ORIGINAL CONTRIBUTION

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Aspirin desensitization for ASA triad patients - a prospective study of the rhinologist's perspective*

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SUMMARY

Objectives/Problem: *To determine the sinonasal effect of aspirin salicylic acid (ASA) desensitization in patients with nasal polyps, asthma and aspirin intolerance (ASA triad).*
Methods of study*: Patients with ASA triad were recruited from the outpatient otolaryngology clinic. They underwent a program of ASA desensitization (2005-2008) with prospective assessment of subjective and objective responses. Incremental doses of aspirin were given to reach a target of 625 mg twice daily during a period of 3-5 days. A maintenance dose was then given for the study period. The patients also received inhaled and topical nasal steroids, antihistamines and beta agonists for asthma control, but no systemic steroid treatment.*
Main results: *Of the original 27 enrolled subjects, 10 elected to discontinue treatment and five dropped out because of treatment complications. The objective evaluation of the polypoid sinonasal disease in the remaining 12 patients (4 males, 8 females, age range 22-63 years) revealed only mild improvement. In contrast, the patients' subjective feeling of nasal congestion, nasal discharge and overall discomfort improved significantly.*
Conclusions: *Aspirin desensitization has a favorable subjective effect on certain nasal symptoms among ASA triad patients, but the objective effect on polypoid mass is not significant.*

Key words: ASA triad, aspirin, desensitization, polyposis, asthma, prospective study

INTRODUCTION

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a common disease of the upper airways. Its main symptoms are nasal obstruction, anosmia and rhinorrhea, all of which have a significant negative impact on the individual's quality of life. Endoscopic examination and computed tomography (CT) reveal polypoid tissue of varying degrees and centered at the ethmoidal complex, which causes obstruction of the sinonasal passages and secondary chronic infection of the paranasal sinuses. Although it is not clear whether polypoid tissue is the cause or the effect of chronic sinonasal infection, these two co-existing processes create a vicious cycle. In the presence of asthma, polyposis tends to take a more aggressive and refractory form [1,2]. Sinonasal disease is especially severe in patients with asthma and aspirin sensitivity (ASA triad, aspirin exacerbated respiratory disease [AERD], Samter's triad) [3-5]. For them, exposure to even a small quantity of medications from the non-steroidal anti-inflammatory drug group can cause acute exacerbation of allergic and asthmatic symptoms.

Despite extensive research in the past, the optimal treatment modality for CRSwNP remains elusive, with endoscopic sinus surgery currently being the mainstay of treatment. Surgery usually has a clear positive effect on asthma and polyposis by providing relief of the obstructive and inflammatory symptoms, but the polypoid disease recurs in 10-27% of cases [6-8]. Moreover, patients with concomitant CRSwNP and asthma or allergy have significantly higher recurrence rates than non-asthmatic and non-allergic patients (80% recurrence rate in CRSwNP and asthma and 73% in CRSwNP and allergy) [2]. This failure rate indicates that surgery alone is inadequate treatment for CRSwNP, and that adjuvant medical therapy (currently mainly topical and systemic corticosteroids) is needed to control the disease.

Desensitization to aspirin was first described as a means of enabling its use for treating asthma in ASA-sensitive patients [9]. Since then, several studies have demonstrated the efficacy of ASA desensitization in improving asthma and nasal symptoms in ASA triad patients [10-12]. Desensitization is performed by giving incremental doses of aspirin in a hospital setting and then monitoring airway function. The dose is increased gradu-

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ally to a maintenance dose of up to 650 mg twice daily. If the patient discontinues treatment, the sensitized state is resumed within 48-72 hours and therefore compliance is crucial.

The aim of this study was to prospectively evaluate and follow-up selected subjective and objective nasal measurements during ASA desensitization in a group of ASA triad patients.

MATERIALS AND METHODS

Experimental Design

The study protocol was approved by the Tel Aviv Sourasky Medical Center ethics committee. During the 27-month period between December, 2005 and March, 2008, all patients with nasal polyposis and asthma who were treated in the rhinology outpatient clinic were referred for aspirin challenge at the institutional allergy clinic. A trial dose of aspirin was given to all potential study participants and full desensitization was carried out (described below) if symptoms of hypersensitivity appeared. The final study group consisted of all patients with asthma, sinonasal polyposis and proven aspirin sensitivity. Exclusion criteria were history of peptic disease, anticoagulation therapy and previous major bleeding episodes. Patients who had sinus surgery 6 months prior to referral to the allergy clinic were also excluded.

Pre-Treatment Evaluation

After signing informed consent, all ASA triad patients underwent an evaluation that included a visual analog symptom (VAS) score questionnaire and recording of pre treatment CT score, as well as polypoid disease severity score. The scoring systems were chosen based on the recommendations of the sinusitis staging and therapy task force (Lund and Kennedy) [13].

The symptom score of the self-reported questionnaire consisted of six common chronic sinusitis complaints, including facial pain, headache, olfactory disturbance, nasal congestion, nasal discharge and overall discomfort. Each symptom was scored on a scale of 1-10, with 1 being least severe and 10 most severe (maximal total score of 60). The endoscopic score was given on a scale from 1-4 and on each side of the nose, as follows: 1) polyps confined to the middle meatus, 2) polyps protruding to the nasal cavity, 3) polyps touching the inferior turbinate but located above the superior half of the inferior turbinate, and 4) polyp involvement below the superior half of the inferior turbinate (maximal total score of 8 for both sides). The CT score ranged from 0-2 for each sinus group and 0-2 for the nasal cavity (maximum of 12 on each side and total score of 24).

All patients responded to specific questions on atopy and underwent allergy skin prick tests, followed by the recording of positive allergens.

Desensitization Protocol

Upon completion of the pre-treatment evaluation, the aspirin-intolerant patients began the desensitization process at the allergy and pulmonology clinic. They were desensitized following baseline spirometry: each patient was given incremental doses of aspirin, beginning with 15 mg and doubled every 60-90 minutes. The aspirin dose was adjusted if significant allergic symptoms appeared. The patients were sent home overnight and returned to continue treatment the following morning. After the last aspirin dose of each day, the patients were observed for two hours in the clinic before discharge. The treatment target dose was 625 mg twice daily, which took 3-5 days to achieve. Peak expiratory flow and asthma-related symptoms were recorded after each dose of aspirin. A maintenance dose of 625 mg twice daily was then given for the rest of the study period. The patients also received inhaled and topical nasal steroids, anti-histamines and beta agonists for asthma control, but there was no systemic steroid treatment to exclude the confounding effect of steroids on nasal polyps. The treatment with nasal steroids and anti-histamines given before the beginning of the study remained unchanged during the aspirin treatment period to make sure that these drugs had no confounding effect on the assessment of the nasal polyps.

Treatment was discontinued upon patient request or if there was any bleeding or allergic complication. The endoscopic and symptom scores were prospectively collected after 1, 3, 6 and 12 months of treatment. If no subjective and objective improvement could be seen at the first follow-up visit (1 month of treatment) and the patient requested to discontinue treatment, the subjective and objective scores were prospectively recorded and the patient's data were included in the study.

Statistical analysis

The study results were analysed by the two-tailed Student's t test, and a p-value less than 0.05 was considered significant.

RESULTS

Twenty-seven patients (16 females and 11 males, mean age 47.1 ± 11.6 years) were enrolled in the study. Sixteen patients had undergone sinus operations (mean 1.67, range 0-5) before entering the study. The mean CT score was 18.9 ± 4.1.

Five of the 27 patients (18.5%) had ASA-related complications during desensitization, mandating early discontinuation of treatment after a few days: specifically, three patients had asthma exacerbation (one of them was admitted to the hospital) and two patients had abdominal pain (one had duodenitis requiring hospitalization). The rate of patients who were hospitalized for desensitization complications was 7.4%. Ten other patients either discontinued treatment before completion of a minimum of one month into the study, or stopped taking the medication and did not come for follow-up visit, and their data were not included in the analysis. The data on the 12 remaining patients were sufficient to prospectively analyse the effect of aspirin desensitization on sinonasal disease.

All ASA triad patients taken together, 24 of 27 had pre-treatment endoscopic staging which showed no significant difference in nasal polyp severity between the atopic (12 patients) and non-atopic (12 patients) groups (mean endoscopic staging 6.75 and 5.92, respectively, $p = 0.35$). Table 1 details the specific positive allergens in the atopic group. A wide variety of

Table 1. All ASA triad patients taken together, a total of 12 cases had atopy (five had adequate follow-up and seven did not complete the study). These patients were sensitive to a wide variety of allergens, the most common being dust (83%). Five patients were sensitized to one allergen and seven patients were allergic to two or more allergens.

Patient	Allergens								
No.	Dust	Grass	Cockroach	Olive	Dog	Feathers	Cat	Mold	Mugworth
Patients with adequate follow-up									
1	+	+			+	+			
2	+								
3	+								
4	+								+
5							+		
Patients who did not complete the study									
6	+	+							
7				+					
8	+	+							
9	+							+	
10	+		+						
11	+		+						
12	+								

allergens were detected, with dust being the most common (10 patients - 83%).

For the 12 patients who were followed up prospectively (Table 2), reduction of polypoid mass could be seen after aspirin treatment even though the endoscopic score did not change significantly (pretreatment score of 7, post-treatment score of 6.08, p = 0.12). After subdividing these 12 patients into atopic and non-atopic groups, the polypoid disease in both the 7 atopic and the 5 non-atopic patients failed to show any significant response to aspirin. Specifically, the mean pre treatment endoscopic score was 7.4 and the mean post-treatment score was 6.6 for the atopic group (p = 0.13) and 6.71 and 5.71, respectively, for the non-atopic group (p = 0.29).

Table 2. Pre- and post-ASA desensitization endoscopic score of the 12 prospectively followed patients (5 atopic and 7 non-atopic). Each nasal cavity can score up to 4 points, yielding a total of 8 points. Although reduction in polyp size could be seen after aspirin therapy in both the atopic and non-atopic patients, the change did not reach a level of significance.

Patient No.	**Pre-treatment endoscopic score**		**Post-treatment endoscopic score**
Non-atopic patients			
1	8		5
2	6		4
3	8		8
4	4		4
5	7		8
6	6		4
7	8		7
Mean non-atopic	**6.71**		**5.71**
p-value		**0.29**	
Atopic patients			
8	8		6
9	7		6
10	7		7
11	8		8
12	7		6
Mean atopic	**7.4**		**6.6**
p-value		**0.13**	
Mean - Total	**7**		**6.08**
p-value - Total		**0.12**	

The pre- and post-treatment symptom scores of the 12 study patients are presented in Table 3. Nasal congestion, nasal discharge and overall discomfort were significantly improved by aspirin therapy (p = 0.008, 0.004 and 0.002, respectively). Facial pain, headache and olfactory disturbance as well as total symptom score improved during aspirin therapy, but the extent did not reach a level of significance.

DISCUSSION

Aspirin might be effective medical treatment in ASA triad patients, helping to avoid revision surgery and improving the patients' symptoms. The mechanism(s) involved in ASA desensitization is only partially understood. The response to aspirin ingestion can be divided into the acute phase (the first

Table 3. Mean pre- and post-ASA desensitization symptom score. Each symptom can score up to 10 points, yielding a potential total symptom score of 60. Nasal congestion, nasal discharge, and overall discomfort improved significantly while scores for facial pain, headache and olfactory disturbance as well as total symptom score did not reach a level of significance.

Symptom	**Pre-treatment score(mean)**	**End of treatment score (mean)**	**p-value**
Facial pain	2.49	1.56	0.12
Headache	4.56	2.44	0.1
Olfactory disturbance	8.77	7.11	0.32
Nasal congestion	8.22	4.11	**0.008**
Nasal discharge	8	3.67	**0.004**
Overall discomfort	9.44	5	**0.002**
Total symptom score	36.9	27.5	0.08

hours after ASA exposure) and the chronic phase (two or more weeks of treatment) [14]. In the acute phase, ASA is thought to cause down-regulation of the E4 leukotriene receptors in the airway [15], resulting in a decrease in bronchial responsiveness to allergen exposure, although the levels of leukotrienes and other inflammatory mediators in the tissue remain high. Down-regulation of endothelial leukotriene receptors in the blood vessels of the mucous-secreting glands of the nasal mucosa also results in improvement of nasal symptoms. In the chronic phase, there is a drop in the tissue levels of the leukotrienes B4 and E4 [16,17], and this also contributes to a reduction in upper and lower airway hypersensitivity.

Some studies have reported changes in subjective measures, such as the sense of smell or nasal congestion, after aspirin desensitization among patients with ASA triad. We are unaware of any studies that have monitored both objective and subjective sinonasal polypoid reactions to ASA desensitization by endoscopy and prospective follow-up analyses.

CRSwNP presents a challenge to the rhinologist since surgical treatment is frequently only a temporary solution and medical management with systemic steroids, although effective, carries a risk for serious side effects and therefore must be used judiciously. Kim et al. showed that patients with Samter's triad had 10 times more previous surgeries than non-Samter's patients in addition to significantly more recurrence rates [18]. Rowe-Jones et al. recently reported that postoperative topical steroid treatment significantly decreased recurrence rates in CRSwNP [19].

Our interdisciplinary team measured the effect of ASA desensitization on nasal polyps and sinonasal symptoms in a total of 27 patients with ASA triad. Prospective data were obtained in 12 of these patients, all of whom had severe disease (with a mean Lund-MacKay CT score of 18.9 ± 4.1). Our study as well as other reports [20] have shown a substantial dropout rate in ASA desensitization which might be a confounding factor in the final result analysis. Treatment was discontinued due to severe asthma or gastrointestinal complications in five of our patients, of whom two needed to be admitted to hospital. This represents a substantial complication rate that should be taken into consideration when desensitization is offered to a patient. Moreover, the possibility of severe asthma attack mandates the proximity of full intensive care facilities.

Our study design did not include a placebo control group since the ingestion of aspirin causes an immediate hypersensitivity response, which will be apparent to the patient and might also be apparent to the otolaryngologist and allergy specialist who perform follow-up.

Three of the six subjective symptoms (nasal congestion, nasal discharge and overall discomfort) significantly improved following desensitization, while the other three (facial pain, headache, and olfactory disturbance) did not, and so the total symptom score failed to show improvement. Stevenson et al. [20] concluded that some nasal symptoms, sinus pain and nasal congestion improved with ASA treatment, and Mardiney et al. [10] reported significant reduction in systemic steroid consumption, improvement of sense of smell and less acute sinus infections after ASA desensitization. The significant subjective improvement in congestion, discharge and overall score that we witnessed during the current study supports the use of aspirin in patients who are at high risk or refuse to undergo surgery and in those who have undergone multiple surgeries and want to improve their nasal symptoms.

The data in this series do not seem to support the assumption that atopy was a significant factor in influencing disease severity or response to aspirin. Twelve of the 24 patients who were enrolled into the current study (50%) and who had been given pre-treatment endoscopic scores had atopy, yet they did not have worse polypoid disease compared to the 12 non-atopic patients. The polypoid disease did not respond significantly to aspirin either in the 7 atopic or in the 5 non-atopic patients among the 12 patients for whom prospective follow-up was available.

CONCLUSIONS

Although the objective effect on polypoid sinonasal mass is minor, aspirin desensitization is an effective treatment for improving some important nasal symptoms in ASA triad patients. As such, aspirin may be considered a substitute for systemic steroid treatment for symptom relief for patients who are at high risk for surgery and for those who refuse surgery.

We recognize that the substantial dropout rate in this study might have affected the reported results.

The role of desensitization following surgery should be investigated to better understand the efficacy of aspirin as an adjuvant therapy in the treatment of ASA triad patients.

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