CLINICAL STUDY ON THE APPLICATION OF VINSALPIUM IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): SHORT-TERM EVALUATION AND COMPARISON WITH A BRAND NAME DRUG WITH THE SAME SUBSTANCE

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ABSTRACT

Background and objectives: Vinsalpium is a combined short-acting bronchodilator (beta$_2$ adrenergic agonist and anticholinergic), produced domestically with international standard processes in the form of an aerosol solution and has been licensed for circulation in Vietnam (register number: VD-33654-19). This study aimed to evaluate short-term efficacy of the drug in patients with COPD (exacerbation and non-exacerbation) in terms of clinical effectiveness, functionality and side effects compared with brand name drug with the same active element (Combivent, Boehringer Ingelheim. ***Subjects and methods***: Study patients were recruited from 5 treatment facilities with respiratory specialist activities distributed nationwide. The cases included in the study were diagnosed of COPD. Patients were randomly divided into 2 groups, each of which received an aerosol dose of the study drug (Vinsalpium) or the control drug (Combivent). Assessment of clinical symptoms and pulmonary function before and after drug administration was compared between the two groups. ***Results and discussion***: There were 260 patients in the study, 130 patients in each group. The percentage of patients under management with spirometry were 74.2% and without it were 3.8%. The number of patients with frequent exacerbations were 119 (45.8%), the number of patients with at least one admitted severe exacerbation were 104 (40.00%). The number of patients attending by appointment were 163 (67.20%). The number of patients who received medication (including at least one of the short-acting bronchodilators, long-acting bronchodilators, and corticosteroids) prior to examination were 213 (82.00%). The average VAS score before the drug administration was 4.50. The number of patients with old tuberculosis leisons on chest Xray were 33 (12.70%). There were no differences in patient characteristics in the study between the two groups (except that the number of patients with combined old TB lesions were greater in the group using the study drug (p=0.005) than the other). The efficacy and safety of the investigational drug (Vinsalpium) compared to the control drug (Combivent) was equivalent. There were small differences in blood pressure stability pre and post-medication, post-medication VAS score, and VAS score via telephone interview favoring the study drug (p values: 0.03; 0.028; and 0.013, respectively). ***Conclusions***: In 260 study patients, most of them had been diagnosed COPD, were being managed and treated. The study showed that there were patient characteristics that need to be noted in terms of indications for drug, treatment efficacy

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and BMI value. There were no differences in patient characteristics in study between the two groups (except that the number of patients with combined old tuberculosis lesions was greater in the group using the study drug than the other). Efficacy and safety of the study drug (Vinsalpium) compared to the control drug (Combivent) are equivalent. There were small differences in blood pressure stability pre and post-medication, post-medication VAS score, and VAS score via telephone interview favoring Vinsalpium.

I. BACKGROUND AND OBJECTIVES

In COPD, the foundational treatment is bronchodilators and inhalers which are preferred over oral agents. In stable COPD, short-acting bronchodilators are indicated for patients with fewer symptoms and exacerbations. During exacerbations, combination short-acting bronchodilators of beta-2 agonist and muscarinic antagonist is the preferred choice for initial therapy [1]. Combining two drugs with two different mechanisms of action (beta2-adrenergic agonist and cholinergic antagonist) increases the bronchodilator effect [4]. The combined formulation improves ventilation better than either ingredient alone and reduces the number of separate inhalations, simplifies therapy and improves adherence compared to either medication alone [5]. In current clinical practice, Combivent (Boehringer Ingelheim's Ipratropium/Salbutamol) is recommended for stable COPD and exacerbations treatment [2]. Generic drugs with the same active ingredients as Combivent have been produced domestically according to international standard processes. Aerosol solution form, the same content as the original drug called Vinsalpium which has been licensed for circulation in Vietnam (Register: VD-33654-19). This study aimed to evaluate the short-term effectiveness of the drug in COPD patients (with and without exacerbations) in terms of clinical effectiveness, functionality and side effects of the drug.

II. PATIENTS AND METHODS

Study patients were cases who visited Respiratory clinics (sites) of participating units (including: Hai Phong International Hospital, Central Lung Hospital, Pham Ngoc Thach Hospital in Ho Chi Minh City HCMC, Ngoc Minh Clinic in Ho Chi Minh City, Can Tho Central General Hospital). The patients were diagnosed COPD with 3 selection criteria: either i) Patients who had measured spirometry, firmly diagnosed with COPD and are being managed and treated with records, or ii) Patients are being managed and treated as a COPD cases but have not had a lung function test, or iii) Patients who have not been managed and treated, have not had a lung function test but they had dyspnea on exertion disproportionate to their age, a 20-pack- year history of smoking, more than twice going to see a doctor for respiratory symptoms or at least once hospitalization for respiratory symptoms in the past 12 months. There are no contraindications for lung function test with a spirometer [3]. There were no contraindications to use the drug in the study: being treated for diseases or suspected to be present such as: hyperthyroidism, diabetes, unstable hypertension, angle-closure glaucoma, urination disorders (urinary retention, benign prostatic hyperplasia).

We excluded from the study the following cases: failure to diagnose COPD, severe exacerbations requiring hospitalization, contraindications for lung function test by

spirometer and to use investigational drugs, do not agree to participate in the study (do not sign the consent form). Exclusion also applied if spirometry measurements were incorrectly performed.

All patients in the study were examined and assessed for dyspnea by using a visual analog scale VAS, electrocardiogram, chest X-ray, spirometry, and side effects were recorded after 30 minutes and by telephone interview after 24-hour medication administration. All patients were explained and used bronchodilators once without knowing the specific type of medication before the second spirometry with: 2.5ml of Salbutamol 2.5mg/Ipratropium 0.5 mg solution by a compressed air nebulizer (Omrion NE-C801) provided and used only in patients in this study. Study drug: Vinsalpium, control drug: Combivent. The data collection process steps are shown in **Figure 1**.

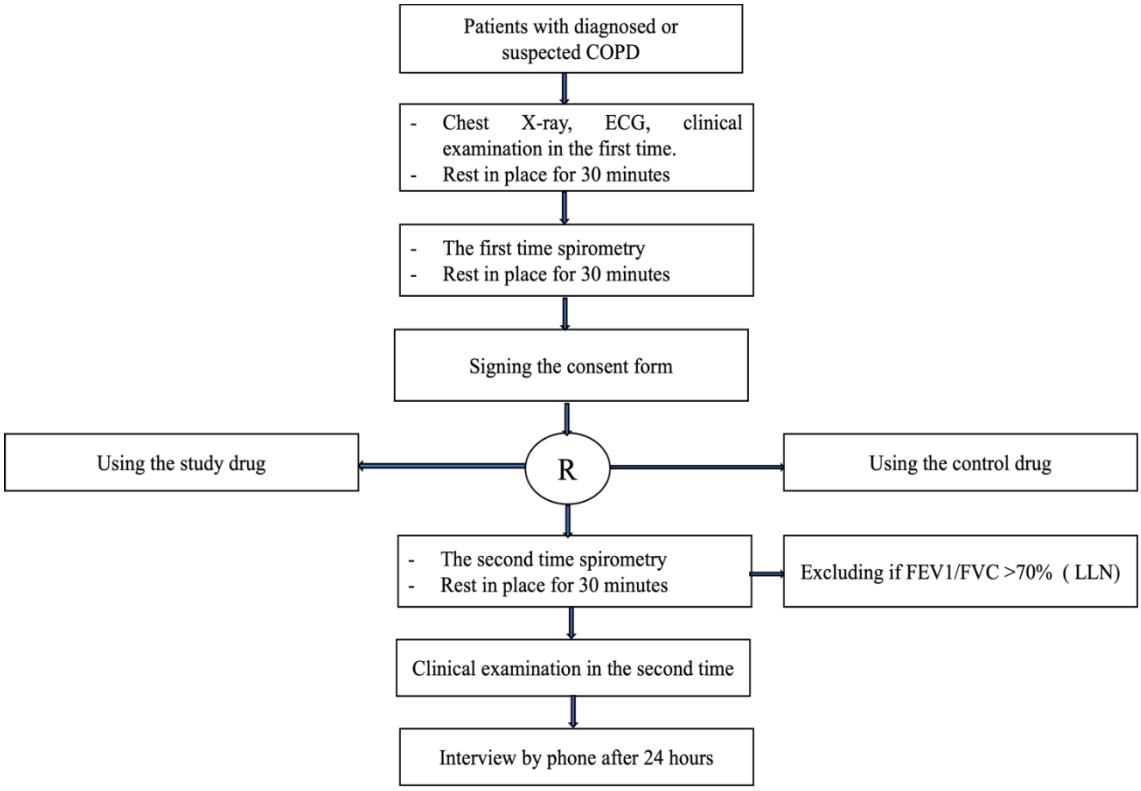

Figure 1. ***Diagram for research data obtaining process***

This is a non-inferiority trial on the short-term effects of Vinsalpium with a brand name drug. It was designed as a prospective, multicenter, randomized, single-blind study. The study used FEV1 index as the main outcome variable. Refer to changes in FEV1 values according to the study "*Tashkin et al. Bronchodilator responsiveness in patients with COPD D.P. Eur Respir J 2008; 31: 742–750*", the sample size calculation formula for a two-sample study with randomized controlled comparison was applied. The number of patients required for the study was 150, and the study recruited 260 patients for sufficient subgroup analysis.

Patients participating the study were randomly divided by even-odd days into two groups: the study drug group (vinsalpium) and the control drug group (combivent).

Evaluating the internal consistency reliability for 3 groups of variables: i) Questioning method (diagnostic characteristics of COPD with characteristics of drug administration), ii) Direct exchange method (VAS score in three times) and iii) Examination method (pulse on examination with heart rate on ECG) by randomly selecting 20% CRF per site for verification by Cronbach's α test with the requirement R ≥ 0.8. Specifically, i) R=0.915, ii) R=0.837 and iii) R=0.967. Statistical analysis by descriptive statistical tests, mean comparison and correlation analysis on SPSS software version 20.

III. RESULTS AND DISCUSSION:

3.1. General characteristics of study patients in 2 groups (using study drug and control drug)

A total of 260 patients were included in the study and divided into two groups, each group had 130 patients. The data table below shows the general characteristics of the study patients in terms of gender, age, diagnosis of COPD, medication management and treatment, exercise capacity before examination, reason for seeking medical attention, VAS score, clinical symptoms (pulse, blood pressure, respiratory rate), SpO2, BMI, chest X-ray images, ECG and use of respiratory drugs before examination in two groups (**table 1**), lung function values before and after using medication (**table 2**), and adverse effects after using the drug (**table 3**).

Table 1. ***Clinical and laboratory characteristics of patients by groups***

Characteristics	Patients use study drug	Patients use control drug	P Value
Age (Mean, SD)	66,62 (8,84)	67,08 (9,35)	0,84
Using medicine before examination (N, %) - Do not taking medicine - SABDs - LABDs - CRS - LABDs + CRS	 21 (16,15) 8 (6,15) 46 (33,38) 43 (33,10) 12 (9,23)	 26 (20,00) 9 (6,92) 37 (28,46) 40 (30,77) 18 (13,85)	 0,58
Exacerbations in the previous 12 months - The average number of exacerbations (mean, SD) -The average number of severe exacerbations requiring hospitalization (mean, SD) -The number of patients with frequent exacerbations (N, %) -The number of patients with at least 1 severe exacerbation requiring hospitalization (N, %)	 1,31 (1,87) 0,76 (1,38) 58 (44,61) 51 (39,23)	 1,48 (1,88) 0,86 (1,22) 61 (46,92) 53 (40,76)	 0,47 0,57 0,71 0,23
The limitation of physical activity before examination (N, %) - Normal - Mild limitation - Moderate limitation - Severe limitation	 8 (6,15) 51 (39,23) 59 (45,38) 12 (9,23)	 5 (3,85) 54 (41,54) 55 (42,31) 16 (12,31)	 0,69
Reasons for going to see the doctor (N, %)			

Characteristics	Patients use study drug	Patients use control drug	P Value
- By an appointment - Because of acute symptoms - Because of chronic symptoms	84 (64,62) 23 (17,69) 23 (17,69)	79 (60,77) 15 (11,54) 36 (27,69)	0,09
VAS score for both groups before and after using medicine (mean, SD)	4,50 (1,80) vs 3,37 (1,73)		**0,0001**
Pre- medication VAS score in each group (mean, SD)	4,36 (1,92)	4,65 (1,68)	0,20
Post- medication VAS score in each group (mean, SD)	3,14 (1,71)	3,61 (1,73)	**0,028**
VAS score via telephone interview in each group (mean, SD)	3,3 (1,7)	3,8 (1,7)	**0,013**
BMI (mean, SD)	20,55	20,64	0,80
Chest X-ray and ECG (N, %) - Emphysema image - Old tuberculosis lesions - Abnormal ECG	 74 (56,69) 24 (18,46) 9 (6,92)	 81 (62,31) 9 (6,92) 13 (10,00)	 0,38 **0,005** 0,37
Pre and post- medication pulse for both groups (mean, SD)	84,07(11,37)vs84,18 (11,11)		0,80
Pre and post- medication pulse in each group - Pre-medication pulse (mean, SD) - Post-medication pulse (mean, SD)	 83,73 (11,20) 84,42 (11,56)	 83,66 (10,95) 84,71 (11,27)	 0,98 0,93
Pre and post-medication hypertension for both groups (mean, SD)	38 (14,61) vs 29 (11,15)		**0,0001**
pre and post- medication hypertension in each group - Pre-medication hypertension (mean, SD) - Post-medication hypertension (mean, SD)	 18 (13,85) 9 (6,92)	 20 (15,38) 20 (15,38)	 0,43 **0,03**
Crackles before and after medication (N, %) - Pre-medication crackles (mean, SD) - Post-medication crackles (mean, SD)	 9 (6,92) 3 (2,30)	 12 (9,23) 4 (3,07)	 0,50 0,70
Using accessory respiratory muscle before and after medication (N, %) - Pre-medication - Post-medication	 4 (3,07) 3 (2,30)	 5 (3,85) 1 (0,76)	 0,73 0,63
Pre and post- medication SpO2 (TB, SD) - Pre-medication - Post-medication	 96,4 (1,80) 96,65 (1,77)	 96,4 (1,97) 96,74 (1,48)	 0,97 0,65

The study enrolled patients from 5 research units with specialized medical examination and treatment activities for COPD. These units are distributed across regions of the country. Therefore, this may be considered a representative study sample for patient characteristics and the situation of COPD treatment and management in Vietnam. **Table 1** presents the characteristics of COPD patients being managed and treated

with the following highlights: the great majority are men (95.00%), 78.07% patients are being managed, most patients has been diagnosed by spirometry and is being treated according to specialized guidelines (74.23% and 74.00%, respectively). VAS score at an unacceptable level (≥ 5 points) is 30%. The number of patients being treated with inhaled corticosteroids (ICS) accounted for a high rate of 45%. However, the proportion of COPD patients using ICS in this study was much lower than in the ENHANCE study with the same research sites in 2018 (45% vs 92,7%) [4]. The average number of exacerbations in previous 12 months in the study was 1.39. The number of exacerbations was higher than in a UK study in 2015, which reported 0.89 [5]. According to the classification of exacerbation risk from the GOLD Guideline, the proportion of patients with frequent exacerbations in the study was 45.76%. This rate, although still high compared to the world medical literature [6], is much lower than in the ENHANCE study cited above, which reported 77.3% [4]. Notably, the proportion of patients with at least one acute exacerbation requiring hospitalization in the previous 12 months in this study was 40%. There was no significant difference in the number of exacerbations between the group of patients being managed and treated and the group of patients undergoing self-treatment (p=0.54). This rate is also higher than in the UK study as cited above, which was 22.6% [5]. The number of patients with sequelae of old tuberculosis lesions on chest X-ray in the study was 33 (13.7%). This rate is equivalent to a study in Turkey (2016) which reported 15.5% [7]. However, it should be noted that among 33 patients with old pulmonary tuberculosis sequelae on chest X-ray, 12 patients (36.36%) were on maintenance therapy with ICS-containing regimens.

3.2. Comparing the effects of investigational and control drugs on respiratory function

Table 2. ***Comparison of pulmonary function between 2 groups pre and post-medication***

Characteristics	Patients use study drug	Patients use control drug	pValue
%FVC and %FEV1 pred before and after medication for both groups (mean, SD)			
- %FVC pred before and after medication	79,81 (18,50) vs 108,37 (12,30)		**0,0001**
- %FEV1pred before and after medication	55,46 (18,19) vs 59,76 (18,80)		**0,0001**
%FVC pred before and after medication (mean, SD) in each group			
- %FVC pred before medication(mean, SD)	79,78 (19,97)	79,85 (16,97)	0,98
- %FCV pred after medication(mean, SD)	109,13 (13,18)	107,60 (11,35)	0,32
%FEV1 pred before and after medication in each group			
- pre-medication %FEV1 pred (mean, SD)	53,52 (18,75)	56,56 (17,55)	0,18
- post-medication %FEV1 pred (mean, SD)	109,93 (11,23)	108,80 (11,51)	0,46
- Number of patients with post-medication %FEV1 pred. ≥12% (N, %)	50 (38,46)	43 (33,08)	0,37

All reported cases of side effects were mild and specifically presented in **Table 3.**

Table 3. ***Comparison of side effects between 2 groups after medication***

Characteristics	Patients use study drug	Patients use control drug	Total	P-value
Side effects after using the drug (N, %)	14 (10,77)	29 (22,31)	43 (16,54)	0,07
- Headache	1	1		
- Dizziness	1	5		
- Dry mouth	9	21		
- Palpitation	3	2		
Patient's feelings when using the drug (N, %)				0,13
- The same as other drugs	90 (69,23)	77 (59,23)		
- More uncomfortable than other drugs	1 (0,77)	4 (3,08)		
- Have no ideas	39 (30,00)	49 (37,69)		

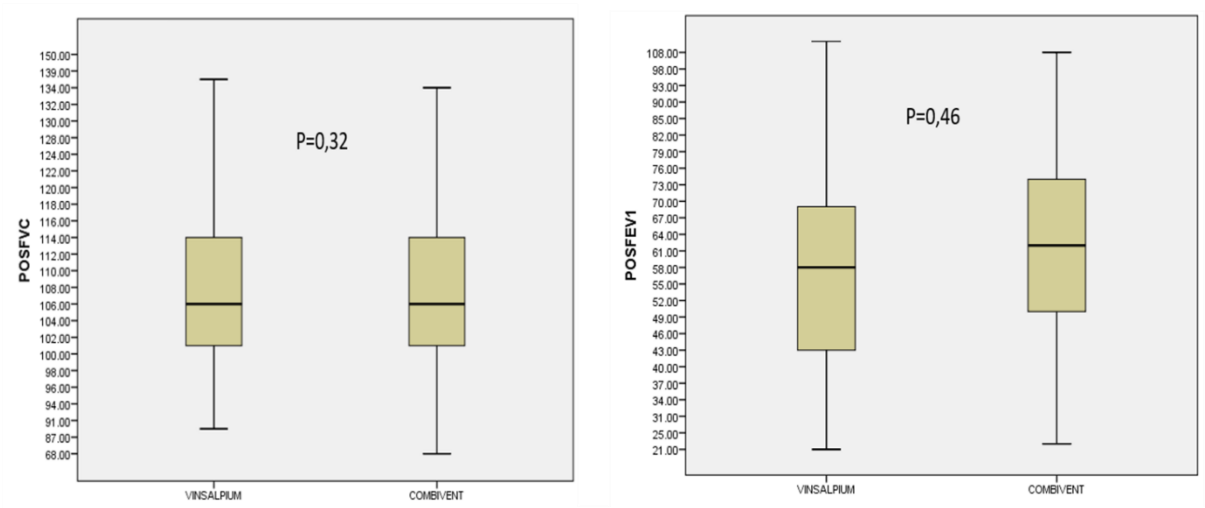

Figure 2. ***The Boxplot chart distributes the mean and SD values of %FVC pred. (left image) and %FEV1 pred. (right image) after using study and control drug.***

Comparison of clinical, laboratory, management and treatment characteristics between the group using the study drug and the group using the control drug showed that there were no fundamental differences **(Table 2)** except that the number of patients in the group using the study drug were more pulmonary tuberculosis sequelae than the group using control drug: 24 (18.46%) versus 9 (6.92%), $p < 0.005$.

The mean pre-medication VAS score between the two groups was not different (4.36 vs 4.65, p=0.20). The mean post-medication VAS score in the group using the study drug decreased significantly more than the group using the control drug (3.14 vs. 3.61, p=0.028). Similarly, the average VAS score after taking the study drug was also significantly lower than the group taking the control drug (3.3 vs. 3.8, p=0.013). The proportion of patients with pre-medication hypertension between the two groups was not different (14% vs. 15%, p = 0.43), but the proportion of patients with post-medication hypertension in the group using the study drug significantly lower than the group using

control medication (6.9% vs. 15.4%, p=0.03).

Comparisons of the change of %FVC pred and %FEV1 pred value before and after medication between the two groups did not show any significant differences. This demonstrates The non-inferiority of the study drug compared to the control drug in terms of the change of %FVC pred. and %FEV1 pred value before and after medication as shown in **Figure 2**.

Side effects of the drug in the study were few and mild. In addition to the side effects that patients reported after taking the drug as shown in Table 3, it is also necessary to pay attention to the effects of beta2 adrenergic receptor agnonist plus muscarinic receptor antagonist in the study drug and the control drug on cardiovascular system, specifically pulse and blood pressure.

Hypertension is a common comorbidity in COPD patients. However, this study did not show that using the study and control drug had an impact on cardiovascular status and blood pressure even though the number of patients with hypertension before taking the drug was significantly higher than after taking the drug (p=0.0001). Because the study design did not include ECG measurement after drug administration, it could not evaluate the impact of the drug on heart rate and conduction.

IV. CONCLUSIONS

Over 260 study patients, most of them have been firmly diagnosed with COPD and are being managed and treated. However, the study points out features that need attention including medication indications, treatment effectiveness and physical characteristics measured by BMI.

There were no differences in patient characteristics at study entry between the two groups, except that the number of patients with combined old tuberculosis lesions was greater in the group using the study drug. Efficacy and safety of the study drug (Vinsalpium) compared to the control drug (Combivent) were equivalent. There were modest differences in term of the stability of blood pressure before and after using drug, post-medication VAS score and via phone interview VAS score favor Vinsalpium.

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