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Investigation of the Relationship between Aspirin-Sensitivity and Poor Response to Medical Management in NSAIDs-exacerbated Respiratory Disease Patients with Sinonasal Polyposis

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Abstract

Background: NSAID-exacerbated respiratory disease (N-ERD) is a highly heterogeneous disorder with various clinical symptoms. The aspirin challenge test is a gold standard method for its diagnosis, and there are still no reliable in vitro diagnostic biomarkers yet. Oral challenge tests are time-consuming and may be associated with a risk of severe systemic reactions. This study aimed to evaluate whether patients with poor responses to medical management are more susceptible to being aspirin-sensitive.

Methods: In this cohort study, after CT scanning of all patients and subject selection, conventional medical treatment was started as follows and continued for three consecutive months: at first, saline nose wash twice per day, intranasal beclomethasone spray one puff in each nostril twice per day, montelukast 10 mg tablet once daily, a ten-day course of oral prednisolone starting with the dose of 25 mg per day and taper and discontinued thereafter. Sinonasal outcome test 22 (SNOT22) was used for the evaluation of symptom severity. Statistical analyses were performed with SPSS version 23, and data were analyzed using an independent samples T-test, paired T-test, and Receiver operating curve analysis

Results: 25 males and 53 females were enrolled in this study, with an average age of 41.56 ± 11.74 years old (18-36). Aspirin challenge test results were positive in 29 (37.2%) patients. The average SNOT22 scores before the treatment were 52.97 ± 17.73 and 47.04 ± 18.30 in aspirin-sensitive and aspirin-tolerant patients, respectively, and decreased to 27.41 ± 16.61 and 24.88 ± 16.72 in aspirin-sensitive and aspirin-tolerant patients after the treatment, respectively. There was no significant difference in SNOT22 scores between the groups.

Conclusion: The severity of symptoms before treatment and clinical improvement after treatment are not good predictors of N-ERD.

Keywords: N-ERD, Aspirin-sensitive, Aspirin-tolerant, Chronic rhinosinusitis, Nasal polyposis, Asthma, SNOT22

Conflicts of Interest: *None declared*
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↑What is "already known" in this topic:
The aspirin oral challenge (AOC) test is the gold standard method for the diagnosis of NSAID-exacerbated respiratory disease (N-ERD), and there are no reliable in vitro diagnostic biomarkers yet. AOC test is time-consuming and may be associated with a risk of severe systemic reactions.

→What this article adds:
The clinical symptom severity before medical treatment and/or the degree of clinical response to conventional medical treatments in patients with nasal polyposis is neither a good proxy of aspirin sensitivity nor a suitable indicator for the selection of candidates for the aspirin challenge trial.

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Introduction

Rhinosinusitis is the inflammation of the nose and the paranasal sinuses, and it is called chronic rhinosinusitis when the duration of symptoms takes more than 12 weeks with no complete resolution of symptoms (1). Nasal polyposis is considered a subgroup of chronic rhinosinusitis (CRSwNP) (1).

Aspirin (acetylsalicylic acid, ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs), as widely prescribed drugs, are among the main causes of hypersensitivity reactions to medications.

Hypersensitivity reactions to NSAIDs are categorized into 1) Pharmacologic reactions include NSAID-exacerbated respiratory disease (N-ERD), NSAID-induced urticarial/angioedema (N-IUA), and NSAID-exacerbated cutaneous disease (N-ECD) 2) Selective reactions include single NSAIDs-induced delayed hypersensitivity reactions (SNIDHR) and single NSAIDs-induced urticaria, angioedema and/or anaphylaxis (SNIUAA). N-ERD is the main phenotype among cross-intolerant types of NSAID hypersensitivity and had been named ASA-sensitive asthma, ASA-induced asthma, and ASA-intolerant asthma; nevertheless, NERD and ASA exacerbated respiratory disease (AERD) is commonly used (2).

N-ERD includes CRSwNP and bronchial asthma, which usually appear in the third or fourth decade of life. Aspirin (acetylsalicylic acid=ASA) sensitivity is suspected after a typical respiratory reaction that can be confirmed by oral provocation tests. Respiratory reactions related to ASA and other NSAIDs (i.e., agents that inhibit both cyclooxygenase 1,2 (COX)), often present with asthma attacks/bronchospasm (which may be severe), laryngeal spasm, rhinorrhea, nasal congestion, ocular itching and tearing, periorbital edema and generalized flushing. The onset of symptoms after ingesting full therapeutic doses of an offending agent (Aspirin) typically occurs within 30 minutes to 3 hours. A minority of patients present both dermatological and respiratory symptoms (“blended” reactions) (3).

Approximately 40% to 80% of patients with aspirin sensitivity suffer from polyposis, as well as about 15% of patients with sinonasal polyposis have aspirin sensitivity (4). The prevalence of N-ERD in adults with asthma is estimated to be as much as 25% and even is higher among those with nasal polyps (up to 40%) or asthma and nasal polyps (5). The condition affects women more than men in most populations by a ratio of 3:2. The prevalence of N-ERD seems to increase with the severity increment of the underlying disorders (6). Additionally, the degree of polyp hypertrophy of the sinus mucosa and the severity of inflammation is more extensive in patients with N-ERD than in ASA-tolerant individuals (7, 8). Most patients suffer from severe nasal obstruction, postnasal drainage, and nasal polyps characteristically undergo rapid regrowth, thereby resulting in an average of several sinus surgeries or polypectomies in each patient (8, 9).

The diagnosis of ASA hypersensitivity is based on a history of adverse reactions caused by ASA or other NSAIDs. Some patients have a definitive history of adverse reactions to ASA and NSAIDs; however, 50% have not. In patients without a clear history, challenge tests are necessary to confirm or exclude ASA hypersensitivity (8-10). Diagnostic oral challenge tests are time-consuming procedures requiring well-experienced personnel, and may be associated with a risk of severe systemic reactions (11, 12).

In patients with N-ERD, desensitization not only improves upper and lower respiratory symptoms in most patients but also permits the use of NSAIDs which are typically considered to be cross-reactive (13). N-ERD patients with CRS may benefit from ASA desensitization with subjective sinonasal symptom improvement (14). Desensitization is also a specific therapy for patients with N-ERD. In addition, ASA desensitization is clearly useful in patients who require NSAIDs for concomitant inflammatory diseases (14). Pooled data from 3 double-blind, placebo-controlled trials (DBPCTs) showed that CRSwNP patients with ASA desensitization had significantly fewer overall nasal and paranasal complaints, and less quality-of-life impairment by nasal and paranasal complaints, and better general health condition (15). Therefore, in this study, we aimed to evaluate whether the severity of clinical symptoms and response to conventional treatment quantified by SNOT22 scores, could be a clue to finding which patient is eligible to undergo aspirin challenge tests.

Methods

Patient selection

This cohort study was performed in the Department of Allergy and Clinical Immunology, Rasoul Akram Hospital, Tehran, Iran. Informed consent was obtained from all participants before enrollment in the study, and the patient’s information remained confidential. Also, this study was approved by the Ethics Committee of Iran University of Medical Sciences with an ethics code: IR.IUMS.REC.1394.25461.

All patients with symptoms of chronic rhinosinusitis underwent paranasal sinus computed tomography (CT) scanning provided that they met the inclusion criteria, and if nasal polyposis was confirmed on CT scan, the patients were included in the study. The inclusion criteria consisted of not having other serious underlying diseases such as gastrointestinal, rheumatologic, renal, cardiac, hepatic, and psychological disorders, and also bleeding tendency, mastocytosis, cystic fibrosis, immunodeficiency, and not using anticoagulants, topical or systemic beta-blockers, and not being in pregnancy or nursing period. Patients with FEV1 (forced expiratory volume in 1 s) less than 70% of the predicted at the time of aspirin challenge, patients reluctance to participate, non-adherence patients, and patients with prior history of anaphylactic reactions to aspirin or NSAIDs were excluded from the study. Non-random and consecutive patient selection was made within one year. Data were collected by a questionnaire containing the patient’s age, sex, history of prior reaction to NSAIDs or aspirin, results of aspirin challenge tests, and the severity of symptoms, according to the validated Per-

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sian copy of sinonasal outcome test version22 (SNOT22) scores (16), and severity of paranasal sinus involvement according to CT scan results.

The Glicklich et al. classification was used to grade the severity of sinus disease on CT-PNS findings. It is classified as Grade 0: Less than 2 mm mucosal thickening on any sinus wall, Grade 1: All unilateral disease or anatomic abnormalities, Grade 2: Bilateral disease limited to the ethmoid or maxillary, Grade 3: Bilateral disease with involvement of at least one sphenoid or frontal sinus, Grade 4: Pansinus disease.

Aspirin desensitization

After including patients with nasal polyposis, conventional medical treatment was started for all patients as follows: at first, saline nose wash twice per day, intranasal beclomethasone spray one puff in each nostril twice per day, montelukast 10 mg tablet once daily, a ten-day course of oral prednisolone starting with the dose of 25 mg per day and taper and discontinued thereafter. Oral antihistamines were administered depending on the individual patient's symptoms. This regimen was continued for three consecutive months, and all patients who did not follow the treatment regimen as scheduled above were excluded from the study.

After finishing a three-month course of medical treatment, the SNOT22 questionnaire was refilled by participants, and then a diagnostic aspirin challenge test was performed for each participant to determine their aspirin sensitivity state. The six-step oral aspirin challenge (OAC) test, which is the gold standard for diagnosis of N-ERD, was performed on two consecutive days (Table 1). Physical examination and spirometry were done before the first dose and then every 30 min and the interval dose was one and a half an hour if the patient was symptom-free and spirometry was acceptable. The test was considered positive if the FEV1 falls to 20% of baseline or lower and also equivocal extra bronchial symptoms (e.g., severe nasal congestion, pronounced rhinorrhea). Respiratory symptoms accompanied by FEV1 fall to 15% of baseline or lower. The test was considered negative if the maximum cumulative dose of aspirin (662.5 mg) was achieved without a fall in FEV1 of 20% or greater and in the absence of nasoocular symptoms. In cases of aspirin intolerance, e.g., severe gastrointestinal complications, the test was withheld and considered inconclusive. In patients with a history of reactions to NSAIDs who tolerated 662.5 mg aspirin without reactions or showed equivocal symptoms, an additional 325 mg aspirin tablet was given and if no reactions occurred after two hours, the test was considered negative.

Table 1. Aspirin challenge test protocol

Time	Day 1	Day 2
Dose1	25 mg	162.5 mg
Dose2 (after 1.5 hours)	50 mg	325 mg
Dose3 (after 3 hours)	100 mg	325 mg (if needed)
Cumulative Dose	175 mg	812.5 mg

Statistical Analysis

Statistical analyses were performed with SPSS version 23.0 (SPSS Inc., Chicago, Illinois, USA), and data were analyzed using an independent sample T-test, paired T-test, and Receiver operating curve analysis (17). Moreover, the Kolmogorov-Smirnov test was used for normality. A P-value of less than 0.05 was considered statistically significant.

Results

Totally, 174 patients with CRS and sinonasal polyposis were visited in the allergy and clinical immunology department for one year, 65 of whom were excluded (severe gastrointestinal problems (peptic ulcer disease) (n=9), prior history of anaphylactic reaction to aspirin or NSAIDs (n=5), rheumatoid arthritis (n=1), multiple sclerosis (n=1), chronic myelocytic leukemia (n=1), major thalassemia (n=1), severe cardiac disease (n=2), pregnant and nursing mothers (n=8), aging above 65 (n=5) and below 18 years old (n=3), unwillingness to participate in the study (n=29) and did not continue the follow-up visits regularly (n=11), and did not take the drugs correctly (n=8)). There were still 12 patients who were candidates for oral aspirin challenge testing, but it was not possible because of poorly controlled asthma.

Eventually, 78 patients, including 25 males (32.1%) and 53 females (67.9), completed the study course, and the mean ± SD age of the patients was 41.56± 11.7 (18-63) years old. The mean ± SD age of asthma onset was 32.77± 13.04, diagnosis of polyposis was 33.28 ± 11.99, and symptoms of CRS were 26.76 ± 11.48. Among 58 (74.4%) patients who suffered from persistent asthma, 23 (39.7%) were aspirin-sensitive and 35 (60.3%) were aspirin-tolerant, whereas out of 29 aspirin-sensitive and 49 aspirin-tolerant patients, 23 (79.3%) and 35 (71.4%) had persistent asthma, respectively. However, the difference was not significant. 31 patients mentioned a previous history of polypectomy, including 22 patients who underwent one, 7 patients who underwent two, 1 patient who underwent five, and 1 patient who underwent eight polypectomies. Among the patients with a history of two or more polypectomies, 4 individuals were aspirin-tolerant and 5 were aspirin-sensitive. Nevertheless, the difference in the number of polypectomies was not significant. The extent of sinus involvement in CT scans was not significantly different between aspirin-sensitive and aspirin-tolerant patients. In terms of the grade of paranasal sinus involvement in CT scan, the grade 4 involvement was significantly more prevalent than other grades in the aspirin-sensitive group but not in the aspirin-tolerant group (P = 0.001) (Table 2).

Treatment complications occurred in 14 patients, nasal burning due to intranasal steroid usage in 4 patients and minimal epistaxis in 6 patients. 2 people developed epigastric pain after taking oral prednisolone, which led to premature discontinuation of prednisolone. 2 patients who were taking montelukast reported headache after taking it when the drug was discontinued. Overall, among 78 patients with nasal polyposis, 23 individuals had a history of

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Table 2. The characteristic and clinical findings of aspirin-sensitive and tolerant-patients

Parameters		Aspirin-sensitive patients	Aspirin-tolerant patients	*P*-value
Frequency (%)		29 (37.2)	49 (62.8)	-
Age		40.8 ±12.36	42.02 ± 11.47	0.661
Gender, Female/Male (%)		21/8 (72/28)	32/17 (65/35)	0.513
BMI		25.5 ± 4.13	25.8 ± 3.73	0.822
Asthma (%)		23 (79.3)	35 (71.4)	0.441
Asthma age		32.7 ± 12.8	32.8 ±13.3	0.931
Polypectomy		14 (46.3)	17 (34.7)	0.241
GER (%)		13 (44.8)	19 (38.8)	0.611
History of Aspirin Sensitization (%)		15 (51.7)	8 (16.3)	0.001
SNOT22 score (0-110)	Before treatment	52.97± 17.73	47.04 ± 18.30	0.171
	After treatment	27.41±16.61	24.88±16.72	0.522
	Difference between before and after treatment	25.55±15.99	22.16±15.45	0.361
Paranasal CT scan involvement (Grade 0-4)	Grade 2	2 (6.9)	6 (12.2)	0.451
	Grade 3	3 (10.3)	21 (42.9)	0.003
	Grade 4	24 (82.8)	22 (44.9)	0.001

*Data are SNOT22 scores and presented as mean ± SD

prior reactions to NSAIDs, eight of whom were aspirin-tolerant and 15 of whom were aspirin-sensitive. Regarding NSAIDs suspected to cause reactions, ibuprofen was the most prevalent, and diclofenac and aspirin were the second and third most prevalent causes of reaction, respectively. Other common drugs were acetaminophen, acetaminophen codeine, and naproxen.

In terms of the history of reactions to NSAIDs, 23 patients had a history of acute reactions to NSAIDs or aspirin. The patient's reaction data are shown in Table 2. Single reactors were 80% ($P = 0.040$). Mild or moderate prior reactions were associated with 84% and 80% positive OACs (oral aspirin challenges), respectively, whereas 100% of the patients with severe prior reactions had positive OACs ($P = 0.007$). The severity of previous reactions was classified into three categories according to the World allergy organization grading system; grade 1, grade 2 and 3, and grade 4 and 5 were considered mild, moderate, and severe, respectively. There was no significant difference in terms of SNOT22 score between aspirin-tolerant and aspirin-sensitive patients before ($P = 0.171$) and after ($P = 0.522$) treatment (Figure 1A and 1B). However, there was a significant decrease in SNOT22 scores before and after treatment in both groups ($P < 0.001$) (Figures 1C and 1D).

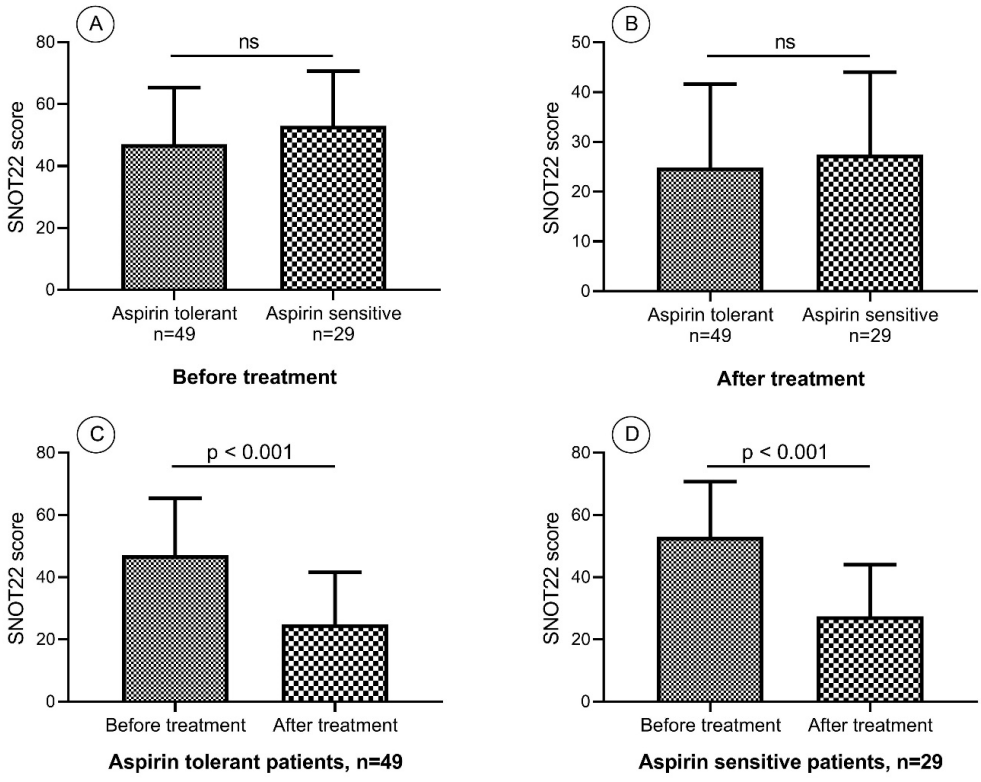

Figure 1. Average SNOT22 scores before and after treatment in aspirin-sensitive and aspirin-tolerant groups. There was no significant difference in terms of SNOT22 score between aspirin-tolerant and aspirin-sensitive patients before ($P = 0.171$) and after ($P = 0.522$) treatment (Figure 1A and 1B). However, there was a significant decrease in SNOT22 scores before and after treatment in both groups ($P < 0.001$) (Figures 1C and 1D).

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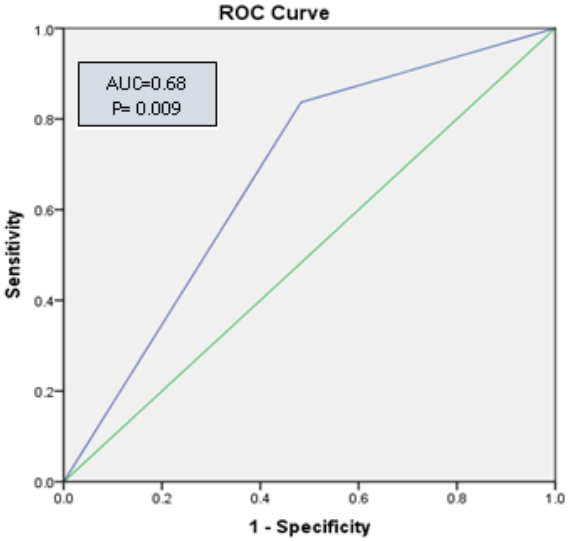

Figure 2. The prediction value for the history of reactions to aspirin versus aspirin challenge as the gold standard in the aspirin-sensitive and -tolerant groups. The area under curve (CI, *P*-value) was 0.68 (0.55-0.81, *P* = 0.009).

The frequency of positive history of reactions in the aspirin-sensitive and -tolerant groups was 15 (51.7%), and 8 (16.3%), respectively (*P* = 0.001), and the Odds ratio (confidence interval: CI) was 5.49 (1.9-15.7). Furthermore, the prediction value of the history of reactions to NSAIDs in patients with N-ERD was compared with the results of the oral aspirin challenge as the gold standard by the Receiver Operating Curve (17) analysis. The significant area under the curve (AUC) was 0.68 (CI: 0.55-0.81, *P* = 0.009), which is shown in Figure 2. Furthermore, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the history of reactions to NSAIDs were 83.7 %, 51.7 %, 65.2%, and 74.6%, respectively.

Discussion

Aspirin desensitization is a highly effective treatment option when standard treatment protocols are not effective or daily ASA/NSAID administration is required, but it is underutilized.

The main barrier to the more widespread use of aspirin desensitization is the potential for aspirin-induced severe bronchospasm, laryngospasm, and/or extra-respiratory side effects (cutaneous and gastric) (13, 18, 19). In this study, the prevalence of N-ERD was found to be 37.1% (29 out of 78 CRS patients). The overall incidence of ASA hypersensitivity among adult asthmatics, if assessed by history alone, ranges from 4.3% to 12% in various populations. When aspirin hypersensitivity was assessed by oral provocation; however, the incidence increased to 21.1% as recorded in a systematic review of 15 studies (10, 17, 20). The prevalence of aspirin sensitivity in patients with nasal polyposis was 15% in one study, but other studies have reported a higher prevalence of up to 30-40% (21, 22). Yunping et al. reported a low prevalence of N-ERD (0.57%) in patients with CRS (23). The difference in the prevalence of N-ERD among different studies may be attributed to different ethnic groups, as Esmailzadeh et al. has found differences in HLA between N-ERD and aspirin-tolerant patients (24). Furthermore, in another study, Seung-Hyun et al. proposed that N-ERD was related to HLA-DPB1*0301 in Polish and Korean ethnic groups (25).

We found that the frequency of aspirin sensitivity in patients with polyposis did not correlate with the patient's age or sex. In the study by Dursun et al., sex, atopy, the number of sinus infections per year, and the number of sinus surgical procedures were studied as predictors of N-ERD, which were not associated with positive oral aspirin challenges. Patients with two or more prior aspirin- and NSAID-associated respiratory reactions had an 89% chance of having a positive OAC compared with single reactors (80%). Patients with previous mild or moderate reactions were associated with 84% and 80% positive OACs, whereas 100% of the 45 patients with previous severe reactions had positive OACs. Except for hospitalizations, treatment sites for previous reactions (home or emergency department) did not seem to make a difference in response to the OAC test. This study identified age, sense of smell, and multiple prior reactions as independent risk factors associated with positive oral aspirin challenges (11). We found no significant difference between the two studied groups in the case of the number of polypectomies per patient. Overall, polypectomy has been done in 48% of N-ERD patients and in 34% of aspirin-tolerant patients, in which the difference was not significant.

In a study by Mascia et al., patients with N-ERD were distinguished by the higher sinus CT scores and considerably, they were more likely to have nasal polyps. In our study, severe paranasal sinus involvement in paranasal sinus CT scan was found in 82.8% of the aspirin-sensitive group versus 44.9% of the aspirin-tolerant group. Therefore, we concluded that if you visit a patient with N-ERD, it is highly possible that she/he has severe pansinusitis in the paranasal sinuses (PNS) CT scan. But if you visit a patient with pansinusitis, the probability of being N-ERD is only about 52%. Therefore, the severity of paranasal sinus involvement is not a single predictor of N-ERD. In addition, N-ERD patients demonstrated increased total lung capacity, indicating a trend toward increased air trapping (26, 27). In a study by Esmaeilzadeh et al. coexistence of asthma with nasal polyposis was an indicator of aspirin sensitivity (28). In our study, the prevalence of asthma in patients with nasal polyposis was not significantly different between aspirin-sensitive and aspirin-tolerant patients. Generally, as the coincidence of asthma with CRSwNP is highly variable (20-70%) and the findings are diverse, this coincidence does not necessarily lead to the diagnosis of N-ERD. Therefore, the decision to perform aspirin desensitization in patients with N-ERD should not be made until they receive optimal medical treatment and don't show a favorable outcome.

The degree of polypoid hypertrophy of the sinus mucosa and the severity of inflammation is more extensive in patients with N-ERD than in ASA-tolerant individuals (6-8, 12, 29). Nasal polyps characteristically re-growth rapidly

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in N-ERD, resulting in an average of three sinus surgeries or polypectomies per patient (7, 8).

A distinctive feature of CRS in N-ERD patients is a rapid recurrence of nasal polyps and mucosal hypertrophy following standard polypectomy or even functional endoscopic sinus surgery. It has been documented that patients with non-erosive reflux disease have ten times increased risk of polyp recurrence after Functional Endoscopic Sinus Surgery (FESS) compared to aspirin-tolerant patients (12, 30, 31).

Regrowth of polyps after endoscopic sinus surgery in patients with both CRSwNP and ASA sensitivity is related to severe mucosal inflammation refractory to long-term corticosteroid treatment using intranasal sprays or drops. Those patients exhibit more frequently an eosinophilic inflammation pattern related to disease severity (32, 33).

In addition, the ratio of polypectomies to the number of N-ERD patients was 0.82%, which was lower than most other studies. This finding may demonstrate the orientation of physicians visiting these patients about the fact that considering the recurrent nature of the disease, avoiding traumatic surgical procedures as much as possible is a rational approach. Generally, as nasal polyposis is usually recurrent in N-ERD, therefore making a decision about polypectomy should be done more cautiously by an expert ENT specialist.

In our study, there was no difference in the SNOT 22 scores neither before nor after treatment between aspirin-sensitive and aspirin-tolerant groups. However, on average, SNOT22 scores decreased by about 50% for both groups as a result of the treatment. In a study by Hopkins et al., the clinical improvement was studied according to SNOT22 scores after FESS. They found a minimal percentage of improvement among patients whose scores were zero to 10 before treatment and maximal improvement among patients whose SNOT22 scores were 91-100 before treatment. In our study, the clinical improvement was 40.6% (18.5 scores) in patients with SNOT22 scores of 41-50, which was close to the average scores of aspirin-tolerant patients, and 42.5% (23.5 scores) in patients with scores of 51-60, which was close to aspirin-sensitive patients. Compared to the study by Hopkins et al., the improvement in average SNOT22 scores in both groups of patients in our study was remarkable and comparable to the results of surgical interventions. This finding was in opposition to our previous knowledge, as we expected poor response to medical management in N-ERD patients (12, 34).

The reason for the good clinical improvement of patients in this study, which was close to the results of surgery in some studies, was that most of the patients in this study were not receiving the appropriate treatment or had discontinued their treatment. Another reason was the administration of a combination of topical and systemic medications, especially a medium course of oral prednisolone, and close monitoring of patients during the treatment course which is effective in a significant reduction of symptoms, although the problem will return with a reduction of medications and this is a reason for repeated surgical interventions and also a reason for patient's non-adherence. On the other hand, the exclusion of all patients who did not continue the complete course of the treatment was another explanation for a remarkable response to exclusive medical management (27).

In a study by Vishal et al., the average SNOT22 scores before endoscopic sinus surgery were 44.2 and 45.1 in patients without and with polyps, respectively, and decreased to 22.74 and 17.37 after surgery, with 48% and 70% improvement in patients without and with polyps, respectively (35). In another study by Deal et al. SNOT20 scores were studied in CRS patients with and without polyposis before and one year after FESS. There were 85% and 81% improvements in SNOT20 scores in patients without and with polyps, respectively (31).

In our study, the improvement in average SNOT22 scores after medical treatment was lesser than the average improvement after surgical management that was observed in the two above-mentioned studies, and this was expected in the short term. Compared with surgical treatment, the superiority of medical treatment is the possibility of prolonged use, thereupon prolonged control of symptoms, whereas surgical treatment has a high rate of recurrence and there may be a need for multiple surgeries and much more complications may occur, as mentioned above. In contrast, FESS is more efficient in patients who do not respond to medical treatment or experience frequent recurrences. In such patients, a combined medico-surgical approach is the most efficient treatment.

In summary, data analysis showed no significant relation between aspirin and NSAID sensitivity and symptom severity, concomitant asthma, age, sex, and pansinusitis in PNS CT scan, either separately or concomitantly. Although the treatment significantly reduces SNOT22 scores in patients with CRSwNP, our study did not provide a suitable differentiation marker for predicting aspirin sensitivity. However, obtaining an appropriate history of aspirin reactions was the only significant predictor of aspirin sensitivity.

Finally, this study meets some limitations, including very heterogeneous comorbidity profiles of the selected patients, and this heterogeneity couldn't be characterized in more detail in the study.

Conclusion

According to these findings, it seems that clinical symptom severity before medical treatment and/or the degree of clinical response to conventional medical treatments in patients with nasal polyposis is neither a good proxy of aspirin sensitivity nor a suitable indicator for the selection of candidates for aspirin challenge trial. Therefore, there may be some other points in aspirin-sensitive patients to be considered before selecting candidates for the aspirin challenge trial, including paraclinical findings, medical history, and accompanying asthma.

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Ethical Approval

This cohort study was approved by the Ethics Committee of Iran University of Medical Sciences with an ethics code: IR.IUMS.REC.1394.25461.

Conflict of Interests

The authors declare that they have no competing interests.

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