

Long Term Follow-Up of Sulfur Mustard Related Bronchiolitis Obliterans Treatment

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Abstract- Bronchiolitis obliterans (BO) is the most remarkable pulmonary sequels of war-related sulfur mustard inhalation. There is little if any data about long-term efficacy of associated BO treatment. Five years spirometric records of three groups of patients with obstructive pulmonary diseases (asthma, COPD, BO) and documented sulfur mustard inhalation were evaluated. The BO patients were treated with inhaled Seretide 125-250/25 (2 puffs BID), azithromycin (250 mg, three times/week) and N-acetylcysteine (1200-1800/day). Asthma and COPD patients were treated according to existing guidelines. Seventy-three (38 asthma, 16 COPD and 19 BO) patients completed the 5 years follow-up. Basal and final FEV₁ in BO patients (2.69±0.81 and 2.39±0.65 respectively) were not significantly different from COPD patients (2.46±0.56 and 1.96±0.76 respectively). There was also no significant difference between the yearly FEV₁ decline in BO patients compared to COPD patients (60±84 cc vs. 99±79 cc respectively, *P*=0.163). The non-significant difference of FEV₁ decline in BO compared to COPD patients suggests the effectiveness of azithromycin, inhaled steroid and N-acetyl cysteine in BO patients. Considering safety and possible effectiveness, this treatment is recommended until more data is available from controlled clinical studies.

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Introduction

Sulfur mustard (SM) is a potent alkylating agent that was used during the First World War and also extensively during the Iran-Iraq war against Iranian population. Various types of late respiratory complications are described in patients following SM inhalation, including bronchiolitis obliterans (BO), pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma and large airway narrowing (1,2).

BO is the most distinct and remarkable pulmonary consequence in war-related SM victims (2-5). It was also recently reported in American soldiers returning from Iraq and Afghanistan (6). Bronchiolitis obliterans, also known as constrictive bronchiolitis, initiate as nonspecific inflammatory damage, primarily affecting the small airways with consecutive peribronchial fibrosis. It usually spares a substantial portion of interstitial tissue of the lung.

Most studies on the course and treatment of BO have been done after lung and bone marrow transplantation (7-9). A few studies have been done on the treatment of SM associated pulmonary disease that suggest the beneficial effects of macrolide antibiotics, antioxidants notably, N-acetylcysteine (NAC) and inhaled corticosteroids in SM victims (10-18). However, there is little if any data about the long-term efficacy of these therapies in SM associated BO.

We retrospectively assessed 5 years of spirometric parametric changes in SM victims to evaluate the efficacy of BO treatment in comparison to standard management of asthma and COPD in these patients.

Materials and Methods

Patients

We evaluated retrospectively the spirometric records of SM victims who visited in our specialized chemical center in Sasan hospital in Tehran from September 2008

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till May 2014. These patients were all victims of the Iran-Iraq war who had well-documented SM inhalation during 1984 to 1987 confirmed by Iranian war victim's organization (Bonyad_e_Shahid). Three groups of SM victims with obstructive pulmonary diseases (asthma, COPD, and bronchiolitis obliterans) were included in our study. The BO in most SM victims was diagnosed based on significant air-trapping (>25% of hypo-attenuation area) on full expiratory chest HRCT after a six-week course of inhaled steroid (to exclude asthma) (19). The diagnosis was confirmed in patients with inconclusive HRCT findings with open lung biopsy. Those with recognized cardiopulmonary disease before SM exposure or any suspicious occupational and environmental exposure were excluded from our study.

Study design

Patients with at least 5 years follow-up were entered in this study. All patients had baseline audiometry, EKG, and mycobacterial study in those with sputum. They have been visited regularly in the clinic and were monitored with spirometry every two months. The BO patients were treated with our protocol using inhaled Fluticasone/Salmeterol (Seretide 125-250/25 µg 2 puff BID), azithromycin (250 mg/3 times per week) and N-acetylcysteine (Flumucil 1200-1800/day). Those with asthma and COPD were treated based on their diagnosis according to GINA and GOLD guidelines (20,21). Because the patient's records were evaluated retrospectively, the institutional Ethics committee waived the need for patient consent.

Pulmonary function tests

Spirometry was performed at each 2-month visit using spirometry device (ZAN®, Messgrate GmbH, Germany) by trained technicians under the supervision of a physician according to American Thoracic Society/European Respiratory Society guideline (22). Best values of forced expiratory volume in 1st second (FEV₁) and forced vital capacity (FVC) at first and last year was used for analysis.

Statistical methods

The spirometric results of these 3 groups were analyzed by one-way analysis of variance (ANOVA), using SPSS for windows 13.0 (SPSS Inc., Chicago, IL, USA). *P*.value of <0.05 was considered significant.

Results

Seventy-three of 98 male SM victims with obstructive lung disease who had 5 years' follow-up were included in the analysis. Patients were categorized in 3 groups: Asthma (n=38, 52.0%), COPD (n=16, 21.6%) and BO (n=19, 26.2%). In 3 patients, BO diagnosis was made by open lung biopsy, and in 16 other cases with compatible clinical and HRCT findings and documented SM exposure. Age at the time of SM exposure and at the first visit was not significantly different between the 3 groups (Table 1).

Table 1. Baseline and final demographic/spirometric characteristics of the patients in Asthma, COPD and BO group

Variable	Asthma group (n=38)	COPD group (n=16)	BO group (n=19)
Age at first visit years	42.57 ± 6.16	46.6 ± 9.53	44.53 ± 7.27
Age at time of exposure to SM years	22.02 ± 6.56	25.60 ± 12.02	22.66 ± 7.23
Current smoker no. (percent)	2 (5.2)	3(18.8) [#]	1(5.2)
Pack. year smoking	5.23 ± 8.90	10.25 ± 13.78	2.86 ± 2.20
Basal FEV ₁ liter	3.13 ± 0.56*	2.46 ± 0.56	2.69 ± 0.81
Basal FEV ₁ %predicted	79.28 ± 10.94*	61.43 ± 16.58	68.73 ± 20.52
Basal FVC liter	3.78 ± 0.57**	3.07 ± 0.71	3.49 ± 0.79
Basal FVC % predicted	79.65 ± 9.32**	63.50 ± 16.76	71.73 ± 15.15
Final FEV ₁ liter	3.08 ± 0.63 [§]	1.96 ± 0.76	2.39 ± 0.65
Final FEV ₁ % predicted	83.17 ± 8.66 [§]	50.73 ± 20.97	69.08 ± 18.05
Final FVC liter	3.64 ± 0.63 [¶]	2.76 ± 0.75	3.05 ± 0.54
Final FVC %predicted	78.95 ± 11.94 [¶]	60.66 ± 17.05	70.18 ± 12.80
5 years FEV ₁ change liter	-0.055 ± 0.412 [‡]	-0.497 ± 0.398	-0.300 ± 0.414
5 years FVC change liter	-0.144 ± 0.465	-0.319 ± 0.606	-0.441 ± 0.717
Yearly FEV ₁ change liter	-0.011 ± 0.082 [‡]	-0.099 ± 0.079	-0.060 ± 0.084
Yearly FVC change liter	-0.029 ± 0.093	-0.063 ± 0.121	-0.088 ± 0.143

P.value <0.05 compared to BO group, * *P*.value <0.05 compared to each COPD and BO group, ** *P*.value <0.05 compared to COPD group, § *P*.value <0.05 compared to each COPD and BO group, *P*.value <0.001 and <0.05 compared to COPD and BO respectively, ‡ *P*.value <0.05 compared to COPD group

There were no significant differences in mean basal

and final FVC and FEV₁ between COPD and BO groups

(Table 1). Mean FEV₁ decline per year was significantly higher in COPD and BO patients compared to asthma group (99±79 cc vs. 11±82 cc, $P=0.001$ and 60±84 cc vs. 11±82 cc, $P=0.038$ respectively). However, there were no significant differences in mean FEV₁ decline in BO patients compared to COPD groups ($P=0.163$). There was no QT prolongation, audiometry changes and positive mycobacterial culture in BO patients during azithromycin use. Three patients reported some gastrointestinal discomfort that declined with continuing treatment. Two patients discontinued N-acetylcysteine due to gastrointestinal intolerance. Seretide had been discontinued in two BO patients without any subjective or spirometric changes after its discontinuation. There was no mortality in these 3 groups during this period

Discussion

It is estimated that at least 34,000 patients in Iran are still suffering from long-term pulmonary consequences of mustard gas, mandating considerable care and costs in medical services (23). In many specialized chemical centers in Iran, referral physicians developed protocols for management of SM associated pulmonary disease based on short-term studies, their experience with SM victims and expert opinions. However, there are few if any studies about long-term efficacy of the existing protocols in these patients. This is the first study to address the 5 years' follow-up of SM related pulmonary diseases and the efficacy of treatment in one of these referral centers.

We retrospectively assessed 5 years FVC and FEV₁ changes to evaluate the efficacy of BO management by azithromycin, inhaled steroid and N-acetyl cysteine in comparison to standard management of asthma and COPD in SM victims. Considering the poorer natural history of BO in comparison with COPD (19,24-26), the non-significance of mean FEV₁ decline in BO group compared with COPD group suggests the effectiveness of BO treatment during the 5 years' follow-up. There was also no mortality in all three groups during this period.

There are elevated levels of inflammatory markers including cytokines and CRP in the bronchoalveolar lavage and serum of SM-exposed victims (27,28). Macrolides have anti-inflammatory action in BO with various etiologies including those associated with SM. (10-12). This could suggest the possible mechanism of azithromycin effectiveness in our study and previous short term studies in SM associated BO patients. Also, considering previous studies that suggest short term

effectiveness of N-acetyl cysteine and inhaled steroids in BO (11,14-17), the usefulness of these agents in long-term management of BO could be expected.

During the 5 year's follow-up with close clinical monitoring and serial laboratory tests, ECG and audiometry, there was no significant side effects attributing to the use of three doses per week of azithromycin in BO patients. This suggests the safety profile of this agent in long-term treatment of SM associated BO.

In COPD group with standard treatment, FEV₁ had greater reduction per year than previous reports of yearly FEV₁ changes in non-SM COPD patients (25,26). This may indicate the worse prognosis of COPD in SM-exposed patient. However, considering the total number of our COPD patients, this result must be interpreted with caution. Meanwhile, the FEV₁ decline in asthma group was within physiological ranges (29).

Limitations of the study

In this study, the diagnosis of BO in the majority of patients was made based on compatible HRCT and clinical findings. Although, open lung biopsy is the most specific means of BO diagnosis, the compatible HRCT findings in the setting of a BO risk factor can also be diagnostic (19). To exclude asthma, inspiratory/expiratory HRCT was done after at least 6 weeks treatment with inhaled steroid (30). In three cases with discrepancy between clinical and HRCT findings, BO was diagnosed by open lung biopsy.

Regarding the short term efficacy of BO management with azithromycin and reports of possible efficacy of inhaled steroid and NAC and good safety profile of these agents, BO patients in our center were managed with azithromycin, inhaled steroid and N-acetyl cysteine. So the efficacy of BO management was assessed by comparing these patients with historical BO natural history and COPD and asthmatic SM victims. Further studies are required to assess the long-term efficacy of BO management with different protocols and considering other important outcomes such as dyspnea score, exercise capacity, annual exacerbation rate, and overall mortality rate.

Ghanei *et al.*, reported FEV₁ response in 27 % of BO patients after 2 months of inhaled steroid trial. They proposed possible discontinuation of steroid inhaler in FEV₁ non-responders and considering macrolides in these patients (18). However, HRCT was done before steroid inhaler trial without repeating HRCT after steroid inhaler trial. So asthma could not be ruled out in steroid responders in their study. The inhaled steroid in

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BO patients, even in FEV1 non-responders was continued in our center as an adjunct for anti-inflammatory effect of azithromycin. We were unable to determine the efficacy of each component of our BO management. Further studies are needed to determine the role of azithromycin, inhaled steroid, and NAC in BO management.

Considering safety and possible effectiveness of treatment of war-related BO with Azithromycin, N-acetyl cysteine, and inhaled steroid (with or without long-acting β -agonists), the long-term use of these drugs in war-related BO patients is recommended until more data from controlled studies becomes available.

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