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Original Article

The Effect of Concurrency of Colchicine and Simvastatin in Improvement of Clinical Signs of Mustard Gas-Wounded Patients

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ABSTRACT

Introduction: ninety years after the first application of mustard gas in Belgium as a chemical weapon, after World War II, the largest and the most extensive chemical attacks during the history occurred against soldiers and civilians in invasion of Iraq to Iran. The use of chemical weapons in this war has led to multiple complications especially in the respiratory system of wounded soldiers. Since the treatment of these patients is associated with high costs, so finding effective medications to treat this illness has great importance. Several studies have shown that both colchicine and simvastatin medications have reducing inflammation and oxidative effects and the cumulative effect of these two medications in this study may be effective (on creation of delayed effects of mustard gas).

Methods: this study was conducted as double-blind intervention during 2 months. The population society was consisted of 40 mustard gas-wounded patients. Their illness had previously been approved by Foundation of Oppressed and the Crippled and other valid government agencies. These patients were referred as OPD for treatment to pulmonary clinic related to Shiraz University of Medical Sciences (Motahari, Imam Reza and Shahid Faghihi Clinics). The studied patients in this study were divided into two groups: 1- The placebo group that included 20 patients who did not receive colchicine and simvastatin. 2- The medication group included 20 patients who received simultaneously colchicine and simvastatin with daily dosage of 1 mg/d and 10 mg/d, respectively. Then height, weight and age of the patients were evaluated and recorded before and after the intervention in order to evaluate pulmonary function tests. The lung spirometry and plethysmography tests were performed to assess the lung function.

Results: the obtained results showed that no significant changes were observed in RV/TLC, RV, TLC, FVC/FEV1, FEV1, IC and VC tests in the medication group compared to the placebo group. This indicates lack of effect of the medicines on improving of the lung of chemical wounded patients.

Discussion and Conclusion: according to the above as well as the obtained results of this study, it was found that both medicines (colchicine and simvastatin) were not effective in the treatment of pulmonary diseases in mustard gas-exposed patients and this can be concluded that the prescription of these two medicines is not recommended for treatment of the signs of these patients.

Keywords: Colchicine, Simvastatin, Clinical Signs, Mustard Gas

INTRODUCTION

Chemical weapons are tools or materials that may be used to target human and/or other living organisms. By direct contact of these materials with any part of the body of a living organism, the body becomes infected and the organism will be affected to a variety of illnesses (general

disease or exclusive disease of the chemical materials). These materials can be used as solid, liquid or gas [1]. Despite the ratification of 1925 Geneva Protocol, the Iraqi regime by violation of this international treaty during the war between Iran and Iraq was committed the second largest chemical attacks after the First World War [1]. Based on the reports of United Nations (UN) weapons inspectors, mustard gas and also deadly nerve agents were used in several cases against Iranian soldiers and civilians in rural and border cities of Iran from 1984 to 1988 [1].

Mustard gas or sulfur mustard by chemical formula of 1,5-dichloro-3-thiapentane is a chemical compound containing of chlorine and sulfur and has been synthesized for the first time by Despretz in 1822 [2]. Mustard gas in its pure form is a colorless oily liquid. However, this gas typically varies from pale yellow to dark brown. Sulfur mustard smells garlic or horseradish [2, 3]. The first report of delayed complications of exposure to sulfur mustard in 236 Iranian wounded patients showed that the most damaging effects observed in the respiratory tract (78%), central nervous system (45%), skin (41%) and eyes (36%), respectively. These complications were recorded 2 to 28 months after the exposure [4]. Comparison of early (one week after contact) and delayed (two years after contact) complications of 77 patients with chemical injuries showed that ocular lesions did not change much over time; cutaneous complications were tended to decrease and the respiratory complications generally found their strength [5,6].

The respiratory ducts in mustard gas-exposed patient become sensitive to foreign substances and as a result of contact with these materials, the ducts become constricted. So among the causes of shortness of breath can mention in summary to tightness of respiratory ducts caused by lesions, destruction of air sacs, increased sensitivity of respiratory ducts, contraction of respiratory ducts, increased secretion of mucus, thickening of mucus, thickening of blood and so on [7]. The cause of permanent sputum is that both the size and the number of mucus-producing cells in respiratory tracts increase due to local inflammation and stimulation. As a result, mucus secretion is increased [8, 9]. It has also been indicated that both respiratory ducts and blood vessels that enter to these ducts have been damaged in person affected by chemical fumes. Sometimes when you are coughing, a number of capillaries in respiratory ducts break due to the pressure that enters the air sacs and the blood vessels. As a result, small amounts of blood and sputum mixed and emerge accompanied by cough [7].

Colchicine is placed in anti-metabolite treatment class of medicines and is an anti-gout drug that pharmacologically classified as alkaloid from colchicum autumnale. This medicine is taken orally in Iran and its injectable form is not present in Iran pharmacopoeia. The half life of medicine is 9.3-10.6 hours [10]. Colchicine is used for relief of acute gout as well as for prophylaxis of acute attacks, especially in the first months of treatment with Allopurinol and/or Uricosurics. By reducing the inflammatory responses to urate crystals, colchicine causes therapeutic response to acute gout [10] and given to its anti-inflammatory role has been considered in the present study.

Simvastatin marked under the trade name Zocor is a group of cardiovascular medicines and is pharmacologically a component of HMG-CoA inhibitor that is anti-blood fat and cholesterol lowering medicine. Its products are available in tablets of 10 and 20 mg [10]. It was stated in previous studies that simvastatin does not have a significant effect on inflammatory markers and the lung function test in bronchiectasis caused by mustard gas [11].

According to the above as well as high costs of treatment for persons injured by mustard gas, finding a proper medicine to reduce the costs of these patients can be of great help to them. Since

there are conflicting reports about the efficacy of colchicine and simvastatin on improvement of the lung function in chemical wounded patients, so this study tries to investigate the effect of these two medicines on improvement of the lung function in chemical wounded patients.

Methods

This study was conducted as double-blind intervention during 2 months. All rules and ethical issues approved by Islamic Countries, Iran Ministry of Health and Shiraz University of Medical Sciences were taken into consideration and after face to face explanation and completion of moral questionnaire; patients with complete knowledge and understanding were enrolled to the study. The population society was consisted of 40 mustard gas-wounded patients and their illness had previously been approved by Foundation of Oppressed and the Crippled and other valid government agencies and they have had chemical wounded patients' card. These patients were referred as OPD for treatment to pulmonary clinic related to Shiraz University of Medical Sciences (Motahari, Imam Reza and Shahid Faghihi Clinics).

The studied patients in this research were divided into two groups as follows:

1- The placebo group that included 20 patients who did not receive colchicine and simvastatin.
2- The medication group included 20 patients who received simultaneously colchicine and simvastatin with daily dosage of 1 mg/d and 10 mg/d, respectively.

It should be noted that patients and researchers were kept unaware of the name of groups and the type of taken medicine during the study period. The patients were prevented from taking new drugs and they were evaluated in terms of incidence of side effects of taking medicine during the verbal interviews and the medication was discontinued when it was required. Then height, weight and age of the patients were evaluated and recorded before and after the intervention in order to evaluate pulmonary function tests. The lung spirometry and plethysmography tests were performed to assess the lung function. The amount of the air that a person can inhale and exhale is measured in spirometry. It also measures the speed of inhalation. If indicated values by spirometry are less than average limit it reflects the fact that the lungs are not functioning well. Some of tests used in this study were included: RV/TLC, RV, TLC, FVC/FEV1, FEV1, IC and VC.

The obtained data were analyzed using SPSS 16 and the Wilcoxon signed-rank test as a statistical test was used to evaluate RT and total lung capacity (TLC) before and after the intervention. Mc Nemar test was also used to examine FEV1/FVC, RV/TLC and FEV1 before and after the intervention.

Results

Two people of twenty patients, who took the medicines, were smoker. Their average weight was 75.9 kg, their mean age was 50.4 years and the average height was 167 cm. Two people of twenty patients in the placebo group were smoker, too. Their average weight was 80.65 kg, their mean age was 51.2 years and the average height was 172 cm.

VC and IC

The plotted curves related to each patient were first investigated and data were evaluated based on the curves. The plethysmography was performed in initial testing on twenty patients who took the medicines. VC for 13 patients was less than 80% and IC for 14 patients was less than 80% and after taking the medicines, VC was less than 80% for 10 patients and IC was less than 80% for 9 patients (Table 1). The plethysmography was performed in initial testing on twenty patients who took the placebo. VC for 13 patients was less than 80% and IC for 12 patients was less than 80% and after taking the medicines, VC was less than 80% for 12 patients and IC was less than 80% for 14 patients (Table 2). The Mc Nemar test was used to analyze

pretest-posttest study that no significant relationship was observed in VC before and after the treatment (P value: 0.5). This means that the medicines had no effect in improvement of VC. No significant relationship was also observed in IC before and after the treatment (P value: 0.5). This means that the medicines had no effect in improvement of IC. As can be expected, no significant relationship was observed in VC before and after the treatment (p value: 1) and in IC before and after the treatment (p value: 0.5) in the placebo group. This means that the placebo did not have impact on remission of the patients in terms of VC and IC.

Table 1- The frequency in terms of VC and IC before and after treatment in the medication group

The percentage volume	Initial VC	VC after treatment	Initial IC	IC after treatment
80≤	7 (35%)	10 (50%)	6 (30%)	11 (55%)
80>	13 (65%)	10 (50%)	14 (70%)	9 (45%)

Table 2- The frequency in terms of VC and IC before and after treatment in the placebo group

The percentage volume	Initial VC	VC after treatment	Initial IC	IC after treatment
80≤	7 (35%)	8 (40%)	8 (40%)	6 (30%)
80>	13 (65%)	12 (60%)	12 (60%)	14 (70%)

FEV1:

The initial FEV1, in twenty patients received the medicine, was normal for 8 patients. This number increased to 10 after taking the medicine. However, no significant relationship on FEV1 was observed before and after taking the medicine (p value: 0.64). This means that the medicine had no effect on improvement of FEV1 (Table 3). The initial FEV1, in twenty patients received the placebo, was normal for 7 patients. This number remained unchanged, as expected, after taking the medicine. No significant relationship on FEV1 was observed before and after taking the placebo (p value: 0.95). This means that the placebo had no effect on improvement of FEV1 (Table 4).

Table 3- The frequency of patients in terms of FEV1 before and after taking the medicines

The percentage of lung volume of FEV1	Before taking the medicine	After taking the medicine
75<	8 (40%)	10 (50%)
60-75	6 (30%)	5 (25%)
50-59	2 (10%)	1 (5%)
49>	4 (20%)	4 (20%)

Table 4- The frequency of patients in terms of FEV1 before and after taking the placebo

The percentage of lung volume of FEV1	Before taking the placebo	After taking the placebo
75<	7 (35%)	7 (35%)
60-75	4 (20%)	3 (15%)
50-59	0	1 (5%)
49>	9 (45%)	9 (45%)

FEV1/FVC:

The initial FEV1/FVC, in twenty patients received the medicine, was less than 70% for 2 patients. According to FEV1 these two patients had severe obstruction. The initial FEV1/FVC in 18 patients was more than 70% that with respect to FEV1 and FVC, 13 patients had restriction and 5 patients were normal. In after treatment FEV1/FVC, two patients had FEV1/FVC less than 70% that based on FEV1, these two had severe obstruction. In this condition, 18 patients had FEV1/FVC more than 70% that based on FEV1 and FVC these two had restriction and 10 patients were normal (Table 5). The initial FEV1/FVC, in twenty patients received the placebo, was less than 70% in three patients that based on FEV1 the three had severe obstruction. This amount was less than 70% in 17 patients that based on FEV1 and FVC, 11 patients had restriction and 6 people were normal. In after treatment FEV1/FVC, the level of FEV1/FVC in 3 patients was less than 70%. These three patients had severe obstruction according to FEV1. In after treatment FEV1/FVC, the level of

FEV1/FVC in 17 patients was more than 70%. These three patients had restriction and 6 patients were normal, given to FEV1 and FVC (Table 6). No significant relationship was observed in related to FEV1/FVC before and after taking the medicines (p value: 1). This means that the medicines did not have influence on improvement of FEV1/FVC. No relationship was also observed in pulmonary restriction before and after taking the placebo (p value: 1). No significant relationship was observed in related to FEV1/FVC before and after taking the placebo (p value: 1). This means that the medicines did not have influence on improvement of FEV1/FVC. No relationship was also observed in pulmonary restriction before and after taking the placebo (p value: 1).

Table 5- The frequency of initial FEV1/FVC before and after treatment in patients received the medicines

The percentage volume	initial FEV1/FVC	FEV1/FVC after treatment
70≤	18 (90%)	18 (90%)
70>	2 (10%)	2 (10%)

Table 6- The frequency of initial FEV1/FVC before and after treatment in patients received the placebo

The percentage volume	initial FEV1/FVC	FEV1/FVC after treatment
70≤	17 (85%)	17 (85%)
70>	3 (15%)	3 (15%)

TLC and RV:

The initial RV in twenty patients taking the medicines was in the normal range (80-120) in 7 patients, less than 80 in 4 patients and more than 120 in 9 patients. RV after taking the medicines was in the normal range (80-120) in 11 patients, less than 80 in 1 patient and more than 120 in 8 patients. In terms of initial TLC in patients received the medicines was in the normal range (80-120) in 12 patients, less than 80 in 6 patients and more than 120 in 2 patients. TLC after taking the medicines was in the normal range (80-120) in 16 patients, less than 80 in 3 patients and more than 120 in 1 patient (Table 7) (Chart 1 and 2).

Table 7- The frequency of RV and TLC before and after taking the medicines

The percentage volume	RV before treatment	RV after treatment	TLC before treatment	TLC after treatment
120-80	7 (35%)	11 (55%)	12 (60%)	16 (80%)
80>	4 (20%)	1 (5%)	6 (30%)	3 (15%)
120>	9 (45%)	8 (40%)	2 (10%)	1 (5%)

Chart 1: The frequency of TLC before and after taking the medicines

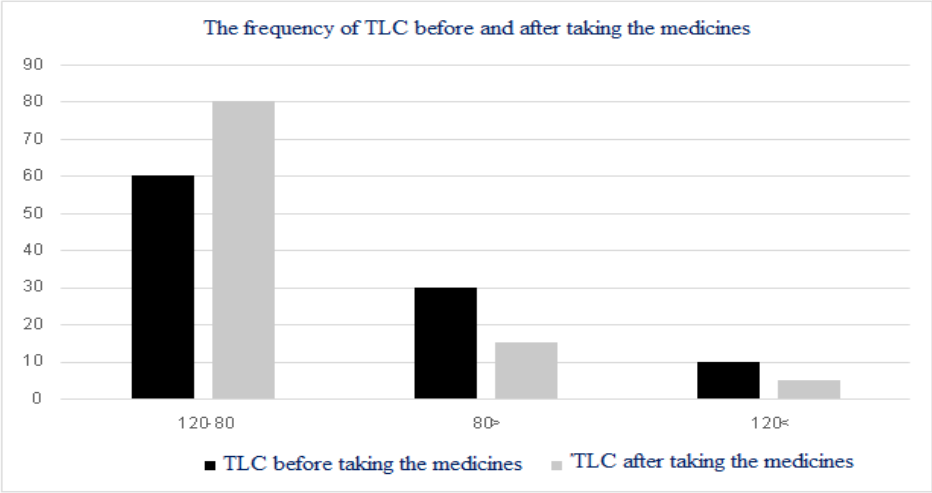
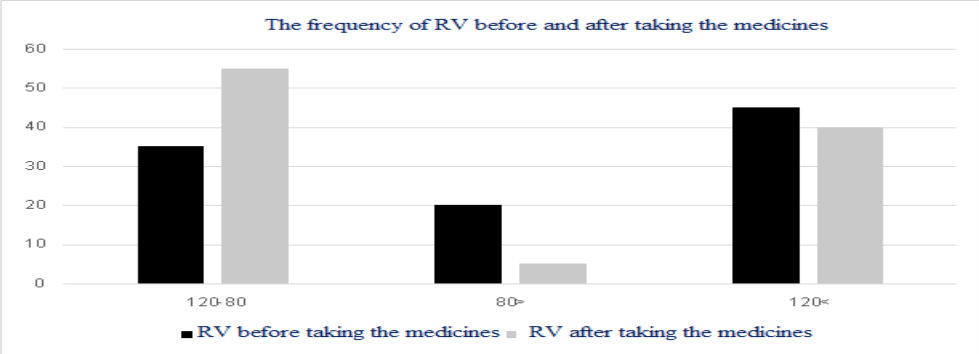


Chart 2- The frequency of RV before and after taking the medicines



Among twenty patients received the placebo, the initial RV was in the normal range (80-120) in 3 patients, less than 80 in 1 patient and more than 120 in 16 patients. RV after taking the placebo was in the normal range (80-120) in 2 patients, less than 80 in 1 patient and more than 120 in 17 patients. In terms of initial TLC in patients received the placebo was in the normal range (80-120) in 16 patients, less than 80 in 2 patients and more than 120 in 2 patients. TLC after taking the medicines was in the normal range (80-120) in 15 patients, less than 80 in 4 patients and more than 120 in 1 patient (Table 8) (Charts 3 and 4)

Table 8- The frequency of RV and TLC before and after taking the placebo

The percentage volume	RV before taking the placebo	RV after taking the placebo	TLC before taking the placebo	TLC after taking the placebo
120-80	3 (15%)	2 (10%)	16 (80%)	15 (75%)
80>	1 (5%)	1 (5%)	2 (10%)	4 (20%)
120>	16 (80%)	17 (85%)	2 (10%)	1 (5%)

Chart 3: The frequency of TLC before and after taking the placebo

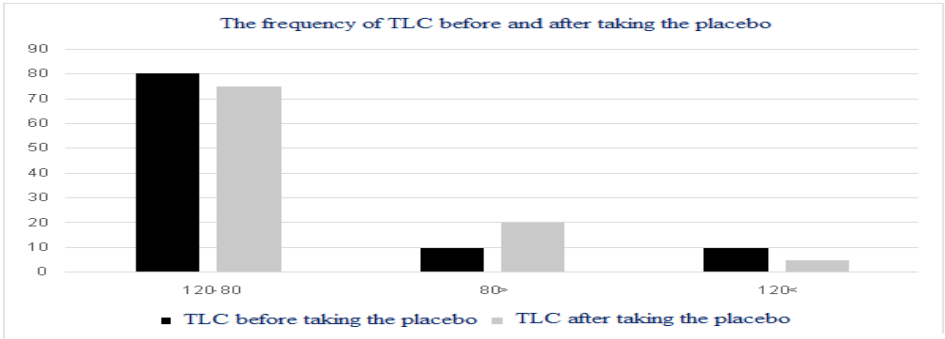
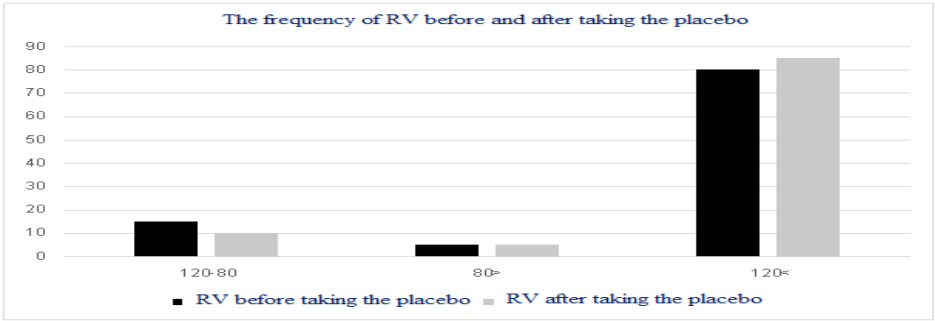


Chart 4- The frequency of RV before and after taking the placebo



No significant relationship was observed in related to RV before and after taking the medicines (p value: 0.42). This means that the medicines did not have any effects on

improvement of RV and no significant relationship was observed in related to TLC before and after consumption of the medicines (p value: 0.09). This means that the medicines did not have any effects on improvement of TLC, too. No significant relationship was observed in related to RV before and after taking the placebo (p value: 0.3). This means that the placebo, as can be expected, did not have any effects on improvement of RV and no significant relationship was observed in related to TLC before and after consumption of the placebo (p value: 1). This means that the placebo did not have any impact on improvement of TLC, too.

RV/TLC:

RV/TLC before taking the medicines among twenty patients who were taking the medicines was normal in three patients and RV/TLC remained unchanged in these three patients after taking the medicines. No significant relationship was observed in before and after the treatment (p value: 1) (Table 9).

RV/TLC before taking the placebo among twenty patients who were taking the placebo was normal in one patient and this amount change to two patients after taking the medicines. No significant relationship was observed in before and after the treatment (p value: 1) (Table 10).

Table 9- The frequency of patients in terms of RV/TLC before and after taking medicines

RV/TLC	Before taking the medicines	After taking the medicines
Normal	3 (15%)	3 (15%)
Abnormal	17 (85%)	17 (85%)

Table 10- The frequency of patients in terms of RV/TLC before and after taking placebo

RV/TLC	Before taking the medicines	After taking the medicines
Normal	1 (5%)	2 (10%)
Abnormal	19 (95%)	18 (90%)

DISCUSSION AND CONCLUSION

The results of this study indicated that initial FEV1 of 8 patients was normal. This number increased to 10 by taking the medicines. However, no significant relationship was observed on FEV1 before and after taking the medicines. This means that the medicines did not have any effect on FEV1 improvement. The results also indicated that FEV1/FVC in 2 patients, who had severe obstruction according to FEV1, was less than 70%. This condition did not also change after taking the medicines. This means that the medicines did not have any effect on FEV1/FVC improvement. Also, no significant relationship was observed in pulmonary restriction before and after taking the medicines.

It was stated in previous studies on evaluation of FEV1 and FEV1/FVC and pulmonary chronic lesions in mustard gas-wounded patients that abnormal changes of bronchioles play an important role in pathogenesis of pulmonary chronic complications caused by mustard gas in mustard gas-exposed patients. It was also stated that obstruction of respiratory ducts in mustard gas-exposed patients is partially reversible [12, 13]. Studies suggested that FEV1 and PFT are reliable tests for evaluation of adverse consequences of systemic inflammation in pulmonary diseases and are used to evaluate the effectiveness of the treatment [14, 15]. As in the past and 25 years evaluation on a chemical plant workers exposed to sulfur mustard (mustard gas) reported that FEV1, FEV1/FVC and FVC in these people had been less than people who had less contact with the gas and also healthy individuals. After a while these people were affected by bronchiectasis and advanced emphysema and in a few cases they caught cancer and bronchioles. This shows that mustard gas is very effective in reduced vital capacity of the lungs as well as in power of lungs. It also decreased the lungs functioning during evaluation of pulmonary tests [16].

Due to obstruction and destruction of respiratory ducts as well as lack of correct breathing, a weakness usually exists in FEV1 and other pulmonary tests of these patients. Studies suggested that Statins may be considered as a

useful drug to reduce inflammation and lung related complications [17]. On the other hand, it was stated that the role of Statins is still unknown in treatment of chemical injuries [18, 19]. Retrospective studies suggest that statin therapy may have beneficial impacts on some clinical complications in chemical wounded patients and among which can be mentioned to increase in the pulmonary function [20, 21]. It was also suggested in studies that statin drugs, especially atorvastatin will be resulted in significant improvement in the lung function and FEV1 is treated after 6 months [14, 15]. Aside from that colchicine is a component of idiopathic pulmonary fibrosis treatment protocol as well [22] and its preventative effects have been approved in development of pulmonary fibrosis [23]. The results related to pulmonary tests, in this study, showed that no significant changes in the lung function were observed in the medication group (colchicine and simvastatin). This is contrary to the results of previous researches that can possibly be due to differences in conditions and quality of implementation of researches and studied patients. Increased in the lung function was observed in the present study only in certain treated groups and this is not significant compared to the initial groups and the placebo group. Plethysmography initial test showed that no significant changes were observed in variation of VC and IC in the patient groups. This indicates that the medicines (colchicine and simvastatin) were not effective in treatment and increase of the lung function. Therefore, use of these medicines in patients is not recommended. So that in studies conducted on the effects of atorvastatin as an anti-inflammatory drug on variation of FEV1 in mustard gas-exposed patients revealed that atorvastatin had failed to make significant changes in FEV1 after 4 weeks compared to placebo group. This shows that atorvastatin had been ineffective in treatment and in variation of TEV1 chemical wounded patients and the consumption of this drug is recommended for probably more effective treatment [17]. Some studies stated that short-term treatment with atorvastatin does not change the lung function. However, it will enhance the quality of life in patients with mild asthma [24]. Another study that was performed for investigation of Statins on variation of pulmonary tests and especially on FEV1 reported that no significant changes especially in improvement of pulmonary diseases in mustard gas-wounded patients was observed in the short-term consumption of these drugs. They also stated that long-term use of this class of medicines may improve pulmonary tests in these patients [25]. Previous studies about evaluation of Statins on improvement of pulmonary signs in smokers showed that this class of medicines does not have any impact on the lung function and FEV1 in short-term period [26, 27].

It was found in this study that no significant changes were observed in the lung function compared to the placebo group within two months of consumption of the evaluated medicines. This is consistent with the results of the other mentioned researches and its consumption is not recommended to enhance the performance and improvement of pulmonary tests in chemical wounded patients. Various studies have also stated that the duration and the kind of treatment as well as various stages of injury with mustard gas impact on the results related to pulmonary tests. So this study improves the results of previous studies.

The findings of this study showed that the results of plethysmography before and after drug therapy in the studied groups did not have significant change. This indicates that the medicines did not have any effect on treatment of RV and TLC in mustard gas-wounded patients. It had suggested in studies that pulmonary fibrosis caused by production of free radicals induced by mustard gas and its alkylating properties, which destroy the lung tissue and reduce the lung

efficiency, is a case that can lead to decrease the lung efficiency in mustard gas-wounded patients [28-31]. An amount of air always remains in the lungs after a deep exhalation, in natural conditions and in a healthy human. The amount of remaining air or residual volume (RV) cannot be measured by spirometry, and since determination of the amount of RV and measurement of its enhancement and reduction has great importance respectively to determine the severity of obstructive disease and to prove the lung tissue diseases, so plethysmography device is used to measure it.

In this study, the number of people with normal RV and TLC was increased after treatment with colchicine and simvastatin, and vice versa the number of people with RV and TLC levels more than 80 and 120 was reduced that represents the severity of obstructive disease. This is not statistically significant compared to the placebo group and indicates that the medicines were not effective in improvement of the clinical signs related to plethysmography test.

Probably, the lack of effectiveness of these medicines in mustard gas-wounded patients can be due to the lung damages and adverse pulmonary fibrosis depending on the severity of the disease, as studies reported that the percentage of alveolar space will reduce in chemical wounded patients due to collagen deposition, incidence of pulmonary fibrosis, and chronic inflammatory of the lungs. This can lead to variation in RV and TLC compared to normal individuals [32]. It was also stated that the reduction in alveolar space as well as reduced capacity of the lungs can be due to infiltration of inflammatory cells [30], so that any medicine which can improve the alveolar space and pulmonary volume causes the symptoms related to the lung function and its tests to be more successful. In this study, the consumption of the medicines (colchicine and simvastatin) could not be effective on variation of RV and TLC. So, there is lack of reduction of inflammation, fibrosis as well as reduced alveolar spaces. The performed pulmonary tests are supporting this subject.

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