Original article

Effects of fenoterol/ipratropium bromide on FEV1 and hyperinflation in Thai COPD patients

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Background: Patients with chronic obstructive pulmonary disease (COPD) usually suffer from breathlessness caused by chronic progressive worsening of airway obstruction and lung hyperinflation.
Objective: This study aimed to evaluate the effects of fenoterol hydrobromide and ipratropium bromide combination on lung function parameters in Thai COPD patients. We also compared the effects from two commercially available products; Aerobidol® metered-dose inhaler (MDI) and Berodual® inhaler.
Methods: A double-blind, randomized cross-over study was conducted in 31 COPD patients from outpatient service, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. To compare the responses of both inhalers on lung volume parameters, patients were randomized to be challenged by either Aerobidol® MDI or Berodual® inhaler. Spirometry and body plethysmography were performed before and after 60 min of each inhalation administration. All patients were switched to the other inhaler in the same manner after one-week washout period. A change of lung volume parameters including forced expiratory volume in the first second (FEV_1), inspiratory capacity (IC), functional residual capacity (FRC), and residual volume (RV) were statistically compared by using analysis of covariance.
Results: Thirty-one COPD patients were recruited into the study. Their average of age was 66.6 years with a median value of smoking of 40 pack-years. Severity of COPD according to post bronchodilator FEV_1 % predicted was mainly in GOLD stage 2 and 3. Both Aerobidol® MDI and Berodual® inhaler significantly increased FEV_1 and decreased RV from baseline values. No statistical difference in changes of FEV_1, IC, FRC, and RV between these two inhalers were observed.
Conclusion: Acute bronchodilating effects of Aerobidol® MDI is comparable to Berodual® inhaler in Thai COPD patients.

Keywords: COPD, fenoterol, ipratropium bromide, lung volume, FEV_1, hyperinflation.

Chronic obstructive pulmonary disease (COPD) is characterized by chronic persistent airflow limitation which progressively worse. COPD is a major cause of morbidity and mortality throughout the world.[1] The patients usually suffer from daily symptoms such as breathlessness on exertion and cough leading to limited physical activities, physical deterioration, and poor quality of life.

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Hyperinflation of the lung is one of major pathophysiologic determinants of dyspnea in COPD. [1] The lung become more hyperinflated during exercise. Therefore, inhaled medications used in relieving dyspnea should have effects on decreasing of lung hyperinflation, which may result in improvement of exercise capacity and daily physical activities.

The combination of β_2-agonist and anticholinergic inhaler has been recommended for treatment of COPD by several COPD guidelines, and has been widely studied for relieving dyspneic symptom through different mechanisms.[2, 3] The combination therapy can achieve greater bronchodilation effect than that of either drug alone.[4] Fenoterol hydrobromide and ipratropium bromide combination have been

studied for improvement of forced expiratory volume in 1 second (FEV_1)[5], and provided effective bronchodilation of similar degree and duration to that achieved in metered dose inhaler (MDI) or dry powder inhaler (DPI) dosage form.[6] However, its effect on lung hyperinflation was limited.

The commercial product of fenoterol hydrobromide and ipratropium bromide is originally from Boehringer Ingelheim under the trade name of Berodual® inhaler. [7] Thai pharmaceutical product under the trade name of Aerobidol® MDI manufactured the generic of Berodual® inhaler. The present study aimed to evaluate the effects of Aerobidol® MDI on its bronchodilating properties, focusing on improvement of FEV1 and decrease of hyperinflation, compared with Berodual® inhaler.

Materials and methods

Study design and patients

This open, randomized, single-dose, two-way crossover study was conducted in COPD patients in King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The protocol was approved by the Ethics Committee, Faculty of Medicine, Chulalongkorn University. Eligible patients were symptomatic COPD patients aged more than 40 years. Diagnosis of COPD were defined by GOLD criteria [1] including smoking more than 10 pack-years, and post-bronchodilator FEV_1/forced vital capacity (FVC) less than 70.0%. Patients who suspected of other possible diagnoses that may interfere symptoms and response to bronchodilators such as lung cancer, bronchiectasis, severe tracheobronchomalacia, were excluded. All patients had no exacerbation, respiratory infection, or changing the doses or types of bronchodilators during a previous 4 weeks prior to entering the study. Patients who cannot perform spirometry and body plethysmography were also excluded.

After obtaining written informed consent, baseline characteristics were collected from the patients directly and outpatient medical records including gender, age, number of cigarettes per day, duration of smoking, symptoms, comorbid diseases, and medication use.

Randomization and procedures

Following an initial screening, the patients were randomized into 2 groups depending on Aerobidol® MDI or Berodual® inhaler was first used for bronchodilator challenge. The first group of 15 patients was started with Aerobidol® MDI, and the second group of 16 patients was started with Berodual® inhaler Figure 1. Aerobidol® MDI and Berodual® inhaler were obtained from the Pharmacy Department, King Chulalongkorn Memorial Hospital.

Procedures

Spirometry was performed, then followed by body plethysmography (VIASYS; Vmax V20-7) with subjects at rest, before and 60 minutes [8, 9] after 2 puffs of 50/20 mcg of fenoterol hydrobromide/ ipratropium bromide (Aerobidol® MDI or Berodual® inhaler) metered dose inhaler via Allens Hanburys Volumetric TM Spacer Device with a volume of 750 mL (Allen & Hanburys Limited, Uxbridge, London, UK). Spirometry provided forced expiratory volume at 1 second (FEV1), vital capacity (VC) and inspiratory capacity (IC) whilst body plethysmography provided information on other lung volume parameters, including, functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC). Procedures for lung function measurements were performed and standardized according to manufacturer's instructions and European Respiratory Society/American Thoracic Society recommen-dations.[10] On the study day, the subjects were asked to attend the PFT laboratory in the early morning after withholding short-acting bronchodilators for at least 8 hours and long-acting bronchodilators for at least 48 hours as recommended. [10, 11] The reference values used were determined according to equations: Crapo RO, *et al*. [12] for spirometry and Quanjer PH, *et al*. [13] for plethysmographic lung volumes.

The patients were appointed for the second inhaler tests after 7-day washout period in the same manner. The sequences of lung volume study in our study depicted in Figure 1. After a completion of tests, the patients were asked to use Aerobidol® Inhaler whenever felt breathlessness for 4 weeks. Satisfaction of the patients in relieving dyspnea symptom and side effects were interviewed by phone.

Assessment and outcome measurements

The lung volume parameters after challenge with both inhalers were analyzed to compare an efficacy of Aerobidol® MDI with Berodual® inhaler in term of improving in FEV_1, IC, and decrease of RV and FRC.

Statistical analysis

The sample size was calculated according to Equation [14]:

$$N \text{ of pairs} = [(Z_\alpha + Z_\beta)\ \sigma_d/\Delta]^2$$
$$= [(1.96 + 0.84) / 0.5]^2 = 31 \text{ patients}$$

Where the power of analysis is 95.0%, $\alpha = 0.01$, $Z_\alpha = 1.96$, $Z_\beta = 0.84$. From the Equation 1, the number of samples is 31 which is enough to detect differences.

Descriptive statistics were described in a ratio and percentage. Changes of lung volume parameters between Aerobidol® MDI and Berodual® inhaler were compared using Student's unpaired *t* - test.

Results

A patient deposition in this study is shown in Figure 2. Thirty-one patients were enrolled and grouped into 2 crossover treatment with a 7-day washout period. All subjects completed the study.

The demographic data and baseline characteristics are shown in Table 1. Twenty- nine of male COPD patients and 2 of female COPD patients were in this study. The average of age was 66.6 years. Smoking history in male patients were 53.5 ± 70.7 pack-years which were varied and higher than female patients (10.0 ± 0.0 pack-years). CAT score assessment indicated that 12 patients (41.4%) were mild in symptoms (CAT score < 10 or modified Medical Research Council dyspnea scale; MMRC = 0 to 1), while the others were moderate to severe. There are 3, 17, 10, and 1 patient were GOLD severity staging of 1, 2, 3, and 4, respectively, evaluated by the FEV_1 % predicted. Twenty-six patients had comorbid diseases with cardiovascular diseases such as hypertension, ischemic heart disease, and cerebrovascular disease. Two patients were found to have lung cancer and colon cancer, respectively. Neither osteoporosis nor depression was observed.

Effects of inhaled bronchodilators on lung volume parameters were shown in Table 2 and Figure 3. We found that FEV_1 and IC were significantly increased whereas FRC and RV were significantly decreased after either Aerobidol® MDI or Berodual® inhaler was tested. Compared with baseline, the changes of lung volume parameters in percentage of FEV_1, IC, FRC, and RV after challenge by Aerobidol® MDI or Berodual® inhaler were comparable. No statistically significant difference was detected.

Analysis of variance is shown in Table 3 to analyze whether a sequence, treatment, and period of treatment would affect a change of lung volume parameters. The results showed that only a sequence of treatment significantly affected a change of IC and FRC ($P < 0.05$) but did not affect FEV_1 and RV, while the treatment and period of treatment had no effect to lung volume parameters. The sequence of treatment is also affected at 90.0% of FEV_1. There is no difference in effect of FEV_1 between the two medications. The period of treatment also shows no difference between the two medications.

Patients' satisfaction on clinical efficacy and adverse effects from Aerobidol® MDI during the 4-week period after the lung volume study was analyzed. No subject reported any adverse effects from using the inhaler. All subject felt better after using the inhaler to relieve dyspneic symptoms.

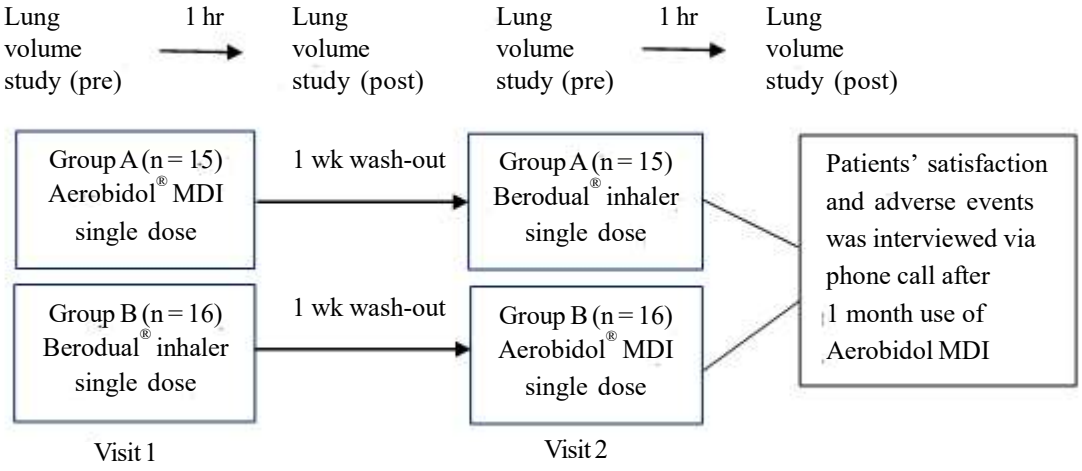


Figure 1. Study design and patient´s allocation of the 2-period cross-over sequences.

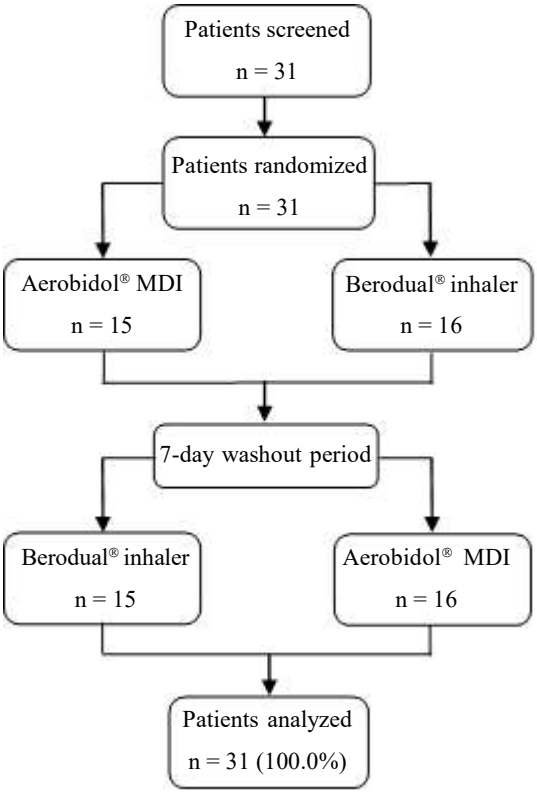


Figure 2. Patient deposition (randomized cross over study design). Thirty-one patients were screened and randomized. All patients completed the study. MDI, metered dose inhaler.

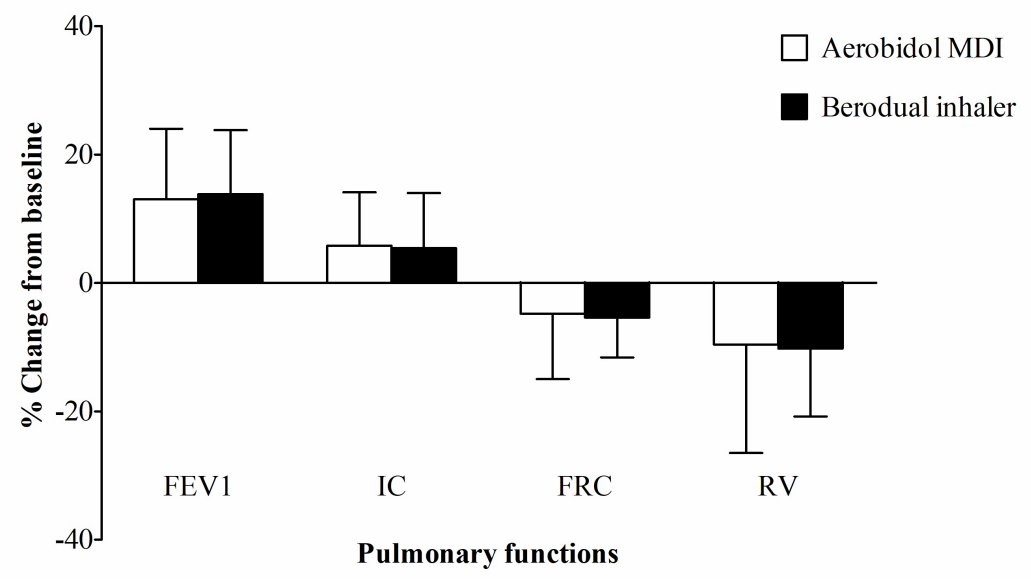
Table 1. Patient demographics and baseline characteristics.

Number of patients	**N = 31 (%)**
Gender	
Male	29 (93.5)
Female	2 (6.5)
Age (years)	66.6 ± 9.7
Smoking history (pack-years)	50.0 ± 68.8
CAT score	
Mild (<10)	9 (29.0)
Moderate to severe (>10)	22 (71.0)
Exacerbation (times)	1.0 ± 1.0
GOLD classification	
1 FEV1 ≥ 80.0% predicted	3 (9.7)
2 FEV1 ≤ 80.0% predicted ≥ 50.0% predicted	17 (54.8)
3 FEV1 ≤ 50.0% predicted ≥ 30.0% predicted	10 (32.3)
4 FEV1 < 30.0% predicted	1 (3.2)

Table 2. Lung function parameters includes FEV1, IC, FRC, RV before and after challenge with fenoterol/ipratropium bromide in both groups.

Lung function parameters	Aerobidol		Berodual	
	Pre	Post	Pre	Post
*FEV_1 (L)	1.4 ± 0.6	1.6 ± 0.6	1.4 ± 0.6	1.5 ± 0.6
*IC (L)	1.8 ± 0.5	1.9 ± 0.5	1.8 ± 0.5	1.9 ± 0.5
*FRC (L)	3.1 ± 1.0	3.0 ± 0.9	3.1 ± 1.0	3.0 ± 1.0
*RV (L)	2.2 ± 0.9	1.9 ± 0.7	2.2 ± 0.9	2.0 ± 0.8

Data are mean ± SD or n (%). * indicates a significant difference of data between pre- and post-treatment of the patients, $P < 0.05$. FEV_1 = forced expiratory volume in one second, IC = inspiratory capacity, FRC = functional residual capacity, and RV = residual volume.



Lung volume parameters	Aerobidol MDI mean (SD)	Berodual inhaler mean (SD)	*P* - value
FEV_1 change	13.0 (11.0)	13.8 (10.0)	0.74
IC change	5.8 (8.3)	5.4 (8.6)	0.90
FRC change	- 4.8 (10.2)	-5.4 (6.2)	0.76
RV change	- 9.6 (16.9)	-10.2 (10.6)	0.86

Figure 3. Change in percentage of pulmonary functions after treatment with Aerobidol MDI and Berodual inhaler. Data were calculated and compared to the pre-treatment values. FEV_1= forced expiratory volume in one second, IC = inspiratory capacity, FRC = functional residual capacity, and RV = residual volume.

Table 3. Cross over study variation analysis.

	Partial SS	MS	F	*P*-value
FEV_1 (%change)				
Sequence	502.5	502.5	3.4	0.07
Treatment	7.2	7.2	0.1	0.74
Period	39.9	39.9	0.6	0.43
Period IC (%change)				
Sequence	755.6	755.6	11.1	0.01
Treatment	0.9	0.9	0.0	0.90
Period	21.0	21.0	0.4	0.53
FRC (%change)				
Sequence	409.1	409.1	6.0	0.02
Treatment	6.4	6.4	0.1	0.76
Period	15.3	15.3	0.2	0.63
RV (%change)				
Sequence	507.7	507.7	2.1	0.15
Treatment	4.8	4.8	0.0	0.86
Period	0.6	0.6	0.0	0.95

FEV_1 = forced expiratory volume in one second, IC = inspiratory capacity, FRC = functional residual capacity, and RV = residual volume

Table 4. Effects of fenoterol/ipratropium bromide combination on lung function parameters including FEV1, VC, RV, TLC; compared with the previous studies. Data were shown in mean (SD); nd :no data.

Lung function parameters	Changes after inhalation of fenoterol/ipratropium bromide (ml)				
	Hughes JA, *et al.*[21] 1982	**Teale C, *et al.*[22] 1991**	**Kilfeather SA, *et al.*[23] 2004**	**Hanania NA, *et al.*[24] 2011**	**Our study**
FEV1	210 (30)	120 (150)	200 (165)	229 (100)	174 (136)
IC	nd	nd	nd	nd	96 (152)
FRC	nd	-250 (400)	nd	nd	-168 (246)
RV	nd	-330 (430)	nd	nd	-257 (309)
VC	560 (120)	160 (340)	nd	468 (200)	nd

Discussion

The prevalence of COPD in Thailand is 5.0% in patients with ages more than 30 years old characterized by persistent airflow limitation.[15] The improvement of airflow obstruction in response to inhaled bronchodilators in COPD is evaluated by an increase in FEV_1.[16] However, FEV_1 correlates weakly with exercise capacity and dyspnea, and changes in FEV_1 following bronchodilator therapy are poorly predictive of improved symptoms and exercise endurance.[17] Effects on other pulmonary function parameters such as RV, IC, and FRC reflecting lung hyperinflation are also the crucial determinants in evaluation of physiologic changes after administration of bronchodilators in COPD.[18] Significant reduction in lung hyperinflation occurred in the absence of a change in FEV1 after low-dose short acting bronchodilator has been observed in patients with advanced emphysema.[19] Improved lung hyperinflation, evaluated by decrease of RV, FRC, and TLC, may have better correlation with patients' symptom than FEV1. Therefore, the efficacy of bronchodilators on breathlessness in COPD patients could be better evaluated by both an increase of FEV1 and a decrease of hyperinflation. [20]

Inhaled fenoterol hydrobromide and ipratropium bromide combination has been generally accepted as a mainstay in relieving acute breathlessness in COPD. [1, 2, 6] In the present study, we found that Aerobidol MDI was equivalence to the original Berodual inhaler in improvement of lung functions; an increase of FEV1 and decrease of lung hyperinflation estimated by an increase of IC and decrease of FRC and RV. This short-term

bronchodilating effect may imply the clinical equivalence between Aerobidol MDI and Berodual inhaler when COPD patients become breathlessness.

The effects of fenoterol/ipratropium bromide were investigated in several studies. The comparison to the previous studies were shown in Table 4.[21 - 24] The results were almost comparable except from Hughes's study which showed high bronchodilator responsiveness. The high doses of fenoterol 400 mcg in Hughes's study; others use 100 μg; may take part in the differences in responses.

There are some limitations in our study. Firstly, the physiologic changes of inhalation of bronchodilator was tested in COPD patients in stable condition, without any symptoms. This may not reflect the changes of lung volume parameters while taking the inhalers during breathlessness in the real situation. Although the results may be influenced by several uncontrolled factors such as the particle size, inhaler techniques, we designed the study in a crossover study and use volumetric spacer to assure the equal amount of inhalers. Secondly, the number size of COPD patients is quite small, and may not have enough power to evaluate clinical efficacy and adverse events.

Conclusions

Acute physiologic effects of fenoterol hydrobromide and ipratropium bromide combination inhaler in COPD patients is an increase of FEV_1 and a decrease of hyperinflation. The changes of lung function parameters after inhalation of Aerobidol® MDI and of Berodual® inhaler are comparable.

Conflict of interest

The study is supported by AeroCare CO.,LTD.

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