
High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study

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Background: It is important to determine whether chronic cough is associated with asthma and can be helped by treatment with inhaled corticosteroids.

Objective: To compare the effects of beclomethasone and placebo in patients with chronic cough for at least 8 weeks after excluding those with cough due to postnasal drip and gastroesophageal reflux disease.

Methods: A prospective, randomized, double-blind, placebo-controlled study comprising 64 patients was performed for 2 weeks. The active group received metered-dose inhaler chlorofluorocarbon-beclomethasone (1,500 $\mu\text{g}/\text{d}$), and the placebo group received identical-appearing placebo inhalers. All the participants completed a respiratory questionnaire and underwent bronchoprovocation testing (BPT) with methacholine and allergy skin testing. The primary outcome measure was a decrease in daily cough scores (symptom diary and visual analog scale) during the 2-week treatment period.

Results: The active group comprised 44 patients and the placebo group 20 patients. Cough duration averaged 20 weeks. At the end of treatment 82% of the active group and 15% of the placebo group had complete resolution of cough. In the active group 22 patients (50%) had positive BPT results, and in the placebo group 10 patients (50%) had positive results. There was no correlation between treatment response and responses on the respiratory questionnaire, allergy skin testing, or BPT.

Conclusion: Therapy with high-dose inhaled beclomethasone provided an excellent response in a subgroup of patients with chronic cough that did not correlate with atopy or airway hyperresponsiveness.

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INTRODUCTION

Worldwide, the prevalence of chronic cough ranges from 5% to 40%.^{1–3} In Brazil, chronic cough is responsible for an estimated 1.5 million visits to the physician's office per year.⁴ Cough has been classified into 3 categories: acute (persisting for <3 weeks), subacute (persisting for 3–8 weeks), and chronic (persisting for >8 weeks).⁵ This classification system is currently used.^{6,7} Chronic cough with bronchial hyperresponsiveness (BHR) and no other cause is termed *cough variant asthma* (CVA).^{8,9} This is one of the most common causes of chronic cough in adults¹⁰ and seems to respond to bronchodilators^{8,11} and corticosteroid medications.¹² Chaudhuri et al¹³ noted an improvement in cough severity after fluticasone was administered to patients with chronic cough. Ponsioen et al,¹⁴ on the other hand, found limited benefits from inhaled corticosteroid therapy in nonasthmatic patients with cough.

In guidelines published recently by the American College of Chest Physicians,⁵ Dicpinigaitis¹⁵ listed 13 studies that involved treatments for CVA, but only 2 used inhaled corti-

costeroids (beclomethasone), in a few patients and with a low response rate. Only 1 study compared inhaled corticosteroid treatment with placebo therapy. Therefore, the recommendations to use inhaled corticosteroids for CVA had only fair quality of evidence. All recommendations for the therapeutic approach to CVA are based on treatment results being similar to those of asthma, with modest literature evidence. One study¹⁶ has shown an 85% reduction in chronic cough with placebo treatment, suggesting that a placebo-controlled trial is necessary. To investigate whether a high-dose inhaled corticosteroid for a short period is better than placebo in the treatment of a subgroup of patients with chronic cough, we designed a prospective study in which the primary outcome measure was decrease in daily cough scores during a 2-week treatment period.

METHODS

A prospective, randomized, double-blind, placebo-controlled study was conducted with parallel groups. The medical ethics review board of the Federal University of São Paulo approved the study, and written informed consent was obtained from the participants. This protocol was part of a larger study of chronic cough.¹⁷

Patients and Study Procedures

Adults 18 to 70 years of age with cough for at least 8 weeks⁵ were recruited from the Outpatient Respiratory Clinic of the Hospital São Paulo at the Federal University of São Paulo,

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from the community (general practitioners, 89%), and from hospital clinics (11%). Requirements for the study included normal findings on a chest radiograph, plain sinus radiographs in 4 positions, and ears, nose, and throat examination. Exclusion criteria were a previous gastroesophageal reflux disease diagnosis, positive 24-hour esophageal pH measurement, concurrent respiratory tract infections, and a history or medical diagnosis of asthma, chronic obstructive pulmonary disease, or chronic rhinosinusitis (postnasal drip syndrome) and evidence of airflow limitation with a forced expiratory volume in 1 second (FEV₁)/forced vital capacity of 70% or less, and patients needed not to have taken any medications for cough in the 4 weeks leading up to entry into the study.

Before the study patients completed an unvalidated modified epidemiologic respiratory questionnaire¹⁸ consisting of 83 questions about medical history, current medication use, family history of allergy symptoms or noncommunicable diseases, physical activity, disability, smoking habits, occupation, education, and details of cough. After inclusion in the protocol, patients underwent spirometry; allergy skin prick testing for various inhaled allergens, and bronchoprovocation testing (BPT) with methacholine, which was performed according to the standard protocol.¹⁹ Figure 1 reflects the flow of the protocol.

Lung Function

Spirometry (MultiSPIRO Inc, San Clemente, California) was performed in the morning according to the accepted criteria of the American Thoracic Society.²⁰ Airway responsiveness was measured by means of methacholine BPT using a modified protocol.^{21,22} Two methacholine solutions (0.2% and 1% in phosphate-buffered saline solution [PBS]) (Sigma-Aldrich Corp, St Louis, Missouri) were prepared by a local pharmacy and were delivered by means of a DeVilbiss 646 nebulizer using compressed air (DeVilbiss, Somerset, Pennsylvania) using a dosimeter (MultiSPIRO Inc). The nebulizer was pressurized at 20 psi and was calibrated to an output of 0.01 mL per inhalation that produces aerosol particles ranging from 0.5 to 5 μ m in diameter. The nebulizer was loaded with 3 mL of methacholine solution for each concentration. Inhalations were conducted with the patient in the sitting position and wearing a nose clip. Nebulized solution was inhaled through a mouthpiece, and the best FEV₁ was recorded. Spirometry was performed 30 and 90 seconds after each dose. Slow inspirations from functional residual capacity to total lung capacity with breath holding for at least 3 seconds were performed, and aerosol delivery time was set to 1 second and pause time to 6 seconds. After 5 breaths of aerolized PBS solution, patients inhaled 1, 1, 2, and 4 breaths of the 0.2% solution of methacholine (equivalent to 0.1, 0.1, 0.2, and 0.4 μ mol of methacholine),

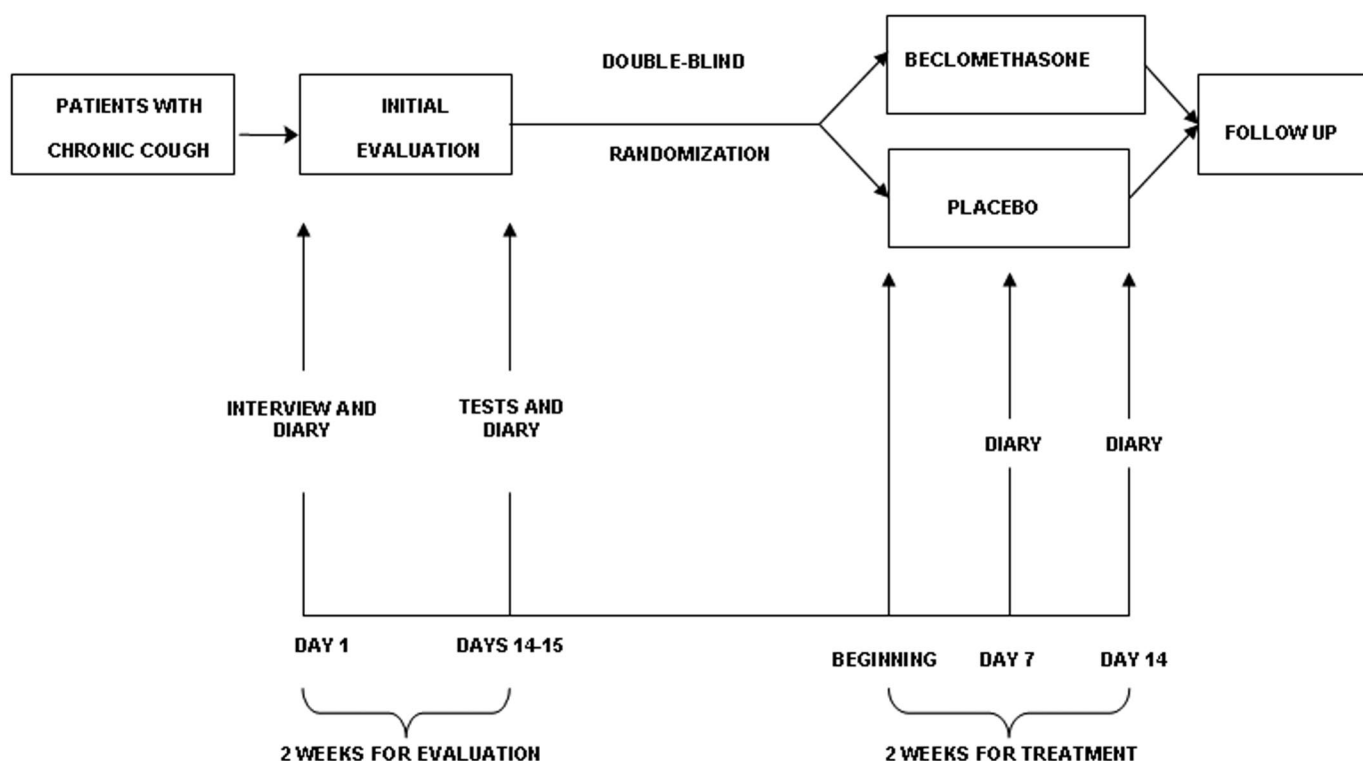


Figure 1. Study flowchart.

followed by 1, 2, 4, and 8 breaths of the 1% solution (equivalent to 0.5, 1, 2, and 8 μ mol of methacholine).

Methacholine responsiveness is expressed as the provocation dose that caused a decline in FEV₁ of 20% from the baseline value (PD₂₀) and was calculated by means of an interpolation from the slope of the logarithmic dose-response curve.²³ The methacholine PD₂₀ was used as the threshold of BHR with a value less than 8 mg/mL.²⁴

Skin Testing

Allergy skin tests for the airborne inhaled allergens were performed using the prick method. House dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis* [10,000 AU/mL each]), indoor fungi (*Aspergillus fumigatus*, *Penicillium notatum*, and *Alternaria alternata* [10,000 BAL/mL each]), pollens (*Avena sativa*, *Tritium sativum*, *Dactylis glomerata*, *Cynodon dactylon*, *Poa pratensis*, *Festuca rubra*, *Juniperus sabinoides*, and *Eucalyptus* species [10,000 BAU/mL each]), and animal dander samples (*Canis familiaris* and *Felis domesticus* [10,000 BAU/mL each]) and histamine (1/1,000) and normal saline (International Pharmaceutical Immunology do Brasil, Sao Paulo) were used. Atopy was defined by the presence of 1 or more positive test reactions (wheal diameter >3 mm greater than the saline control).

Symptom Diaries

Patients were asked to keep a 2-week symptom diary²⁵ noting frequency (throughout the day), severity (on arising and throughout the day), and duration of coughing (on arising and throughout the day) on a scale from 0 to 4 and sleep interruption (throughout the night). Cough severity was also measured using a bipolar visual analog scale (VAS).²⁶ The VAS for the evaluation of cough resolution consisted of a 100-mm horizontal linear scale, where 0 mm indicated no cough (right end) and 100 mm indicated worst cough (left end). All the ratings are reported as percentage of line length (range, 0%–100%).

Study Design

Patients were randomized using a simple randomization in an unbalanced design by an outside observer manually by means of a random number table into 2 groups at a ratio of 2:1 (active treatment vs placebo) in a double-blind manner to receive treatment. Because no expected anti-inflammatory effect should have occurred from placebo, we minimized the number of patients in the placebo group. Calculation of the number needed to treat was based on the assumption that there would be a difference between treatment and placebo groups of 90% power to detect a 20% difference (assuming a 2-sided test with $\alpha = .05$ and $\beta = .1$) between active treatment and placebo for the primary variable that was considered clinically significant. Therefore, 60 patients (40 in the active group and 20 in the placebo group) would be needed on each side of the study to show this difference. Patients in the study group received metered-dose inhaler chlorofluorocarbon-beclomethasone, 1,500 μ g/d (250 μ g per

dose; 2 puffs in the morning, 2 in the afternoon, and 2 in the evening), whereas those in the control group were given a metered-dose inhaler chlorofluorocarbon-placebo (vehicle; 2 puffs 3 times a day), and both received these treatments for 14 days. All other treatments for cough were not allowed by the protocol. Packaging of the study and placebo medications was identical in appearance and taste and identically marked.

After 2 weeks the patients returned to the clinic and turned in their diaries, VASs, and medication. We used symptom diaries and VASs to define a response to treatment higher than that obtained with the use of placebo (>75%), similar to Chang et al.²⁷ The minimal response on the VAS is an improvement greater than 75% and a decrease for each question in the diaries of at least 2 points. Adherence to medication was verified by the weight of the inhalers before and after the study.

Statistical Analysis

Statistical calculations were obtained using a software program (SPSS version 10; SPSS Inc, Chicago, Illinois). The demographic and clinical data are expressed as mean $\pm$ SD. Patients already responding to PBS were assigned a PD₂₀ value of half the lowest dose applied.²⁸ Patients not responding to the highest dose of methacholine were assigned a value of twice the highest dose applied.²⁹ Variables with normal distribution were compared using the paired *t* test. The Fisher exact test was applied to evaluate the questionnaire responses. Corticosteroid treatment and placebo use were compared using 1-way analysis of variance, followed by multiple comparisons using the unpaired *t* test. The relationship of the subjective perception evaluated using the diaries and the VAS to the questionnaire or the BPT was studied using linear regression analysis on a within-subject basis. The effect of inhaled corticosteroids on diary variables and VAS scores was analyzed using the paired *t* test. We applied the logistic regression model to correlate the corticosteroid response with the various tests used. The minimum level of significance adopted was $P < .05$.³⁰

RESULTS

Clinical Variables

Of 147 patients evaluated at the Outpatient Respiratory Clinic of the Hospital São Paulo at the Federal University of São Paulo, 64 were included in and completed the study. All 64 participants completed the respiratory questionnaire; underwent spirometry, skin prick testing, and BPT; and were assigned to a group: 44 to the active group and 20 to the placebo group. Anthropometric and functional data are given in Table 1.

Twenty-five patients had previously (at least 6 months before) received corticosteroids in varying doses and durations of treatment for cough, without diagnosis of obstructive disease. There was no significant difference in response to beclomethasone in those who had or had not received corticosteroids earlier ($r^2 = 0.12$; $P = .08$).

Table 1. Clinical, Demographic, and Functional Characteristics of Patients in the Active and Placebo Groups

Variable	Active group (n = 44)	Placebo group (n = 20)
Sex, M/F, No.	18/26	4/16
Age, mean $\pm$ SD, y	46 $\pm$ 17	50 $\pm$ 18
Duration of cough, median (variation), wk	20 (8–540)	19 (8–192)
FVC, mean $\pm$ SD, % predicted	102 $\pm$ 13	108 $\pm$ 18
FEV ₁ , mean $\pm$ SD, % predicted	98 $\pm$ 15	103 $\pm$ 18
FEV ₁ /FVC, mean $\pm$ SD, % predicted	96 $\pm$ 7	96 $\pm$ 10
PD ₂₀ , mean $\pm$ SD, mg	5.35 $\pm$ 3.2	4.56 $\pm$ 3.7 ^a
Cough VAS, mm	94 (87–100)	93 (85–100)
Cough diaries score	3 (0–4)	3 (0–4)
Smoking history, mean (SD), pack-years	4 (5)	2 (6)
Current smokers, Y/N, No.	0/44	0/20
Atopic status, Y/N, No.	22/22	11/9

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PD₂₀, methacholine provocation dose that caused a decline in FEV₁ of 20%; VAS, visual analog scale.

^a $P < .05$.

The median cough duration in weeks was similar in both groups ($P = .09$), and the modified respiratory questionnaire revealed that there was no significant difference ($P = .07$) between the active group and the placebo group in each item, regardless of the question category. None of the questions on the respiratory questionnaire were found to correlate positively with BPT ($r = 0.12$), but in the active group the patients answered more frequently for constant wheezing (50% vs 41%; $P = .59$), wheezing during cold or influenza (66% vs 45%; $P = .52$), and cough caused by running or walking fast (43% vs 40%; $P = .54$).

Lung Function and Allergy Skin Testing

In the active group, 22 patients (50%) had positive BPT results, as did 10 patients (50%) in the placebo group. The PD₂₀ was higher in the active group than in the placebo group (5.35 vs 4.56 mg/mL; $P = .01$). The skin test result was positive in 22 patients (50%) in the active group and 11 (55%) in the placebo group.

Treatment Response

At the end of the 2-week study, 36 of the 44 patients (82%) in the active group who had been treated with the corticosteroid had complete resolution of cough, and 8 (18%) showed no improvement. Of the 20 patients treated with placebo, cough cessation was observed in 3 (15%), and cough persisted in 17 (85%). Compliance was greater than 95% with beclomethasone and placebo inhalers. During the study period, β -adrenergic bronchodilator therapy of any type was not allowed. Furthermore, no major adverse effects were noted by anyone in either group. Only 2 patients in the active group reported sore throat as an adverse event.

Symptom Diaries

Most patients had moderate cough scores (Table 1). There was a significant difference in the cough diaries and VASs before and after beclomethasone treatment compared with before and after placebo use (difference of differences, 1.0;

95% confidence interval, 0.4–1.5; $P < .002$ for diaries; and difference of differences, 1.1; 95% confidence interval, 0.6–1.8; $P < .01$ for the VAS). In the beclomethasone group the mean $\pm$ SD cough score decreased from 3 at baseline to 0 ± 1 at the end of treatment. In the placebo group the baseline score was 3 and remained at 3 ± 1 with no change. In the active group, the mean VAS score decreased from 94 (range, 87–100) at baseline to 3 (range, 0–10) at the end of treatment, and in the placebo group the baseline score was 93 (range, 85–100) and remained at 91 (range, 76–100). Neither cough diaries nor VAS scores correlated with questionnaire ($r = 0.12$; $P = .07$) or BPT ($r = 0.23$; $P = .06$) findings. When symptom diaries were compared with VAS data, there was a significant difference between the active and placebo groups at the end of the protocol ($P < .001$) (Figs 2 and 3). When we compared the response to the treatment, none of the answers to any of the questions on the respiratory questionnaire were found to correlate with patient improvement ($r = 0.11$). Also, there are no correlations with BHR (positive or negative response) and response to treatment ($r = 0.09$).

During follow-up we treated 25 patients in whom the study treatment failed (8 in the active group and 17 in the placebo group) with prednisone (20 mg) in an open-label manner for 15 days. Cough cessation was observed in 21 of these patients. In 4 patients (1 in the active group and 3 in the placebo group), after 1 more course of prednisone and oral omeprazole, 40 mg twice daily for at least 12 weeks, the cough finally resolved.

DISCUSSION

Therapy with a high-dose inhaled corticosteroid provided an excellent response, resulting in complete resolution of cough in 82% of the patients with chronic cough where extrapulmonary causes, such as postnasal drip and gastroesophageal reflux disease, had been excluded. As a defining variable, we adopted a cough duration of at least 8 weeks,⁵ as opposed to

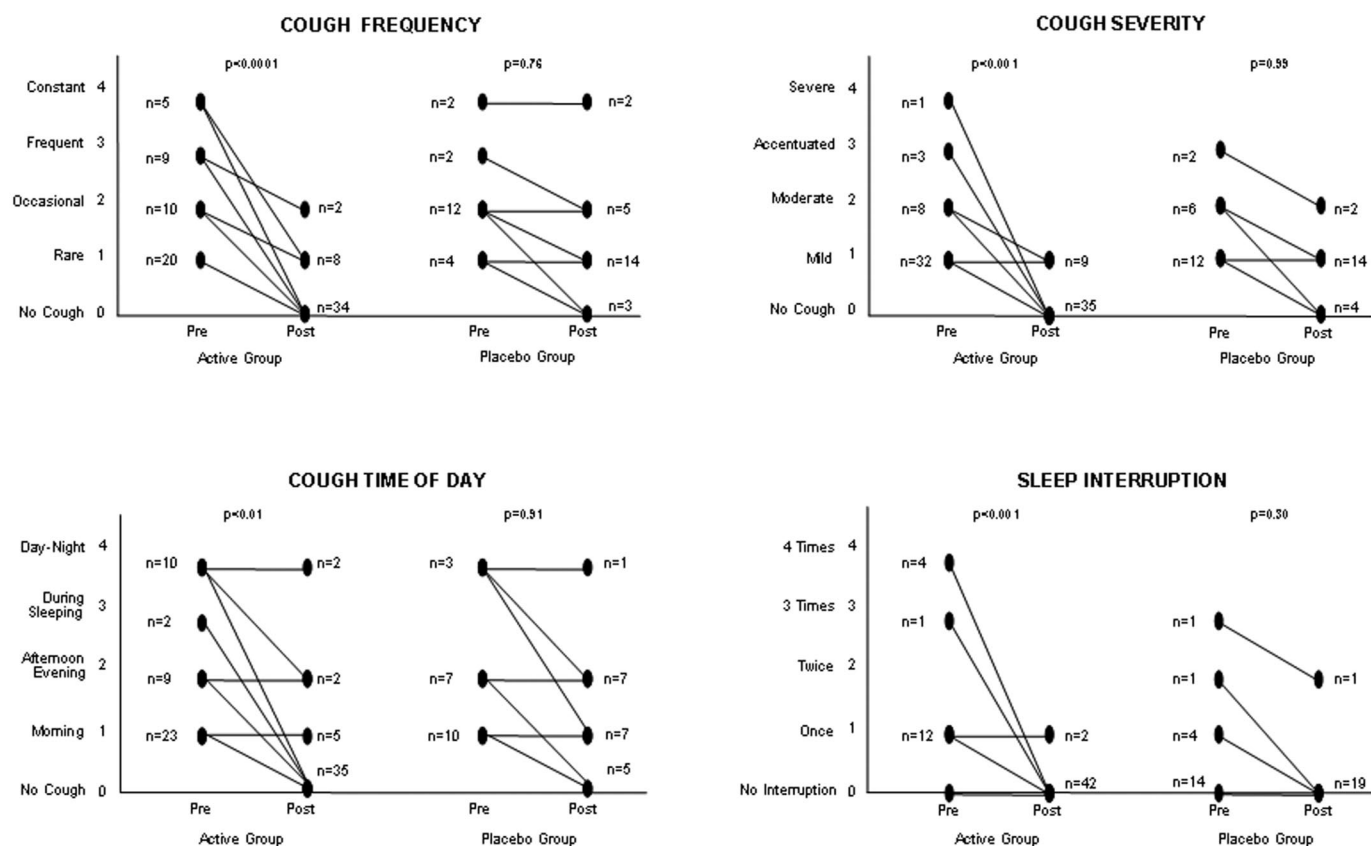


Figure 2. Pretreatment and posttreatment cough frequency, severity, time of day, and sleep interruption at night reported in a diary by patients in the active (n = 44) and placebo (n = 20) groups.

3 weeks,³¹ thereby minimizing confounding causes, such as sinusitis, bacterial respiratory infections, and allergic rhinitis. The median cough duration in the present study was 20 weeks, with wide variation, which was higher than the average duration in other studies.^{10,32} This can be explained by difficulties and delays in receiving medical attention, inadequate or no investigation, and self-medication.

In the present study, as in that by O'Connell et al,³³ we found that questions related to characteristics such as constant wheezing, wheezing during cold or influenza, and cough caused by running or walking fast were more closely correlated with BHR in the active group than in the placebo group. We found no differences between the active and placebo groups in any of the questions on the questionnaire. Nevertheless, none of these questions were found to have a significant predictive value for a satisfactory response to treatment. The relative strengths of the relationship observed differed by symptom, being much less strong for cough. This may reflect the fact that cough and airflow obstruction are manifestations of 2 different pathologic processes—cough arising from mucosal inflammation and mucous hypersecretion and airflow obstruction from emphysematous change—and that although these processes frequently coexist in the lung, cough and

sputum production are not necessarily associated with airflow obstruction.

The various functional variables did not differ between the active and placebo groups in either the means or the predicted values. This is in agreement with studies on CVA that reported no abnormalities for these variables.^{8,12} The BPT initially was used as a tool to determine whether cough could be the only manifestation of asthma.¹¹ Prospective studies^{10,32} have been performed to evaluate the usefulness of BPT predicting when asthma is the cause of chronic cough. Irwin et al¹⁰ also stated that this was the only manner in which to detect the prevalence of asthma among the patients in their study.

Thirty-two patients (50%) tested positive for methacholine on BPT. Mean values of PD₂₀ were higher in the active group than in the placebo group. However, the PD₂₀ values in those with a positive BPT result were higher than those in patients with asthma (usually <4 mg/mL) and fall into a "gray area" because this degree of hyperresponsiveness can also be found in healthy individuals. In a study by Fujimura et al,³⁴ the median PD₂₀ for methacholine in a group with CVA was 5.18 mg/mL.

IMPROVEMENT OF COUGH

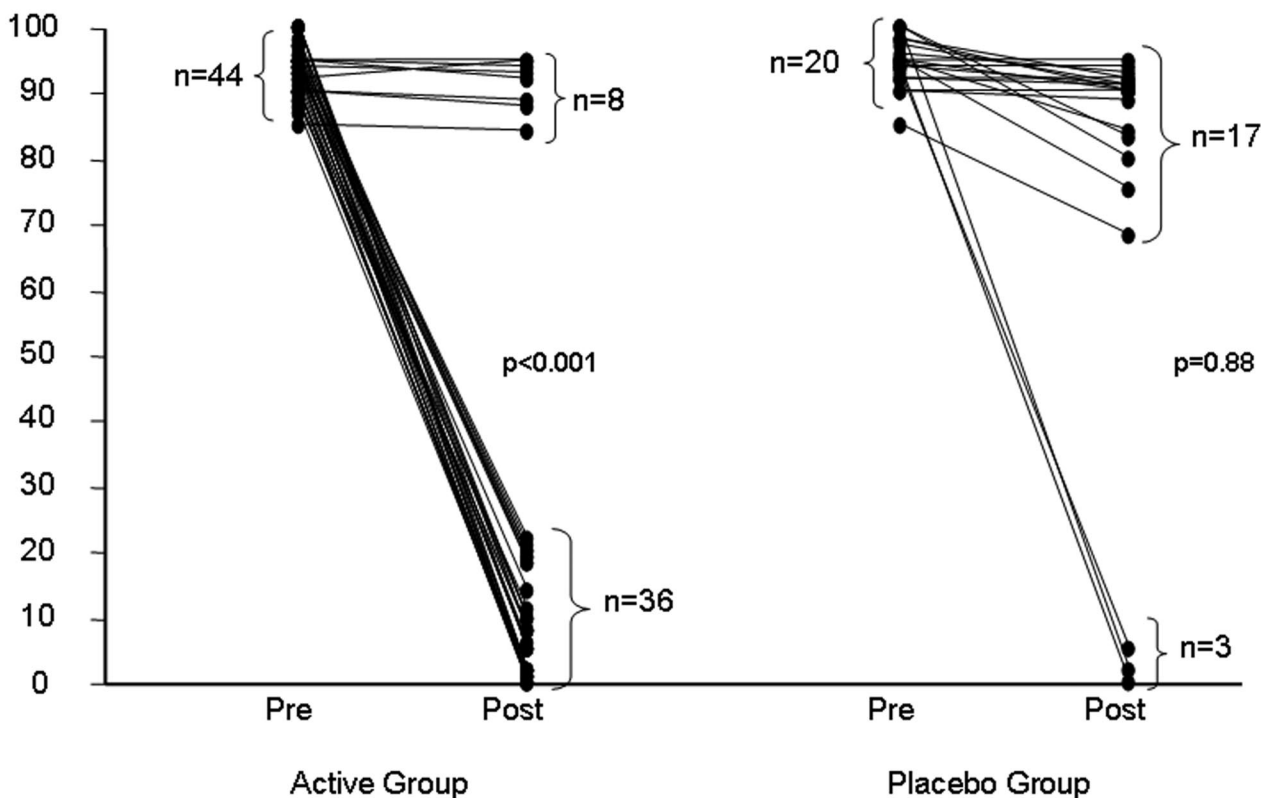


Figure 3. Pretreatment and posttreatment cough improvement reported on a visual analog scale by patients in the active (n = 44) and placebo (n = 20) groups.

The effects of fluticasone on cough in asthmatic patients are frequently seen within 2 weeks.³⁵ Two others studies, one in children³⁶ and the other in adults,³⁷ examined the effect of corticosteroids on cough and found no benefit. Two major reviews in the Cochrane Database by Tomerak et al (1 with inhaled corticosteroid therapy³⁸ and 1 with inhaled bronchodilator therapy³⁹) showed small improvement with very high-dose inhaled corticosteroid compared with placebo and no difference between salbutamol and placebo in reducing the frequency of cough. In this study, of the 44 patients treated with a corticosteroid, 36 resolved their cough after 2 weeks. Twenty-one patients had positive BPT results and were, therefore, diagnosed as having CVA. The number of positive BPT results plus response to the treatment is higher than that found in other studies and is probably attributable to the inclusion and exclusion criteria and the higher dose of corticosteroid that we chose.

Fifteen patients who responded to treatment had negative BPT responses. This might be due to nonasthmatic eosinophilic bronchitis, although we did not perform eosinophil counts in induced sputum as recommended by

Gibson et al.⁴⁰ Some investigators,^{12,41} based on the efficacy of corticosteroids, have frequently made a CVA diagnosis.

In evaluating patients with CVA, Hannaway and Hopper⁴² reported that 55% of the patients responded positively to allergy skin prick testing with various inhaled allergens. In the present study, positive results were found in 50% of patients in the active group and in 55% of patients in the placebo group. There was no correlation with response to treatment. Consequently, these tests should not be used to predict patient improvement with the use of medication. The symptom diary and the VAS proved to be useful tools in the evaluation of cough and can be used in everyday practice in the follow-up and monitoring of this symptom.

In adults with or without asthma, no correlation was found between cough receptor sensitivity and BHR in patients with chronic cough. One can speculate that persistent cough in patients with BHR may be triggered by bronchoconstriction, whereas that in patients without BHR and who do not develop asthma may be induced by hypersensitivity of airway irritant receptors.

There are various alternatives for the treatment of chronic cough due to asthma, such as the use of bronchodilators alone, oral and inhaled corticosteroids, and leukotriene receptor antagonists. To date, there has been no standardization of dosing schedules or treatment duration. Our choice of the type of corticosteroid (beclomethasone), administration route (inhaled), dose (1,500 μg), and treatment duration (14 days) was based on the availability of the medication and the placebo for the study and the good response that asthmatic patients have to this treatment because patients with chronic cough are similar to asthmatic patients in several ways. Chaudhuri et al¹³ found an increase in many markers before treatment for chronic cough with inhaled corticosteroids and a decrease in others after this treatment, similar to asthma. In contrast to Pizzichini et al,⁴³ who found no response to a trial of inhaled corticosteroids in individuals with chronic cough with asthma, postnasal drip syndrome, and gastroesophageal reflux disease, Chaudhuri et al¹³ found partial response to fluticasone regardless of the cause of the cough. Shirahata et al⁴⁴ found significant efficacy of inhaled corticosteroid in a CVA trial, but the study was not placebo controlled.

The present results are different from those of these authors^{10,41} because they included different causes of chronic cough, whereas we excluded extrapulmonary factors and concentrated on pulmonary causes. We showed that beclomethasone, 1,500 $\mu\text{g}/\text{d}$, delivered in a metered-dose inhaler regimen exhibited a significant overall effect on daily cough scores in a subgroup of patients with chronic cough.

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