Evaluation of the effectiveness of Tadalafil on improving pulmonary function and asthma severity in severe asthmatic patients: a randomized controlled trial study

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Abstract

Phosphodiesterase inhibitors elevate the levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate, which have been associated with various anti-inflammatory effects that can help alleviate asthma symptoms. This study aims to assess the impact of Tadalafil, a selective phosphodiesterase inhibitor, on pulmonary function in patients with asthma. This study was a randomized, double-blind clinical trial conducted in 2021 at Imam Khomeini Hospital in Ahvaz, Iran. The study enrolled 44 patients with severe asthma, who were divided equally into a Tadalafil group and a placebo group. The Tadalafil group received 20 mg/day of Tadalafil, while the placebo group received a placebo at the same dose. The patients' spirometry tests, asthma quality of life questionnaire, 6-minute walking distance, and quality of life were measured at the beginning of the study and one month later. The study results indicated that there was no statistically significant difference between the Tadalafil group and the placebo group in terms of pulmonary parameters ($p>0.05$). Furthermore, the scores for patients' quality of life ($p=0.167$) and the 6-minute walking test ($p=0.148$) at the end of the study did not show any statistically significant improvement compared to the placebo group. Results showed that the use of Tadalafil (20 mg) once daily for one month in patients with severe asthma did not affect clinical and laboratory outcomes.

Introduction

Asthma is a chronic respiratory disease affecting over 300 million individuals worldwide [1]. This condition is caused by the immune system's reaction to allergenic substances and particles, resulting in increased mucus secretion, inflammation, hyperresponsiveness of the respiratory tract mucosa, smooth muscle contraction, and difficulty breathing during asthma attacks [2,3]. The primary objective of asthma treatment is to reduce airway inflammation and reverse bronchoconstriction [4,5]. Phosphodiesterases (PDEs) are isoenzymes that are expressed in various lung cell types, including airway and vascular smooth muscle cells, epithelial cells, fibroblasts, inflammatory cells, and immunity [6]. PDE catalyzes the adenosine monophosphate cycle and cyclic guanosine monophosphate (cGMP), essential second messengers in asthma. Modulation of the intracellular concentrations of these cyclic nucleotides regulates their signaling pathways, which in turn regulates a wide range of biological responses [7,8]. PDE inhibitors are among the most effective treatments for asthma, as they reduce airway inflammation and the impact of inflammatory chemokines and cytokines. Elevated cGMP levels have bronchodilator, anti-inflammatory, and

pulmonary vasodilator effects [9-11]. Tadalafil, a selective PDE-5 inhibitor, prevents the degradation of cGMP and increases its levels [5]. However, the limited human studies on the effects of specific PDE inhibitors on pulmonary function have led to the need for experimental studies. Therefore, our study aimed to investigate the effect of Tadalafil, a selective PDE inhibitor, on improving lung function and asthma severity in patients with severe asthma.

Materials and Methods

Study design and patients

The present study was a double-blind, randomized controlled clinical trial conducted at Imam Khomeini Hospital in Ahvaz, Iran in 2021. A total of 52 patients with severe asthma based on a history of characteristic symptom patterns and evidence of severe variable obstructive patterns (Global Initiative for Asthma guideline) who met the inclusion criteria were enrolled [12]. Inclusion criteria were severe asthma, forced expiratory volume in one second (FEV1) <60%, and inadequate control of symptoms despite receiving standard current treatments, such as high-dose inhaled corticosteroids, long-acting β-agonists, inhaled long-acting anticholinergics, and oral corticosteroids. A pulmonologist confirmed the asthma diagnosis based on medical history and spirometry data. Exclusion criteria consisted of patients with mild to moderate disease, receiving immunosuppressants and corticosteroids in doses exceeding 5 mg/day, uncontrolled hypertension, advanced liver failure, use of nitrates, advanced renal failure, pregnancy, and concomitant untreated diseases such as gastroesophageal reflux disease, sinusitis, or allergic bronchopulmonary aspergillosis.

The sample size was calculated based on a similar study by Borsi *et al.* in 2019 [13], where the mean ± standard deviation (SD) of FEV1 in the intervention group and the placebo group were 2463±350 and 2207±244, respectively, considering α=0.05 and the power of 80%, the final sample size of 22 patients in each group was estimated. The sample size formula is shown below [Eq. 1].

$$n = \frac{(s_1^2 + s_2^2)\ (z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2}{(\bar{x}_1 - \bar{x}_2)^2} \qquad \text{[Eq. 1]}$$

The eligible patients were randomly assigned to two groups using a four-block randomization method. Allocation concealment was implemented by concealing the random allocation sequence from those assigning participants to the intervention and placebo groups. The first group received Tadalafil 20 mg/day, and the other group received a placebo at the same dose. Both medications were similar in shape, color, and size. Additionally, both groups received standard current treatments for their asthma stage, including high-dose inhaled corticosteroids, long-acting β-agonists, inhaled anticholinergics, and 5 mg oral corticosteroids.

The placebo was prepared at the Faculty of Pharmacy laboratories at Tehran University of Medical Sciences.

Implementation and tools

Before starting the study, spirometry and a 6-minute walking test (6MWT) were performed based on the American Thoracic Society guidelines [14]. Patients also completed the Asthma Quality of Life Questionnaire (AQLQ) [15]. In this study, we utilized a validated and reliable tool previously used by Borsi *et al.* (2019) [13] in Iran to assess the impact of sildenafil on lung function and quality of life in patients with severe asthma. Spirometry and 6MWT were repeated and the questionnaires were re-evaluated to determine their score at the end of the study period. All patients were monitored by the same pulmonologist at predetermined intervals.

This study was approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code IR.AJUMS.REC.1398.920) and registered with the Iranian Registry of Clinical Trials under the number IRCT20200823048482N1. Written informed consent was obtained from each patient before they participated in the study. Figure 1 illustrates the study's flow diagram.

Statistical analysis

The statistical analysis in this study was conducted using IBM SPSS version 22 software (Chicago, IL, USA). Descriptive statistics for the quantitative variables were reported as mean ± SD, while the qualitative variables were presented as numbers (percentage). The normality assumption of the data distribution was tested using the Shapiro-Wilk test. Differences between the two groups were compared using either the *t*-test or the Mann-Whitney U test, as appropriate. A p-value less than 0.05 was considered statistically significant.

Results

There were 10 females in the Tadalafil group (50.0%) and 12 females in the placebo group (60.0 %), and the rest were men (p=0.525). The present study evaluated various pulmonary parameters, including spirometry data, 6MWT, and quality of life questionnaire scores. Before the intervention, no significant differences were observed between the two groups in terms of FEV1, forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity (FEF25-75), FEV1/FVC, and AQLQ (p>0.05) (Table 1). However, a statistically significant difference was noted between the two groups in terms of the 6MWT parameters before intervention (p=0.028). Specifically, the 6MWT and questionnaire scale scores in the Tadalafil group were higher than the placebo group before the intervention (Table 1).

The Tadalafil group exhibited statistically significant differences (p<0.05) in the variables of FEV1, FVC, FEF25-75 and 6-minute walking distance (6MWD), before and after the intervention, whereas FEV1/FVC and AQLQ before and after the intervention did not have statistically significant differences (p>0.05). Similarly, in the placebo group, all variables, including FEV1, FVC, FEF25-75 and 6MWD, before and after placebo intervention had significant differences (p<0.05), except for FVC (%), which did not have statistically significant difference (p=0.082) (Table 2).

There was no statistically significant difference between the Tadalafil and placebo groups (p>0.05). Table 3 presents a comparison of pulmonary function tests, 6MWD, and AQLQ measurements between the two groups. A total of 5 patients experienced headaches after starting the drug, which led to discontinuation of the drug in 3 patients.

Discussion

This study aimed to investigate the impact of Tadalafil on pulmonary function, 6MWT, and the quality of life of individuals with severe asthma. The findings indicate that Tadalafil did not have a significant effect on pulmonary parameters, such as FEV1, FVC, FEF25-75, FEV1/FVC, or the quality of life.

Table 1. Comparison of pulmonary function parameters and 6-minute walking distance between two groups before intervention in patients with severe asthma.

Variable	Trial	n (%)	p
Age	Tadalafil	38.51±6.50	0.122
	Placebo	42.10±7.80	
FEV1 (L)	Tadalafil	1.27±0.26	0.338**
	Placebo	1.20±0.19	
FVC (L)	Tadalafil	2.22±0.42	0.075**
	Placebo	2.02±0.26	
FEF25-75 (L)	Tadalafil	0.95±0.30	0.218*
	Placebo	0.84±0.28	
FEV1/FVC	Tadalafil	64.95±7.30	0.093*
	Placebo	60.70±8.24	
6MWD (m)	Tadalafil	381.50±43.07	0.028**
	Placebo	352.00±38.47	
FEV1 (%)	Tadalafil	49.40±7.62	0.271**
	Placebo	46.45±9.01	
FVC (%)	Tadalafil	60.65±7.36	0.788*
	Placebo	60.10±5.35	
FEF25-75 (%)	Tadalafil	29.85±5.55	0.328*
	Placebo	31.60±5.60	
AQLQ	Tadalafil	14.95±2.70	0.604*
	Placebo	14.50±4.74	

*p-value from independent samples t-test; **p-value from Mann-Whitney U test; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25-75, forced expiratory flow between 25% and 75% of vital capacity; 6MWD, 6-minute walking distance; AQLQ, Asthma Quality of Life Questionnaire.

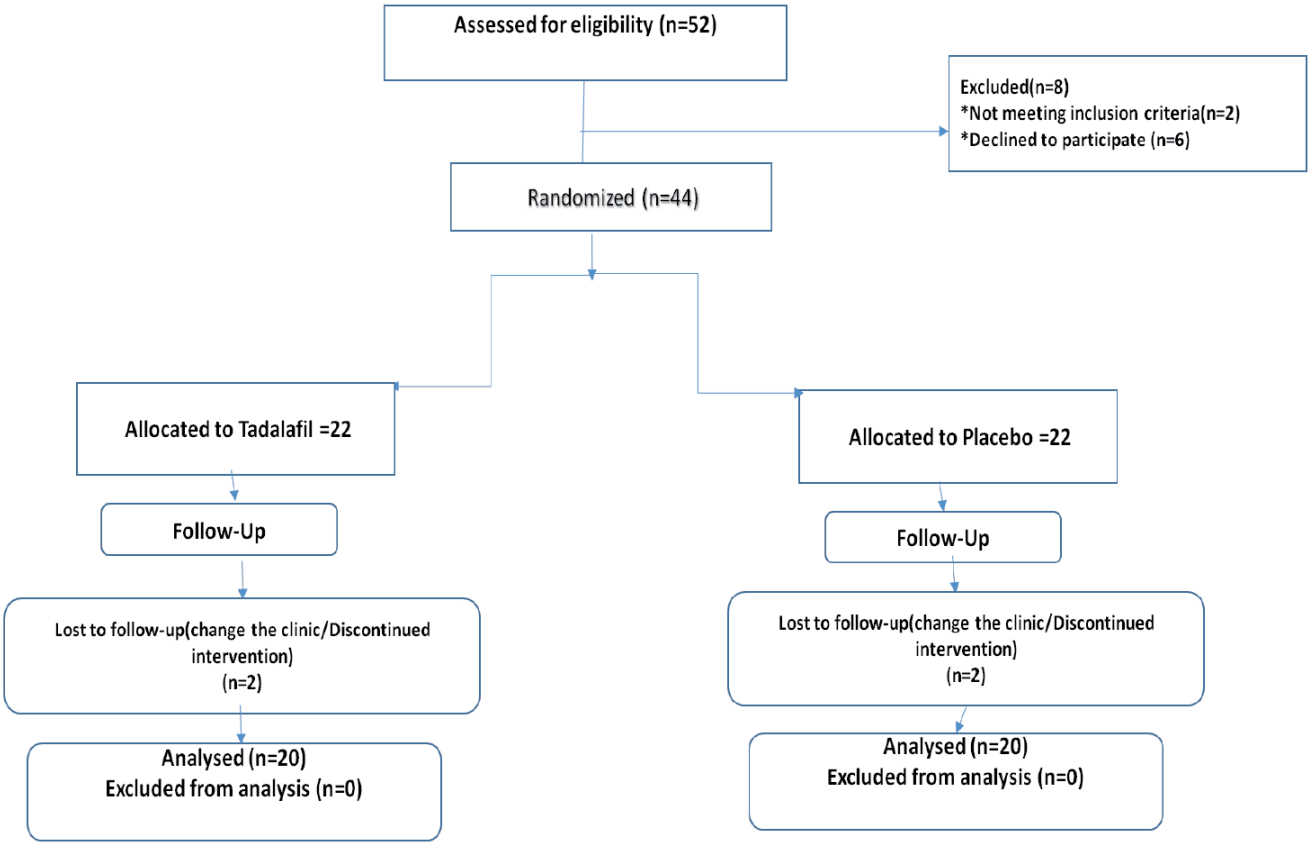

Figure 1. The CONSORT flow diagram of the study.

Furthermore, there was no notable difference between the two groups regarding 6MWD. To date, only a few studies have explored the impact of Tadalafil on asthmatic patients, with most of them limited to experimental animal models or case reports of other lung diseases [5,16]. Puthiyaveettil *et al*. found a significant difference in 6MWD between Tadalafil-treated and control groups, as well as an increase in FEV1, FEF25-75, and peak expiratory flow rate (PEFR) in the former while studying the impact of Tadalafil on patients with respiratory and pulmonary complications [16]. However, their results are contradictory to those of our study, potentially due to differences in the diseases studied and our relatively small sample size.

In a study by Kim *et al.* on the effects of Tadalafil on patients with chronic obstructive pulmonary disease (COPD), the results showed a significant increase in FEF, FEV1, and PEFR levels compared to the placebo group after 4 weeks of treatment with Tadalafil. The mean 6MWD in the two groups was also statistically different [17]. However, these findings are inconsistent with our study, which focused on patients with asthma.

Goudie *et al*. conducted a study on the effects of Tadalafil on 6MWT and quality of life in patients with COPD and mild pulmonary hypertension. Their results showed no significant differences in the 6MWD and quality of life between the Tadalafil and placebo groups [18], which is consistent with our study.

In recent years, specific PDE inhibitors, such as Tadalafil, have been considered for the treatment of pulmonary diseases. Tadalafil, prescribed as a single daily dose compared to sildenafil with a shorter half-life, is more readily accepted by patients. Studies have been conducted on the effects of specific PDE inhibitors, including sildenafil, on pulmonary function [19,20].

Table 2. The comparison of pulmonary volumes, 6-minute walk distance, and Asthma quality of life questionnaire before and after intervention in each group separately.

Trial		Mean ± SD	p
Tadalafil			
	FEV1 (post) (L) FEV1 (pre) (L)	1.49±0.34 1.27±0.26	0**
	FVC (post) (L) FVC (pre) (L)	2.42±0.47 2.22±0.42	0**
	FEF25-75 (post) (L) FEF25-75 (pre) (L)	1.20±0.41 0.95±0.30	0*
	FEV1/FVC (post) FEV1/FVC (pre)	68.25±8.03 64.95±7.30	0.053*
	6MWD (post) (m) 6MWD (pre) (m)	414.75±41.72 381.50±43.07	0*
	FEV1 (post) (%) FEV1 (pre) (%)	54.95±10.58 49.40±7.62	0**
	FVC (post) (%) FVC (pre) (%)	66.50±9.60 60.65±7.36	0.003*
	FEF25-75 (post) (%) FEF25-75 (pre) (%)	38.05±7.46 29.85±5.55	0*
	AQLQ (post) AQLQ (pre)	15.90±4.56 14.95±2.70	0.268**
Placebo			
	FEV1 (post) (L) FEV1 (pre) (L)	1.42±0.21 1.20±0.19	0*
	FVC (post) (L) FVC (pre) (L)	2.23±0.31 2.02±0.26	0*
	FEF25-75 (post) (L) FEF25-75 (pre) (L)	1.05±0.39 0.84±0.28	0*
	FEV1/FVC (post) FEV1/FVC (pre)	66.00±8.98 60.70±8.24	0**
	6MWD (post) 6MWD (pre)	394.75±31.60 352.00±38.47	0**
	FEV1 (post) (%) FEV1 (pre) (%)	52.20±10.92 46.45±9.01	0**
	FVC (post) (%) FVC (pre) (%)	65.20±11.71 60.10±5.35	**0.082****
	FEF25-75 (post) (%) FEF25-75 (pre) (%)	37.05±6.54 31.60±5.60	0*
	AQLQ (pre) AQLQ (post)	14.50±2.74 16.90±3.49	0.001*

*p-value from independent samples *t*-test; **p-value from Mann-Whitney U test; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25-75, forced expiratory flow between 25% and 75% of vital capacity; 6MWD, 6-minute walking distance; AQLQ, Asthma Quality of Life Questionnaire.

Table 3. Comparative analysis of pulmonary volumes, 6-minute walking distance, and Asthma Quality of Life Questionnaire between Tadalafil and placebo groups.

Variable	Trial	Mean	p
Difference_FEV1 (L)	Tadalafil	0.222±0.182	0.966*
	Placebo	0.220±0.148	
Difference FVC (L)	Tadalafil	0.195±0.187	0.672**
	Placebo	0.218±0.136	
Difference_FEF25-75 (L)	Tadalafil	0.247±0.209	0.641*
	Placebo	0.217±0.190	
Difference_FEV1/FVC	Tadalafil	3.30±7.17	0.321*
	Placebo	5.30±5.26	
Difference_6MWD (m)	Tadalafil	33.25±18.52	0.148**
	Placebo	42.75±21.97	
Difference_FEV1 (%)	Tadalafil	5.55±4.65	0.904**
	Placebo	5.75±4.78	
Difference_FVC (%)	Tadalafil	7.83±5.85	0.821*
	Placebo	12.43±5.10	
Difference-FEF25-75 (%)	Tadalafil	8.20±5.04	0.079*
	Placebo	5.45±4.57	
Difference_ AQLQ	Tadalafil	3.72±0.95	0.167**
	Placebo	2.70±2.40	

*p-value from independent samples *t*-test; **p-value from Mann-Whitney U test; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25-75, forced expiratory flow between 25% and 75% of vital capacity; 6MWD, 6-minute walking distance; AQLQ, Asthma Quality of Life Questionnaire.

Vijayalaxmi *et al*. investigated the effects of Sildenafil and Tadalafil on the anti-inflammatory, antioxidant, and anti-stress potential of nitrous in an animal model of bronchial asthma. Their results showed that treatment with Sildenafil and Tadalafil significantly reduced proinflammatory cytokines interleukin 4 and tumor necrosis factor-α in rat serum and bronchoalveolar fluid. Both medications inhibited oxidative and nitrous stress in the animal model of bronchial asthma and could have therapeutic potential in bronchial asthma [20]. However, our study differed in that we evaluated the clinical and paraclinical effects of Tadalafil in human subjects.

Another study by Borsi *et al*. concluded that pulmonary volumes, quality of life questionnaire scores, and 6MWD showed no significant differences between the sildenafil and placebo groups [13]. These findings are consistent with the results of our study, which showed no significant differences between the Tadalafil and placebo groups in terms of pulmonary function, quality of life, or 6MWD.

Overall, our study contributes to the growing body of research on the effects of specific PDE inhibitors on pulmonary diseases, particularly in patients with asthma.

The study by Clayton *et al.* found that type 3 and 5 PDEs did not demonstrate any impact on reducing inflammatory markers in laboratory settings. Conversely, type 4 PDE inhibitors exhibited anti-inflammatory properties [21]. However, it is worth noting that this study was conducted on laboratory animals and differs from our investigation, which involved human samples. Nonetheless, their findings align with ours in that Tadalafil did not affect lung function. Further research is warranted to establish the efficacy of these drugs in reducing inflammation.

It is important to acknowledge the limitations of our study, including a small sample size, short follow-up duration, and the inclusion of only severe asthma patients. PDEs may potentially affect mild or moderate asthma cases.

Conclusions

The results indicate that administering a daily dose of Tadalafil (20 mg) for one month in patients with severe asthma did not exhibit any impact on clinical or subclinical outcomes, such as improvements in lung volume (FEV1, FVC, FEV1/FVC, FEF25-75), 6MWD, and overall quality of life. Further investigation with larger sample sizes and longer follow-up periods is necessary to evaluate the clinical and laboratory effects of other PDEs.

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