Reviews

Long-term effects of mustard gas on respiratory system of Iranian veterans after Iraq-Iran war: a review

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【**Abstract**】To review long-term respiratory effects of mustard gas on Iranian veterans having undergone Iraq-Iran war. Electronic databases of Scopus, Medline, ISI, IranMedex, and Irandoc sites were searched. We accepted articles published in scientific journals as a quality criterion. The main pathogenic factors are free radical mediators. Prevalence of pulmonary involvement is approximately 42.5%. The most common complaints are cough and dyspnea. Major respiratory complications are chronic obstructive pulmonary disease, bronchiectasis, and asthma. Spirometry results can reveal restrictive and obstructive pulmonary disease. Plain chest X-ray does not help in about 50% of lung diseases. High-resolution CT of the lung is the best modality for diagnostic assessment of parenchymal lung and bronchi. There is no definite curative treatment for mustard lung. The effective treatment regimens consist of oxygen administration, use of vaporized moist air, respiratory physiotherapy, administration of mucolytic agents, bronchodilators, corticosteroids, and long-acting beta-2 agonists, antioxidants, surfactant, magnesium ions, therapeutic bronchoscopy, laser therapy, placement of respiratory stents, early tracheostomy in laryngospasm, and ultimately lung transplantation. High-resolution CT of the lung is the most accurate modality for the evaluation of the lung parenchyma and bronchi. The treatment efficacy of patients exposed to mustard gas depends on patient conditions (acute or chronic, upper or lower respiratory tract involvement). There are various treatment protocols, but unfortunately none of them is definitely curable.

Key words: ***Lung injury; Chemical warfare; Mustard gas***

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During the war between Iran and Iraq (1980-1988), more than 1 000 tons of mustard gas against Iranian forces was used. The attacks left more than 50 000 injured people.[1] Over 22 years after the war ended, several studies have been done on the survivors, in which each of them has focused on a particular aspect of the subject. Khateri et al[2] in one study conducted on 34 000 victims of chemical warfare and reported that 42.5% of the victims (14 450 patients) were suffering from respiratory problems. According to intensity of the lesions, the problems were divided into 3 categories. Among them, 12 580 persons (37%) were mild lesions, 1 530 (4.5%) were moderate and 340 (1%) were in a severe status. In another study, Emad and Rezaian[3] reported the prevalence of respiratory complications. Among 197 injured patients 10 years after exposure, the results were as follows: bronchitis, 58.80% cases; pulmonary fibrosis, 12.18%; asthma, 10.67%; airway narrowing due to granulation tissue, 9.64%; and bronchiectasis, 8.60%. The main purpose of this study was to review the long-term effects of mustard gas on respiratory system in Iranian veterans related to Iraq-Iran war.

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Sources

For gathering information, electronic databases, including Scopus, Medline, ISI, IranMedex, and Irandoc sites were used. We used the following key words in national and international sources: (chemical war) OR (chemical warfare) OR (chemical combat) OR (chemical

fight) OR (sulfur mustard). About the quality of articles, added evaluations were not performed and we accepted only publication of the articles in scientific journals as a quality criterion.

Titles and abstracts were assessed by two expert persons separately and unrelated reports were excluded from the study list. Then subjects were classified and used.

Predisposing factors

Zarchi et al[4], in a retrospective cohort study on 1 337 soldiers exposed to mustard gas, have determined the association between some factors and long-term pulmonary complications. These factors include: age, smoking, frequencies of the exposure and use of masks. They have revealed that the cumulative incidence rate of pulmonary complications is 31.6% and determined that when the age increases, the risk of pulmonary complications significantly rises. So the risk is 0.75 per thousand in the first year after exposure and 9.76 per thousand in the seventh year. They have also reported that the risk of pulmonary complications is reduced with the use of masks and it appears that the gas concentration, duration of exposure and high environmental temperature also affect the incidence and severity of the diseases. Smoking, with unknown reasons, is not relevant to higher incidence of pulmonary complications. Ghanei et al[5] in one study have stated that the effects of sulfur mustard are not dependent on the severity of exposure.

Pathology

One of the pathological factors in pathogenesis of pulmonary diseases due to mustard gas effects is free mediated radicals.[6] Sulfur mustard, by free mediated radicals and other factors, exerts their effects on the airways and the lung parenchyma. When it is absorbed from the respiratory system, it causes inflammation of the tracheobronchial epithelium with severe leukocyte infiltration, alveolar hemorrhage with thrombus formation, and vacuolization of the lung parenchymal cells.[7] Some pathological changes that develop after exposure to mustard gas are asthma, chronic obstructive pulmonary disease (COPD), and chronic bronchitis.

The most striking feature of asthma is airway hyperresponsiveness against methacholine and other stimuli. In addition to asthma, airway hyperresponsiveness may be seen in COPD, chronic bronchitis, smoking as well as chemical victims.[8,9] Mirsadraee et al[10] in one study conducted on 15 chemical victims (cases) and 15 normal volunteers (controls). They concluded that airway hyperresponsiveness against methacholine among most of chronic chemical victims increass and this might be related to chronic inflammation or irreversible airway changes. Airway hyperresponsiveness phenomenon can cause burn-like effect (acid-like burning sensation) on the vocal cords and this phenomenon can cause laryngitis and hoarseness. Granulation tissue may also increase narrowing of the airways.[11] Aghanouri et al[12] in one study conducted on 126 veterans with chronic lung disease and observed that transforming growth factor type B1 (TGF-B1) in the bronchoalveolar lavage is increased. So theoretically impaired lung TGF-B1 can facilitate lung fibrosis.

Signs and symptoms

Mustard gas has both acute (short term) and chronic (long term) effects on the respiratory system.[13-15] Usually after exposure to mustard gas, acute symptoms such as irritated throat, sore threat, increased nasal discharge, sneezing, and discomfort in the nose and sinuses, and in more severe exposures, dry cough and tracheobronchitis will appear. Other acute upper respiratory system findings are hoarseness, dry cough, and bleeding from the nasal mucosa, which are the early poisoning symptoms following mustard gas exprosure.[16]

Symptoms of acute lower respiratory involvement usually include cough, dyspnea and burning sensation in the chest beyond the sternum, hemoptysis, airway inflammation, and some degrees of pneumonia and even acute respiratory failure.[17]

Over the time, these symptoms gradually become chronic. For example in Ghanei et al's study[18], the main symptoms are chronic cough, dyspnea and sputum. In Emad et al's study[19], chest pain, esophagogastric reflux, hemoptysis, and chronic bronchitis are seen in 59% out of 197 people. Other chronic signs may be night waking, cyanosis, decreased lung voice, and clubbing. These findings are obtained from the studies carried out on 287 veterans from Kashan and Isfahan[16], 34 chemical veterans[18], and 408 injured peple.[20]

Upper respiratory tract complications

Early complications Usually several hours after exposure, tracheobronchitis occurs.[20] Ferietag et al[11]

in one study conducted on 21 Iranian soldiers injured with mustard gas and showed that early lesions of the lung include hemorrhagic inflammation in tracheobronchial trees.

Late complications In one study on the injured survivors of World War I (1914-1918), the most common pattern of pulmonary function tests (PFT) was obstructive pattern and the most important long-term complications were bronchitis and emphysema. Secondary complications were chronic infections and purulent bronchitis.[11]

Overall, long-term effects of mustard gas on the respiratory system include dyspnea, irritant cough, and frequent respiratory infections. These effects are mostly associated with complications such as obstructive pulmonary disease, chronic bronchitis, asthma, bronchiolitis, bronchiectasis, COPD and narrowing of large respiratory ways.[17-20]

A few weeks after acute exposure to sulfur mustard, the severity of acute disease drops, but the symptoms continue and gradually convert into the chronic form of disease, i.e. COPD.This condition has a progressive trend and after several years it will convert to a typical bronchiolitis. According to WHO reports, one of the main respiratory complications among Iranian chemical victims is laryngitis.

Akhavan et al[21] have studied laryngeal abnormal findings in 50 cases 20 years after acute chemical exposure. In this study, they evaluated the patient's speech and found some degrees of dysphonia including harshness in 14% cases, hoarseness in 32% and more often chronic laryngitis. According to this study, vocal cord paralysis may result in long neurotoxic effects of mustard, while synechia and vocal cord nodules may be caused by infections of the larynx and bronchi. In addition, there may be false vocal cords hypertrophy due to inability to use the edematous true vocal cords, and thus dysphonia occurs. All these synptoms approve the presence of chronic laryngitis. According to several reports, chronic bronchitis is the most common delayed respiratory disease among more than 50% of Iranians who have been exposed to mustard gas during Iraq-Iran war. [21] According to another report, the most common complication in veterans 15 years after exposure is bronchiolitis and airways hypersensitivity can be the first manifestation of this disease.[22]

In some victims exposuring to mustard gas, tracheobronchomalasia will appear after 15 years.[23] In a series of bronchoscopies conducted on patients with chronic cough, tracheobronchomalasia is observed in 14% of cases.[23] Tracheobronchomalacia is usually due to weakness in the wall of the airway cartilages and supportive areas, and the central airways may develop severe collapse. Tracheobronchomalasia occurs in two forms: primary and secondary. Primary type causes stridor and lung infections in children, and in the second type, bronchial involvement occurs. Extensive panbronchiolitis may play a role in exacerbation of tracheobronchomalasia.[20]

Lower respiratory tract complications

Respiratory failure, secondary pneumonia and occasionally hemorrhagic pulmonary edema are usually due to fatal exposures.[23]

Lung complications are the most major effects and also the most causes of late complaints in mustard gas-exposed people. Its prevalence in various studies is 15% to 27%.[6] Pulmonary complications of mustard gas are in the lowest rate in the first year and increases with the time. Zarchi et al[4] in one study conducted on 1 337 fighters and stated that 31.6% of pulmonary complications occur in delayed phases. The major pulmonary complications in mustard gas victims manifested as COPD, bronchiectasis, asthma, and narrowing of major airways.[21]

Late effects of mustard gas in the lungs is dependent on the gas concentration and duration of contact.[6] When sulfur mustard particles in the size of 1 to 5 microns reach to small bronchiolus, their effects will occur. One study on mustard gas victims observed that persistent pulmonary complications occur in 78% of cases as asthma-like symptoms. We can point to the other late effects of gene mutations for developing cancer, especially laryngeal and pulmonary cancers.[24] Epidemiological studies clearly show that mustard gas causes lung cancer.[25] In a survey conducted on soldiers who implicated in sulfur mustard exposure in World War I, it was found that the relative risk for lung cancer was 1.3 and the death rate from lung cancer was 400% more than the normal population.[26] In another study conducted

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on the workers who worked in the mustard gas production line in the years 1929 to 1945, the upper airway cancer was 37 times over the normal population.[27] However, It should be noted that these workers have regular and long time contact with mustard gas, but soldiers often encounter in one dose with higher amounts of gas.

There is no relationship between lung cancer and hemoptysis. The main symptoms associated with cancers and respiratory infections will appear at least 16 to 20 years after the first exposure to mustard gas.

Sulfur mustard depending on the concentration and duration of exposure can also cause respiratory failure.[24] Roushan et al[28] in their study conducted on 266 support troops and found that 15-18 years after exposure, the incidence of bronchioltis was 13.1% , fibrosis 2.3%, COPD 17.6%, asthma 16.6%, and chronic bronchitis 2.3%.

Diagnosis

Plain chest X-ray By chest X-ray, we can observe obstructive lung disease findings, such as hyperinflation, air retention, increased marking around the bronchioles (bronchial wall thickness) and bronchiectasis.[6,13,18] Multiple studies have showed that plain radiographs in symptomatic patients are normal in 17%-54% of cases.[6,16,29] As we see, the range of reported normal and abnormal findings on chest radiographs of the victims is very wide. Therefore, plain radiography is a nonspecific diagnostic measure and does not help us too much in diagnosis of the respiratory problems in exposed people.

Spirometry One of the best ways for diagnosis is to assess PFT. The most common PFT pattern is an obstructive pattern.[14] In a study on 202 chemical war veterans, spirometry results showed that 142 patients (70%) were abnormal and 60 (30%) were normal. Abnormal spirometry results included obstructive pattern in 43% of cases, restrictive views in 16% and a combination of obstructive and restrictive forms in 10%. These abnormal findings were more evident after 7 years from their exposure, but between abnormal spirometry findings and the time of injury is not a significant relationship. The likelihood of abnormal spirometry caused by obstructive and restrictive lesions is more frequently seen in patients with persistent dyspnea than those with intermittent dyspnea.[16]

High-resolution CT High-resolution CT is the most accurate modality for diagnostic evaluation of bronchial and lung parenchyma.[30] Ghanei et al[20], in a study on 300 patients exposed to mustard gas, found the evidences of tracheal collapse in 13 cases (4.3%) and air retention in 137 cases (45.7%). A significant correlation was found between the presence and severity of air retention and tracheal collapse in high-resolution CT. Bagheri et al[30]conducted a study on 50 cases of chemical war victims and found at least one abnormal point in all the patients by high-resolution CT, while these findings were observed in 80% of cases on plain chest X-rays. In this study, the most common high-resolution CT finding was bronchial wall thickening (bronchitis and peribronchitis) in 100% cases, and other important findings were interstitial lung disease in 80% of cases, bronchiectasis in 26%, and emphysema in 24%; whereas nodular pulmonary involvement, pulmonary masses, traction bronchiectasis and lung parenchymal calcification were not seen. It is concluded that lung high-resolution CT is much more sensitive than plain chest X-rays. Among the exposed support troops 15 to 18 years after exposure, the normal view on high-resolution CT was 64% of the cases, partial retention of air 17%, and significant air retention 12%.[28]

Bronchoscopy Bronchoscopy often shows bronchial trees full of the pus, from which staphylococcus aureus, haemophilus influenza and pseudomonas aeroginosa are isolated. Antibiotic therapy does not inhibit the purulent sputum production because the function of respiratory cilia is destroyed. Mucus secretions are so thick and sticky that even the young victims are unable to pass it with an effective cough. In many patients, hypoxia and increased respiratory rate (hypercapnea) occur. In histological study, there is tissue necrosis and nonspecific granulation in bronchial tree.[11] Eosinophilia in bronchoalveolar lavage may indicate the presence of asthma as one of the main effects of chemical exposure in the victims.[9] Ghanei et al[5], in a study on 15 chemical warfare victims with chronic respiratory disease who exposed to mustard gas at least 17 years before the study, concluded that lung surgical biopsy in the diagnosis of difficult cases, such as symptomatic constrictive or obstructive bronchiolitis in which high-resolution CT and PFT are normal may be helpful.

Other diagnostic measures Rouhi and Ganji[31] have also performed echocardiography and arterial blood

gas analysis for patients and the evaluation results suggest that the right ventricular pressure is significantly higher than normal but not significant changes in left ventricular pressure. The results of arterial blood gases analysis are normal too.

Overall, in the current time, perhaps the most helpful diagnostic tests for veterans are spirometry and lung high-resolution CT.

Treatment

There is no definite curative treatment for mustard lung, but effective treatment is available,[18] consisting of repeated (periodic) clinical examinations[29], oxygen administration, use of vaporized moist air, respiratory physiotherapy,[17] administration of mucolytic agents like acetylcysteine, bronchodilators such as salbutamol, ipratropium bromide[18], oral corticosteroids, inhaled corticosteroids, interferon inhaled corticosteroids and long-acting beta-2 agonists[18,32], antioxidants[33,34], surfactant[35], magnesium ions[1], therapeutic bronchoscopy, laser therapy, placement of respiratory stents[11], ICU admission depending on the patient's condition[17], early tracheostomy in laryngospasm and steridor and hoarseness in critical patients[36], ultimately lung transplantation[11].

Conclusion

According to our study on Iranian veterans of Iraq-Iran war, the incidence of pulmonary lesions among Iranian veterans is approximately 42.5%. Age, exposure frequency, exposure duration, gas concentration and amount, high temperature of environment and the use of masks are the factors influencing the results. The most common complaints are cough and dyspnea. Major pulmonary complications among mustard gas victims are COPD, bronchiectasis, asthma, and narrowing of the large airways. Spirometry results show restrictive and obstructive lung disease. Plain chest X-ray is not helpful for diagnosis in about 50% of cases. Currently, high-resolution CT of the lung is the most accurate modality for the evaluation of the lung parenchyma and bronchi. The treatment efficacy of respiratory patients exposed to mustard gas depends on patient conditions (acute or chronic, upper or lower respiratory tract involvement). There are various treatments, but unfortunately none of them is definitely curable.

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