagonist (montelukast) effectively reduced AHI by 2.80 events/h.[15] Additionally, a recent systematic review revealed that AHI was lower by 4.18 events/h and the lowest oxygen saturation was higher by 4.76% after treatment of OSA with montelukast combined with intranasal corticosteroids.[16] The 2018 French Society for Otolaryngology and Head and Neck Surgery (SFORL) guidelines state that intranasal corticosteroids can be used in children with mild to moderate OSA associated with nasal obstruction. Montelukast (possibly in combination with a nasal corticosteroid) can be used in asthmatic children with mild to moderate OSA for three months before reassessment of symptoms.[17]

Despite the large body of evidence on the effectiveness of drug therapy, many questions remain unanswered. For example, reportedly, the size of the adenoids of a child can be reduced by the use of intranasal corticosteroids or leukotriene receptor antagonists. However, no such effect is reported to have been exerted on the tonsils. Therefore, further research is needed to determine the appropriateness of the treatment of children with mild OSA caused only by tonsil hypertrophy with medication alone. Concerning the duration of medication use, a range from 1 to 16 weeks was previously reported.[18] To date, no studies

with long-term follow-up have been focused on OSA recurrence after medication withdrawal. Indeed, in this respect, the SFORL guideline states that results of medium and long-term clinical follow-up of treatment with intranasal corticosteroids or montelukast must be reported in the light of the current lack of published reports on the long-term efficacy and safety of these treatments.[19]

Additionally, the benefits of combining intranasal corticosteroids and montelukast versus the administration of a single medication are still not established, because no randomized controlled trials comparing these two treatments have been conducted so far.[16]

Non-invasive intervention

In children with craniofacial and upper respiratory malformations or extreme obesity, adenotonsillectomy may only partially solve the problem of airway obstruction. Furthermore, in some children, upper airway obstruction is not originally caused by adenotonsillar hypertrophy, or surgery is contraindicated. NIV is especially useful in such cases.[20]

Commonly used modes of NIV in children include continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP). NIV treatment of pediatric patients is being increasingly reported with the rising research interest in sleep apnea and improvements in medical technology. Girbal et al[21] summarized their experience of CPAP treatment in children with complex OSA over the past 15 years; these authors found that 45% of those children had improvement in their symptoms or had undergone surgery, resulting in NIV discontinuation.

During the use of NIV, an assessment of clinical characteristics, such as compliance and effect of ventilation, and a follow-up sleep study should be conducted at least annually. Additionally, PSG measurements should also be repeated when the efficacy of the therapy decreases, the child's BMI z-score changes, or additional therapies included.[19] Furthermore, adverse effects of CPAP therapy may appear, including nasal symptoms, eye irritation, and skin damage. Younger children may develop midface hypoplasia from the pressure, especially if PAP is used for prolonged periods.[22] Periodic assessment of maxillofacial growth is, therefore, recommended.[19,22,23]

The adherence to NIV treatment in children is generally lower than that in adults and thus less experience with the application of this therapeutic option in children has been accumulated. In earlier investigations, the duration of the NIV treatment during night-time sleep was only 3.3—5.3 h, with reported rates of adherence to the NIV treatment of only 30%—60%.[24—27] Objective compliance monitoring is important because parents often overestimate CPAP use. Adherence can be assessed objectively by the PAP device via a secure digital card or uploading onto an online server via a modem.

Studies examining the barriers to PAP compliance have shown that age,[28] gender,[29] asthma,[28] family economic status,[30] level of family support, maternal education, strong caregiver self-efficacy,[31] and the use of humidification and warming are associated with adherence to PAP use in children.[32] The compliance with NIV use in the early stage or the first month of treatment is often indicative of whether the NIV treatment would be sustainable,[33,34] suggesting that timely supervision and guidance with multidisciplinary comprehensive management may improve the overall adherence to NIV treatment in children.

Other non-surgical treatments

Orthodontic treatment

Orthodontic treatment [e.g., rapid maxillary expansion (RME)], mandibular advancement devices (MADs)] is an effective treatment option for pediatric OSA in selected children. For example, it can be used as an auxiliary measure in children with maxillofacial anomalies.[35]

RME is an orthodontic treatment that increases the transverse diameter of the hard palate by reopening the mid-palatalsuture through an expandable dental appliance inserted into the mouth close to the hard palate. It also has a secondary impact on the placement of the mandible.[36] MADs enlarge the upper airway by pushing the mandible and tongue forward.[37]

A meta-analysis found that the AHI decreased by 6.2 events/h after the use of RME and by 5.1 events/h after that of MAD.[38] Regarding the optimal age for orthodontic treatment, a systematic review established that rapid arch expansion was significantly more effective before puberty.[39] Another systematic review found that a mandibular advancement device reduced AHI in both younger (6—9.5 years) and older children (9.5—13 years), suggesting that these devices can be used to treat OSA before the age of 13 years. However, no data are available for older adolescents.[40] Of note, the children included in the aforementioned studies had defective dental occlusion; thus, these findings may not be applicable to children without malocclusion.

Orofacial myofunctional therapy

Orofacial myofunctional therapy (OMT) reeducates the muscles of the face and mouth, which is crucial for the maintenance of craniofacial integrity andthe achievement of normal nasal breathing.[41] OMT emphasizes a strong sucking and good mastication, employing both sides of the jaw, as well as normal swallowing and tongue position, and nasal breathing with the lips in good contact at rest.[42] Children with persistent OSA after adenotonsillectomy reportedly achieved a decrease in AHI from 4.9 to 1.8 events/h within two months after OMT, whereas minimal changes in AHI (4.6—4.1 events/h) were observed in the control group.[43] A meta-analysis showed that OMT is effective in children with postoperative residual OSA and open-mouth breathing.[44] However, another meta-analysis revealed a negative effect of OMT in children with OSA, with the 95% confidence interval for reduced AHI crossing the zero thresholds.[44] Hence, further studies of OMT in childhood OSA are warranted.

High-flow nasal cannula

A constant stream of humidified air is delivered by high-flow nasal cannulas (HFNCs) via the insertion of a soft plastic nasal cannula into the upper airway. The mechanism by which HFNC improves OSA is unclear. One theory

explains its therapeutic effect by the delivery of heated and humidified air to the nasopharynx at higher than the usual flow rates, which may activate or reactivate the protective airway reflex via nasopharyngeal mechanoreceptors or thermoreceptor stimulation, as well as by reducing the dryness-associated irritation, swelling, and congestion.[45] In some studies, significant improvements in AHI without carbon dioxide retention were observed after the use of HFNCs.[46–48] Nevertheless, larger investigations are needed to further evaluate the mechanism of action and the effectiveness of this therapeutic approach. This therapy can be considered in younger patients with OSA and children who are intolerant of CPAP. However, carbon dioxide levels have to be carefully monitored.

Nasal expiratory positive airway pressure(NEPAP) valves
This device comprises two small adhesive disposable valves applied to both nares. The valves have negligible resistance during inspiration, but generate resistance during expiration, creating positive end-expiratory pressure from 4 to 17 cmH_2O(1 cmH_2O = 0.098 kPa).[49] No patient characteristics, history, or physical exam findings were identified as predictors of favorable response to these devices. Moreover, the obstructive apnea index (OAI) was significantly improved by the use of NEPAP in 8–16 years old children, whereas aggravation was observed in a few of them, suggesting that PSG monitoring should be implemented for assessment of its effects and emphasizing the need for further research in that area.[50]

Weight loss
Obesity is a well-known risk factor for OSA, and obese children have higher rates of residual OSA after adenotonsillectomy. A systematic review found that behavioral weight loss measures (dietary restriction, physical activity, and psychological support) reduced AHI in obese children with OSA.[51] In a study of a cohort (mean age 17.8 years, BMI 55.2 kg/m^2) who underwent bariatric surgery, AHI declined postoperatively from baseline by 9.2 events/h at 3 weeks and 9.1 events/h at 5 weeks.[52] Bariatric surgery in specific patient groups and weight loss interventions in others were found to reduce AHI in children with OSA.[51] Although sustained weight loss can be achieved in children, the process is time-consuming and often requires motivated families and an adequate system for child support.

Watchful waiting
In the CHAT study, OSA was resolved in 79% of the children who underwent adenotonsillectomy. Interestingly, the AHIs of 46% of the patients in the watchful waiting group were normalized without any intervention. A systematic review showed that approximately two-thirds of the children with mild OSA (AHI 1–5 events/h) obtain relief on their own with age advancement.[10] Factors associated with non-resolution of OSA with watchful waiting include obesity,[11] progressive tonsillar hypertrophy,[11] male sex,[11] low socioeconomic status,[53] asthma,[54] African American ethnicity,[55] and moderate to severe OSA.[7] Watchful waiting is, therefore, an acceptable option in patients with mild OSA who have no significant risk factors for progression.

Conclusions

A large number of surgical and non-surgical options for treatment of childhood OSA have shown efficacy. However, little published evidence is available on comparative assessments of these interventions. Therefore, these therapeutic options should be tailored to the specific needs of each child, considering also the comorbidities and the availability and expertise of the practitioner. The optimal solution would be that a multidisciplinary team of doctors would beformed and a thorough discussion regarding the benefits and risks of all available treatment options would be hold with the patients and their parents or guardians, followed by an consensus on the potentially most effective treatment plan.

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Declaration of competing interest

None.

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