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Diagnostic and Therapeutic Value of Short-Term Corticosteroid Therapy in Exacerbation of Mustard Gas-Induced Chronic Bronchitis

Mostafa Ghanei, Ali Reza Hosseini Khalili, Mohamad Javad Arab, Mojtaba Mojtahedzadeh, Jafar Aslani, Mahbob Lessan-Pezeshki, Yunes Panahi and Farshid Alaeddini

Baqiyatallah Medical Sciences University, Research Center of Chemical Injuries. Tehran, Iran

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Abstract: Chronic bronchitis is the most frequent late respiratory disease among Iranians exposed to mustard gas during the Iraq-Iran war. The aim of this study was to investigate efficacy of oral and intravenous corticosteroid therapy in improving lung function in mustard gas induced chronic bronchitis patients. 65 mustard gas-exposed chronic bronchitis patients, who were not responsive to standard treatments in exacerbation occasions, were randomly divided into two groups: an intravenous group (39 patients) receiving 500 mg intravenous methylprednisolone daily, and an oral group (26 patients) receiving 1 mg/kg oral prednisolone daily. Corticosteroid was tapered over the study period in both groups. Spirometery was performed on admission and on day 8 of therapy for assessment of effectiveness of therapy. There was significant improvement in spirometery indexes of both groups in approximately half of the patients over the study period. Furthermore, there was no difference between the pulse corticosteroid versus oral corticosteroid therapy in these patients. Since short-term corticosteroid therapy has a significant effect on lung function of almost fifty percent of patients with mustard gas-induced chronic bronchitis in exacerbation occasions, we suggest a short-term bolus steroid treatment to triage the patients into responders and non-responders for subsequent treatment.

Mustard agents are alkylating agents, which cause acute and chronic effects on different organs following exposure (Ghanei *et al*. 2003). Mustard gas was employed widely by Iraqi forces against Iranians during the Iraq-Iran war (UN 1986), which led to disorders among exposed individuals mainly in respiratory system, skin and eye (Khateri *et al*. 2003). Thousands of Iranians are suffering from late respiratory complications of mustard gas exposure (Khateri *et al*. 2003). Chronic bronchitis, asthma and bronchiolitis obliterans account for the most frequent long-term respiratory diseases in these patients (Emad & Rezaeian 1997; Thomason *et al*. 2003; Ghanei *et al*. 2004). Despite some differences between asthma and chronic bronchitis in pathological features causing air flow obstruction, some studies have shown that corticosteroids should be as effective in some exacerbated chronic bronchitis patients as they are in most asthmatic patients. There is some evidence suggesting that steroids are effective in acute exacerbation of chronic obstructive pulmonary disease and can increase the patients' FEV1 considerably more than non-treated patients with steroids (Albert *et al*. 1980; Murata *et al*. 1990; Davies *et al*. 1999; Niewoehner *et al*. 1999; Fein & Fein 2000). However, according to reports from some investigators, their use in exacerbation of chronic obstructive pulmonary disease remains controversial (Eliansson *et al*. 1986; Emerman *et al*. 1989).

The aim of this study was to investigate whether corticosteroid therapy would be effective in improving lung function of patients with mustard gas-induced chronic bronchitis or not. Furthermore, we wanted to determine if the effect of intravenous pulse corticosteroid therapy is superior to that of oral administration. The need for such research is emphasized by the fact that there is no investigation on the role of corticosteroids on exacerbation of mustard gas-induced chronic bronchitis.

Materials and Methods

Patients and groups. This randomized clinical trial study was carried out over a period of 6 months (between April 2002 and November 2002). One investigator took a detailed medical history and examined patients on admission.

Sixty-five patients with mustard gas-induced clinical history of chronic bronchitis, determined by the American Thoracic Society (ATS) criteria (ATS statement 1995; Pauwels *et al*. 2001), who were referred to the Emergency Department of the Sasan and Baqyatallah Hospitals (the referral centers for chemically injured cases) were enrolled in this study. The patients had documented exposure to mustard gas during the Iran-Iraq war, certified by veteran's affairs (Janbazan) organization. None of these patients had other causative factors such as cigarette smoking, occupational exposition and α-1-proteinase inhibitor deficiency which could be responsible for the development of chronic obstructive pulmonary disease.

According to documented FEV1 results, the patients did not respond to high dose of inhaled corticosteroids and bronchodilators. We excluded patients if they had personal or family history of asthma before the exposure to mustard gas (defined as episodic wheezing or dyspnoea that rapidly improved with treatment), atopy,

Author for correspondence: Mostafa Ghanei, Baqiyatallah Medical Sciences University, Research Center of Chemical Injuries, P.O. Box 19945-546, Mollasadra Street, Tehran, Iran (fax +98 (21) 8040106, e-mail m.ghanei@bmsu.ac.ir).

Table 1.

Response to treatment in both intravenous and oral groups.

	Complete response % (N)	Partial response % (N)	No response % (N)	Total
Intravenous group	15.4 (6)	28.2 (11)	56.4 (22)	39
Oral group	11.5 (3)	34.6 (9)	53.8 (14)	26
Total	13.8 (9)	30.8 (20)	55.4 (36)	100 (65)

allergic rhinitis, or nasal polyposis, uncontrolled left ventricular failure, or received intravenous or oral corticosteroids within a month before admission. Written consent was obtained from all participants. The study protocol was approved in the ethical committee of our research center.

Therapy. The 65 patients were randomly divided into two groups. Thirty-nine of the patients were enrolled in the intravenous group, and 26 into the oral group. The duration of the therapy was from the time of admission to the time of discharge (8 days). Both groups of patients received standard treatment on admission, including antibiotics (except those with antiinflammatory effect, e.g. macrolide) when indicated (the presence of increased dyspnoea, sputum volume and sputum purulence), Felixotide 2 puffs (125 mg/puff) twice a day, 2 puffs Servent (125 mg/puff) twice a day and controlled oxygen therapy.

The patients in the intravenous group received 500 mg methylprednisolone in 250 ml normal saline serum infusion over 2.5 hr. After 3 days the dose was reduced to 250 mg. Treatment continued until the 6th day. On days 7 and 8 they took 150 mg and 100 mg prednisolone, respectively. In the oral group, 1 mg/kg oral prednisolone per day was given instead of pulse methylprednisolone, and then the dosage was gradually reduced.

Treatment assessment. Spirometry was performed before and after inhalation of long acting β-2 agonist on admission and on day 8 of therapy, using a portable spirometer (Jaeger) according to the established ATS criteria (ATS Update 1987). This included measurements of forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and peak spirometry flow (PEF). Airflow measurements were compared with normal predicted values. During each session, a minimum of two forced flow-volume loops of good quality were obtained. If the FEV1 and FVC values were not within 10% of one another an additional measurement was taken. The flow-volume loop with the best FEV1 and FVC was used. Response to treatment was defined as >15% increase in FEV1, while no responsive treatment was defined as FEV1 rise less than 15%. Among patients responsive to corticosteroid therapy, those who reached normal spirometry were categorized as complete response, and those who did not reach normal PFT were categorized as partial response to therapy, while increase in PFT indices less than 15% was defined as unresponsiveness group.

Statistical analysis. Data from this study was analyzed using paired t-test to compare spirometry findings before and after treatment, and t-test to compare responsiveness to treatment in the intravenous and oral groups. A value of $P<0.05$ was taken to indicate statistical significance. All data are reported as mean±S.D.

Results

This study was conducted on 39 intravenously and 26 orally treated patients. The mean ages (±S.D.) were 38.4±9.9 years for the intravenous and 38.2±6.9 for the oral group. The average time lapse from injury was 14.2±2.1 and 14.5±3.2 years for the intravenous and oral groups respectively. Table 1 illustrates the overall response to corticosteroid in both the intravenous and oral groups. As can be seen, half of the patients showed complete or partial response, while the rest did not respond to corticosteroid therapy.

Nevertheless, the spirometry indices were not significantly different between the intravenous and oral groups before and after the therapy (table 2). This result is further confirmed by comparing the amount of change (improvement) in spirometry indices following the therapy between the intravenous and oral groups. As shown in table 3, from a statistical point of view, no priority has been seen for pulse corticosteroid therapy over the oral corticosteroid administration in exacerbation of chronic bronchitis.

Discussion

Since the latter half of the twentieth century, corticosteroids have been used to improve the airflow obstruction seen in acute deterioration of chronic obstructive pulmonary disease. However, this has been controversial, as some studies have demonstrated that corticosteroids can significantly improve the symptoms and lung function of patients within 12 hr of treatment (Niewoehner *et al*. 1999). Contradictory data suggest that corticosteroids do not improve the patients' lung function and symptoms (Emerman *et al*. 1989). The results of the present study show that short-term intravenous pulse or oral corticosteroid therapy has a statistically significant effect on the lung function of patients with mustard gas-induced chronic bronchitis in exacerbation occasions. However, there was no considerable difference between the two groups in the variation of spirometry indexes.

Table 2.

Comparison of PFT indices between the intravneous and oral groups, before and after therapy.

	Before treatment			After treatment		
	FVC	FEV1	PEF	FVC	FEV1	PEF
Intravenous group	67.4±9.9	50.2±18.4	50.0±22.3	76.2±14.6	59.0±18.7	55.7±19.8
Oral group	74.1±28.1	74.8±25.5	74.1±33.4	80.5±25.7	82.2±24.1	80.9±26.5

Table 3.

Comparison of changes (improvement) in PFT indexes between case and control groups.

	FVC (%)*	FEV1 (%)*	PEF (%)**
Intravenous group	19.5±33.2	25.9±45.6	26.9±66.3
Oral group	11.0±41.0	14.8±30.6	18.7±37.3

*P=0.3, **P=0.5.

On the other hand, after evaluation of the responsiveness to corticosteroid therapy in these patients, considerable diagnostic conclusions can be drawn. According to the results, complete and partial response to pulse and oral corticosteroid therapy was observed in 13.8% and 30.8% of the both groups respectively, while no response was seen in the rest of these patients (55.4%) in exacerbations of chronic bronchitis.

Previous studies have shown the presence of chronic bronchitis in the majority of patients exposed to mustard gas (Emad *et al*. 1997; Bijani & Moghadamnia 2002). In the present study, the different response can be attributed to accompanying pulmonary disorders, such as asthma (Emad *et al*. 1997) and bronchiolitis obliterans (Thomason *et al*. 2003; Ghanei *et al*. 2004) observed in mustard gas-exposed patients suffering from late respiratory complications of exposure.

It has been demonstrated that the inflammatory process in chronic bronchitis is considerably different from that in asthma, with different inflammatory cells, mediators, inflammatory effects and response to therapy. Airway inflammation in asthma, characterized by an eosinophilic inflammation affecting all the airways but not lung parenchyma, is linkedto airway hyperresponsiveness (Barnes 1996 & 2000). In chronic obstructive pulmonary disease, there is a predominantly neutrophilic inflammation in the airways (Keatings *et al*. 1997; Culpitt *et al*. 1999). Parenchymal destructionis an important irreversible feature which leads to airflow obstruction through dynamic compression. The eosinophilic inflammation inasthma is markedly suppressed by corticosteroids, but they have little or no appreciable effect on the inflammation in chronic obstructive pulmonary disease, consistent with the failure of long-term corticosteroids to alter the progression of the disease (Keatings *et al*. 1997; Culpitt *et al*. 1999). Therefore, complete response to corticosteroid treatment in 13.8% of our patients indicates the presence of an asthmatic pattern. These patients can be defined as having chronic asthmatic bronchitis, which was also pointed out in a previous study (Hosseini *et al*. 1999). Relative response in 30.8% of our patients can be attributed to airway hyperresponsiveness and bronchospasm which were previously observed in chronic obstructive pulmonary disease patients (Sohrabpour & Maleki 1988; Nefedov & Shergina 2000). As reported in a recently performed study, the presence of more than 25% air trapping in chest high resolution CT scans of a great number of mustard-exposed patients was considered suggestive for bronchiolitis obliterans (Ghanei *et al*. 2004). Accordingly, 50% failure in response to treatment may be attributable to the presence of bronchiolitis obliterans, along with chronic bronchitis.

From a practical point of view, we conclude that short-term bolus steroid treatment can triage patients into responders and non-responders for subsequent treatment with corticosteroids. Since the intravenous pulse of corticosteroid showed no benefit over the oral corticosteroid, the latter is preferred for, given the side effects of pulse corticosteroid. However, follow-up studies of these patients are needed to confirm the predictive value of short-term therapy.

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