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Evaluation of efficacy of topical corticosteroid for the clinical treatment of nasal polyposis: searching for clinical events that may predict response to treatment

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SUMMARY

The objective of the present study was to evaluate the clinical response to topical budesonide in patients with nasal polyposis (NP) and to evaluate if there is any clinical event that may predict the response to treatment. Twenty patients with NP were assessed by a clinical questionnaire, nasal endoscopy and sinusal computed tomography. The patients were then medicated with budesonide, 256 μg/nostril/day, for a 2-month period and afterwards they were submitted to a new clinical questionnaire and a new endoscopy. Post-treatment endoscopy revealed a significant reduction of polyp size's score (4.25 vs. 2.90, $p < 0.01$), which was associated to improvement of nasal symptoms: posterior rhinorrhea, headache, hyposmia, anterior rhinorrhea, and sneezing ($p < 0.05$). There was also a significant improvement of the sum of scores (20.10 vs. 10.30, $p < 0.0001$). Cacosmia and nasal itching did not respond to medical treatment. Patients with a higher tomographic extension of the polyp presented a significantly worse clinical response ($p < 0.05$). We conclude that there was partial, but significant, improvement of nasal symptoms and polyp size after treatment with nasal budesonide and that this clinical improvement was inversely correlated to the tomographic extension of NP at diagnosis.

Key-words: nasal polyposis, topical corticosteroid, budesonide, clinical treatment

INTRODUCTION

Nasal polyposis (NP) is a common disease with an incidence of 1 to 4% in the general population [1], and it affects mainly males from 40 years or up. The etiology of NP is not fully understood, but the nasal mucosa is known to undergo extensive histological changes, becoming thickened and showing an increase in goblet cells. The stroma shows increased fibroblast production associated with recruitment of inflammatory cells such as lymphocytes, mast cells, plasmocytes, and mainly eosinophils [1,2]. Finally there is thickening of the basement membrane. This chronic inflammatory process usually starts in the region of the osteomeatal complex.

Several factors have been proposed to trigger the onset of the inflammatory process, such as local hypoventilation, the presence of fungi or superantigens in nasal secretion, changes in epithelial cells, altered production of nasal secretion favoring local edema (an important factor in the pathogenesis of cystic fibrosis) [3]. One of those stimuli can trigger a chronic inflammatory process by the production of pro-inflammatory cytokines (such as IL-5, GM-CSF, TNF-α, and some others), of chemokines (including RANTES, eotaxin), and of adhesion molecules (such as ICAM-1), in addition to inhibition of anti-inflammatory cytokines such as TGF-β, and uteroglobulin [3]. Allergy is currently not believed to be a causal factor, but it may increase the symptoms and the extension of NP by altering the pattern of the local immune response [3].

The most common symptoms of NP are nasal obstruction, anosmia, rhinorrhea, headache, and recurrent sinusitis. These symptoms considerably impair the quality of life of the patient, as demonstrated by Alobid et al. [4].

In view of the high recurrence rate among patients with NP treated solely by surgery (31% on average) [5], the currently recommended treatment is clinical and based on glucocorticosteroids. The 2002 international NP consensus [6], the 2005 European paper on Rhinosinusitis and Nasal Polyposis [3], as well as several investigators [2,9] have recommend topical corticosteroid as the medication of choice to control NP. The rate of success of NP treatment with a topical corticosteroid ranges from 60.9 to 80% [5,7,8]. The objective of clinical treatment should be the improvement of nasal obstruction and anosmia, the reduction of the nasal polyp and the prevention (or reduction) of recurrence of

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symptoms [9]. In those cases where isolated topical corticosteroid treatment does not control the symptoms, systemic corticoteroid or surgical treatment may be indicated [3,4,6]. The operation of choice is functional endoscopic sinus surgery (FESS).

For a more effective action, corticosteroids must be used over a prolonged period of time. Due to their minimal systemic side effects, topical corticosteroids became very important because of their capacity of chronic administration. Among topical corticosteroids, fluticasone [3,9] and budesonide [3,9] have a proven anti-inflammatory action. Momethasone, despite the lack of a randomized clinical study proving its efficacy, has been increasingly used for this purpose [2].

The response to corticosteroids, however, varies widely among individuals, probably due to cellular mechanisms of resistance to these drugs [10-14].

The objectives of the present study were:

- to assess the clinical response to the topical corticosteroid budesonide to patients with NP.
- to correlate this response with:
  - total score for signs and symptoms before treatment;
  - clinical data regarding allergic symptoms in pre-treatment period;
  - endoscopic dimensions of the polyp in the nasal cavity before treatment; and
  - sinusal extension of NP determined by computed tomography.

PATIENTS AND METHODS

Patients

The studied patients were evaluated at the Rhinology outpatient clinic of the Discipline of Otorhinolaryngology, University Hospital of Ribeirão Preto, University of São Paulo. The patients had NP without history of associated diseases such as asthma, aspirin intolerance (Samter triad), ciliary dyskinesia or cystic fibrosis. Patients with bilateral polyposis who had not been treated with a topical or systemic corticosteroid or with an antihistamine for at least 2 months before the study were included. The study was approved by the Research Ethics Committee of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo (document no. 1090/2003), and by the National Research Ethics Committee (CONEP).

Evaluation and treatment

After an initial evaluation, the patient signed an informed consent form and responded to a clinical questionnaire regarding symptoms of nasal obstruction, posterior and anterior rhinorrhea, cacosmia, hyposmia or anosmia, headache, sneezing, and nasal itching. The patient was asked to score each symptoms on a scale from 0 to 4, where 0 = absence of symptom, 1 = mild/occasional symptom, 2 = moderate/-persistent symptom, 3 = severe symptom, 4 = extremely severe symptom, strongly impairing the quality of life.

The patient was then submitted to nasal endoscopy, always performed by the same investigator (FCPV) and the polyp was graded from 0 to 3 in each nostril according to Lund et al [2], with the total score ranging from 0 to 6. After the procedure, budesonide, 64 μg, was provided to the patient. Each patient was instructed about the correct use of the medication by the same investigator (FCPV). They were oriented to administer it in 2 sprays per nostril twice a day (a total dose of 264 μg/nostril/day) for a continious period of 2 months.

At the beginning of this period, and before medical treatment was started, CT of the facial sinuses was scheduled for each patient. The CT scan score was based on the study of Lund and Mackay [15], which is recommended by the 2005 European position paper on Rhinosinusitis and Nasal Polyposis [3] and on the 2002 international NP consensus [6]. On this basis, the sinusal involvement was graded from 0 to 24. After the 2 month-treatment, the patients who completed the treatment were re-evaluated, through the same questionnaire protocol and endoscopy.

Statistics

The endoscopic score before treatment was correlated to the CT score through Pearson correlation. The pre- and post-treatment scores were compared one to the other by the nonparametric Mann-Whitney test.

Clinical improvement was evaluated according to the clinical improvement score (CIS):

CIS = pre-treatment score - post-treatment score/ pre-treatment score.

The median CIS value was obtained and the patients were divided into two subgroups, with 10 patients in each: patients with a poor response the topical corticosteroid (G1) and patients with a better response to the treatment (G2). The two subgroups were compared one to the other in terms of the total clinical score before treatment (TOT1), the pretreatment clinical score for allergic symptoms (anterior rhinorrhea, sneezing and nasal itching) (AS1), endoscopic score of the polyp before treatment (End1), and sinusal extension of the polyp evaluated by the CT scan (CT).

The variables were compared between groups by the nonparametric Mann-Whitney test, with the level of significance set at $p<0.05$.

RESULTS

The study was conducted on 20 patients (4 females and 16 males) aged 15 to 69 years (mean: 44.5 years). Three of these patients had been previously submitted to FESS because of NP (mean post-operatory period: 5.3 years), whereas the remaining 17 patients had never been operated for this reason.

The patients had moderate symptoms (mean total score: 20.10 out of 36), associated to extensive polyps at endoscopy (mean score of 4.25 out of 6) and at CT (mean score of 15.6 out of 24) before treatment. The endoscopic extension of the polyps before treatment correlated positively to the CT score ($r = 0.4567$, $p < 0.05$).

The individual clinical and endoscopic scores obtained before and after treatment and the p values for the comparison between the two time points are listed in Tables 1 and 2. There was a significant decrease in endoscopic polyp size score from 4.25 to 2.90 ($p < 0.01$). This objective reduction was followed by an improvement in clinical symptoms, with a statistically significant reduction in scores of nasal obstruction (2.80 vs. 1.25, $p < 0.005$), posterior rhinorrhea (2.35 vs. 0.85, $p < 0.005$), headache (1.60 vs. 0.70, $p < 0.05$), hyposmia (3.30 vs. 2.05, $p < 0.05$), anterior rhinorrhea (1.50 vs. 0.70, $p < 0.05$), and sneezing (2.25 vs. 0.95, $p < 0.005$). Only cacosmia and nasal itching did not differ significantly between time points (respectively: 0.50 vs. 0.25 and 1.55 vs. 0.65, $p > 0.05$), but these symptoms were already scarcely present among patients before treatment. Regarding the sum of the scores for the clinical and endoscopic data (total score), there was a statistically significant difference between the two evaluated points (20.10 vs. 10.30, $p < 0.0001$).

Table 1. Comparison of the mean scores of individual symptoms and of endoscopy obtained before and after treatment, using the Mann-Whitney test.

	Pretreatment mean	Post-treatment means	p
Nasal obstruction	2.80	1.25	0.0011
Posterior rhinorrhea	2.35	0.85	0.0019
Cacosmia	0.50	0.25	NS
Headache	1.60	0.70	0.017
Hyposmia – Anosmia	3.30	2.05	0.0214
Nasal itching	1.55	0.65	NS
Anterior rhinorrhea	1.50	0.70	0.0431
Sneezing	2.25	0.95	0.0026
Endoscopic score	4.25	2.90	0.0064

NS: non-significant

Table 2. Endoscopic scores before and after treatment, as well as CT scores, for each patient, and mean values.

Patient number	Pretreatment endoscopic score	Post-treatment endoscopic score	CT score
1	4	3	11
2	6	4	17
3	3	4	12
4	4	3	22
5	3	2	4
6	5	3	20
7	6	6	23
8	5	5	20
9	4	4	21
10	4	2	19
11	5	5	24
12	4	2	11
13	3	2	15
14	4	4	19
15	3	2	9
16	4	2	14
17	5	4	18
18	5	0	11
19	5	0	7
20	3	1	15
mean	4.25	2.9	15.6

Table 3. Comparison of subgroups G1 and G2 by the Mann-Whitney test regarding the variables AS1, End1, TOT1 and CT, and levels of significance.

	G1		G2		
Scores	Mean	SD	Mean	SD	p
EA	6	2.44	4.6	3 .83	0.3252
End	4.6	0.96	3.9	0.87	0.1477
TOT	22	4.76	18.2	6.39	0.2262
CT	18.7	4.37	12.5	5.08	0.014*

When comparing subgroups, there was no significant difference regarding the total score (TOT1), allergic symptoms (AS1) and endoscopic polyp dimension (End1) before treatment (Table 3). However, the subgroup with a smaller tomographic extension of NP presented a significantly better improvement, suggesting that clinical improvement is inversely correlated to the sinusal extension of NP.

Out of the 20 patients studied, only 1 achieved complete remission of the nasal polyposis when evaluating endoscopy and symptoms, while 11 patients had an important improvement and decided to maintain their clinical treatment; however, 6 had only partial improvement, and 2 worsened their symptoms, requiring adjuvant surgical treatment.

DISCUSSION

Regarding the prevalence of NP, the findings of the present study are in accordance to those reported in the literature [1], showing that NP is more prevalent among men (65%) at the forth decade of life. In a study conducted on 109 patients, Alobid et al. [4] reported that 68% of the patients with NP were males.

The patients had extensive polyposis at endoscopy and CT prior to the treatment, and presented moderate symptoms on average. There was a significantly positive correlation between endoscopic and tomographic scores before treatment.

After 8 weeks of treatment with topical budesonide spray, there was a statistically significant improvement of nasal obstruction, posterior rhinorrhea, headache, anosmia/hyposmia, anterior rhinorrhea and sneezing, in addition to endoscopic improvement. Only cacosmia and nasal itching did not improve significantly, but these were symptoms formerly with low prevalence in the studied population.

Tos et al. [6] evaluated the efficacy of budesonide spray during 6 weeks of treatment in 138 patients with NP and observed an improvement of the symptoms of nasal obstruction, rhinorrhea, sneezing and anosmia/hyposmia, as well as an endoscopic reduction of nasal polyps. The substantial or total improvement of symptoms (60.9%) observed by these authors was similar to that observed in the present study (12 out of 20 patients).

Lund et al. [2] evaluated 10 patients with NP over a period of 12 weeks of treatment with fluticasone spray at the dose of 200

μg/nostril/day and observed a significantly greater endoscopic reduction of the nasal polyp in the studied group compared to 9 patients treated with placebo. This improvement was mainly due to nasal obstruction, whereas there was no significant improvement in symptoms such as sneezing, itching, hyposmia or headache. Tuncer et al. [5] treated 17 patients with NP with a 16-day pulse of methylprednisolone and nasal fluticasone for 2 months and observed clinical improvement in 15 of them. However, complete regression of the polyp occurred in only 2 patients, while 9 required surgical treatment for symptom remission. Alobid et al. [4] observed an improvement of quality of life in patients treated only with topical corticosteroid, which was identical to that observed in patients submitted to FESS, after 1 year of follow-up.

To date, reports correlating clinical improvement to pretreatment clinical factors are absent in literature. The present study demonstrates a significant inverse correlation between clinical improvement and tomographic sinusal extension of NP, indicating that more extensive polyposis is less amenable to adequate treatment with topical corticosteroids. This confirms the hypothesis raised by Badia and Lund [9], who stated that a possible cause of the failure of clinical treatment with a topical corticosteroid could be the localized action of the drug, which would not reach all NP sites.
Thus, cases of extensive NP should not be treated exclusively with topical corticosteroids, but rather with adjuvant therapy, such as pulse therapy with a systemic corticosteroid [3] or prolonged antibiotic therapy [16]. Surgical treatment should be contemplated in cases that are refractory to clinical treatment.

The nasal extension of NP at endoscopy, the intensity of the nasal symptoms and the presence of associated allergic symptoms are not sufficient to predict the clinical response to topical corticosteroid treatment. The site of extension of the polyps seems to be an important aspect, since polyps with large extension to the nasal cavity (evaluated through endoscopy) might be more amenable to clinical improvement than extensive polyps at sinus cavities (evaluated through CT scans).
The concern about the mechanisms of NP resistance to glucocorticosteroids is currently increasing because they continue to be the most effective medication for the treatment of this condition. Cellular genetic and epigenetic mechanisms leading to corticosteroid resistance are being increasingly discussed. However, studies that point out clinical events that might predict the corticosteroid response are also necessary. In the present study, the sinusal extension of NP significantly interfered to the treatment outcome.

CONCLUSIONS

Based upon this study, we can conclude that:
1) There was a statistically significant improvement of NP symptoms and reduction of polyp size observed by endoscopy after 2 months of treatment with topical budesonide.
2) Clinical improvement was not influenced by the sum of symptoms, allergic symptoms or polyp score before treatment.
3) Clinical improvement was negatively influenced by the tomographic extension of NP.

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