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Review Article

Alternatives to surgery in children with mild OSA

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Abstract Precision medicine requires coordinated and integrated evidence-based combinatorial approaches so that diagnosis and treatment can be tailored to the individual patient. In this context, the treatment approach to mild obstructive sleep apnea (OSA) is fraught with substantial debate as to what is mild OSA, and as to what constitutes appropriate treatment. As such, it is necessary to first establish a proposed consensus of what criteria need to be employed to reach the diagnosis of mild OSA, and then examine the circumstances under which treatment is indicated, and if so, whether and when anti-inflammatory therapy (AIT), rapid maxillary expansion (RME), and/or myofunctional therapy (MFT) may be indicated.

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What constitutes mild obstructive sleep apnea (OSA)?

In the last decade, both the parents of our patients and, of course, medical practitioners have come to expect that a personalized and precise approach to their child's sleep problems is needed. We have further identified that such precision requires much better definition of the spectrum of disease with accurate decision trees that enable reliable categorization in "severity cells" that carry specifically tailored and optimized interventions. For example, emerging data in adults have recently shown that sleep duration, sleep quality, sleep continuity, and sleep regularity are all fundamentally important determinants of end-organ morbidities associated with sleep disorders.[1–4] In otherwise healthy children, the presence of irregular sleep schedules has also been associated with obesity risk, and as a corollary with cardiovascular and metabolic risk.[5]

In the context of OSA, clinical history and physical examination, the pillars of medical practice for centuries are notoriously inaccurate in predicting who among symptomatic patients actually suffers from OSA when compared to an overnight sleep study (PSG) as the diagnostic tool. Consequently, symptom-based assessments are poor discriminators of those children who despite typical symptoms of OSA will display evidence of a "normal" PSG based on current consensus criteria. Not so long ago, many of our clinical colleagues endorsed an approach that stipulated that every child who is symptomatic, e.g., habitually snores during sleep, should undergo adenotonsillectomy (AT), without requiring any diagnostic test such as a PSG. Since then, professional associations such as the American Academy of Pediatrics, American Academy of Sleep Medicine, American Academy of Otolaryngology-Head and Neck Surgery Foundation, European Respiratory Society, have further suggested that in the presence of characteristic OSA symptoms and some supportive physical findings, implementation of simplified testing procedures could replace the gold standard PSG in the form of home-based multichannel respiratory recordings or even single channel overnight oximetry.[6–34] We have been among the latter, particularly based on the concern of limited access to PSG testing for children along with excessive financial costs. Development of such validated scalable diagnostic tools that can be automated would substantially reduce financial burden as well as time consuming labor involved in scoring and interpretation of polysomnograms.[6–34] Such approaches if adopted more universally, would result not only in expedited evaluation of many children who currently are required to wait for long periods of time before being diagnosed, but would also facilitate access to pediatric sleep laboratories for those children in whom the diagnosis is uncertain, or the clinical presentation is more complex and requires more sophisticated diagnostic approaches.

For the sake of an example, please consider the scenario in which a 3-year-old otherwise healthy girl is referred to the sleep clinic by her primary care physician because of seasonal allergic rhinitis, occasional sinus infections and otitis media, habitual snoring, frequent nightmares and occasional night terrors, difficulty to wake up in the morning, and falling asleep in the car or in daycare while also displaying inattentive and disruptive behaviors in class. Let's now assume multiple options: (a) PSG shows an obstructive apnea-hypopnea index (AHI) of 8 events/hour of sleep, in which case AT is clearly the unanimous consensus for treatment; (b) PSG shows an AHI $>$ 2 but $<$5 events/hour or (c) PSG shows an AHI $<$1 events/hour. Indeed, if the apnea-hypopnea index (AHI) of this child is less than 1/hour TST, we will tell the parents that the PSG is normal, and this will be the end of the consultation, while if option (b) is the one, some may recommend AT, while others will recommend non-surgical treatment approaches. However, option (c) reflects a consultation prompted by the underlying symptoms, and even though the sleep study is normal does not necessarily mean that this child is fine and does not suffer from sleep disordered breathing.

What cut-off values of PSG-derived measures (i.e. AHI, ODI 3%, hypoxic burden, respiratory arousal index, end-tidal CO_2) should we then subscribe to as a reliable method demarcating normal from pathological? How would the use of statistical classifiers be helpful in this setting? For example, would 2, 3, or even 5 standard deviations beyond the mean of the sleep measure of interest that was obtained by evaluating a representative cohort of healthy community children spanning the whole pediatric age range be the accurate way of determining whether the individual patient's result is pathological and requires treatment? Or more importantly, how do we measure the degree of "pathological" or even more critically provide an accurate prediction of the risk of morbidity? And if such measures were available, how would such classifiers affect the clinical decision tree? How many symptomatic children would be designated as "normal", and of these how many would be really true (test specificity) or false negatives?

So, as we consider the topic of this review, we need to clarify first how we reach that decision to treat or not to treat. The now well-established poor correlation between phenotype and OSA severity based on PSG measures generates a high level of uncertainty in everything we decide to recommend, and as such the reader is alerted already here of this uncertainty and may seek to establish his/her own approach and conclusions.

A large body of work in the last 4 decades has somewhat conclusively established that two of the major consequences of upper airway obstructive events during sleep, namely repeated arousals (i.e. sleep fragmentation) and intermittent hypoxia are possible determinants of a complex cascade of pathophysiological processes that ultimately increase the risk of adverse neurocognitive, behavioral and cardiovascular consequences in children.[35–37] Considering the importance of such systems in overall wellness and one's future social and financial success, and health-related longevity, treatment of OSA should be viewed as rather urgent in children, particularly when daytime symptoms such as hyperactivity, inattention, somnolence, or poor school performance are detected by either parents or school teachers.[38] AT has emerged as the most common treatment for OSA,[39] yet is not only painful but also has the potential of complications, such as bleeding, post-surgical apnea, and oxyhemoglobin desaturations, as well as adverse intra-operative anesthetic events. Furthermore, after adenotonsillectomy, 20%~50% of the operated children may still have some degree of residual OSA, as dictated by the PSG

criteria used to define residual OSA.[40,41] Thus, the search for a test or group of tests that can accurately and reliably measure the morbidity of sleep-disordered breathing in a given child is ongoing.

Non-surgical anti-inflammatory therapy for "mild OSA"

Considering that inflammation as well as increased collapsibility are consistently present in adenotonsillar tissues and upper airway tissues in children with OSA,[42–44] treatment with either systemic or topical anti-inflammatory agents may reverse these processes and resolve the underlying OSA. Indeed, several studies have emerged in the last 15 years supporting nonsurgical anti-inflammatory treatment approaches in children with OSA.

Mechanisms of action for anti-inflammatory agents

We need to consider that the location and cellular composition of the upper airway is in contiguity with the lower airways, and that substantial commonalities exist between these two artificially divided compartments. Similar to bronchial asthma or allergic rhinitis, anti-inflammatory medications such as nasal corticosteroids and leukotriene receptor antagonists reduce or block the activation or migration of innate inflammatory cells and corresponding molecular cascades into the airway, and mitigate the magnitude of the inflammatory processes in the airway. As is readily apparent, the local inflammation in the upper airway is the end-result of a complex interaction of networks involving production of a multitude of cytokines, chemotactic mediators, and adhesion molecules and upstream signaling pathways.[45] Accordingly, application of anti-inflammatory agents aims to reduce the lifespan of inflammatory cells, including eosinophils, neutrophils, T and B-cell lymphocytes, and mast cells. Corticosteroids are particularly effective at such tasks via their binding to corticosteroid receptors and their translocation to the nucleus where they operate via transcriptional, epigenetic, and post-translational regulatory processes. We should also point out, that the expression of cysteinyl-leukotriene receptors is markedly enhanced in the tonsillar and adenoid tissues of children with OSA, and are predominantly located in T-cell lymphocytes (both CD4+ helper T cells and even more so in CD8+ cytotoxic T cell lymphocytes). In vitro studies from our laboratory using mixed cell cultures of either adenoids or tonsils showed that addition of leukotriene D4 to the media resulted in increased cellular proliferation and release of pro-inflammatory cytokines.[46,47] When such cultures were treated with leukotriene receptor antagonists or with corticosteroids, dose-dependent reductions in proliferation and cytokine release occurred.[46–49]

Intranasal corticosteroids

The initial study aiming to examine the potential use of systemic corticosteroids in OSA in children was conducted over a period of 5 days and resulted in no significant changes in the severity of OSA.[50] In 2001, the same group led by Brouillette conducted the first randomized, triple-blind controlled trial investigating the use of nasal fluticasone over a period of 6 weeks in children with OSA who were waiting for AT. Significant reduction of the AHI occurred in the fluticasone group (from 10.7/h to 5.8/h), while the AHI modestly increased from 11.0/h to 13.1/h in the placebo-treated group.[51]

In an ulterior randomized double blind crossover study involving a larger cohort, intranasal budesonide for 6 weeks in PSG diagnosed children with mild OSA (defined as AHI < 5 events/hour sleep) resulted in significant reductions in AHI and lateral X-rays of the upper airway showed that the size of the adenoids had also declined. Importantly, no evidence of rebound adenoid growth or AHI surges occurred within the first 8 weeks after discontinuation of the treatment.[52] Criscuoli et al[53] reported that significant clinical improvement was detectable after 2 weeks of nasal corticosteroid therapy in a cohort of 53 children. However, even though the improvements were long-lasting among responders, only 45% actually showed improved nasal obstruction and respiratory patterns during sleep. A large number of studies have been published on intranasal corticosteroids, but the majority did not assess the children using PSG (Table 1) such that the current evidence, albeit favorable to the use of these compounds for periods between 2 and 12 weeks, is still limited.[54]

Montelukast

After the initial study by Goldbart et al[55] in 2005, which showed improvements in AHI in children with mild OSA in an open label trial, two double-blind, placebo-controlled studies have been conducted and revealed that oral montelukast therapy for a period of 12–16 weeks improves nocturnal symptoms, reduces the size of adenotonsillar tissues, and significantly reduces PSG-derived measures in the context of mild OSA.[56,57] However, the emergence of side effects related to montelukast, particularly in the neuropsychiatric realm, raises a red flag that should prompt caution when making the decision to use this compound over an extended period of time.[58–61]

Comparison of treatment efficacy: nasal corticosteroids versus montelukast

Studies comparing head-to-head intranasal corticosteroids and oral montelukast revealed rather similar improvements in children with OSA.[62,63] Based on these results, both therapies seem to be of comparable efficacy.

Combination nasal corticosteroids and montelukast

The rationale for using both montelukast and nasal corticosteroids as a combined therapy emerged after the individual success of each medication for reducing OSA severity. It also provides the option to achieve an initial suppression of the inflammatory processes described above, and then, continued treatment with montelukast over a longer period should induce a long-term sustained effect. In a large retrospective study that included 752 children with mild OSA, Kheirandish-Gozal et al[64] indicated that approximately

Table 1 Comprehensive summary of published studies on montelukast and/or nasal corticosteroids for mild OSA.

Study	Design	Patients number (age)	PSG	Treatment	Dose	Duration	Control
Corticosteroids							
Brouillette 2001	RCT	25 (1—10 y)	AHI $>$ 1/h	Fluticasone	50 μg c/12 h,1 week; 50 μg/24 h, 5 weeks	6 weeks	Placebo
Yilmaz 2003	RCT	28 (12—18 y)	No PSG	Mometasone	200 μg	6 weeks	—
Criscuoli 2003	RCT	53 (3.8 $\pm$ 1.3 y)	No PSG	Beclomethasone	400 ug	2 weeks, 24 weeks	—
Cengel 2006	RCT	122(3—15 y)	No PSG	Mometasone	100 μg	6 weeks	—
Berlucchi 2007	RCT	60 (3—7 y)	No PSG	Mometasone	100 μg	40 weeks	—
Kheirandish-Gozal 2008	RCT, crossover	62 (6—12 y)	Mild OSA	Budesonide	32 μg $\times$ nostril	6 weeks, washout, 6 weeks	Placebo
Barghawa 2014	RCT	100 (2—12 y)	No PSG	Mometasone	200 μg	8 weeks	—
Barghawa 2014	RCT	60 (2—12 y)	No PSG	Mometasone	200 μg	8 weeks	—
Hassanzadel 2013	RCT	40 (4—12 y)	No PSG	Mometasone	400 μg	4 weeks	—
Rehman 2013	RCT	112 (3—8 y)	No PSG	Mometasone	NR	8 weeks	—
Montelukast							
Goldbart 2005	RCT	24 (2—10 y)	AHI 1—8/h	Montelukast	4/5 mg	12 weeks	Placebo
Kheirandish-Gozal 2016	RCT	64 (2—14 y)	PSG-Mild OSA (AHÍ $<$ 7/h)	Montelukast	4/5/10 mg	16 weeks	Placebo
Montelukast and corticosteroids							
Kheirandish-Gozal 2014	Retrospective	752 (2—14 y)	PSG-Mild OSA (AHÍ$<$5/h)	Montelukast and corticosteroids	variable	12 weeks	—
Tuhaniouglu 2017	RCT	120 (4—10 y)		Mometasone Montelukast Both None	100 μg 4/5 mg	12 weeks	Corticosteroids

RCT: randomized controlled trial; OSA: obstructive sleep apnea; PSG: polysomnography.

80% of the children has virtual resolution of their mild OSA after 1-year or longer follow-up (AHI dropped from 4.5 ± 2.0 to 1.4 ± 0.0.9 events/h, $p < 0.001$). Interestingly, in a recent systematic review on the efficacy of these anti-inflammatory approaches for pediatric OSA, oral montelukast alone ($n = 166$ patients) led to an average reduction on 56% in the AHI (6.2 ± 3.1 events/h *vs* 2.7 ± 2.7 events/h),[65] while the combination of the two approaches in 502 children resulted in remarkably similar results to those reported by Kheirandish-Gozal et al (4.7 ± 2.1 events/h pre-treatment to 1.4 ± 1.0 events/h post-treatment, with a mean difference of −4.2 events/h; $p < 0.001$).

Orofacial myofunctional exercise

Orofacial myofunctional exercises are designed to achieve improved function and balance of the orofacial muscles, particularly revolving around swallowing, breathing, speaking, and chewing. The sustained rehabilitation efforts usually consist of isometric and isotonic exercises involving all the oropharyngeal cavity, and aim to promote proprioception, range of motion, coordination, and strength of the orofacial structures.[66]

The intention to reduce the use of adenotonsillectomy (AT) as the immediate approach to pediatric OSA has led to initial exploration of myofunctional therapy as a non-surgical approach in selected children. The first issue that needs to be emphasized is that a great level of commitment, cooperation and adherence by the child and the family is required. Poor adherence signifies failure of the intervention, and adherence to MT cannot yet be tracked at this stage, such that more objective methods of delineating adherence will need to be developed in parallel with novel intervention strategies. In a study of 54 children (mean age 7.1 ± 2.5 years, 29 males) with OSA, MT led to improvements in mean oxygen saturation and in the oxygen desaturation index 3% (5.9 ± 2.3 *vs* 3.6 ± 1.8, $p = 0.001$) only in the children assigned to the treatment group compared to the no intervention group.[67] Other open studies in which mouth breathing and altered tongue position at rest and during sleep are identified in children with OSA and are more often associated with dento-skeletal malocclusions, have led to implementation of MT. In most of these studies, improvement in tongue function within 2 months of oropharyngeal exercises was accompanied by better oximetry parameters during sleep among those children who followed the recommendations of oropharyngeal exercises, with an aim to eliminate mouth breathing and recover nasal breathing.[68–70]

In a recent study, the short-term therapeutic effect of passive myofunctional therapy using an oral appliance that advances the mandible during sleep was evaluated in children with OSA.[71] Patients were instructed to wear their appliances and use their tongue to roll the bead inside the appliance (i.e. passive myofunctional therapy) during sleep every night. Improvements in AHI were noted after 6 months. In a similar study, we implemented an intraoral appliance that provided not only mandibular advancement but also imposed tongue repositioning passive exercises in 24 children with OSA and compared to 16cuildren who were left untreated over a period of 6 months (corresponding to the wait time before undergoing AT).[72] Significant improvements in sleep related symptoms and improvements in the pharyngeal minimum cross-section area and volume occurred only among those who received the appliance.

Rapid maxillary expansion

Enlarging the intraoral and upper airway space will minimize airflow resistance and foster upper airway patency. Therefore, many different approaches have been developed aiming to achieve rapid maxillary expansion (RME). RME usually involves the placement of a fixed appliance with an expansion screw anchored to opposing teeth. This screw serves to expand the appliance gradually and to open the mid-palatal suture. Such expansion will therefore gradually increase the transverse diameter of the hard palate over the course of several months. It remains unclear whether RME alone is sufficient for treatment of mild OSA if significant adenotonsillar hypertrophy is present. In addition, only small uncontrolled studies with a relatively short follow-up period are currently available.[73,74] Overall, it would appear that RME may have a role in carefully selected young patients, more specifically in those suffering from obvious malocclusion (high, narrow palate associated with deep bite, retrusive bite or crossbite) and OSA.[75,76] Further studies are clearly needed to evaluate more critically how to proceed with the optimal selection of patients with mild OSA who may benefit from RME, to define the optimal ages for RME intervention, and to establish the anticipated criteria for success.

The "do nothing" option

In the initial multicenter trial assessing the outcomes of AT for pediatric OSA (CHAT study),[77,78] the control group was assigned to watchful waiting for 7 months. Among these children, the majority of which had mild OSA, a significant proportion exhibited normalization of their respiratory disturbances during sleep.[79] Similar findings have been recently reported by another group of investigators.[80]

Conclusions

Nasal corticosteroids and oral montelukast have now been incorporated into the armamentarium of the treatment of mild OSA and have emerged as the preferred options when AT is not the preponderant and definitive equipoise selection. However, identifying those children who are more likely to benefit from such non-surgical treatments, and deciding what PSG criteria or other criteria are needed to reach such decision in an evidence-based manner, remain issues of contention. Since obesity and older age are apparent risk factors associated with increased failure rate of medical treatment, should we opt for alternative approaches in such cases? The duration of treatment is also not standardized and will undoubtedly require more evidence. In summary, there is no doubt that the symptomatic child referred for evaluation of snoring merits a well-structured and evidence-based treatment plan that is based on both the pathophysiological determinants of the

upper airway collapsibility and of treatments that optimize the risk benefit ratios of such selection. Much remains to be done, but hopefully we are on the correct trajectory to achieve such goals.

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Declaration of competing interest

None.

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