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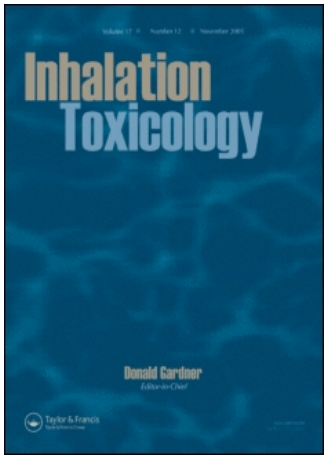

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Inhaled Corticosteroids and Long-Acting β2-Agonists in Treatment of Patients with Chronic Bronchiolitis Following Exposure to Sulfur Mustard

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We examined the role of two regimens of combination inhaler therapy on amount of reversibility of chronic lung complications in mustard gas exposed patients. In a phase III, prospective, randomized clinical trial, 105 participants received either combination form of fluticasone propionate and salmetrol, 500/100 μg daily (group 1; $n = 52$) or beclomethasone, 1000 μg daily, and salbutamol inhaler, 800 μg daily (group 2; $n = 53$) for 12 wk. Pulmonary function test (PFT) indices and respiratory symptoms (including dyspnea, night awakening due to dyspnea and cough) were assessed at baseline and in each visit. Thirty-six patients in group 1 and 30 patients in group 2 completed study course. Both medication regimes increased pretreatment forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC%, and peak expiratory force (PEF) by the end of 12 wk. It seems that these improvements are more constant in group 1 than in group 2. Reversibility, that is, 10% increase of FEV1 in the second month was seen for 27% of patients in the group 1 and for 7% in the group 2. VAS scores have decreased in two groups during treatment period ($p = .003$) and after follow-up period it remained sustained in group 1 alone. Inhaled corticosteroids and long-acting β2-agonists are effective in treatment of patients with chronic bronchiolitis following exposure to sulfur mustard. However, a medium dose of fluticasone/salmeterol has the same effect on the airways reversibility, rather than a very high dose of beclomethasone with only the short-acting beta-agonist.

Bronchiolar abnormalities play an important role in the pathogenesis of chronic lung complications in mustard gas-exposed patients (Beheshti et al., 2006). Bronchiolitis obliterans (BO) is an inflammatory process that involves the small airways and often results in progressive, irreversible obstructive pulmonary disease (Fullmer & Dishop, 2005). Unfortunately, the common feature of BO has generally poor response to treatment (Perrin-Fayolle, 1995); consequently, therapy is based on symptomatic therapy, and the use of corticosteroids is controversial but common (Ezri et al., 1994). In one study the efficacy of high-dose inhaled fluticasone in BO patients following sulfur mustard exposure has been investigated (Ghanei at al., 2005). In contrast, in another study inhaled fluticasone propionate in infants recovering from acute bronchiolitis was ineffective (Wong et al., 2000). Several pivotal studies have clearly demonstrated in adults the superiority of adding long-acting β2-adrenoceptor agonist (LABA) (salmeterol or formoterol) to inhaled corticosteroids (ICS) (fluticasone propionate or budesonide) compared with doubling the dose of ICS in terms of improving asthma (Shrewsbury et al., 2000) and chronic obstructive pulmonary disease (COPD) control (O'Brien et al., 2001) versus single therapy. O'Brien et al. evaluated discontinuation of ICS in COPD patients and observed a significant deterioration in lung function (O'Brien et al., 2001).

It has been shown that there are partial responses to short-term bolus steroid treatment in chemical-injured patients (CIPs) (Ghanei et al., 2005); however, the outcome of inhaler maintenance therapy in these patients is not clear. Since due to frequent chemical attacks by the Iraqi ex-regime a large number of adult chronic bronchiolitis cases in Iran are available, we examined the impact of two regimens of combination inhaler therapy to find amount of reversibility in these patients.

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METHODS AND MATERIALS

Study Participants

We enrolled outpatient CIPs who came to our centers, Baqiyatallah Hospital, and Sasan Hospital, Tehran, Iran. These hospitals have specialized clinics for CIPs as referral centers for whole of the country. The protocol and procedures as described earlier received institutional approval from the University of Baqiyatallah Research Ethics Board, and all patients had provided written informed consent. A sample size of 50 patients was calculated to detect a 10% difference in FEV1 at the 5% significance level with 90% power. Considering 20% loss to follow-ups 60 patients were enrolled to each group.

Inclusion criteria were: patients with official certificate of exposure to sulfur mustard (SM), according to clinical and pulmonary function tests (PFTs), and significant air trapping in their chest shown via high-resolution computed tomography (HRCT)—significant air trapping generally means a fairly significant and long-standing condition.

Exclusion criteria were: active respiratory infection, ongoing regular oxygen treatment, systemic corticosteroids during 3 mo before the study, monoamine oxidase (MAO) inhibitors, tricylic antidepressants, beta blockers or other drugs that had interaction with the study medication like persons already on LABA or ICS, lung transplantation, smoking or exposure to air pollutions, drug abusing, and patients' signs and symptoms worsening. Exacerbations were defined as a worsening of respiratory symptoms that required treatment with antibiotics, oral corticosteroids, and even sometimes hospitalization. These patients were withdrawn from the study. Of 210 visited chemical-injured patients, 105 cases met the inclusion criteria of the study whom were divided to two groups randomly: 52 patients in group 1 and 53 patients in group 2.

Study Design

The general design of the study was a phase III, prospective, randomized clinical trial. Participants received either combination form of fluticasone propionate and salmetrol (i.e., Seretide metered dose inhaler; GlaxoSmithKline, Greenford, UK), 500/100 μg daily (group 1), or beclomethasone, 1000 μg daily, and salbutamol inhaler, 800 μg daily (group 2), for 12 wk. Patients who satisfied the eligibility criteria were assigned an exclusive study code. Neither the examiners nor pulmonary function test (PFT) technicians were aware of the patients' codes. For each patient a standard questionnaire was completed, including demographic data, medical history, and chemical exposure history. Respiratory symptoms (including dyspnea, and night awakening due to dyspnea and cough) were assessed using three multiple-choice questions before and after medical interventions. In addition, dyspnea status was assessed by the Visualized Analogue Scale (VAS) at wk 0, 4, 8, 12, and 14. The study protocol has been summarized in Figure 1.

Spirometry

After collection of an appropriate number of included cases (through interview and clinical examination by a general

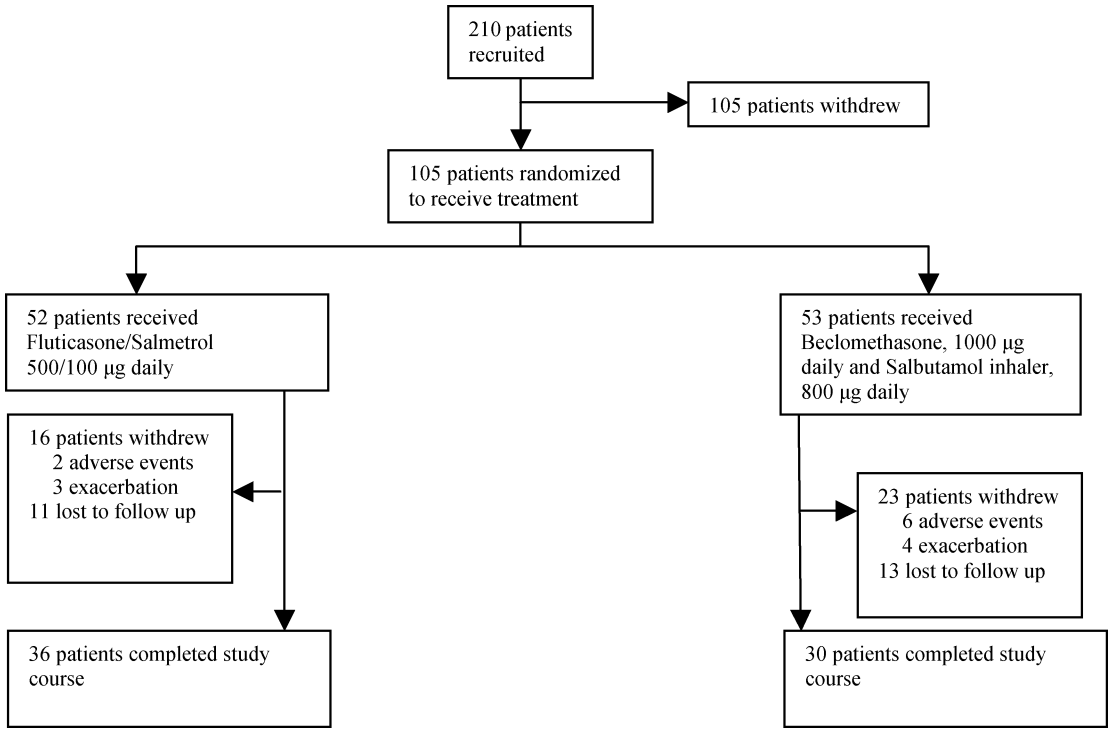

FIG. 1. Study profile.

practitioner) the first step was PFTs. All PFTs were done at the same time of day for all patients (4–6 p.m.), by the same technician and device (Chest HI-801). Spirometry was performed for each participant at each visit in accordance with the guidelines from the American Thoracic Society (1979). A test session consisted of several repeated forced vital capacity (FVC) maneuvers. Each FVC maneuver required the subject to take the deepest possible breath and exhale into a spirometer as hard, fast, and completely as possible. The spirometer recorded the volume of air exhaled as a function of time. Each subject performed at least three FVC maneuvers. For a maneuver to be acceptable, it needed to be a maximal exhalation free from cough, excessive hesitation, leak, obstructed mouthpiece, variable effort, or early termination. The best result of each maneuver was saved and printed for interpretation. The next step was a respiratory subspecialist visit for a thorough respiratory examination and spirometry interpretation. After this step and only with our respiratory subspecialist's agreement, the patient was eligible to receive medication.

Medication

We used a randomization schedule to allocate patients to study treatment groups. All agents were delivered via pressurized metered-dose inhaler (MDI) spacer. Unfortunately, due to the difference in half-time of prescribed drugs it was not feasible to run the study as a double-blind study. Inhaled salbutamol was used as relief medication throughout the study in both groups. All nonrespiratory medication that did not interfere with study drugs continued. Intervention lasted for 12 wk, and during this period patients were followed by fortnightly phone calls to assess whether they were using drugs correctly and whether there were any adverse reactions to medication. Also each patient came monthly for PFTs and dyspnea VAS. The occurrence of acute respiratory exacerbation was investigated in these visits. An increase in mean FEV1 in each group by 10% was the endpoint of study as time passed.

After 12 wk of medication all inhalers except relief salbutamol were discontinued for 2 wk. After this period all patients were revisited and underwent PFTs and VAS again. They were followed for 4 wk after stop of medications. After this period they were assessed again by clinical examination and PFTs.

Statistical Analysis

Continuous variables were reported as mean and standard deviation (mean $\pm$ SD), and comparisons between groups were based on a two-sample t-test (parametric) or the Mann–Whitney (nonparametric) test. Categorical variables were summarized as percentages, and group comparisons were based on the chi-squared test. A mixed model used for comparison of the two groups for variables (FEV1, PEF, and VAS) because of repeated measurement and adjustment for baseline differences. Study drop-outs were considered as missing data. Analysis was performed using SPSS software version 13.

RESULTS

There was only one female in group 1. The mean values $\pm$ SD for age (yr) in group 1 ($n = 36$) and group 2 ($n = 30$) were 42.15 ± 6.45 and 41.73 ± 6.2, respectively ($p = .73$).

There was no difference in demographic characteristics and baseline VAS scores; however, pretreatment FEV1 and FVC values differed slightly between the two groups (Table 1). These minor imbalances in baseline data were accounted for in the statistical analysis since these values were used as covariates in analyses where appropriate.

TABLE 1
Comparison of baseline variables between two groups

Variables	Fluticasone/salmeterol ($n = 52$)	Beclomethasone and salbutamol ($n = 53$)	p Value
Mean age at exposure (mean $\pm$ SD, yr)	22.67 $\pm$ 6.4	22.31 $\pm$ 6.32	.77
Mean time after exposure (mean $\pm$ SD, yr)	19.48 $\pm$ 1.37	19.59 $\pm$ 1.77	.73
Baseline FEV1 (%predicted $\pm$ SD)	72.75 $\pm$ 15	79.63 $\pm$ 15	.02
Baseline FVC (%predicted $\pm$ SD)	79 $\pm$ 13	86 $\pm$ 14	.01
Baseline FEV1/FVC % ($\pm$ SD)	77.4 $\pm$ 6.8	76.6 $\pm$ 8.3	.67
Baseline PEF (%predicted $\pm$ SD)	74.5 $\pm$ 16	81.5 $\pm$ 24	.09
Baseline MMEF (%predicted $\pm$ SD)	63 $\pm$ 25	69 $\pm$ 25	.25
Baseline VAS score $\pm$ SD	55.57 $\pm$ 19.552	52.36 $\pm$ 19.356	.40

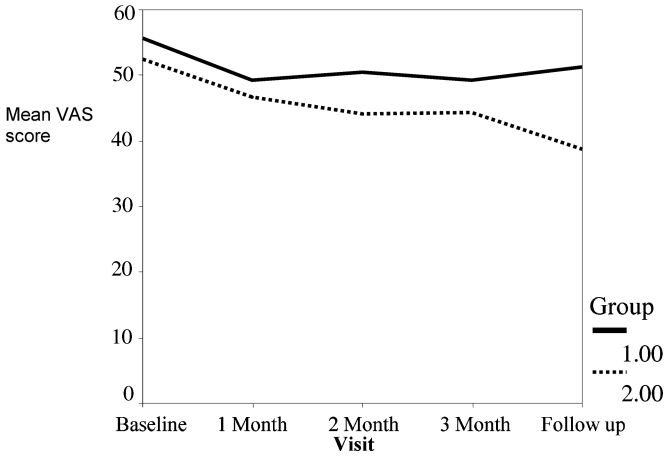

FIG. 2. VAS score of dyspnea in two groups.

Withdrawal rate, that is, exacerbation and adverse effect, in groups 2 and 1 was 3 (12.2%) and 4 (20%), respectively ($p = .318$). There was no difference between rate of loss in group 1 (11; 21%) and group 2 (13; 24.5%) ($p = .681$). The difference in mean of withdrawal time due to exacerbations and serious adverse events was not statistically significant between group 1 (63.25 ± 69.1 days) and group 2 (45.2 ± 29.7 days) ($p = .94$).

Acute respiratory exacerbation occurred in 3 cases in group 1 and 4 cases in group 2. VAS scores decreased in the two groups during the treatment period, but patients who received combination therapy in group 2 had an increase in dyspnea VAS score after mo 3. However, these differences were not statistically significant between the two groups ($p > .05$) without the follow-up time in the model and were statistically near significance ($p = .055$) with the follow-up time in the model.

Both medication regimes increased pretreatment FEV1, FVC, FEV1/FVC%, and PEF by the end of 12 wk. It seems that these improvements are more constant in group 1 than in group 2. These values dropped again after the follow-up period (Figures 3 and 4). The rises in PFT indices during medication associated with combination therapy (Flu/Sal MDI) versus beclomethasone and salbutamol inhaler therapy were not statistically significant ($p > .2$). Also comparison of results between two groups was not significant ($p > .05$).

The value of 10% improvement of FEV1 in the combination group rises significantly by wk 8, but it decreases again during mo 3 and then after discontinuing the medication during the follow-up period (Table 2). Comparison of dyspnea, cough, and night awakening between two groups is shown in Table 3.

DISCUSSION

ICS and long-acting $\beta 2$-agonists are effective in treatment of patients with chronic bronchiolitis following exposure to sulfur mustard (SM). Fortunately, 27% of patients showed a reversible pattern and had a 10% increase in FEV1 in month 2. It seems there is a considerable reversible component in small-airway

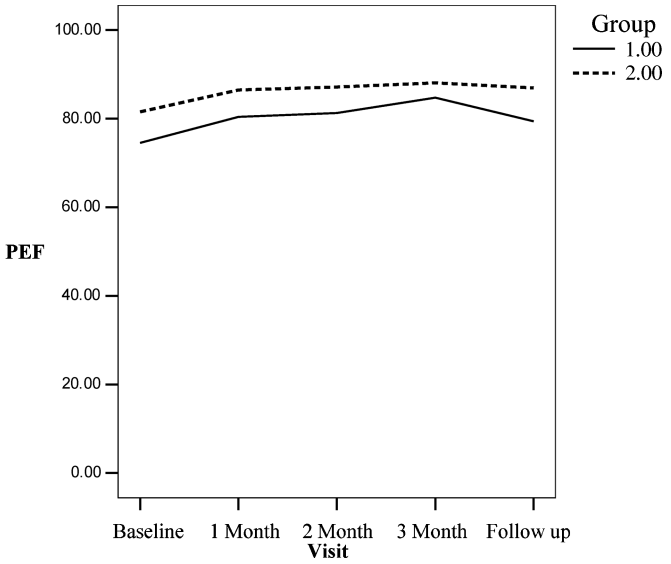

FIG. 3. Mean of FEV1 in two groups in each visit.

obstruction of chemical-injured victims. It has been shown that increased airway responsiveness of most chemical warfare victims to methacholine, which correlated with the FEV_1 value, may be related to chronic airway inflammation and airway hyperresponsiveness (Mirsadraee et al., 2005). However, still about 70% of CIPs do not have any response to ICS and $\beta 2$ agonist treatment.

Previous study by Chacon et al. (2000) showed that simple spirometry indices are useful for detection and evaluation of response to treatment of inpatients with BO due to lung transplantation. In our study the improvement in FEV1, FVC, PEF, and FEV1/FVC indices after 3 mo of therapy and their decrease to baseline values after a follow-up period in both groups is an indicator of reversibility of airway obstruction and usefulness of spirometry for their follow-up. There was almost the same effect with two strategies of therapy. It is of note that the dose of administered corticosteroid in the fluticasone/salmeterol

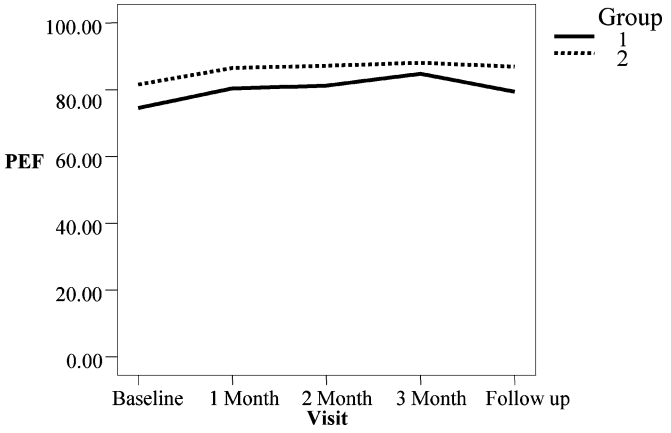

FIG. 4. Mean of PEF in two groups in each visit.

TABLE 2
Number (%) of patients who had 10% or more increase in FEV1

	Month 1	Month 2	Month 3	Follow-up
Group 1, number (%)	5 (15.6)	9 (27.3)	5 (15.6)	3 (12)
Group 2, number (%)	2 (7.1)	2 (7.1)	4 (14.8)	1 (5.3)
p	.43	.051	.61	.41

group was half that of the beclomethasone and salbutamol inhaler group. Considering this fact, note that ICS have differences in pharmacokinetics, in that budesonide and fluticasone have a lower oral bioavailability than beclomethasone dipropionate, resulting in reduced systemic absorption from the fraction of the inhaled drug that is swallowed (Martin et al., 2002). At high doses (>1000 μg), budesonide and fluticasone have less systemic effects than beclomethasone dipropionate and triamcinolone, and are preferred in patients who need high doses and long-term treatment with inhaled corticosteroids (Mason, 2005). It is worth considering that the VAS improvements in dyspnea might warrant the risks associated with long-term ICS use.

As shown in the graphs, PFT indices have the same pattern of changes in both groups. This shows that even with a larger sample size the same results will be obtained again. Dyspnea in group 1 improved obviously more than in group 2. Also, the dyspnea score reached the baseline value after follow-up in both groups. The rate of worsening was high in group 2 (27%), while none of the patients in group 1 showed worsening of dyspnea during the intervention period. The night awakening remained without changes, but dyspnea improved only after 1 mo of therapy. This is inconsistent with previous reports that reported that inhaled LABA improve airflow obstruction, control of symptoms, and health status in patients with COPD over 3–4 mo and have several potentially beneficial nonbronchodilatory effects (Calverly et al., 2003). The main reasons for withdrawing from our study were lost to follow-up in both groups and there was a high rate of unresponsiveness in our series (24 cases). However, frequency of withdrawal was lower but not significantly so in group 1, where the members used a treatment combination in a single inhaler.

There is little information regarding pathophysiology of respiratory problems following exposure to SM. However, the CIPs in Iran are managed and treated by respiratory physicians empirically and mainly on the basis of their individual experiences. So it is necessary to establish evidence-based guidelines for management of CIPs. Conventional medications including ICS and β2 agonists (e.g., belomethasone and salbutamol) have been prescribed for many years in other settings. The CIPs are often resistant to conventional medical treatments. So there is a great concern about finding new effective treatments for SM-injured patients to improve their respiratory functions and returning them to ordinary function.

A previous report showed that ICS in combination with LABA were effective in COPD patients (Soriano et al., 2002). Considering the point that BO is classified in the COPD diseases, our results make clear the fact that BO cases with COPD have more benefit from using ICS. Fluticasone propionate/salmeterol (Advair or Seretide) is a combination ICS and long-acting bronchodilator that was recently approved for use in COPD in the United States. Fluticasone propionate/salmeterol is a potent bronchodilator and also appears to have important effects on the frequency of exacerbations and the overall quality of life for some patients with COPD (Dransfield & Bailey, 2004). As was described for COPD patients, the aim of treatment of these patients is to prevent and control symptoms and exacerbations while improving lung function and health status (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2001). In patients with moderate-to-severe COPD, twice-daily inhaled salmeterol/fluticasone propionate 50/250 or 50/500 μg for 24–52 wk improves predose FEV1 significantly more than salmeterol monotherapy, improves postdose or postbronchodilator FEV1 significantly more than fluticasone propionate monotherapy, and results in clinically significant improvements in health-related quality of life. Salmeterol/fluticasone propionate 50/500 μg significantly reduced annual COPD exacerbations, especially

TABLE 3
Comparison of respiratory symptoms between two groups

	Group 1			Group 2			
Respiratory symptoms	Improved	No difference	Worsened	Improved	No difference	Worsened	*p* Value
Dyspnea (%)	18 (51.5)	17 (48.5)	0 (0)	16 (55)	6 (20.5)	7 (24)	.003
Night awakening (%)	9 (25.5)	22 (63)	4 (11.5)	9 (31)	14 (48.5)	6 (20.5)	.443
Cough (%)	15 (43)	12 (34.5)	8 (23)	11 (38)	10 (34.5)	8 (27.5)	.888

in severe COPD. The dry powder inhaler combining a corticosteroid and LABA provides benefits over monotherapy and may encourage patient compliance in COPD (Fenton & Keating, 2004). Considering the emphasis on combination therapy benefit in previous reports and also our derived results, we recommend the usage of combination rather than monotherapy in adult patients with bronchiolitis.

CONCLUSION

A 2-mo trial course of fluticasone/salmeterol therapy can be administered. If patients respond to this therapy they should be considered as responsive and fluticasone/salmeterol can be continued. The remaining subjects (e.g., 70% in our study) should be considered for other types of therapy, such as macrolides antibiotics, as one of the effective medications in sulfur mustard-induced BO, like other subjects with lung transplants. This can save both time and money in the treatment of these patients. However, we recommend making decisions case by case to choose suitable therapy in this setting. Further studies are required to assess the effect of long-term therapy by fluticasone/salmeterol in annual exacerbation rate, annual hospitalization rate, and overall mortality rate of CIPs.

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