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Respiratory Complications Due to Sulfur Mustard Exposure

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ABSTRACT

Sulfur mustard (SM) or bis (2-chloroethyl) sulfide is a vesicant and alkylating chemical weapon. SM was used in the 1980s against Iran by Iraqi forces.After exposure to SM in initial acute phase the greatest damage is incurred by the eyes, skin and lungs and the highest damage is caused to the lungs. This injury not only in the acute phase but also in the long-term has the highest prevalence among these patients. Clinical symptoms of people after exposure to SM start with irritation of the nose and sinuses in the mild doses to the runny nose and pain at higher doses and even irritation of the airways and bronchial engagement in very high doses. Respiratory complications in patients exposed to SM have been associated with long-term symptoms and these symptoms add to the intensity of the complication. Bloody sputum, feeling of tightness in the chest and shortness of breath over nights are among common symptoms; also the main respiratory symptoms including generalized wheezing, rale (crackle), decreased breath sounds and cyanosis and Apparently FEV1 is reduced by 50 mL/year.In these patients there are changes in blood cells especially in white blood cells and neutrophils and systemic inflammation and systemic changes with other comorbidities are observed. Although SM pulmonary patients' treatment is based on bronchodilators and long-acting –β2 agonists, paying attention to the comorbidities with prior systemic changes in these patients is a reason for the need to change treatment strategies of these patients with systemic and extra-pulmonary therapy.

Key Word:*Sulfur Mustard, Respiratory, Chronic Diseases*

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INTRODUCTION

Sulfur mustard (SM) is a chemical compound with the chemical name bis (2-chloroethyl) sulfide which is a vesicant and alkylating chemical weapon and in IUPAC the name 1-chloro-2-(2-chloroethylsulfanyl) ethane is defined for $ClCH_2CH_2SCH_2CH_2Cl$ [1-2]. The gas was used for the first time by the Germans in the First World War and then it was synthesized and used by other countries as well [3]. This gas due to its ease of synthesis has a special place in the war; unfortunately it was used in the later wars and even terrorist attacks [4]. It was used in the 1980s against Iran by Iraqi forces. Although the death rate of SM is less than other chemical weapons, its range of injuries is much more than other weapons [5] such than in the attacks by Iraq against Iran by SM more than 100 thousand people were injured (6). SM due to its environmental stability can lead to the exposure of people, food and agriculture in the long-term; but most recorded cases are associated with battle field exposure at the time of chemical attack(7). SM enters human body through inhalation, skin, the anterior surface of the eye and gastrointestinal tract after consumption of contaminated food [8]. Also detection, identification and measurement of mustard gas is possible through layer chromatography (TLC), gas chromatography (GC), gas chromatography - mass spectrometry (GC-MS), high performance liquid chromatography (HPLC) and liquid chromatography / mass spectrometry (LC / MS) [1].

COMPLICATIONS OF EXPOSURE TO SULFUR MUSTARD

After exposure to SM in initial acute phase the greatest damage is incurred by the eyes, skin and lungs [9]. Studies have shown that the highest damage is caused to the lungs and usually the patients with skin and eye lesions suffer from pulmonary complications [10]. It should be noted that SM has no anti-duty and all acute and chronic phase treatments are supportive and there is no antidote factor for SM at the time of

exposure [11]. In general, studies conducted on the patients in the acute phase indicate that after major conflict in the eyes, skin and lungs; it might involve the endocrine system complications, blood cells and neuromuscular system [12]. Complications caused by SM continue in the long term and can even cause more damage to some tissues or even cause new complications in other body systems. Studies show that although eyes, skin and lungs of patients are involved in the chronic phase, the highest complication in the long term is associated with the pulmonary complications in patients and it is believed that in SM chemical patients after the Iraqi war against Iran, about 30 thousand people still suffer from pulmonary complications [13-14].

Pulmonary complications caused by SM

As was mentioned the highest damage observed in patients exposed to SM is pulmonary and this injury not only in the acute phase but also in the long-term has the highest prevalence among these patients and it is necessary to evaluate all patients exposed to mustard gas in terms of pulmonary complications. Since there are different symptoms among the patients exposed to mustard gas in acute and chronic phases, first the pulmonary complications in the acute phase and then the chronic phase are presented.

Pulmonary complications caused by SM in the acute phase

Obviously, in the pursuit of toxic effects of various substances, including SM, the exposure dose and its duration play the fundamental role in the development of clinical symptoms and complications. Unfortunately, studies conducted on the patients exposed to mustard gas have not discussed the dose and duration of exposure in the acute phase accurately. But, clinical symptoms of people after exposure to SM start with irritation of the nose and sinuses in the mild doses to the runny nose and pain at higher doses and even irritation of the airways and bronchial engagement in very high doses [15].In fact, with increasing doses of SM the increased symptoms and breathlessness, cough, bloody sputum and involvement of the lower respiratory tract are observed [16]. Also bronchopneumonia caused by airway infection occurs less than two days after exposure and even lead to death in less than a month [17,18].Of course the studies conducted on the acute phase of these patients have not mentioned significant details about the clinical symptoms of these patients and unfortunately the lack of access, advanced diagnostic devices and the absence of adequate conditions for examination and more analyses during the war have deprived us about more information about acute phase pulmonary complications.

Pulmonary complications caused by SM in chronic phase

Long-term complications of SM include a wide range of symptoms in the tissues and body organs but the most common damage is respiratory complication [10]. In fact, respiratory complications in patients exposed to SM have been associated with long-term symptoms and these symptoms add to the intensity of the complication. In other words, long-term pulmonary effects in these patients are after the direct effect of SM on the patient's lungs and on the other hand following the complications, the changes occurred in patients' bodies lead to increased symptoms and complications. It should be noted that it is possible that a patient after exposure to SM has no clinical symptom but has incurred pulmonary injuries which is observed by more specialized tests and examinations [19-21].

The mentioned clinical symptoms in the studies of SM pulmonary patients indicate that chronic cough is the most complaint among these patients. Three symptoms of cough, phlegm and shortness of breath were observed in more than 80% of Iranian veterans three years after the exposure [22]. Bloody sputum, feeling of tightness in the chest and shortness of breath over nights are among common symptoms; also the main respiratory symptoms including generalized wheezing, rale (crackle), decreased breath sounds and cyanosis(23). Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1 / FVC (FEV1%) may be lower than the non-exposed healthy subjects as well as the chemical injured veterans that have used the mask at the time of attack [24]. Apparently FEV1 is reduced by 50 mL/year [25].

Different diagnoses are presented in the case of long-term pulmonary complication in patients exposed to SM and the important thing is that the treatment of these patients depends on the diagnosis of the disease in these people. In fact, like other pulmonary inhalation poisonings, the most common complication is bronchiolitis and bronchiolitis is proven in these patients but other forms of lung disease and complications have been reported in these patients. Similarity between the patients exposed to SM and chronic obstructive pulmonary disease (COPD) is addressed in the studies and this result helps to follow up the treatment and manage these patients. Therefore, learning about COPD and identifying its similarities and differences of the chemical and COPD patients can provide the better treatment for these patients.

Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) has defined this disease as follows: "a state of disease by airflow limitation [expiration] that is not fully reversible [with bronchodilation]. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of lungs to harmful particles or gases [26]." Spirometric ventilation values include Forced Expired Volume in 1

second (FEV1) and Forced Vital Capacity (FVC). If after the maximum bronchodilation FEV1/FVC ratio is less than 70%, it indicates airflow limitation. GOLD has classified the COPD severity into the stage 1 (FEV1 ≥ anticipated 80%), stage 2 (FEV1 = anticipated 50-79%), stage 3 (FEV1 = anticipated 30-49%) and stage 4 (FEV1 < anticipated 30%) [27]. Right now there are substantial evidences implicating the involvement of neutrophils as the dominant effective cell based on their damaging effects; also it is possible that there is a genetic predisposition to susceptibility to COPD, however the specific genes are not identified yet and the existing evidences are contradictory [28-29]. Although COPD is primarily a lung disorder, it is associated with a variety of systemic effects and coexisting conditions and the most common coexisting conditions include ischemic heart disease, osteoporosis, cachexia, chronic kidney disease and lung cancer as well as cognitive and emotional symptoms such as depression [30]. The common factor between all coexisting diseases is the systemic inflammation. Increased plasma levels of pro-inflammatory cytokines (TNFα, 6- IL and 8- IL), adipokines (leptin, ghrelin) and acute phase proteins (C-reactive protein (CRP), fibrinogen) can be seen in many of these diseases and all independent risk factors are associated with systemic inflammation [31]. Right now there is no drug therapy that prevents the disease progression or exacerbations or mortality significantly. For years bronchodilators have been the best COPD treatment and the only significant advancement only in the treatment has been creating long-acting –β2 agonists [32].

The reason for COPD detailed explanation to understand the similarities between the pulmonary patients exposed to SM and COPD patients. In fact, in chemical patients as well as patients with COPD there is irreversible airflow limitation. In these patients there are changes in blood cells especially in white blood cells and neutrophils and systemic inflammation and systemic changes with other comorbidities are observed. Changes in inflammatory factors such as interleukins, metalloprotease matrix and C-reactive protein are not only changed locally in the lung but also changed in patients' blood circulation system [33-36] and these systemic inflammatory changes have led to other complications such as cardiovascular disease [37]. Meanwhile the chemical pulmonary patients have never has an effective medicine so far and they only rely on bronchodilators and long-acting –β2 agonists such as COPD patients [38-39]. However, for several years a type of COPD known as Mustard lung is defined in these patients that indicate the COPD in these patients associated with decreased lung capacity and systemic and inflammatory pathology [40].

CONCLUSION

SM is a chemical warfare agent with vesicant and alkylating symptoms that in addition to acute complications acute complications that has the highest prevalence in patients' lung, has long-term chronic symptoms that appear in the lungs more than the rest of organs. Over time in addition to the direst effects of SM, changes in the patient's body lead to the spread of disease, the incidence of systemic effects and diseases such as cardiovascular disease. Although SM pulmonary patients' treatment is based on bronchodilators and long-acting –β2 agonists, paying attention to the comorbidities with prior systemic changes in these patients is a reason for the need to change treatment strategies of these patients with systemic and extrapulmonary therapy.

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