



Efficacy of Levosalbutamol/Ipratropium Combination in Early Bronchodilator Reversibility

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Authors' contributions

This work was carried out in collaboration among all authors. All authors have contributed sufficiently in the conception and design of the study, data collection and interpretation as well as manuscript preparation. All authors read and approved the final version of the manuscript.

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ABSTRACT

Objective: The bronchodilator test is a useful method for measuring the changes in lung capacity with spirometry after inhaling a short-acting bronchodilator drug to diagnose patients with obstructive lung disease. Although its liquid form was available, the inhaler form of levosalbutamol is a relatively new short-acting bronchodilator. To measure the efficacy of levosalbutamol in acute bronchodilator reversibility, in this study, we aimed to compare the effects of salbutamol and new levosalbutamol/ipratropium combination on early reversibility and FEV1 changes observed in bronchodilator tests.

Methods: Bronchodilator test results of forty-two patients who were selected according to the inclusion criteria were retrospectively analyzed. The results of spirometry analysis were evaluated for twenty-four patients who received salbutamol (Group I) and eighteen patients who received levosalbutamol/ipratropium combination (Group II). Reversibility levels were evaluated as the absolute and percentage changes in FEV1.

Results: The changes of absolute and percentage values of mean FEV1 were 159±118 mL,

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12.2%±11.4% in salbutamol (Group I) group and 233±191mL, 18.8%±15.6% in levosalbutamol / ipratropium (Group II) combination (p=0.025 and 0.048, respectively). Although no significant difference was observed in the reversibility results, Group II showed significantly improved FEV1 values compared to Group I.

Conclusion: To the authors' knowledge, this is the first study demonstrating that the combination of inhalation therapy with levosalbutamol and ipratropium bromide is more beneficial than salbutamol alone in terms of FEV1 improvement in bronchodilator test. We suggest that this combination can be a good candidate for utilization in diagnostic bronchodilator tests since it proved a specific higher improvement in FEV1 values.

Keywords: Asthma; COPD; spirometry; reversibility; bronchodilator agents; levosalbutamol; ipratropium bromide.

1. INTRODUCTION

Obstructive lung diseases such as asthma, chronic bronchitis, and emphysema are the most common pulmonary diseases worldwide which are characterized by chronic airway inflammation and airway obstruction. They are also characterized by reduced airflow related to airway narrowing which was caused by an increased airway resistance [1]. Spirometry is used as a complementary tool for the diagnosis of obstructive lung diseases. Therefore, assessment with spirometry helps making a diagnosis by differentiating between obstructive lung diseases, such as asthma or chronic obstructive pulmonary disease (COPD), and restrictive lung disorders, such as interstitial pneumonia [2].

In general, spirometric determination of a postbronchodilator FEV1/FVC<0.7 is used to confirm the COPD diagnosis. However, fixed or non-reversible airway obstruction that is characteristic of COPD complicates the differential diagnosis by spirometry alone. Although airway obstruction is not fully reversible in such patients, bronchodilator responsiveness is common and bronchodilator medications are used both for diagnosis and management [3]. Since it was stated that acute bronchodilator reversibility may predict both inflammatory characteristics and long-term prognosis, it is important to investigate acute bronchodilator reversibility responses to different therapeutic regimens in COPD [4]. American Thoracic Society recommends using a short-acting β 2-adrenoceptor agonist, such as salbutamol, or an anticholinergic, such as ipratropium bromide, for reversibility testing [5].

The bronchodilator test is a useful method for measuring the changes in the lung capacity after inhaling a short-acting bronchodilator drug. Until

recently, conventional short-acting bronchodilators such as β 2-agonists (e.g, salbutamol) were used to obtain possible reversibility in these tests [2]. All of the β 2-agonists that are currently in use are racemic mixtures that are composed in equal amounts of R- and S- enantiomers, except levosalbutamol, which is mainly composed of R-salbutamol. Therefore, levosalbutamol has 100-fold greater affinity to β 2-receptor than S-salbutamol and 2-fold greater binding affinity than racemic salbutamol. Several clinical and mechanistic studies have demonstrated that R-salbutamol alone provides the bronchodilator and bronchoprotective effects through β 2-agonist activity that is required for the relief, while S-isomer being inert [6,7].

Together with the advances in pharmacotherapy, new drugs which require lower doses and have fewer side effects have become available in the market. Although its liquid form was available, the inhaler form of levosalbutamol is a relatively new short-acting bronchodilator used in the treatment of asthma and COPD via a pressurized metered-dose inhaler [8,9]. The discovery of a new route of administration for levosalbutamol started a research area for its further possible indications owing to its different pharmacodynamic properties. Currently, new combination formulas of levosalbutamol with ipratropium bromide is available in the market and used for better management of COPD patients. Since not all the COPD patients show a positive response to reversibility test with same agent, the use of different therapeutic regimens is crucial to reduce differences on patient basis. To measure the efficacy of levosalbutamol in acute bronchodilator reversibility, in this study, we aimed to compare the effects of salbutamol and levosalbutamol/ipratropium combination on early reversibility and the changes in forced expiratory

volume at the first second (FEV1) in patients with obstructive airway disease.

2. MATERIALS AND METHODS

2.1 Patient Selection

Patients consulted our clinics who were meeting the inclusion criteria specified below between August 2019 - October 2019 were evaluated:

- (I) Symptomatic patients (cough, dyspnea, and/or wheezing);
- (II) Obstructive breath sounds on chest auscultation;
- (III) Presence of airway obstruction in spirometry (FEV1/ FVC \leq 70% of expected);
- (IV) Patients who had never used bronchodilators before, or;
- (V) Patients who had not received short- or long-acting inhaled bronchodilator therapy within the recent 12 hours.

Forty-two patients who met the inclusion criteria and consulted to clinics between aforementioned time period were retrospectively evaluated.

2.2 Pulmonary Function Test and Reversibility Assessment

The basal FEV1 and FEV1/FVC values were measured using the MIR MiniSpir PC-Based USB Spirometer by the same physician following a 30-min resting period in an outpatient clinic setting. It was assured that the test was performed in the seated position, when the nose was clamped, and nasal respiration was hindered. The patients performed the forced expiratory maneuver at least three times and the maximum FEV1 value was recorded as the basal value.

2.3 Reversibility Test

The patients with similar characteristics and demographic hallmarks who were found to receive two different drug formulas were selected for comparison. Group I were constituted with patients who received salbutamol (Ventolin® 100 mcg inhalation aerosol, total dose 400 mcg, Glaxo Wellcome, UK) and and Group II was composed of patients who received levosalbutamol/ipratropium combination (Ipralev® 50/20 mcg, inhalation aerosol, total dose 200/80 mcg, Neutec, Turkey) via a pressurized metered-dose inhaler with a spacer. Reversibility levels were evaluated as the

absolute change in FEV1 and the percentage of change from the initial FEV1, calculated as $FEV1\ \%\Delta_{init} = \frac{\text{post FEV1} - \text{pre FEV1}}{\text{pre FEV1}} \times 100$ (according to American Thoracic Society guidelines) and bronchial reversibility is defined as a drug-induced increase in FEV1 of ≥ 200 mL and $\geq 12\%$ from baseline.

2.4 Statistical Analysis

Results are presented as means \pm standard errors of means. P value < 0.05 was considered as statistically significant and indicated with an asterisk. Descriptive group data were compared using the unpaired Student t-test and Pearson chi-square test.

3. RESULTS

Total 42 patients were evaluated, consecutively. The characteristics of patients were shown in Table 1. The mean age of patients was 59.1 ± 16.6 years and the male-to-female ratio was 33/9. The baseline pulmonary function test results were as following: mean FVC; 2329 ± 1125 mL and $63.9\% \pm 21.3\%$, mean FEV1; 1463 ± 808 mL and $49.5\% \pm 19.5\%$, mean FEV1/FVC; $61.7\% \pm 7.7\%$. Overall, the observed absolute change and percentage of change in FEV1 were 191 ± 156 mL and $15.1\% \pm 13.6\%$, respectively. Reversibility after drug administration was observed in total 23 (54.8%) of patients. No adverse effect has seen in any patients.

We aimed to compare the effects of salbutamol (Group I) and levosalbutamol/ipratropium (Group II) combination on early reversibility. Therefore, we compared the two groups according to the patients' characteristics and the results of spirometry analysis, as shown in Table 2. There was no significant difference in demographic data and baseline pulmonary function test results between two groups. The changes of absolute and percentage values of mean FEV1 were 159 ± 118 mL, $12.2\% \pm 11.4\%$ in salbutamol (Group I) group and 233 ± 191 mL, $18.8\% \pm 15.6\%$ in levosalbutamol/ipratropium (Group II) combination ($p=0.025$ and 0.048 , respectively). Group II showed a statistically significant changes in FEV1 values (in the means of $\text{abs}\Delta$ -mL and $\%\text{init}$; $\text{mean} \pm \text{SD}$) compared to Group I. The reversibility test was positive in 13(54.1%) of patients in salbutamol (Group I) and 10(55.5) in levosalbutamol/ipratropium (Group II) combination ($p=0.929$). There was no statistically significant relationship for reversibility results between two groups.

Table 1. The characteristics of the patients

Characteristics	Values
Patient number	42
Age; Mean years \pmSD	59.1 \pm 16.6
Male/Female	33/9
Smoking status (n, %)	
Mean packet/years \pm SD	28.8 \pm 19.2
Non-smoker	10(23.8)
Current smoker	15(35.7)
Ex-smoker	17(40.5)
Spirometry Results	
FVC	
mL \pm SD	2329 \pm 1125
%pred-mean \pm SD(min-max)	63.9 \pm 21.3(26-110)
FEV1	
mL \pm SD	1463 \pm 808
%pred-mean \pm SD(min-max)	49.5 \pm 19.5(24-95)
FEV1/FVC; %pred-mean \pm SD(min-max)	61.7 \pm 7.7(40.5-70)
Reversibility	
Yes(n, %)	23(54.8)
No(n, %)	19 (45.2)
FEV1 change	
abs Δ -mL	191 \pm 156
%init;mean \pm SD(min-max)	15.1 \pm 13.6(0-47)

Table 2. The spirometry test results and comparisons between two groups

Characteristics	Group I	Group II	p
Patient number(n, %)	24(57.1)	18(42.9)	
Age; mean years \pmSD	57.9 \pm 18.8	60.7 \pm 13.4	0.307
Male/Female	19/5	14/4	0.914
Smoking			
Mean packet/years \pm SD	27.9 \pm 20.7	30 \pm 17.6	0.317
Spirometry Results			
FVC			
mL \pm SD	2478 \pm 1181	2131 \pm 1046	0.703
%pred-mean \pm SD	68.8 \pm 20.6	57.2 \pm 21.1	0.775
FEV1			
mL \pm SD	1505 \pm 866	1406 \pm 743	0.675
%pred-mean \pm SD	51.5 \pm 20.8	46.7 \pm 17.9	0.556
FEV1/FVC			
%pred-mean \pm SD	59.3 \pm 8.6	64.8 \pm 5	
Reversibility			
Yes(n,%)	13(54.1)	10(55.5)	0.929
No(n,%)	11(45.9)	8(44.5)	
FEV1 change			
abs Δ -mL	159 \pm 118	233 \pm 191	0.025*
%init;mean \pm SD	12.2 \pm 11.4	18.8 \pm 15.6	0.048*

4. DISCUSSION

In this study, we have demonstrated that combination of inhalation therapy with levosalbutamol and ipratropium bromide is more beneficial than salbutamol alone in terms of

FEV1 improvement in bronchodilator test. Starting from this, it can be suggested that this combination can be a good candidate for utilization in diagnostic bronchodilator tests since it proved a specific higher improvement in FEV1 values.

Several factors may influence bronchodilator reversibility, including disease severity, criteria used to define reversibility, and method and drug used for reversibility testing [5]. In this study, we only investigated the effect of drug choice in reversibility. It is well known that short and long acting bronchodilator drugs are commonly used in clinical practice for the bronchodilator test. The combination approach for bronchodilators with different mechanism and duration of action may increase the degree of bronchodilation with same or lesser side effects [10,11]. Salbutamol and salbutamol/ipratropium combination are the most common bronchodilators which are used for the reversibility test. In a comprehensive review, it has been concluded that S-salbutamol is an unnecessary component of racemic salbutamol and produces no clinical benefit, furthermore, it may undermine the desired therapeutic bronchodilator effects and cause detrimental effects such as a greater accumulation of S-salbutamol over time (a circumstance that might paradoxically contribute to the underlying disease process by causing to take additional doses and further aggravate the process). On the other hand, R-Salbutamol provides all of the benefits of racemic salbutamol but eliminates some important drawbacks by demonstrating more effective and rapid bronchodilation at a lower dose with fewer side effects and a reduced cost [6].

Levosalbutamol is the R-isomer of salbutamol which is more efficacious than racemic salbutamol in terms of improvement of PEFr, SPO₂ and it also has less adverse effects like tachycardia and hypokalemia. With the increased availability of levosalbutamol, the fixed dose combinations of levosalbutamol and ipratropium bromide are started to be used. Another benefit of levosalbutamol is the requirement of lesser concentrations of ipratropium bromide (50 mcg versus 100 mcg) in combination formulas to achieve a similar degree of bronchodilation. Ipratropium, when added in combination with levosalbutamol, also resulted in improved maximal airflow which is longer-lasting [8,9]. In their study, Kamshette et al. also suggested that the combination of inhalation therapy with levosalbutamol and ipratropium bromide is more beneficial than either of the agents used alone [12,13]. Although the benefits of salbutamol and ipratropium combination has proven to be superior than salbutamol alone, utilization of levosalbutamol in this combination is a new approach in the diagnosis and treatment of obstructive lung diseases.

In our study, the ratio of patients who showed reversibility after drug administration were similar between two groups. However, the changes in absolute and percentage values of mean FEV₁ were significantly higher in group II. As expected, the levosalbutamol/ ipratropium combination provided a higher increase in FEV₁ values than salbutamol alone. We suggest that this combination can be a good candidate for utilization in diagnostic bronchodilator tests since it indicates a more reliable result due to higher improvement in FEV₁ values. However, the limitations of this study may include the small size, diverse characteristics of the patient population, and a follow-up and observation of clinical outcomes of the patient group. Further larger randomized studies may be required to demonstrate the beneficial effects of this combination for the improvements on positive results of reversibility tests. Also, other beneficial effects of this combination should be investigated from the perspective of lesser side effects and longer duration of action.

5. CONCLUSION

In conclusion, to the authors' knowledge, this is the first study demonstrating that the combination of inhalation therapy with levosalbutamol and ipratropium bromide is more beneficial than salbutamol alone for early reversibility in bronchodilator test in terms of FEV₁ improvement.

CONSENT AND ETHICAL APPROVAL

The study was performed in accordance with the ethical principles in the Good Clinical Practice guidelines, and Declaration of Helsinki. All the participants were informed about the study and their written informed consents were obtained. Approval for this study procedure was obtained from the local Ethics Committee and Institutional Review Board of the concerned tertiary health care institution.

DATA AVAILABILITY

The research article data used to support the findings of this study are available from the corresponding author upon request.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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