

Short course of systemic corticosteroids in sinonasal polyposis: A double-blind, randomized, placebo-controlled trial with evaluation of outcome measures

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Background: Topical and systemic corticosteroids are the first choice in medical treatments for sinonasal polyposis, but surprisingly, there is no high-level evidence for the efficacy of oral corticosteroids.

Objective: The aim of this study was to establish the efficacy of a short course of oral prednisolone in ameliorating the symptoms of sinonasal polyposis, as well as reducing mucosal inflammation assessed by means of nasendoscopy and magnetic resonance imaging (MRI). A secondary aim was to evaluate the relationship between outcome measures.

Methods: Subjects with symptomatic endoscopically diagnosed sinonasal polyposis received 50 mg of prednisolone daily for 14 days or placebo. Outcome was quantified by using the modified 31-item Rhinosinusitis Outcome Measure questionnaire, physician's assessment, nasendoscopy with photography, and MRI.

Results: There were 20 subjects in each treatment group. Only the prednisolone-treated group showed significant improvement in nasal symptoms ($P < .001$). The Rhinosinusitis Outcome Measure score improved in both groups, but the prednisolone-treated group had significantly greater improvement than the placebo group ($P < .001$). Objectively, there was significant reduction in polyp size, as noted with nasendoscopy ($P < .001$) and MRI ($P < .001$), only in the prednisolone-treated group. The outcome measures correlated with each other; the highest level of correlation was between the objective measures of nasendoscopy and MRI ($R^2 = 0.76$, $P < .001$). There were no significant adverse events.

Conclusion: This trial clearly establishes clinically significant improvement in the symptoms and pathology of sinonasal polyposis with a short course of systemic corticosteroids.

MRI scanning and quantitative nasendoscopic photography are objective and valid tools for assessing the outcome of treatment in this condition.

Clinical implications: A 14-day course of 50 mg of prednisolone is safe and effective therapy for symptomatic nasal polyposis. (J Allergy Clin Immunol 2006;118:128-33.)

Key words: Nasal polyps, corticosteroids, medical treatment, 31-item rhinosinusitis outcome measure, endoscopy, magnetic resonance imaging, outcome, randomized, double blind, placebo controlled

Sinonasal polyposis is a chronic disorder with a major effect on the quality of life of affected individuals. The management options for sinonasal polyposis are medical treatment, surgery, or a combined approach. It is a common practice to use systemic or topical corticosteroids as the first therapeutic choice, followed by surgery for resistant or recurrent cases. There is good evidence, in the form of randomized controlled trials, to support the use of topical nasal corticosteroids.^{1,2} Short courses of systemic corticosteroids are also widely used in clinical practice to provide rapid relief of symptoms, followed by the use of long-term topical corticosteroids.^{3,4} The efficacy of systemic corticosteroids is well reported; there is usually a dramatic reduction in symptoms, and it has been termed a *medical polypectomy*. However, it is surprising to note that there have been no published randomized placebo-controlled trials of systemic corticosteroids to confirm their efficacy on the symptoms and pathology of sinonasal polyposis.⁵

Various outcome measures have been used to analyze the results of intervention in this patient population.^{6,7} Most of these are questionnaire-based visual analogue scores of symptoms and quality of life. Intranasal polyps can be visualized by means of nasendoscopy, and sinonasal polyp tissue can be shown by using imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI); these approaches offer more objective methods of measuring treatment response. Many previous studies have shown a poor relationship between symptoms and objective measurements of pathology.⁸⁻¹⁰ In this article we describe a randomized,

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Abbreviations used

CT: Computed tomography
MRI: Magnetic resonance imaging
RSOM-31: Thirty-one-item rhinosinusitis outcome measure

double-blind, placebo-controlled trial of a short course of systemic corticosteroids, using as outcome measures the physician history, a patient questionnaire (the 31-item Rhinosinusitis Outcome Measure [RSOM-31]), MRI of the paranasal sinuses, and nasendoscopy. We have used a novel but simple method of nasendoscopic quantification of nasal polyp size, validated it against the other outcomes, and assessed the correlation between these measures.

METHODS

Patients

Forty-one subjects aged 18 to 65 years drawn mainly from allergy outpatient clinics who had symptomatic polyp disease diagnosed on nasendoscopy were included in the study. Exclusion criteria included previous use of oral steroids, unstable asthma, recent sinus surgery, acute infection within 1 month of recruitment, polyps caused by cystic fibrosis or mucociliary disorders, diabetes mellitus, cataract, glaucoma, fungal sinusitis, contraindications for MRI scanning, or any other significant comorbid condition that contraindicated the use of systemic corticosteroids. Subjects were allowed to continue the use of regular antihistamines, topical corticosteroids, or both. These patients were randomized by the hospital pharmacy to receive the study medication, which consisted of 50 mg of prednisolone or placebo daily for 14 days, and were blinded to their treatment status. This dose was selected as the maximum safe dose in adults that could be given for 14 days without inducing lasting adrenal suppression, thus allowing drug cessation without tapering.¹¹ Immediately on completion of the study investigations, the subjects were unblinded by an independent physician (study personnel were not informed of the patient's treatment status until all assessments were completed) and offered open treatment; all who had taken placebo were offered and accepted a course of prednisolone. Therefore in this study we did not undertake long-term follow-up of the subjects because all of them ultimately received prednisolone. The study was approved by the Medical Ethics Committee of the Royal Adelaide Hospital.

Physician assessment

Baseline assessment included full history; physical examination; ear, nose, and throat examination; skin prick testing; pregnancy testing (in female subjects of childbearing age); and blood glucose level measurement. Physician assessment at both entry and exit visits included grading nasal symptoms (6 scales: congestion, hyposmia, rhinorrhea, sneezing, postnasal drip, and itch) and other related symptoms (4 scales each for eyes and ears and 2 scales for general well-being) on a visual analog scale of 1 to 5 (mild to severe) based on the patient history. Adverse symptoms were recorded at visit 2, and subjects were also asked about symptoms after cessation of the study drug on subsequent follow-up.

RSOM questionnaire

The RSOM-31 questionnaire⁶ assesses 6 nasal symptoms (congestion, rhinorrhea, sneezing, hyposmia, postnasal discharge, and thick nasal debris) and 25 other symptoms in several domains (ocular,

ear, sleep, general symptoms, practical problems, and emotional consequences) by using a visual analog scale score of 1 to 5 for symptom severity and 1 to 5 for symptom importance. Patients were asked to fill out the questionnaire at baseline and after 2 weeks of therapy, without assistance from the medical personnel. We used a modification of this questionnaire; subjects had difficulty understanding the importance parameter, and therefore we used severity scores only. We note that in a subsequent development of the RSOM-31 by the group that developed it, the 20-item Sinonasal Outcome Test score,⁷ the importance parameter was relinquished. We did not use the Sinonasal Outcome Test because it omits questions on nasal congestion and anosmia, cardinal features of polyposis.

MRI of the paranasal sinuses

MRI of the paranasal sinuses was done immediately before and after 2 weeks of prednisolone treatment. T1 and T2 scans were scored by 2 experienced observers who were blind to treatment status. Pretreatment and posttreatment scans were scored independently according to defined criteria; each sinus group (maxillary, ethmoid, frontal, and sphenoid), right and left, and the nasal cavity itself was scored as follows, which produced a theoretic maximum score of 40: score 0, normal—mucosa of less than 1 mm and no polyp; score 1, mild—mucosa of 1 to 3 mm and a polyp of less than 6 mm; score 2, moderate—mucosa of 3 to 6 mm and a polyp of 6 to 12 mm; score 3, severe—mucosa of greater than 6 mm and a polyp of greater than 12 mm; and score 4, obliterated—sinus/nasal cavity filled with polyp/mucosa.

Nasendoscopy

Nasendoscopy was carried out immediately before commencement of prednisolone treatment and after 2 weeks of treatment by using an Olympus rigid telescope (30°, 4 mm; A7595A; Tokyo, Japan) with a 300-W Xenon light source (CLV-S30), a video adapter 1.2× (AR-SX12E), a camera control unit (OTV-SX2C), and a triple-chip camera head (MAJ-387N). Images were recorded with a Sony Digital Still Image Capture Adaptor (MVC-FDR3E; Tokyo, Japan). To document the position at which images were captured, the nasendoscope was calibrated in centimeters with an indelible marker, and the distance of passage of the endoscope past the nasal tip in centimeters, as well as the angle (superior, middle, and inferior), was recorded. After treatment, repeat photographs were taken by using the same distance/angle measurements to reproduce the original field of view as closely as possible. For scoring, we compared pretreatment and posttreatment groups of images paired for each study subject according to comparable fields of view. The photographs were viewed on the computer screen; observers were blind to active/placebo treatment status and to pretreatment/posttreatment order. Observers selected the group of images showing the more extensive/larger polyps and estimated the percentage reduction in polyp size in the other group. The results from the assessment of 4 clinicians (3 immunologists and 1 ear, nose, and throat surgeon) were pooled for analysis. The intraclass correlation analysis showed a good measure of consistency among the 4 raters (0.96). The measure of absolute agreement among the raters was 0.57. The predicted reliability of these measurements using a mean of 3 replicate measurements resulted in a reliability of 0.80.¹² Grades were also assigned at the time of endoscopy according to the system of Lund and Mackay¹³; however, polyp grading was not suitable for evaluation of treatment because it is a qualitative scale.

Statistics

The χ^2 and Student *t* tests were used to determine the significant differences between the 2 treatment arms. Comparison between different outcome measures was done by using the Spearman correlation coefficient. Intraclass correlation analysis was estimated as part of an

TABLE I. Baseline characteristics of the study population

Baseline characteristics	Active treatment group (n = 20)	Placebo group (n = 20)
Average age, y	49 ± 13	48 ± 12
Age of symptom onset, y (range)	30.05 (12-61)	29.4 (16-60)
Sex, male/female	7/13	12/8
Past recurrent sinus infections	10	09
History of atopy	18	20
History of aspirin sensitivity	2	6
Smokers	3	6
Previous polyp operations	17 in 8 subjects	23 in 13 subjects
Use of intranasal corticosteroids	11	11
Use of antihistamines	7	6
Prior use of nasal decongestants	5	4
Other modalities*	8	7

*Saline washes, mucolytics, and alternative remedies.

ANOVA analysis with Statistica version 6.1 (StatSoft Inc, Tulsa, Okla). A *P* value of less than .05 was considered a significant difference. Power calculations using conservative assumptions based on previous studies¹⁴ required recruitment of 33 subjects in each treatment group to achieve a power of 90%. We could recruit only 20 patients in each arm in the available time; however, this did produce statistically significant results.

RESULTS

Patients

A total of 41 subjects were randomized to receive either 50 mg of prednisolone or placebo for 14 days. One subject (in the placebo group) withdrew within the first week because of a lack of efficacy; evaluable data were not available for this subject. Relevant baseline characteristics were similar in both groups (Table I).

RSOM scores

All 31 parameters of the RSOM were averaged for each subject; the group mean of these average scores was higher in the placebo group than in the active group before treatment, but this was not significant (2.2 vs 1.87, *P* = .25; Fig 1, A). Significant improvement was noted in the total RSOM score with both active and placebo treatments (53% improvement [*P* < .001] vs 21% improvement [*P* < .005]). Importantly, it was found that the subset of nasal-specific RSOM scores (6 parameters) showed significant improvement only in the group treated with prednisolone (64% [*P* < .001] vs 11% [*P* = not significant] in the placebo group; Fig 1, B). Individual symptoms of stuffy/blocked nose, runny nose, sneezing, decreased sensation of smell, and postnasal drip showed significant improvement after treatment with corticosteroids (*P* < .05) as opposed to placebo. By using the average of the 6 nasal subscores, 95% of prednisolone-treated patients improved

by more than 20%, whereas 5% deteriorated (63% improved by >40%). In the placebo group 37% improved by more than 20%, 53% did not change, and 10% deteriorated (16% improved by >40%). An improvement of greater than 20% is considered clinically significant.⁷

Physician history assessment scores

Symptom scores were not significantly different between the 2 groups before treatment. After treatment, both groups showed significant symptom score reduction, but the degree of improvement was significantly greater in the actively treated group (37% vs 16%, *P* < .001). The nasal-specific physician history assessment score showed similar improvement, again significantly greater in the actively treated group (38% vs 12%, *P* < .001). The difference between posttreatment scores in the prednisolone versus placebo group was significant (mean score, 1.56 vs 2.48; *P* < .001).

MRI

Before treatment, the mean MRI score for the entire group was 21 (of 40); the lowest score was 5, and 97% of the group had scores of 8 or greater. Mean MRI scores did not change in the placebo group (Fig 1, C; *n* = 19 evaluable scan pairs), whereas there was a 45% reduction in the score for the prednisolone-treated group (*n* = 17, *P* < .001). Scores reduced by more than 20% in 78% of prednisolone-treated individuals but only in 5% of placebo-treated individuals. By these criteria, 4 (22%) of the prednisolone-treated patients could be classified as nonresponders; however, no score worsened, and these 4 individual scores reduced by between 10% and 20%.

Nasendoscopy

Paired, evaluable, nasendoscopic photographs were available for 15 and 17 patients in the prednisolone- and placebo-treated groups, respectively. As shown in Fig 1, D, there was a significant reduction in polyp size, as assessed by means of nasendoscopy, in the prednisolone-treated group (mean change, 48%), with no change in the placebo-treated group (mean change, 0%). Ten (63%) patients in the prednisolone-treated group had more than a 40% reduction in polyp size. One patient in the placebo-treated group had a 50% reduction, and 2 patients showed a 10% reduction in polyp size. There was an increase in polyp size in 8 (48%) patients treated with placebo. No enlargement of the polyps was noted in the prednisolone-treated group.

Correlation of outcome measures

For each outcome parameter, the change in score between pretreatment and posttreatment assessments was expressed as a percentage. Correlations between these changes were then calculated with Spearman ranking (Table II). Relatively high correlation values were obtained for the 2 objective outcome measures of MRI and nasendoscopy and for the change in scores of the physician's and the patient's assessment of nasal-specific symptoms. In general, somewhat lower correlation scores were

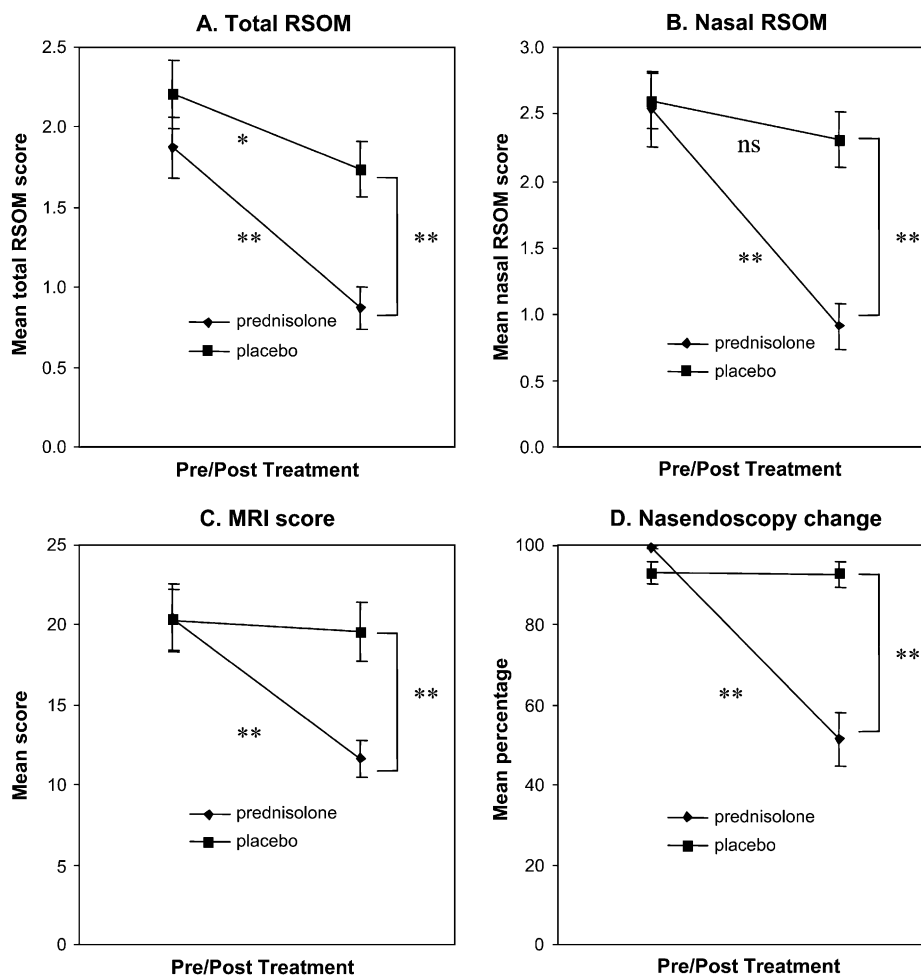


FIG 1. Scores at baseline and after treatment of subjects with sinonasal polyposis with 50 mg of prednisolone or placebo daily for 14 days. **A**, Mean $\pm$ SEM of average (modified) RSOM-31 score for all 31 parameters ($n = 20$ in each group). **B**, Mean $\pm$ SEM of average RSOM score for nasal subscales only (6 parameters, $n = 20$ in each group). **C**, Mean $\pm$ SEM MRI score ($n = 17$ in prednisolone-treated and $n = 19$ in placebo-treated patients). **D**, Mean $\pm$ SEM percentage change in polyp size on nasendoscopy (largest polyps normalized to 100%, $n = 15$ in prednisolone-treated and $n = 17$ in placebo-treated patients). * $P < .05$; ** $P < .005$ (Student t test).

obtained for the relationship between change in symptoms and the 2 more objective tests, yet positive and significant correlations were still found in most cases. It should be noted that because of the sample size, the 95% CIs of the 2 values are wide, so that only limited conclusions can be drawn about the relative strength of correlations.

Adverse effects of prednisolone

Insomnia was noted more frequently in subjects being treated with prednisolone (Table III). Other side effects were infrequent and no different than those with placebo. No patient reported significant adverse symptoms during the days immediately after cessation of prednisolone.

DISCUSSION

This is the first randomized, double-blind, placebo-controlled trial to quantify the efficacy of a short course of

high-dose oral corticosteroids in sinonasal polyposis. The outcome measures used were clinician assessment based on patient history, symptom scores on a patient questionnaire (RSOM-31), change in the size of intranasal polyps determined by means of nasendoscopy, and pretreatment and posttreatment MRI scans with scoring of the extent of sinonasal mucosal disease.

Our patient group included those with endoscopically visible chronic nasal polyps. Patients were mostly drawn from an allergy clinic, hence the high rate of atopy. However, a previous open-label trial¹⁴ has indicated that atopic status does not increase the likelihood of response to corticosteroids. Polyps were of grades 1 to 4.¹³ Previous systemic corticosteroid treatment was an exclusion criterion, so that enrollment would not be biased toward known corticosteroid responders. MRI scans indicated that intranasal polyps were accompanied by significant sinus mucosal abnormalities. Radiologic mucosal thickening is seen in

TABLE II. Spearman correlation between outcome measures in sinonasal polyposis

Outcome parameters	R ²	CI	P value
Total RSOM vs PAS	0.48	0.19 to 0.70	<.005
vs PASn	0.67	0.45 to 0.82	<.001
vs NE	0.45	0.10 to 0.70	<.05
vs MRI	0.41	0.10 to 0.65	<.05
Nasal scores vs PASn	0.67	0.45 to 0.82	<.001
vs NE	0.52	0.18 to 0.74	<.005
vs MRI	0.46	0.15 to 0.68	<.005
PAS vs NE	0.42	0.12 to 0.66	<.01
vs MRI	0.54	0.22 to 0.76	<.01
PASn vs NE	0.63	0.38 to 0.79	<.001
vs MRI	0.36	−0.01 to 0.64	NS
NE vs MRI	0.76	0.55 to 0.88	<.001

Correlations were determined between percentage change in each of these parameters across the entire group (active and placebo treated).

Nasal scores, Patient-assessed nasal symptom scores (nasal subset of RSOM questionnaire); *PAS*, physician assessment scores; *PASn*, physician assessment of nasal symptoms; *NE*, nasendoscopy; *NS*, not significant.

some healthy individuals, and a score of up to 4 (of 24) is part of the range of normality in the Lund and Mackay CT scan scoring system.¹⁵ By extrapolation, a score of up to 7 of 40 might be considered normal in our system; however, 97% of our subjects had a score of 8 or greater.

The treatment of sinonasal polyposis is debated. Surgical treatment, medical treatment, or both have been advocated as the treatment of choice. However, sinonasal polyposis is a chronic recurrent disease and often requires multiple surgical procedures. In a long-term follow-up evaluation of 41 patients, it was found that 85% of patients had persistent disease after 20 years, with 8 patients requiring more than 10 surgical procedures each during this period.¹⁶ Medical treatment has been shown to be of comparative efficacy to the surgical approaches in terms of reduction in the symptomatic scores, improvement of quality of life, and long-term outcome in randomized controlled trials¹⁷⁻¹⁹ and large case series.³ Although there have been many published review articles advocating the use of systemic corticosteroids for sinonasal polyposis, either as primary therapy or before surgery,^{5,20,21} we were surprised to find no level 1 evidence. One uncontrolled study addressed the efficacy of this treatment, showing a significant effect for some months, with an improvement of symptoms in 72% of the subjects and a reduction of polyp size and sinus opacification on the CT scan in 52%.¹⁴ Several randomized studies (not blinded or placebo controlled) demonstrated efficacy of combined systemic and topical corticosteroids.^{3,4,19} This is the first double-blind, placebo-controlled study to demonstrate the effects of a short course of corticosteroids on the symptoms of sinonasal polyposis, as well as the size of polyps on MRI and nasendoscopy.

The outcome measures used in the current study included subjective measures (RSOM and physician assessment scores) and objective measures (nasendoscopy and MRI). The aim was to identify the usefulness of these

TABLE III. Adverse events

Adverse events	Active treatment	Placebo
Insomnia	8*	2
Mood disturbance	5	2
Headache	2	0
Dyspepsia	3	2
Increased appetite	2	0
Fatigue	2	0
Backache	1	0
Diarrhea/GI disturbance	2	1
Acne	1	0
Edema feet	1	0

**P* < .05.

GI, gastrointestinal.

measures to detect a change over a period of time and to correlate them with each other. There was a statistically significant improvement in the physician scores and total RSOM scores in both the placebo-treated and actively treated groups of patients, but the level of improvement was significantly greater in the prednisolone-treated group. Importantly, the nasal-specific subset of the RSOM scores improved with prednisolone treatment only. We chose to use the RSOM-31 because it includes symptoms relevant to sinonasal polyposis, in particular anosmia and congestion. In the current study the nasal-specific dimensions of the RSOM were more responsive to prednisolone than the total score, suggesting a limitation of applying a global QOL measure in a short-term study.

In the recent European Academy of Allergology and Clinical Immunology position paper,²² it has been agreed that for the purpose of research, the differentiation between chronic rhinosinusitis and nasal polyposis must be based on outpatient endoscopy. There have been many published and validated scoring systems for the nasendoscopic staging of nasal polyposis.^{13,23} We decided to use a different methodology because the aim of our study was to document the difference in the size of the polyps after treatment. Photographs were taken by video capture and saved to disk, with controlled positioning of the field of view, allowing offline polyp size comparisons to be made. This technique was reliable, and there was good correlation between observers. This methodology is very accessible with current digital technology, and having been validated, it is applicable for future use in research on medical treatment of polyps, as well as for outpatient management and follow-up.

MRI was essential to this study to obtain an objective assessment of the total polyp mass, including sinus polyposis. Although the improvement in patients was noted in both arms by the subjective measures of RSOM scores and physician assessment, objective improvement with nasal endoscopy and MRI was noted only in the actively treated group. Moreover, the degree of change identified by using MRI correlated with nasal endoscopy findings. This underscores the importance of having both subjective and objective measures of assessment in

analysis of treatment response in this condition. The placebo response is a well-known phenomenon in chronic diseases and should be countered with objective measures to examine change in the underlying pathology. The correlation of nasal endoscopy (which measures intranasal polyposis) with MRI (measures predominantly sinus disease) is consistent with a common pathology in the nasal and sinus mucosa.

Previously, a lack of a direct relationship between the severity of patient symptoms and the extent of sinonasal polyposis determined by using imaging methods has been noted.⁸⁻¹⁰ These studies were based on static measurements. In the present study correlation was seen between self-assessed improvement in symptoms (both nasal and global) and change in the size of nasal and sinus polyps, but this correlation was in the moderate range. Interestingly, the 4 subjects who did not respond to prednisolone, as determined on the basis of MRI criteria, did report subjective improvement (nasal scores reduced by 29% to 86%). It is noteworthy that the majority of our patients were atopic, suggesting the possibility that treatment of allergic symptoms with prednisolone might partially account for the relatively poor correlation between symptom scores and objective measures. However, the improvement of symptom scores in the placebo group suggests that this effect was probably minor. Numbers were too small to perform subgroup analysis to determine predictors of nonresponse.

No significant adverse effects were seen in this study. The dose of corticosteroid in this study was slightly higher than that seen in most previously published studies, and tapering was not used. The dose was chosen after reviewing the literature regarding corticosteroid use in asthma,¹¹ showing no evidence of adrenal suppression at a similar dose after a short course. Moreover, no clinically significant symptoms or signs of adrenal suppression were found in our study. There is a risk of osteonecrosis after a short course of oral corticosteroids, but this appears to be extremely rare.

The current study was not designed to look at the long-term outcome of these patients. There is a considerable published literature regarding the efficacy of short-term systemic steroids followed by intranasal steroids.^{3,4,14,17,19} The duration of the effect of systemic corticosteroids is varied and usually lasts between 1 and 6 months. This study fulfills the long-awaited need for evidence of the efficacy of systemic steroid therapy in sinonasal polyposis. It also underlines the importance of using a combination of objective and subjective measures of outcome while analyzing the effect of an intervention in studies on sinonasal polyposis. Future research might focus on the optimal dose or duration of prednisolone therapy, as well as the effect of combined treatment with systemic and nasal steroids on the subsequent requirement for surgery.

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