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Review

Newer treatment modalities for pediatric obstructive sleep apnea

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EDUCATIONAL AIMS

THE READER WILL BE ABLE TO:

- Discuss the current evidence supporting newer treatments for paediatric obstructive sleep apnoea.
- Appreciate the role of anti-inflammatory therapy in the treatment of paediatric obstructive sleep apnoea.
- Describe the indications of dental treatments for paediatric obstructive sleep apnoea.

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Weight loss

SUMMARY

The obstructive sleep apnea syndrome is common and its prevalence is expected to increase with the current obesity epidemic. If left untreated, it is associated with important morbidity such as growth failure, neurocognitive impairment, systemic and pulmonary hypertension, and endothelial dysfunction. Recent research has shown that many children, especially the obese or those with other underlying medical conditions, have residual obstructive sleep apnea after adenotonsillectomy (the primary treatment for childhood obstructive sleep apnea). These children could be effectively treated with continuous positive airway pressure but poor adherence is a significant limitation of this therapy. Therefore, new treatment modalities for the pediatric obstructive sleep apnea syndrome are needed. Current research has focused on newer therapies for pediatric obstructive sleep apnea, such as anti-inflammatories, dental treatments, high-flow nasal cannula, and weight loss. However, there are few randomized controlled trials assessing the effectiveness of these therapies. Further research is warranted.

INTRODUCTION

The obstructive sleep apnea syndrome (OSAS) is common, affecting 2–3% of children.[1,2] Its peak incidence occurs between 2 and 8 years of age, probably due to the relative size of lymphoid tissue to airway diameter. OSAS is characterized by upper airway collapse during sleep as a consequence of an imbalance between upper airway structural load due to factors such as adenotonsillar hypertrophy or obesity, and upper airway neuromotor tone.[3] If left untreated, it is associated with significant morbidity such as growth failure,[4] cognitive impairment,[5] systemic[6–8] and pulmonary hypertension,[9,10] and endothelial dysfunction.[11,12] Therefore, untreated OSAS can result in a significant health burden for the patients.

Classically, adenotonsillectomy (AT) has been the treatment of choice for pediatric OSAS.[5,13] However, many children, especially the obese, those with underlying medical conditions such as Down syndrome or craniofacial anomalies, and those with more severe OSAS, require further treatment after this surgery.[14–19] Continuous positive airway pressure (CPAP) delivered via a nasal interface is the most common non-surgical therapy for pediatric OSAS. However, poor adherence can be a significant limitation of this treatment.[20–23] In addition, the AT risk benefit ratio in children with very mild OSAS is not clear. This particular group of children may benefit from less invasive therapies. Hence, one of the challenges that pediatric sleep specialists face is finding new treatments for OSAS, especially as the prevalence of OSAS is expected to increase along with the current obesity epidemic.[24,25]

The current review will focus on newer treatment modalities for OSAS, including anti-inflammatories, dental treatments, high-flow nasal cannula, and weight loss.

ANTI-INFLAMMATORY DRUGS

An open-label pilot study published in 1997 demonstrated that a five-day prednisone course was ineffective in reducing the severity of pediatric OSAS.[26] However, the same group showed in

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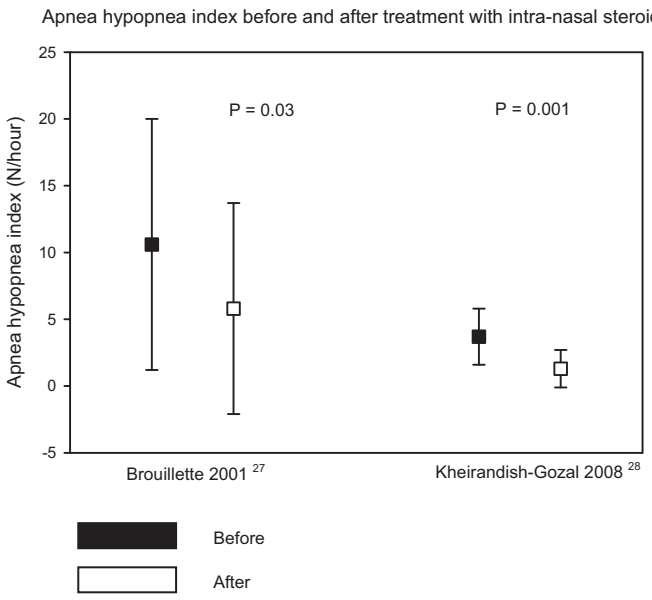

Figure 1. Apnea hypopnea index before and after treatment with intra-nasal steroids. The Y axis represents the apnea hypopnea index (N/hour). The box represents the mean. The whiskers represent the standard deviation (SD). Of note, the SD was calculated for the purpose of this paper. The original articles by Brouillette[27] and Kheirandish-Gozal[28] reported standard error of the mean (SEM). The AHI decreased significantly after treatment with inhaled corticosteroids, overall in children with mild OSAS.

2001 that the intra-nasal steroid fluticasone could be useful in pediatric OSAS (Figure 1).[27] Twenty-five children with OSAS were randomly assigned to nasal fluticasone vs. placebo. The apnea hypopnea index (AHI) decreased from a mean (SEM) of 10.7 ± 2.6/hour to 5.8 ± 2.2/hour in the treatment group ($p = 0.03$), and increased from 10.9 ± 2.3/hour to 13.1 ± 3.6/hour in the control group ($p = 0.04$). This was a significant improvement but the mean AHI of the treatment group did not normalize. Since then, intra-nasal steroids clinical trials have included children with milder OSAS, and the efficacy of other intra-nasal steroids for the treatment of mild OSAS, such as budesonide, has been demonstrated. Kheirandish-Gozal et al performed a double-blind, randomized, crossover trial of intranasal budesonide (32 micrograms per nostril at bedtime) or placebo for 6 weeks, followed by a 2-week washout period and an additional 6-week treatment in the alternative treatment arm (Figure 1).[28] Sixty-two children with polysomnographically diagnosed mild obstructive sleep apnea syndrome were recruited, and 48 completed the study. The authors reported that in the treatment group the mean (SEM) AHI decreased from 3.7 ± 0.3 to 1.3 ± 0.2 ($p < 0.001$). More importantly, this level I trial showed that the positive effect of intra-nasal steroids persisted for at least 8 weeks after discontinuation of budesonide. Specifically, 25 children who were randomly assigned to the initial treatment arm completed the second phase of the protocol. Therefore, this allowed for assessment of whether discontinuation of intranasal budesonide for a period of 8 weeks (2 weeks of washout plus 6 weeks of placebo) would result in worsening of the severity of OSAS. The mean (SEM) AHI at the end of the 6-week budesonide treatment was 1.8 ± 0.3/hour, similar to that at 8 weeks after treatment discontinuation, 1.4 ± 0.2/hour ($p = NS$). Recently, the same research group studied cell cultures from harvested tonsils of children with OSAS to further characterize the steroid efficacy mechanisms. They established that a variety of different potency steroids reduced proliferation rates of lymphoid tissue in a dose-dependent manner. Further, these steroids also enhanced cellular apoptosis.[29]

Tonsillar and adenoidal tissues have been found to express an array of leukotrienes and leukotrienes receptors.[30,31] Leukotrienes in children with OSAS modulate the inflammatory signaling pathway and promote proliferation of adenotonsillar tissue.[32] Subsequently, clinical studies have evaluated the effectiveness of leukotrienes receptor antagonists in children with OSAS. A 16-week open-label trial of a leukotriene receptor antagonist in a few children with mild OSAS showed a very small but statistically significant improvement in breathing parameters.[31] In this study, twenty-four children with mild obstructive sleep apnea were treated with montelukast during 16 weeks. The mean (SD) AHI decreased from a pre-treatment value of 3 ± 0.2 to 2 ± 0.3/hour post-treatment ($p = 0.017$). One small open label trial assessed the effectiveness of a 12-week treatment with a combination of intranasal steroids and a leukotriene receptor antagonist in children with residual mild OSAS post-adenotonsillectomy.[33] Twenty-two consecutive children received the pharmacologic intervention and 14 untreated children with residual mild OSAS post-adenotonsillectomy served as controls. The mean (SD) pre-treatment AHI in the intervention group was 3.9 ± 1.2, and 0.3 ± 0.3/hour post-treatment ($p < 0.001$) whereas no significant changes occurred in the control group. However, the benefit of this combination therapy vs. intra-nasal steroids alone remained unknown. Blinded randomized controlled trials are needed.

In summary, intra-nasal steroids may be useful for the treatment of mild OSAS but the evidence to support treatment with anti-leukotrienes is sub-optimal as no double-blind randomized controlled trial has been published to date. It is important to point out that intra-nasal steroids are most useful in mild OSAS as the AHI improvement is consistent but rather modest. Despite these encouraging trials, several questions remain unanswered. For example, it is unknown whether atopic children would respond better to these treatments, how long the treatment should last, whether a follow up polysomnogram is necessary and if so, when is the optimal timing to repeat it?

DENTAL TREATMENTS

Oral appliances

Mandibular anterior repositioning appliances are effective in adults with mild to moderate OSAS.[34] However, to date there has been only one clinical trial in children assessing its effectiveness. This small, unblinded, randomized controlled trial aimed at analyzing the clinical usefulness and tolerability of oral appliances in children was published in 2002.[35] 32 children with OSAS and orthodontic abnormalities (deep and retrusive bite and cross-bite) were recruited and randomly assigned to 6 months of treatment with 24-hour use of a customized oral appliance vs. a 6-month observation period with no treatment for OSAS. Participants underwent a baseline clinical polysomnogram and a research sleep study at the end of the 6-month period. Authors reported a mean (SD) reduction in the AHI from 7.1 ± 4.6/hour to 2.6 ± 2.2/hour ($p < 0.001$), and a decrease in parental reporting of snoring, restless sleep, irritability, oral breathing, and nasal congestion. However, the AHI normalized in only 50% of the treated children. Despite its randomized controlled design, this study has some important limitations such as unblinded design, a small sample size (14 treated children and 9 controls were included in the final analysis), and an orthodontic evaluation and classification after enrollment. This is an important point as the study was not designed to answer whether the initial severity of malocclusion or other possible orthodontic anomalies were predictive factors for treatment success. This information would be very useful for clinicians to decide which children to treat with oral appliances.

Rapid Maxillary Expansion (RME)

Patients with a maxillary transverse deficiency or "cross-bite" may benefit from rapid maxillary expansion. Clinically, a maxillary