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The Effect of Aspirin on Moderate to Severe Asthmatic Patients with Aspirin Hypersensitivity, Chronic Rhinosinusitis, and Nasal Polyposis

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ABSTRACT

Asthmatic patients may have aspirin-exacerbated respiratory disease and experience acute dyspnea and nasal symptoms within 3 hours after the ingestion of aspirin. This study aimed to evaluate the effect and outcome of daily low-dose aspirin in the treatment of moderate to severe asthma in patients with concomitant aspirin hypersensitivity and chronic rhinosinusitis with nasal polyposis (CRSwNP).

This clinical trial was conducted from February 2014 to February 2015 on 46 adult patients with moderate to severe asthma accompanied by CRSwNP. Patients with a positive aspirin challenge were blindly randomized in three groups receiving placebo/day (A); aspirin 100 mg/day (B); and aspirin 325mg/day (C), respectively. Clinical findings, FEV1 and ACT scores were recorded and compared before, during, and after treatment for 6 months (IRCT2015061521970N2).

Of 46 participants at baseline, 30 patients completed this 6-month trial study. The level of asthma control was significant; based on Asthma Control Test (ACT) when comparing the results in groups A and C and also groups B and C, but it was not significant when comparing ACT scores between groups A and B. FEV1 before and after treatment was significant when comparing groups A and B, groups A and C, and groups B and C.

To conclude, aspirin desensitization with a daily dose of 325 mg aspirin resulted in the

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improvement of long-term control of asthma. A daily aspirin dose of 100 mg was not associated with such an increase in ACT score.

Keywords: Aspirin; Asthma; Nasal polyps

INTRODUCTION

Asthma is a heterogeneous disease of the airways, with various phenotypes and characteristics according to the clinical manifestations, type of airway inflammation, lung function, and triggering factors. A subpopulation of asthmatic patients have aspirin-exacerbated respiratory disease (AERD) and experience acute dyspnea usually accompanied by nasal symptoms (rhinorrhea and/or nasal congestion) within 30 minutes to 3 hours after ingestion of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). These patients have the aspirin triad, including chronic rhinosinusitis with nasal polyposis (CRSwNP), moderate to severe bronchial asthma and, hypersensitivity reactions to aspirin or other NSAIDs.[1-3] The diagnosis of AERD is made via clinical suspicion and an aspirin challenge test, however, definitive diagnosis of AERD is only done via an aspirin challenge.[4,5]

The recommended approaches for the management of asthma with NSAID sensitivity include guideline-based treatment of bronchial asthma,[6,7] medical and surgical interventions for concomitant CRSwNP,[8] leukotriene-modifiers, avoidance of Cyclooxygenase-1 (COX-1) inhibitors, and in some patients, aspirin desensitization followed by daily treatment of high-dose aspirin. Aspirin desensitization is an effective modality in corticosteroid-dependent asthma.[9] Previous studies indicated that this procedure had resulted in a considerable reduction in disease activity, improvement in the quality of life, improvement in nasal and asthma symptom scores, reduction in sinusitis as well as the rate of hospitalizations for polyp surgery, and also corticosteroid requirements.[9] The daily suggested doses of aspirin were not the same in different studies, with a range between 100 mg to 1300 mg.[10] After aspirin desensitization, a maintenance dose of 650 mg twice daily was established for 6 months, which if tolerated was reduced to 325 mg twice daily.[4,11]

Considering the adverse effects of high-dose aspirin mentioned in some previous studies,[12] this study aimed to evaluate the effect and outcome of daily low-dose aspirin in the treatment of moderate to severe asthma in patients with concomitant aspirin hypersensitivity and CRSwNP.

PATIENTS AND METHODS

Participants

This double-blind placebo-controlled randomized clinical trial was conducted from February 2014 to February 2015 at the Allergy Department, Hazrat Rasoul-E-Akram Hospital, Iran University of Medical Sciences, Tehran. A total of 65 patients between the ages of 18 to 65 with moderate to severe asthma and CRSwNP were enrolled in this study. Moderate to severe asthma was defined according to the Expert Panel Report 3(EPR-3)[6] and the Global Initiative for Asthma (GINA) 2014 guidelines.[7] Diagnosis of CRSwNP was established by physical examination and paranasal sinus CT scan. Patients with serious systemic diseases (including bleeding disorders, gastrointestinal diseases, rheumatologic diseases, malignancies, renal diseases, cardiac diseases, hepatic diseases, psychologic diseases, and mastocytosis), pregnancy or breast-feeding, history of life-threatening anaphylactic reactions precipitated by NSAIDs, forced expiratory volume in 1 second (FEV1 less than 70% of predicted at the time of aspirin challenge), and patients receiving warfarin, beta-blockers, and angiotensin-converting enzyme inhibitors were excluded from the study. Signed informed consent was obtained from the patients following the Code of Ethics of the World Medical Association (Declaration of Helsinki). This research has been confirmed in the Iranian Registry of Clinical Trials with a registration reference of IRCT2015061521970N2. The protocol for the research project has been approved by the Ethics Committee of Hazrat Rasoul-E-Akram Hospital with the registration code of IR.IUMS.REC.1394.25458.

Study Design

A questionnaire including demographic data including sex, age, body mass index (BMI), history of co-morbidities including gastroesophageal reflux

disease (GERD) (empirical diagnosis of GERD is made based on the presence of typical esophageal symptoms), history of aspirin/ NSAID sensitization, smoking or second-hand exposure was completed by a physician for all participants. The level of asthma control was assessed using an Asthma Control Test (ACT). Spirometry was also performed for all patients. The patients with moderate to severe asthma were treated with a combination of inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA), a short-course (maximum 5 days) of oral corticosteroid if needed, and Leukotriene receptor antagonist (LTRA), according to guidelines [6,7] for three months. Concurrent GERD and rhinosinusitis were also treated. Clinical findings and ACT scores were recorded monthly.

An oral aspirin challenge was performed for all participants during two consecutive days. Drug withdrawal before the oral aspirin challenge includes LTRA, 1 week; short-acting antihistamines, 3 days; LABA, tiotropium bromide and theophylline, 48 hours and short-acting beta-agonists and ipratropium bromide, 8 hours. FEV1, vital signs, nasoocular and respiratory symptoms were recorded before the tests, and then every 30 min after aspirin administration. If the baseline FEV1 was at least 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 under intensive monitoring. If the patient had a history of a severe hypersensitivity reaction to aspirin or NSAIDs, the test was started with slightly lower doses of 10 and 15 mg aspirin. The challenge was interrupted if a decrease of at least 20% in FEV1 was observed (positive reaction) or when the maximum cumulative dose of aspirin (1000 mg) had been reached without a fall in FEV1 of 20% or greater and in the absence of nasoocular symptoms (negative reaction). The aspirin challenge was also considered as positive when a decrease of more than 15% was observed in FEV1, in association with severe extra-bronchial symptoms including nasal stuffiness and rhinorrhoea.

Patients with a positive aspirin challenge were assigned to one of the three distinct groups; using balanced blocked randomization (Group A received placebo/day, group B received aspirin 100 mg/day, group C received aspirin 325 mg/day. Patients were visited monthly and their clinical findings, possible adverse effects, and treatment adherence were recorded carefully. At the end of these 6 months, the patients were evaluated again using ACT and FEV1, and the results were compared with those obtained at the beginning of the study.

Statistical Analysis

Statistical analysis was performed; using relevant statistical tests where $p<0.05$ was considered significant. This study used common software (SPSS, version 16).

RESULT

Of the 46 participants at baseline, 30 completed this 6-month trial study, with 8 patients in group A, 9 patients in group B, and 13 patients in group C. Figure 1 displays the flowchart of the study and the reasons why several were lost to follow-up.

Major characteristics of the three groups of patients have been demonstrated in Table 1. Normality for age, FEV1 (pre-and-post), ACT scores, and their differences

Table 1. Major characteristics of the three groups of patients

Variable	Group			*P*	*P*	*P*
	A (N=8)	B (N=9)	C (N=13)	*a*	*b*	*c*
Sex Female	37.5%	89%	69.2%	**0.05***	0.2*	0.36*
Age (mean± SD) year	44.87±9.51	39±10.16	39.61±12.65	0.24	0.33	0.9
FEV1 (mean±SD) L/second	64.62±9.10	71.56±7.89	70.77±9.46	0.11	0.16	0.84
ACT (mean±SD)	13±4.78	14.56±3.32	15.77±3.04	0.44	0.12	0.39

* Mann-Whitney U test was applied. a) comparing group A and group B, b) comparing group A and group C, c) comparing group B and group C, Group A: Placebo Group B: Aspirin 100 mg/d Group C: Aspirin 325 mg/d,
ACT: asthma control test, FEV1: forced expiratory volume in 1 second

before and after aspirin consumption were determined which were indicative of well-modeled normal distribution (Table 2 and 3).

There was no significant difference between the age, gender of patients, asthma control score (using ACT), and FEV1 (before and after treatment) in the three groups.

As shown in Table 4, differences found in FEV1 before and after 6 months of treatment, were significant when comparing groups A and B, groups A and C, and groups B and C. But the FEV1 increments between groups A and C (-11.3), and groups B and C (-7.48) with a *p*-value of 0.001 were much more significant compared to groups A and B (-3.82) with a *p*-value of 0.04.

The changes in ACT scores before and after treatment were compared; using the Mann-Whitney U test (Table 5). ACT score was meaningful when comparing the results in groups A and C and also groups B and C ($p<0.001$), but it was not significant in comparing ACT scores between groups A and B ($p=0.09$).

Table 2. A comparison of forced expiratory volume in 1 second (FEV1) in the three studied groups

	FEV1 (mean±SD)		*p*	Mean difference
	Before	After		(95% CI of difference)
Group A (N=8)	64.62±9.10	67.25±9.13	0.17	-2.63 (-6.08 to 0.83)
Group B (N=9)	71.56±7.86	78±5.83	**0<0.001**	-6.44(-8.82 to -4.07)
Group C (N=13)	70.77±9.46	84.69±9.35	**0<0.001**	-13.92(-17.38 to -10.46)

Group A: Placebo, Group B: Aspirin 100 mg/d, Group C: Aspirin 325 mg/d

Table 3. A comparison of asthma control test (ACT) scores in the three studied groups

	ACT score (mean±SD)		*p*	Mean difference
	Before	After		(95% CI of difference)
Group A (N=8)	13±4.78	14.62±3.78	0.09	-1.62(-3.62to 0.37)
Group B (N=9)	14.56±3.32	18.11±2.93	**<0.001**	-3.55(-4.65 to -2.46)
Group C (N=13)	15.77±3.03	22.15±2.48	**<0.001**	-6.38(-7.56 to -5.21)

Group A: Placebo, Group B: Aspirin 100 mg/d, Group C: Aspirin 325 mg/d

Table 4. Comparison of forced expiratory volume in 1 second (FEV1) differences between each two specific groups

comparison	FEV1 mean difference (mean±SED)	*p* (95% CI of difference) a	*p* (95% CI of difference) b	*p* (95% CI of difference) c
Group A and B	-3.82±1.76	**0.046** (-7.56 to -0.75)		
Group A and C	-11.3±2.33		**<0.001** (-16.41 to -6.41)	
Group B and C	-7.48±2.10			**<0.001** (-11.86 to -3.10)

a) Comparing group A and group B, b) comparing group A and group C, c) comparing group B and group C, Group A: Placebo Group B: Aspirin 100 mg/d, Group C: Aspirin 325 mg/d

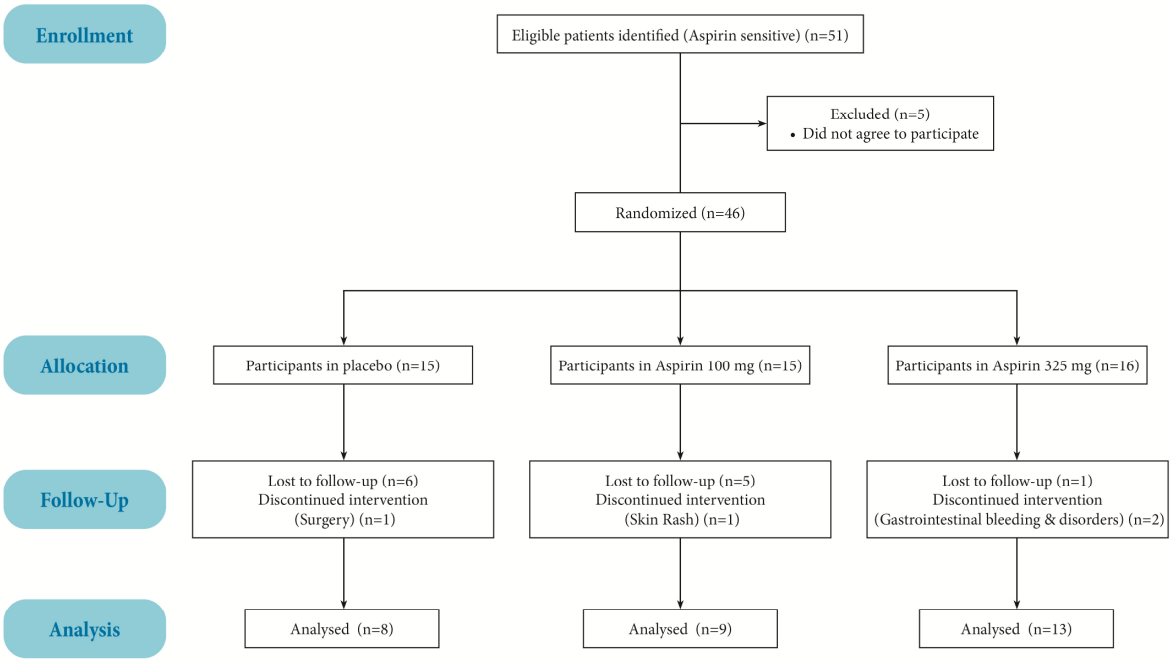

Figure 1. Recruitment and participation flow through the study based on the consort diagram. A total of 128 patients with CRSwNP and asthma were screened for aspirin hypersensitivity and 51 were eligible. Of them, 46 agreed to participate in this study. The patients were randomized into three groups receiving placebo, 100 mg aspirin, and 325 mg aspirin daily, respectively. Of 15 patients assigned to the placebo arm, 6 were lost in follow-up, and one discontinued participation due to surgical intervention. Six participants in the active arm received 100 mg aspirin daily doses left the study (5 were lost in follow-up and one discontinued participation because of a skin rash). From 16 patients assigned to the active arm with 325 mg aspirin daily doses, only one was lost in follow-up, but two discontinued the study because of gastrointestinal disorder.

Table 5. Comparison of asthma control test (ACT) score differences (before and after treatment) between two specific groups

Comparison	ACT difference (mean± SED)	p^* (95% CI of difference) a	p^* (95% CI of difference) b	p^* (95% CI of difference) c
Group A and B	-1.93±0.94	0.09 (-3.93 to 0.07)		
Group A and C	-4.76±0.75		**<0.001** (-6.75 to -2.77)	
Group B and C	-2.83±0.76			**0.001** (-4.41 to -1.24)

* Mann-Whitney U test was applied. a) comparing group A and group B, b) comparing group A and group C, c) comparing group B and group C, Group A: Placebo, Group B: Aspirin 100 mg/d, Group C: Aspirin 325 mg/d

DISCUSSION

In this study, we investigated the effect of low-dose aspirin in moderate to severe asthmatic patients with aspirin hypersensitivity and CRSwNP. We performed a comparative analysis using the data obtained from our patients suffering from concomitant moderate to severe asthma and aspirin sensitivity with two daily doses of

100 mg and 325 mg after successful aspirin desensitization procedures, in which daily doses of 325 mg were associated with a better improvement in asthma control scores compared to 100 mg daily doses.

The classic triad of symptoms including aspirin sensitivity, asthma, and nasal polyposis is known as aspirin-exacerbated respiratory disease (AERD).[13] Rajan et al have detected AERD in 7% of adult asthmatic patients, and twice that in severe asthmatic patients.[14] Therefore, AERD usually indicates a poor response to the therapeutic agents and therefore a more challenging asthma disease course.

Sweet et al performed a study with a daily aspirin dose of 1300 mg and found a significant reduction in the rate of emergency visits and hospitalizations in their asthmatic patients[3] Berges-Gimeno et al found improvements in the ACT score of their patients with less need for short-courses of systemic corticosteroid therapy, lower doses of inhaled corticosteroid therapy, and lower rates of hospitalizations with the same mentioned dose of aspirin in their patients.[2] Rozsasi et al compared two doses of aspirin after the desensitization procedure in their patients and concluded that 300 mg of daily aspirin intake was efficacious in the management of their patients resulting in a decreased need for asthma medication and improved pulmonary function tests.[15] Swierczynskan-Krepa performed a double-blind study on two groups of patients with aspirin-sensitive asthma and aspirin tolerant asthma and concluded that daily aspirin doses of 624 mg were beneficial only in those patients with aspirin sensitivity resulting in better ACT scores with less need for inhaled corticosteroids after 6 months of treatment.[16] In 2015, Esmailzadeh et al conducted a 6-month double-blind study with twice-daily doses of 625 mg aspirin which was associated with considerable improvements in ACT scores and pulmonary function tests in the treatment group compared with the group of patients who received a placebo.[17] Our results with low doses of aspirin were similar to Rozsasi et al which was associated with better asthma control and improvement in pulmonary function tests with a daily dose of 300 mg of aspirin, while daily doses of 100 mg were only associated with improvement in pulmonary function tests without achieving better asthma control. The clinical efficacy of aspirin treatment after desensitization in patients with AERD and its cost-effectiveness has been documented previously both in observational studies and in double-blind placebo-controlled trials.[18,19] However, considering the most common adverse effects including cutaneous flushing, urticaria, gastrointestinal bleeding, epistaxis, and asthma exacerbation,[19] the optimal maintenance dose after desensitization becomes an important issue in these patients. For example, gastrointestinal irritation has been reported in <3% of patients receiving doses of 100 mg aspirin.[19] In those studies with lower doses of daily aspirin, the frequency of gastrointestinal complications and the number of patients who dropped out from the study due to their intolerance to the drug, seemed to be significantly lower compared to those investigating high doses of daily aspirin (650 mg daily), although a statistically significant relationship was not demonstrated.[19] In the present study, the efficacy of daily doses of 325 mg was associated with a better improvement in asthma control scores compared to 100 mg daily doses.

However, there are some limitations to this study, of which the first was the low number of criteria investigated for a clinical response to treatment (ACT score and FEV1). Other limitation is the small number of patients who participated in the study and the large number of participants who left the study because of aspirin intolerance or their non-compliance in taking the drug continuously.

To conclude, it was demonstrated that aspirin desensitization with a daily dose of 325 mg aspirin may result in improvement in long-term control of asthma with significant increases in ACT score and pulmonary function test. Although daily aspirin doses of 100mg could increase ACT score and FEV1, it was not associated with a considerable improvement in asthma control in the patients. Further studies with larger sample sizes and more clinical and paraclinical criteria with a longer duration of evaluation are required for a more accurate determination of the most appropriate daily doses of aspirin to improve the management of patients with AERD.

CONFLICT OF INTEREST

None

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