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EVALUATION OF 17 PATIENTS SEVERELY INJURED WITH SULFUR MUSTARD

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ABSTRACT

In this article, we evaluated 17 Iranian soldiers who were exposed to mustard gas utilized by the Iraqi forces in the war fronts. Their clinical symptoms and signs, laboratory tests, and other parameters were carefully assessed, an attempt was made to identify a finding of prognostic significance, and patients who recovered from the acute phase were followed to determine possible long-term effects. Our results, as well as a general review, are presented.

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INTRODUCTION

Unfortunately, chemical, microbiological and nuclear warfare agents have been used in war in the past, but to date nowhere have chemical agents been used as extensively as they have been used by Iraqi forces against the Iranian combatants, despite all international conventions and regulations.

The chemical agents which are used in wars are of different nature. One of the agents used by Iraq extensively on the battlefronts and even against civilian targets (for instance, the city of Sar-Dasht), is sulfur mustard.

Sulfur mustard, or mustard gas, is an alkylating agent with a $Cl\text{-}CH_2\text{-}CH_2\text{-}S\text{-}CH_2\text{-}CH_2\text{-}Cl$ formula. This dichloroethyl sulfide is vesicant and similar to other alkylating agents, undergoes strong electrophilic chemical reactions through the formation of carbonium ion intermediates, or transition complexes with target molecules. These reactions result in the formation of covalent linkages (alkylation) with various nucleophilic substances, such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl and imidazole groups. The cytotoxic effect and other effects of alkylating agents are directly related to the alkylation of components of DNA, especially the 7-nitrogen atom of guanine, but other atoms of purine and pyrimidine bases of DNA and phosphate atoms of DNA chains and the proteins associated with DNA may be alkylated to lesser degrees.[1]

This agent can produce dermatological, ophthalmological, gastrointestinal, and respiratory lesions upon direct contact with these tissues in the form of either a liquid or a vapor; as well as systemic lesions (bone marrow, reproductive and nervous systems) when absorbed through skin, respiratory or gastrointestinal tracts. Urinary tract lesions may also result during the excretion of the agent or its metabolites.

In this article, Iranian fighters (who were quite healthy prior to their engagement in the war) suffered dermatological and ophthalmological lesions, in addition to severe respiratory distress resulting from inhalation of gas. They were hospitalized at Shahid Rajai Heart Hospital in Tehran, from February, 1985 to January, 1986. They are being evaluated here to determine their clinical symptoms and signs, laboratory abnormalities, and to search for parameters to predict the prognosis of patients with these symptoms and to follow those who recover from the acute phase.

During the period mentioned above, because of the availability of facilities (particularly for respiratory assistance), Shahid Rajai Heart Hospital was elected as the referral center for those needing assisted ventilation and intensive respiratory care. (In other words, only those who were critically ill were transferred to our department).

PATIENTS AND METHODS

Most of the patients on admission, because of their critical condition, were unable to give the exact date upon which they came in contact with the chemical agent. However, according to their medical records, all were transferred from other institutions one to four

TABLE I

No	AGE	DAYS OF HOSPITALIZATION	DAYS ON RESPIRATOR	OUTCOME
1	21	35	13	DISCHARGED
2	21	35	15	DISCHARGED
3	16	1	1	DIED
4	21	3	2	DIED
5	19	›1	›1	DIED
6	19	8	8	DIED
7	21	13	9	DIED
8	21	12	7	DIED
9	21	7	6	DIED
10	30	8	8	DIED
11	20	5	4	DIED
12	24	4	4	DIED
13	19	5	3	DIED
14	18	6	6	DIED
15	20	6	2	DIED
16	20	6	5	DIED
17	18	35	13	DISCHARGED

* SEE THE TEXT

days after exposure.

The age of the patients ranged from 18 to 30 years, with a mean age of 21.7 years. All patients had extensive dermal erythema, large blisters, keratitis and severe conjunctivitis associated with blepharospasm and photophobia, and severe mucous lesions of the upper respiratory tract and mouth. All patients were in respiratory distress and needed ventilatory assistance with volume-limited respirators such as MA1 either on admission or at most five days following hospitalization (Table I).

RESULTS

1) 14 of the 17 victims expired despite all efforts during the first 13 days after admission. Of these, 13 patients died while on respirators; one patient expired one day after he was extubated and transferred to another hospital (Table II). The three patients who survived were intubated for 13-15 days and stayed in the hospital for 35 days (Table II, see also Followup).

2) Blood pressure in patients was usually normal until the time of demise, at which time they became hypotensive, not responding to vasopressors.

3) Temperature fluctuated in most patients; some had normal temperautres and some had temperatures as high as 40.5° centigrade

4) Nasal, oral, and respiratory tract secretions were abundant.

5) All patients had sinus tachycardia with occasional atrial or ventricular ectopic beats, and had sinus bradycardia followed by stand-still at the time of death, not responding to different medications.

6) Cultures from blood, skin, urine and respiratory tract were usually negative.

TABLE II

DAYS OF HOSPITALIZATION	1-3	4-6	7-9	10-12	›13
NO.OF PATIENTS	3	6	2	1	4*

* Of these 4 patients who were hospitalized for 13 days or more, one died and the other 3 were discharged.

7) Some patients became comatose despite having no apparent blood metabolic derangement.

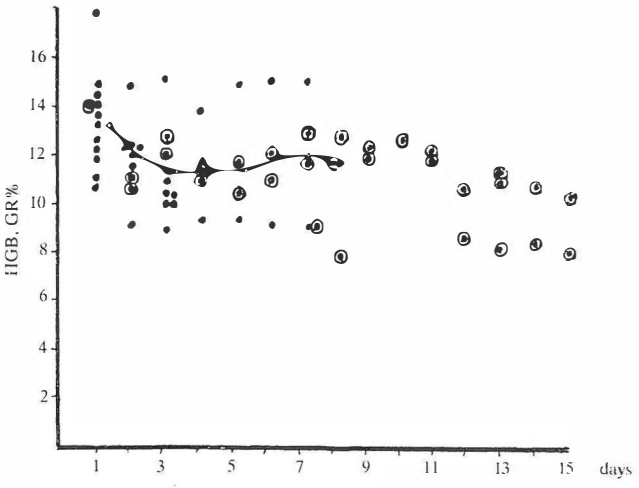
8) There was no relation between the extent of skin burn and blisters and the patient's outcome. The three patients who survived had extensive skin lesions. Among those who died were some who had limited skin involvement, confined to the head and neck.

9) All patients had severe conjunctivitis, keratitis and photophobia. The three patients who survived had keratitis for about six months.

10) Despite severe respiratory distress, some patients showed no remarkable changes on chest roentgenogram and in some, patchy infiltrates were seen. In one patient who repeatedly had atelectasis of the right lung and underwent bronchoscopy twice, the X-ray changes were remarkable. This patient showed extensive burns and sloughing of bronchial epithelium, and after removal of the necrotic epithelium, atelectasis continued to recur repeatedly.

11) Figures 1-12 show different parameters obtained from Hgb, WBC, percentage of polymorphonuclear cells (PMN) and lymphocytes, platelet count, arterial partial pressure of oxygen, CO_2, total bicarbonate, base excess and pH.

The levels of hemoglobin were not predictive of the patients' outcome (Figure 1). Indeed, the three pa-



• Patients who died
⊙ Patients who survived

Figure 1

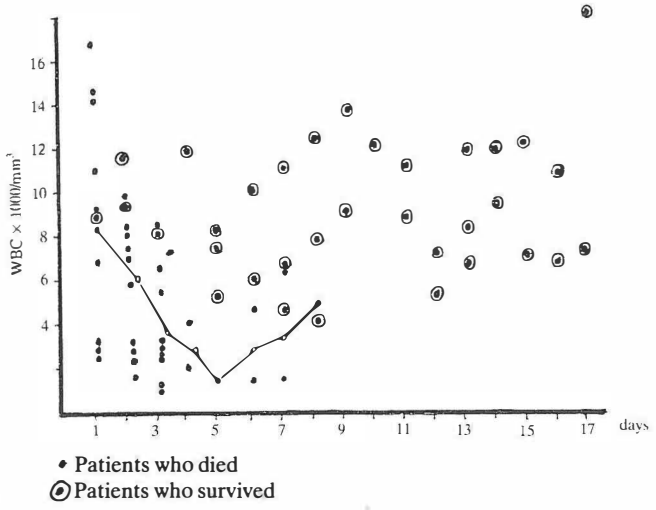


Figure 2

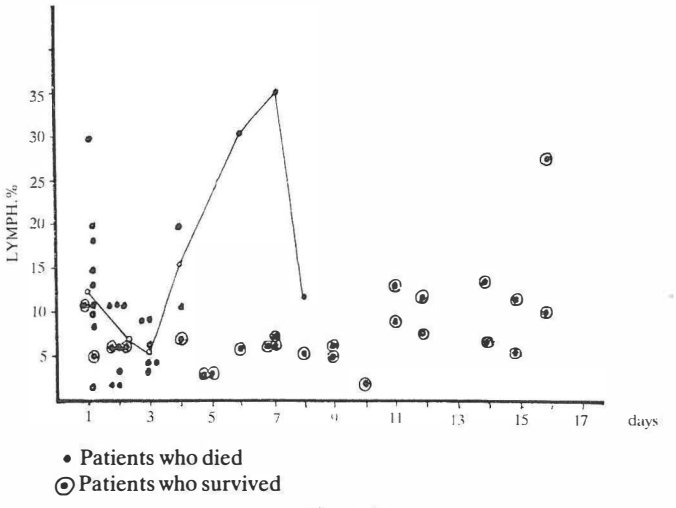


Figure 4

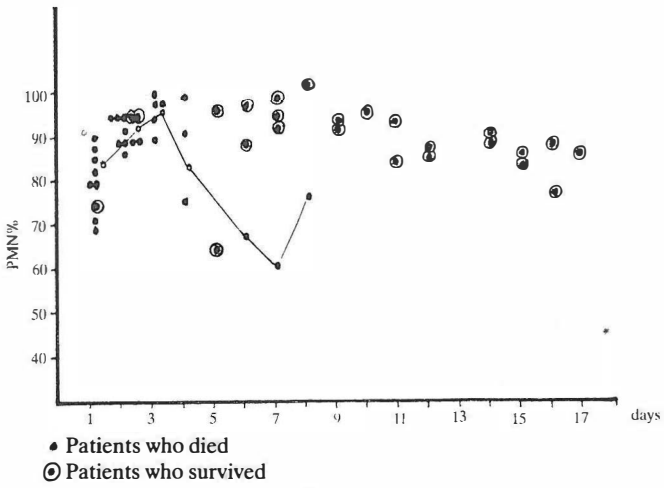


Figure 3

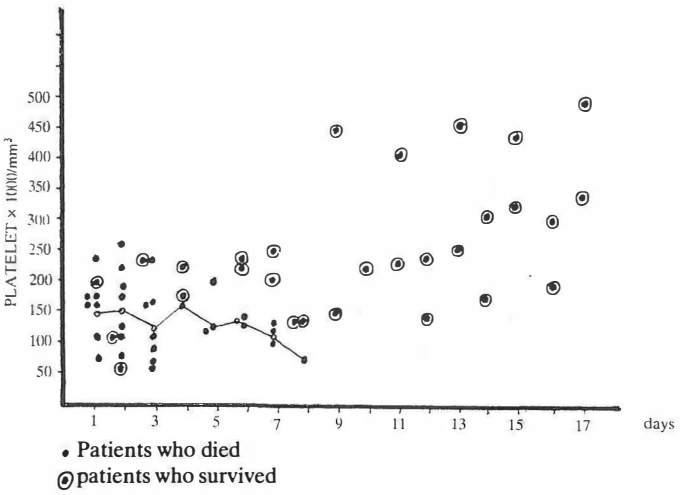


Figure 5

tients who survived had lower levels of hemoglobin when compared to the others.

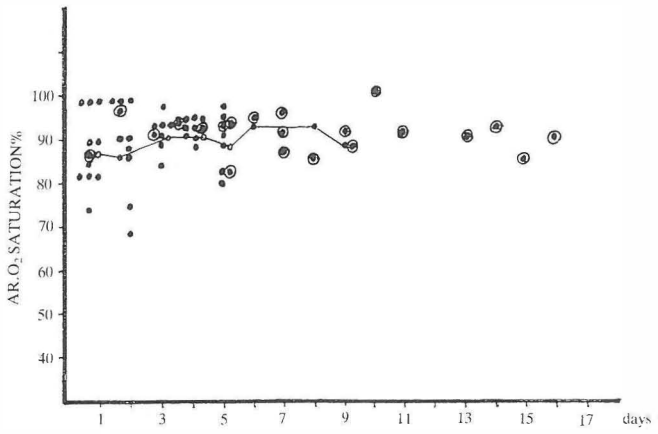
From Figures 2-4, it is obvious that the number of WBC,PMN and lymphocytes gradually decreased in most cases. There was no relation between the parameters and the patients' outcome. There were patients who had low white blood counts which increased after hospitalization, but nevertheless expired (Patient No.6, Table I). The decreases in WBC, PMN and lymphocytes were ominous signs, and no patient survived with a WBC count of less than 1400/cubic millimeter. Chronologically, the time of these declines coincided with deterioration of pulmonary status. After the first week of hospitalization, in those patients who survived, the WBC count waxed and waned every four to six days, and continued to do so until the time of discharge.

12) Figure 5 shows a rapid increase in the platelet count after the first week if the patient survived; in one of the patients it reached 480,000/cubic millimeter on the 13th day of hospitalization.

ESR was elevated in all patients. However, in two of three paitents who survived, it had been slightly lower on admission.

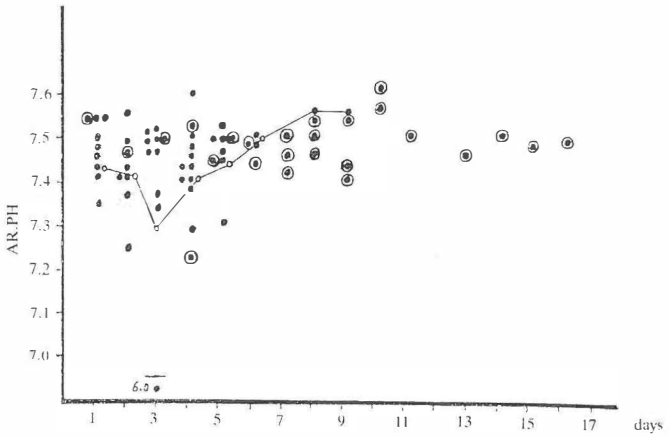
Figures 6-11 are for ABG's and pH which show no significant change on different days, but these results represent a mixture of different conditions of various patients who were on different percentages of oxygen either by mask, nasal cannula, volume-limited respirators with and without PEEP, and cannot be used as baseline levels for ventilation.

13) Other parameters such as eosinophil count,



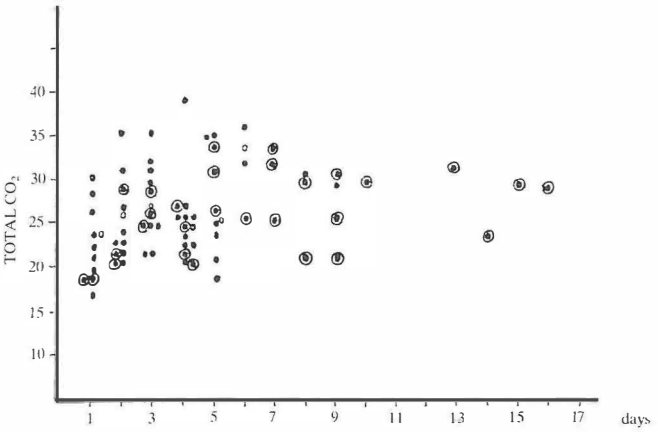
• Patients who died
⊙ Patients who survived

Figure 6



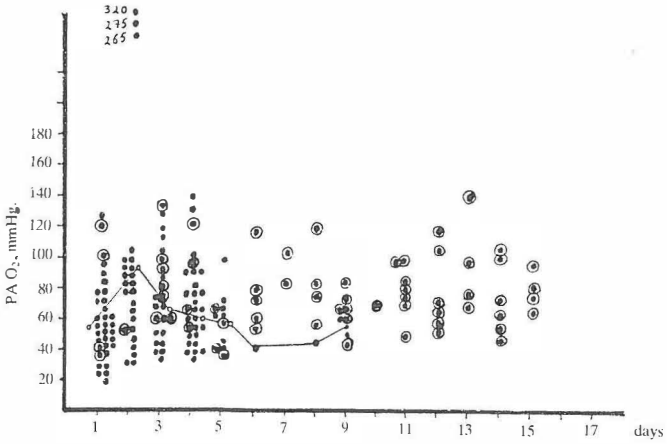
• Patients who died
⊙ Patients who survived

Figure 9



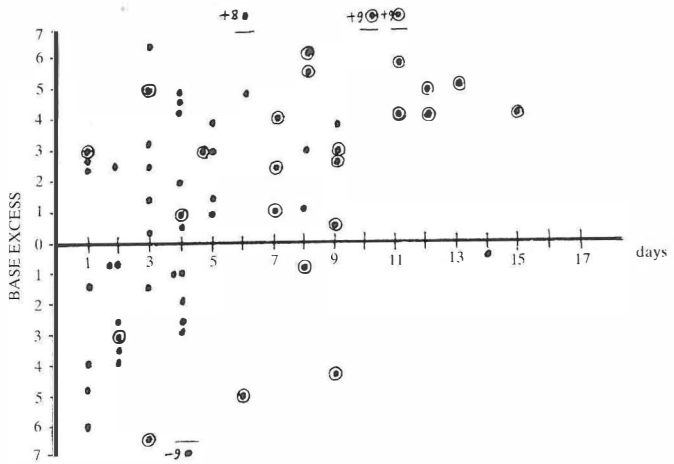
• Patients who died
⊙ Patients who survied

Figure 7



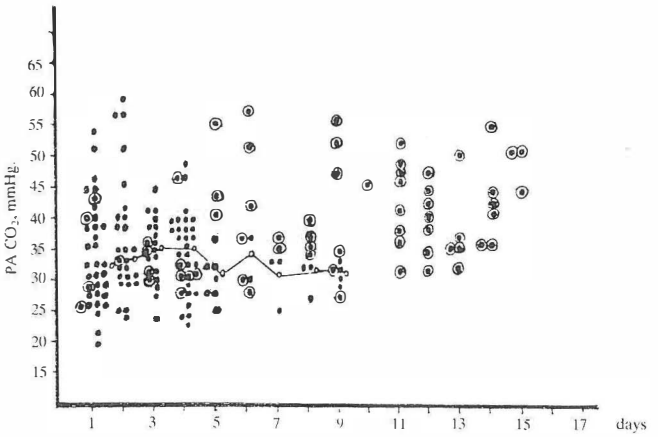
• Patients who died
⊙ Patients who survived

Figure 10



• Patients who died
⊙ Patients who survived

Figure 8



• Patients who died
⊙ Patients who surviven

Figure 11

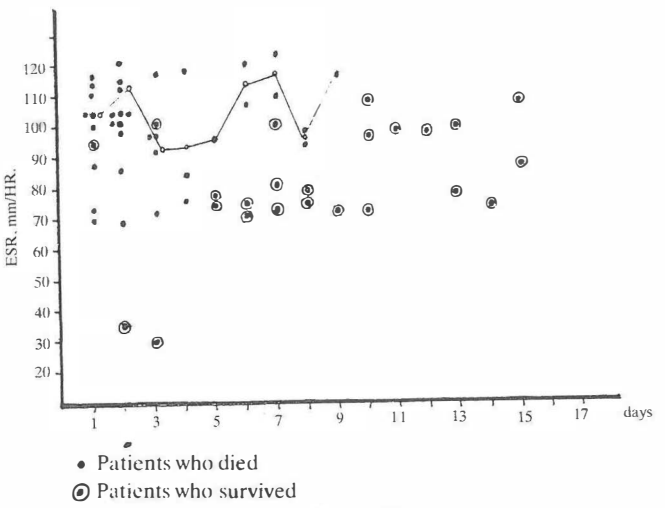


Figure 12

number of monocytes, reticulocyte count, BUN,uric acid, creatinine, Na,K and urinalysis were not of any predictive value.

14) Non of the patients died from infection.

Followup

The three patients who survived were thin, and have been followed for more than two years. All of them have severe chronic productive bronchitis, bronchospasm and pulmonary fibrosis. Their physical activities are limited because of their pulmonary condition. They produce about 100-200 cc of yellow to green, thick sputum and frequently have episodes of lower respiratory tract infection which show different pathogens including *Staphylococcus aureus* and *Pseudomonas*, requiring hospitalization and treatment with oral or parenteral antibiotics. In the interim, they receive bronchodilators and mucolytics. Chest X-rays show hyperinflated lungs, and signs of cor pulmonale have appeared with deviation of electrocardiographic axis to the right. Blood tests including hemoglobin, WBC and differential, reticulocytes, platelets, blood sugar, BUN, uric acid, ESR,Na,K and urinalysis are normal up to the present time.

DISCUSSION

There is either no or very little information in classic textbooks of medicine[2-4] and medical journals[5-6] regarding the clinical studies of chemical warfare agents. A search in the Abridged Index Medicus from January 1980 to March 1988 contains only one short report by Wulf, et al.,[5] and Wada, et al.,[6] regarding mustard gas. Recently there was a brief report in the JAMA[7] regarding protective measures against chemical warfare agents. Therefore, most of the recent clinical information is from Iran,[8,9] published mostly in the Persian language, and some in English.[10-12]

In the present report, of 17 victims who inhaled sulfur mustard, it is quite apparent that pulmonary involvement was the major determinant of the patient's outcome not the extent of dermal, gastrointestinal and ophthalmological lesions. The deterioration of pulmonary function occurs when the bone marrow function is suppressed, however the lethal factor is the patient's pulmonary status. Farhoodi from Mashad, Iran, also confirms this opinion.[8]

The three patients who survived the acute stage were thin and in the past two years have had progressive chronic bronchitis, bronchospasm and pulmonary fibrosis, interrupted by recurrent episodes of pulmonary infection with different pathogens. Signs of cor pulmonale are emerging in these patients.

In conclusion, those who are exposed to sulfur mustard and inhale the gas are at risk. If protective masks are used, the victims can survive despite transient bone marrow suppression, skin lesions and involvement of other systems. Those who survive the acute pulmonary problems will develop progressive chronic lung disease. So far, no teratogenic or carcinogenic effects have been observed in the three patients who have survived and have been followed for two years.

The patients heart rate, temperature, blood pressure and respiratory rate were checked every one to three hours, or more frequently as needed. Secretions of the nose, mouth, throat and trachea were suctioned regularly. If the patients had no tracheal tube, they were given heated humid air enriched with oxygen. When they were intubated, most of the patients were put on positive end-expiratory pressure (PEEP) ventilation. For skin lesions, silver sulfadiazin ointment was used twice daily; and cycloplegic drops, sulfacetamide solution and tetracycline ointment were used for eye involvement, according to the recommendation of ophthalmologists. All patients received intravenous glucose and saline solutions. Cephalothin (4-6 grams per day in divided doses), as well as one of the aminoglycosides (i.e. gentamicin, 180-240 mg per day in divided doses), were given as prophylaxis. Oral or intravenous aminophylline, salbutamol and mucolytics were given for bronchospasm and heavy secretions, respectively. Patients were given a high protein formula either by mouth or through nasogastric tube. Most of the patients received oral or intravenous cimetidine as well as oral antacids to prevent stress ulcers. Some patients received corticosteroids intravenously with no apparent benefit. When patients did not cooperate with the ventilators, muscle relaxants were given. Some patients received whole blood, packed cells, platelet concentrates, and white blood cell concentrates when needed.

Laboratory workup

All patients repeatedly had portable chest X-ray and arterial blood gas measurements. Measurements of hemoglobin, white blood cell count and differential were taken at least daily. Platelet and reticulocyte counts, blood urea nitrogen, creatinine, glucose, uric acid, sodium, potassium. erythrocyte sedimentation rate and urinalysis were also evaluated. If a patient's temperature was high, cultures were taken from blood, sputum, urine, and skin blisters.

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