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Original Article

Evaluating the effectiveness of Tiotropium Bromide on severe Asthma patients referred to Ali ibn Abi Talib hospital in Zahedan, southeastern Iran

Nezarali Moulaei[1*], Seyyed Mohammad Ali Mirjahanbakhsh[2], Mohammad Kazem Momeni[3], Mosayeb Shahryar[4], Hossein Ansari[5]

[1] Assistant Professor of Pulmonary Diseases, Department of Internal Medicine, School of Medicine, Infectious Diseases and Tropical Medicine Research Center, Zahedan University of Medical Sciences, Zahedan, Iran. [2] Resident of Internal Medicine, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran. [3] Assistant Professor of Pulmonary Diseases, Department of Internal Medicine, School of Medicine, Clinical Immunology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran. [4] Assistant Professor of Pulmonary Diseases, Department of Internal Medicine, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran. [5] Associate Professor of Epidemiology, Department of Biostatistics and Epidemiology, School of Health, Health Promotion Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

Correspondence: Nezarali Moulaei, Assistant Professor of Pulmonary Diseases, Department of Internal Medicine, School of Medicine, Infectious Diseases and Tropical Medicine Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

ABSTRACT

Introduction: Asthma is a chronic respiratory symptom that causes inflammation, hypersensitivity, and spasm of the airways. Asthma is one of the most common chronic diseases in the world. It is estimated that there are 235 million asthma patients in the world. Therefore, the present study aimed to evaluate the effectiveness of tiotropium bromide on severe asthma patients. **Methods:** The present study was a Randomized Placebo-Controlled Crossover Trial. The study population were the 60 patients referred to the Respiratory Department of the Ali ibn Abi Talib in Zahedan. The patients were divided into placebo and experimental groups. Tiotropium bromide was prescribed in combination with the routine treatment in the experimental group. After four weeks, the FEV1 level and the score of the Asthma Control Test (ACT) were evaluated, and the groups were interchanged after a washout period of 4 weeks. Then the placebo group received tiotropium bromide, and the tiotropium bromide group received the placebo; and after four weeks, the FEV1 level and the score of the ACT were re-evaluated. Tiotropium bromide and the placebo were coded, making the study a double-blind one. Finally, the data were statically analyzed using SPSS. **Results:** The results showed that In the tiotropium bromide group, 14 (46.7 %) of the patients were male, and 16 (53.3 %) of them were female, and in the placebo group, 16 (53.3 %) of the patients were male, and 14 (46.7 %) were females. The mean age in the tiotropium bromide and the placebo groups was 26.366 ± 7.430 and 30.266 ± 8.423, respectively. The period of the disease in the tiotropium bromide and the placebo groups was 3.036 ± 4.766 and 3.002 ± 3.866, respectively. Finally, our results showed that tiotropium bromide has a role in controlling asthma and improving the mean FEV1. **Conclusion:** The researchers of this study found tiotropium bromide to be beneficial in the treatment of severe asthma patients. Moreover, adding tiotropium to the asthma treatment regimen was found to be beneficial in lowering the dosage of corticosteroids.

Keywords: tiotropium bromide, severe asthma.

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Introduction

Asthma is a chronic respiratory symptom that causes inflammation, hypersensitivity, and spasm of the lung airways [1]. The chronic inflammatory disease of the airways has complicated pathophysiology. Many etiologies have been attributed to it, making it a disease with heterogeneous clinical course and severity [2]. The main characteristic of inflammation of the airways is the infiltration of the bronchial walls by eosinophils, activated mast cells, and T-lymphocytes. Other clinical features

of asthma include increased mass of soft tissue and reversible contraction. The airway inflammation, mucus aggregation, and bronchospasm are factors responsible for the dyspnea, whizzing, cough, and chest tightness [1].

It is estimated that there are 235 million asthma patients in the world, comprising 1-18% of the population in different countries [3]. The prevalence of asthma is increasing because of the urban lifestyle; namely, it has increased from 7.3 % in 2001 to 8.4 % in 2010 [4]. It is estimated that the number of asthma patients will be increased by 100 million until 2025 [3].

According to the available data, it seems that the prevalence of Asthma in Iran is higher than the global average. Moreover, the prevalence of asthmatic symptoms and the economic, social, and health care costs are rising in the country. According to the previous studies on the prevalence of asthma symptoms in Iran based on the meta-analysis of national studies, the estimation of the country's asthma prevalence is much higher than reported by international organizations. Moreover, it seems that Iran's share of the disease prevalence in the world and the region is higher than the global and regional average, which is justifiable, given the urbanization, industrialization, the climatic conditions, the pollution caused by the industrial conditions, and the unbalanced development of the country [5].

Although the current medical treatments are useful in most asthma patients, controlling the disease is complicated in some subgroups. In fact, despite the therapeutic protocols, asthma is not adequately controlled in more than 5 % of asthma patients. A subgroup of patients require high doses of drugs, and they still experience the resistance and the exacerbation symptoms [6]. It seems that some subgroups of patients respond better to the anticholinergic agents [7, 8]. The previous studies on some subgroups of asthma patients showed that patients with nocturnal symptoms, chronic asthma with evidence of recurrent, consistent airway obstruction, a long period of internal asthma, and atopic asthma respond better to the anticholinergic agents [9].

Tiotropium bromide, which is a synthetic and relatively new class of anticholinergic agents, was primarily used to treat patients with Chronic Obstructive Pulmonary Diseases (COPDs) [10]. Tiotropium bromide is an inhaled long-acting muscarinic antagonist (LAMA). This drug has a high efficacy as a selective antagonist for the muscarinic acetylcholine receptors [11]. Tiotropium bromide is the first anticholinergic drug recommended for children and adults with poorly controlled asthma [12]. A systematic review of 5 clinical trials, regarding the effectiveness of adding tiotropium bromide to the treatment regimen of asthma, showed that taking tiotropium in combination therapy with an ICS alone, or in addition to a LABA, leads to improvement in lung function; moreover, the effects will not be diminished with lowering the doses of glucocorticoids and LABA [13]. Although the previous studies have shown significant lung function results, consistent improvement of respiratory symptoms was not observed, and more research is required in this field [6]. In comparison to the LABAs, tiotropium bromide has the same effects for the maintenance treatment of asthma in combination with ICSs. Because of its effects on inflammation, airway remodeling, mucus production, cough reflex, optimal safety profile, and the wide range of effectiveness in different phenotypes of the disease, this drug is an appropriate option for treating the poorly-controlled asthma patients [12].

Kerstjens et al. studied the effects of tiotropium on 912 poorly-controlled patients in 2012. The results of the study showed that adding tiotropium to the treatment regimen of the poorly-controlled asthma patients [14]. Price et al. in their study found that adding a LAMA, e.g., tiotropium to the treatment regimen of asthma patients leads to a significant decrease of exacerbations and prescription of antibiotics for treating the lower respiratory tract infections in the follow-up years [15].

Considering the high asthma prevalence in Iran and the importance of controlling and treating the disease, and the absence of a clinical trial regarding the effectiveness of tiotropium in the treatment of asthma patients inside the country, the researchers aimed to study the effects of tiotropium on the severity of the symptoms in severe asthma patients.

Materials and Methods

This crossover clinical trial study was performed on 30 persons with asthma in the case group and 30 healthy persons in the control group in 2018 in southeastern Iran. The inclusion criteria included age of above 18 years, not taking a muscarinic anticholinergic drug, absence of other respiratory diseases, and not being a smoker or a history of fewer than ten pack-years of smoking. The exclusion criteria included pregnancy, breastfeeding, not taking contraceptive pills or devices in those with a high probability of conceiving, a history of taking other anticholinergic drugs, vocal cord dysfunction, contraindications to the treatment, and presence of other respiratory diseases, e.g., COPD and respiratory infection. The sample size was 30. The sampling method used was convenience sampling. All of the Helsinki principles were applied in this study. The patients under treatment for severe asthma were chosen for further analysis and follow-up upon the approval of the Ethics Committee of Zahedan University of Medical Sciences.

After obtaining approval of the ethics committee, the profiles of the patients under treatment for severe asthma were extracted with the help of the secretary of the center. Before the treatment with tiotropium bromide, the demographic information, i.e., age, sex, and the Asthma Control Test (ACT) and spirometry questionnaires were completed; then, the patients were divided into placebo and experimental groups using permuted block randomization. Tiotropium bromide was prescribed in combination with the routine treatment in the experimental group. After four weeks, the FEV1 level and the score of the ACT were evaluated, and the groups were interchanged after a washout period of 4 weeks; namely, the placebo group received tiotropium bromide, and the tiotropium bromide group received the placebo. After four weeks, the FEV1 level and the ACT score of the two groups were re-evaluated. Tiotropium bromide and the placebo were coded, making the study a double-blind one.

As for data description, central tendency, index of dispersion, and tables with statistical charts were used. A paired T-test and an independent T-test were used to compare the experimental group and to evaluate the Carryover Effect, respectively. Data were analyzed using SPSS version 22, and the p-value was defined as less than 0.05.

Results

According to Table 1, the number of men and women in the case group with thiothropium bromide was 14 (46.7%) and 16 (53.3%), respectively, and in the placebo group was 16 (53.3%) and 14, respectively. (46.7%) (P> 0/07).. On the other hand, the mean age in the tiotropium bromide and the placebo groups were 26.366 ± 7.430 and 30.266 ± 8.423, respectively. The period of the disease in the tiotropium bromide and the placebo groups were 3.036 ± 4.766 and 3.002 ± 3.866, respectively (P>0.05).

Table 1: Demographic properties of the participants in the experimental and the placebo group.

Factor	Group	Intervention	Placebo	P
		Frequency (% N)	Frequency (% N)	
Sex	Male	14 (46.7 %)	16 (53.3 %)	0.07
	Female	16 (53.3 %)	14 (46.7 %)	
Age (sd)		26.366 ± 7.430	30.266 ± 8.423	0.06
Period of the disease (sd)		4.766 ± 3.036	3.866 ± 3.002	0.253

As shown in Table 2, the mean and the standard deviation (SD) of the experimental and the placebo group were 60.833 ± 9.02 % and 54.8206 ± 10.86 % before the treatment, respectively. The results of the independent T-test showed that there was not a significant difference in FEV1 mean between the two groups before the treatment (P>0.25). The mean and SD of the ACT score in the experimental and the placebo group were 19.733 ± 2.863 and 20.566 ± 1.590 before the experiment, respectively. The results of the independent T-test showed that there was not a significant difference between the two groups in the mean of the ACT score before the treatment (P>0.07).

Table 2: Mean of FEV1 and the ACT score in the experimental and placebo group, prior to the treatment

	Experimental group		Placebo group		P
	Mean	SD	Mean	SD	
FEV1	60.833	9.02	54.206	10.86	0.25
ACT score	19.733	2.863	20.566	1.590	0.07

As shown in Table 3, the mean and SD of FEV1 in the experimental group after phase I of the study is 55.800 ± 8.087. After a period of four weeks, the tiotropium group received the placebo. The mean and the SD of FEV1 in the new placebo group was 69.966 ± 9.499. The results of the independent T-test showed that there was not a significant difference in the mean FEV1 between the phase I and II experimental groups (P>0.825); therefore, there is not a significant difference between the experimental group in phase I with the same group which received placebo in phase II of the study. The mean and the SD of FEV1 in the placebo group after phase I are 58.066 ± 13.516 %. The placebo group received tiotropium bromide after a period of four weeks. The mean and SD of FEV1 in the new experimental group was 60.833 ± 9.029. The results of the independent T-test showed that there was a significant difference in the mean FEV1 between the placebo bromide group in phase I and II of the study (P<0.05); therefore, there is a significant difference between phase I placebo group and the same group which received tiotropium in phase II of the study. The improvement in the tiotropium group was greater, given the mean of the two groups. On the other hand, the mean and SD of the ACT in the experimental group after phase I of the study are 13.933 ± 3.600. The experimental group received a placebo after a period of four weeks. The mean and the SD of the ACT in the new placebo group was 20.233 ± 5.775. The results of the independent T-test showed that there is not a significant difference in the ACT mean of the experimental group in phase I and II of the study (P>0.891); therefore, there was not a significant difference between the phase I experimental group and the same group which received placebo in phase II. On the other hand, the results showed that the mean and SD of the ACT in the placebo group was 19.166 ± 2.804 after phase I of the study. The placebo group received tiotropium bromide after four weeks. The ACT mean and SD of the new experimental group was 20.233 ± 5.775. The results of the independent T-test showed that there was a significant difference between the ACT mean of the phase I placebo group and the phase I experimental groups in the and phase I and II of the study (P<0.04), indicating that there was a significant difference between the phase I placebo group and the same group which received tiotropium in phase II. The improvement of the experimental group was greater, given the mean of both groups.

Table 3: FEV1 mean and the ACT score in the experimental and the control group after phase I and II of the study

	Phase I experimental group		Phase II placebo group		P
	Mean	SD	Mean	SD	
The experimental group FEV1	55.800	8.087	69.966	9.499	0.825
The control group FEV1	58.066	13.516	60.833	9.029	0.05
The ACT in the experimental group	13.933	3.600	18.766	2.725	0.891
The ACT in the control group	19.166	2.804	20.233	5.775	0.04

Finally, our results showed that the rise in the mean of tiotropium drug is indicative of better asthma control, and the correlation degree and the significance level between tiotropium indicated an increased level of asthma control is followed by an increased percentage of FEV1.

Discussion

Our results showed no significant difference in the mean FEV1 between the experimental and the placebo group before the study. Also, the independent T-test results showed no significant difference in the mean of ACT score between the experimental and the placebo group before the study. On the other hand, the FEV1 mean was not significantly different in the experimental groups of phase I and II of the study; therefore, the group which received tiotropium in phase I was not significantly different from the same group which received placebo in phase II. The independent T-test results showed that the FEV1 mean in the two placebo bromide groups was significantly different in phase I and II of the study; therefore, the group which received placebo in phase I was significantly different from the same group which received tiotropium bromide in phase II. The improvement of the drug group was greater than the other, given the mean of the two groups. The independent T-test results showed that the mean score of ACT was not significantly different between the two experimental groups in phase I and II of the study; therefore, the group which received tiotropium in phase I was not significantly different from the same group which received placebo in phase II. In a study designed to determine the effects and safety of tiotropium in the treatment of asthma in 2016, Huib et al. concluded tiotropium has long-lasting effects, safety, and an adequate level of tolerance in patients with asthma. Moreover, the study results showed that the drug is comparable with ICSs and LABAs regarding safety and efficacy, making it an appropriate choice for treatment [16]. The results of the study were in line with our findings. In a study similar to ours conducted by Murata et al. in 2020, the researchers found that the drug's clinical efficacy was significant in children with severe asthma. Moreover, they found tiotropium to be an appropriate choice for prophylaxis of therapy-resistant asthma recurrence [17]. In another similar study, conducted by Huib et al. in 2011, the researchers found that adding tiotropium to an ICS and a LABA has significant effects in promoting lung function of patients with severe, uncontrolled and resistant asthma [18].

Also, our results showed that there was a significant difference between the mean ACT score of the phase I placebo group and that of phase II experimental group in phase I and II of the study, indicating that the group which received placebo in phase I was significantly different from the same group which received tiotropium in phase II. The improvement was greater in the drug group, given the mean of the two groups. Finally, our studies showed that tiotropium has a role in controlling asthma and improving FEV1. In a similar study in 2008 by Iwamoto et al., aimed at determining the effects of tiotropium bromide in non-eosinophilic severe asthma, the researchers found that tiotropium has significant effects in treating patients with non-eosinophilic severe asthma [19]. In a systematic review and meta-analysis over fourteen Randomized Clinical Trials (RCTs) with similar aims in 2019, the researchers concluded that tiotropium has significant effects in the treatment of moderate-to-severe asthma. Moreover, tiotropium has a role in improving the morning and afternoon PEF and FEV [20]. Their findings were consistent with that of the present study. Also, in a case report with consistent results with our study, conducted in 2009 by Kapoor et al., the researchers found that tiotropium is effective in treating patients with severe asthma, and in lowering the therapeutic doses of Systemic Corticosteroids (SCS) [21]. Finally, by studying the similar articles in a review article by Chari et al., they found that it is tolerable for children and adults with severe asthma and that it has significant effects in treating patients with severe and therapy-resistant asthma [22].

Conclusion

Considering the results of the present study and that of the others, it was conceivable that tiotropium is useful in treating patients with severe asthma. Moreover, adding tiotropium to the treatment regimen of asthma was found to lower the therapeutic dose of corticosteroids. Thus, we suggest that a study be conducted in a larger target population, aimed at determining the effects of tiotropium in lowering the therapeutic doses of ICSs and SCSs.

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