

The effect of sildenafil on the mustard gas induced pulmonary artery hypertension

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Abstract

BACKGROUND: One of the causes of pulmonary artery hypertension (PAH) is mustard gas poisoning, which is a destructive factor in chemical bombs that contaminated Iranian soldiers during Iraq-Iran war. This study was designed to evaluate the effect of sildenafil, an effective drug for PAH, on symptoms of PAH caused by mustard gas.

METHODS: In a quasi-experimental study on 20 patients with a history of mustard gas poisoning and PAH symptoms, pulmonary artery pressure was measured with a transthoracic echocardiography (TTE). Patients took a 6-minute walking test (6-MWT), and then, they were treated for 12 weeks with 50 mg daily sildenafil. Finally, echocardiography and 6-MWT were repeated.

RESULTS: All patients were men with a mean age of 42.8 ± 3.9 years. Mean pressure of pulmonary artery at the beginning of the study was 37.7 ± 8.2 mmHg, and the walked distance at 6-MWT was 263.3 ± 2.2 meters. After 12 weeks, these values were 29.1 ± 6.5 mmHg, and 291.3 ± 82.3 meters, respectively, which were significantly higher.

CONCLUSION: This study showed that sildenafil improves mustard gas PAH. On the basis of our findings, even a single daily dose of sildenafil can have a good effect on these patients.

Keywords: Pulmonary Artery Hypertension, Mustard Gas Poisoning, Sildenafil.

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Introduction

Pulmonary artery hypertension (PAH) is defined as a group of diseases with the characteristic of progressive resistance of pulmonary arteries. This disease finally leads to right heart failure and death.^{1,2} Despite the increase in pulmonary artery pressure, lack of sufficient blood flow during physical activity causes dyspnea and fatigue.³ The ultimate treatment of PAH is simultaneous heart and lung transplantation, which is costly, and inaccessible for many patients. Other available treatments have limited benefit because of the cost, and are less effective because of non-compliance.^{4,5} Recently, phosphodiesterase-5 (PDE5) inhibitors were approved by the US Food and Drug Administration (FDA) for treating PAH. Sildenafil is one of the drugs approved by FDA for this purpose in 2005.⁶ Some studies showed its effect on reducing fatigue and dyspnea during physical activity.^{7,8}

Mustard gas is an alkaloid chemical agent that was

extensively used during World War I, and during Iraq-Iran war. With regard to its adverse effects, Iranian researchers have been seeking appropriate treatments for soldiers and civilians afflicted by it. A study in 2005, investigated late adverse effects of mustard gas poisoning in 40 patients who were contaminated 16-20 years before. It showed chronic obstructive pulmonary disease, asthma, narrowing of large airways, and pulmonary fibrosis were the most common pulmonary disorders in these patients.⁹

One of the problems arising from these disorders is PAH. Because no documents were found about the application of sildenafil in treating mustard gas induced PAH, this study was conducted to examine the amount of physical activity and pulmonary artery pressure after administration of sildenafil.

Materials and Methods

In a quasi-experimental before-after study, 20 male victims of mustard gas attack during Iraq-Iran war

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who had PAH were studied. The subjects were selected using convenience sampling from patients referred to Amiralmomenin Hospital in Isfahan, Iran. The criteria for pulmonary hypertension were the presence of minimum pulmonary artery pressure of 30 mmHg according to Bernoli formula in Doppler echocardiography, in absence of other secondary causes of this disease such as heart failure, chronic obstructive pulmonary disease (COPD), and systemic diseases. Bernoli formula is based on failure of tricuspid valve and the following equation and pulmonary arterial pressure was calculated by this. Pulmonary Arterial Pressure (PAP) = $4 \times V^2 + \text{Jugular Venous Pressure}$

Patients with a history of other pulmonary diseases, all cardiac diseases, systemic diseases or sildenafil consumption were excluded from the study. All participants signed a written consent form. At the beginning of the study, Doppler echocardiography was carried out and demographic and medication data was collected. Then 6-minute walking test (6-MWT) was taken to check their exercise capacity.

The intervention was administered a single dose of 50 mg sildenafil for 12 weeks. Patients were blind to the name and possible side effects of the drug till the end of the study. During the study, patients took the other drug, but did not take any new drugs. Patients were weekly followed up by physician by phone asking for drug side effects including blur vision, diplopia, hot flashes, and change in urine color. In case of any side effects, patients were examined in person, and if needed, the drug was discontinued. All participants were examined in the middle of the course (6th week). After 12 weeks, Doppler echocardiography (measuring PAP), and 6-MWT were repeated.

Data were analyzed using SPSS (version 15; SPSS Inc., Chicago, IL., USA). To compare distance in 6-MWT and PAP before and after intervention, paired t-test was used. P-value less than 0.05 was considered significant. All data were reported as mean \pm SD.

Results

Participants aged between 36 and 48 years with mean of 42.8 ± 3.9 years. Duration of presence at war was between 12 and 33 months with mean of 22.5 ± 5.3 months. The number of times each person was exposed to mustard gas was two times in 2 people (10%), and once in others. Eleven patients (55%) did not mention a history of hospitalization, but 6 patients (30%) were hospitalized once and 3 subjects (15%) were hospitalized twice for pulmonary problems. Salbutamol spray was used by 16

participants (80%) and fluconazole by one (5%). Five people (25%) used prednisolone, and 6 ones (30%) took antibiotics. In primary examinations, mean systolic blood pressure was 119 ± 20 mmHg, and diastolic blood pressure was 69 ± 8 mmHg. Mean heartbeat rate was 71 ± 7 and mean respiratory rate was 16 ± 3 per minute.

Of 20 patients, 19 completed the treatment course, and only one person discontinued the pill after 6 weeks because of digestive adverse effects. At the beginning of the study, mean PAP was 37.7 ± 8.2 mmHg, and 6-MWT was 263.3 ± 82.2 m. After 12 weeks, mean PAP was 29.1 ± 6.5 mmHg, and 6-MWT was 291.3 ± 82.3 m. The difference for PAP during the 12 weeks was a reduction of 8.65 ± 4.91 mmHg ($P < 0.001$). There was a 28 ± 10.88 increase in 6-MWT ($P < 0.001$). Four subjects (20%) reported sexual disorders, 2 (10%) had headache and 3 patients (15%) had dyspepsia. There were no reports of reduced visual acuity or urinary frequency.

Discussion

Nowadays, sildenafil is one of the modern treatments of primary and secondary PAH.^{10,11} Among PDE5 inhibitors, this drug increases cellular cGMP in vascular smooth muscles leading to their relaxation and reduced PVR and PAP.^{12,13} So far, several uncontrolled clinical trials have been conducted and approved of the therapeutic effects of sildenafil on functional class, exercise capacity, right ventricular hypertrophy, and quality of life in patients with PAH.^{10,14-15}

One of the studies conducted by Garg et al. on the effect of this drug on patients with PAH showed a stable improvement in clinical symptoms by taking sildenafil for 3 months. This study showed significant efficiency of oral sildenafil on indexes such as functional class, PAP, cardiac output, and patients' symptoms.¹⁴

In a double-blind randomized cross over study, Singh et al. studied patients with severe primary PAH in Eisenmenger. Two groups of 10 people were treated with sildenafil and placebo for 6 weeks. The studied indexes in this study were functional class, PAP, and clinical symptoms. Sildenafil improved these indexes. With regard to functional class and patients' clinical status, the improvement continued until treatment continued. The advantage of this study was that each patient was considered as control after passing a wash out period.¹⁶

One of the few controlled clinical trials on sildenafil was a multicenter study conducted on patients with PAH. In this study, patients were divided into 4

groups. One group was treated with placebo, and the others were treated with daily doses of 20, 40, and 80 mg of sildenafil. Functional class and hemodynamic symptoms improved in the treatment groups, and the effect was more as the dose was increased. The least side effects were seen in this study.¹⁷

Another study by Oudiz et al. showed the therapeutic effect of sildenafil. This randomized clinical study was conducted on two groups of 13 people with PAH. The results showed the effect of sildenafil on functional class and clinical symptoms. In addition, the effect of the drug on pulmonary ventilation in patients with PAH was shown. Based on their findings, it can be said that the effect of this drug on PAH was because of improvement in ventilation.⁶

In our study, improvement in functional class and PAP was seen after 12 weeks of treatment, which corresponds with that of other studies. The main difference between this study and others was the reason for PAH in our patients. Our participants were contaminated with mustard gas. During Iraq-Iran war, around 100000 people were contaminated, out of whom 45000 were afflicted with chronic poisoning adverse effects including its pulmonary ones.¹⁸ One of the therapeutic predicaments in these patients is PAH, which disables patients, reduces quality of life and finally kills them. Therefore, finding a cheap, accessible, and acceptable treatment is of priority for them. The results of this study, especially when only one person discontinued treatment shows that sildenafil is an appropriate treatment for this group of patients.

The treatment regimen was single dose of 50 mg sildenafil in this study. With regard to its short half-life, treatment was previously divided into dosages,¹⁹ but the results of our study showed that even a single dose regimen can have appropriate therapeutic effects. Another finding of this study was that sildenafil's side effects were less than those in other studies. Only dyspepsia, headache and diarrhea were seen in our study. The headache was less than that in a similar study, but dyspepsia was the same.¹⁷

In conclusion, we can recommend sildenafil for patients with PAH caused by mustard gas. In these patients, administration of the least dose once a day improves the symptoms, increases functional class and reduces PAP.

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Conflict of Interests

Authors have no conflict of interests.

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