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【 ORIGINAL ARTICLE 】

Bronchodilator Effect of Tiotropium via Respimat® Administered with a Spacer in Patients with Chronic Obstructive Pulmonary Disease (COPD)

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Abstract:

Objective Among elderly patients with chronic obstructive pulmonary disease (COPD), there are some patients who cannot inhale tiotropium via Respimat® due to poor hand-lung coordination. This study aimed to examine whether or not tiotropium inhalation therapy using Respimat® with a spacer increased the forced expiratory volume in 1 s (FEV_1) in patients with COPD.

Methods A randomized, crossover, single-center study was conducted in 18 patients with stable COPD. Tiotropium (5 μg) via Respimat® with or without a spacer (AeroChamber®) was administered for 2 weeks. Following a 2-week washout period using a transdermal tulobuterol patch (2 mg per day), participants were then crossed over to the other inhalation therapy with respect to spacer use. The trough FEV_1 was measured at every visit using a spirometer. A questionnaire regarding inhalation therapy was administered to patients at the final visit.

Results The administration of tiotropium via Respimat® both with and without a spacer significantly increased the trough FEV_1 from baseline during each treatment period, with mean differences of 115.0±169.6 mL and 92.8±128.1 mL, respectively. There was no significant difference in the change in the trough FEV_1 between the 2 procedures (p=0.66). A total of 86% of patients reported that inhalation using a spacer was not difficult, and more than half also rated both the usage and maintenance of the AeroChamber® as easy.

Conclusion Tiotropium inhalation therapy administered via Respimat® using a spacer exerted a bronchodilatory effect similar to that observed with tiotropium Respimat® alone.

Key words: chronic obstructive pulmonary disease, tiotropium, Respimat®, spacer

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Introduction

Increases in the worldwide prevalence of chronic obstructive pulmonary disease (COPD) are expected, and there are estimated to be 5.3 million patients with the disease in Japan (1). The majority of patients with COPD are elderly and may have an impaired cognitive function and manual dexterity. Inhaled bronchodilators, such as long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), are the mainstay of management for patients with stable COPD, according to both strategy documents for the diagnosis, management, and prevention of COPD published by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2) and the COPD guideline of the Japanese Respiratory Society (3).

Many inhaler devices have been developed by various pharmaceutical companies, and COPD patients may need to learn adequate inhalation techniques for each device. Patients with severe COPD or asthma-COPD overlap syndrome (ACOS), requiring triple inhalation therapy [LAMA plus LABA plus inhaled corticosteroid (ICS)], must learn to operate two or more devices. If patients cannot generate a sufficient inspiratory flow rate for a dry powder inhaler

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Figure 1. Tiotropium Respimat® attached to an AeroChamber®.

(DPI), they must be administered inhalation therapy via pressurized metered-dose inhaler (pMDI) devices. Inhalation using a pMDI is often difficult for elderly patients because of the requirement for adequate hand-lung coordination. The addition of a spacer has been designed to aid in the delivery of drugs via pMDI, minimize coordination difficulties, reduce the oropharyngeal deposition, and increase the lung deposition.

No form of drug delivery for LAMAs via pMDI exists in Japan; however, the Respimat® SoftMist™ Inhaler for tiotropium has been developed. Respimat® has lower aerosol velocity and longer aerosol cloud duration than pMDIs, which should allow patients to coordinate handling and breathing more easily. Although this device is a valuable addition to inhalers currently available for inhalation therapy for patients with COPD, some elderly patients display incorrect hand-lung coordination in the use of Respimat®. Inhalation via Respimat® with a spacer has not been recommended because data regarding its efficacy and safety are lacking. As such, instructions provided to patients with severe COPD or ACOS for inhalation therapy using pMDIs with a spacer for ICS/LABAs and Respimat® without a spacer may lack coherence.

The aim of this randomized, open-label, crossover study was to investigate the efficacy of tiotropium inhalation therapy using Respimat® with a spacer through the measurement of the forced expiratory volume in 1 s (FEV_1) in patients with COPD.

Materials and Methods

Between February 2014 and May 2016, 20 stable COPD patients (18 men and 2 women) were recruited for this study. COPD was defined according to the GOLD criteria. The inclusion criteria were stable mild-to-severe COPD (FEV_1 >30% predicted), ≥20 years of age, continuing use of tiotropium Respimat® or intention to receive tiotropium Respimat®, and no use of inhaled LABAs or ICS/LABAs. Stable COPD was defined as the absence of exacerbation in the last two months. Patients were excluded if they had a history of drug hypersensitivity; they had either benign prostatic hypertrophy or glaucoma, which were contraindications to tiotropium; they could not purchase an AeroChamber® spacer; or they could not use tiotropium Respimat® with inhalation assistance.

This trial was approved by the ethics committee of our hospital (Approval No. 37, 2013) and registered in the university medical information network (Registration date: May 17, 2014; UMIN000013980). All patients provided their written informed consent.

Study design

This was a prospective, single-center, open-label, randomized, crossover study of tiotropium Respimat® with a spacer (Fig. 1) versus without a spacer conducted at Hamamatsu Medical Center. Following a two-week observational washout period, eligible patients were randomized equally to one of two groups (Fig. 2). Randomization was performed using a computer-generated randomization scheme with blocks of four. Participants received once-daily tiotropium 5 μg (2 puffs of 2.5 μg) via a Respimat® SoftMist™ Inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) with or without a spacer (AeroChamber®) in the evening for 2 weeks. Each treatment period was separated by a washout period of two weeks. During the washout period, participants were treated with a transdermal tulobuterol patch (2 mg, once a day) to prevent worsening of symptoms due to bronchodilator withdrawal. After the washout period, participants again received once-daily tiotropium 5 μg for 2 weeks, this time having crossed over to the other method with respect to spacer presence. After a clinical examination by physicians at every visit, pharmacists educated all participants on the usage of the Respimat® SoftMist™ Inhaler with or without the AeroChamber®. Adverse effects were recorded at every visit.

Trough FEV_1 and forced vital capacity (FVC) were measured at visits two to five, using a spirometer (CHESTAC-8800; Chest, Tokyo, Japan) in accordance with the method described by the American Thoracic Society and the European Respiratory Society task force (4). The primary endpoint was the mean difference in trough FEV_1 during the treatment period. The secondary endpoints were the mean differences in FVC, $\dot{V}50/\dot{V}25$, and the COPD Assessment Test (CAT) score (5) during the treatment period, adverse effects, and responses to a questionnaire regarding preferences in relation to the use of a spacer. This questionnaire comprised five questions on the following topics: preference for inhaled drug versus transdermal drug, inhalation without spacer, inhalation with spacer, spacer use, and ease of maintenance of the AeroChamber®.

Statistical analyses

For the primary endpoint, enrollment of 20 patients provided 80% power to detect a difference in FEV_1 of 100 mL, assuming a standard deviation of 140 mL, with a 2-sided test at a 0.05 significance level and an expected dropout rate of 10%. The data are expressed as either the number (proportion) or mean (standard deviation), as appropriate. We compared the differences in FEV_1 during the treatment period using a paired *t*-test. The differences in FEV_1, FVC,

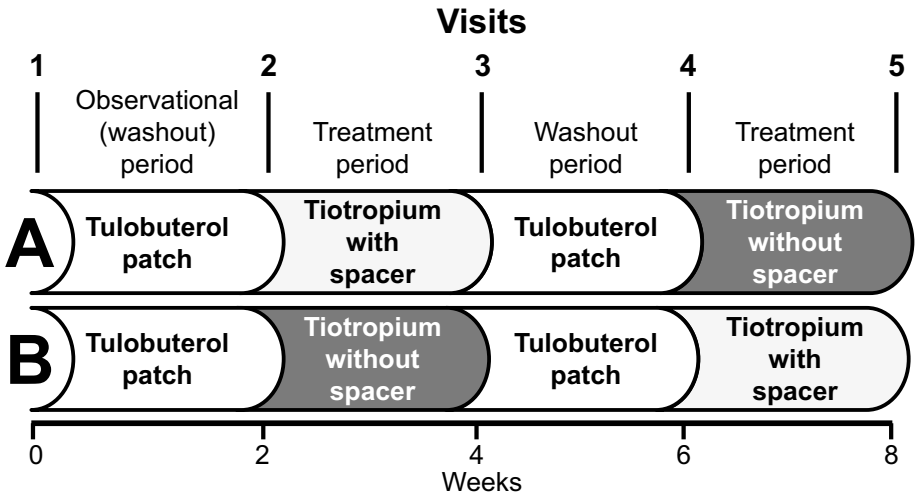

Figure 2. **Study design.**

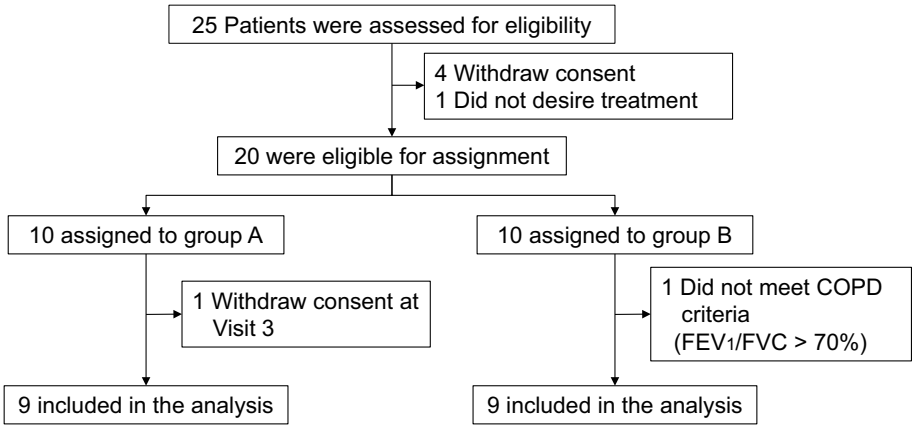

Figure 3. **Participant flow chart.**

and $\dot{V}50/\dot{V}25$ between inhalation with and without a spacer were analyzed using an unpaired *t*-test. Fisher's exact test was used to analyze the incidence of adverse effect and the responses to the questionnaire. All analyses were performed in accordance with the per-protocol principle. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.2.2) (6). More precisely, it is a modified version of R commander (version 2.2-3) designed to add statistical functions that are frequently used in biostatistics (7).

Results

Of the 25 patients screened, 20 were ultimately included in the study and underwent randomization (Fig. 3). Nineteen participants completed all study visits, with one participant withdrawing their consent at visit 3. One participant was excluded because their FEV_1/FVC ratio increased more than 70% during the study, resulting in that patient no longer meeting the diagnostic criteria for COPD. Table 1 shows the demographic data and baseline clinical characteristics of the remaining 18 eligible participants. The mean age of all patients was 75.3 years, and the majority (89%) were men. Seven participants were current smokers at the time of study recruitment but quit before visit 1. All participants were inhalation therapy-naïve, and none had received treatment with tiotropium. The mean baseline FEV_1 values were 1,465±485 mL.

The mean changes in trough FEV_1 (ΔFEV_1) were 115.0 mL after 2 weeks of tiotropium treatment administered with a spacer and 92.8 mL without a spacer (Table 2). There was no significant difference in the ΔFEV_1 between tiotropium therapy delivered with and without a spacer [p=0.66, difference in the mean ΔFEV_1 between the groups: 22.2 mL (95% confidence interval: -79.6 to 124 mL)]. There were also no significant differences between tiotropium therapy with and without a spacer with respect to ΔFVC, $\Delta\dot{V}50/\dot{V}25$, and the CAT score at the 2-week time-point. Although the FEV_1 and FVC were significantly increased after tiotropium treatment with or without a spacer, the $\dot{V}50/\dot{V}25$ and CAT did not show any significant changes.

The overall incidence of adverse effects was 16.7% and

Table 1. Baseline Patient Demographics and Characteristics.

Characteristics	n=18
Age, mean (SD), yr	75.3 (11.7)
Male, no. (%)	16 (89)
Body weight, mean (SD), kg	54.7 (14.1)
Body mass index, mean (SD), kg/m^2	20.7 (4.6)
Current smoker, no. (%)	7 (39)
Pack-years, mean (SD)	43.5 (30.2)
Baseline FEV_1, mean (SD), mL	1,465 (485)
Severity of COPD, no. (%)	
Group A	5 (28)
Group B	11 (61)
Group C	0 (0)
Group D	2 (11)
Comorbidities, no (%)	
Hypertension	6 (33)
Atrial fibrillation	2 (11)
Myocardial infarction	2 (11)
Heart failure	1 (6)
Diabetes mellitus	1 (6)

COPD: Chronic obstructive pulmonary disease, FEV_1: Forced expiratory volume in 1 s

11.1% with and without a spacer, respectively (p=0.99). The only reported adverse effect was dry mouth, and all participants experiencing dry mouth were able to continue the study drug. There were no participants who experienced heart palpitation or arrhythmia.

Of the 18 participants, 14 (78%) responded to the questionnaire regarding inhalation therapy. A total of 79% of the respondents preferred the inhaled drug, while 21% preferred the transdermal drug (Fig. 4). Inhalation with a spacer was reported to be easier than that without a spacer, but no to a significant degree (p=0.20). There was no relationship between age and preference. For example, a 90-year-old participant preferred the inhaled drug and felt that inhalation with a spacer was easy, whereas a 93-year-old participant preferred the transdermal drug and felt that inhalation with a spacer was slightly difficult. The respondents who answered that inhalation with a spacer was very easy were all over 75 years of age. More than half of the respondents felt that both the usage and the maintenance of the AeroChamber® were easy.

Discussion

The present study demonstrated that delivery of tiotropium with a spacer is equally effective in terms of increased FEV_1 values compared to delivery without a spacer. Before examining the clinical benefit of tiotropium with a spacer for elderly patients with poor inhalation skills, we first aimed to examine whether or not tiotropium with a spacer had a bronchodilatory effect. If patients with COPD are unable to use Respimat® adequately because of cognitive impairment or poor lung-hand coordination, or if they cannot push the button of this device because of rheumatism in their fingers, tiotropium administered via Respimat® using a spacer may be an alternative inhalation method and a more effective treatment option than transdermal LABA.

Regarding the main outcome of this study, the FEV_1 improved significantly after the administration of tiotropium with or without a spacer, but none of the changes in the pulmonary function tests differed significantly between the two groups. An increase of 100 mL in the trough FEV_1 was considered the minimal clinically important difference (MCID) (8), since tiotropium administered via Respimat® with a spacer met the minimal criteria for an MCID. However, the difference in the mean ΔFEV_1 between the groups (lower limit of 95% confidence interval: -79.6 mL) was not <-100 mL. This result did not demonstrate the non-inferiority of tiotropium with a spacer, because the present study was not designed as a non-inferiority trial, and -100 mL might be inappropriate as the non-inferiority margin of FEV_1. Although we feared that tiotropium might be absorbed by the inner surface of the AeroChamber®, resulting in decreased deposition of tiotropium to small airways, the value of $\dot{V}50/\dot{V}25$, which reflected the airflow obstruction of small airways, did not differ regardless of whether or not a spacer was used. Tiotropium inhalation therapy via Respimat® using the AeroChamber® may therefore have a sufficient bronchodilatory effect.

Adding a spacer to a pMDI helps to minimize difficulties with hand-lung coordination as well as to reduce adverse effects and increase therapeutic efficacy. Among inhaler devices, pMDIs are the most difficult for patients with COPD or asthma to use (9). It has been shown that more than 60% of patients were unable to use a pMDI correctly (10). Patients with asthma using spacers with pMDIs for the delivery of ICS were found to have better control than those using pMDIs alone (11). Incorrect inhaler use increases with age and with the severity of airflow obstruction (12). It is considered important for physicians or pharmacists to repeat the instructions for inhaler techniques to elderly patients with poor inhalation skills; however, elderly patients may have learning difficulties due to an impaired cognitive function as well as impaired vision and fine motor skills. Since elderly patients with severe COPD often have decreased inspiratory flow rates, a pMDI with a spacer is the ideal and most strongly recommended treatment option for patients with these and other related problems (13). In the present study, we selected the AeroChamber® as a spacer, and the majority of participants found the use or maintenance of this device relatively easy. Although the Respimat® device is easier to use and provides smoother inhalation than a pMDI, the AeroChamber® with a Respimat® device may be a treatment option for COPD patients who are unable to coordinate the press of a button with their breathing. Although there was no significant difference between the devices, many participants in the present study felt that inhalation with the AeroChamber® was not difficult. Inhalation therapy with the AeroChamber® may be useful for care assistants

Table 2. Changes in the Lung Function Parameters and COPD Assessment Test Results.

	Tiotropium without spacer			Tiotropium with spacer		
	Before	After	p value	Before	After	p value
FEV_1 (mL)	1,524 (511)	1,617 (484)	0.007	1,492 (476)	1,607 (537)	0.01
ΔFEV_1 (mL)	92.8 (128.1)			115.0 (169.6)		
FVC (mL)	2,786 (720)	2,912 (646)	0.03	2,746 (630)	2,863 (706)	0.01
ΔFVC (mL)	126.1 (233.0)			117.8 (182.5)		
$\dot{V}50/\dot{V}25$	3.06 (1.16)	2.91 (1.03)	0.32	3.22 (1.09)	3.36 (1.58)	0.54
$\Delta\dot{V}50/\dot{V}25$	-0.146 (0.601)			0.132 (0.903)		
CAT	11.6 (9.1)	10.4 (8.9)	0.76	12.3 (6.6)	13.0 (7.6)	0.71

FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, CAT: COPD assessment test
Values are mean (SD).

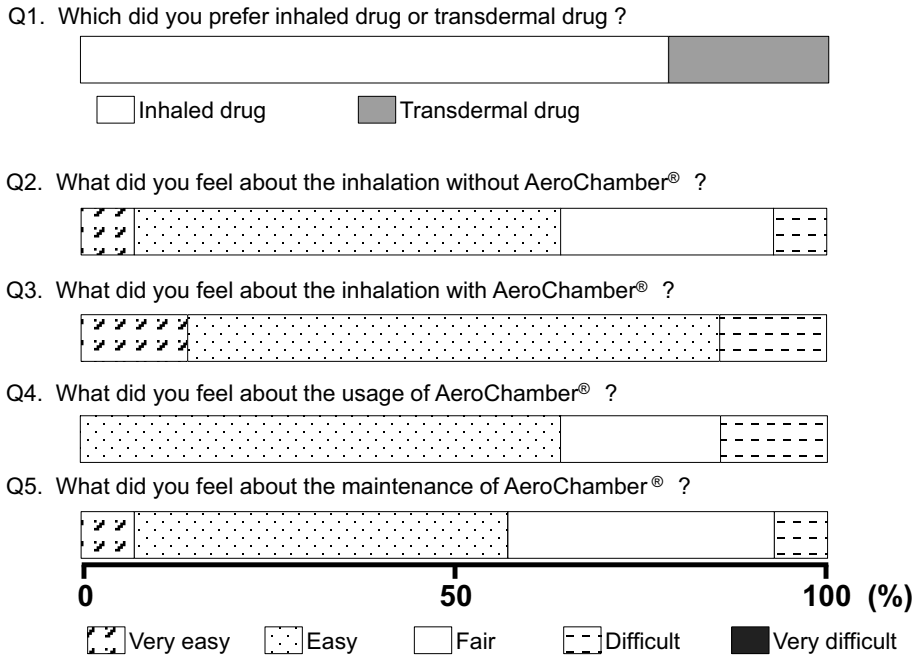

Figure 4. Results of a preference questionnaire regarding inhalation using the AeroChamber®.

providing inhaler assistance to elderly patients with COPD and dementia.

Although there was concern that the delivery of tiotropium by Respimat® might increase mortality due to cardiovascular disease, the Tiotropium Safety and Performance in Respimat (TIOSPIR) trial demonstrated that tiotropium Respimat® had a favorable safety profile with respect to cardiovascular adverse effects (14). In the present trial, no participants reported heart palpitations during this short-term use. Dry mouth is the most commonly reported adverse effect of tiotropium (15). The results of our study are compatible with the pooled analysis by Kesten (16). No participants discontinued tiotropium because of symptoms of dry mouth during the treatment period, and participants were able to continue tiotropium therapy following the study. Our data suggest that inhalation therapy via Respimat® using the AeroChamber® does not enhance or reduce the adverse effects of tiotropium.

Several limitations associated with the present study warrant mention. First, patients were administered a transdermal tulobuterol patch to prevent worsening of symptoms during the washout periods; therefore, ΔFEV_1 did not simply represent the bronchodilatory effect of tiotropium delivered by Respimat®. Second, the FEV_1 after bronchodilation (e.g. inhalation of short-acting β_2-agonists [SABAs]) was not measured in this trial. SABAs require different devices in combination with Respimat®, and thus it is necessary for patients to learn how to manage another device. Therefore, changes in the FEV_1 might be affected by the delivery of SABAs, so we measured only the trough FEV_1 in this trial. Third, we were unable to completely assess the cardiovascular adverse effects, because neither electrocardiograms nor echocardiographic examinations were routinely performed at all visits. Questioning of the participants by pharmacists and auscultation by physicians provided the only data that guided decision-making with regard to cardiovascular adverse effects. Fourth, elderly patients with dementia or poor handling skills preferentially did not participate in this trial. It is

therefore unclear whether or not tiotropium with a spacer has a clinically beneficial effect on elderly patients with these conditions, warranting further examination.

In conclusion, as measured by the change in the FEV_1, tiotropium inhalation therapy administered via Respimat® using a spacer had a comparable effect to that of tiotropium Respimat® alone. Tiotropium with a spacer may be an alternative treatment option for elderly patients with poor inhalation skills.

The authors state that they have no Conflict of Interest (COI).

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