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REVIEW ARTICLE

Use of intranasal corticosteroids in adenotonsillar hypertrophy

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Abstract

Objectives: This review examined the efficacy of intranasal corticosteroids for improving adenotonsillar hypertrophy.

Method: The related literature was searched using PubMed and Proquest Central databases.

Results: Adenotonsillar hypertrophy causes mouth breathing, nasal congestion, hyponasal speech, snoring, obstructive sleep apnoea, chronic sinusitis and recurrent otitis media. Adenoidal hypertrophy results in the obstruction of nasal passages and Eustachian tubes, and blocks the clearance of nasal mucus. Adenotonsillar hypertrophy and obstructive sleep apnoea are associated with increased expression of various mediators of inflammatory responses in the tonsils, and respond to anti-inflammatory agents such as corticosteroids. Topical nasal steroids most likely affect the anatomical component by decreasing inspiratory upper airway resistance at the nasal, adenoidal or tonsillar levels. Corticosteroids, by their lympholytic or anti-inflammatory effects, might reduce adenotonsillar hypertrophy. Intranasal corticosteroids reduce cellular proliferation and the production of pro-inflammatory cytokines in a tonsil and adenoid mixed-cell culture system.

Conclusion: Intranasal corticosteroids have been used in adenoidal hypertrophy and adenotonsillar hypertrophy patients, decreasing rates of surgery for adenotonsillar hypertrophy.

Key words: Hypertrophy; Adenoids; Tonsil; Sleep Apnea; Obstructive; Steroids

Introduction

Adenotonsillar hypertrophy causes mouth breathing, nasal congestion, hyponasal speech, snoring, obstructive sleep apnoea (OSA), chronic sinusitis and recurrent otitis media. In the long term, OSA can lead to complications including growth failure, cardiovascular morbidity, neurocognitive abnormalities, learning and behavioural problems, hyperactivity, and poor attention.[1]

In children with adenotonsillar hypertrophy, poor brain development, sleep problems and emotional disturbances may occur. In a study of six- to nine-year-old children, scores of emotional instability were higher in the adenotonsillar hypertrophy group than in healthy controls.[2] When obstruction was related to adenotonsillar hypertrophy, the behaviour of most of the children improved 3–10 months after surgery (adenotonsillectomy). Obstruction was not related to age, gender, parents' education or monthly income.[3–5]

Inflammation has been suggested to have a role in adenotonsillar hypertrophy and OSA, given the increased expression of various mediators of inflammatory responses in the tonsils and improvement following treatment with anti-inflammatory agents such as corticosteroids.[6,7] In addition, many steroid receptors are found in adenoid tissue.[8] Intranasal corticosteroids reduce cellular proliferation and the production of pro-inflammatory cytokines in a tonsil and adenoid mixed-cell culture system.[7] Nasal corticosteroids are used to treat adenoidal hypertrophy and OSA.[9]

In children with OSA, there is nasal and oropharyngeal inflammation. This might add to the pathogenesis of breathing issues during sleep.[10,11] In these children, inflammatory markers (local and systemic) and pro-inflammatory cytokines are increased, which additionally advance lymphoid tissue proliferation.[6] To reverse tonsillar enlargement, systemic or topical anti-inflammatory agents may help.[7,12–15]

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This paper reviews the use of nasal corticosteroids in adenotonsillar hypertrophy.

Adenotonsillar hypertrophy

The adenoids are a pyramid-shaped aggregation of lymphoid tissue in the nasopharynx.[16] Adenoidal hypertrophy may cause 'bilateral nasal obstruction, rhinorrhea, cough, snoring, hyponasal speech, hypopnea, and sleep apnea'.[17] When tonsillar hypertrophy is also present, OSA syndrome (OSAS) can manifest. If adenoid hypertrophy causes nasopharyngeal obstruction, adenoidectomy is performed. In some cases, nasal corticosteroids are used to decrease the severity of nasal symptoms and the adenoidal mass.[17]

The tonsil consists of a mass of lymphoid follicles supported by a connective tissue framework. The lymphocytes are dense in the centre of each nodule, an area commonly referred to as the germinal centre because of lymphocyte proliferation. The tonsillar crypts penetrate nearly the whole thickness of the tonsil and are distinguishable histologically from other lymphoid organs.[18] The luminal surface of the tonsil is covered with non-keratinising stratified squamous epithelium continuous with that of the rest of the oropharynx.[19–21]

The adenoid is secured by a pseudostratified ciliated columnar epithelium that is plicated to frame various surface folds.[22] The nasopharyngeal epithelium lines mucosal folds, around which the lymphoid parenchyma is organised into follicles and is subdivided into four lobes by connective tissue septa. Seromucous glands exist in the connective tissue, and their conduits stretch out through the parenchyma and come to the nasopharyngeal surface.[19,21]

The palatine tonsils are composed of lymphoid tissue and are situated in the lateral part of the oropharynx, limited by the palatoglossus, palatopharyngeus and prevalent constrictor muscles. Both the tonsils and adenoid are components of Waldeyer's ring, the ring of lymphoid tissue in the pharynx required in the production of immunoglobulins and development of both B and T cells.[19,23] The size of the tonsil varies with age, hereditary qualities and pathological status. At the fifth or sixth year of life, the tonsils quickly increment in size, achieving their most extreme size at pubescence. At pubescence, the tonsils measure 20–25 mm in vertical distance across and 10–15 mm in transverse diameter.[20,21]

In all children, the adenoid volume increases with age, up to age five or six years, and afterward diminishes step-by-step by age eight or nine years.[24] In an overview of 663 youngsters aged 6–15 years, enlarged adenoids were seen in 25 per cent of the children, and were 3 times more common in 7-year-olds (39 per cent) than in 14-year-olds (12 per cent).[25]

Microbial stimuli and external aggravations (e.g. tobacco smoke) may stimulate adenoidal hypertrophy.[26] Adenoidal hypertrophy can be associated with sleep disorders ranging from snoring to OSA, which may produce both evening and daytime sequelae (i.e. discontinuous sleep, sleepwalking, morning headache, trouble concentrating, drowsiness and enuresis).[27,28]

Paediatric OSA prevalence is estimated at 1 per cent, and most often affects youngsters aged around two to six years, when the adenoids and tonsils are largest with respect to the pharyngeal space.[1,6,7]

In atopic youngsters, atopy was associated with increased numbers of immunoglobulin-E positive cells and FcεRI+ cells in adenoidal tissue.[29] Sensitisation to inhalant allergens modifies the immunology of adenoidal tissue, resulting in more eosinophils, cluster of differentiation 1+ Langerhans cells, and interleukin (IL)-4 and IL-5 messenger RNA^+ cells.[30,31]

Glucocorticoid receptor expression is apparent in the adenotonsillar tissue of youngsters with OSA. The glucocorticoid receptor-α/-β proportion is higher and glucocorticoid receptor-α expression is greater in patients with OSA versus those with recurrent upper airway infection.[32]

Topical nasal corticosteroids

Topical corticosteroids are associated with fewer and milder adverse effects than oral corticosteroids. The local side effects of intranasal steroid therapy – primarily dry nose, crusting, bleeding and candidiasis – have been well described in the literature.[33] It has been suggested that both nasal and inhaled corticosteroids can reach ocular structures in levels sufficient to provoke an ocular hypertensive response and posterior subcapsular cataracts formation in susceptible individuals.[34,35]

The topical potency of beclomethasone is more than 600 times that of dexamethasone, and is 5000 times that of cortisol.[36] Additionally, there is some evidence that the liver metabolises budesonide more rapidly than beclomethasone; therefore, it might be expected to cause fewer ocular side effects.[35,37]

Age restrictions

All topical nasal steroids are pregnancy category C, except budesonide which is pregnancy category B. The age restriction for fluticasone furoate and mometasone is two years and older. In the UK, the age restriction is different. It is six years and older for fluticasone furoate, and four years and older for mometasone. The age restriction for beclomethasone, budesonide, ciclesonide and flunisolide is six years and older. The age restriction for fluticasone propionate and triamcinolone is 12 years and older.[38]

Potency

Of the low-potency topical nasal steroids, both triamcinolone acetonide and mometasone have a relative potency of 1. Of the medium-potency agents, flunisolide has a relative potency of 3 and beclomethasone has a relative potency of 5. Of the higher potency agents, both budesonide and fluticasone propionate have a relative potency of 10.[38]

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Mometasone furoate nasal spray has lower bioavailability. It has a broad first-pass metabolism and a moderately higher binding affinity for the glucocorticoid receptor compared with the other intranasal corticosteroids. It does not suppress the hypothalamic–pituitary–adrenal axis when administered at doses of 100–200 mcg/day, which was clinically relevant.[39]

Long-term utilisation of beclomethasone is not associated with the degradation of typical respiratory epithelium to squamous epithelium seen in chronic atrophic rhinitis. Fluticasone and Nasonex® seem to have less bioavailability than older nasal steroids (e.g. beclomethasone).[40]

Topical corticosteroids, even when used for a prolonged period, are unlikely to have systemic effects on growth, bone metabolism and the adrenocortical axis because the daily doses (e.g. 100–200 μg/d fluticasone) are low.[41,42] The nasal mucosa comprise a much smaller area than the pulmonary mucosa, so topical nasal corticosteroid use results in substantially less systemic absorption than when corticosteroids are inhaled to manage asthma.[43] Newer topical steroids such as fluticasone are ineffectively consumed when swallowed and are quickly metabolised in the liver, thereby diminishing systemic availability.[43]

Topical nasal steroids affect the anatomical component. They decrease inspiratory upper airway resistance at the nasal, adenoidal or tonsillar levels. Corticosteroids may decrease adenotonsillar hypertrophy via their lympholytic or anti-inflammatory effects.[12]

Treatment of adenotonsillar hypertrophy

Surgical treatment

The most common reasons for adenotonsillectomy in the paediatric population include 'history of recurrent tonsil infection, including peritonsillar abscess, and tonsil hypertrophy with associated sleep disordered breathing (SDB) and obstructive sleep apnea (OSA)'.[44] A variety of surgical techniques and instruments such as 'cold dissection, electric monopolar cautery, bipolar cautery, harmonic scalpel, bipolar radiofrequency (coblation), and PEAK PlasmaBlade (Medtronic)' have been used for adenotonsillar hypertrophy surgery.[45–48] Various methods and devices have been employed to decrease post-operative pain and intra-operative bleeding, increase surgical speed, and decrease the risk of post-surgical haemorrhage.[45–48]

Lane *et al*. evaluated 1780 patients who underwent tonsillectomy or adenotonsillectomy.[44] Twenty-one of the patients (1.2 per cent) had a primary bleed and 69 (3.9 per cent) had a secondary bleed. The majority of bleeds (58.9 per cent) occurred with coblation; Peak PlasmaBlade was associated with only 17.8 per cent of bleeds and cautery with 23 per cent of bleeds.[44] An estimated 2–3 per cent of patients experience haemorrhage, and 1 in 40 000 patients die from tonsillectomy-related bleeding.[49–51]

Electrodissection increases pain in comparison to sharp dissection for tonsillectomy. However, intraoperative blood loss and operative time were decreased using monopolar electrocautery techniques.[52] Post-operative haemorrhage rates are not significantly different when the two methods are compared.[52]

Complications associated with tonsillectomy (with or without adenoidectomy) include 'adverse effects related to anesthesia, bleeding, infection, and dehydration'.[53] Major complications (e.g. delayed bleeding requiring intervention) occur in approximately 3 per cent of cases.[53] As reported by the Royal Australasian College of Physicians and Australian Society of Otolaryngology Head and Neck Surgery,[54] a recent surgical audit in England and Northern Ireland showed that in 33 921 tonsillectomies, of which 72 per cent were performed on paediatric patients (aged 0–15 years), the incidence of haemorrhage was 1.9 per cent in those aged 0–4 years, 3.0 per cent in those aged 5–15 years and 4.9 per cent in adults.[55]

Approximately 7–13 per cent of patients revisit the emergency department or out-patient setting following tonsillectomy, of whom approximately 15 per cent require in-patient admission.[53,56–58] Revisits are most commonly because of: bleeding (24–30 per cent), pain (15–18 per cent), and nausea, vomiting and dehydration (25–37 per cent).[53]

Post-operative respiratory complications vary in severity, ranging from 'transient desaturations requiring supplemental oxygen' to 'severe airway obstruction and/or apnea requiring positive pressure ventilation'.[53] Respiratory complications are higher in children with OSA.[53]

Other complications include: weight loss; post-operative airway obstruction due to uvular oedema, haematoma and aspirated material; pulmonary oedema; vocal changes; and temporomandibular joint dysfunction.[51] To avoid these complications, additional treatments have been needed in patients with adenotonsillar hypertrophy.

Adenoidectomy can be performed using suction diathermy ablation or curettage adenoidectomy.[59] Jonas *et al*. investigated a group of 100 children undergoing adenoidectomy alone or in combination with tonsillectomy.[59] These children were randomised into two groups, and underwent either suction diathermy or curettage adenoidectomy performed by a single surgeon. For adenoidectomy alone, there was no significant difference in duration of surgery between the curette and suction diathermy groups. When performing tonsillectomy and adenoidectomy together, suction diathermy took significantly longer to complete than curettage ($p < 0.001$). The post-operative comparison at six months showed a significant difference in the residual adenoidal size between the two groups, with that in the suction diathermy group being generally smaller than in the curettage group.[59]

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Nasal corticosteroid treatment

Allergic rhinitis is closely associated with OSA and tonsillar and adenoidal hypertrophy. Tonsillectomy and adenoidectomy are considered to resolve OSA. In a study of sixth grade children, 8 per cent of the children without tonsillar hypertrophy had allergic rhinitis, whereas nearly 30 per cent of the children with tonsillar hypertrophy had allergic rhinitis.[60] Intranasal corticosteroids are suggested to be effective for the treatment of nasal congestion due to allergic rhinitis.[61]

Adenoidal hypertrophy occurs more frequently in children with allergic diseases such as allergic rhinitis, bronchial asthma or atopic dermatitis (40.4 per cent) than in healthy children (22.3 per cent). Allergic inflammation in the nasal mucosa may contribute to adenoidal hypertrophy.[62]

Three months of treatment with intranasal corticosteroids and antihistamine significantly reduced adenoidal hypertrophy (measured by endoscopy and acoustic rhinometry) and obstructive airway symptoms.[63] A meta-analysis similarly found a five-fold reduction in adenoid size following intranasal corticosteroids treatment, but this was not statistically significant because of the small sample size.[64]

Brouillette *et al*. reported that a six-week course of fluticasone nasal spray administration decreased the severity of paediatric OSA symptoms.[12] They concluded that nasal corticosteroids affect the anatomical component of OSA by reducing the inspiratory upper airway resistance at the nasal, adenoidal or tonsillar levels. Both Ciprandi *et al*.[65] and Varricchio *et al*.[66] found that intranasal flunisolide (administered for either 8 weeks or 12 months) lowered rates of adenoidectomy.

In a study by Jazi *et al*., 39 adenoidal hypertrophy patients were randomised to receive fluticasone or azithromycin for 6 weeks.[67] Tonsillar size, adenotonsillar hypertrophy level and OSA symptoms (sleep apnoea, hyponasal speech, snoring and mouth breathing) were assessed, via a self-administered questionnaire, before treatment, and at one week and eight weeks after treatment. Mouth breathing, snoring, hyponasal speech and sleep apnoea improved significantly in both groups ($p < 0.05$). In both groups, the grade of obstruction was also significantly reduced. One week after treatment, apnoea and hyponasal speech values were better in the azithromycin group. The authors concluded that azithromycin is more effective than fluticasone in improving adenoidal hypertrophy related symptoms, though the difference was more significant in the short term than in the long term.

Fluticasone propionate spray was shown to reduce the severity of OSA in children with adenotonsillar hypertrophy.[68] A total of 25 children (aged 1–10 years) received one 50 µg spray per nostril twice daily (200 µg/day) for the first week and once daily (100 µg/day) for the subsequent five weeks. The mixed or obstructive apnoea/hypopnea index decreased in the 13 subjects treated by fluticasone propionate and increased in the 12 placebo-treated subjects. Baseline values of tonsillar size, adenoid size and OSA symptom scores did not differ significantly between the treatment groups.[68]

Demain and Goetz showed that 24-week treatment with topical nasal corticosteroids reduced adenoidal size and improved nasal airway obstruction symptoms.[9]

A double-blind, randomised crossover trial compared intranasal budesonide (32 µg per nostril at sleep time) with a placebo over a 6-week treatment period in 62 children.[69] Adenoid size decreased and polysomnographic measures of sleep quality and respiratory disturbance improved after treatment. Normalisation of sleep measures was observed in 54 per cent of treated children, which was sustained at eight weeks after the discontinuation of treatment.[69]

The role of inflammatory mediators and increased expression of these mediators have been implicated in the pathogenesis of adenotonsillar hypertrophy and OSA. Corticosteroids act as an anti-inflammatory agent, which explains why patients benefit from corticosteroids.[6,7] Brouillette *et al*. reported that nasal corticosteroids are effective in the treatment of OSA.[12]

In a study by Criscuoli *et al*., 53 of 60 children completed a 4-week crossover trial. They were given aqueous beclomethasone (total of 400 µg/d).[70] In 45 per cent of the children, nasal obstruction significantly decreased with intranasal corticosteroid usage, whereas no child improved when saline solution was used. Clinical improvement was observed when a lower dose steroid was used over 24 weeks, and the need for adenotonsillectomy was reduced compared to the children (55 per cent) who had no benefit with initial 2-week steroid treatment.

Kuyucu *et al*. administered cefuroxime axetil (CEF®) and mometasone furoate nasal spray combination to 128 children (aged 3–14 years) for 4 weeks.[71] After the cessation of therapy, the children were followed up for two months. The authors concluded that this combination therapy may delay, or be a substitute for, surgical intervention in mild to moderate adenoidal hypertrophy.[71] Intranasal corticosteroids significantly affect the production and/or activity of a variety of 'proinflammatory mediators, including cytokines, adhesion molecules, mast cells, eosinophils and T lymphocytes', probably through local actions in the nasal mucosa.[72] Intranasal corticosteroids additionally diminish vascular permeability and oedema. Hence, these profound anti-inflammatory effects may reduce the immunological activation shown in hypertrophied adenoid tissue and decrease the adenoid size.[71]

A short course of oral steroids (oral prednisone, 1.1 ± 0.1 mg/kg/day for 5 days) was reported as ineffective in treating paediatric OSAS caused by adenotonsillar hypertrophy.[13] However, Brodsky *et al*. found that tonsillar size was directly proportional to

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bacterial density (expressed as colony forming units per gram of tonsil).[73] Therefore, Al-Ghamdi *et al*. suggested that antibiotics might be effective against these organisms.[13] Although these authors reported that a short course of steroids was ineffective in adenotonsillar hypertrophy related paediatric OSAS, they suggested that antibiotics plus a short course of high-dose corticosteroids could potentially reduce adenotonsillar hypertrophy, lessen OSAS severity and decrease the need for surgery.[13]

Corticosteroid treatment safety

Safety issues and potential side effects of systemic exposure to corticosteroids (oral or parenteral) include hypothalamic–pituitary–adrenal axis suppression induced growth inhibition.[1,74,75] The newer intranasal corticosteroid agents, such as mometasone furoate, fluticasone propionate and fluticasone furoate, have favourable pharmacokinetic characteristics that minimise systemic bioavailability and the risk of systemic adverse effects.[1]

Conclusion

As surgery-related complications may occur during and after adenoidectomy or adenotonsillectomy, non-surgical treatment methods have been considered for use in appropriate patients. Intranasal corticosteroids, used alone or with antibiotics, might reduce cellular proliferation and pro-inflammatory cytokine production in a tonsil and adenoid mixed-cell culture system. They may reduce tonsillar, adenoidal or adenotonsillar hypertrophy, decreasing rates of surgery for adenotonsillar hypertrophy.

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