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ORIGINAL ARTICLE

Investigation of the efficacy of generic and brand-name tiotropium bromide in the management of chronic obstructive pulmonary disease: A randomized comparative trial

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KEYWORDS

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Anticholinergic;
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Abstract *Introduction*: The beneficial effects of tiotropium bromide, a long acting anticholinergic bronchodilator, in the management of chronic obstructive pulmonary disease have been shown in previous studies. The present study aimed to compare the efficacy and safety of generic (Tiova®) and brand-name (Spiriva®) tiotropium preparations in patients with COPD. *Methods and materials*: In this randomized double-blind parallel-group trial, 79 patients with documented COPD were assigned to Tiova® or Spiriva® for a period of 4 weeks. Assessment of pulmonary function (using spirometry), quality-of-life (using St. George respiratory Questionnaire [SGRQ]) and severity of

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respiratory symptoms (using breathlessness, cough and sputum scale [BCSS]) was performed at baseline and at the end of treatment period. *Results*: There were significant increases in FEV_1 and reductions in FVC by the end of study in both Tiova® and Spiriva® groups. FEV_1/FVC ratio did not change significantly neither in the Tiova® nor in Spiriva® group. Overall SGRQ score as well as subscale scores of symptoms, activity and impacts were improved by both drugs. In the BCSS scale, the frequency and severity of three main symptoms (dyspnea, cough and sputum) was decreased by both drugs. Baseline as well as post-treatment values of spirometric parameters, SGRQ and BCSS scores was comparable between the groups, apart from a lower post-treatment frequency of cough and sputum in the Spiriva® versus Tiova® group. There was no report of adverse events in either of the study groups. *Conclusion*: The findings of this comparative trial showed equivalent efficacy and safety of Spiriva® and Tiova® in lessening the symptoms as well as improving the quality of life in patients with COPD. This finding has an important translational value given the significantly lower costs of generic versus brand-name products.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a pathologic state which is characterized by chronic, progressive and irreversible airflow obstruction, leading to impaired pulmonary function. Smoking is the major risk factor for COPD (Currie, 2010). According to WHO estimates, 65 million people had COPD in 2005 and more than 3 million people died because of COPD in this year, amounting to 5% of all deaths globally. COPD was the 5th cause of death in 2002 all over the world and currently it is the third cause of death, preceded by ischemic heart disease and stroke. Moreover, 90% COPD-associated deaths occur in low- and middle-income countries. In Iran, COPD was among the four main non-communicable diseases which led to death in 2012 (Semba et al., 2014).

COPD is a chronic state that is accompanied by symptoms such as productive coughs and dyspnea. By progression of COPD, exacerbations become more frequent and are often triggered by respiratory bacterial infections, predisposing to several life-threatening conditions such as left ventricular failure, cardiac arrhythmia, pneumothorax, pneumonia and pulmonary thromboembolism (Longo et al., 2011). Although complete control of COPD is difficult, pharmacotherapy can alleviate the symptoms, slow the disease progression, reduce the frequency and severity of exacerbations and also prevent mortality. Bronchodilators and inhaled corticosteroids are routinely administered medications for COPD management (Hanania and Sharafkhaneh, 2010). Bronchodilators have also been shown to be helpful in patients with increased airway hypersensitivity. Combination of a β_2-agonist (e.g. salbutamol) and an anticholinergic (e.g. ipratropium bromide) has been found to be more effective than any of the other bronchodilators used alone (Balali-Mood and Hefazi, 2005).

Anticholinergic bronchodilators are widely used as standard treatments of COPD. Anticholinergics are indicated in all stages of COPD and are available in two forms: short-acting (ipratropium bromide) and long-acting (tiotropium bromide) (Vestbo et al., 2013). These bronchodilators block muscarinic receptors, resulting in relaxation and dilatation of airways and attenuation of mucus secretion (Kato et al., 2006). Tiotropium bromide is preferred over ipratropium bromide because of its specific inhibition of M3 receptors and longer duration of action (Vestbo et al., 2013). Tiotropium bromide is marketed under two trade names Spiriva® (manufactured by Boehringer-Ingelheim, Germany) and Tiova® (manufactured by Cipla, India). Tiova® is a generic product that is less expensive than the brand-name product (Spiriva®) (Tan and de Haan, 2014). Hitherto, only Spiriva® has been available and prescribed in Iran.

The present study aimed to compare the efficacy and safety of brand and generic products of tiotropium bromide in patients suffering from COPD.

2. Material and methods

This study was designed as a randomized double-blind clinical trial. Subjects were recruited from those referring to the Respiratory Clinic of the Baqiyatallah Hospital (Tehran, Iran). Inclusion criteria were documented history of COPD, age between 30 and 60 years, absence of spirometry contraindication, and a negative history of coagulopathy, prostate hypertrophy and glaucoma. Subjects with a history of hypersensitivity to tiotropium bromide, cigarette smoking, occupational exposure to toxic chemicals, allergic rhinitis or any other type of allergy, asthma, tuberculosis, lung cancer, systemic diseases with pulmonary complications (e.g. heart failure, renal dysfunction, hepatitis, cirrhosis and connective tissue disorders), anemia or polycythemia, and acute respiratory infection were excluded from the study.

2.1. Treatment

Eligible subjects were randomized to receive either Spiriva® ($n = 33$) or Tiova® ($n = 46$). Patients were instructed to take one capsule of either of the drugs daily at 12:00 a.m. Each capsule contained 18 μg of tiotropium bromide dry powder. Both study drugs were inhaled by the aid of appropriate apparatus i.e. Revolizer® (made by Cipla Ltd. For the use of Tiova®) and Handihaler® (made by Boehringer-Ingelheimmade Ltd. for the use of Spiriva®). During the study, all patients continued their standard COPD treatment regimen including Seretide® inhaler (containing Fluticasone and Salmeterol; one puff every 12 h), and N-acetylcysteine (600 mg every 12 h).