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Aspirin Sensitivity in Patients with Moderate to Severe Asthma

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ABSTRACT

Asthma induced by ingestion of aspirin occurs when symptoms arise within 30 minutes to three hours after aspirin consumption. Previous data indicate that sensitivity to aspirin may be associated with poorly controlled asthma. This study aims to evaluate the frequency of aspirin sensitivity in patients with moderate to severe asthma receiving conventional asthma therapy.

This clinical trial was conducted on 65 patients aged 18 to 65 years with moderate to severe asthma from February 2015 to February 2016 at the Allergy Department, Hazrat-e-Rasoul Hospital, Iran University of Medical Sciences, Tehran. To assess treatment responses in patients, forced expiratory volume in the first second (FEV1) and asthma control test (ACT) scores were measured at baseline and after 3 months.

The results of the oral aspirin challenge revealed a prevalence of 35.38% for sensitivity to aspirin. Hypersensitivity reactions to aspirin were detected in 60.9% of the patients with moderate asthma and 39.1% of the patients with severe asthma. All patients with positive aspirin challenge tests suffered from rhinosinusitis and in 56.5% of cases, history of previous hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) was detected. No meaningful differences were found between those patients with aspirin sensitivity and those with aspirin tolerance neither in mean pre-bronchodilator FEV1 nor in ACT scores pre- and post-treatment.

To conclude, aspirin sensitivity was not found to have an association with an unfavorable response to conventional treatment in patients with uncontrolled asthma.

Keywords: Asthma; Aspirin; Hypersensitivity

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INTRODUCTION

Asthma is a chronic inflammatory condition with airway hyperresponsiveness and inflammation.[1] Various factors may trigger asthma exacerbation including allergens, exercise, cold exposure, chemical sensitizers, air pollutants, respiratory viral infections[2] and non-steroidal anti-inflammatory drugs(NSAIDs).[3] Aspirin Induced Asthma (AIA) is defined as asthma occurring30 minutes to 3 hours after ingesting aspirin.[4] The prevalence of NSAIDs hypersensitivity has been estimated as 0.3-0.9% in the general population,[5] reaching 26% in patients with asthma[6] and in 30-40% of patients with asthma and nasal polyposis.[5] AIA develops between the third to fourth decade of life,[7] is not an immunological phenomenon, and the only established way for its definite diagnosis is through the aspirin provocation challenge.[8,9] Since NSAIDs are frequently used as over-the-counter drugs, asthmatic patients must be aware of the possibility of their asthma being exacerbated by the use of these drugs.[10,11]

This study was conducted to evaluate the frequency of aspirin hypersensitivity in patients with uncontrolled asthma receiving standard treatment.

PATIENTS AND METHODS

This study was a randomized clinical trial conducted from February 2015 to February 2016 at the Allergy Department, Hazrat-e-Rasoul Hospital, Iran University of Medical Sciences, Tehran. The Ethics Committee of Hazrat-e-Rasoul Hospital approved the study protocol. The Iranian Registry of Clinical Trials confirmed this research with registration reference of IRCT2015042721970N1.

Patients between the ages of 18 to 65 years with a diagnosis of moderate to severe asthma according to the Expert Panel Report 3(EPR-3) guideline,[12] were included.

All patients with the following criteria were excluded from the study: those with any serious systemic disorders (including hemorrhagic, gastrointestinal, rheumatologic, cardiac, renal, psychological, malignant disorders or systemic mastocytosis); those with a history of previous experience of IgE-mediated reactions to Aspirin or other NSAIDs; those with concomitant use of beta-blockers, warfarin or angiotensin-converting enzyme inhibitors; those with high-risk occupational or lifestyle conditions; pregnant or lactating woman; and those with Forced expiratory volume in 1 second (FEV1) of <70% at the time of aspirin challenge.

Signed informed consent was obtained from the patients following the code of ethics of the world medical association (declaration of Helsinki). A questionnaire including demographic data and relevant variables including sex, age, body mass index (BMI), history of comorbidities comprising gastro esophageal reflux disease (GERD), rhinosinusitis, aspirin sensitization, and smoking was completed for each participant. All patients underwent asthma control evaluations according to the asthma control test (ACT) scores and FEV1 values. All the patients with moderate to severe asthma were then treated with a combination of daily inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) according to the guideline (10) for at least 3 months, and in those with inadequate treatment response, a daily leukotriene receptor antagonist (LTRA) and/or a short course of oral corticosteroid was added if needed. Comorbid GERD and rhinosinusitis were also treated. At the end of the 3 months, ACT scores and FEV1 values were measured again and compared with the initial data obtained before treatment.

The patients were recommended to suspend LTRA drugs for 1 week, short-acting antihistamines for 3 days, LABA, tiotropium bromide and theophylline for 2 days, and short-acting beta 2 agonists (SABA) and ipratropium bromide for 8 hours before performing the challenge. A two-day oral challenge test with aspirin was considered for those patients with stable asthma and FEV1>70% of the predicted value. The test was carried out with increasing doses of 25, 50, and 100 mg of aspirin on the first day and 162.5, 325 and 325 mg on the second day administered at 1.5 hour intervals. In patients with a previous history of severe hypersensitivity reactions (severe dyspnea or cyanosis) to aspirin or NSAIDs, the test was initiated with 10 and 15mg of aspirin. The patients were examined every 30 minutes and FEV1 was measured before each aspirin dose and every 30 minutes thereafter.

A positive aspirin challenge-response was characterized by a≥20% decline in FEV1 or a decline in FEV1 of<20% combined with subjective symptoms (including the nose and eye pruritus) or isolated obvious nasal-ocular reactions including nasal stuffiness and nasal discharge. The challenge was interrupted when a cumulative dose of aspirin (1000

mg) was reached without any of the above-mentioned criteria (negative reaction). At the end of the aspirin challenge, the patients with aspirin hypersensitivity were treated for any respiratory or other complications with appropriate treatments.

Statistical analysis was performed using Chi-square and paired t-Test for FEV1 and ACT. SPSS software version 19 was used. In all tests $p<0.05$ was considered significant.

RESULTS

A total of 65 patients were eligible for the oral aspirin challenge (OAC) test. The mean age was 40.86±11.53 years. Nineteen (23.29%) were male and 46 (77.71%) were female. Twenty-seven (41.5%) patients were diagnosed with moderate asthma and thirty-eight (58.5%) with severe asthma. Eighteen patients (27.7%) had a previous positive history of hypersensitivity reactions to aspirin or other NSAIDs. All the patients underwent oral aspirin challenge, of whom 23 patients (35.4%) showed positive results. Positive results were defined as:

Naso-ocular symptoms (found in 1 patient [4.3%])

FEV1 decline (found in 6 patients [26.1%] and Both naso-ocular symptoms and FEV1 decline (found in 16 patients [69.6%]). Therefore, the prevalence of aspirin sensitivity was 35.38% based on OAC results. In 61.1% of aspirin-sensitive patients, hypersensitivity reactions occurred in less than an hour and in 38.9% of them within 12 hours of OAC test.

Table 1 demonstrates a comparison of ACT scores before and after asthma treatment regarding the OAC results.

Table 2 shows mean FEV1 values in participants according to OAC results.

We could not find any significant difference between age, BMI, gender, smoking status, and GERD between those with and without aspirin sensitivity.

Table 1. Comparison of ACT before and after asthma treatment regardingthe OAC result

ACT score	positive OAC (N=23)	Negative OAC (N=42)	*p*
Before treatment (Mean ± standard deviation)	11.1 ±4.3	10.6 ±4.4	0.607
After treatment (Mean ± standard deviation)	22.2 ±3.1	22.1 ±3.6	0.912
Alteration (Mean ± standard deviation)	11.1 ±5.3	11.6 ±5.3	0.726

ACT: Asthma Control Test, OAC: Oral Aspirin Challenge

Table 2. Mean FEV1 in participants according to OAC result

FEV1	positive OAC (N=23)	negative OAC (N=42)	*p*
Pre bronchodilator FEV1 (Mean±standard deviation)	65.1 ±8.3	63.7 ±10.9	0.576
Pre bronchodilator FEV1 Alteration (Mean±standard deviation)	21.8 ±8.8	24.9 ±12.6	0.289

FEV1: Forced Expiratory Volume in the first second, OAC: Oral Aspirin Challenge

A positive history of chronic rhinosinusitis (CRS) in patients with moderate to severe asthma was associated with a significant correlation with positive aspirin challenge test (p=0.03). Surprisingly, all patients (100%) with positive results for the aspirin challenge test suffered from CRS. In this study, 60.9% of the individuals among the aspirin-sensitive patients had moderate asthma, and 39.1% of them had severe asthma. Moderate asthma was detected in aspirin-sensitive patients with a significant difference compared to severe asthma (p=0.019). A history of previous hypersensitivity reactions to NSAIDs was associated with positive aspirin challenge test in 56.5% of the patients.

DISCUSSION

The mean age[7] and the gender[9] of the patients in this study were similar to previous studies with most of the cases occurring in the fourth decade of life with the majority of patients being female, however, without a significant difference (*p* values 0.7 and 0.3, respectively). We found aspirin sensitivity in 35.4% of the patients according to OAC in our study. This high prevalence of aspirin sensitivity in our patients may be explained by the inclusion criteria of the participating patients with moderate and severe asthma (excluding mild cases) and the high association of the nasal polyposis with chronic rhinosinusitis in patients attending our center (as a referral center for nasal polyposis surgeries). Aspirin sensitivity,[13] GERD and sinusitis have been reported more often in severe asthma.[14] Previous studies underline the importance of timely recognition of aspirin sensitivity because of its predominant occurrence in patients with severe asthma.[13,15] In these studies, increased morbidities including more severe pulmonary function impairment, increased risk of ICU admission, a further need for higher doses of ICS and repeated bursts of systemic corticosteroids have been associated with fixed airway disease and repeated asthma attacks.[13] Our data in the current study was different from the mentioned previous studies. ACT scores and FEV1 did not have significant differences in both groups with and without aspirin hypersensitivity. Paradoxically, we found aspirin hypersensitivity more common in patients with moderate asthma and not with severe asthma, which could be explained not only by the lower number of the participants with severe asthma in the present study but also by their inability to perform the aspirin challenge test because of their severe condition. Also, various definitions of asthma severity and the method of AIA diagnosis in different studies can explain this distinct result. Aspirin sensitivity was not detected by the aspirin challenge test in 27% of patients in this study who had reported a history of a previous aspirin sensitivity reaction. The most common explanation is the possibility of misdiagnosis of the original reaction which led to erroneously attributing the symptoms to aspirin. The second one is that perhaps the patients had lost their sensitivity over time by dissipating IgE responses. The third possibility is undiagnosed concomitant viral infections at the time of the previous reactions which had lowered the threshold for aspirin hypersensitivity at that time. And finally, this possibility of lower cumulative dose in the performed challenge test compared to the dose which had previously resulted in hypersensitivity reactions in the patients.

Previous studies have demonstrated that patients suffering from asthma associated with aspirin hypersensitivity not only had poorly controlled asthma but also showed less appropriate responses to standard treatment.[3,13,16] In this study we could not find a meaningful difference in FEV1 and ACT scores in both groups of patients with and without aspirin hypersensitivity. We attributed these inconsistencies by the short follow-up period and the small sample size of the patients in our study.

To conclude, there was no association between aspirin sensitivity and poor response to the asthma standard treatment in patients with moderate to severe asthma.

CONFLICT OF INTEREST

None

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