ORIGINAL ARTICLE

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Comparison of extrafine and non-extrafine inhaled corticosteroids/long-acting β2-agonists as maintenance and reliever therapy in asthma: a randomized open-label crossover trial

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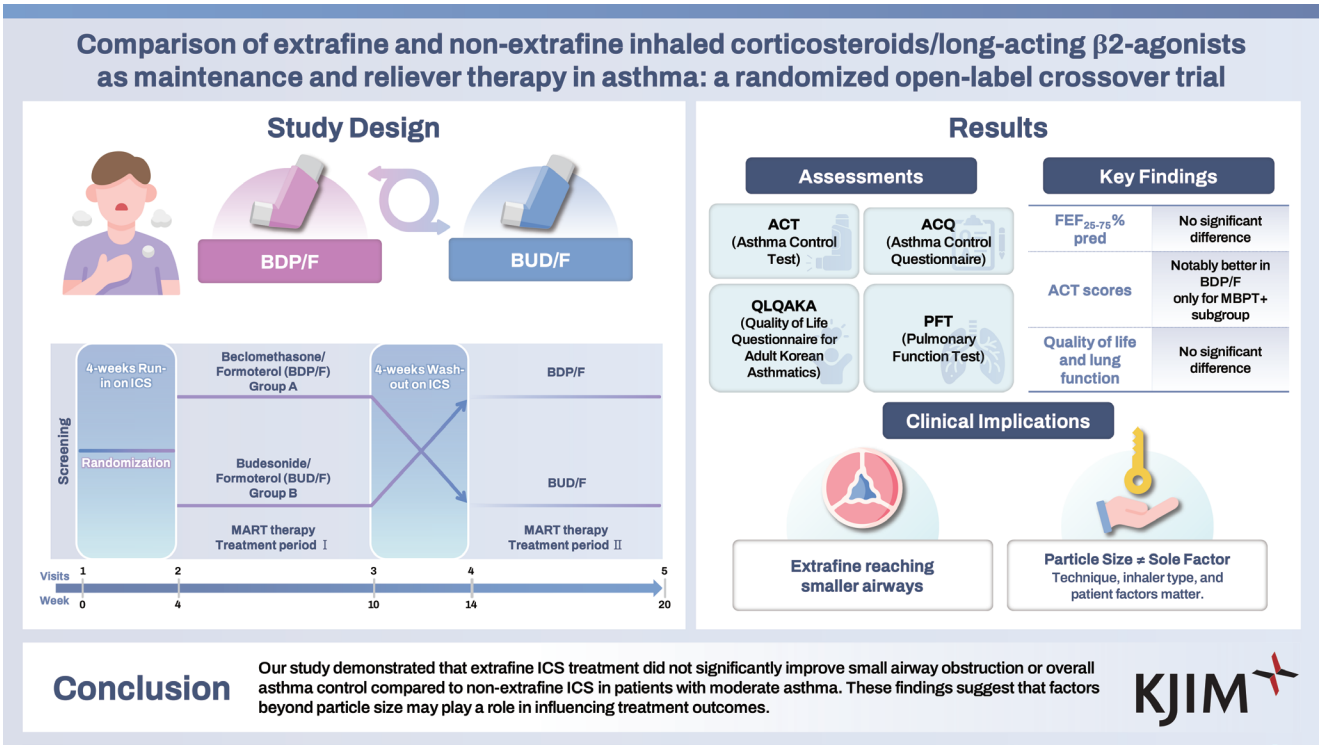

Background/Aims: Asthma is characterized by chronic inflammation. Inhaled corticosteroids (ICS) remain the cornerstone of anti-inflammatory therapy, targeting both the large and small airways.

Methods: This randomized open-label crossover trial included 30 patients receiving step 3 inhaled medication according to the Global Initiative for Asthma (GINA). Patients received beclomethasone/formoterol (BDP/F) for maintenance and reliever therapy for 6 weeks, followed by budesonide/formoterol (BUD/F) for 6 weeks, or vice versa, with a 4-week washout period

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in between. Assessments at each visit included the Asthma Control Test (ACT), Asthma Control Questionnaire, Quality of Life Questionnaire for Adult Korean Asthmatics, and pulmonary function test. The primary endpoint was the change in forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$% pred).

Results: Twenty-four patients (15 females, mean age 39.3 years) completed the study. The changes in $FEF_{25–75}$% pred were comparable between BDP/F and BUD/F (5.79 ± 38.34 vs. -1.36 ± 14.93, $p = 0.399$). No significant differences were observed between the BDP/F and BUD/F groups in terms of improvement in asthma control or quality of life. However, in the subgroup of patients with positive methacholine bronchial provocation tests, BDP/F significantly improved ACT scores compared to BUD/F (0.92 ± 2.25 vs. -1.31 ± 3.04, $p = 0.044$).

Conclusions: Our study demonstrated that extrafine ICS treatment provided no significant advantage over non-extrafine ICS in improving small airway obstruction or overall asthma control in moderate asthma. This suggests that factors other than particle size may contribute to treatment outcomes.

Keywords: Asthma; Beclomethasone; Budesonide; Forced expiratory flow between 25% and 75% of vital capacity; Treatment outcome

INTRODUCTION

Asthma is a chronic inflammatory respiratory condition characterized by episodic airway obstruction and increased bronchial responsiveness, leading to symptoms such as wheezing, shortness of breath, chest tightness and cough [1]. Suppressing chronic airway inflammation is increasingly being recognized as a critical component of asthma management. Consequently, anti-inflammatory maintenance therapy remains the cornerstone of asthma treatment in contemporary practice [2,3]. Among anti-inflammatory medications, inhaled corticosteroids (ICS) are regarded as the most effective option, demonstrating safety at appropriate doses for long-term use in both children and adults with asthma. Additionally, ICS can be combined with long-acting inhaled β2-agonist (LABA) to achieve effective asthma control in patients whose symptoms are not adequately managed with ICS alone [4,5]. Small airways, defined as those with an internal diameter of less than 2 mm, occur in all stages of asthma and contribute significantly to its pathophysiology [6]. Asthma-related airway inflammation involves both the large and small airways. Therefore, enhancing total lung deposition, with a focus on targeting both large and small airways, may amplify the anti-inflammatory effects of ICS and potentially improve asthma outcomes [7,8]. ICS formulations differ in particle size owing to variations in their composition and propellants. For effective deposition in the lower respiratory tract beyond the carina, particles must be less than 5 μm in diameter. Specifically, particles smaller than 2 μm, referred to as the "extrafine particle fraction," are considered the most effective for deposition in small airways [9].

A previous study comparing two pressurized metered-dose inhalers (pMDIs) found that using pMDIs with extrafine particles (beclomethasone/formoterol, BDP/F) may better alleviate small airway obstruction than non-extrafine particle inhalers (budesonide/formoterol, BUD/F), despite no significant differences in overall treatment outcomes [10]. According to the Global Initiative for Asthma (GINA) guidelines, ICS and formoterol combinations (BDP/F and BUD/F) are the preferred treatments for symptom relief in mild asthma (Steps 1 and 2) and for daily maintenance and reliever therapy (MART) in moderate to severe asthma (Steps 3, 4, and 5) [11]. Furthermore, studies have demonstrated that dry powder inhalers (DPIs) are as effective as pMDIs in delivering ICS and formoterol combinations [12,13]. In this study, we conducted a comprehensive evaluation of the clinical benefits of extra-fine particle ICS delivered via DPI in combination with MART, focusing on symptom control and improvements in both small and large airway functions—an area that has not yet been thoroughly investigated.

METHODS

Study design

This was a 20-week, single-center, randomized, open-label crossover trial. At enrollment and during each visit, patients

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were educated on proper inhaler use. During the study period, including the run-in and washout phases, all patients used an inhaled corticosteroid (fluticasone propionate 250 μg) twice daily along with a short-acting β2-agonist (salbutamol 100 μg) as a reliever. After a 4-week run-in period, patients were randomized into two groups using an Excel program (Microsoft, Redmond, WA, USA) with a block size of 10. Subsequently, they were assigned in a crossover design to receive open-label treatment with either BDP/F (beclomethasone dipropionate 100 μg/formoterol fumarate dihydrate 6 μg, extra-fine particles) or BUD/F (budesonide 160 μg/formoterol fumarate dihydrate 4.5 μg) for 6 weeks. Patients received one inhalation of either BDP/F or BUD/F twice daily as maintenance therapy (two inhalations per day) and one inhalation as needed for symptom relief. Total daily inhalations were limited to a maximum of eight per day, and the same criteria were applied to both inhalers based on the findings of a study involving Korean asthmatic patients (Fig. 1) [14].

Enrollment

Patients attending the outpatient clinic were enrolled if they met the following inclusion criteria: (1) aged 19 years or older; (2) exhibited typical asthma symptoms such as wheezing, shortness of breath, chest tightness, or coughing, exacerbated by triggers including exercise, colds, changes in climate or diurnal temperature, allergens, air pollution, tobacco smoke, or strong odors; (3) demonstrated a bronchodilator response (BDR) or treatment response through repeated lung function tests (defined as a ≥ 200 mL and ≥ 12% increase in forced expiratory volume in 1 second [FEV_1] from baseline after salbutamol inhalation or appropriate asthma treatment) or airway hyperresponsiveness (AHR) confirmed by a methacholine challenge test (provocative concentration of methacholine causing a 20% drop in FEV_1 [PC20] ≤ 16 mg/mL); (4) were on initial asthma treatment as defined by GINA guidelines, specifically low-dose ICS/LABA (Step 3); and (5) demonstrated the ability to be trained in the correct use of a DPI device.

Outcome measurements

Various indicators are available for assessing small airway obstruction. The primary outcome of this study was the effect on small airway obstruction, assessed by the percentage of predicted values for forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$% pred), comparing extrafine and non-extrafine ICS treatments. This study aimed to validate previous findings by comparing the effects of extrafine particle transition from pMDI to DPI formulations [10].

Secondary outcomes included changes in asthma control and asthma-specific quality of life (Asthma Control Test [ACT], Asthma Control Questionnaire [ACQ], Quality of Life Questionnaire for Adult Korean Asthmatics [QLQAKA]) and lung function tests. Local and systemic adverse events (AEs) were recorded after each 6-week treatment period.

Statistical analysis

This study explored the effects of particle size differences in inhaler therapy in patients with asthma. Based on previous inhaler studies, sample size calculation was performed using the mean difference (62.58%) and standard deviation (SD) (94.80%) of $FEF_{25–75}$% pred, a marker of small airway obstruction [10]. Using a two-sided test with $\alpha = 0.05$ and $\beta = 0.2$, the required sample size was 24.112. Accounting

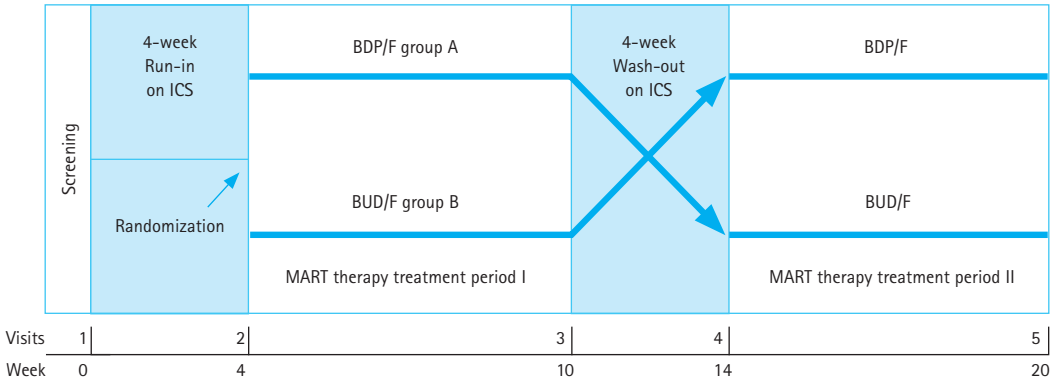

Figure 1. Study design. ICS, inhaled corticosteroids; BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol; MART, maintenance and reliever therapy.

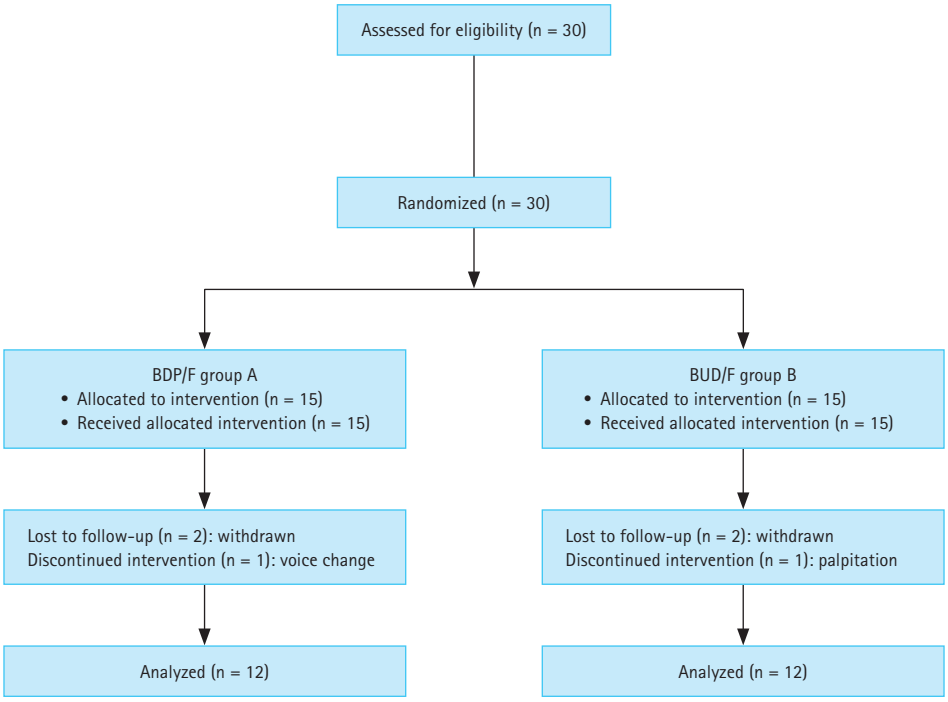

Figure 2. CONSORT diagram illustrating the participant flow. BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol.

for a 20% dropout rate, the final number of patients was determined to be 30. Continuous variables between groups were compared using the Student's t-test, and categorical variables were analyzed using the chi-square test or Fisher's exact test. Data are expressed as mean ± SD for continuous variables and as frequencies (%) for categorical variables. Intervisit differences between groups were analyzed using a paired t-test. Unadjusted changes in lung function and symptom control status in each treatment group were analyzed using a Linear Mixed Model. Statistical significance was set at $p < 0.05$. All analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical consideration

The study protocol was reviewed and approved by the Institutional Review Board of Gachon University Gil Medical Center (approval number: GCIRB2021-222). This study was registered in the Clinical Research Information Service of the Republic of Korea (CRIS KCT0006933). All participants were enrolled after obtaining their informed consent.

RESULTS

Baseline characteristics

Of the 30 enrolled patients, 24 (12 in group A [BDP/F followed by BUD/F], and 12 in group B [BUD/F followed by BDP/F]) completed the study. This discrepancy was due to withdrawal (n = 2) and loss to follow-up (n = 4) (Fig. 2). The mean age of the enrolled patients was 39.3 ± 15.2 years, and 62.5% were female. The mean body mass index (BMI) was 27.6 kg/m^2, and 20.8% of the patients were classified as obese (BMI ≥ 30.0 kg/m^2). The mean duration of asthma symptoms was 16 months and the mean frequency of exacerbations in the past year was 2.8 ± 1.7. The baseline scores for ACT, ACQ, and QLQAKA were 15.9, 2.0, and 3.4, respectively. Approximately 80% of the patients had partly controlled (41.7%) or uncontrolled (37.5%) asthma based on the GINA criteria [11]. Thirteen patients (54.2%) exhibited AHR in the methacholine challenge test and 15 (62.5%) showed a BDR, defined as an FEV_1 increase of 200 mL and 12% from baseline after salbutamol inhalation. The baseline percentages of the predicted values of FEV_1, FEV_1/FVC, and $FEF_{25–75}$ were 82.5 ± 14.5%, 73.7 ± 9.0% and 64.9 ± 24.2%, respectively. The fractional exhaled nitric oxide (FeNO) values and blood eosinophil counts were 71.7 ±

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Table 1. Baseline demographic and clinical characteristics

Characteristic	Overall (n = 24)	BDP/F group A (n = 12)	BUD/F group B (n = 12)	*p* value
Age (yr)	39.3 ± 15.2	40.8 ± 14.9	37.8 ± 15.9	0.648
Sex, female	15 (62.5)	9 (75.0)	6 (50.0)	0.400
Body mass index (kg/m^2)	27.6 ± 6.9	28.7 ± 7.0	26.5 ± 6.9	0.452
Obese	5 (20.8)	4 (33.3)	1 (8.3)	0.317
Smoking status				0.623
Non-smoking	9 (37.5)	3 (25.0)	6 (50.0)	
Ex-smoking	7 (29.2)	3 (25.0)	4 (33.3)	
Current smoking	8 (33.3)	6 (50.0)	2 (16.7)	
Comorbid allergic diseases				
Allergic rhinitis	14 (58.3)	7 (58.3)	7 (58.3)	> 0.999
Atopic dermatitis	3 (12.5)	2 (16.7)	1 (8.3)	> 0.999
Chronic urticaria	5 (20.8)	3 (25.0)	2 (16.7)	> 0.999
Drug allergy	3 (12.5)	1 (8.3)	2 (16.7)	> 0.999
Symptom duration (mo)	16.4 ± 26.8	10.9 ± 16.7	21.9 ± 34.0	0.325
Asthma exacerbation in last 1 year	8 (33.3)	2 (16.7)	6 (50.0)	0.193
Asthma exacerbation frequency in last 1 year	2.8 ± 1.7	3.0 ± 1.4	2.7 ± 1.9	0.828
FEV_1 (L)	2.8 ± 0.8	2.6 ± 0.6	3.0 ± 0.9	0.181
FEV_1 (% of predicted value)	82.5 ± 14.5	81.2 ± 13.6	83.9 ± 15.9	0.653
FVC (L)	3.8 ± 0.9	3.7 ± 0.7	4.0 ± 1.1	0.403
FVC (% of predicted value)	91.5 ± 15.0	91.7 ± 10.2	91.3 ± 19.2	0.958
FEV_1/FVC (%)	73.7 ± 9.0	71.7 ± 9.2	75.7 ± 8.7	0.285
$FEF_{25–75}$ (L)	2.3 ± 1.1	2.0 ± 0.9	2.6 ± 1.3	0.152
$FEF_{25–75}$ (% of predicted value)	64.9 ± 24.2	59.5 ± 23.5	70.3 ± 24.7	0.286
Post FEV_1 (L)	3.0 ± 0.7	2.9 ± 0.6	3.2 ± 0.9	0.379
Post FEV_1 (% of predicted value)	89.0 ± 13.5	90.3 ± 12.6	87.8 ± 14.8	0.670
Post FVC (L)	3.9 ± 0.9	3.8 ± 0.8	4.0 ± 1.1	0.563
Post FVC (% of predicted value)	92.7 ± 14.9	94.0 ± 9.9	91.3 ± 19.0	0.670
Post FEV_1/FVC (%)	78.3 ± 8.1	77.3 ± 7.8	79.3 ± 8.6	0.572
Post $FEF_{25–75}$ (L)	2.9 ± 1.2	2.7 ± 1.0	3.1 ± 1.4	0.375
Post $FEF_{25–75}$ (% of predicted value)	83.7 ± 26.7	82.0 ± 24.9	85.3 ± 29.3	0.767
FeNO (ppb)	71.7 ± 65.0	96.2 ± 76.7	47.2 ± 40.6	0.063
Positive MBPT	13 (54.2)	7 (58.3)	6 (50.0)	0.682
Positive BDR	15 (62.5)	7 (58.3)	8 (66.7)	> 0.999
WBC (×10^3/uL)	8.2 ± 2.5	7.8 ± 1.7	8.6 ± 3.1	0.443
Eosinophil (%)	4.6 ± 3.0	5.2 ± 2.7	4.1 ± 3.3	0.401
Eosinophil_counts (/μL)	875.0 ± 356.8	418.8 ± 252.0	294.8 ± 210.5	0.204
ACT	15.9 ± 3.9	16.8 ± 4.1	14.9 ± 3.7	0.426
ACQ	2.0 ± 1.2	1.8 ± 1.2	2.2 ± 1.1	0.243
QLQAKA	3.4 ± 0.8	3.5 ± 0.8	3.4 ± 0.8	0.664

Table 1. Continued

Characteristic	Overall (n = 24)	BDP/F group A (n = 12)	BUD/F group B (n = 12)	*p* value
Asthma control by GINA				
Well controlled	5 (20.8)	4 (33.3)	1 (8.3)	0.592
Partly controlled	10 (41.7)	3 (25.0)	7 (58.3)	
Uncontrolled	9 (37.5)	5 (41.7)	4 (33.3)	

Values are presented as mean ± standard deviation or number (%).
We compared continuous variables between groups using the Student's t-test and analyzed categorical variables using the chi-square test or Fisher's exact test.
BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; FeNO, fractional exhaled nitric oxide; MBPT, methacholine bronchial provocation test; BDR, bronchodilator response; WBC, white blood cell; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics; GINA, Global Initiative for Asthma.

Table 2. Intervisit difference in group A (BDP/F-BUD/F group) (n = 12)

	Treatment period I		*p* value	Treatment period II		*p* value
	Visit 2	Visit 3		Visit 4	Visit 5	
$FEF_{25–75}$ (L)	3.03 ± 1.04	3.13 ± 0.93	0.085	3.08 ± 0.98	2.96 ± 0.77	0.355
$FEF_{25–75}$ (% of predicted value)	91.17 ± 25.89	94.67 ± 22.48	0.085	92.50 ± 22.87	89.17 ± 14.29	0.420
FEV_1 (L)	2.96 ± 0.62	3.03 ± 0.64	0.122	2.99 ± 0.62	2.99 ± 0.55	> 0.999
FEV_1 (% of predicted value)	91.42 ± 10.52	93.50 ± 11.95	0.081	92.25 ± 10.81	92.42 ± 7.79	0.914
FVC (L)	3.69 ± 0.81	3.76 ± 0.85	0.304	3.72 ± 0.79	3.78 ± 0.75	0.096
FVC (% of predicted value)	91.42 ± 9.95	93.33 ± 13.09	0.267	91.92 ± 10.62	93.83 ± 10.06	0.083
FEV_1/FVC (%)	80.42 ± 5.78	80.92 ± 4.78	0.477	80.50 ± 5.11	79.46 ± 4.37	0.194
ACQ	0.77 ± 0.59	0.99 ± 1.00	0.367	0.64 ± 0.50	0.79 ± 0.66	0.381
ACT	20.92 ± 3.26	20.08 ± 4.34	0.404	21.83 ± 2.76	20.83 ± 2.79	0.172
QLQAKA	4.24 ± 0.48	4.17 ± 0.79	0.669	4.23 ± 0.61	4.11 ± 0.55	0.270
Control status						
Well controlled	7 (58.3)	8 (66.7)		8 (66.7)	10 (83.3)	
Partly controlled	5 (41.7)	3 (25.0)		4 (33.3)	1 (8.3)	
Uncontrolled	0 (0.0)	1 (8.3)		0 (0.0)	1 (8.3)	

Values are presented as mean ± standard deviation or number (%).
Intervisit differences between groups were analyzed using the paired t-test.
BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics.

65.0 ppb and 875.0 ± 356.8/μL, respectively. No significant differences were observed in the baseline characteristics between the treatment groups (Table 1).

Asthma treatment outcomes

During the two 6-week treatment periods, the mean number of inhalations per day was 2.55 ± 1.13, with a mean as-needed usage of 0.55 ± 1.13 inhalations per day. A total of 16 patients (66.7%) used inhalers for maintenance therapy, incorporating as-needed usage. The mean daily inhalations of BDP/F and BUD/F were 2.76 ± 1.29 and 2.44 ± 0.94, respectively, while the mean as-needed inhalations

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were 0.67 ± 1.29 and 0.44 ± 0.94, respectively. There were no significant differences between the groups in terms of inhalation pattern or usage.

Intervisit differences in lung function and symptom control status

No statistically significant differences in lung function or asthma control were observed between the start and end of each treatment phase in groups A and B. However, ACT scores in group B significantly increased during BDP/F treatment, raising from 18.00 ± 3.88 to 20.42 ± 2.27 (Tables 2, 3).

Comparison of BDP/F and BUD/F in the lung function and symptom control status

The treatment effects on small airway function, as assessed by $FEF_{25–75}$% pred, were similar between the BDP/F and BUD/F (5.79 ± 38.34 vs. -1.36 ± 14.93, $p = 0.399$) (Fig. 3). Similarly, there were no differences between the BDP/F and BUD/F groups in the average changes from baseline in FEV_1, FVC, and FEV_1/FVC ratios. BDP/F exhibited improvement trends in ACT, ACQ, and QLQAKA scores over the 6-week treatment period; however, these trends were not statistically significant (Supplementary Table 1). Subgroup analyses were conducted based on FeNO levels (≥ 40 ppb, n = 15), blood eosinophil counts (≥ 300/μL, n = 13), positive BDR (n = 15), and

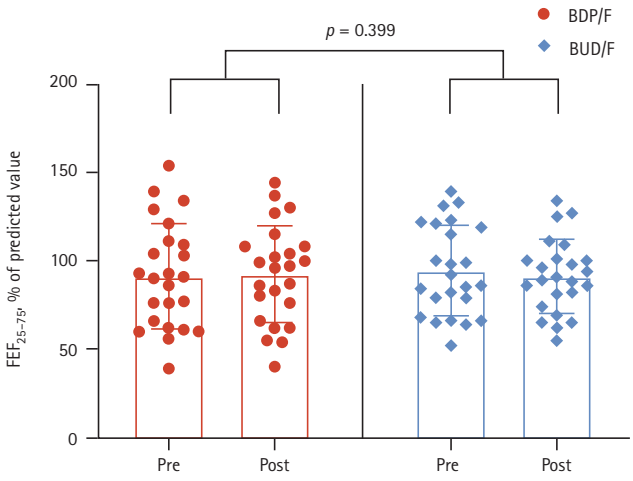

Figure 3. Change in $FEF_{25–75}$% of the predicted value after 6-week treatments. $FEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol; Pre, pretreatment; Post, posttreatment.

Table 3. Intervisit difference in group B (BUD/F-BDP/F group) (n = 12)

	Treatment period I		*p* value	Treatment period II		*p* value
	Visit 2	Visit 3		Visit 4	Visit 5	
$FEF_{25–75}$ (L)	3.51 ± 1.42	3.43 ± 1.46	0.602	3.41 ± 1.68	3.29 ± 1.53	0.495
$FEF_{25–75}$ (% of predicted value)	96.50 ± 28.84	93.17 ± 26.17	0.503	91.33 ± 34.41	90.17 ± 32.60	0.869
FEV_1 (L)	3.33 ± 0.85	3.34 ± 0.89	0.931	3.30 ± 0.97	3.25 ± 0.90	0.650
FEV_1 (% of predicted value)	93.42 ± 15.02	93.08 ± 14.69	0.860	91.67 ± 18.21	90.50 ± 14.91	0.729
FVC (L)	4.06 ± 1.00	4.10 ± 1.11	0.525	4.07 ± 1.07	4.01 ± 1.05	0.526
FVC (% of predicted value)	93.17 ± 17.56	93.75 ± 18.77	0.721	93.33 ± 19.63	91.83 ± 17.44	0.461
FEV_1/FVC (%)	82.17 ± 7.02	81.83 ± 8.23	0.780	80.67 ± 9.52	81.08 ± 8.65	0.783
ACQ	1.05 ± 0.80	1.11 ± 0.63	0.846	1.22 ± 0.89	0.96 ± 0.63	0.138
ACT	19.08 ± 3.15	18.67 ± 3.37	0.778	18.00 ± 3.88	20.42 ± 2.27	0.016
QLQAKA	4.15 ± 0.45	3.92 ± 0.50	0.276	3.89 ± 0.61	4.04 ± 0.43	0.346
Control status						
Well controlled	4 (33.3)	3 (25.0)		4 (33.3)	5 (41.7)	
Partly controlled	6 (50.0)	9 (75.0)		6 (50.0)	7 (58.3)	
Uncontrolled	2 (16.7)	0 (0.0)		2 (16.7)	0 (0.0)	

Values are presented as mean ± standard deviation or number (%).
Intervisit differences between groups were analyzed using the paired t-test.
BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics.

a positive methacholine bronchial provocation test (MBPT) (n = 13). The MBPT subgroup revealed significant differences in ACT scores between BDP/F and BUD/F treatments (0.92 ± 2.25 vs. -1.31 ± 3.04, $p = 0.044$). However, no significant differences were observed in the subgroups based on the BDR, blood eosinophil counts, or FeNO levels (Supplementary Table 2).

AEs

Two patients (8.3%) reported at least one treatment-emergent AE during the BDP/F treatment. The reported AEs included coughing, sputum production, and palpitations; however, all patients completed the study without discontinuation. No serious AEs or deaths were reported.

DISCUSSION

This crossover study, designed to evaluate the impact of extrafine particle size ICS in patients with moderate asthma, did not demonstrate significant improvements in symptom control, large airway function (measured by FEV_1 and FEV_1/FVC), or small airway function (measured by $FEF_{25–75}$% pred) compared to non-extrafine ICS. The ACT scores in group B, treated with BDP/F, showed statistically significant improvements. However, intervisit difference analysis did not account for factors such as individual patient characteristics or order effects. To address these limitations, the mixed-effects model was employed, offering greater robustness and reliability than intervisit difference analysis. These findings, which contrast with our previous study, illustrate that evaluating clinical benefits in inhalation therapy cannot be based solely on particle size, as multiple complex variables influence treatment outcomes [10].

Asthma, previously thought to affect only the large airways, is now recognized as a condition characterized by chronic inflammation throughout the lungs. Inflammation is characterized by mucus plugging, increased T cells, activated eosinophils, and major basic proteins in both the central and small airways [15]. Novel ICS formulations, such as beclomethasone dipropionate and ciclesonide, have been specifically designed to target small airway inflammation [16]. These formulations yield smaller particles, which facilitate better access to the distal airways. Imaging studies have suggested that these formulations produce beneficial changes in the distal airways [17,18].

Smaller particle sizes may confer additional clinical benefits by penetrating smaller airways and enhancing efficacy [19-21]. However, the practical impact of these benefits remains inconclusive, as evidenced by our study and meta-analysis [22]. El Baou et al. [22] conducted a meta-analysis of 23 trials and found no significant differences between standard and small-particle ICS in changes in FEV_1, morning peak expiratory flow (PEF), or $FEF_{25–75}$% pred. Additionally, benefit-risk plots across five efficacy endpoints, including FEV_1, morning PEF, $FEF_{25–75}$%, asthma symptoms, and rescue medication use, did not reveal clinically meaningful differences.

Although extrafine particles are more effectively distributed in peripheral airways [23], it is commonly believed that particles smaller than 1 μm are largely exhaled due to their extremely low settling velocity, which consequently limits their therapeutic activity within the lungs. The rapid relief of airway constriction achieved with initial ICS treatment may lessen the incremental benefits provided by smaller particles [24].

In studies using the same extrafine ICS, DPIs did not demonstrate significant improvements in small airway obstruction, in contrast to the findings observed with pMDIs [10]. This discrepancy may stem from differences in aerosol generation mechanisms, reliance on patient inhalation efforts for particle delivery efficiency, or variations in the particle deposition patterns between the two devices. Moreover, some patients may struggle to achieve the necessary inspiratory flow for effective DPI use, potentially reducing the therapeutic benefits of extrafine particles in treating small airway obstructions. Collectively, these results suggest that targeted aerosol delivery to the conducting or peripheral airways is not solely dependent on particle size, but is instead determined by a complex interplay of various factors [25-27].

Given the non-significant results across all parameters in this crossover study, subgroup analyses were performed. Notably, BDP/F significantly improved ACT scores in patients positive for MBPT. Mild-to-moderate asthmatic patients with small airway dysfunction (SAD), as assessed by impulse oscillometry (IOS), exhibit excessive bronchoconstriction during methacholine challenge, highlighting the significant role of small airways in bronchial hyperresponsiveness [28]. These findings emphasize the importance of small-particle aerosols in the management of patients with AHR. Additionally, future studies should investigate the impact of extrafine particles in a patient group exhibiting both AHR and reversibility,

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which are the two key characteristics of airway variability.

Asthma control is significantly influenced by treatment adherence, which is enhanced by combining MART in a single inhaler and by using a device optimized for ease of use [29,30]. Few studies have evaluated the potential correlation between extrafine particles and the benefits of MART in asthma control, lung function, and quality of life [31,32]. In this study, the mean as-needed inhaler usage for symptom relief was aligned with previously published data on MART usage in real-life settings among Korean and European patients, despite thorough education on MART use provided at every visit [14,33]. We observed no statistically significant differences in either group even with the application of MART. These findings underscore the need for further investigation through prospective trials or real-world studies to assess whether extrafine particles enhance MART by uniformly addressing airway inflammation.

Our study has two major strengths. First, it focused on a well-defined population of patients with a clinical need for ICS/LABA and provided evidence supporting the use of MART for moderate asthma. Second, all subjects received fluticasone propionate as a controller medication during the 4-week run-in and washout periods to mitigate the potential carryover effects of ICS/LABA in the crossover design, considering the half-life of ICS medications. Furthermore, a mixed-effects model was employed for statistical analysis to evaluate treatment effects and account for potential carryover effects. However, this study has some limitations. First, the small sample size and short study duration limited the statistical power, although the crossover design partially offsets this limitation. We acknowledge that the small sample size may affect the generalizability of our findings and limit the precision of subgroup analyses. Second, despite education and monitoring of inhaler use, we could not evaluate the impact of factors beyond particle size on asthma control, owing to the lack of robust verification methods. The particle size of the inhaler was not independently measured in this study; instead, the designation of extrafine particles relied entirely on the limited information obtained from radiolabeling studies conducted on a small sample and data provided by the manufacturer [34,35]. Practically, it is challenging to directly measure the particle size in such studies. Third, while $FEF_{25–75}$% pred is a commonly used marker of SAD, it may not fully capture the nuanced changes in small airway pathology. Some studies have indicated that even parameters specific to small airways lack validated clinical significance and reliability [36,37]. Postma et al. [38] showed that no single variable defines SAD; however, tools such as IOS, multiple breath nitrogen washouts, lung volumes, and spirometry can contribute. Fourth, we only recruited patients categorized according to GINA step 3. SAD is prevalent across all asthma severities but is particularly significant in severe diseases [38,39]. Future studies should also focus on patients with moderate to severe asthma (GINA step 3–5) to comprehensively evaluate the role of extrafine ICSs. Fifth, it has been reported that the maximal effect of ICS typically requires 3–6 months to manifest [40]. Extending the treatment period beyond six weeks may have provided a more robust evaluation of the impact of ICS particle size, allowing for a more accurate assessment of its effectiveness. Finally, the comparison would have been more accurate if the two inhalers had shared identical components and formulations, differing only in particle size. Such a distinction would enable a more precise evaluation of the impact of the particle size on the performance and efficacy.

In conclusion, our study demonstrated that extrafine ICS treatment did not result in significant improvements in small airway function or overall asthma control compared to non-extrafine ICS treatment in moderate asthma. These results suggest that, while particle size plays a role, other factors, such as patient-specific and inhalation characteristics, may be equally important in determining clinical outcomes. Identifying patient subgroups that could benefit the most from extrafine ICS should be a priority for future research, paving the way for a more personalized approach to asthma management. Moreover, long-term studies incorporating advanced tools to assess small airway function are necessary to explore the enduring effects of extrafine particles on asthma.

KEY MESSAGE

1. Existing studies suggest that while extrafine particles may penetrate the small airways more effectively, their clinical significance remains uncertain owing to mixed evidence.
2. Our study showed that extrafine particle ICS treatment did not result in significant improvements in small airway function or overall asthma control compared to non-extrafine ICS treatment in patients with moderate asthma.

3. These findings highlight that factors beyond particle size, such as patient-specific characteristics and inhalation techniques, are critical for determining treatment outcomes.
4. Further research with larger sample sizes and more advanced tools is needed to evaluate the potential long-term benefits of extrafine particles in asthma management.

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Supplementary Table 1. Effectiveness of BDP/F compared to BUD/F in asthma

Overall (n = 24)	Changes after BDP/F	Changes after BUD/F	*p* value
Delta $FEF_{25–75}$ (L)	-0.01 ± 0.46	-0.10 ± 0.48	0.496
Delta $FEF_{25–75}$ (% of predicted value)	5.79 ± 38.34	-1.36 ± 14.93	0.399
Delta FEV_1 (L)	0.01 ± 0.26	0.00 ± 0.17	0.917
Delta FEV_1 (% of predicted value)	1.38 ± 12.68	0.27 ± 6.32	0.704
Delta FVC (L)	0.01 ± 0.27	0.05 ± 0.18	0.516
Delta FVC (% of predicted value)	0.58 ± 7.90	1.41 ± 4.99	0.663
Delta FEV_1/FVC (%)	0.46 ± 3.90	-0.69 ± 3.34	0.280
Delta ACQ	-0.02 ± 0.73	0.10 ± 0.78	0.578
Delta ACT	0.79 ± 3.49	-0.71 ± 3.84	0.163
Delta QLQAKA	0.05 ± 0.53	-0.17 ± 0.54	0.164

Values are presented as mean ± standard deviation using the Linear Mixed Model.
BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; QLQAKA: Quality of Life Questionnaire for Adult Korean Asthmatics.

Supplementary Table 2. MBPT-based subgroup analyses comparing BDP/F and BUD/F in asthma

MBPT (n=13)	Changes after BDP/F	Changes after BUD/F	*p* value
Delta $FEF_{25–75}$ (L)	-0.18 ± 0.36	-0.13 ± 0.56	0.780
Delta $FEF_{25–75}$ (% of predicted value)	-5.61 ± 12.04	-1.80 ± 15.87	0.498
Delta FEV_1 (L)	-0.04 ± 0.22	-0.02 ± 0.17	0.860
Delta FEV_1 (% of predicted value)	-1.39 ± 6.71	-0.79 ± 5.80	0.809
Delta FVC (L)	0.02 ± 0.26	0.02 ± 0.14	0.926
Delta FVC (% of predicted value)	0.79 ± 6.68	0.30 ± 4.07	0.821
Delta FEV_1/FVC (%)	-1.38 ± 2.22	-0.73 ± 3.77	0.582
Delta ACQ	-0.10 ± 0.46	0.11 ± 0.77	0.408
Delta ACT	0.92 ± 2.25	-1.31 ± 3.04	0.044
Delta QLQAKA	0.09 ± 0.51	-0.27 ± 0.60	0.111

Values are presented as mean ± standard deviation using the Linear Mixed Model.
MBPT, methacholine bronchial provocation test; BDP/F, beclomethasone/formoterol; BUD/F, budesonide/formoterol; $FEF_{25–75}$, forced expiratory flow between 25% and 75% of vital capacity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACT: Asthma Control Test; QLQAKA: Quality of Life Questionnaire for Adult Korean Asthmatics.

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