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Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray*

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SUMMARY

Chronic rhinosinusitis (CRS) is a recalcitrant inflammatory process which has a marked detrimental impact on quality of life. At the present there is no cure for this condition, measures are taken to stop progression, and provide symptomatic relief. Topical corticosteroids are commonly prescribed in the management of CRS, but few trials show effectiveness in clinical settings. We set up a randomized, double-blind, placebo-controlled trial to study the effectiveness of a topical corticosteroid agent – fluticasone propionate aqueous nasal spray (FPANS) in patients with CRS. We measured symptoms, diary card, and rigid endoscopy scores, acoustic rhinometry, middle meatal swabs, blood tests – CRP, ESR, WBC, and eosinophil count. Measurements were done at the start of the trial, at 8 weeks, and 16 weeks where possible. Twenty-two patients completed the trial, 9 received FPANS, and 13 had placebo. There was no difference between the 2 groups on all counts. When patients were considered as one group, there was an improvement in the diary card scores (p=0.054), comparing baseline to 8 or 16 weeks. There was no evidence that the regular use of topical corticosteroid increased the risk of developing an infection. An important observation was that the topical corticosteroid did not precipitate acute sinusitis. There is compelling evidence that topical corticosteroids down-regulate cytokine expression, and it is likely that a larger, and longer multi-centre trial may prove their efficacy in CRS.

Key words: chronic rhinosinusitis, topical corticosteroids, treatment, trial, placebo-controlled, randomized, sinusitis.

INTRODUCTION

Intranasal corticosteroid therapy is a popular, and widely used modality of treatment in the medical management of chronic rhinosinusitis (Gwaltney et al., 1995; Benniger et al., 1997; Kaliner, 1997). The International Rhinosinusitis Advisory Board has defined the various forms of rhino sinusitis, and mention topical corticosteroids as part of the pharmacologic measures (Lund et al., 1995).

The effectiveness of intranasal corticosteroid therapy in allergic rhinitis has been proven in controlled trials (Meltzer et al., 1990; Godthelp et al., 1996). Also, a significant effect has been demonstrated in patients with nasal polyposis (Chalton et al., 1985; Lidholt et al., 1995; Lund et al., 1998). However, there have been few trials (Cuenant et al., 1986; Sykes et al., 1986; Qvarnberg et al., 1992; Meltzer et al., 1993; Puhakka et al., 1998) designed to study the role of topical corticosteroid therapy in patients with chronic rhinosinusitis. Thus, we decided to undertake such a study, including patients selected on the basis of well established criteria (Lund et al., 1991; Lund et al., 1995). These patients took part in a randomised, double-blind, placebo-controlled trial in which the 'active' group received fluticasone propionate aqueous nasal spray (FPANS).

MATERIALS AND METHODS

Subjects

Twenty-nine patients who fulfilled the inclusion and exclusion criteria for chronic rhinosinusitis were selected from our Rhinology clinic. All had a history (>3 months) of recurrent discoloured rhinorrhoea (>2 weeks/episode), accompanied by more than 2 of the following symptoms: nasal obstruction, headache, facial pain, fever. The history was supported by endoscopic, and/or CT scan evidence of chronic rhinosinusitis at some

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stage. Patients with an acute exacerbation in the previous 2 weeks, on oral or depot corticosteroids in the previous 3 weeks, on intranasal corticosteroid in the previous 2 weeks, or with other severe concurrent illness were not considered for the study. Selected patients were given an information sheet regarding the trial, and consent obtained prior to enrollment. The study was approved by the local Ethics committee.

Study parameters

The following assessments were undertaken at the start of the trial, at 8 weeks, and at 16 weeks where possible.

1. *Symptom score:* A visual analogue scale routinely used in our Rhinology clinic was employed. Patients were asked to mark a point on a 10 cm line, a higher mark denoting greater severity of a particular symptom. The symptoms considered were blockage, sense of smell, sneezing, discharge from front of nose, discharge from back of nose, nose bleeds, facial pain, headaches, itchiness of the nose, throat, and ear. The measures (in cms) were added to obtain a score at the start and end of study.
2. *Endoscopy*: A rigid endoscope (Hopkins rod lens system 2.7 mm, 0^0) was used for this purpose. The signs evaluated included discharge, oedema, crusting, polyps, and scars or adhesions. Each sign was rated on a 0-2 scale (Lund et al., 1995).
3. *Middle meatal swabs:* These were obtained from both nasal cavities at the time of rigid endoscopy. Cotton wool on wire was used, and the specimen immersed in gel, and sent for laboratory analysis.
4. *Acoustic rhinometry:* A *gm* instruments acoustic rhinometer was used. We measured the minimum cross sectional area and volume (0 to 7 cm). The protocol used has been described previously (Taccariello et al., 1999).
5. *Blood tests:* Samples were collected for total white cell and eosinophil count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).
6. *Diary card:* Patients maintained a diary scoring their symptoms, once every week. The first week score was compared to the final week score. Symptoms included nasal blockage, nasal discharge (anterior), nasal discharge (posterior), headache, and facial pain.

Trial medication and randomisation

Patients were randomised to receive Fluticasone propionate or placebo, 2 sprays on each side, twice daily. This provided a dose of 400μg/day to the fluticasone propionate group patients. The randomisation code was generated and maintained by personnel in the pharmacy. The investigators were not involved in the process of randomisation. Placebo spray had benzalkonium chloride in the same concentration as fluticasone propionate, and both had rose scent to mask any differences in smell. The study medications were prepared and supplied by Glaxo Wellcome Research and Development Public Limited (Uxbridge, Middlesex, UK).

Statistical analysis

Collected data was entered into a statistical package Statview&Graphics v.1 for Macintosh. A baseline comparison between groups was done using the Chi squared test. Baseline measures were compared to final visit measures using Wilcoxon signed-rank test. To compare the 2 treatment groups, percentage changes were calculated for all parameters, such that positive values indicated an improvement. Comparison of these changes between groups was done using Mann Whitney U test. Significance level was set at $p<0.05$ for all tests.

RESULTS

Twenty-nine patients were enrolled, and 22 completed the trial. Of these 13 were re-assessed at 8 weeks only, and 9 at both 8 and 16 weeks. Of the 7 patients not completing the trial, 5 did not attend follow-up, 1 stopped using his trial medication prematurely at 3 weeks (drop-out), and 1 patient was withdrawn as his nasal swab taken at the initial visit grew multi-resistant *staphylococcus aureus* (MRSA). A diary card was maintained by the patient who dropped-out, and hence data from it was used in analysis. Following randomization 14 patients received fluticasone propionate aqueous nasal spray (FPANS), and 15 received placebo. However, of the 22 subjects completing the trial 9 belonged to the FPANS group, and 13 to the placebo group. Both groups were comparable for age, sex, atopic status, asthma, nasal polyps, and immunoglobulin levels (Table 1).

Table 1. Clinical data of the 22 patients completing the study.

	FPANS group	Placebo group	p value
Number of patients	9	13	
Age (mean ± SD)	45.1±10.7	38±20	0.55
Gender (M:F)	2:7	7:6	0.30
SPT (+ve:-ve)	7:2	8:5	0.63
Asthma (Y:N)	2:7	3:10	0.5
Nasal polyps (Y:N)	2:7	2:11	0.53
Number of sinus operations: mean±SD (range)	5±6.3 (0-17)	2.8±3.4 (0-11)	0.26
Low immunoglobulin (Y:N)	3:6	5:8	0.68

SPT: skin prick test; Y: yes; N: no

No significant difference could be demonstrated between the placebo and FPANS groups for all parameters (Table 2). When all the patients (FPANS plus placebo) were considered together, and their baseline diary card scores were compared to end of study scores, we found a trend towards improvement (p=0.054).

Table 2. Percentage changes - mean [standard deviation] - in various parameters evaluated at the beginning and end of trial. p values derived using Mann-Whitney U test comparing the 2 groups. (+ve changes indicate an improvement).

Parameters	Group and % change (mean [SD])		p value
	FPANS	placebo	
Symptom scores	71.3 [32.9]	-5.6 [73]	.77
Diary card scores	29.4 [37]	16.9 [48.5]	.39
Endoscopy scores	22.3 [6..8]	18.9 [38.3]	.18
Acoustic rhinometry			
• Area	11.3 [19.2]	1.3 [16.4]	.27
• Volume	-1.8 [22.4]	13.6 [30.2]	1
C-reactive protein	103.8 [257.2]	21.4 [179.9]	.45
ESR (mm/hour)	39.4 [172.8]	47.. [107.6]	.57
White cell count	9.8 [24.2]	-4.8 [16.3]	.35
Blood eosinophil count	21 [75.1]	5.3 [99.7]	.89

This is illustrated in Figure 1. No patient from either group had an acute exacerbation of their rhinosinusitis requiring an 'emergency' visit, and treatment with antibiotics. Results of middle meatal swabs indicate that 4 patients in the FPANS group grew *Staphylococcus aureus* de novo whereas 3 patients from the placebo group grew pathogenic bacteria (1=β *Haemolytic streptococcus*; 1=*Streptococcus pneumoniae*; 1=MRSA).

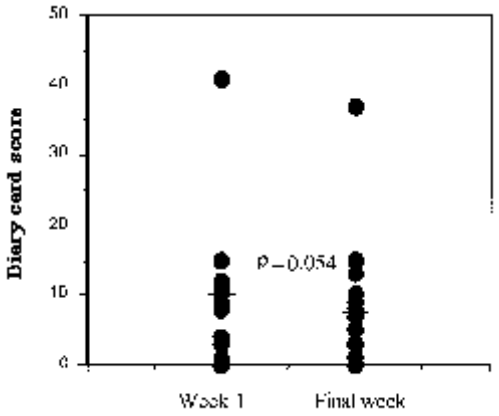

Figure 1. Comparison of diary card scores (all patients).

DISCUSSION

Chronic rhinosinusitis is a persistent, dynamic inflammatory process involving the mucous membrane of the nose, and paranasal sinuses (Kaliner et al., 1997). Histopathology of this lining shows mucosal oedema, exudation, inflammatory cell infiltration, goblet cell hyperplasia, and in some patients formation of polyps (Norlander et al., 1994). The hallmark of such an inflammatory process in the sinuses is marked tissue eosinophilia (Harlin et al., 1998). In the short term the inflammatory response can be viewed as a host defence mechanism but its persistence can result in what has been termed "overrepair" denoting fibrosis, scar formation, and self-sustaining eosinophilic disease (Bachert et al., 1997). Corticosteroids are potent anti-inflammatory agents which exert their effects by binding to a cytoplasmic steroid receptor (Kamada et al., 1995; Siegel, 1991). The formation of such a complex within pro-inflammatory cells such as eosinophils, macrophages, and lymphocytes translates into inhibition of cytokine/mediator release. This reduces exudation, oedema, and further chemotaxis of pro-inflammatory cells. Thus, there appears to be a strong physiologic basis for advocating the use of topical corticosteroids in chronic rhinosinusitis.

There have been few studies evaluating the effect of topical corticosteroids in patients with sinusitis (Cuenant et al., 1986; Sykes et al., 1986; Qvarnberg et al., 1992; Meltzer et al., 1993; Puhakka et al., 1998). Puhakka et al. (1998) have shown that the use of fluticasone propionate for 6 days at the onset of a cold reduces progression to paranasal sinusitis, whereas Meltzer et al. (1993) found that intranasal flunisolide was more effective than placebo when used in conjunction with antibiotic in resolving symptoms and signs of maxillary sinusitis. Studies on chronic sinusitis patients (Sykes et al., 1986; Cuenant et al., 1986; Qvarnberg et al., 1992) have also shown the benefits of topical corticosteroid treatment. Qvarnberg et al. (1992) found that the addition of budesonide spray to sinus washouts and oral antibiotics as compared to placebo, significantly reduced facial pain (p=0.001) with a trend towards significance for reduction in maxillary mucosal swelling on radiology. Cuenant et al. (1986) compared the use of corticosteroids plus antibiotic and antibiotic alone, both in solution form, for irrigating maxillary sinuses in patients with chronic sinusitis. Both solutions were effective, but the one with corticosteroid was significantly more so (p=0.04) throughout the 11 day period of treatment. In their study, Sykes et al. (1986) show that a topical corticosteroids/decongestant combination in patients with CRS was effective in improving nasal mucociliary clearance, and reducing nasal obstruction.

We studied the effectiveness of fluticasone propionate aqueous nasal spray (FPANS 200μg twice daily), a halogenated corticosteroid, in the management of patients with chronic rhinosinusitis. In this randomised, double-blind, placebo-controlled trial we were unable to show a significant difference between the placebo and FPANS groups in symptom scores (visual analogue scale), rigid endoscopy scores, acoustic rhinometry measurements (minimal cross-sectional area; volume), or haematologic parameters (total white cell count, eosinophil count, ESR, C-reactive protein). Comparison of the two groups did not demonstrate a significant difference in diary card scores but, when all patients were grouped together, there was a trend towards improvement (p=0.054; Wilcoxon signed ranks test). We have recently published our findings of a study on nasal douching and its beneficial effects in chronic rhinosinusitis (Taccariello et al., 1999). Thus, we consider the tendency towards improvement in diary card scores a reflection of the douching properties of any intranasal spray.

In our study, the results of the middle meatal swabs suggest that there is no evidence of increased intranasal infection even in predisposed patients such as these, with the regular use of topical corticosteroid. There is some controversy surrounding the use of topical corticosteroids following endoscopic sinus surgery (Mostafa, 1996; Birchall, 1997; Rowe-Jones et al., 1997). Mostafa (1996) has shown that using topical corticosteroids after surgery increases the chances of postoperative infection whereas Rowe-Jones et al. (1997) have shown that this is not the case in twice as many patients. Our findings would support the latter study.

The reason for the lack of efficacy of topical corticosteroids in our trial could be due to a variety of factors. A large proportion of trials demonstrating the benefits of topical corticosteroid therapy have been focused on patients with nasal polyposis (Chalton et al., 1985; Lindholt et al., 1995; Lund et al., 1998). These patients form a subgroup of chronic rhinosinusitis, often labeled as "chronic hyperplastic sinusitis" (Bachert et al., 1997). Amongst our patients (n=22) only 4 had nasal polyps. Thus, it seems likely that the patients studied had a different underlying cellular/cytokine profile. Our patients may have a neutrophil dominated inflammation, which responds poorly to topical corticosteroids. Another factor appears to be the duration of thera-

py. Most trials on nasal polyp patients lasted in excess of 6 months. In our study the maximal follow-up period was 3.5 months. We think that a longer period of follow-up (9-12 months) is more likely to give a definitive answer. Our study was relatively small due to recruitment difficulties, largely because chronic rhinosinusitis patients did not wish to risk the use of placebo over a winter. A larger sample size might have shown a treatment difference and thus, in the future, larger possibly multi-center trials need to be designed.

Recent investigations have shown that the eosinophilic inflammation in chronic rhinosinusitis is due to an upregulation of Th-2 cytokines, in particular interleukins IL-4, IL-5, and IL-13 (Hamilos et al., 1995; Ghaffar et al., 1998). In addition, these studies show that topical corticosteroid use downregulates the receptor expression of these cytokines (Wright et al., 1998; Al-Ghamdi et al., 1997). This supports our use of this therapy but, again it is likely that these agents have to be used over a prolonged period before such effects as seen on a cellular level are translated into clinical improvement when disease is established. This contrasts with uncomplicated allergic rhinitis where 2 weeks of fluticasone propionate markedly reduces the response to nasal allergen challenge (Scadding et al., 1994), and where clinical improvement has been shown to occur within 3 days of its use (Wang et al., 1998). It has been suggested that intranasal medication does not reach the paranasal sinuses, and hardly reaches the ostiomeatal complex. However, a recent paper (Negley et al., 1999) showed that sinus deposition of nasal aerosols occurred in three out of five normal healthy subjects. This may, of course, be reduced where there is nasal and sinus inflammation.

Another possibility is that our patients were too advanced in the course of their disease. Chronic inflammation/infection has been shown to reduce primary defence mechanisms such as mucociliary clearance (Scadding et al., 1995), which is vital in maintaining a healthy sinus milieu. We have also found low levels of nitric oxide in some patients with chronic rhinosinusitis. It may be that corticosteroid treatment should be initiated early in the course of disease in order to reverse the inflammation prior to secondary damage – a concept which has recently been accepted in asthma (Pedersen, 1998).

In conclusion, although there is evidence to show that topical corticosteroids reduce inflammation at the cellular level (Ghaffar et al., 1998; Wright et al., 1998; Appenroth et al., 1998), the clinical results are not yet sufficiently strong enough to advocate their routine use in the medical therapy of chronic rhinosinusitis. Further longer studies need to be undertaken. Future trials designed to study the clinical effects should be prolonged (9-12 months), and the patient population more clearly defined. This may mean a further subclassification of chronic rhinosinusitis into patients with nasal polyps, allergy, or immunodeficiency. Patients with a short history should be preferentially investigated. There is no evidence that topical corticosteroids increase nose and sinus colonisation by pathological bacteria.

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