의학석사 학위 논문

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College of Medicine

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by

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A thesis submitted to the Department of Clinical Medical Sciences in partial fulfillment of the requirements for the Degree of Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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ABSTRACT

Introduction: The association of inhaler use with hemoptysis has rarely been reported in patients with non-cystic fibrosis (CF) bronchiectasis. We aimed to elucidate the effect of inhaler use on the development of hemoptysis in patients with non-CF bronchiectasis.

Methods: In a case-crossover study of 192 non-CF bronchiectasis patients with a history of hemoptysis and inhaler use, the risk of hemoptysis associated with the use of inhalers was elucidated. Two inhaled corticosteroids/long-acting β_2-agonists (ICS/LABA), one long-acting muscarinic antagonist (LAMA), and one short-acting β_2-agonist (SABA) were evaluated. The case and control periods were defined respectively as 0-30 days and 180-210 days before hemoptysis.

Results: The risk of hemoptysis during the case period was 3.51 times higher than during the control period with any use of inhalers (95% confidence interval (CI), 1.96-6.28). The results of clinically significant hemoptysis showed good agreement with those of total events. These associations were consistent with the sensitivity analyses. In the sub-analysis according to inhaler type, ICS/LABA and SABA were significantly associated with an increased risk of hemoptysis (aOR 2.62, 95% CI 1.25-5.45; aOR 2.51, 95% CI 2.23-5.15).

Conclusions: In patients with non-CF bronchiectasis, the use of inhalers, especially including β_2-agonist, was associated with an increased risk of hemoptysis.

Key words: Bronchiectasis; Hemoptysis; Inhaled corticosteroids; Bronchodilators

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Contents

List of tables and figures

List of abbreviation

BMI: Body mass index

CF: Cystic fibrosis

COPD: Chronic obstructive pulmonary disease

CT: Computed tomography

DPI: Dry power inhaler

ER: Emergency room

FEV1: Forced expiratory volume in 1s

FVC: Forced vital capacity

ICS/LABA: Inhaled corticosteroids/long-acting β-agonists

LAMA: Long-acting muscarinic antagonists

MDI: Metered-dose inhaler

SABA: Short-acting β-agonists

TB: Tuberculosis

Introduction

Bronchiectasis is a chronic lung disease that results from repeated cycles of airway infection and inflammation. In the course of its progression, bronchiectasis may induce variable complications such as airflow limitation, combined infection, and hemoptysis. Hemoptysis is rare, but potentially life-threatening. Bronchiectasis is the main cause of hemoptysis, accounting for ~20% of cases.[1]

Besides hemoptysis, airflow limitation is another clinical issue in non-cystic fibrosis (CF) bronchiectasis, which presents with a physiology of chronic obstructive pulmonary disease (COPD).[2,3] Supporting inhaled corticosteroids (ICS) and bronchodilator therapy, ICS have been reported to improve clinical outcomes, including symptoms, exacerbation frequency, quality of life, and lung function.[4-7] Also, inhaled β_2-agonists and anticholinergics can improve symptoms and lung function in bronchiectasis.[8,9] Therefore, in practice inhaler therapy is commonly applied to control respiratory symptoms even though there is insufficient evidence to recommend their routine use.[4,10,11]

Despite the prevalent use of inhalers in bronchiectasis, few well-designed studies have reported an association of inhaler use with development of hemoptysis. Several case reports suggested that salbutamol or its excipient might be a cause of hemoptysis in patients with bronchiectasis,[12,13] and there are web-based consumer reports of hemoptysis development during inhaler use in less than 1% of patients.[14] In this context, we aimed to elucidate the effect of inhaler use on the development of hemoptysis in patients with non-CF bronchiectasis.

Methods

Study design and participants

A case-crossover study was performed at the Seoul National University Hospital and its affiliated Boramae Medical Center between January 2007 and December 2011. We applied the case-crossover design, which is a variation of case-control study and has been used when the exposures of a specific factor temporarily increase a risk of development of acute event. The risk period (case period) is defined as a time interval immediately prior to the hemoptysis events, while the control periods are time intervals that are prior to and equal in the length of the risk period in the absence of hemoptysis (Figure 1). The risk of development of hemoptysis can be evaluated by comparing with the exposures to inhalers in case and control periods, and calculating the average incidence rate ratio.

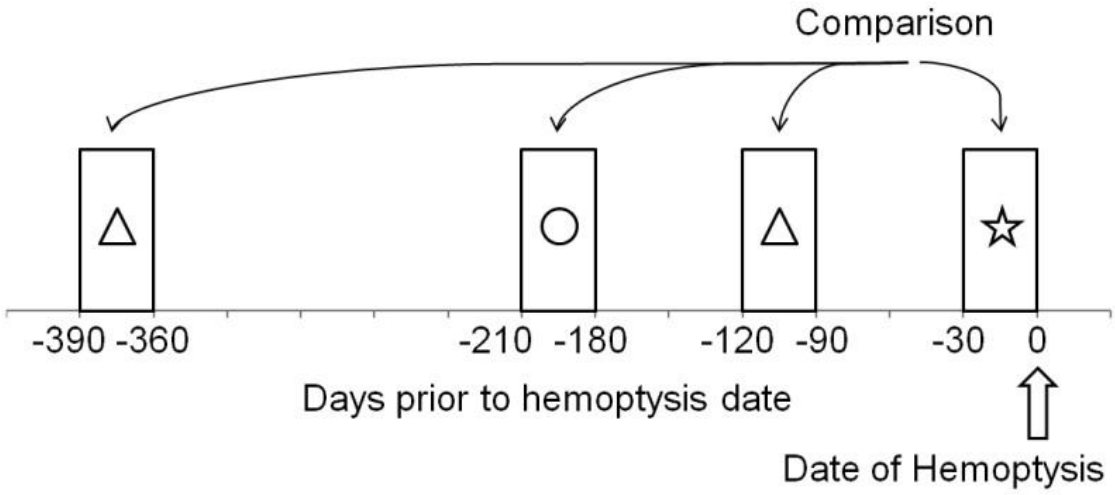

Figure 1 Case-crossover design of the study

A star indicates the case period of 0-30 days before the date of the hemoptysis event. An empty circle indicates the main control period of 180-210 days before hemoptysis. The empty triangles indicate additional control periods of 90-120 and 360-390 days before hemoptysis. Inhaler prescriptions during the control and the case periods were compared.

We considered the hypothesis that the inhaler effect is relatively short-term,[15,16] and whether it is caused by substances itself or the mechanical effects of inhalers when designing the study.

Among adult patients with non-CF bronchiectasis confirmed by chest computed tomography (CT), we enrolled patients with documented events of hemoptysis and a history of inhaler use during 390 days preceding hemoptysis. Patients with hemoptysis following a procedure or surgery were excluded.

The underlying severity of bronchiectasis or the development of hemoptysis itself can influence the decision to prescribe inhalers to patients with non-CF bronchiectasis. As the case period and control period are defined in the same subjects in the case-crossover study, the results of study were not affected by individual factors, such as age, sex, and comorbidities, to minimize the selection bias due to disease severity.

This retrospective data collection was approved by the Institutional Review Board of Seoul National University (IRB No.: H-1205-062-410) and Boramae Medical Center (IRB No.: 06-1212-98), and was performed in accordance with the Declaration of Helsinki.

Definitions of hemoptysis, case, and control periods

Hemoptysis was defined as an expectoration of any amount of blood requiring a clinic visit, medications or imaging evaluation. Clinically significant hemoptysis was defined as hemoptysis requiring an emergency room (ER) visit, admission or embolotherapy.

The case period was defined as the 30 days preceding the hemoptysis event, because usual inhaler dosages are prescribed on a monthly basis and highlight the acute or cumulative effect of inhaled drugs. The duration of inhaler use would be expected to be approaching approximately 3 months before occurrence of an hemoptysis event (inhalers are usually prescribed monthly and stable patients will visit outpatient clinics every 2 or 3 months in study institutes), so we selected 180-210 days before hemoptysis as the main control period. Additionally, 90-120 and 360-390 days before hemoptysis were selected as the control periods in the following analyses.

Types of inhaler

Two types of ICS/LABA (fluticasone/salmeterol and budesonide/formoterol), one type of LAMA (tiotropium), and one type of SABA (salbutamol) were evaluated. Short-acting

muscarinic antagonists were excluded because their administration has been decreasing due to concern regarding an increased cardiovascular risk. ICS monotherapy was also excluded, because they are not usually recommended in patients with a physiology of COPD and the small number of users.

Assessment of hemoptysis risk

All prescriptions including the targeted inhalers during the case and control periods were recorded. The risk of hemoptysis development was assessed according to exposure to targeted inhalers during each period by calculating the odds ratios. To correct for the effect of underlying disease severity or medications during each period, we adjusted the results according to the frequency of hospitalization (visit to emergency room (ER) and/or admission) and the prescription of anticoagulants and anti-platelet agents during each period and then calculated the adjusted ORs (aOR). Due to the mechanical effect of inhaler devices, additional analysis was performed after classification of inhalers as dry power (DPI) or metered-dose (MDI) inhalers.

Assessment of bronchiectasis severity and comorbidities

The study population was classified by age, Charlson comorbidity index[17], airflow limitation measured by FEV_1% predicted, bronchiectasis severity measured by the bronchiectasis scoring system, the presence of tuberculosis (TB)-destroyed lung, and bronchial arterial hypertrophy. Pulmonary function test results during a stable status were recorded. Chest CT images around the case period were selected, and the bronchiectasis score was calculated in the manner that total lung area was divided into the right upper lobe, the right middle lobe, the right lower lobe, the left upper lobe except the lingular segment, the lingular segment, the left lower lobe, and then, the number of areas involved were counted. TB-destroyed lung was defined as a destructive parenchymal change due to the preceding pulmonary TB, with the involvement of more than one lobe. Bronchial artery hypertrophy was defined as bronchial arteries with a diameter greater than 2 mm.

Statistical analysis

The data are presented as median and IQR for age and durations, and means and standard deviations for the other continuous variables, and as numbers (%) for categorical variables. The risk of development of hemoptysis was estimated by conditional logistic regression. Time-dependent changes in confounding variables were evaluated by linear mixed regression. OR and aOR are presented with 95% confidence intervals (CI).

Acute exacerbation during the case period increases the use of inhalers, which might make assessment of whether the increased use of inhalers induces hemoptysis difficult. To avoid this protopathic bias, aOR was also assessed by sensitivity analysis after exclusion of inhalers prescribed within 7 days before hemoptysis events. Subgroup analyses according to the severity of bronchiectasis or comorbidities were performed.

Statistical significance was determined with a p value of 0.05. Data were analyzed using PASW Statistics, version 18 (IBM, Armonk, NY, USA).

Results

Baseline characteristics of the study population

A total of 417 candidates who had bronchiectasis and a history of hemoptysis were screened for the study at Seoul National University Hospital and its affiliated Boramae Medical Center between January 2007 and December 2011. 225 patients were excluded because they had non-pulmonary bleeding or procedure/operation-related bleeding, or no history of inhaler use for 390 days before hemoptysis event, so 192 patients were included in the analysis. Baseline characteristics of the study population are shown in Table 1. There were 115 (59.9%) male patients, and the median age was 68 years [IQR 59, 74]. Pulmonary function data were available in 167 patients and showed a significant degree of airflow limitation, and 43.7% of subjects had a history of smoking. Airway hyperresponsiveness was found in 9.4%. The most common type of inhaler was ICS/LABA (59.4%). The median duration from the latest prescription of inhalers to hemoptysis event was 53 days [IQR 22, 91]. Clinically significant events that required an ER visit, admission, and/or embolotherapy occurred in 89 cases (46.4%).

Table 1 Baseline characteristics of study subjects

A. Demographics

	Total (N=192)
Male, n (%)	115 (59.9)
Age, years, median (Q1, Q3)	68 (59, 74)
BMI, kg/m^2	21.2 ± 4.0
Follow-up duration, months, median (Q1, Q3)	84 (47, 132)
Pulmonary function test (n =167)	
FEV1 (L) *	1.29 ± 0.56
(% predicted)	56.9 ± 23.4

FVC (L) *	2.32 ± 0.84
(% predicted)	74.7 ± 49.8
FEV1/FVC (%)	57.0 ± 18.0
Bronchodilator response, n (%)	18 (9.4)
History of smoking	
Never, n (%)	91 (47.4)
Ex, n (%)	53 (27.6)
Current, n (%)	31 (16.1)
Unknown, n (%)	17 (8.9)
Pack-year	38.2 ± 20.7
Charlson comorbidity index	2.1 ± 1.6

B. History of inhaler use

	Total (N=192)
Inhaler use (at least 1 time), n (%)	
ICS/LABA	114 (59.4)
LAMA	98 (51.0)
SABA	91 (47.4)
Inhaler use pattern, n (%)	
Single device	99 (51.6)
Multiple devices	93 (48.4)
Inhaler type (at least 1 time), n (%)	
Dry power inhaler	168 (87.5)
Metered dose inhaler	91 (47.4)
Duration from last inhaler prescription till hemoptysis (days), median (Q1, Q3)	53 (22, 91)

C. Hemoptysis events and other confounders

	Total (N=192)
Clinically significant events, n (%)	89 (46.4)
Emergency room visit	85 (44.3)
Admission	64 (33.3)
Embolotherapy	47 (24.5)
Anticoagulation, n (%)	8 (4.2)
Anti-platelet therapy, n (%)	19 (9.9)

* Post-bronchodilator FEV1 and FVC were presented.

Data expressed as mean (SD) unless otherwise indicated.

Risk of hemoptysis according to inhaler use

In patients with experience of any inhaler, the risk of hemoptysis during the case period was 3.51 times higher than during the control period (95% CI, 1.96-6.28) (Table 2), when the frequency of inhaler use during the case period was compared with that during the control period, defined as 180-210 days before hemoptysis. With regard to inhaler types, ICS/LABA and SABA increased the risk of hemoptysis significantly (aOR 2.62, 95% CI 1.25-5.45; aOR 2.51, 95% CI 2.23-5.15).

When the hemoptysis event was restricted to only those clinically significant and requiring a visit to the ER, admission and/or embolotherapy, any inhaler use during the case period was associated with a higher risk of hemoptysis (aOR 2.98, 95% CI 1.26-7.01). Additionally, LAMA increased the risk of hemoptysis in patients with non-CF bronchiectasis as well as ICS/LABA and SABA.

Table 2 Risk of hemoptysis according to inhaler use

	Control period* n (%)	Case period† n (%)	Univariate OR (95% CI)	P value	Adjusted OR‡ (95% CI)	P value
Total events (n=192)						
Any inhaler	118 (61.5)	156 (81.3)	3.53(1.99-6.27)	<0.001	3.51 (1.96-6.28)	<0.001
ICS/LABA	68 (35.4)	89 (46.4)	2.91 (1.47-5.77)	0.002	2.62 (1.25-5.45)	0.010
LAMA	64 (33.3)	76 (39.6)	2.20 (1.04-4.65)	0.039	1.50 (0.68-3.32)	0.317
SABA	31 (16.1)	53 (27.6)	3.0 (1.52-5.94)	0.001	2.51 (2.23-5.15)	0.012
Clinically significant events (n=89)						
Any inhaler	59 (66.3)	74 (83.1)	3.14 (1.34-7.36)	0.008	2.98 (1.26-7.01)	0.013
ICS/LABA	34 (38.2)	41 (46.1)	2.62 (1.38-4.96)	0.047	2.34 (1.19-4.63)	0.036
LAMA	31 (34.8)	38 (42.7)	3.40 (1.68-6.88)	0.047	2.80 (1.34-5.84)	0.046
SABA	17 (19.1)	23 (25.8)	2.73 (1.51-4.94)	0.36	2.46 (1.33-4.56)	0.036

* Control period: 180-210 days before hemoptysis

† Case period: 0-30 days before hemoptysis

‡ Adjusted by the frequency of hospitalization, the concomitant inhaler use, the prescription of anticoagulants and anti-platelet agents during each period

Aggravation of the underlying disease or acute exacerbation of respiratory disease can affect inhaler prescription and use pattern. To avoid this protopathic bias, sensitivity analysis was performed after exclusion of patients who were prescribed an inhaler in the 7 days preceding the hemoptysis events (Table 3). The results in terms of an increased hemoptysis risk in patients using any type of inhaler, ICS/LABA, and SABA were persistent. However, restriction of the analysis to clinically significant events resulted in an increased risk of hemoptysis with use of any inhaler, while the type of inhaler lost its statistical significance.

Table 3 Risk of hemoptysis - sensitivity analysis excluding patients prescribed an inhaler in the last 7 days

	Control period*	Case period†	Univariate OR	P	Adjusted OR‡	P
	n (%)	n (%)	(95% CI)	Value	(95% CI)	Value
Total events (n=192)						
Any inhaler	118 (61.5)	153 (79.7)	3.33 (1.87-5.94)	<0.001	3.28 (1.83-5.88)	<0.001
ICS/LABA	68 (35.4)	90 (46.9)	3.2 (1.57-6.51)	0.001	2.97 (1.38-6.38)	0.005
LAMA	64 (33.3)	74 (38.5)	2.0 (0.94-4.27)	0.074	1.26 (0.56-2.83)	0.583
SABA	31 (16.1)	51 (26.6)	2.82 (1.42-5.61)	0.003	2.34 (1.14-4.83)	0.021
Clinically significant events (n=89)						
Any inhaler	59 (66.3)	73 (82)	3.0 (1.28-7.06)	0.012	2.80 (1.18-6.65)	0.020
ICS/LABA	34 (38.2)	42 (47.2)	2.31 (0.94-5.68)	0.109	2.01 (0.79-5.16)	0.087
LAMA	31 (34.8)	37 (41.6)	3.0 (0.81-11.08)	0.099	1.79 (0.44-7.34)	0.474
SABA	17 (19.1)	22 (24.7)	1.83 (0.68-4.96)	0.232	1.45 (0.51-4.10)	0.490

* Control period: 180-210 days before hemoptysis

† Case period: 8-30 days before hemoptysis

‡ Adjusted by the frequency of hospitalization, the concomitant inhaler use, the prescription of anticoagulants and anti-platelet agents during each period.

The combined use of two inhalers was associated with a higher risk of hemoptysis compared to the sum of single uses of each inhaler (Table 4). A combination regimen that increased the risk of hemoptysis was SABA with ICS/LABA and ICS/LABA with LAMA. SABA with LAMA showed a tendency to increased risk, albeit not significantly.

In the analysis of inhaler type (*i.e.*, DPI or MDI), the risk of hemoptysis increased irrespective of device type (aOR 2.99, 95% CI 1.58-5.66 for DPI; aOR 2.60, 95% CI 1.27-5.33 for MDI).

Table 4 Risk of hemoptysis according to inhaler combination

Type of inhaler combination (n=192)	Control Period* n (%)	Case period† n (%)	Univariate OR (95% CI)	P value	Adjusted OR‡ (95% CI)	P value
SABA and ICS/LABA						
SABA single or ICS/LABA single	55 (28.6)	76 (39.6)	3.10 (1.52-6.32)	0.002	3.12 (1.46-6.68)	0.003
SABA with ICS/LABA	30 (15.6)	43 (22.4)	5.33 (1.55-18.30)	0.008	5.52 (1.53-20.01)	0.009
SAMA and LAMA						
SABA single or LAMA single	59 (30.7)	75 (39.1)	1.94 (1.08-3.49)	0.026	1.92 (1.07-3.45)	0.029
SABA and LAMA	27 (14.1)	34 (17.7)	4.5 (0.97-20.83)	0.054	3.61 (0.69-19.00)	0.130
ICS/LABA and LAMA						
ICS/LABA single or LAMA single	73 (38.0)	95 (49.5)	3.0 (1.52-5.94)	0.002	3.07 (1.53-6.17)	0.002
ICS/LABA with LAMA	33 (17.2)	41 (21.4)	5.0 (1.10-22.82)	0.038	4.76 (1.02-22.24)	0.048

* Control period: 180-210 days before hemoptysis

† Case period: 0-30 days before hemoptysis

‡ Adjusted by the frequency of hospitalization, the prescription of anticoagulants and anti-platelet agents during each period

Risk of hemoptysis according to control period

With the control period of 90-120 days before hemoptysis, inhaler use did not affect development of hemoptysis (Figure 2). However, with control periods of 180-210 days and 360-

390 days before hemoptysis, the risk of hemoptysis during the case period increased significantly (aOR 3.51, 95% CI 1.96-6.28 for 180-210 days; aOR 3.13, 95% CI 1.88-5.21 for 360-390 days). Analysis of clinically significant events showed strong agreement with the total events results.

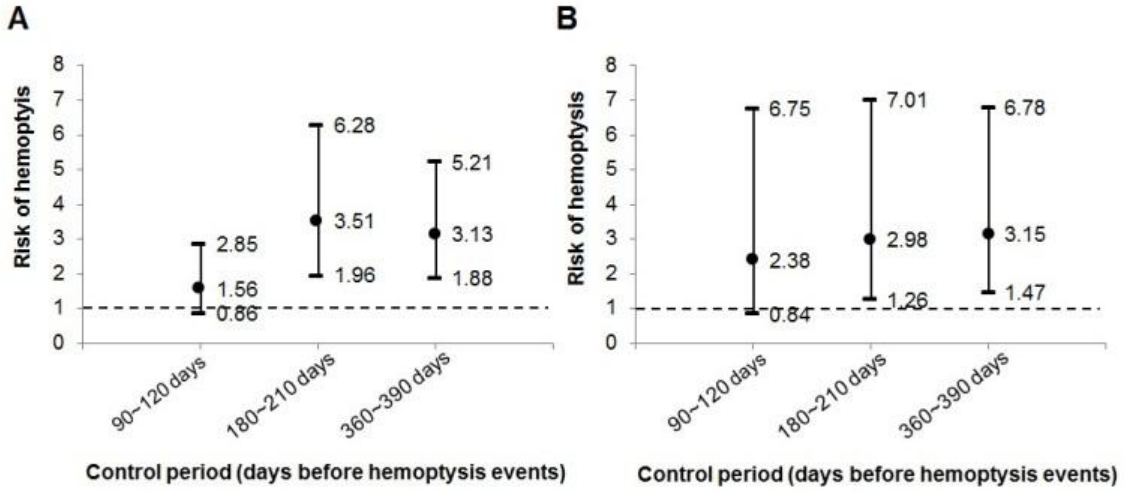

Figure 2 Assessment of the risk of hemoptysis according to control period.

The vertical lines indicate 95% CI, and the black dots indicate adjusted ORs. The dotted lines show an aOR value of 1. (A) Risk of total hemoptysis events (B) Risk of clinically significant hemoptysis events.

Subgroup analysis

Subgroup analyses were performed according to age, Charlson comorbidity index, severity of airflow limitation measured by FEV_1% predicted, bronchiectasis score, presence of TB-destroyed lung, and the presence of bronchial artery hypertrophy (Figure 3). Inhaler use during the case period increased the risk of hemoptysis compared with that during the control period irrespective of subgroup variables, except in patients with more comorbidities and bronchial arterial hypertrophy. In subgroups classified by the presence of TB-destroyed lung and bronchial artery hypertrophy, the difference in hemoptysis risk between the groups was more marked.

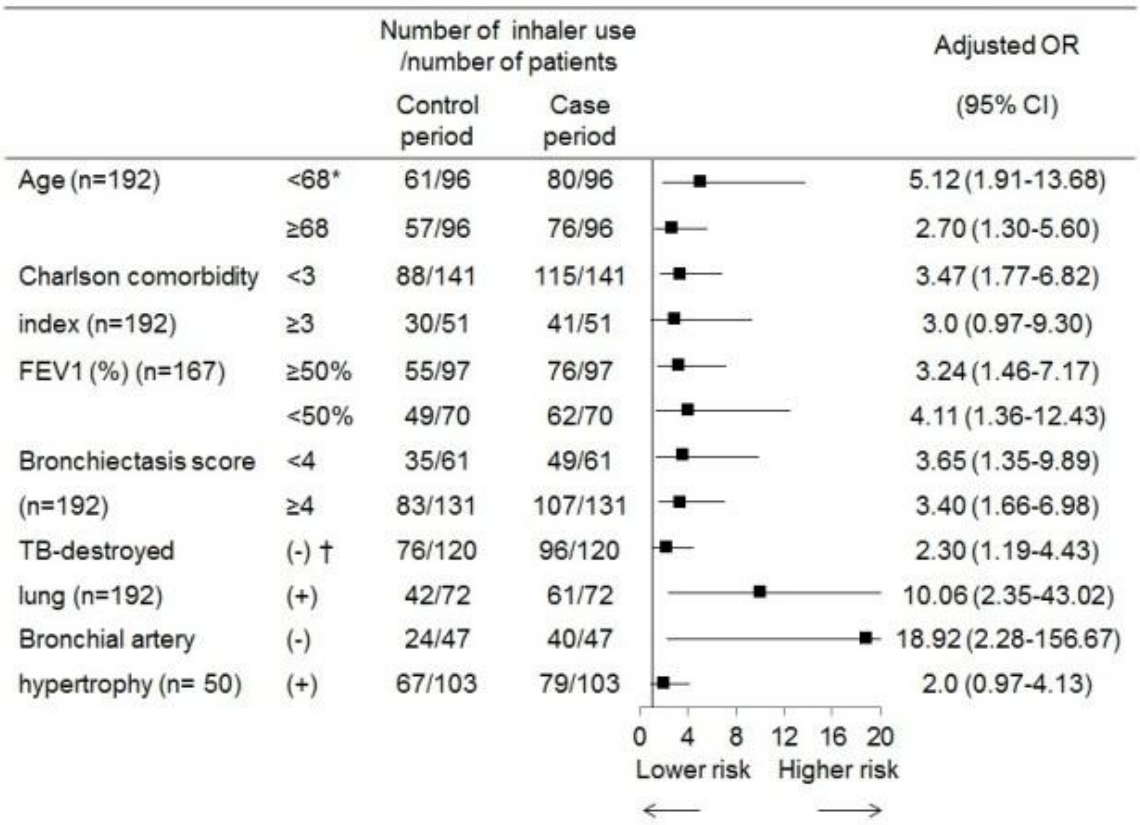

Figure 3 Risk of hemoptysis in subgroup analyses.

Risks of hemoptysis associated with the use of inhalers compared with the control period (180-210 days before hemoptysis) are shown together with the 95% CIs.

* Median age of the study population is 68 years.

† (-) and (+) respectively mean the absence and presence of the condition.

Discussion

Inhaled therapy, especially with inhalers containing ICS and bronchodilators, has been used to target airway diseases such as COPD and asthma. Despite their benefits, various adverse events related to the aerodynamic characteristics of the drugs have been reported.[18] In clinical settings, bronchodilators with/without ICS are prescribed in bronchiectasis patients with airflow limitation, but some patients complain of hemoptysis despite improvement in dyspnea. Our results suggest this not to be a baseless complaint.

This case-crossover study of 192 patients with non-CF bronchiectasis revealed that the use of inhalers containing ICS/LABA and SABA is associated with development of hemoptysis. The increased risk of hemoptysis was consistent regardless of inhaler type and control period, and in the sensitivity and subgroup analyses. The association of total and clinically significant hemoptysis events was prominent in patients who used ICS/LABA and/or SABA.

The mechanisms underlying this association cannot be confirmed due to the scarcity of reports. Nevertheless, we are focusing on the vasodilating effects of inhaler therapy on airway vasculature. In bronchiectasis, chronic airway inflammation leads to the hypertrophy and tortuosity of bronchial vessels; rupture of these vessels results in hemoptysis. In an animal study, β-adrenergic stimulation induced dilations of arterioles and venules.[19] Inhaled β_2-agonists affect the airway vascular smooth muscles and cause vasodilation and increased airway blood flow.[20,21] The use of β_2-agonists likely accentuate vasodilation of vulnerable or ruptured vessels and recruitment of blood flow, resulting in development of hemoptysis in susceptible populations.

Anticholinergic agents including LAMA also have vasodilatory effects because activation of the muscarinic M3 receptor, which is inhibited by LAMA, is responsible for pulmonary vessel contraction in murine models. However, their vasodilatory potency is less than that of β_2-agonists.[22-25] This may explain why LAMA use increased the risk of hemoptysis only in more severe cases in our analysis. However, β_2-agonists have a dual mechanism of action: direct stimulation of β_2-receptors and indirect inhibition of cholinergic neurotransmission.[26]

Subsequent LAMA use can potentiate the indirect anticholinergic effect of β_2-agonists,[27] and this synergistic effect may increase the risk of bleeding from fragile vessels during intensified vasodilation. Our analysis of the combination regimen also suggested a synergistic effect.

ICS monotherapy has a transient, short-term vasoconstrictive action in the airway mucosa.[16,28,29] However, when ICS is used in combination with a β_2-agonist, it inhibits the local disposal of the β_2-agonist and the down-regulation of β_2-receptors, and potentiates the vasodilatory effect of the β_2-agonist.[30-34] Thus ICS/LABA can increase airway blood flow compared to use of β_2-agonists alone, and promote the development of hemoptysis. Also, our data suggest that ICS/LABA with SABA has a more potent effect in terms of increasing the risk of hemoptysis compared with ICS/LABA alone.

While the vasodilatory effect of β_2-agonists may be beneficial to patients with asthma in clearing inflammatory mediators,[30] it may be a double-edged sword in vulnerable bronchiectasis patients. Considering the dose-response relationship of the effect of β_2-agonists on airway receptors,[21] the weakening of the statistical association in the sensitivity analysis after exclusion of events that occurred within 7 days of the prescription suggests that exposure to a higher dose during acute exacerbation exaggerates hemoptysis events. Alternatively, the effect of β_2-agonists on the development of hemoptysis may be due to a relatively acute reaction.

In terms of an acute response to inhaled β_2-agonists, the mean airway blood flow may have increased with a peak around 60 min and returned to baseline by 240 min after inhalation.[30] However, there is to our knowledge no report of the long-term effect of β_2-agonists on vasodilation and recruitment of blood flow in the airway. Additionally, the median duration from the most recent inhaler prescription to hemoptysis was somewhat long (53 days) to be able to explain our acute reaction findings. However, the lack of previous reports may be an obstacle to evaluate the biological plausibility of our findings.

In the subgroup analysis, classification according to age, Charlson comorbidity index, severity of airflow limitation measured by FEV_1% predicted, and the bronchiectasis severity score had no effect on the level of hemoptysis risk. While the patients with TB-destroyed lung had a higher risk of hemoptysis compared to those without, this finding suggests that inhaler use can potentiate the bleeding tendency in patients with TB-destroyed lung which itself is one of

the cause of hemoptysis.[35]

This study has strength in the fact that it is the first scientific report of an association of inhaler use with the risk of hemoptysis in non-CF bronchiectasis. We believe that this study may help to focus attention on the adverse events of inhaled drugs in this vulnerable population suffering hemoptysis, and may lead to further studies of inhaled drugs used in bronchiectasis. Additionally, the application of a case-crossover design allowed adjustment for time-independent factors and minimization of the effect of the heterogeneity of the population with non-CF bronchiectasis.

This study also had a few weaknesses. First, the level of evidence is limited by the retrospective design and small population. Also, healthy individuals or non-users of inhalers were not included. As all types of inhalers were not evaluated, generalization of our results to other inhaled drugs is not possible. Moreover, this study may not be free of selection bias. Additionally, even though we performed the sensitivity analysis to minimize the confounding by indication, the exclusion of inhalers prescribed in the 7 days prior to the event is unlikely to be enough to prevent it. In other words, it is quite plausible that patients with hemoptysis due to bronchiectasis might have been taking more treatment than usual in the month before they actually presented with hemoptysis.

In conclusion, our findings suggest that the use of inhalers containing ICS/LABA and SABA is associated with an increased risk of hemoptysis in patients with non-CF bronchiectasis. Based on our findings, physicians should exercise caution when prescribing inhaled therapies to improve airflow limitation of patients with bronchiectasis. Further studies will be required to replicate our findings and reveal the underlying mechanisms.

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초 록

서론: 기관지확장증 환자에서 흡입기의 사용과 객혈은 연관성에 대한 보고는 드물다. 이에 기관지확장증 환자에서 흡입기의 사용이 객혈 발생에 미치는 영향을 평가해보고자 하였다.

방법: 기관지확장증을 진단받고 객혈의 병력이 있으면서 흡입기의 사용력이 있는 192명을 대상으로 환자-교차연구를 통해 흡입기 사용과 연관된 객혈의 위험을 평가하였다. 연구에는 두 종류의 흡입스테로이드/지속성 베타항진제, 한 종류의 지속성 항콜린제, 한 종류의 속효성 베타항진제가 포함되었다. 위험기간과 대조기간은 각각 객혈 발생으로부터 0-30일전과 180-210일전으로 정의하였다.

결과: 위험기간 동안의 객혈의 위험도는 어느 흡입기를 사용할 경우에나 대조기간에 비해 3.51배 높았다. (95% 신뢰구간 1.96-6.28) 임상적으로 의미있는 객혈만을 대상으로 분석하였을 경우, 결과는 전체 객혈을 대상으로 하였을 때와 일치하였으며, 이러한 연관성은 민감도 분석 결과에서도 유지되었다. 흡입기 종류에 따른 하위그룹분석에서는 흡입스테로이드/지속성 베타항진제와 속효성 베타항진제가 객혈의 위험도를 유의하게 증가시켰다. (교차비 2.62, 95% 신뢰구간 1.25-5.45; 교차비 2.51, 95% 신뢰구간 2.23-5.15)

결론: 기관지확장증 환자에서 흡입기, 특히 베타항진제의 사용은 객혈 발생의 위험을 유의하게 증가시킨다.

주요어: 기관지확장증; 객혈; 흡입스테로이드; 기관지확장제

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