Rhinology, 23, 49-59, 1985

Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy

A randomized, double blind, parallel, placebo controlled study

G. Dingsør, J. Kramer, R. Olsholt and T. Søderstrøm, Bergen-Odo, Norway

SUMMARY

This double blind, parallel study compared flunisolide 2 × 25 mcg in each nostril twice daily, with placebo in the prophylaxis of nasal polyposis recurrence after surgery. The treatment lasted for 12 months. The study was conducted according to the recommendations of the Declaration of Helsinki, and the patients gave verbal consent to participate. The study was reviewed by the Norwegian Medicines Control Authority.

Forty-one patients with first or recurrent polypectomy were enrolled. Thirty-seven patients completed the 12 months' period. Four patients dropped out prematurely for reasons unrelated to the test drug.

Flunisolide was significantly superior to placebo in preventing recurrence of polyps during 6 to 12 months' treatment, both with respect to number ($p = 0.05$) and size ($p = 0.03$) of polyps.

Nasal symptoms of sneezing and stuffiness decreased significantly for flunisolide treated patients during treatment. In the placebo group, there was a significant increase in stuffiness throughout the year. For runny nose, there was no difference between the treatments.

Six flunisolide patients and 10 placebo patients reported side effects during the one year treatment, transient mild itching being the most common complaint. Three cases of secretion with bloody traces were reported. No patient withdrew for drug related reasons.

In this study, flunisolide was significantly more effective than placebo in preventing recurrence of nasal polyposis during one year's treatment after polypectomy.

INTRODUCTION

Nasal polyposis is regarded as a common suffering, but our knowledge of the polyp formation and its etiology is still in dispute. The condition is troublesome to the patient as the polyp often develop to block the nasal passages completely, and must be removed surgically. Recurrent polypectomies are often required because there is a frequent tendency to recurrence for the polyposis. Due to the

temporary relief after surgery, there has been a search for treatment to prevent recurrence, and the steroids have been regarded to be of value.

Two short term trials with beclomethasone diproprionate (Mygind et al., 1975; Deuschl and Drettner, 1977) demonstrated beneficial effect over placebo of clinical symptoms, but no changes of the polyps themselves. A long-term treatment follow-up study (Pedersen, 1976) indicated good symptom control, but perhaps doubtful effect on polyps of bigger size. Virolainen et Puhakka (1980) showed in a one year study that normal patency and absence of polyps were mostly controlled by beclomethasone diproprionate nasal spray.

A placebo-controlled study with flunisolide in 22 patients (Drettner, 1982) showed beneficial effect in symptom score, but a tendency for decreasing the polyps in the flunisolide group was not statistically significant.

The documentation for the topical steroids in treatment of allergic and some forms of non-allergic rhinitis is considerable (Mygind, 1982) and long-term studies with flunisolide have stated that there is no evidence of any systemic effects of the steroid in therapeutic doses (Sahay, 1980).

The aim of the present study was to evaluate the prevention of recurrence of nasal polyposis after polypectomy followed by 1 year's treatment with Lokilan nasal spray (flunisolide) compared to placebo.

METHODS

This study was performed in two ENT-departments, at Florida Hospital in Bergen and Ullevål Hospital in Oslo. It was a placebo controlled, double blind, parallel design, comparing the efficacy of flunisolide nasal spray with that of vehicle spray. Each patient was followed for one year after surgery of nasal polyps. Patients were randomly assigned to one of the two treatment groups, according to a computer-generated code.

Male or female patients aged 18 to 65 years were to be recruited. The patients' diagnosis was nasal polyposis, and patients with first time or recurrent surgery were included. All polypectomies were carried out under local anesthesia. Nasal and/or sinus infections were to be cleared clinically by appropriate antibiotic and decongestant therapy prior to entry to the trial.

Excluded were patients with radical surgery of the maxillary sinus, as well as recurrent epistaxis. Also patients who had received corticosteroids the last three months were excluded, together with patients with unstable treatment regimens for severe asthma or allergic rhinitis, or if other conditions made use of corticosteroids contraindicated. Patients with tuberculosis, active peptic ulcer, ocular herpes simplex, chickenpox, acute psychosis, or any major uncontrolled illness were not included in the trial. Neither were females who were or intended to become pregnant or were breast feeding during the trial period, or patients unlikely to adhere to the protocol.

Patients were seen 4 weeks after surgery and then 6 weeks, 3, 6, 9 and 12 months thereafter.

Flunisolide was provided as a 0.025% solution, Lokilan® nasal spray "Astra-Syntex". The dosage was 2 sprays in each nostril morning and evening, each spray containing 25 mcg flunisolide to give a total of 200 mcg per day. The placebo was administered as a vehicle spray identical in appearance to that containing flunisolide, and according to the same dosing schedule.

Patients were not allowed to use other local corticosteroid medication while on study medication, and use of systemic symptomatic therapy was to be reported on the patient record forms, together with other concomitant medication.

Hyposensibilization therapy was allowed as long as the dose frequency was stabilized. The patients, prior to entering the study, were informed of the nature of the drug, possible side effects, and the meaning of the trial and gave verbal consent to participate. The study was conducted according to the recommendations of the Declaration of Helsinki, and the patients had the freedom to withdraw at any time and of any reason. The Norwegian Medicines Control Authority reviewed the scientific aspects of the study before start.

Upon admission the patients' demographic data, allergic and polyposis history, and medication history were recorded.

The presence and size of polyps on admission were examined by anterior rhinoscopy of the nasal cavities, and a visual judgement of the nasal mucosa and secretion was made. Nasal secretion was cultured for bacteria. Symptoms of sneezing, stuffiness, and runny nose were graded as mild, moderate or severe.

An ACTH-test was made for cortisol evaluation. The number of eosinophilic granulocytes in blood were counted, and sinus X-rays were taken. The patients were instructed in the use of the nasal spray, and given a record card to fill in each week. Information recorded were severity of the nasal symptoms: sneezing, stuffiness, and runny nose, graded as none, mild, moderate or severe. These gradings were defined. Use of any concomitant medication was also recorded together with sleep disturbances because of symptoms, or comments about infections, colds etc.

At each follow-up visit, after 6 weeks, 3, 6, 9 and 12 months, a physical examination was made by anterior rhinoscopy, amd polyp number, size and nasal symptoms were recorded. Infections or common cold during the last treatment period were recorded with the duration of these. Side effects were elicited with the indirect question "How is the treatment suiting you?" Any side effects were evaluated for severity and relationship to the test drug. Changes in concomitant medication usage were recorded.

After 6 and 12 months an ACTH-test was done, and eosinophils counted. Nasal secretion was cultured for bacteria. An overall evaluation of the treatment was made and recorded as: total control of nasal symptoms, substantial, but not com-

plete control, minor control, minor aggravation or substantial aggravation of nasal symptoms. Polyp size was graded as substantial or minor decrease, no change, minor or substantial increase. After 12 months a new X-ray of the sinuses was taken.

The side effects which occured during the trial were recorded, their severity, duration, and the investigators' opinion of the relationship of the effect to the medication.

For patients who withdrew prematurely from the study, time and reason for drop-out were recorded. Patients dropping out for reasons unrelated to medication were allowed to be replaced. Patients dropping out because of side effects or lack of effect were to be included in the final analysis, and not replaced.

Per patient data listings were provided and summary statistics computed for medical and allergy history data, laboratory examination results and side effects.

The comparability of the two treatment groups at admission was to be analyzed, using t-test for continuous variables, Mann-Whitney two sample test for ordered categorical variables and X^2- or Fischer's exact-test for discrete variables.

The efficacy analysis comparing the two groups was done using Mann-Whitney two sample test for ordered categorical variables, X^2- or Fischer's exact-test for linary responses. Baseline-treatment comparisons were performed using Wilcoxon matched pairs signed rank test for ordered variables or McNemars test for linary coded variables.

RESULTS

Forty-one patients were admitted to the trial. Thirty-seven patients completed one year's treatment. Of the four patients terminating prematurely, three had additional steroid therapy (two of them because of worsening of asthma) and the other wished to discontinue because of an infection and a suspicion of lung tumor. This was later disproved.

For all patients, the age ranged between 18 and 73 with a mean of 49,4 years. Thirty-six males and five females were entered. Patients had a mean disease duration of 9 years, ranging from 1 to 20 years. Nine patients had their first polypectomy, the total mean was 1,7. The two treatment groups did not significantly differ on any of these variables at admission. No significant difference between the two groups was found in allergic history.

Tables 1 to 3 summarize the rhinoscopic findings at baseline and during treatment. Table 2 shows the number of polyps at each visit. Patients in the placebo group showed statistically significant increase from admission in number of polyps at visit 3 to 5. In the flunisolide group no such change was observed. At visit 4 and 5 there is a significant difference between the treatment in favour of flunisolide.

Table 2 summarizes the size of polyps during treatment compared to baseline.

Table 1. Number of polyps during treatment, right and left side summarized.

	flunisolide (n = 20)	P-value*	placebo (n = 21)	P-value†	P-value††
baseline					
no polyps	13		13		0.84
single polyps	5		4		
multiple polyps	1		4		
single + multiple polyps	0		0		
2 × multiple polyps	1		0		
visit 1					
no polyps	14	0.50	10	0.72	0.48
single polyps	4		6		
multiple polyps	2		3		
single + multiple polyps	0		1		
2 × multiple polyps	0		0		
not stated/drop out	0		1		
visit 2					
no polyps	13	0.55	11	0.14	0.66
single polyps	1		4		
multiple polyps	3		4		
single + multiple polyps	1		0		
2 × multiple polyps	0		1		
not stated/drop out	1		1		
visit 3					
no polyps	11	0.89	10	0.05*	0.33
single polyps	3		2		
multiple polyps	3		5		
single + multiple polyps	1		0		
2 × multiple polyps	0		2		
not stated/drop out	2		2		
visit 4					
no polyps	13	0.60	9	0.01*	0.05*
single polyps	1		2		
multiple polyps	4		3		
single + multiple polyps	0		2		
2 × multiple polyps	0		3		
not stated/drop out	2		2		
visit 5					
no polyps	13	0.55	9	0.008*	0.05*
single polyps	2		2		
multiple polyps	1		1		
single + multiple polyps	0		2		
2 × multiple polyps	1		5		
not stated/drop out	3		2		

† = change from baseline - Wilcoxon matched pairs test.
†† = difference between treatments - Mann-Whitney U-test.

Table 2. Size of polyps before and during treatment, right and left side summarized, mean ± SD

	flunisolide (n = 20)	P-value**	placebo (n = 21)	P-value**	P-value***
size of polyps latest operation	4.4 ± 1.1 (n = 19)		3.6 ± 1.3		0.04
size of polyps during treatment					
baseline	0.4 ± 0.7		0.5 ± 0.7		0.58
visit 1	0.3 ± 0.6	0.46	1.0 ± 1.3 (n = 20)	0.11	0.08
visit 2	0.5 ± 0.8 (n = 19)	0.50	0.8 ± 0.9 (n = 20)	0.12	0.41
visit 3	0.6 ± 0.8 (n = 18)	0.35	1.2 ± 1.5 (n = 19)	0.02*	0.33
visit 4	0.6 ± 1.0 (n = 18)	0.50	1.3 ± 1.6 (n = 19)	0.01*	0.10
visit 5	0.4 ± 0.9 (n = 18)	0.94	1.7 ± 1.9 (n = 19)	0.005*	0.03*

* = score for *one* nostril: 0 = no polyps
1 = small polyps
2 = moderate polyps
3 = large polyps.
** = change from baseline - Wilcoxon's matched pairs test.
*** = difference between treatments - Mann-Whitney U-test.

The mean size increased significantly in the placebo group, but not in the flunisolide group. The difference between groups is significant at visit 5, after 12 months.

Table 3 summarizes the appearance of the nasal mucosa during treatment. There was difference between groups, except for visit 5, where significantly more patients showed a polypoid mucosa in the placebo group.

For nasal secretion and sneezing there were a decrease in the flunisolide group and no corresponding decrease in the flunisolide group and no corresponding decrease in the placebo group, but the difference was not significant.

Table 4 summarizes the mean score for stuffiness. There was statistically significant increase in stuffiness from admission in the placebo group, starting at the first follow up visit and becoming more marked through the year. This increase did not occur in the flunisolide group. After one year's treatment the difference between treatments reached significance. The scores for runny nose showed no difference between the groups.

In overall control of symptoms, there was no difference between the patients in the two groups after 6 months' and 1 year's treatment.

There was no change in positive pathogen bacteria cultures either within or between groups.

Further, there was no statistical difference between the flunisolide treated and the vehicle treated patients as far as X-rays findings are concerned.
A few patients experienced nasal infections during the year, but there were no statistically significant differences between groups. The same applied for common cold.
There was no difference between the groups on number of patients with eosinophilia, using a count of 450 as upper normal limit. No connection was shown between high eosinophil values and steroid response.

Table 3. Conditions of nasal mucosa during treatment.

	flunisolide	placebo	P-value (between treatments chi-square-test)
normal			
baseline	10 (n = 20)	9 (n = 21)	0.63
visit 1	12 (n = 20)	9 (n = 20)	0.34
visit 2	12 (n = 19)	8 (n = 20)	0.15
visit 3	11 (n = 18)	9 (n = 19)	0.40
visit 4	11 (n = 18)	10 (n = 19)	0.60
visit 5	10 (n = 18)	5 (n = 19)	0.07
odematous			
baseline	8 (n = 20)	9 (n = 21)	0.85
visit 1	6 (n = 20)	8 (n = 20)	0.51
visit 2	6 (n = 19)	11 (n = 20)	0.14
visit 3	6 (n = 18)	7 (n = 19)	0.82
visit 4	6 (n = 18)	6 (n = 19)	0.91
visit 5	8 (n = 18)	6 (n = 19)	0.42
athropic			(Fischer's exact test)
baseline	1 (n = 20)	1 (n = 21)	1.00
visit 1	0 (n = 20)	0 (n = 20)	1.00
visit 2	0 (n = 19)	1 (n = 20)	1.00
visit 3	0 (n = 18)	0 (n = 19)	1.00
visit 4	0 (n = 18)	1 (n = 19)	1.00
visit 5	0 (n = 18)	1 (n = 19)	1.00
polypoid			
baseline	1 (n = 20)	2 (n = 21)	1.00
visit 1	1 (n = 20)	5 (n = 20)	0.18
visit 2	1 (n = 19)	2 (n = 20)	1.00
visit 3	1 (n = 18)	2 (n = 19)	1.00
visit 4	1 (n = 18)	2 (n = 19)	1.00
visit 5	0 (n = 18)	6 (n = 19)	0.02*
congested			
baseline	3 (n = 20)	1 (n = 21)	0.34
visit 1	2 (n = 20)	1 (n = 20)	1.00
visit 2	1 (n = 19)	2 (n = 20)	1.00
visit 3	0 (n = 18)	3 (n = 19)	0.23
visit 4	0 (n = 18)	3 (n = 19)	0.23
visit 5	0 (n = 18)	4 (n = 19)	0.11

Table 4. Stuffiness during treatment, mean ± SD†

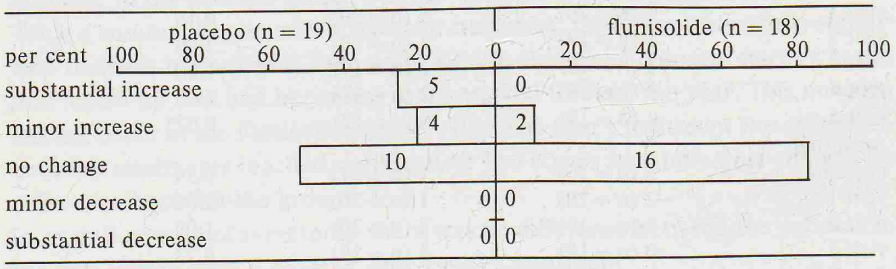
	flunisolide (n = 20)	P-value†† (change from baseline Wilcoxon (n = 18)	placebo (n = 21)	P-value†† (change from baseline Wilcoxon (n = 19)	P-value (between treatments Mann-Whitney)
baseline	0.5 ± 0.7		0.2 ± 0.5 (n = 20)		0.16
visit 1	0.3 ± 0.5	0.50	0.6 ± 0.7 (n = 20)	0.02*	0.25
visit 2	0.4 ± 0.5 (n = 19)	0.72	0.4 ± 0.5 (n = 20)	0.04*	0.91
visit 3	0.3 ± 0.5 (n = 18)	0.72	0.5 ± 0.6 (n = 19)	0.02*	0.34
visit 4	0.4 ± 0.8 (n = 18)	0.79	0.7 ± 0.7 (n = 19)	0.008*	0.16
visit 5	0.4 ± 0.6 (n = 18)	0.80	1.1 ± 1.0 (n = 19)	0.003*	0.05*

† score = 0 = none
1 = mild
2 = moderate
3 = severe

†† change from baseline:
tested for patients completed all visits.

No patients had plasma cortisol values outside the normal range at the visit after 12 months as measured by the Synacthen test.

Six patients in the flunisolide group reported 6 side effects. Five of them were mild itching after spraying, the last one secretion with blood traces during two weeks in the first period. Ten receiving vehicle reported 13 side effects during one year of treatment. Of these, 6 were mild itching, 1 severe itching, and 1 sore throat after spraying. Two patients complained of mild transient sneezing, two reported blood traces in secretion and one patient experienced mild nausea in the beginning of the treatment. No patients withdrew from the study because of side effects.



P-value between treatment (chi-square-test) = 0.03*

Figure 1. Overall evaluation, change in polyp(s) size - visit 12 months.

Figure 1 illustrates the changes in polyp size after 6 and 12 months. At the end of the 12 months' treatment period only two of the flunisolide patients stated minor increase, while the numbers for placebo are 4 minor and 5 substantial increase. The difference at the last recording is statistically significant.

DISCUSSION AND CONCLUSION

A beneficial effect of flunisolide for prevention of recurrence of nasal polyposis has been demonstrated by the present study. Flunisolide was superior to placebo in preventing new polyps developing, and Table 2 indicates that the flunisolide treatment also decreases the size of already present polyps as is the case for systemic steroids. The difference becomes statistically significant after 6 to 12 months' treatment, and this may explain why earlier studies over 3–6 months were not able to demonstrate any convincing effect. By extending the treatment period we have been able to demonstrate this beneficial effect statistically.

After one year's continuous treatment with flunisolide there seem to be no difference between the two groups in the mucosa appearance. This supports the earlier findings that there is little chance for developing atrophy in the mucosa tissue during topical steroid treatment.

The increasing stuffiness in the placebo group during treatment is probably mostly due to the recurrence of polyps. The difference between groups is significant after one year in favour of flunisolide, and this corresponds to the development of nasal polyposis in the placebo group.

Steroids are known to mask infections. In this study there is no difference detected in growth of pathogen cultures from the nasal secretion from those who received flunisolide and those on placebo. Neither was there any difference in the sinus X-rays taken. During treatment both groups developed more sinus affections, but this was due to mucus thickening, and not as sign of active infection.

The short ACTH-test has its weaknesses, but the full test requires measurements during 3 consecutive days which is difficult to manage with out-patients. The results from the test taken was regarded as clinically normal. There is nothing in these results that indicates that there was any systemic effect on the adrenal function after long-term use.

The most reported side effect was, as expected, mild itching just after spraying. It was not regarded as troublesome by any of the patients, and none of the patients stopped treatment because of side effect.

As a conclusion this trial demonstrates Lokilan® nasal spray as an effective and safe therapy for prevention of recurrent polyposis after polypectomy.

ZUSAMMENFASSUNG

Diese "double-blind", parallele Untersuchung, baut auf einem Vergleich von Flunisolide 2×25 mcg in den beiden Nasenoffnungen zweimal täglich mit

Placebo in der Prophylaxe bei erneuten Ausbruch von nasalen Polypen nach Chirurgie. Die Behandlung dauerte 12 Monate. Die Untersuchung erfolgte auf Empfehlung und Veranlassung der "Declaration of Helsinki" und die Patienten gaben ihr mündliches Einverständnis zur Teilnahme daran. Das Studium wurde von der Norw. Medizinischen Kontroll-Behörde überprüft.

Einundvierzig Patienten mit erstem oder erneutem Ausbruch von Polypen wurden registriert. Siebenunddreissig Patienten vollführten die 12 Monate-lange Untersuchungsperiode. Vier Patienten fielen vorzeitig aus, jedoch aus Gründen, die nichts mit dem getesteten Medikamente zu tun hatten.

Flunisolide war erheblich besser als Placebo zur Verhinderung von Rückfällen von Polypen in der Behandlungsperiode von 6–12 Monaten. Dies sowohl was Anzahl ($p = 0{,}05$), als Grösse ($p = 0{,}03$) der Polypen angeht.

Nasale Symptome von Niessen und Verstopfung wurden bei Flunisolide-behandelten Patienten bedeutend reduziert. In der "Placebo-gruppe" kam es zu Verstopfung im Laufe des Jahres. Für rinnende Nase gab es keinen Unterschied zwischen den Behandlungen.

Sechs Flunisolide-behandelte und 10 Placebo-behandelte Patienten berichteten von Nebenwirkungen im Laufe des Behandlungs-Jahres. Vorbeigehend leichteres Jucken war haüfigste Klageursache. Drei fälle von Sekretion mit Blutspuren wurden rapportiert. Keine Patienten zogen sich im Zusammenhang mit dem Medikamente von der Untersuchung zurück.

Die Untersuchung ergab, dass Flunisolide bedeutend wirkungsvoller war als Placebo in der Verhinderung von Rückfällen von Nasenpolypen im Laufe einer Behandlungszeit von einem Jahr nach Polypectomie.

REFERENCES

1. Deuschl H, Drettner N. Nasal polyps treated by beclomethasone nasal aerosol. Rhinology 1977; 15:17–23.
2. Drettner B, Ebbesen A, Nilsson M. Prophylactive treatment with flunisolide after polypectomy. Rhinology 1982; 20:149–58.
3. Mygind N, Pedersen CB, Prytz S, Sørensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. Clin Allergy 1975; 5:159–64.
4. Mygind N. Topical steroid treatment for allergic rhinitis and allied conditions. Clin Otolaryngol 1982; 7:1–10.
5. Pedersen CB, Mygind N, Sørensen H, Prytz S. Long-term treatment of nasal polyps with beclomethasone dipropionate aerosol II. Acta Otolaryngol (Stockh) 1976; 82:256–9.
6. Sahay JN, Ibrahim MBN, Chatterjee SS, Nassar WY, Lodge KV, Jones CW. Long-term study of flunisolide treatment in perennial rhinitis with special reference to nasal mucosa histology and morphology. Clin Allergy 1980; 10:451–7.
7. Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. Rhinology 1980; 18:9–18.

G. Dingsør, M.D.
Lars Hillesgate 20B
N-5000 Bergen
Norway