Comparison of Medical and Surgical Treatment of Nasal Polyposis

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Nasal polyposis is the end result of a variety of pathologic processes. The aims of treatment are to relieve nasal blockage, restore olfaction, and improve sinus drainage. Treating any accompanying rhinitis is also an aim, which requires that medical treatment be given to all patients with an inflammatory problem. Most forms of nasal polyp recur after treatment, whether medical or surgical. There are few direct comparisons of medical and surgical treatment in the literature. Those that exist suggest that most patients should be treated medically, with surgery reserved for patients who respond poorly. Large prospective randomized trials of surgical versus medical therapy are needed in groups of well-characterized patients to determine the optimum approach for each and to decrease relapse rates. Topical corticosteroids are the mainstay of treatment. All patients with inflammatory polyps should receive topical corticosteroid treatment in the long-term, unless there is a compelling contraindication. Adverse effects of surgery are rare but can be devastating. The major side effects of medical therapy are those of oral corticosteroids, which need to be used carefully. The choice of topical corticosteroid is important because long-term use is necessary; the least absorbed should be used. No cost-benefit analysis has been undertaken in this area, although medical therapy is probably cheaper and involves less work/school absence than sinonasal surgery, even when the latter is performed with an endoscope.

Introduction

Nasal polyps, which are symptomatic in 1% to 4% of the population [1], are the end result of several pathologic processes. They can be classified in the same way as rhinitis (Table 1). This review focuses on inflammatory nasal polyps (*ie*, those that are eosinophilic or neutrophilic).

The aims of treatment are to relieve nasal obstruction, restore the sense of smell, improve sinus drainage, and treat the accompanying symptoms of rhinitis. Because treating the accompanying symptoms of rhinitis is not amenable to surgical therapy, surgery always needs to be accompanied by some form of medical treatment [2].

Recurrence of polypoid disease is common in the nose and is most frequent in patients with many eosinophils (*ie*, aspirin sensitivity, allergic fungal sinusitis [AFS]) [3•,4•], and in those with an underlying condition such as cystic fibrosis [5•,6•,7]. Several studies have shown that topical corticosteroids reduce recurrence rates [8••]; topical furosemide also appears to do so [9].

Treatment has included medical and surgical approaches since Byzantine times [10]. However, direct comparisons between the two are few. It is difficult to compare results from separate studies because patient populations and outcome measures differ. Recent staging and classification systems have been presented that should help to clarify the situation [11,12].

Medical Treatments

The mainstay of treatment, as with allergic rhinitis, consists of topical nasal corticosteroids [8••]. Several placebo-controlled studies demonstrate the efficacy of betamethasone sodium phosphate nasal drops, beclomethasone dipropionate, fluticasone dipropionate, fluticasone propionate drops, and budesonide nasal sprays. Beclamethasone dipropionate, budesonide, and flunisolide sprays have been shown to delay the recurrence of polyps after surgery.

The physiologic changes in patients after treatment involve a reduction in the number and activation of T cells and eosinophils and in the number of mast cells and antigen-presenting cells [13].

Controlled trials show that, although topical corticosteroids reduce nasal obstruction, they have little or no effect on the sense of smell, even when used as drop formulations with the patient's head inverted [14•]. However, they reduce rhinitis symptoms.

Topical corticosteroid therapy may fail when polyps are very large and obstructive, when inflammation is predominantly neutrophilic as in cystic fibrosis, or after long-term use (Scadding, personal observation), indicating the possibility of steroid-resistance.

Systemic corticosteroids, either oral (prednisolone, dexamethasone) or produced in response to stimulation by synthetic adrenocorticotrophic hormone (ACTH) injection are effective in reducing polyp bulk and restoring

Table 1. Classification of nasal polyps*

Allergic-type	Infective	Structural	Other
Allergic fungal sinusitis, eg, aspirin sensitivity Churg-Strauss syndrome	Cystic fibrosis Chronic infections rhintis	Antrochoanal	Inverted papilloma

*Nasal polyps can be classified in the same way as in rhinitis. Allergic-type polyps contain plentiful eosinophils but are not necessarily associated with positive skin prick test results.

olfaction, especially if administered with topical corticosteroids. Adverse effects [15•] mean that only short-term (< 2 weeks) use is possible; however, the course can be repeated at no less than three monthly intervals. My practice is to administer prednisolone 1 mg/kg for 5 days plus betamethasone nasal drops 2 per nostril three times daily for 5 days, twice daily thereafter for one bottle. The major contraindications are diabetes, hypertension, glaucoma, previous tuberculosis, and peptic ulceration. Infection may increase; the coadministration of antibiotic is sensible in patients with muco-pus in sinus secretions.

Antileukotrienes

The recent development of antileukotriene drugs, either synthesis inhibitors (zileuton) or leukotriene D4 receptor antagonists (montelukast, zafirlukast), has enabled treatment to be directed at a part of the inflammatory response unaffected by steroids. Leukotrienes are produced by mast cells and eosinophils and are present in the early and late phases of the allergic response. They contribute to congestion and to mucus production and are known mediators in asthma [16•]. Leukotrienes are also involved in nasal polyposis, particularly in aspirin-sensitive disease. Recent open studies have suggested that antileukotrienes help approximately 50% of patients with polyps, with no evidence for any predisposing factor such as age, sex, aspirin-sensitivity, skin prick test positivity, or disease duration. Our studies [17] involving the addition of montelukast to topical corticosteroid therapy showed clinical subjective improvement in nasal polyposis in 64% of aspirin-tolerant (AT) patients ($P < 0.01$) and in 50% of aspirin-sensitive (AS) patients ($P > 0.05$). Improvement in asthma occurred in 87% of AT patients and 61% of AS patients ($P < 0.05$ for both groups), with objective changes in peak flow occurring in only the AT patients ($P < 0.05$). The change in asthma score correlated significantly with the change in polyp score at the 95% confidence level. Ulualp *et al.* [18] found similar results with nine of 15 patients with aspirin triad (Samter's triad) disease showing some improvement.

Zileuton has been shown to affect a return of olfaction in nasal polyposis [19]. We have observed this phenomenon in a few patients administered montelukast.

Antibiotics

The recent demonstration of high levels of immunoglobulin E (IgE) directed against staphylococci in nasal polyps [20••] has led to a reappraisal of the role of antibiotics in this condition. There have been few placebo-controlled studies, but several clinical reports, largely from Japan, state that long-term low-dose macrolide antibiotics are effective in treating chronic sinusitis incurable through surgery or the use of topical corticosteroids [21]. Improvements vary from 60% to 80% in different studies. Macrolides increase mucociliary transport, reduce goblet cell secretion, and accelerate neutrophil apoptosis in animal studies. In vitro, they can reduce interleukin (IL)-6 and IL-8 gene expression and inhibit the expression of intercellular adhesion molecule 1. They also reduce the tissue damage caused by chronic bacterial colonization without eradicating the bacteria. Double-blind, placebo-controlled trials are necessary.

Antifungals

Double-blind, placebo-controlled trials are also necessary with respect to topical antifungal treatment in the nose for nasal polyposis. This has been subjected to two open studies with benefit to patients in both [22•].

Aspirin

Aspirin is a known anti-inflammatory agent. Oral aspirin "desensitization" has been proven to reduce the recurrence rate of polyps, asthma exacerbations, and hospitalization in patients with Samter's triad (nasal polyposis, asthma, and aspirin-sensitivity) [23•]. However, side effects such as gastrointestinal bleeding are eventually found in approximately 40% of patients on long-term therapy.

Studies have been undertaken using the only truly soluble form, lysine acetylsalicylate (LAS), topically for nasal polyposis. Patriarca *et al.* [24] reported improvement more marked in AT patients. Long-term follow-up studies have been reported recently [25]. An open study in AT patients demonstrated a reduction in polyp recurrence similar to that given by topical corticosteroids [26]. Our most recent double-blind trial has involved topical LAS or placebo in addition to regular topical fluticasone propionate in AT patients. The results are being analyzed.

The mechanism of action of LAS is unknown. LAS inhibits growth of fibroblasts from nasal polyps and from normal skin [27]. Recently completed studies demonstrate that topical LAS used in a double-blind, placebo-controlled, cross-over study decreased the deterioration of the nasal airway over a 6-month period in AS patients. From our LAS topical desensitization study, we have preliminary evidence of down-regulation of LTC4 receptors, which are increased in polyps of AS patients compared

with polyps of AT patients (Sousa, manuscript submitted). The nature of AS and AT rhinosinusitis has been reviewed recently [28••].

Other medical treatments

Many other forms of treatment are being explored, including topical azelastine, topical diuretics, omeprazole and anti–IL-5. Sodium cromoglycate has been shown to reduce eosinophilic infiltration in patients with asthma [29] but appears ineffective in nasal polyposis. Immunotherapy is practiced in the United States mainly in the treatment of AFS. However, there are no placebo-controlled trials.

Surgical Treatment

Considerable changes have occurred in the past 20 years. The advent of the endoscope and the computed tomography (CT) scan has enabled earlier detection and more precise and less traumatic surgical treatment. Endoscopic sinus surgery can be undertaken through the nasal cavity, being directed mostly at the ostiomeatal complex [30]. Long-term outcomes are thought to be better in patients with the "halo" sign on a CT scan (*ie*, those with uninvolved mucosa still present). However, our studies on the inferior turbinates of polyps of AS patients demonstrate significant eosinophilia even where no polyp tissue exists [31•]. Therefore, the inflammatory process is probably generalized throughout the mucosa, with polyp formation being determined largely by hemodynamic factors. More than 80% of polyps occur around the ostiomeatal complex, possibly because of the Bernoulli effect.

Drake-Lee [32] suggests that, on principle, the simplest and least invasive operation should be tried first. Zhang [33] noted that laser surgery was marked by less bleeding and a lower recurrence rate (40.6% vs 66.6% found in routine removal). Stammberger [3•] advocates a more aggressive approach in patients with Samter's triad and in those with AFS, together with combined therapy with corticosteroids. Marple [34•] notes recurrence rates of 10% to 100% in AFS and the need for surgical and nonsurgical therapy, which is also advocated by Schubert [4•]. Although it makes sense to remove any remaining fungal tissue, in Samter's triad, there is little evidence that extensive surgery is any better than a simple procedure or no surgery. Patients with this condition tend to relapse quickly, but the relapse rate is reduced by oral desensitization with aspirin [23]. Endoscopic sinus surgery is less effective in patients with cystic fibrosis.

Holmberg and Karlsson [2] advocate complete intranasal or transantral ethmoidectomy for patients who require polypectomy several times a year or suffer from recurrent rhinosinusitis. Freidman *et al.* [35,36] report long-term nasal airway improvement and a reduction or elimination of recurrent sinusitis, with a recurrence rate of less than 20% and a major complication rate of less than 1% in 1300 spheno-ethmoidectomies. However, recurrence in other series are still common [37], possibly as a result of incomplete marsupialization of the ethmoid [38].

Olfactory improvement after endoscopic sinus surgery has been studied by Ohtori *et al.* [39] who noted that younger patients (< 30 years of age) showed more improvement than older patients (> 50 years of age). Revision surgery resulted in similar rates compared to the original procedures. There was no clear correlation between preoperative CT changes at the olfactory cleft and ethmoid sinuses and the degree of improvement. Unsatisfactory surgical results such as adhesions or polyp recurrence were associated with lower improvement rates compared to those with satisfactory surgical outcomes. In these series, there was a high postoperative olfactory improvement rate of 78.8%, which is higher than that seen in most series.

Comparative Studies

Lildholdt *et al.* [40•] undertook a randomized double-blind comparison of two doses of topical budesonide compared to placebo supplemented with surgical removal or intramuscular betamethasone. One hundred twenty-six patients with nasal polyps who had bilateral disease entered a 2-year study. In phase I, they were randomized, double-blind to treatment with budesonide powder 800 µg, budesonide powder 400 µg, or placebo for 1 month. At the end of this phase, failed therapy was supplemented by randomized treatment involving surgical removal or a single injection of sustained-release betamethasone. Afterward, the patients received randomized, double-blind treatment with budesonide powder 800 µg or 400 µg daily. At the end of phase II, the medication was discontinued and the patients monitored for 1 more year. Approximately 85% of the patients rated total or substantial symptom control. The two doses of budesonide showed equal results. At the end of the nontreatment phase, 50% of the patients needed treatment after 4 months, and 34% managed without further treatment for 1 year. Medical treatment with betamethasone injection had better results than surgical polyp removal. In a second study [41], acoustic rhinometry demonstrated that the nasal airway improved significantly a few days after the steroid injection compared to surgery. Lildholdt [41] suggested that the primary treatment of nasal polyposis should be medical, with surgery being recommended only for cases resistant to medical therapy.

Blomquist *et al.* [42•] have undertaken a randomized controlled prospective study to determine whether surgical treatment has an effect additive to medical treatment of nasal polyposis. Thirty-two patients with nasal polyposis and symmetrical disease were randomized to unilateral endoscopic sinus surgery after pretreatment with oral steroids for 10 days and local nasal budesonide bilaterally for 1 month. Postoperatively, budesonide was administered nasally. Patients were followed up for 12 months and were evaluated with nasal endoscopy, symptom scores, and

olfactory thresholds. Their sense of smell was improved by the combination of local and oral steroids; surgery had no additional effect. Symptom scores improved significantly with medical treatment alone, but surgery had additional benefits on nasal obstruction and secretion. After surgery, the polyp score decreased significantly on the operated side but remained the same on the nonoperated side. Twenty-five percent of the patients were willing to undergo surgery on the nonoperated side at the end of the study. They concluded that medical treatment is sufficient for most symptoms of nasal polyposis. When hyposmia is a symptom, no additional benefit is gained from surgical treatment. If nasal obstruction is the main problem after steroid treatment, surgical therapy is indicated. Selection of the patients who will benefit from surgery should be based on the patients' symptoms and not on the examiner's polyp scores [42•].

Studies (Ragab, MD thesis) have randomized patients with chronic polypoid and non-polypoid rhinosinusitis to medical or surgical treatment once they have failed initial therapy with 6 weeks of dexa-rhinospray and nasal douching. A CT scan was undertaken and randomization occurred. Surgical therapy involved endoscopic sinus surgery; patients also received antibiotics, a short course of oral corticosteroids in addition to long-term topical corticosteroids. Medical therapy involved oral corticosteroids, long-term antibiotics, leukotriene inhibitors, or a combination of these in addition to regular topical corticosteroids. Patients were followed up for 1 year, and the effects on the lower and upper respiratory tracts evaluated. The results of medical treatment were equivalent to those of surgical treatment for the upper respiratory tract signs and symptoms in nasal polyposis, but were superior when effects on the lower respiratory tract were considered. No patient deteriorated on medical therapy. However, after polyp surgery, one patient's asthma became significantly worse. The observation of deterioration of the patient or precipitation of asthma after polypectomy was initially made several years ago and has recently been attributed to poor anesthesia in the past. However, it appears to be a real, although probably rare, entity.

Adverse Effects of Therapy

Surgical polypectomy, unless it is a simple snare removal of the obstructing polyps under a local anesthetic, will involve a general anesthetic and a brief stay in the hospital. It is uncomfortable for the patient, and costly. In addition, there are possible (although rare) serious sequelae such as epistaxis and infection. Very rarely, there is the possibility of blindness or central nervous system problems. In a recent UK survey [43•], the complication rate of endoscopic sinus surgery was 0.69%.

The major side effects of medical therapy involve oral corticosteroids (although these are also used as an adjunct to surgery). Oral corticosteroids can increase blood pressure, cause gastric hemorrhage, precipitate diabetes and glaucoma, or reduce resistance to infection. Topical corticosteroids have few side effects, the major one being epistaxis, which occurs in approximately 10% of the patients. Hypothalamic-pituitary-adrenal axis suppression and Cushing's syndrome have been seen when patients have been maintained on long-term therapy with first-generation corticosteroids such as betamethasone or dexamethasone [44,45]. Long-term therapy with first-generation corticosteroids should be circumvented using the newer molecules such as fluticasone propionate (available in spray and drop form), or mometasone. Topical steroid safety has been reviewed recently [15•].

Leukotriene receptor antagonists have minor side effects in approximately 10% of patients, largely involving dyspepsia, difficulty sleeping, or nausea. A rare serious complication is the Churg-Strauss syndrome [46], which may be related to steroid withdrawal. Topical lysine aspirin has no major problems; oral aspirin can cause gastric hemorrhage. If desensitization is not continued regularly, serious exacerbation of aspirin and rhinitis can occur if aspirin is ingested.

Costs

In the UK, surgery is an expensive option, with costs of approximately £800.00 per patient. A 1-year supply of montelukast costs £365.00; topical corticosteroid for 1 year costs approximately £50.00. Oral aspirin and oral corticosteroids are cheap. The cost of long-term antibiotic depends on the molecule used.

Conclusions

Treatment of nasal polyps should be primarily medical, with surgery reserved for patients responding poorly, or for those in whom the primary diagnosis is uncertain because polyps may represent inverted papilloma [47] or hide a malignancy. Unilateral nasal polyps always require operation and histologic examination. Large prospective randomized trials of surgical versus medical therapy are needed in groups of well-characterized patients to determine the optimum approach for each and to decrease relapse rates. All patients with inflammatory polyps should be administered long-term topical steroid treatment unless there is a compelling contraindication.

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