

Original Article



Multifaceted interventions to reduce acute exacerbations in elderly asthmatics

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ABSTRACT

Background: Although many risk factors are known to be associated with poor asthma outcomes in the elderly, the literature on the effect of risk factor control on asthma outcomes in the elderly is very sparse.

Objective: To evaluate the role of multifaceted interventions in reducing acute exacerbations in elderly asthmatics.

Methods: A total of 100 subjects were randomly selected from our prospective cohort of elderly asthmatics aged 65 years or older and were provided multifaceted intervention for 1 year. Our multifaceted interventions included repeated education on asthma and inhaler technique for patients and their caregivers, provision of an action plan to cope with acute exacerbations, short message service to prevent follow-up losses, and oral replacement of magnesium. The primary outcome was an acute asthma exacerbation rate compared to the previous year.

Results: Ninety-two subjects completed this study, although only 58 subjects continued to take magnesium. Compared to the previous year, the acute asthma exacerbation rate showed a significant reduction from 67% to 50% ($p = 0.001$) and significant improvement was observed in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) ($p = 0.04$, $p = 0.036$ for each). Interestingly, a subgroup analysis revealed that predicted value of FEV₁ increased significantly in subjects who continued to take magnesium from 79.6% to 87.1% ($p = 0.008$).

Conclusion: To reduce acute exacerbations in elderly asthmatics, a multifaceted approach to increase medical awareness, proficiency and adherence to inhaler, assistance of caregivers and correction of micronutrients deficiency is likely to be effective. In addition, a continuous oral replacement of magnesium may increase FEV₁ in elderly asthmatics.

Keywords: Asthma; Aged; Exacerbation; Education

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INTRODUCTION

The socio-economic burden due to the rapidly increasing number of elderly people with asthma is of concern in aging societies. The clinical characteristics of asthma in the elderly are different from those of young adults. Moreover, in the elderly, a combination of a poor perception of asthma symptoms and multiple comorbidities may make rapid diagnosis and treatment difficult. For this reason, the rates of hospitalization and mortality due to asthma are higher in the elderly than in other age groups [1, 2], and the burden of asthma has increased.

Despite ongoing research, the pathophysiology and the risk factors of asthma in the elderly are not yet fully understood, and the literature concerning the effects of risk factor control on asthma outcomes in the elderly is limited.

Previously, we evaluated the risk factors to predict asthma exacerbation in elderly people with asthma and our results indicated that a state of depression, low cognitive function, poor proficiency in using inhaler devices, poor medication adherence, and a previous history of asthma exacerbations at baseline were important risk factors [3]. In addition, the absence of a caregiver and a micronutrient deficiency (magnesium and vitamin D) were also found to be risk factors for asthma exacerbations in elderly with asthma [4]. On the basis of these results, we designed multifaceted interventions to improve risk factors for asthma exacerbation, and aimed to examine their effects on asthma outcomes in the elderly with asthma.

MATERIALS AND METHODS

Study design

We established a prospective multicenter cohort study with planned 5-year follow-up (2008–2013) in Korea [3] in which approximately 1,000 patients had been recruited from 9 referral hospitals. We conducted subgroup analysis every year and this study was performed at the fifth year of cohort study as a single-arm interventional study with historical controls. A total of 100 subjects were selected from our cohort study and patient selection was randomized using an online random number generator (www.random.org). All participants were aged 65 years or older and had a history of asthma exacerbation within the last 3 years. The diagnosis of asthma was made by immunology physicians, based on a clinical history and the documented presence of a reversible airway obstruction: a positive bronchodilator response or $\geq 12\%$ and 200-mL improvement in forced expiratory volume in 1 second (FEV₁) after antiasthmatic treatment [5].

Baseline assessment at recruitment included sex, age, asthma control status, body mass index, smoking status, atopy, the Korean version of asthma control test (ACT) score [6], medication adherence, cognitive function and mood states, proficiency in using inhaler devices, and a history of previous exacerbations, as described in previous studies [3, 5]. The predicted percentage values for FEV₁ (FEV₁ %pred) and forced vital capacity (FVC %pred) were obtained using the Morris methods [7]. Serum magnesium levels were measured using colorimetry methods, and the reference range was 1.5–2.5 mg/dL.

Multifaceted interventions

The patients were treated by allergic physicians according to the Global Initiative for Asthma guidelines [8], and received multifaceted interventions to target known risk factors associated with asthma exacerbation. Our multifaceted approach included repeated

education on asthma and on improving inhaler techniques for patients and their caregivers, provision of an action plan to manage acute exacerbations, a brief message service to avoid losses to follow-up, and oral magnesium replacement therapy (48-mg tablet, 2 tablets 3 times daily). The participants with abnormal renal function or serum magnesium level higher than normal range (>3.0 mg/dL) were excluded from magnesium replacement therapy.

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (approval number: 1205-083-410) and we received informed consent from all patients.

Outcomes

The primary outcome for the multifaceted intervention efficacy was evaluated as an acute asthma exacerbation rate compared to the rate 12 months previously. The patients were requested to visit the clinic at regular 3-month intervals, over a total follow-up period of 12 months. At every visit, any occurrence of asthma exacerbation over the previous 3 months was checked. An asthma exacerbation was recorded when one of the following criteria was reported: (1) the use of systemic corticosteroids, or an increase in the stable maintenance dose for at least 3 days; (2) unscheduled visits to the outpatient clinic; and (3) hospitalization or an emergency department visit, due to an asthma attack.

The secondary outcomes were lung function improvement and the ACT score, and both were reviewed at each visit, according to the original cohort protocol. We compared the value of the baseline with that of the last visit.

Statistical analysis

The groups were compared using the *t* test, the Mann-Whitney *U* test, the chi-square test, or the Kruskal-Wallis test. A comparison of the asthma exacerbation rate for the current year and the year prior was performed using McNemar test. All statistical analyses were undertaken using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). A *p* value of < 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the study participants are presented in **Table 1**. The mean age was 73.8 years, and female patients comprised 48% of the study population. Sixty one patients (62.2%) were diagnosed with asthma when aged over 65 years. A total of 8 patients (8%) were lost to follow-up, mainly due to consent withdrawal.

Analysis for the primary outcome indicated that 46 events of acute asthma exacerbations occurred in 46 patients and the exacerbation rate (46 of 92, 50.0%) was significantly lower than that of the previous year (67 of 100, 67.0%) ($p < 0.001$) (**Fig. 1**).

Analysis for the secondary outcome showed that lung function test measurements, evaluated as FEV₁ %pred and FVC %pred, improved significantly after multifaceted interventions ($p = 0.004$, and $p = 0.036$, respectively). However, there was no difference in the ACT score either pre-, or postinterventions (**Fig. 2**).

Among 100 participants, 67 patients (67%) had experienced acute asthma exacerbations in the previous 12 months. There was no significant difference in the baseline characteristics except

Table 1. Baseline characteristics (n = 100)

Characteristic	Value
Age (yr)	73.8 ± 4.9
Female sex	47 (47.0)
Body mass index (kg/m ²)	23.5 ± 2.9
Asthma diagnosis > 65 yr	61/98 (62.2)
Smoking	
Never smoker	57/99 (57.6)
Ex-smoker	32/99 (32.3)
Current smoker	10/99 (10.1)
Pulmonary function	
FEV ₁ %pred	74.5 ± 25.2
FVC %pred	83.7 ± 21.1
FEV ₁ /FVC	67.9 ± 12.5
PNS abnormalities	61/99 (61.6)
MBPT positivity	80/93 (86.0)
PC ₂₀ (mg/mL)	6.9 ± 6.4
Peripheral eosinophils counts (/μL)	326.9 ± 273.6
Sputum eosinophil (%)	8.4 ± 10.3
Total IgE (IU/mL)	198.9 ± 327.3
ACT score	20.9 ± 4.2
Micronutrients	
Magnesium (mg/dL)	2.2 ± 0.2

Values are presented as mean ± standard deviation or number (%).

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PNS, paranasal sinuses; MBPT, methacholine bronchial provocation test; PC₂₀, provocative concentration of methacholine in a 20% fall in FEV₁; ACT, asthma control test.

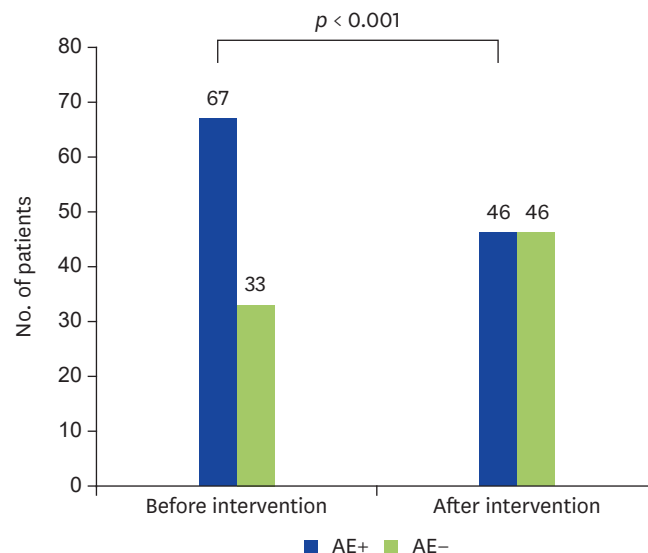


Fig. 1. Acute exacerbations before and after multifaceted interventions. AE+, patients with acute exacerbations; AE-, patients without acute exacerbations.

for lung functions and ACT score between the 2 groups with or without asthma exacerbations during the previous 12 months (Table 2). In the current study, acute exacerbations occurred in 42 patients (66.7%) in the group with prior acute exacerbations and in 4 patients (13.8%) in the group without prior acute exacerbations ($p < 0.001$). The history of acute exacerbations in the previous 12 months correlated significantly with the recurrence of acute exacerbations.

Among 92 participants who completed the study, only 60 patients (65.2%) continued with the magnesium supplement therapy. The reasons given for discontinuation of magnesium

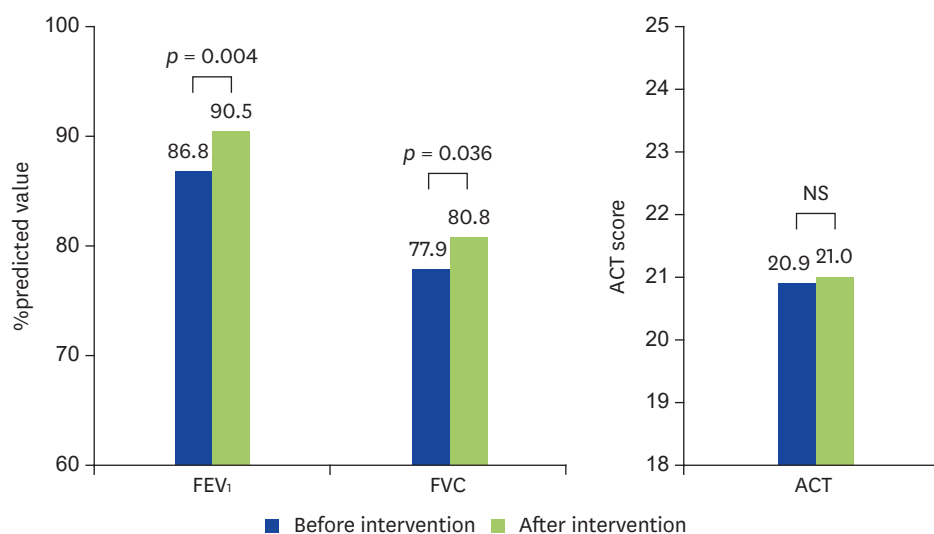


Fig. 2. Change of lung functions and symptom score according to the interventions. FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ACT, asthma control test; NS, not statistically significant.

therapy were as follows: 8 patients (25%) reported taking too many medications, 7 patients (21.9%) reported adverse reactions, 5 (15%) withdrew from magnesium therapy voluntarily, 4 (12.5%) reported aggravation of a disease other than asthma, and 8 (25%) reported other reasons. Nausea and diarrhea were the common adverse reactions of magnesium supplement therapy. When analyzing the correlation between the magnesium supplement and asthma exacerbations, a significantly lower asthma exacerbation rate was observed in the group with continuous magnesium supplement compared to the group without magnesium supplement (41.6% vs. 65.6%, $p = 0.029$). Moreover, there was significant improvement in FEV₁ %pred and

Table 2. Characteristics between groups with or without exacerbation in the previous year

Characteristic	With exacerbation (n = 67)	Without exacerbation (n = 33)	p value
Age (yr)	73.3 ± 4.4	73.8 ± 6.0	0.290
Female sex	34 (50.7)	13 (39.4)	0.196
Body mass index (kg/m ²)	23.2 ± 2.9	23.9 ± 2.8	0.289
Asthma diagnosis > 65 yr	40 (59.7)	23 (69.7)	0.297
Smoking			0.797
Never smoker	38 (56.7)	19/32 (59.4)	
Ex-smoker	22 (32.8)	10/32 (31.3)	
Current smoker	7 (10.4)	3/32 (9.4)	
Pulmonary function			
FEV ₁ %pred	71.4 ± 27.2	81.5 ± 18.7	0.037*
FVC %pred	80.7 ± 22.7	90.4 ± 15.0	0.014*
FEV ₁ /FVC	67.1 ± 13.9	69.7 ± 8.8	0.274
PNS abnormalities	41 (61.2)	20/32 (62.5)	0.541
PC ₂₀ (mg/mL)	6.3 ± 6.5	7.9 ± 6.5	0.322
Peripheral eosinophils counts (/μL)	308.4 ± 391.7	346.9 ± 612.8	0.728
Sputum eosinophil (%)	9.4 ± 11.0	6.6 ± 8.7	0.362
Total IgE (IU/mL)	154.0 ± 189.5	322.3 ± 558.9	0.430
ACT score	19.6 ± 4.5	23.6 ± 1.2	<0.001*
Micronutrients			
Magnesium (mg/dL)	3.0 ± 5.4	2.3 ± 0.2	0.670

Values are presented as mean ± standard deviation or number (%).

FEV₁, forced expiratory volume in 1 second; FVC, Forced vital capacity; PNS, paranasal sinuses; PC₂₀, provocative concentration of methacholine in a 20% fall in FEV₁; ACT, asthma control test.

* $p < 0.05$, statistically significant differences.

FVC %pred in the group with continuous magnesium supplement (FEV₁ %pred: from 79.6 ± 23.7 to 87.1 ± 20.0, $p = 0.008$, and FVC %pred: from 82.9 ± 25.4 to 91.8 ± 20.6, $p = 0.047$). However, no difference in the ACT score was observed between the groups.

DISCUSSION

Until recently, the well-known risk factors or predictors associated with asthma exacerbations in the elderly were smoking, obesity, combined chronic obstructive pulmonary disease, poor asthma control, poor adherence and proficiency in relation to inhaled corticosteroid (ICS) therapy, depression, and cognitive dysfunction [1, 9-11]. The absence of a caregiver was also found to be a risk factor for asthma exacerbations in elderly participants with asthma in our study (unpublished data), and a recent study has shown that physical performance should be considered as a predictor of asthma exacerbations [12]. Considering these results, a multifaceted approach is needed to improve asthma outcomes in the elderly.

Some studies have examined the effects of risk factor control in the elderly, however the results have not been consistent. In a Japanese study on elderly patients with asthma, caregiver assistance in using ICS therapy effectively improved lung function [13]. In contrast, an American study providing standard educational information and instructions concerning peak flow meter use and asthma action plans failed to improve asthma outcomes in the elderly [14]. Therefore, in elderly patients with asthma, assistance from caregivers appears to be an important component to enhance the effects of education and treatment. The presence of caregivers can be effective in compensating for the negative effect of depression and cognitive dysfunction, which are both very common in elderly patients with asthma. Depression and impaired cognitive function have been associated with poor proficiency and adherence to ICS medication [15]. As such, caregivers may provide important support in maintaining regular medication use. In our study, we also provided repeated education on asthma and inhaler techniques for patients and their caregivers. We consider this to be one reason why we were able to improve asthma outcomes.

Inadequate nutrition is prevalent in the elderly due to tooth loss, impaired digestive function, multiple comorbidities and medications, decreased physical activity, and low income [16]. Previously, we have published data on serum micronutrient levels and the clinical characteristics of elderly study participants with asthma, and showed that lower serum magnesium levels were significantly related to a history of asthma exacerbation [4]. Similarly, one study has reported that lower serum magnesium correlated with more severe asthma, and that magnesium deficiency caused increased bronchial hypersensitivity and airway muscle contraction [17]. On the basis of these results, we provided oral magnesium supplements to the participants in the present study. We observed a significant decrease in the asthma exacerbation rate and an increased lung function in the magnesium supplement group. We consider these results represent the correction of a micronutrient deficiency that could decrease future asthma exacerbations in the elderly. However, 35% of patients failed to continue oral magnesium therapy for varying reasons, which may indicate difficulty in the general use of magnesium supplement therapy. Several studies have reported that nutritional education for caregivers or patients was effective in improving the nutritional status of elderly patients [18, 19]. The improvement plan of adherence to medication and a tailored nutritional education program for the elderly should be considered in a future study.

In this study, a history of acute exacerbations in the previous year was a major predictor of future exacerbations and this is consistent with other literature [3, 20]. Therefore, it is important to be alert concerning elderly with asthma who have a history of prior acute exacerbations, and to aim to prevent further exacerbations through an active multifaceted intervention.

The limitations of this study involve the relatively small study population, the short intervention period and no control arm. A larger randomized controlled study is needed to clarify the efficacy of multifaceted interventions in the elderly.

Nevertheless, given limited data available on the effect of controlling risk factors to prevent an acute exacerbation in a multifaceted way in the elderly with asthma, this study is useful and confirms the need for further targeted research in this area.

In summary, to reduce acute exacerbations in the elderly with asthma, a multifaceted approach to increase medical awareness, proficiency and adherence to inhaler therapy, assistance of caregivers, and correction of micronutrients deficiency is likely to be effective.

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