Original Article

Investigating the effect of sildenafil on improving lung function and quality of life in the patients with severe asthma

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Abstract

Introduction: Phosphodiesterase inhibitors (PDEs) increase intracellular cyclic adenosine monophosphate, which results in a wide range of anti-inflammatory effects and pathologically leads to improve asthma disease. Because no human study has surveyed the effect of PDEs on pulmonary function, except some case reports and animal researches, we decided to perform a pilot study for evaluating the effect of sildenafil (PDE5) on pulmonary function in patients with severe asthma. **Methods:** This randomized controlled trials study was conducted on 20 patients with severe asthma in 2019 in Iran. For case group, was prescribed sildenafil (50 mg) daily and the control group received the placebo. In the beginning of the study and one month later, volume parameters, 6-minute walk distance (6MWD), and the quality-of-life questionnaire were measured and compared in the two groups. **Results:** Twenty patients were entered into this study. 8 patients (40%) were male and 12 (60%) were female. The results showed that mean forced vital capacity 1 in the sildenafil group turned from 1259 ± 170 to 1603 ± 527, while in the placebo group it changed from 1135 ± 125 to 1365 ± 251 (*P*-value = 0.215). There is no statistically significant difference between two groups. In addition, in comparison with placebo, sildenafil did not show any significant improvement in the volume parameters, the quality-of-life questionnaire scale, and 6MWD at the end of the study. **Conclusion:** According to present result can be concluded that sildenafil does not improve the severity of asthma and the quality of life in patients with severe asthma.

Keywords: Lung volumes, quality of life, severe asthma, sildenafil

Introduction

Phosphodiesterase inhibitors (PDEs) increase intracellular cyclic adenosine monophosphate, which results in a wide range of anti-inflammatory effects and pathologically leads to improve asthma and chronic obstructive pulmonary disease.[1-3] Increasing intracellular cyclic adenosine monophosphate concentration contributes to decrease and inhibit the release of inflammatory mediators from mastocytes and eosinophils. It also results in the cessation of inflammatory cytokines products, such as TNF-alpha, IL-2, IFN-α, and IL-4.[4,5] Since no human study has surveyed the effect of PDEs on pulmonary function, except some case reports and animal researches,[6,7] we decided to

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conduct a pilot study for investigating the effect of sildenafil on pulmonary function in patients with severe asthma.

Materials and Methods

This randomized controlled trials study was conducted on 20 patients with severe asthma in 2019 in Imam Khomeini Hospital of Ahvaz, Iran. All patients included in this study developed asthma according to history and spirometry, and whose disease had been diagnosed by the pulmonologist. These subjects suffered a high degree of severe asthma (forced vital capacity [FEV] <60%) and their symptoms were not controlled by treatments (high doses of inhaled corticosteroids—long-acting beta-agonists, anticholinergic inhalers, and oral corticosteroids). Before entering the study, patients with the history of concurrent diseases such as reflux, sinusitis, allergic rhinitis, and other diseases that can affect asthma treatment were diagnosed, and if necessary, before the beginning of the study, comorbidity disease was treated. Patients with advanced liver and kidney failure, uncontrolled hypertension, pregnancy, hypersensitivity to sildenafil, and use of nitrates were excluded. Eligible people were randomly divided into two groups of 10 people. Treatments were commonly prescribed according to the disease stage included high-dose inhaled corticosteroids, long-acting beta-agonists, anticholinergic inhalers, and oral corticosteroids (5 mg). Inhaled anticholinergics (18 μg) were used for tiotropium bromide patients whose inhaled corticosteroid was fluticasone and beta-agonist was salmeterol. The first group received sildenafil (50 mg) daily and the second group received the placebo at the same dose. Before the beginning of the study, spirometry was done and the 6-min walk test (6MWT) was performed following the American Thoracic Society (ATS) guidelines. The quality-of-life questionnaire was designed on GSK (2002) completed by participants. At the end of the study (after one month), spirometry and 6MWT were done again and the questionnaire was recompleted by these patients. The data were analyzed and compared between the two groups.

Statistical analysis

To compare the variables, independent t-test was used for the normal distribution of data. Chi-square test was used for qualitative variables. Data were analyzed by SPSS version 23 and a significant level of 0.05 was considered.

Results

This study was conducted on 20 patients, 8 patients (40%) were male and 12 (60%) were female. The mean age of patients was 40.20 ± 10.01. Other baseline characteristics are shown in Table 1. The results showed that in the intervention group after using sildenafil the mean FEV1 turned from 1259 ± 170 into 1603 ± 527, while in the control group it changed from 1135 ± 125 to 1365 ± 251, which was no significant difference between two groups (*P*-value = 0.215). The mean FVC level in the intervention group turned from 2298 ± 401 into 2463 ± 350 while in the control group, it changed from 2099 ± 292 to 2207 ± 244 which was not a statistically significant difference between two groups (*P*-value = 0.075). The mean score of asthma quality-of-life questionnaire in the intervention group was turned from 12 ± 4.38 into 10 ± 4.21 while in the control group, it changed from 12 ± 4.20 to 12 ± 4.04, which showed no statistically significant difference between the two groups (*P*-value = 0.340). The average of 6MWD in the intervention group turned from 354 ± 33 into 390 ± 33 after using sildenafil while in the control group, it changed from 342 ± 35 to 367 ± 31, which was not a statistically significant difference between two groups (*P*-value = 0.131). The results of other variables and lung volumes were presented in Table 2.

Discussion

This study investigated the effect of sildenafil on sever asthma and our findings showed that sildenafil did not improve lung parameters including FEV1, FVC, forced expiratory flow (FEF25–75), FEV1/FVC, 6MWD, and the quality of life. So far no human studies have been done in this subject except some surveys that have demonstrated the positive effect of sildenafil on increasing lung volume limited to animal models in the laboratory or human case reports that results have been obtained randomly.[6,7]

Mukhallad Aljanabi (2017) conducted a case report in Jordan on sweeper with asthma (FEV1 54%). After receiving consent, 3 days before the beginning of the study the patient discontinued the bronchodilator and after these days, the patient received oral sildenafil (50 mg), and then two hours later the spirometric control was performed. The rate of increase in FEV1, FEF 25–75%, and peak expiratory flow rate was reported

Table 1: Baseline characteristics of patients

Variable	Sildenafil	Placebo	*P*
Gender			
Male	5 (%50)	3(%30)	0.325
Female	5 (%50)	7 (70%)	
Age	37±6.28	40±8.30	0.39
FEV1	1259±170	1135±125	0.07
FVC	2298±401	2099±292	0.22
FEF25-75	861±431	616±199	0.12
FEV1/FVC	58±6.95	59±10.25	0.69
Asthma Q	12±4.38	12±4.20	0.68
6MWD (m)	354±33.8	342±35	0.45

Table 2: Mean differences of variable values after intervention

Variable	Sildenafil	Placebo	*P*
FEV1 (mean differences)	468.343±50.24	230.211±50.53	0.21
FVC (mean differences)	174±165.5	108.137±70.42	0.07
FEV1/FVC (mean differences	37.01±8.9	42.02±1.7	0.228
FEF25-75 (mean differences)	373.531±70.75	211.235±50.53	0.107
6MWD (mean differences)	36.40±16.83	25.20±19.77	0.131
Asthma questionnaire score (mean differences)	2.60±2.45	00.00±4.59	0.34

14%, 26%, and 13%, respectively. Average increase percentage of lung volumes was 304 cc, 450 cc, and 526 cc, respectively.[8] Lung volumes were measured immediately after taking the drug at the early hours, while in our study, sildenafil was prescribed as a maintenance drug, and one month later, its effects on lung volumes were evaluated. Perhaps increasing pulmonary volumes was temporal in which case sildenafil can have clinical value in the treatment of asthma attacks provided that it is proven. The results of this investigation were different from our findings in which sildenafil did not affect the improvement in pulmonary volumes.

Robert A Clayton (2004) studied the anti-inflammatory properties of various PDEs on animals. The results did not indicate the effect of sildenafil (type III PDE) in the laboratory to reduce the anti-inflammatory markers, while phosphodiesterase type 4 inhibitor showed anti-inflammatory properties.[7] However, that study was performed on animals in a laboratory environment and differed from our research conducted on human, their results are similar to our findings in no impact of sildenafil on pulmonary functions. In that survey, inflammatory and laboratory markers were measured but in the current research, clinical and paraclinical markers were evaluated.

The study of Thomas Rothe *et al.* (2009) on 10 young patients with no asthma showed that sildenafil did not affect decreasing fractional exhaled nitric oxide (FeNO) levels and thus reducing inflammation.[9] The small sample size, asthmatic patients, and evaluating clinical and paraclinical effects of sildenafil were the properties of our investigation that causes it to differ from previous research. No influence of sildenafil on reducing inflammation, improving pulmonary volumes, and the quality of life were the similarities of two surveys.

The weaknesses of the present research are the small size of 20 people and shorter half-life of sildenafil than other types of PDEs that were used once a day. Therefore, these factors may lead to no improvement in clinical and paraclinical parameters. Perhaps other types of PDEs with a longer half-life, such as tadalafil, have a more stable effect on the clinical and paraclinical features in the patients with severe asthma which requires targeted studies. The strengths of our study are that it is the first human study in the type of randomized controlled trials evaluating clinical and paraclinical parameters such as pulmonary volumes, 6MWD, and the quality of life of these patients after the intervention.

Conclusion

Administration of sildenafil (50 mg) once a day during one month for the patients with severe asthma did not impact on the clinical and paraclinical findings in improving pulmonary volumes (FEV1 FVC FEV1/FVC FEF25-75), increasing the distance traveled in the 6MWT, and also enhancing the quality of life. It is recommended to evaluate clinical and paraclinical effects of other PDEs with longer half-life such as tadalafil, in a large sample size and a longer time follow-up.

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Conflicts of interest

There are no conflicts of interest.

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