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# Efficacy of omeprazole on cough, pulmonary function and quality of life of patients with sulfur mustard lung injury: A placebo-control, cross-over clinical trial study

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**Background:** Gastro-esophageal reflux disease (GERD) is prevalent and related to more severe disease in patients with respiratory problems. We evaluated the effects of antireflux therapy in warfare victims of exposure to Mustard gas with chronic cough. **Materials and Methods:** This randomized, double-blind, placebo-controlled, cross-over study was conducted on 45 cases of sulfur mustard injury with chronic cough ( $\geq 8$  weeks) and GERD. Patients were randomized into two groups, receiving either 20 mg twice daily omeprazole-placebo (OP) or matching placebo (placebo-omeprazole [PO]) for 4 months, followed by a 1-month washout period and the alternative treatment for 4 months. Assessments included GERD and cough, quality of life, and pulmonary function using spirometry. Leicester Cough Questionnaire and SF-36 were used for measuring quality of life. **Results:** Patients in the OP group experienced a more decrease than those in the PO group in severity of Leicester cough scores during the first 4-month of trial. After crossing the groups, the OP group experienced an increase ( $P = 0.036$ ) and the PO group experienced a nonsignificant decrease ( $P = 0.104$ ) in the severity of scores. The OP group also experienced improvement in GERD symptoms and quality of life at the end of the trial, but changes in the PO group was not significant. There was no significant change in respiratory function indices in any groups. **Conclusion:** Long-term treatment with high-dose omeprazole improved GERD as well as cough, and quality of life, but not changed respiratory function indices in sulfur mustard injured cases with respiratory symptoms.

**Key words:** Chronic cough, gastro-esophageal reflux disease, mustard gas

**How to cite this article:** Emami MH, Talaei M, Panahi Y, Saburi A, Ghanei M. Efficacy of omeprazole on cough, pulmonary function and quality of life of patients with sulfur mustard lung injury: A placebo-control, cross-over clinical trial study. *J Res Med Sci* 2014;19:1027-33.

## INTRODUCTION

Mustard gas or sulfur mustard is a chemical weapon that was used in the Iran-Iraq war by Iraqi military against the Iranian soldiers and defense forces, as well as the Iraqi people, and left destructive impacts on both groups. This sulfide composition (2-chloroethyl) is an alkylizer substance that even in low contact is highly cytotoxic.<sup>[1]</sup> Mustard gas exposure will have harmful effects on all body systems, and mainly involves the eye, skin, and the respiratory system. If it is absorbed through the gastrointestinal tract, systemic and local effects will be left.<sup>[1,2]</sup> With acute destructive effects on various organs, a large number of patients exposed to mustard gas suffer from the delayed and chronic complications, including small airways disease, frequent and persistent corneal ulcers, chronic skin diseases, and various types of cancers.<sup>[1-3]</sup> Pulmonary disorders are the most common delayed complications

in patients exposed to mustard gas, and the Chronic obstructive pulmonary disease (COPD) and prolonged inflammation of small airways are the most common consequences in these patients.<sup>[1,3]</sup> Treatment of these lesions in these patients is a major problem associated with attacks and need to repeated hospitalizations.

A serious disorder that can lead to exacerbation of the clinical course of pulmonary diseases is the gastro-esophageal reflux disease (GERD). Several studies have shown the adverse effects of GERD on the clinical course of pulmonary diseases, including COPD, asthma, and pulmonary fibrosis.<sup>[4-6]</sup> As a result, diagnosis and treatment of GERD in these patients is considerably important. Despite numerous reports on the effects of GERD on the clinical course of COPD and asthma, there are few reports on relevant therapeutic strategies. However, the available evidence not only recommends the antireflux treatment in patients with

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**Received:** 22-11-2013; **Revised:** 17-01-2014; **Accepted:** 17-11-2014

GERD symptoms, but also stresses on the antireflux therapy in asymptomatic, although this issue is controversial.<sup>[7-10]</sup> It has been previously shown that the prevalence of GERD in patients with lung lesions after exposure to mustard gas is high. The anti-GERD treatment appears to be helpful in controlling the respiratory symptoms in these patients. Therefore, the purpose of this research was to study the effect of antireflux treatment on cough and the quality of life of veterans exposed to the chemical warfare with chronic cough and history of exposure to mustard gas.

## MATERIALS AND METHODS

### Study design and population

In a randomized, double-blind, placebo-controlled, cross-over study, 80 patients were selected among 200 individuals meeting the criteria for entering the study and invited to participate in the study. This study was conducted in a medical care unit which was specific for chemical injured patients in Isfahan, Iran during 2009-2011. Among them, 45 subjects finally participated in the project.

### Inclusion criteria

All patients had to have all four of the following conditions:

1. History of contact with mustard gas by Veterans Foundation approval (meaning at least one time exposure to mustard gas with high-doses during the war that has led to temporary or permanent disability of the exposed individuals).
2. Having chronic cough (>8 weeks) or other respiratory symptoms.
3. Having reflux based on clinical symptoms, including retrosternal burning, acid regurgitation and noncardiac chest pain.
4. Ability and willingness to participate in the study.

### Exclusion criteria

In case of any of the following conditions, the patients were excluded from the study:

- Any reason for not performing endoscopy such as respiratory failure or myocardial infarction, history of smoking and recent use of medications such as beta blockers or theophylline, calcium channels blockers as well as gastric antisecretory drugs (such as omeprazole and cimetidine) within 2 weeks before the study.

### Assessments

A special questionnaire and a checklist for clinical and paraclinical data collection were prepared, which were completed by a physician through interview with the patients. The questionnaire included the standard symptoms of GERD, the severity of symptoms and the predisposing factors. Furthermore, the records related to the previous cases of the patients at the Veterans Foundation

were reviewed. Based on the reflux definition, 80 patients were selected. Then, the quality of life questionnaires were completed for through an interview with a physician.

In order to evaluate the symptoms of GERD, a questionnaire consisting of 10 items with grading ratings from 0 = asymptomatic to 5 = symptom severity as disabling level was used, in which higher scores indicate greater severity of GERD and its impact on daily functioning. The psychometric characteristics of the questionnaire were appropriate as the Cronbach's alpha = 0.87. Leicester Cough Questionnaire was used to assess the quality of life in the patient with chronic cough, which consists of 19 items with appropriate psychometric characteristics and response to the treatment. Each item is scored from 1 = never to 7 = always, and higher scores indicate more severity of the cough and its impact on daily functioning.<sup>[11]</sup> The Cronbach's alpha for this questionnaire in our study was equal to 0.89. The quality of life was also evaluated based on the SF-36 questionnaire, which is a very reasonable questionnaire for review of general quality of life with appropriate psychometric characteristics that has been standardized by Montazeri *et al.* for Iranian community. The questionnaire consists of 36 items, 8 dimensions and 2 general dimensions of physical health and mental health. Each dimension is grading from 0 to 100 where higher scores indicate more healthiness.<sup>[12]</sup>

### Interventions

All patients were on low-dose inhaled corticosteroid and Salmeterol and also N-acetyl cysteine during the study period as standard medication. Then, the patients were randomly divided into two groups by a pharmacist who was administering the medications (medication or placebo). The intervention group received omeprazole (20 mg twice daily) for 4 months associated with routine pulmonary medications. Drug dosage was based on available data from trials on pulmonary disease patients.<sup>[7-10]</sup> The control group was given empty omeprazole capsules (20 mg twice daily) plus their medications. All the patients were receiving antacids as needed. All patients participated in the study were examined and evaluated monthly by the physician based on respiratory tests and checklist for complications of used drugs. At the end of the initial 4-month period, the quality of life questionnaire was also completed. Then, the patients passed a period of 1-month without medication, and after that, the medications of the two groups were changed by each other.

At the end of the 9-month period study, the patients unable to tolerate the side effects of omeprazole or who have not responded to the treatment, were selected from both groups and treated by other medications like lansoprazole and were excluded from the study.

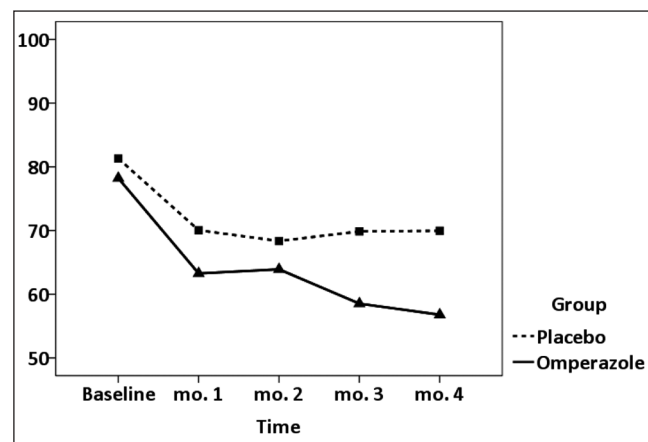
### Statistical analysis and ethics

Data were analyzed in SPSS software (SPSS Inc., Chicago, IL; version 16) using K-S test (checking the normal distribution), independent *t*-test (comparing a quantitative variable between two groups), paired *t*-test (comparing a quantitative variables before and after treatment), and repeated measurement ANOVA (comparing the changes in more level of follow/up). After explaining the study conditions, they were asked to read the consent form and sign it in case of accepting the conditions of the study. This project was approved by Scientific Board Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran. Furthermore, the Ethic Committee of our university approved this study (approval no: P.S/340/3-2620).

## RESULTS

Eventually, 23 patients in the first group (omeprazole-placebo [OP]) and 22 patients in the second group (placebo-omeprazole [PO]) were included in the study. All the patients were male. The average age of the first and second groups, respectively, was equal to  $46.7 \pm 6.6$  and  $50.3 \pm 8.8$  years, and there was no significant differences between age range of the two groups [ $P = 0.133$ , Table 1]. Carryover effect was ruled out by the method introduced by Wellek and Blettner. Accordingly, the cough severity scores throughout both placebo and omeprazole period (10 measurement points) were added together and compared between the two sequences using an independent *t*-test. The sum of scores in PO and OP sequences was  $669 \pm 146$  and  $590 \pm 178$  and no statistically significant difference was observed (0.097). Consequently, it was concluded that washout period was long enough and ordinary statistical analysis like repeated measure is permitted.<sup>[13]</sup>

Also, the difference of the trends of the Leicester cough scores severity between the groups is shown at Table 2.



**Figure 1:** Trend of Leicester cough scores severity during the first 4<sup>th</sup> months of survey

According to the *t*-test, the two groups were similar in terms of severity of Leicester cough scores at the beginning of the study, while at months 3 and 4, the severity Leicester cough scores in the OP group was significantly lower ( $P = 0.005$ ). Also, as shown in the Figure 1, based on repeated measure test, the severity of symptoms significantly reduced in both groups during the first 4 months, but had a more decrease in the OP group [ $P < 0.001$ ]. The severity variations trends of Leicester cough scores after 1-month period without medication and the cross-over of the two groups during the second 4 months in both groups are reported in Table 3.

Based on *t*-test, the severity of Leicester cough scores in the OP group was also significantly lower than in the PO group at the beginning of the second 4 months (respectively,  $P = 0.063$  and  $P = 0.034$ ). Also, as shown in Figure 2, based on repeated measure testing, the changes trend in the severity of symptoms during the second 4 months between the two groups was statistically significant ( $P < 0.001$ ). The severity of Leicester cough scores in the OP group increased significantly ( $P = 0.036$ ), but reduced severity of symptoms in the PO group was not statistically significant ( $P = 0.104$ ).

The trend of change in intensity of Leicester cough scores in the 9-month period of the study is shown in Figure 3. The changes trend in the whole period shows that although the placebo effect has been observed in the control of Leicester cough scores especially at the beginning of study, but the effect of omeprazole was significantly greater than placebo, and by continuing of omeprazole consumption, its effect increased and by stopping its administration, the

**Table 1: demographic and clinical findings at the base line**

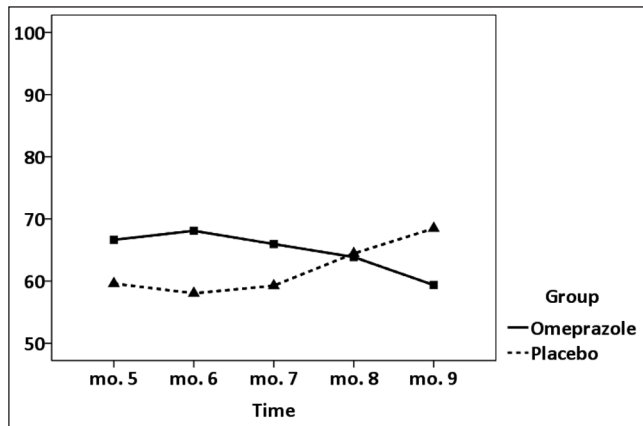
Indicator	PO group <i>n</i> = 22	OP group <i>n</i> = 23	<i>P</i> *
Age	8.8±50.3	6.6±46.7	0.133
Reflux severity score	3.0±7.9	2.4±7.6	0.712
Leicester cough severity score	22.0±81.3	22.5±79.1	0.714
SF-36	19.0±38.5	14.8±32.9	0.275

\*Student's *t*-test; § = Statistically significant; PO = Placebo-omeprazole; OP = Omeprazole-placebo

**Table 2: Trend of Leicester cough scores severity during the first 4<sup>th</sup> months of survey**

Stage	PO group <i>n</i> = 22	OP group <i>n</i> = 23	<i>P</i> *
Baseline	22.0±81.3	22.5±79.1	0.741
1 <sup>st</sup> month	19.2±70.0	19.3±62.8	0.102
2 <sup>nd</sup> month	21.3±68.3	20.3±63.5	0.213
3 <sup>rd</sup> month	19.8±69.8	19.0±59.4	0.036§
4 <sup>th</sup> month	20.7±69.9	17.3±56.7	0.012§
<i>P</i> **	0.047§	0.001§	
<i>P</i> ***	<0.001§		

\*Student's *T*-test; \*\*Repeated measure - within group; \*\*\*Repeated measure - between group; § = Statistically significant; PO=Placebo-omeprazole; OP=Omeprazole-placebo



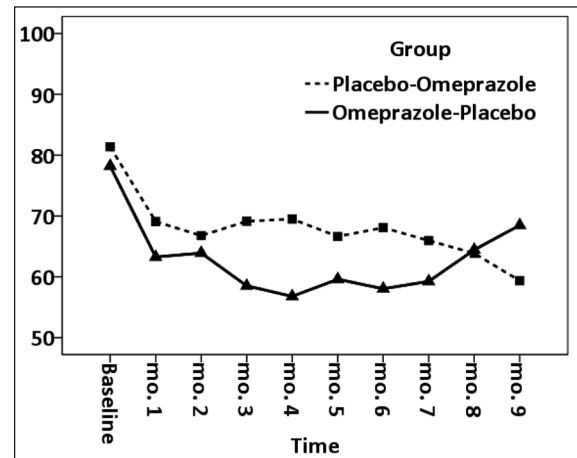
**Figure 2:** Trend of Leicester cough scores severity during the second forth months of survey

therapeutic effect is gone. The severity of reflux symptoms at the beginning and end of the study are reported in Table 4. The severity of reflux symptoms in the OP group ( $P = 0.002$ ) had significantly reduced at the end of the study but had no significant reduction in the PO group ( $P = 0.089$ ).

The quality of life scores based on the SF-36 questionnaire at the beginning and end of the study are shown in Table 5. The overall score for quality of life as well as both dimensions of physical health and mental health scores had significantly increased in the OP group at the end of the study, while in the PO group, the quality of life score or its dimensions scores had no significant changes compared to the baseline. Spirometric indicators at the beginning and end of the study are presented in Table 3. As shown in Table 6, changes in forced expiratory volume (FEV1%), forced vital capacity (FVC), or FEV1/VC% were not statistically significant in any group.

## DISCUSSION

The aim of this study was to evaluate the effectiveness of long-term treatment with high-dose omeprazole in reducing the symptoms of chronic cough, GERD, and the quality of life in veterans exposed to chemical warfare in the city of Isfahan. As demonstrated by the results, in the first 4 months, the severity of respiratory symptoms in a group received omeprazole were significantly lower than the placebo group and the severity of symptoms during the first 4 months in the group receiving omeprazole had reduced compared to the placebo group. Also, therapeutic effect of the drug in the omeprazole treatment group has continued in a progressive trend from 2<sup>nd</sup> to 4<sup>th</sup> months. It can be assumed that if the first intervention period time was continued >4 months, the recovery process would be continuing to reach a plateau level. Consequently, in future studies, it would be better that the duration of intervention will increase to specify at least the intervention period by which the symptoms reach to their



**Figure 3:** Trend of Leicester cough scores severity during the survey

**Table 3:** Trend Leicester cough scores severity during the second 4<sup>th</sup> months of survey

Stage	PO group n = 22	OP group n = 23	P*
Baseline	17.8±66.6	14.5±59.1	0.063
1 <sup>st</sup> month	19.6±68.0	17.3±57.9	0.034§
2 <sup>nd</sup> month	19.7±65.9	16.3±59.9	0.132
3 <sup>rd</sup> month	17.4±63.8	20.8±64.4	0.458
4 <sup>th</sup> month	16.8±59.3	25.7±67.0	0.239
P**	0.104	0.036§	
P***	<0.001§		

Student's T-test; \*\*Repeated measure - within group; \*\*\*Repeated measure - between group; § = Statistically significant; PO = Placebo-omeprazole; OP = Omeprazole-placebo

**Table 4:** Reflux severity scale during the study based on two groups

Stage	PO group n = 22	OP group n = 23	P*
Base line	11.8±8.8	13.5±6.1	0.527
9 <sup>th</sup> month	8.9±8.8	8.1±6.9	0.74
P**	0.089	0.002§	

\*Student's t-test; \*\*Paired t-test; § = Statistically significant; PO = Placebo-omeprazole; OP = Omeprazole-placebo

**Table 5:** Quality of life changes during the survey

Indicator	PO group n = 22		P*	OP group n = 23		P*
	9 <sup>th</sup> month	Base line		9 <sup>th</sup> month	Base line	
SF-36	2.24±18.2	5.83±19.0	0.369	7.24±19.3	9.23±14.8	0.002§
Mental health	8.93±19.0	8.83±23.1	0.819	6.93±17.9	9.92±16.7	0.019§
Physical health	3.14±17.3	4.53±15.3	0.098	1.14±19.4	3.23±13.0	0.029§

§ = Statistically significant; PO = Placebo-omeprazole; OP = Omeprazole-placebo

**Table 6:** Spirometric parameters during the survey

Indicator	PO group n = 22		P*	OP group n = 23		P*
	9 <sup>th</sup> month	Base line		9 <sup>th</sup> month	Base line	
FEV1%	23.9±73.9	28.1±67.5	0.078	122.6±100.6	25.4±90.7	0.723
FVC%	42.5±93.8	26.1±83.1	0.203	57.9±80.8	21.3±96.1	0.286
FEV1/VC%	23.9±61.2	27.9±51.6	0.084	49.1±70.2	28.8±74.2	0.717

\*Student's t-test; § = Statistically significant; PO = Placebo-omeprazole; OP = Omeprazole-placebo; FVC = Forced vital capacity; FEV = Forced expiratory volume



lowest levels. After replacing the two groups, changes trend in the severity of symptoms during the second 4 months between the two groups was not statistically significant, and in the group crossed from omeprazole to the placebo, stabilization of pulmonary symptoms has continued about 3 months after discontinuation of omeprazole, and then the symptoms have gradually increased. It supports the effect of omeprazole in improvement of pulmonary symptoms and symptoms exacerbation in about 3 months after stopping the medication. The changes trend of respiratory symptoms in the whole period show that although the placebo effect has been observed in the control of respiratory symptoms, especially at the beginning of study, but the effect of omeprazole has been significantly greater than the placebo and its effect has increased by continuing the omeprazole intake; by stopping the drug intake, its therapeutic effect is gone.

According to our results reflux symptoms reduced in both groups after the end of the study, but further reduction in the group that had received omeprazole at the beginning of the study. These findings are compatible with reduced lung symptoms resulted from omeprazole receiving, and strengthen the existing evidence regarding reflux as a part etiology of respiratory symptoms in veterans exposed to chemical warfare. The quality of life at the end of the study score has also reduced significantly in the group received omeprazole at the beginning of the study, while in the group received placebo at first, the quality of life score had no significant changes compared to the baseline. This finding shows that not only the use of omeprazole leads to reduced respiratory symptoms and reflux in veterans exposed to chemical warfare, but also effectively improves the patients' quality of life, and therefore can result in increased efficiency and physical and mental stability of the patients of chemical warfare. Despite the positive effects of omeprazole on pulmonary symptoms and reflux symptoms, the changes in spirometric indices were not consistent with the changes in symptoms, and treatment with omeprazole did not result in a significant improvement in the patients' spirometric indices.

In the literature review, no report was found on standard antireflux therapy in patients exposed to chemical warfare. However, GERD is common among patients with respiratory symptoms; however, studies investigating the effect of proton pump inhibitors (PPIs) on asthma or COPD outcomes report conflicting results. In a study by Sharma *et al.* 198 patients with asthma and GERD (based on pH-metry) received omeprazole (20 mg twice daily) and domperidone (10 mg three times daily). The daily and nocturnal symptoms of asthma and reflux symptoms significantly decreased in the group with 16

weeks of antireflux treatment compared to the placebo group. Also, the improvement in morning and evening peak expiratory flow rate, FEV1 and FVC in the antireflux treatment group was significantly better than the placebo group.<sup>[14]</sup> In Littner *et al.* study on 207 patients with asthma and symptomatic reflux, 24 weeks of treatment with lansoprazole (30 mg twice a day) were compared to the placebo. There were no significant effects on the symptoms of asthma, PEF, FEV1, and FVC, but had reduced the occurrence of asthma attacks significantly.<sup>[15]</sup> In another study by Jiang *et al.*, 30 patients with asthma and GERD, taking omeprazole (20 mg daily and 10 mg Domperidone 3 times a day) for 6 weeks showed significant improvement in all parameters of spirometry.<sup>[9]</sup> Sasaki *et al.* studied 100 patients with COPD, treatment with lansoprazole for 12 months significantly reduced the recurrence of COPD exacerbation during 1-year.<sup>[10]</sup>

In contrast, Teichtahl *et al.* found that in 20 patients with asthma and reflux, treatment with omeprazole (40 mg daily) for 4 weeks led to improvement of reflux symptoms, but had no significant effects on asthma symptoms or spirometric indices.<sup>[16]</sup> It seems short-term treatment period is one of the reasons for the negative results. Also, in the study by Boeree *et al.*, 3 months of treatment with high-dose omeprazole (40 mg twice daily) on 36 patients with severe airway hyperresponsiveness and reflux significantly reduced the reflux symptoms, but omeprazole therapy had no significant effect on respiratory parameters.<sup>[17]</sup> In more recent study by Kiljander *et al.* investigated the effect of esomeprazole 40 mg once or twice daily on asthma outcomes in 828 patients with moderate-to-severe asthma and symptomatic GERD. At treatment end, both doses of esomeprazole significantly improved FEV1 function and asthma-related quality of life. However, the improvements were minor and of small clinical significance.<sup>[7]</sup>

In some studies, the results were somewhat in conflict with administration of antiacid treatment in patients with COPD and asthma. It was shown that intravenous ranitidine injection (50 mg) in patients with COPD and severe obstruction led to decrease in FVC and FEV1 in 60 and 120 min after injection.<sup>[18]</sup> In this study, the duration of treatment can also have a negative impact on the results. In a double-blind trial, 412 participants with uncontrolled asthma and with minimal or no symptoms of GERD were recruited to receive either 40 mg of esomeprazole twice a day or matching placebo. Participants were followed for 24 weeks. Episodes of poor asthma control occurred with similar frequency in 2 groups. There was no treatment effect with respect to individual components of the episodes of poor asthma control or with respect to secondary outcomes, including

pulmonary function, airway reactivity, asthma control, symptom scores, nocturnal awakening, or quality of life.<sup>[19]</sup>

Finally, the meta-analysis conducted on relevant clinical trials showed that treatment with PPIs in patients with asthma and symptomatic reflux improves lung function; however, this meta-analysis did not recommend experimental treatment in all patients (asymptomatic).<sup>[20]</sup>

Our study has some limitations. The sample size was small and underlying factors such as BMI, diet, lifestyle, psychological factors and stability of the treatment as potential predicting factors of response to the treatment were not considered. Moreover, we focused on cough as main respiratory complain in this setting and evaluation of other symptoms like dyspnea is necessary. SF-36 is developed as a measure of general health, and assessing effect of respiratory symptom on quality of life, using disease-specific health status questionnaire for measuring health related quality of life such as Chronic Respiratory Questionnaire and the St. George's Respiratory Questionnaire is more specific.

## CONCLUSIONS

The result of the study showed that long-term treatment with high-doses of omeprazole in veterans exposed to chemical warfare, regardless of reflux symptoms, can reduce chronic cough, reflux symptoms and enhance quality of life in both aspects of physical and mental health, but no significant effect on spirometric indices. We suggest performing further and more extensive self-controlled studies on more exposed veterans with increased intervention period time as 1-year. The long-term effects of omeprazole use in reducing the progression of lung disease and on longevity should be taken into consideration in future studies.

## ACKNOWLEDGMENTS

We would like to acknowledge Dr. Elham Nazem, Sanaz Ani, and Najmeh Tavakol for helping us with managing patients. We also thank Amiralmomenin Hospital of Isfahan, and Poursina Hakim Research Institute for collaboration with this study. All authors read and confirmed the draft before submission. The ethic committee of our university approved this study (approval no: P.S/340/3-2620). The project's grant number is "CIRC-No. PU-04".

## AUTHOR'S CONTRIBUTION

This study was based on the idea of MGh and MHE; all authors contributed in the design of the study; MT, MHE and YP collected and analyzed the data; and MHE and MGh wrote the paper. All authors read and confirmed the draft before submission.

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**Source of Support:** This study was funded in full by Baqiyatallah University of Medical Sciences, Tehran, Iran; grant number (CIRC-No. PU-04). **Conflict of Interest:** None declared.