



Comparison of the clinical effects of combined salmeterol/fluticasone delivered by dry powder or pressurized metered dose inhaler



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ABSTRACT

The salmeterol/fluticasone combination (SFC) inhaler is currently the most widely used maintenance drug for asthmatics worldwide. Although the effectiveness of SFC as either a dry powder inhaler (DPI) or a pressurized metered dose inhaler (pMDI) is well documented, there is limited data comparing the clinical efficacies of the two devices. To address this issue, we carried out a randomized crossover trial in which asthmatic patients ($n = 47$; mean age, 62.5 ± 16.5 years old) received a 12-week treatment of SFC DPI (50/250 μg twice daily) or SFC pMDI (four puffs of 25/125 μg daily). After a 4-week washout period, patients received another crossover treatment for 12 weeks. Respiratory resistance and reactance were measured by forced oscillation technique (MostGraph-01), spirometry, fractional exhaled nitric oxide (FeNO), and an asthma control test (ACT) every 4 weeks. The mean forced expiratory volume_{1.0} at the baseline was 2.16 ± 0.86 (L). Respiratory system resistance at 5 Hz (R5), the difference between R5 and R at 20 Hz (R5 – R20), and FeNO improved in both treatment groups, while reactance at 5 Hz (X5) and ACT score improved only in the pMDI group. In patients >70 years old ($n = 21$), R5, R5 – R20, ΔX5 , and FeNO improved only in the pMDI group. These results suggest that SFC by pMDI produces a stronger anti-inflammatory and bronchodilatory effect even in patients whose asthma is well controlled by SFC delivered by DPI.

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1. Introduction

Asthma is a global public health problem that affects up to 300 million people worldwide [1]. Despite recent advances in pharmacological therapies, under-treatment of asthma remains common, especially in terms of long-term maintenance regimens targeting airway inflammation. Although inhalation is an effective delivery route for bronchodilators as well as inhaled corticosteroids (ICS), many asthmatics—especially elderly patients—still have

difficulty in using the inhaler correctly. This along with poor adherence to treatment programs are thought to be common causes of uncontrolled asthma [2,3]. Available types of inhaler device for ICS and long-acting β_2 agonist (LABA) combination therapy now include the dry powder inhaler (DPI) and pressurized metered-dose inhaler (pMDI). Although device preparation and handling techniques vary among brands, some generalizations can be made with regard to optimal inhalation procedure for each type of device: inhalation should be slow and steady with the pMDI, but sharp and rapid with the DPI [4,5]. Additionally, the particle size of each preparation—i.e., mass median aerodynamic diameter—may impact treatment outcome [6]. It has been reported that particle sizes are smaller for pMDI than for DPI products, such that the former can be more widely distributed from central to peripheral airways [7]. However, there have been few clinical trials comparing inhalers for license-equivalent combinations of ICS/LABA.

The salmeterol/fluticasone combination (SFC) inhaler is currently the most widely used product by persistent asthmatics for maintenance therapy. Although the effectiveness of both SFC

Abbreviations: ACT, asthma control test; BUD/FM, budesonide/formoterol; DPI, dry powder inhaler; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume; FOT, forced oscillation technique; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; pMDI, pressurized metered dose inhaler; R5 (20), respiratory system resistance at 5 (20) Hz; R5 – R20, difference between R5 and R20; SFC, salmeterol/fluticasone combination; X5, reactance at 5 Hz.

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DPI and pMDI is well documented, there is limited data comparing their clinical effects, with most studies reporting similar outcomes for the two devices [8–11], and it has been reported that the particle size of SFC pMDI is about half that of DPI [6].

Small airways are difficult to investigate owing to their inaccessibility; several tests are currently available to assess small-airway dysfunction [7]. Reviews of the benefits and limitations of each test have concluded that there is no gold standard for evaluation [12,13]. The forced oscillation technique (FOT) is a noninvasive method that measures respiratory impedance—i.e., the spectral relationship between pressure and airflow. The impulse oscillation system (IOS) is a commercially available version of the FOT that offers respiratory impedance at a wide range of frequencies. MostGraph is a new method of FOT that employs 3-dimensional color images along a time axis to visualize respiratory cycle dependence [14]. MostGraph was recently recognized as a useful tool for evaluating small-airway dysfunction in chronic obstructive pulmonary disease (COPD) and asthmatic patients [15–20], and was therefore used in the present study.

The aim of the present study was to compare the anti-inflammatory or bronchodilatory effect of SFC administered by DPI and pMDI on peripheral small airways in the clinical setting. We hypothesized that the pMDI product with its smaller particle size which might reach peripheral small airways could improve asthma control in patients in which this has already been achieved using a DPI product even in patients with fixed airflow limitation or who are elderly.

2. Methods

2.1. Subjects

The study subjects included outpatients at the National Center for Global Health and Medicine aged ≥ 20 years old with persistent, moderate asthma treated for at least 6 months with a ICS/LABA combination inhaler (equivalent fluticasone propionate ≤ 500 $\mu\text{g}/\text{day}$) and in whom the disease was well or totally controlled—i.e., an Asthma Control Test (ACT) score of 20–25 points. Asthma was diagnosed according to clinical history and based on pulmonary function tests demonstrating variable airflow obstruction by measuring bronchodilator responsiveness, or bronchial hyperactivity by assessing the response to methacholine challenge, which satisfied the criteria of the Global Initiative for Asthma [1]. Patients with non-reversible lung diseases such as COPD or interstitial pneumonitis were excluded from the analysis.

2.2. Study design

The study was a prospective randomized crossover trial. Written, informed consent was obtained from each patient. At first, the patients were divided into two groups based on co-existence of seasonal allergic rhinitis or not to exclude seasonal variation of the fractional exhaled nitric oxide (FeNO) value, which was higher during the pollen scattering than during the non-pollen-scattering season. In this subgroup, after a 4-week washout period with budesonide/formoterol (BUD/FM) combination DPI (320/9 $\mu\text{g}/\text{day}$, Turbuhaler), patients were randomized to receive a 12-week treatment of a SFC DPI (250 μg , two puffs/day, Diskus) or SFC pMDI (125 μg , four puffs/day). After another 4-week washout period, patients received a second crossover treatment for 12 weeks (Fig. 1). The randomization was made based upon computer-generated table of random numbers. At each visit, inhalation technique and adherence to the regimen were verified. The patients with adherence rate less than 80% in wash-out period were excluded. Patients receiving the SFC pMDI were advised to use

antistatic Aero-Chamber Plus as an assistant spacer to produce high availability [21].

The primary end point was the change of respiratory system resistance (R) and reactance (X) before and after 12 weeks of treatment, as measured using MostGraph-01 (Chest MI, Tokyo, Japan). More than 5 technically acceptable MostGraph measurement were performed. Pulmonary function tests are measured by using spirometer (model CHESTAC-8100; CHEST MI, Inc., Tokyo, Japan) at the same visit. FeNO was measured 0, 4, and 12 weeks after treatment using NIOX-MINO (Aerocrine, Solna, Sweden) before any forced expiratory maneuvers; the best value of three readings was used for analysis. All medications for maintenance therapy and short-acting β_2 agonists for reliever use were halted 12 h before Spirometry, MostGraph and FeNO measurements, which were performed in the same order at similar times of the day before inhalation of the morning dose. ACT score and patient preference for the product (DPI, pMDI, or BUD/FM) were also recorded.

R at 5 and 20 Hz (R5 and R20, respectively) was measured and the difference between them (R5–R20) was taken as an indicator of the frequency dependence of R, which is presumed to reflect non-homogeneous ventilatory mechanics. We also determined X at 5 Hz (X5), which reflects elastic and inertial properties of the lung; resonant frequency (Fres), which is the point at which X = 0 and elastic and inertial forces are equal in magnitude and opposite; and low-frequency reactance area, which is the integral of X5 to Fres. Each oscillatory index was expressed as the mean values during a respiratory cycle (whole breath) and the differences between inspiratory and expiratory phases. To clarify the difference of clinical effects among elderly patients between DPI and pMDI, the subdivision in patients aged ≥ 70 and < 70 years old were made and analyzed.

2.3. Statistical analysis

It was determined that a total sample size of 16 subjects per group would provide 80% power at a 2-sided α level of 0.05 to detect a difference of 1 $\text{cmH}_2\text{O}/\text{L/s}$ or greater in R5 (a primary end point), assuming an SD of 1 $\text{cmH}_2\text{O}/\text{L/s}$. And we expected some variables concerning respiratory resistance which might be related to peripheral airway could be change after treatment. Values are presented as mean $\pm$ SD. Differences between groups were evaluated for significance using the χ^2 and Mann–Whitney U tests. Comparisons between baseline and measured values were assessed by repeated-measures analysis of variance. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (revised in 2008). The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM-G-001321-00). The clinical trial registration number was UMIN000009990.

3. Results

Three of the 50 patients enrolled in the study dropped out due to an adverse event; 2 cases hoarseness, and 1 case cough after inhalation. We therefore analyzed data from 47 patients. The male-to-female ratio was 28:19; the mean age was 62.5 ± 16.5 years (range: 24–78 years); mean disease duration was 16.8 ± 14.5 years; and % predicted value of forced expiratory volume (FEV)_{1.0} was $68.0\% \pm 14.1\%$. Concomitant medications were leukotriene receptor antagonist in 19 patients and a theophylline preparation in six patients. The mean ACT score of 23.6 indicated that asthma was

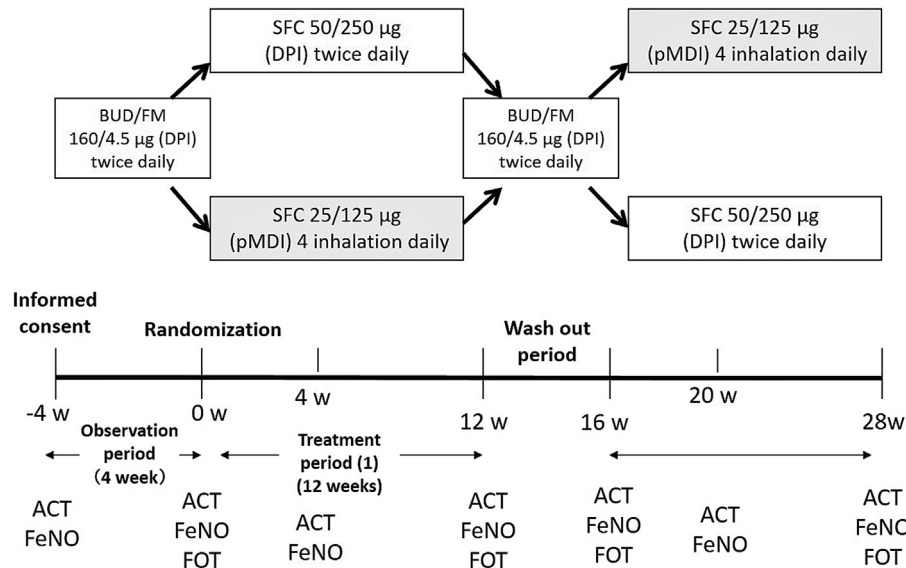


Fig. 1. Randomized crossover controlled trial study design. ACT, asthma control test; BUD/FM, budesonide/formoterol; FeNO, fractional exhaled nitric oxide; FOT, forced oscillation technique; SFC DPI, salmeterol/fluticasone combination dry powder inhaler; SFC pMDI, salmeterol/fluticasone pressurized metered dose inhaler.

controlled in all of the patients. Of the 47 cases, 21 were ≥ 70 years old and had lower $FEV_{1.0}$ and $FEV_{1.0}\%$ as compared to patients < 70 years old; however, there were no significant differences in demographic characteristics among patients (Table 1).

After 3 months of treatment with SFC DPI or SFC pMDI, there were no significant changes in spirometry measurements such as FVC, $FEV_{1.0}$, maximum midexpiratory flow (Table 2). On the other hand, significant changes were observed in the primary endpoints R5 and R5–R20 as measured by MostGraph-01 after SFC DPI and SFC pMDI treatment ($P < 0.05$). In addition, X5 changed from -1.15 ± 1.12 to -1.03 ± 1.18 (cm $H_2O/l/s$) in the SFC pMDI but not the SFC DPI group. FeNO values improved at 4 weeks in both groups, while ACT score improved only after pMDI treatment (Table 3).

Patients ≥ 70 years old were less responsive to SFC DPI treatment (Table 4); i.e., there were no changes in R5 and R5–R20 or

significant improvement of FeNO observed among all patients disappeared in this group. However, the elderly group showed a significant improvement in R5 and R5–R20 as well as in $\Delta X5$ (difference in X5 between inspiratory and expiratory phases) after 3 months of treatment with SFC pMDI but not SFC DPI. Patients in both SFC DPI and SFC pMDI showed significant improvement in FeNO at 4 and 12 weeks in all cases, however, these improvement of FeNO vanished among patients aged ≥ 70 years old (Fig. 2).

4. Discussion

To assess the clinical efficacies of license-equivalent combination ICS/LABA, a medium dose of SFC—currently the most widely used option for inhaled drugs—was administered to patients by DPI and pMDI. A comparison of the clinical effects of SFC by these two modes of delivery has been performed in only three studies to date.

Table 1
Demographic characteristics of all patients.

	All subjects	Patients aged ≥ 70 years old	Patients aged < 70 years old	p value
Patients, number	47	21	26	
Age; Mean $\pm$ SD (years old)	62.5 $\pm$ 16.5	76.2 $\pm$ 4.1	53.2 $\pm$ 13.6	$< 0.01^+$
Sex; male: female	28:19	15:6	13:13	N.S.
Smoking; never: ex-: current	24: 23: 0	11: 10: 0	13:13: 0	N.S.
Allergic; intrinsic	28: 19	11: 10	17: 9	N.S.
Asthma duration (y)	16.8 $\pm$ 14.5	20.7 $\pm$ 14.6	14.8 $\pm$ 14.4	N.S.
$FEV_{1.0}$ (L)	2.16 $\pm$ 0.86	1.60 $\pm$ 0.42	2.53 $\pm$ 0.93	$< 0.01^+$
% $FEV_{1.0}/FVC$ (%)	80.5 $\pm$ 21.3	77.4 $\pm$ 19.4	86.7 $\pm$ 21.6	$< 0.03^+$
$FEV_{1.0}$ predicted (%)	68.0 $\pm$ 14.1	61.7 $\pm$ 11.4	71.5 $\pm$ 14.1	$< 0.01^+$
Rescue medication use/week	3.4 $\pm$ 2.1	4.3 $\pm$ 2.8	3.1 $\pm$ 1.9	N.S.
ACT score	23.6 $\pm$ 1.61	23.6 $\pm$ 1.83	23.5 $\pm$ 1.51	N.S.
FeNO value (ppb)	39.1 $\pm$ 33.9	44.3 $\pm$ 40.3	39.1 $\pm$ 28.5	N.S.
Allergic rhinitis				
None: seasonal: perennial	18: 15: 14	10: 6: 5	8: 9: 9	N.S.
Prior ICS/LABA				
SFC DPI: SFC pMDI: BUD/FM	27: 2: 18	13: 0: 8	14: 2: 10	N.S.
Add-on controller				
None: LTRA: theophyllin	21: 19: 6	13: 5: 2	8: 14: 4	N.S.

Data are presented as mean $\pm$ SD. Statistically significant p values of chi-square test and Mann–Whitney U-test between patients aged ≥ 70 and < 70 years old are shown ($^+$). ACT, asthma control test; BUD/FM, budesonide/formoterol; FeNO, fractional exhaled nitric oxide; FEV, forced expiratory volume; ICS/LABA, inhaled corticosteroids/long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; SFC DPI, salmeterol/fluticasone combination dry powder inhaler; SFC pMDI, salmeterol/fluticasone pressurized metered dose inhaler.

Table 2
Change of spirometric variables before and after the treatment in all subjects (n = 47).

	DPI			p MDI		
	Before	After	p value	Before	After	p value
FVC (L)	3.21 ± 0.95	3.28 ± 1.01	0.45	3.28 ± 0.89	3.33 ± 1.03	0.52
FEV _{1.0} (L)	2.12 ± 0.89	2.18 ± 0.74	0.54	2.22 ± 0.8	2.21 ± 0.71	0.55
% FEV _{1.0} /FVC (%)	79.6 ± 23.6	78.4 ± 20.3	0.46	81.3 ± 18.2	78.4 ± 20.7	0.51
FEV _{1.0} % predicted (%)	68.1 ± 13.2	69.8 ± 18.4	0.28	70.1 ± 14.2	70.9 ± 16.5	0.39
MMF (L/s)	1.98 ± 1.53	1.88 ± 1.44	0.17	2.01 ± 1.68	2.11 ± 1.52	0.24
V ₅₀ (L/s)	1.56 ± 1.21	1.61 ± 1.37	0.41	1.64 ± 1.33	1.69 ± 1.21	0.38
V ₂₅ (L/s)	0.43 ± 0.34	0.47 ± 0.39	0.51	0.48 ± 0.39	0.51 ± 0.41	0.49
V ₅₀ /V ₂₅	3.74 ± 1.08	3.81 ± 1.14	0.29	3.66 ± 1.29	3.77 ± 1.15	0.34

Data are presented as mean ± SD. P values of ANOVA are shown.

Table 3
Change of FOT (MostGraph-01) parameter, ACT score and FeNO value before and after the treatment in all subjects (n = 47).

	DPI			p MDI		
	Before	After	p value	Before	After	p value
R5 (cmH ₂ O/L/s)	3.54 ± 1.25	3.28 ± 1.01	<0.04*	3.49 ± 1.08	3.25 ± 1.14	<0.05*
R20 (cmH ₂ O/L/s)	2.7 ± 0.94	2.55 ± 0.65	0.17	2.57 ± 0.8	2.51 ± 0.89	0.23
R5-R20 (cmH ₂ O/L/s)	0.86 ± 0.59	0.73 ± 0.68	<0.05*	0.83 ± 0.54	0.73 ± 0.476	<0.05*
Fres (Hz)	12.29 ± 5.29	11.96 ± 4.76	0.28	11.39 ± 4.61	11.03 ± 4.75	0.25
ALX (cmH ₂ O/L/s)	8.16 ± 8.89	7.55 ± 8.37	0.17	7.12 ± 7.76	6.75 ± 8.65	0.29
X5 (cmH ₂ O/L/s)	−1.41 ± 1.47	−0.75 ± 2.99	0.08	−1.15 ± 1.12	−1.03 ± 1.18	<0.05*
ΔR5 (cmH ₂ O/L/s)	−0.58 ± 0.64	−0.59 ± 0.83	0.51	−0.65 ± 0.77	−0.66 ± 0.87	0.49
ΔR20 (cmH ₂ O/L/s)	−0.28 ± 0.41	−0.25 ± 0.46	0.27	−0.31 ± 0.42	−0.27 ± 0.44	0.34
ΔR5-R20 (cmH ₂ O/L/s)	−0.31 ± 0.36	−0.34 ± 0.48	0.35	−0.34 ± 0.48	−0.38 ± 0.54	0.29
ΔFres (Hz)	−2.03 ± 2.81	−2.04 ± 3.56	0.49	−1.95 ± 2.91	−2.15 ± 3.48	0.35
ΔALX (cmH ₂ O/L/s)	−4.47 ± 7.14	−3.85 ± 6.39	0.11	−3.52 ± 5.23	−4.17 ± 7.44	0.16
ΔX5 (cmH ₂ O/L/s)	0.04 ± 3.61	0.44 ± 0.69	0.34	0.43 ± 0.65	0.5 ± 0.81	0.19
ACT score	23.53 ± 2.16	23.96 ± 1.99	0.06	23.76 ± 1.49	24.43 ± 1.22	<0.01*
FeNO (ppb)	40.11 ± 32.99	33.7 ± 28.77	<0.01*	38.55 ± 27.3	30.83 ± 19.95	<0.01*

Data are presented as mean ± SD. P values of ANOVA are shown. * revealed statistically significant. ALX, integrated low-frequency reactance area; Δ, difference between inspiratory and expiratory phases (inspiratory - expiratory); X5, respiratory system reactance at 5 Hz; R5 and R20, respiratory system resistance at 5 Hz and 20 Hz; Fres, resonant frequency.

Table 4
Change of FOT (Mostgraph-01) parameter, ACT score and FeNO value before and after the treatment in patients aged more than 70 years old (n = 21).

	DPI			p MDI		
	Before	After	p value	Before	After	p value
R5 (cmH ₂ O/L/s)	3.81 ± 1.34	3.43 ± 0.82	0.08	3.61 ± 1.0	3.35 ± 0.96	<0.05*
R20 (cmH ₂ O/L/s)	2.7 ± 0.94	2.55 ± 0.65	0.12	2.72 ± 0.91	2.62 ± 0.92	0.17
R5-R20 (cmH ₂ O/L/s)	0.98 ± 0.49	0.88 ± 0.36	0.08	0.89 ± 0.42	0.74 ± 0.41	<0.05*
Fres (Hz)	14.6 ± 4.64	13.83 ± 3.71	0.09	13.3 ± 3.41	13.19 ± 4.79	0.45
ALX (cmH ₂ O/L/s)	10.39 ± 9.18	9.32 ± 8.76	0.13	9.25 ± 7.9	8.9 ± 9.21	0.38
X5 (cmH ₂ O/L/s)	−1.75 ± 1.42	−0.5 ± 4.36	0.14	−1.53 ± 1.1	−1.43 ± 1.15	0.21
ΔR5 (cmH ₂ O/L/s)	−0.72 ± 0.74	−0.62 ± 0.85	0.23	−0.70 ± 0.91	−0.67 ± 0.76	0.44
ΔR20 (cmH ₂ O/L/s)	−0.34 ± 0.49	−0.33 ± 0.48	0.45	−0.39 ± 0.47	−0.33 ± 0.44	0.35
ΔR5-R20 (cmH ₂ O/L/s)	−0.38 ± 0.36	−0.24 ± 0.52	0.09	−0.28 ± 0.55	−0.32 ± 0.38	0.36
ΔFres (Hz)	−2.43 ± 2.84	−2.14 ± 3.06	0.27	−2.26 ± 2.34	−2.49 ± 3.19	0.34
ΔALX (cmH ₂ O/L/s)	−6.98 ± 7.29	−4.42 ± 6.23	0.07	−3.92 ± 5.65	−5.93 ± 9.63	0.10
ΔX5 (cmH ₂ O/L/s)	0.24 ± 3.61	0.44 ± 0.69	0.25	0.48 ± 0.69	0.37 ± 1.0	<0.05*
ACT score	23.42 ± 2.52	23.9 ± 1.61	0.10	23.95 ± 1.47	24.1 ± 1.64	0.27
FeNO (ppb)	42.86 ± 38.81	42.38 ± 35.96	0.43	41.52 ± 33.32	32.29 ± 16.84	<0.05*

Data are presented as mean ± SD. P values of ANOVA are shown. * revealed statistically significant. ALX, integrated low-frequency reactance area; Δ, difference between inspiratory and expiratory phases (inspiratory - expiratory); X5, respiratory system reactance at 5 Hz; R5 and R20, respiratory system resistance at 5 Hz and 20 Hz; Fres, resonant frequency.

In one study of moderate–to-severe asthma, patients were randomized to receive a high dose of SFC pMDI or DPI. The two methods were clinically equivalent, as evidenced by mean changes in morning peak expiratory flow (PEF) over 12 weeks. The two groups did not differ in other secondary measures of efficacy including circadian variation in PEF, FEV_{1.0}, and clinical symptoms [8]. Other studies in mild cases with low doses of SFC DPI arrived at similar conclusions, demonstrating that patients can switch to SFC

DPI from other MDI-based asthma treatments safely [9,10]. Only one study in Japan has reported the superiority of pMDI in terms of FeNO, eosinophil cationic protein in sputum, X5, and reactance area using the IOS, which indicates peripheral airway resistance [22]. Moreover, a retrospective observational study in the UK found that compared to the DPI cohort, patients using a pMDI had greater probability of achieving asthma control and the exacerbation rate was lower, although not significantly so [11].

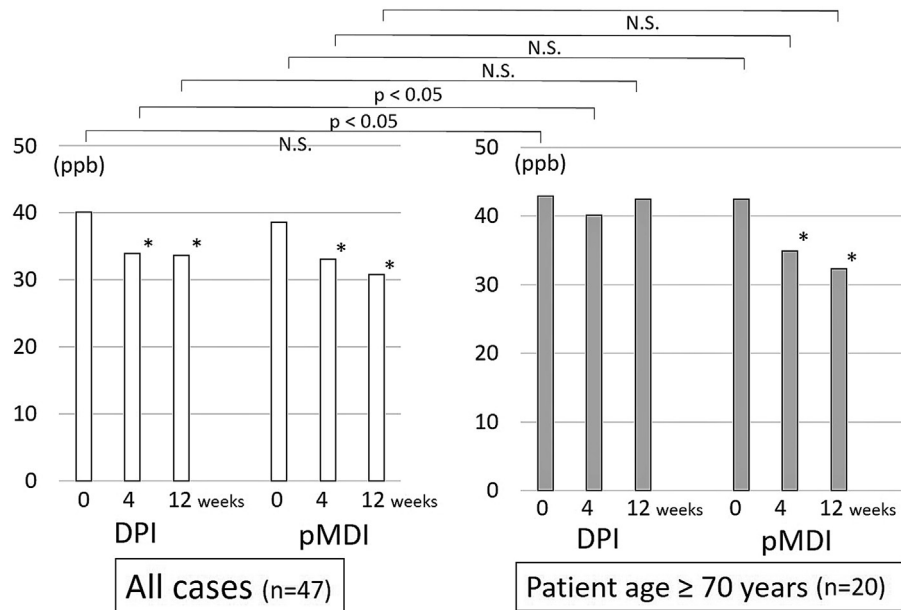


Fig. 2. Change of FeNO values in all cases and elderly patient group. *: $p < 0.05$ vs baseline, ANOVA. FeNO, fractional exhaled nitric oxide; DPI, dry powder inhaler; pMDI, pressurized metered dose inhaler.

Based on these previous reports, we hypothesized that a pMDI could achieve better asthma control in patients who have already had success using a DPI. We therefore examined patients with controlled asthma who showed good adherence, considering that adherence to treatment might have an influence on the results of the protocol. The mean age of patients was 62.5 years old, which was older than that of the general population with asthma. This selection bias is attributable to the fact that adherence is typically better in elderly as compared to younger patients [23–26]. In addition, approximately half of the patients ($n = 27$) had been using ICS/LABA SFC DPI prior to enrollment in the study, which may have also led to a bias in the results; that is, these patients received the same treatment as before, although the present study included a washout period. This may explain why the SFC DPI treatment group did not show a significant improvement in ACT score, which was mainly based on subjective evaluation. The bias in patient enrollment like this could be a major weakness of this study. In addition to that, the results of this study should be considered along with the limitations. First, the study is small with about 50 patients. Second, this study is not designed as placebo-controlled study.

In this study, we observed significant improvements in FOT but not in spirometry parameters in both treatment groups. Previous studies have revealed moderate correlations between $FEV_{1.0}$ and R, including R5, R20, and R5–R20 [19,20], suggesting that spirometry and FOT are not identical but reflect different aspects of airway obstruction. A possible reason for this is the difference between forced expiration and tidal breathing. We also detected improvements in X5 only in the pMDI group and in $\Delta X5$ only in patients ≥ 70 years old. A previous study reported significant correlations between X5 and the phase 3 slope in the nitrogen single-breath washout test (a measure of ventilation non-homogeneity) and between $\Delta X5$ and alveolar nitric oxide concentration (a marker of peripheral airway inflammation) [27]. These findings suggest that improvements in X5 and $\Delta X5$ reflect the delivery of more drugs to peripheral airways by pMDI but not by DPI.

Both R5 and R5–R20 is a measure of airway obstruction. There was an improvement in R5 and R5–R20 in the MDI group of the patients aged over 70 years. Although not statistically significant,

the effect of DPI inhaler still can be seen (the difference in this group is even bigger than in the MDI group), but the baseline values are very different. This difference may suggest the enhanced effectiveness of MDI inhaler on airway obstruction in the patients aged over 70 years compared to the all patients. Another possible reason for this is poor inhaler technique specifically in elderly patients despite being provided with repeated instructions.

A significant improvement in FeNO was observed in the SFC DPI group as a whole but not in elderly patients, who had reduced $FEV_{1.0}\%$. In contrast, FeNO improved even in the elderly group after treatment with pMDI. As noted above, the improvement in R5 and R5–R20 is likely related to outcome, highlighting the benefit either of improvement in inhalation technique or drugs with a small particle size.

As part of this study, we monitored adherence and verified inhalation technique at each visit. The effect of inhaled drugs on peripheral airways, efficiency of drug delivery, and convenience and ease of use are important factors influencing not only individual patient preferences but also patient adherence to treatment and long-term asthma control. In fact, eight of the 27 patients who were using SFC DPI before study enrollment requested to switch to pMDI after the end of the study. Of the eight patients, five were ≥ 70 years old.

In summary, our findings indicate that SFC pMDI is a reasonable treatment choice for elderly patients, not only because the device of pMDI is already being used by the patients for reliever therapy, which may eventually improve patient adherence and compliance and its tolerability [28], but also the airway anti-inflammatory effect of SFC DPI may be attenuated in this group with or without airflow limitation.

Author contributions

M.H. performed primary data analysis and wrote the manuscript. T.S. evaluated data concerning MostGraph and wrote the manuscript. M.I. and J.H. carried out data collection. H.S. contributed to study design and data interpretation. All authors approved the final version of the manuscript.

Conflict of interest

Dr. M. Hojo has, within the last 24 months, received honoraria for lectures from AstraZeneca and Astellas. The other authors declare no conflicts of interest.

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