

Prevention and Treatment of Respiratory Consequences Induced by Sulfur Mustard in Iranian Casualties

Seyed M. Razavi, Payman Salamati¹, Ali Amini Harandi², Mostafa Ghanei³

Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran,

¹Department of Community Medicine, Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran, ²Department of Neurology, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ³Research Center of Chemical Injuries, Baqiyatollah Medical Sciences University, Tehran, Iran

Correspondence to:

Associate Prof. Payman Salamati,
Sina Trauma and Surgery Research Center,
Tehran University of Medical Sciences,
Sina Hospital, Hassan Abad Square,
Imam Khomeini Avenue, Tehran, Iran.
E-mail: psalamati@tums.ac.ir

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ABSTRACT

Background: About 100,000 Iranian have been exposed to chemical weapons during Iraq-Iran conflict (1980-88). After being spent of more than two decades, still about 30,000 of them are under follow-up treatment. The main aim of this study was to review various preventive and therapeutic methods for injured patients with sulfur mustard in different phases.

Methods: For gathering information, we have used the electronic databases including Scopus, Medline, ISI, IranMedex, Irandoc sites. According to this search strategy, 104 published articles associated to respiratory problems and among them 50 articles related to prevention and treatment of respiratory problems were found and reviewed.

Results: There is not any curative treatment for sulfur mustard induced lung injuries, but some valuable experienced measures for prevention and palliative treatments are available. Some useful measures in acute phase include: Symptomatic management, oxygen supplementation, tracheostomy in laryngospasm, use of moist air, respiratory physical therapy, mucolytic agents and bronchodilators. In the chronic phases, these measures include: Periodic clinical examinations, administration of inhaled corticosteroids alone or with long-acting beta 2 agonists, use of antioxidants, magnesium ions, long term oxygen supplement, therapeutic bronchoscopy, laser therapy, and use of respiratory tract stents.

Conclusions: Most treatments are symptomatic but using preventive points immediately after exposure could improve following outcomes.

Keywords: Chemical warfare, lung injury, mustard gas

INTRODUCTION

After more than two decades of Iraq-Iran war, still about 30,000 of Iranian veterans are under follow-up treatment.^[1,2] Khateri *et al.*, in their study conducted on 34,000 subjects who were exposed to sulfur mustard, reported that 14,450 (42.5%) of them were suffering from respiratory problems.^[2]

For paying to remedial and preventive interventions, we should know more about pathological changes related to sulfur mustard. In summary, this alkylating substance leads to DNA damage, cell membrane damage, decrease in glutathione, NFKB

activation, and caspase activation. DNA damage lead to polymerase (PARP) activation and nicotinic adenine nucleotide (NAD) depletion. Glutathione decreasing produce reactive oxygen and these two phenomena may lead to necrosis and cell death.^[3] In addition to cell death, mustard gas has many other adverse effects on cells such as: Alkylation effects, mitosis inhibition (effects on hematologic system, immunologic system, epithelial and germinal tissues), mutagenesis, carcinogenesis, and colinomimethic effects.^[4] Sulfur mustard leads to release of pro-inflammatory cytokines and then releasing of the prostaglandins in acute phase.^[5]

After exposure, there are various types of manifestations in respiratory system. Koch *et al.*, have divided the pathological sequences of sulfur mustard on the respiratory tract into 4 phases: (i) Catarrhal phase (ii) pseudo membranous laryngotracheitis state (iii) pseudo membranous bronchitis and bronchopneumonia and (iv) gangrene and lung abscess formation phase.^[6] Sulfur mustard acts as an immunosuppressant agent^[5] and this fact may lead to a more complex condition. We can use from aforementioned phenomenon in remedial and preventive interventions. Therefore, in this study, we have reviewed the types of respiratory treatment methods in which the doctors have been done for injured patients during more than two decades after the exposure, in different conditions in Iran.

METHODS

This study is a component of a comprehensive systematic review, which includes all the war related studies which have carried out in Iran. The main aim of this study was reviewing chemical warfare related articles in the field of respiratory system.

For gathering information, we have used the electronic databases. These databases were SciVerse scopus, Medline (via PubMed) and ISI for international journals and, IranMedex, Magiran and Irandoc sites for national journals. Chemical injury, chemical warfare, sulfur mustard, mustard gas, mustard lung and respiratory effects of sulfur mustard were used as the key words. Among the nearly 400 articles, which were obtained in a systematic search, there were about 193 articles relevant to chemical war against Iran by Iraq. Among these 193 articles, 104 out of them were

associated with respiratory problems and there were obtained some facts related to prevention and treatment in 50 articles. In addition, if the contents had been repeated in different articles, only one reference would have been used.

RESULTS

Primary prevention

Some recommendations for primary prevention of the adverse effects of mustard gas include the following points:

- Military training on how to deal with chemical terrorism, especially with mustard gas.
- Training the first necessary preventive measures in chemical wars.
- Training on how to transport victims to medical care units with moist area.
- Using the plastic clothing with fine texture if possible. According to researches, mustard gas is able to penetrate leather and ordinary clothes in a few min, but rubber and plastic materials may provide protection for several hours.^[6] Of course, sulfur mustard can penetrate from ordinary and also plastic masks in to the body.^[7]
- Since mustard gas being heavier than air, during the attacks it should be better we take a height of at least 10 meters from the site of bomb landing.^[8]
- All contaminated clothing should be removed from the body, as soon as possible and be destroyed.^[9] Because of, sulfur mustard may persist in the liquid form on contaminated clothing and equipment for many hours or days and effects the biological tissues.^[10]
- Washing the body as soon as possible with the safe and clean water. Soldiers should avoid washing their hand, face and body with water that may be contaminated with the poison.
- Preventing people from entering the contaminated area, because the toxin is able to persist in soil for 10 years.^[7] Sulfur mustard can be found in the place of the battle, in concentrations from 1 to 25 milligrams per cubic meter, in 6 to 12 inches deep of the ground (soil).^[11]
- Using the standard protective equipment such as masques and clothes.
- For decontamination of the environment, calcium hypochlorite and stilbestrol as a

powder and permanganate can be used.^[10] If sulfur mustard is used in the powder form, following decontamination will be difficult.^[12]

Treatment in acute phase

Despite, ongoing researches regarding treatment of the patients, exposed to sulfur mustard, this field still remained controversial. Best treatment in this phase is aforementioned primary prevention and detoxification.^[7]

Management of respiratory complications in acute phase of sulfur mustard poisoning is symptomatic management.^[13] The main points relied for the treatment of respiratory problems are administration of oxygen, vaporized moist air, bronchodilators, antibiotic therapy in the case of respiratory superimposed infection and respiratory physiotherapy.^[14] In fact, early treatments of respiratory problems caused by thick and sticky mucus are mucolytic prescription, chest percussion and postural respiratory physical therapy. In acute cases who exposed to high doses of sulfur mustard, laryngospasm and stridor will occur, in this condition the rapid formation of pseudo membrane in the upper respiratory airways may appear and it needs immediate tracheostomy, and for removing debris and the pseudo membrane bronchoscopic approach may also be required^[15,10] Presence of chemical pneumonia or acute respiratory distress syndrome requiring hospitalization in intensive care unit.^[9]

On the next steps, there will appear scars and narrowing in the airways, and gradually the airways are blocked. In these patients, therapeutic lavage of respiratory tract with using of isotonic sodium solution through fibro optic bronchoscopy is effective, and may decrease mortality. The effects of routine treatment with antibiotics and corticosteroids for prevention of long-term consequences are not clear.^[16]

Studies on animals suggest that, use of materials such as surfactants, anti-inflammatory agents and bronchodilators in the treatment of acute pulmonary poisoning with mustard gas are useful.^[17]

Treatment in late phase

Most studies have been done in Iran are focused on chronic respiratory problems. We have shown some results of these studies.

Simple physical therapies

Pulmonary rehabilitation is one of the most important medical modalities for patients with chronic pulmonary diseases in which sulfur mustard injured victims are not exception. The rehabilitation of respiratory physiotherapy included postural drainage of sputum and chest percussion and vibration applied by devices during deep breathing.^[18]

Abedi *et al.*, in their study in the year 2007 on 27 chemical veterans who were suffering from lung disease, have shown that, utilizing a combination of postural drainage, lung percussion and vibration could improve the spirometry indicators.^[14]

Mucolytic agents

Vaporized moist air, and some mucolytic agents like acetylcysteine in Iranian chemical victims were used.^[8] N Acetyl Cysteine (NAC) is not only a mucolytic drug both also has considerable antioxidant effect. It could reduce signs and symptoms of such patients. Also, NAC improves pulmonary function tests (PFTs), quality of life and it has a good therapeutic effect on fibrozing alveolitis.^[19] Also, NAC could reduce bronchial infections^[20] and COPD exacerbations.^[21] Kasielki and Nowak showed that, administration of NAC in a dose of 600 mg daily for 12 months in patients with COPD can reduce oxidative stress.^[22] Shohrati *et al.*, in a double blind clinical trial conducted on 144 patients with bronchiolitis obliterans due to sulfur mustard, found that administration of NAC (1800 mg daily) for 4 months can improve clinical conditions and PFTs significantly.^[19]

Bronchodilators

Bronchodilators improve the lung function in chemical victims, particularly in moderate and severe cases.^[23] Sohrabpour *et al.*, have proposed the use of combined agents including a beta agonist like salbutamol and an anticholinergic such as ipratropium bromide to improve lung functions among this group of patients.^[24]

To reduce obstruction, the use of bronchodilators such as salbutamol spray (beta 2 agonists) combined with inhaled anticholinergics as ipratropium bromide has been recommended.^[25,26] Mehrdash has studied the effects of these drugs on 30 chemical veterans with a mixed of obstructive and restrictive disorder. He has administered 200 micrograms of salbutamol and 40 micrograms of ipratropium bromide and finally concluded that,

combinative administration of salbutamol and ipratropium bromide, produce more dilation of the bronchi than salbutamol alone.^[26] Also, Boskabady *et al.*, in one study have shown increased airway responsiveness to salbutamol in chemical warfare victims.^[27]

Corticosteroids

According to some reports, administration of corticosteroids for improving some symptoms and problems, such as the existence of the restrictive PFT patterns can be effective. However, according to some other reports, this effect is non significant. Ghanei *et al.*, have reported that, unlike asthma, in which eosinophils of the blood is high and corticosteroids in this condition will be effective, in the mustard lung, the count of blood neutrophils is high (neutrophil dominated inflammatory disease) and medications by corticosteroids have not a significant effect.^[28,29]

Ghanei *et al.* have carried out a RCT study on 65 veterans with chronic bronchitis who were exposed to sulfur mustard in 2002. Their patients were divided into two categories. Intravenous treatment group (39 patients) who received intravenous methylprednisolone acetate 500 mg daily for 6 months and oral treatment group (26 patients) who received oral prednisolone 1 mg/kg daily for 6 months. They revealed that, spirometry indicators were improved in more than 50% of patients in both 2 groups at eighth day of treatment.^[30] However, systemic corticosteroid therapy is only recommended in exacerbation phase.

One of the effective treatments for chemical war veterans, who suffer from chronic bronchitis and chronic obstructive pulmonary disease, is to use of inhaled corticosteroids (ICs) and long-acting beta 2 agonists.^[31] However, it should be considered that ICs systemically enter into the bloodstream through the lungs and can, depending on their dose, reduce BMD (Bone mineral density), and in some studies there has been reported an increase in pathological bone fractures, by using these drugs. Attaran *et al.*, have studied the effects of ICs on bone density of chemical war victims. They compared 35 sulfur mustard exposed suffered from asthma or bronchiolitis obliterans and they received ICs with 75 people who had no any disease and they did not use any drug.

Some studies have shown that when ICs were used in mild to moderate dosages for long periods

of time, did not decrease BMD. Attaran *et al.* in their study have also concluded that, prolonged treatment with ICs, did not lead to decreased bone density but the sever obstruction, can be a risk factor.^[31,32] In other words, ICs can inhibit Hypothalamic-Pituitary-Adrenal axis when they reach in to the blood, and this increases the risk of bruising.^[33]

Gamma interferon

Balance of TH₁ and TH₂ is necessary to regulate immune responses, because TH₁ leads to production of Gamma INF and this agent also reduce TGF-β that is a strong fibrinogenic factor. On the other hand, TH₂ cytokine, causing proliferation of fibroblasts and lead to accumulation and storage of collagen in lung tissue. Therefore, it can be proposed to treat the victims with gamma interferon.^[34]

Short-term administration of oral corticosteroids for exacerbated forms is recommended and when therapeutic response is negative, gamma interferon may be effective.^[30] Ghanei *et al.*, in one randomized controlled trial study, selected two groups of victims with history of an average of 14 years of chemical exposure The case group was treated for 6 months with a combination of 200 mug of interferon gamma-1b (given three times per week subcutaneously) and 7.5 mg of prednisolone (given once a day), while the control group received their previous medications (prednisolone 7.5 mg/day + salbutamol and beclomethasone spray PRN). Clinical findings, PFTs, kidney and liver tests in two groups were compared. In this study, they concluded that with this regimen, dyspnea, hospitalization and need for oxygen were reduced and patients' respiratory functions were improved.^[34]

Anti-inflammatory agents

It has been showed that, use of nonsteroidal anti-inflammatory drugs may be effective. Kehe *et al.*, in their study concluded that, polymerase inhibitors, Matrix Metallo Proteinase inhibitors and anti inflammatory drugs will improve treatment process.^[3] Reports indicate that administration of NAC can also reduce the inflammation phenomena.^[19]

Antibiotics

Antibiotics administration to prevent secondary infections may be helpful. Ghanei *et al.*, during a clinical trial conducted on 30 chemically injured patients with bronchiolitis, because the lack of response to treatment of patients with full

dose corticosteroids, have treated the patients with prednisone and azithromycin. They have concluded that this protocol had not significant results.^[35]

It has been recommended that administration of a 6-month of a combination of clarithromycin and acetylcysteine in chronic bronchitis and bronchiolitis were effective.^[28]

Antioxidants

Oxygen species and free radicals have an important role in the pathophysiology of mustard induced pulmonary lesions. Therefore, administration of certain antioxidants in reducing acute and chronic pulmonary complications could play a major therapeutic role.^[3,19]

Herbal therapy

Thymus vulgaris is a plant from the family of Mint and its essence is a liquid with yellow, brown or red color with a pleasant smell. This material has bronchial antispasmodic, expectorant and anti-microbial properties.^[36]

Bayat *et al.*, in one study conducted on 60 patients with mild chemical bronchitis, were evaluated the effects of the Thyme (*Thymus Vulgaris*) extract on their cough, dyspnea, sputum, wheezing and lung sounds and spirometric indexes. They have concluded that a drop of thyme has no effect in improvement of respiratory symptoms in patients with chemical bronchitis.^[37] Boskabady and Farhadi in a case control study conducted on 40 patients have examined the prophylactic effect of a boiled aqueous extract of *Nigella* seed on 20 chemical war victims and 20 ordinary lung patients and they have suggested a prophylactic effect of *N. sativa* on respiratory symptoms, chest wheezing, and PFT values improvement among chemical war victims.^[38]

Magnesium ions

Magnesium ion has several well-known effects on the respiratory system and can be applied to patients with asthma. The mechanisms of action include stabilization of mast cells,^[39] relaxes smooth muscles in the respiratory system,^[40] decreasing of bronchial responsiveness in tracheobronchial tree,^[41] bronchial dilation.^[42] Administrations of magnesium ions reduce the rate of hospitalization and disability due to disease.^[40] Hyperreactive airway is found in mustard gas victims,^[42,15] and studies indicated that in patients with asthma, magnesium deficiency occurred^[23,43] and treatment

of magnesium deficiency in asthmatic victims can reduce the symptoms.^[44]

Radiation therapy

Polypoid granulations and membranous lesions can be treated by Nd: YAG laser, although recurrence is very common. In some cases, external beam radiotherapy and brachytherapy for the prevention of the scar formation is also very effective.^[16]

Stents

In the case of stenosis of the lower parts of trachea and main bronchi, special silicone stents (Dumon-Type Silicon Stents) may be used, but in some cases, granulation tissues will grow on the wires and the problem become more complicated. In this condition the stent must immediately be removed. Freitag *et al.*, had to remove the stent after 6 months in two of five patients in which the stent was placed for them in their respiratory tract.^[16]

Sildenafil

Mustard gas can cause pulmonary artery hypertension (PAH).^[45] Pulmonary artery hypertension is a complication that ultimately leads to progressive right heart failure and death.^[46,47] Sildenafil is a drug that has been approved by FDA for treatment of PAH in 2005.^[48] Tavakolipour *et al.* in one quasi experimental study, conducted on 20 victims with known PAH due to mustard gas, have been shown that administration of Sildenafil in a dose of 50 mg daily for 12 weeks leads to decreasing the pulmonary artery pressure and may reduces symptoms and emergence of partial recovery.^[45]

Transplantation

In advanced cases, lung transplantation may be indicated. However since chemical victims have long-term survival this method has not usually indication.^[16]

Treatment during exacerbation

In a report has suggested that the use of helium oxygen mixtures with non-invasive ventilation can be decreased airway resistance and work of breathing in subjects with chronic dyspnea following sulfur mustard exposure.^[49] Therefore, helium oxygen mixtures usage may improve impairment of function during exacerbation and also pulmonary in moderate to severe chronic lung effects.

Other therapies during exacerbation are short courses of systemic corticosteroids or inhaled corticosteroids, antibiotics, morphine, oxygen

supplement therapy, mucolytics and chest physiotherapy. However, the optimal choice of antibiotic and length of use are still unclear.

CONCLUSIONS

In this manuscript, various preventive and therapeutic methods for injured patients with sulfur mustard in different phases were reviewed. It was concluded that most treatments are symptomatic but using suggested preventive points immediately after exposure could improve following outcomes.

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