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Clinical and Rhinoscintigraphic Evaluation of Therapeutic Effects of Mometasone Furoate Nasal Spray on Sinonasal Polyposis

Sinonazal Polipoziste "Mometasone Furoate" Burun Spreyinin Terapötik Etkisinin Klinik ve Rinosintigrafik Değerlendirilmesi

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ABSTRACT

Objective: To objectively document the efficacy of mometasone furoate nasal spray (MFNS) in the treatment of sinonasal polyposis (SNP).
Material and Methods: The study was designed prospectively in a group of patients with SNP and negative history of surgery. Ten patients were administered MFNS 100 mcg to each nostril once a day for eight weeks. All patients underwent Tc-99m MAA (macroaggregated albumin) rhinoscintigraphic evaluation of mucociliary activity and endoscopic evaluation before and after the treatments. Response to treatment, in terms of rhinoscintigraphic and endoscopic improvement, was assessed.
Results: Of the 10 patients 8 were male and 2 female, with an average age of 45 years (24-61). Following treatment, mucociliary transport time was significantly reduced ($p< 0.05$) and the polyps were clinically shrunk ($p<0.05$).
Conclusion: It was determined that MFNS treatment was effective in the treatment of SNP. Mometasone furoate (MF) can be considered, as an alternative to other topical steroids, in the treatment of SNP.

Keywords
Sinonasal polyp; nasal polyp; nasal polyposis; mometasone furoate; rhinoscintigraphy; treatment; nasal spray

ÖZET

Amaç: "Mometasone furoate" burun spreyi (MFNS)'nin, sinonazal polipozis (SNP)'in tedavisindeki etkisini objektif olarak ortaya koymak.
Gereç ve Yöntemler: Çalışma SNP'li ve cerrahi geçirmemiş bir grup hastada prospektif olarak planlandı. MFNS, 10 hastanın her bir burun deliğine 100 mcg günde bir kez sekiz hafta uygulanmıştır. Tüm hastalar için, tedavi öncesi ve sonrası, endoskopik değerlendirme ve Tc-99m MAA ("macroaggregated" albumin) rinosintigrafi ile mukosilier transport zamanı değerlendirmesi yapıldı. Tedaviye cevap, rinosintigrafik ve endoskopik düzelme ile değerlendirildi.
Bulgular: Hastalardan 8'i erkek, 2'si bayan, ortalama yaş 45 (24-61) idi. Tedaviyi takiben mukosilier transport zamanı anlamlı derecede azaldı ($p< 0.05$) ve polipler anlamlı derecede küçüldü ($p< 0.05$).
Sonuç: MFNS, SNP'in tedavisinde efektiftir. "Mometasone furoate" (MF), SNP'in tedavisinde diğer topikal steroidlere bir alternatif olarak düşünülebilir.

Anahtar Sözcükler
Sinonazal polip; nazal polip; nazal polipozis; mometasone furoate; rinosintigrafi; tedavi; burun spreyi

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INTRODUCTION

Sinonasal polyposis (SNP) represents an important clinical problem, with several local and/or systemic manifestations. Its prevalence ranges from 0.2 to 4.3% in the general population. SNP is considered to result from a chronic inflammation, and is characterized by edematous masses of inflamed mucosa prolapsing into the nose. Multiple factors, local and/or systemic, can play role in the etiology. It can be sometimes associated with systemic diseases such as asthma, cystic fibrosis, primary ciliary dyskinesia, Aspirin sensitivity, and allergy. Major symptoms are nasal obstruction, increased secretions, loss of smell and headache which may result in reduced quality of life significantly.[1-7]

Management includes medical treatment and/or surgery, and can be quite challenging in certain cases. Disease extension and systemic status are important in making the treatment decision. Medical treatment of various combinations, are considered in the both pre and postoperative periods. Topical and/or systemic steroids are usually the preference of choice. Endoscopic surgery is complementary but recurrences are frequent in the long-term. Therefore even the best surgery should be enhanced by medical treatment.[1-11]

Various topical nasal steroids are used in the treatment of SNP. There are many studies that support the use of them,[7,8,12-31] but those with mometasone furoate are fewer.[7,8,12,13,27,28] The aim of this study was to objectively document the therapeutic effects of mometasone furoate nasal spray (MFNS) on SNP. We utilized rhinoscintigraphy to assess the nasal mucociliary activity and endoscopic examination for staging, in response to treatment.

MATERIAL AND METHODS

Patients and assessment: The study involved 10 adult patients with SNP. The patients who had systemic and/or infectious diseases, history of nasal or systemic steroid application in the last 3 months or any history of sinonasal operations were excluded.

The study was designed prospectively in a single institution and it was approved by the ethical committee of Ankara Numune Hospital. The patients were administered MFNS 100 mcg to each nostril once a day for 8 weeks. Nasal endoscopic examination was used for the clinical assessment of polyps and rhinoscintigraphy for the mucociliary activity. Both examinations were performed before and at the end of the treatment in all patients. Improvement of SNP related symptoms were also evaluated in each patient with a questionnaire. The questionnaires were filled by the patients under the observation of a resident and nasal endoscopies were performed by the authors (HK, ED). Six SNP related symptoms were evaluated, post-treatment new appearing symptoms were not asked specifically.

Nasal examination: Diagnostic nasal endoscopy was done under topical anesthesia in sitting position with a rigid endoscope (4 mm, wide angle 0°). The mass of the polyps in each nostril was assessed and the patients were staged according to the system of Lund and Mackay (Table 1).[32]

Rhinoscintigraphy: A gamma camera (Elscint SPX-6, Haifa, Israel) with a low-energy high-resolution collimator was used. Two radioactive markers were placed on the mastoid and external acoustic meatus and then recorded. The collimator was positioned close to the nasal site with higher amount of polyp, and the patient at sitting position. A 0.5 cc solution of Tc-99m MAA (macroaggregated albumin) (1.85 MBq; 50 μCi) and 2% aqueous propylene glycol was dropped intranasally at anterior region of inferior turbinate. The acquisition was immediately started, storing 128 x 128 matrix sized dynamic images every thirty seconds for 15 minutes of repetetive periods. If no radioactivity was obtained in the nasopharynx at the end of 1 hour, late static images were obtained.

With the aid of radioactive markers, regions of interest were drawn on the images marking the nasal cavity and pharynx. The separation between the palate and the pharynx was identified; where the radioactivity appeared as a downward and backward inclined area at the "end" of the scintigraphic pattern. Time-activity curves were obtained from each region of interest. The exact time when the radioactivity entered the pharynx was individualized using external markers, sequential images, and time-activity curves. The length of the radioactivity path from the hyperactive area corresponding to the dropped radiopharmaceutical to the end of the nasal activity was displayed directly by the computer, transforming the number of pixels into millimeters. Mucociliary transport time (MTT) was then calculated and used for the assessment of mucociliary function. Control rhinoscintigraphic evaluation after the treatment was done on the nasal site examined previously for each patient.

Statistical analysis: Data were analyzed with the use of nonparametric statistics. All data were reported as

Table 1. Special features of all patients before and after the treatment.

Sex	Age	Pre-treatment Stage	Post-treatment Stage	Pre-treatment MTT (minute)	Post-treatment MTT (minute)
M	61	2	2	12.60	07.08
M	60	2	2	18.64	15.75
F	24	1	0	107.0	18.70
F	49	2	1	21.10	18.80
M	52	2	2	41.10	14.50
M	37	2	1	29.10	19.00
M	52	3	1	34.00	30.00
M	49	1	0	27.30	13.56
M	30	2	2	168.0	35.70
M	36	2	2	36.10	19.30

M: male, F: female, n: number of patients, MTT: mucociliary transport time.
The stages as according to nasal endoscopic findings were staged as follows:[11]
Stage-0: No visible polyps.
Stage-1: Polyps confined to the middle meatus.
Stage-2: Polyps beyond the middle meatus but not completely obstructing the nasal cavity.
Stage-3: Polyps completely obstructing the nasal cavity.

medians with the interquartile range unless otherwise stated. Paired comparisons within a group were analyzed with the Wilcoxon signed rank test. Group comparisons were analyzed with the Mann-Whitney *U* test. A *p* value of <0.05 (2-tailed) was considered significant. Statistical Package for the Social Sciences (SPSS) 11.0 for Windows software was used.

RESULTS

Of the 10 patients 8 were male and 2 female, with an average age of 45 years (24-61). Patients were staged endoscopically; 2, 7 and 1 were at stage-1, stage-2 and stage 3 before the treatment, respectively. Two, 3 and 5 patients were at stage-0, stage-1 and stage-2 after the treatment, respectively (Table 1). Five patients were downstaged; and the average of the stages was improved from 1.90 ± 0.57 to 1.30 ± 0.82 after the treatment ($p< 0.05$) (Table 2).

The average MTT was improved from 49.49 ± 49.29 to 19.23 ± 8.17 after the treatment ($p< 0.05$) (Table 3).

Nasal stuffiness was the most common complaint. The improvement scores for the most frequent symptoms were as follows; nasal stuffiness 50%, postnasal drainage 71.4%, nasal drainage 80% in patients (Table 4).

Table 2. The stages before and after treatment.

Stage	Pre-treatment		Post-treatment	
	n	%	n	%
0	0	0	2	20
1	2	20	3	30
2	7	70	5	50
3	1	10	0	0
Median (min-max)	2 (1-3)		1.50 (0-2)	
Mean (mean ± SD)	1.9 ± 0.57		1.30 ± 0.82	

n: number of patients.

DISCUSSION

Treatment of SNP, the most incapacitating benign disease of the nose, is a subject of debate in the area of rhinology. It is a multifactorial disease and the current information about the cause and pathogenesis is inadequate. Several hypotheses have been put forward in the etiology including systemic, local and genetic factors. Aspirin intolerance, epithelial cell defects/gene deletions, cystic fibrosis and ciliary dyskinesia, inhalant or food allergies, and altered Na+ absorption are all considered to be involved. Local mucosal and environmental factors are also important resulting in alteration of aerodynamics with trapment of pollutants and epithelial disruptions.[2,11,33-35] The other possible mechanism involves bacterial colonization of the nasal cavity, causing synthesis and release of enterotoxins that act as superantigens to stimulate the local immune system.[36] The presence of inflammatory mediators is a prominent and common factor in SNP, indicating that chronic persistent inflammation is a major condition irrespective of the etiology.[2,6,8,11,33-35]

Most authors agree on the fact that SNP management should be primarily based on medical treatment followed by complementary endoscopic sinus surgery in persistent cases.[1-11,37] The aim of the medical treatment is to reduce polyp size, relieve symptoms, facilitate operative procedure and prevent recurrences.

Table 3. Mucociliary transport time before and after treatment.

Mucociliary Transport Time			
Mean ± SD		Median (min-max)	
Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
49.49 ± 49.29	19.23 ± 8.17	31.55 (12.60-168)	18.75 (7.08-35.70)

Table 4. Pre-treatment and post-treatment symptoms and their improvement rates.

Symptoms	Pre-treatment		Post-treatment		Improvement	
	n	%	n	%	n	%
Nasal drainage	5	50	1	10	4	80
Postnasal drainage	7	70	2	20	50	71.4
Nasal stuffiness	8	80	4	40	4	50
Headache	5	50	5	50	0	0
Facial pain	3	30	3	30	0	0
Smell disorders	4	40	4	40	0	0

Systemic and/or intranasal (topical) steroids are the mainstay of treatment. Topical steroids can be used long-term either alone in mild cases or combined with systemic steroids and/or surgery in more severe cases.[1,2,6,8-10,37] The efficacy of systemic steroids is well-known, but their usage is limited because of their potential adverse effects even in the healthy population. They are contraindicated and hazardous in a wide spectrum of diseases such as hypertension, diabetes mellitus, obesity, osteoporosis and cataract. Systemic effects of topical steroids are very rare, and use of these drugs does not cause dystrophy or atrophy of the nasal mucosa, but they are associated with some local side effects such as burning sensation, epistaxis, and oral candidiasis. Because of their wide safety margins, these drugs have been used more than systemic steroids in the clinical practice.[10,38]

There is good evidence to support the use of topical nasal steroids. Various steroids such as betamethasone, beclomethasone, budesonide, flunisolide, fluticasone propionate, momethasone furoate, triamcinolone have been demonstrated to be effective in the primary treatment of SNP and these preparations are widely prescribed in spray form.[6-8,12-31] Topical steroids have also been shown to reduce recurrences of polyps post-operatively and to reduce the need for repeated surgery.[8,14,15,17,21,31,39]

MF acts by treating the inflammatory component of the disease. Upon allergen exposure, MF reduces the permeability of the nasal mucosa, thereby reducing the influx of eosinophils and inflammatory mediators during the early- and late-phase responses.[40] Results from *in vitro* glucocorticoid-receptor binding assays show that, on allergen exposure, MF binds to the human glucocorticoid receptor more potently than other intranasal corticosteroids, including fluticasone propionate (FP) or budesonide (BUD). This results in decreased permeability of the nasal mucosa and reduces influx of eosinophils. Furthermore, MF is at least ten times more effective than other intranasal corticosteroids, such as beclomethasone dipropionate (BDP), on inhibiting the synthesis and release of cytokines-the mediators required for the early and late phase inflammatory responses.[41]

MF is a highly potent molecule with a strong anti-inflammatory action that provides powerful relief of the symptoms associated with inflammation and congestion. Long-term use of MF returns the nasal mucosa to its normal state and preserves its integrity, with complete absence of nasal atrophy.[42] MF has proven safety in adult, adolescent and pediatric patients. When administered intranasally, the systemic absorption of MF is negligible. Oral bioavailability of MF is the lowest amongst all intranasal corticosteroids and is no greater than 0.1% in adults. Furthermore, when applied at 20 times the recommended clinical dose (4000 mcg), MF has no effect on the urinary-free and plasma cortisol levels, or on suppression of the hypopituitary-adrenal axis.[43-46]

The studies conducted on SNP in which patients were randomly allocated to receive MFNS 200 mcg OD, MFNS 200mcg BID or placebo, showed that polyp size decreased significantly in the two active treatment groups compared with placebo.[28] In addition, congestion/obstruction symptom scores were significantly improved with MF compared with placebo.[7,8,13,28] These

evidences suggest that MF can be effective in treatment of SNP. Our findings were also parallel to the results of these studies. However, we would like to specify that, after the treatment, five patients still had stage-2 SNP and headache, facial pain and smell disorders symptoms did not improve enough.

In the human nose the mucous flow is predominantly posterior towards the nasopharynx, streaming above and below the tubal opening. Nasal mucociliary transport is disturbed in a variety of conditions which affect the activity of the cilia. If there is a defect associated with pooling of the mucus or with squamous metaplasia, normal mucociliary transport will be lost at this site. SNP is edematous swelling of the nasal mucosa. Their ciliated surface can undergo squamous metaplasia. When the mucociliary blanket is preserved the mucous moves in the normal fashion, but with pedunculated swelling of the mucosa the direction of the mucous flow may be changed. Patients with SNP have disturbed mucociliary function.[47] Mucociliary transport speed is a highly reproducible parameter and can be used to compare the therapy results.[48]

Various well-established methods to study the ciliary activity of nasal mucosa are available. Direct methods such as stroboscopy, roentgenography, and photoelectron techniques are performed to assess the ciliary activity and the frequency of ciliary beat, but they are expensive and unsuitable for routine studies. Indirect methods use soluble, insoluble, or radioactive substances to assess nose-to-pharynx transport times. Saccharine and vegetal-carbon powder testing is the easiest and most inexpensive technique to evaluate nasal ciliary function.[48] But scintigraphy (rhinoscintigraphy) provides the best physiological information about the deposition, dispersion and clearance of particles in the nose.[47,49-52] It follows the movement of many particles once they have been deposited in the nasal cavity, rather than the movement of individual particles or the passage of a substance in solution such as saccharin.[47] Thus, it appears to accomplish some significant goals in research on the ciliary system of the nasal mucosa. However, the equipment is expensive, the patient has to remain in a room suitable for radioactive materials and the subject is exposed to radiation. Various radiopharmaceuticals (colloidal solutions, resin particles, and albumin microspheres) labeled with ^{51}Cr or I-131 have been proposed for rhinoscintigraphy. Tc-99m MAA is preferred by most authors because it is cost effective and has more suitable physical characteristics and does not allow radiation burden. Mucociliary transport speed has been calculated as mean 5.3 mm/min (range 3.3-8.2 mm/min) by rhinoscintigraphy.[48]

In our study we used Tc-99m MAA to compare the therapeutic effects of MF, objectively. The test was successfully applied in all patients without any complication, and we were able to obtain satisfactory data. We determined that MTT decreased from 42.60 ± 34.66 minutes to 19.38 ± 9.28 minutes, which revealed a significant improvement. We also used endoscopic evaluation to monitor the clinical response of the disease. We observed significant clinical improvement in accordance with the findings of rhinoscintigraphy. After the treatment the stages were downgraded from 2.20 ± 0.42 to 1.80 ± 0.42.

Our findings were parallel to those in the literature, which revealed the efficacy of nasal MF in the medical treatment of SNP. The drawback of this study is the limited number of patients. But, it is still possible to recommend that MFNS can be considered as an alternative to other topical steroids in treatment of SNP. Further studies with higher number of patients should be designed to study preoperative and postoperative treatment alternatives.

CONCLUSION

In this study, MF was used in the medical treatment of the SNP. After the MF treatment the polyps' size decreased, symptoms improved and mucociliary transport increased (mucociliary transport time decreased).

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