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Acupuncture and Bronchial Asthma: A Long-Term Randomized Study of the Effects of Real Versus Sham Acupuncture Compared to Controls in Patients with Bronchial Asthma

TULLIO C. MEDICI, M.D.,[1] ELZBIETA GREBSKI, M.D.,[1] JIAMIN WU, M.D.[1]
GEORG HINZ, M.D.,[2] and BRUNELLO WÜTHRICH, M.D.,[3]

ABSTRACT

Background: Acupuncture has traditionally been used in China in the treatment of bronchial asthma and is being increasingly applied in Western countries. Although there are many published studies on acupuncture and asthma, few meet the scientific criteria necessary to prove the effectiveness of acupuncture.

Objective: To examine the short- and long-term effects of real versus sham or no acupuncture in patients with bronchial asthma.

Design: Randomized partially blinded study with three parallel groups.

Subjects: Sixty-six (66) patients of both genders (mean age, 39 years) with mild-to-moderate persistent bronchial asthma.

Interventions: After 2 weeks of run-in, the patients with asthma were randomized to receive either real (23 patients) or sham acupuncture (23 patients) or no acupuncture (20 patients). Two acupuncture periods (each 4 weeks) within the first 4 months were followed by a 6-month observation.

Measurements: Primary outcome was the change of peak expiratory flow (PEF) variability at the end of the two treatment periods. Secondary outcomes were changes in forced expiratory volume in 1 second (FEV_1), airway responsiveness, symptoms of asthma, the use of asthma drugs, and patients' well-being. Moreover, the effect of the intervention on eosinophils and eosinophil cationic protein (ECP) in blood and sputum was assessed.

Results: PEF variability decreased in all groups. In a subgroup of patients whose asthma medication remained fairly unchanged, PEF variability decreased significantly after needling of real as well as sham points at month 4 and 5 compared to controls ($p \leq 0.005$). However, there was no difference in the decrease of PEF variability between patients who had the blinded treatment with real or sham acupuncture. Most of the other functional and clinical variables did not differ from those obtained in controls. Eosinophils and ECP in blood and sputum decreased in all groups, but the only significant differences were found in blood eosinophil count at 4 months between sham acupuncture and the control group ($p < 0.05$) and at 10 months between real and sham acupuncture ($p < 0.05$) suggesting a possible effect on eosinophilic inflammation.

[1]Department of Internal Medicine, University Hospital Zurich, Switzerland.
[2]Medidata, Study Planning and Data Analysis Zurich, Switzerland.
[3]Allergy Unit, Department of Dermatology, University Hospital, Zurich, Switzerland.
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Conclusions: In view of the fact that the effects after real and sham acupuncture compared to controls who had no needling at all were small, in all likelihood clinically irrelevant, our data do not seem to support the use of acupuncture in the management of pharmacologically well-treated patients with mild-to-moderate persistent asthma.

INTRODUCTION

Complementary and alternative medicine is a widespread phenomenon. In Europe, complementary therapies are used by 20–50% of the population, and the popularity of complementary medicine is growing rapidly (Fisher and Ward, 1994). In the United States, a national survey showed that the proportion of the population who use alternative therapies increased from 33.8% to 42.1% between 1990 and 1997 (Eisenberg et al., 1998). More people now visit alternative practitioners than see conventionally trained physicians. Acupuncture has traditionally been used in asthma treatment in China and is increasingly being used in Western countries. Although there are many published studies on acupuncture and asthma, few meet the scientific criteria necessary to prove the effectiveness of acupuncture. In 1991 Kleijnen et al. published a systematic review of the controlled clinical trials in asthma. They concluded that claims of the efficacy of acupuncture in the short- or long-term treatment of asthma are not supported by the results of well-performed clinical trials. Recently, Linde et al. (1997) in a Cochrane Review reached the same conclusion when evaluating the effectiveness of acupuncture for the long-term management of asthma (4). In view of the increased use of acupuncture on the one hand, and lack of interpretable data regarding efficacy of acupuncture in asthma on the other, the authors concluded that there was an urgent need for quality research that should take into account the complex nature of acupuncture use as a treatment modality in asthma.

We therefore undertook a long-term randomized study of the long-term effects of a standardized real acupuncture regimen versus sham and (versus) no acupuncture in patients with allergic bronchial asthma on pulmonary function, airway hyperresponsiveness, clinical symptoms, and consumption of medication as well as eosinophilic inflammation of the bronchial mucosa.

PATIENTS AND METHODS

Patients

Adults of both gender, 16 to 70 years of age who had mild-to-moderate persistent allergic bronchial asthma (Global Initiative for Asthma, 1995) with perennial symptoms for not more than 10 years and who required the daily use of asthma drugs (i.e., inhaled β-agonists, with or without inhaled corticosteroids) were recruited. Peak-flow rate measured in the morning had to be greater than 60% of the predicted value and eosinophils had to be present in a sufficiently high number in induced sputum ($\geq$ 5%). In addition, according to Traditional Chinese Medicine (TCM), the patients had to have the clinical characteristics of an excess (*Shi*)-type asthma (Stux and Pomeranz, 1987).

Patients were excluded if: (1) they had been treated with acupuncture for any clinical condition during the last 12 months; (2) received immunotherapy for allergic rhinitis or asthma in the preceding year; (3) received oral corticosteroids for a prolonged time ($\geq$ 8 weeks per year); (4) inhaled more than 1000 μg of beclomethasone daily or 800 μg of budesonide daily; (5) had a blood clotting disorder, (6) smoked more than 10 cigarettes per day; (7) were not compliant regarding a long-term research study; and/or (8) did not show excess (*Shi*)-type asthma.

The eligibility was verified during the run-in period, before randomization was carried out, in which each criterion for eligibility and ineligibility was confirmed. The eligibility was determined by two independent pneumologists (T.C.M., E.G.). Moreover, a Chinese physician (J.W.) who was trained in Traditional Chinese Medicine as well as orthodox medicine established the diagnosis of excess (*Shi*)-type asthma based on the theory of Chinese medicine.

This type of asthma is caused by external winds and cold influences. Its manifestations are attacks of shortness of breath, cough, and

wheezing. Moreover, as in all Excess or *Shi* type disorders, it is characterized by an excessive amount of qi or blood in organs; the most important signs being reddening of the tongue, redness of the face, and a strong pulse (Stux and Pomeranz, 1987).

Design and interventions

The study course is outlined in Table 1. After a run-in of 2 weeks the subjects were randomly assigned into one of three groups: (1) real acupuncture; (2) sham acupuncture, and (3) controls (de la Torre, 1993; Jobst, 1995). Randomization followed a block design to ensure the continued equivalence of group size. The first group was treated twice weekly for 8 weeks—interrupted by 2 months—with Chinese acupuncture based on standardized acupuncture formulas, and the other group received simulated or sham acupuncture for the same period (Table 1). To ensure that correct techniques were used, real and sham acupuncture were performed by a well-trained, experienced physician (J.W.). She had no other contact with technicians, or physician–evaluators during the experimental sessions. Although traditional acupuncturists select points on an individualized basis for each patient, (Jobst, 1995; Yan Jie, 1992), standardized acupuncture was chosen for this study to ensure that the same type of therapy was administered to each subject (Fig. 1). The 11 points chosen for real acupuncture treatment consisted of points, for which stimulation is believed to have an antiasthmatic effect (*Dazhui*, *Dingchuan*, *Feishu*, *Taixi*, *Yuji*, *Shanyinjiao*), an anti-inflammatory action (*Hegu*, *Quchi*, *Dazhui*, *Tsusanli*), and an antiallergic as well as antihistaminic effect (*Tsusanli*, *Zhagmen*, *Neiguan*) (Yan Jie, 1992).

The sham nonpoints (Jobst, 1995) were in the vicinity of real acupuncture points but at precisely localized regions where no acupuncture points are known to exist.

The acupuncture needles were $1\frac{1}{2}$-inch, 30-gauge, solid stainless-steel needles manufactured in the People's Republic of China. Depth of insertion varied according to the type of acupuncture, the thickness of skin, and subcutaneous fatty tissue. In real acupuncture the depth of the inserted needle ranged from 13 to 40 mm at an angle of 45 or 90 degrees. In sham acupuncture the skin was punctured and the needle inserted to a depth of maximally 10 mm at an angle of 10 degrees according to the suggestions of Vincent and Richardson (1986) concerning the technique of sham acupuncture. The needles were manually manipulated 30 times every 5 minutes during the 20-minute-treatment period in a similar manner for both acupuncture conditions. The subjects, the evaluating physicians, and the technicians were all unaware of which type of acupuncture treatment (real or sham) was performed, fulfilling the criteria of a double-blinded study according to the definition by Jobst (1995).

The third group did not receive any needling; they attended the same clinic visits during the whole study period as the patients who had acupuncture.

Table 1. Tests Performed and Time Course of the Study

	Acupuncture periods												
	Run-in		*Period 1*			*Period 2*					*Follow-up*		
Months	*−0.5*		*0*	*1*	*2*	*3*	*4*[a]	*5*[a]	*6*	*7*	*8*	*9*	*10*[a]
Acupuncture treatment (real/sham)	–	–	x------	x		x------	x	–	–	–	–	–	–
Clinical assessments	x	x	x	x	x	x	x	x	x	x	x	x	x
Diary cards	–	x	x	x	x	x	x	x	x	x	x	x	x
Lung function (FVC, FEV_1, PEF)	x	x	x	x	x	x	x	x	x	x	x	x	x
Methacholine test	–	x	–	x	–	–	x	x	–	x	–	–	x
Blood samples (eosinophils, ECP)	x	x	–	x	–	–	x	x	x	–	–	–	x
Induced sputum (eosinophils, ECP)	x	x	–	x	–	–	x	x	x	–	–	–	x
Skin-prick test	x	–	–	x	–	–	x	–	–	–	–	–	x

[a]Main visits.

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second, PEF, peak expiratory flow; ECP, eosinophil cationic protein.

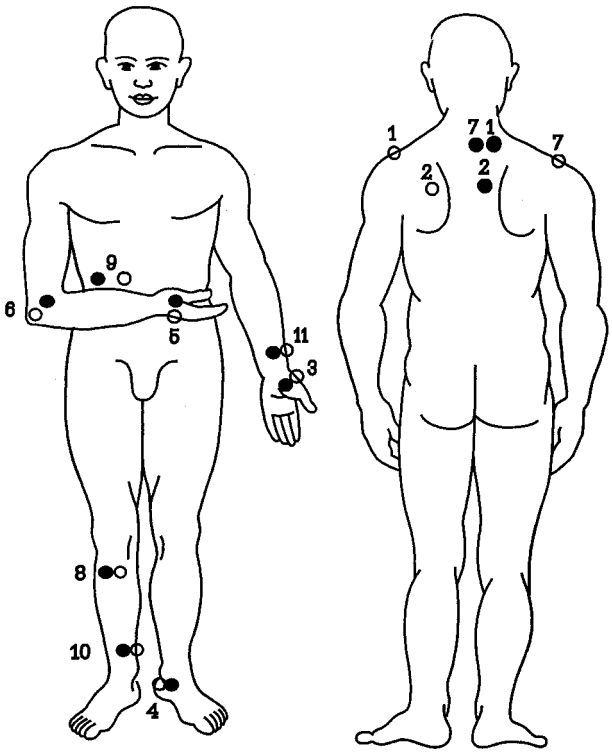

FIG. 1. List of acupuncture points: real points (closed circles), sham nonpoints (open circles): (1) *Dingchuan*; (2) *Feishu*; (3) *Yuji*; (4) *Taixi*; (5) *Hegu*; (6) *Quchi*; (7) *Tazhui*; (8) *Tsusanli*; (9) *Zhangmen*; (10) *San Yinjiao*; and (11) *Neiguan*.

During the treatment periods (period I and II) subjects continued to keep their symptom and medication-use diaries; the subjects were also examined by a physician and had pulmonary function tests. Subjects were asked to keep their regularly scheduled medications throughout the treatment periods at the same level, if possible. Then, 1 month after the end of period II, the subjects could adjust their medication depending on natural fluctuations in asthma status and according to the physician's advice.

Between period I and II, subjects did not receive any form of acupuncture and were evaluated twice (clinical assessment, lung function). During period II, subjects were evaluated objectively and subjectively as during period I. Thereafter, they were studied monthly during a follow-up of at least 6 months.

The institutional ethical committee approved the study. All eligible patients gave written consent to participate.

Measurements

Baseline assessments. On entry into the study, all subjects had their medical histories taken, a physical examination, lung function and skin-prick tests (Soluprick; ALK, Copenhagen, Denmark) with the most common perennial allergens (*Dermatophagoides pteronyssimus*, *Dermatophagoides farinae*, cat, dog, horsehair, and wheat flour) were carried out.

Measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEF) were performed before and after inhalation of 200 μg of salbutamol according to American Thoracic Society criteria (1991) using a wet spirometer (Pulmonary Function Lab 2400; SensorMedics, Bilthoven, The Netherlands).

Methacholine responsiveness was measured using a breath-activated dosimeter (Mefar "MB 3," Bovezzo, Italy), with subjects breathing from functional residual capacity to total lung capacity (Eiser et al., 1983). Subjects took 10 successive tidal breaths of normal saline followed by increasing cumulative doses of methacholine: 100, 250, 500, 1000, and 2000 μg, respectively. The results were expressed as the provocative dose giving a 20% fall in FEV_1, as obtained from the log dose–response curve by linear interpolation of the last two points (PD 20).

Venous blood samples were collected and eosinophils counted using an automated hematology analyzer (H 2, Technicon Instruments Corp., Tarrytown, NY). For ECP determinations, venous blood was taken with the use of 4-mL serum separation tube (SST) vacutainer tubes (Becton Dickinson, Meyran, France), and were allowed to clot at stable room temperature for 60 minutes before centrifugation. The samples were then centrifuged at 1400g for 10 minutes (Megafuge 1.0 R, Heraeus, Zürich, Switzerland) and the serum separated and frozen at -20°C.

To induce sputum, each subject inhaled a sterile 3%-saline solution from an ultrasonic nebulizer (Heyer Mono, Carl Heyer GmbH, Bad Ems, Germany) for 10 minutes. Subjects were encouraged to cough throughout the procedure and to expectorate all secretions (sputum and saliva) into a plastic container. The volume of the samples were measured. One gram of sputum was used to determine the to-

tal cell count with a standard hemocytometer. For that purpose, an equal volume of a 20%-formalin solution was added to protect cells by fixation before liquefying the specimens by ultrasonification as described by Oppenheimer et. al. (1967). Two smears of the unfixed sputum were prepared and stained by the Papanicolaou method. A differential count of the cell types was performed, including all types of inflammatory and bronchial epithelial cells (Chodosh and Medici, 1971; Medici and Chodosh, 1972). Eosinophil percentage, as well as total cell number per milliliter, were determined.

Sputum specimens were then homogenized with an ultrasonic Branson Sonifier (Sonic Power CO, Danbury, CT) for 30 seconds at maximal output, before being centrifuged at 1400*g* for 10 minutes at 4°C. One portion of the supernatant was aspirated and frozen at −80°C.

Serum and sputum ECP concentrations were measured by an ECP fluoroenzyme immunoassay (FEIA) method (Pharmacia CAP system), according to the instructions of the manufacturer (Pharmacia Diagnostics AB, Uppsala, Sweden). The serum samples remained undiluted, those of the sputum were diluted in the ratio of 1:10, and each was assayed twice (Grebski et al., 1998).

Medical assessments. Patients were followed initially for 2 weeks (run-in phase), during which time they kept daily diaries, recording asthma symptoms (i.e., episodes of nocturnal and daytime wheezing, coughing, chest tightness, or breathlessness, and production of sputum). Concomitant medication was recorded. Each subject's prebronchodilator PEF (using the best of three attempts) in the morning and evening was assessed. The patients were asked to record their well-being and episodes of limitation of activity (quality of life). At the initial visit, during the run-in phase, the patients were asked about their motivation to participate in a trial of complementary medicine.

Outcomes

The primary outcome was the change of mean daily PEF variability (maximal PEF − minimal PEF)/(mean daily PEF) × 100% before the use of a bronchodilator at the end of the two treatment periods, (i.e., after 4 months) (Lebowitz and Quanjer, 1997). The mean PEF variability was calculated from the seven daily values preceding the clinical visit.

Secondary outcomes were the changes in airway responsiveness, FEV_1, symptoms of asthma, and the use of asthma drugs (β_2 agonists, inhaled corticosteroids). Moreover, the effect of the interventions on eosinophils and ECP in blood and sputum was assessed.

Statistical analysis

The outcomes after 4 and 5 months were evaluated in a subgroup of patients after having excluded subjects with major changes in the use of asthma medication. In order to detect a possible change in the need of asthma medication, no patient was, however, excluded after the long-term follow-up at 10 months (intention-to-treat population). For the statistical comparisons, changes from baseline (day 0) to months 4, 5, and 10 were calculated. After 4 and 5 months, descriptive statistics were also shown for the "all-patients" group. Because the subgroup comprised fewer patients than the all-patients group, analysis of covariance (ANCOVA) was performed with regard to the primary parameter in order to get more precision and power. The baseline value of the peak flow variability and patient's body weight were found to be the best covariates. In contrast, most of the secondary parameters showed a large variability and had small power to detect group differences.

Regarding peak flow variability and FEV_1, parametric tests (analysis of variance [ANOVA]) were used for comparison among the three treatment groups. All other outcome measures were evaluated with nonparametric statistics (Kruskal-Wallis test), because data transformations (log or square root) did not result in a sufficient approximation to normal distribution. Mean improvement of at least 15% of the functional parameters or transformed parameters as compared to the baseline values was considered to be of clinical importance.

Two-group comparisons with the *t* test or the Wilcoxon-Mann-Whitney test were performed, if the overall tests regarding the three treatment groups showed a p value of 0.10 or less. With

regard to the baseline characteristics of the patients, either ANOVA or Kruskal-Wallis test or χ^2-test were appropriate. The significance threshold was defined with $\alpha = 0.05$ using two-sided tests.

RESULTS

During the recruitment period, 123 subjects were assessed, 66 of whom were eligible. Of those who were not eligible, 41 patients did not fulfill the entry criteria (most of them did not reach 5% of eosinophils in induced sputum), for 11 patients the study was too time consuming and 5 patients could not be included for other causes (anemia, refusal to have blood drawn, or long-term holiday abroad).

All 66 subjects who entered the study did complete the treatment periods. Dropouts occurred only after 5 months. In the group who had real acupuncture 1 patient dropped out at month 5 because of a leg fracture, and 1 patient in the sham acupuncture group moved to a foreign country at month 7. All 20 patients who acted as controls completed the entire study. The baseline characteristics of the 66 subjects are shown in Table 2. There were no statistically significant differences between the subjects of the three groups. Asthma attacks during the day and night ranged from none to 38 and none to 11 attacks per week, corresponding to mild-intermittent-to-moderate persistent asthma according to the classification of the World Health Organization/National Heart, Lung, and Blood Institute workshop report (Global Initiative for Asthma, 1995). However, FEV_1 (percent of predicted) was only mildly reduced and PEF variability was small in the three groups (Table 3, baseline), indicating mild asthma. On the contrary, the median doses of methacholine that provoked a 20% fall in FEV_1 was low, indicating pronounced bronchial hyperresponsiveness. The eosinophils and ECP in blood and induced sputum were increased. None of the differences among the three groups were statistically significant. Regarding the motivation to participate in the study, two thirds of the subjects who received either real or sham acupuncture believed that needling had a positive effect, whereas only one third of the controls did so. The difference was statistically insignificant.

Outcomes at four, five, and ten months

Tables 3 and 4 show the actual values of the primary and secondary outcome variables in all patients at baseline at 4, 5, and 10 months. The changes of the variables for all patients as well as of those for the subgroup whose asthma medication remained fairly stable within the first 5 months are listed in Tables 5 and 6.

At the end of the treatment periods at 4 months, the primary outcome, (i.e., PEF variability) decreased after needling real points or sham nonpoints more than in controls compared to the values observed at baseline (Table 5). The values differed significantly among the three subgroups (i.e., in patients without a major change in asthma drugs) when baseline value and body weight were taken into consideration by ANCOVA ($p = 0.002$). In these patients PEF variability decreased by 57% and 53% after real and sham acupuncture whereas it increased to 6% in the control group. The difference in the decrease of the PEF

TABLE 2. BASELINE CHARACTERISTICS OF THE SUBJECTS

Characteristic	*Real acupuncture (n = 23)*	*Sham acupuncture (n = 23)*	*Control group (n = 20)*
Male—number (%)	11 (48%)	10 (44%)	13 (65%)
Female—number (%)	12 (52%)	13 (56%)	7 (35%)
Age-yr[a]	39.3 ± 11.4	38.4 ± 11.8	40.6 ± 13.5
Height—cm[a]	171.8 ± 10.4	173.1 ± 7.9	171.9 ± 10.0
Weight–kg[a]	69.8 ± 10.8	68.0 ± 10.2	70.9 ± 11.1
Smokers—number (%)	3 (13%)	5 (22%)	4 (20%)
Inhaled corticosteroid use—number (%)	13 (56.5%)	11 (47.8%)	9 (45.0%)

[a]Mean is ± the standard deviation.

TABLE 3. PRIMARY AND SECONDARY VARIABLES DURING THE STUDY

Variable	*Real acupuncture*	n	*Sham acupuncture*	n	*Control group*	n
			PEF-variability median (range)			
PEF-Var (%)						
Baseline	6.4 (1.6–31.8)	22	7.8 (1.7–48.2)	23	7.7 (2.4–45.8)	19
4 month	4.4 (1.3–17.7)	19	4.5 (2.2–30.0)	23	6.7 (1.1–33.6)	17
5 month	4.4 (1.3–11.5)	19	5.3 (1.3–18.0)	22	6.8 (1.4–17.5)	19
10 month	2.9 (0.7–11.6)	20	5.2 (1.3–15.5)	19	4.8 (1.5–18.8)	20
			FEV_1 and PD20 (Mean ± SD)			
FEV_1 (% pred)						
Baseline	91.1 ± 17.2	23	87.0 ± 16.1	23	85.7 ± 18.4	20
4 month	94.0 ± 16.6	23	87.6 ± 15.2	23	90.2 ± 13.4	19
5 month	92.0 ± 17.8	22	90.3 ± 15.4	23	89.9 ± 17.2	19
10 month	90.5 ± 16.9	22	87.3 ± 17.7	22	87.7 ± 17.6	20
PD20 (log μg)						
Baseline	4.86 ± 1.42	23	4.92 ± 1.22	21	4.16 ± 1.14	19
4 month	5.56 ± 1.45	23	4.95 ± 1.46	21	4.63 ± 1.38	17
5 month	5.59 ± 1.32	21	5.44 ± 1.38	21	4.62 ± 1.43	17
10 month	5.57 ± 1.5	21	5.33 ± 1.45	20	4.77 ± 1.47	19
			Blood values median (range)			
Eosinophils (cells × 10^6/L)						
Baseline	365 (120–1390)	21	383 (50–950)	22	405 (105–1075)	19
4 month	300 (85–1125)	21	260 (80–1080)	22	363 (90–895)	18
5 month	350 (85–1250)	19	228 (90–950)	22	325 (95–895)	18
10 month	258 (65–575)	20	285 (155–740)	21	380 (60–745)	19
ECP (μg/L)						
Baseline	16.0 (4.68–72.4)	23	19.3 (6.41–41.1)	23	13.1 (2.49–54.2)	20
4 month	13.3 (4.8–64.9)	23	12.6 (3.83–44.1)	23	15.9 (3.99–56.7)	19
5 month	16.7 (4.05–46.2)	21	17.3 (5.16–43.8)	23	14.6 (6.0–62.7)	19
10 month	16.9 (7.77–38.0)	22	17.6 (3.90–68.2)	23	15.7 (5.80–63.8)	20
			Sputum values median (range)			
Eosinophils (%)						
Baseline	21.6 (2.0–76.1)	21	15.3 (3.6–65.6)	21	18.7 (1.4–60.3)	16
4 month	20.4 (1.5–56.8)	20	8.5 (0.4–64.1)	18	12.4 (0.7–52.3)	15
5 month	18.9 (0–62.7)	19	13.5 (0.8–82.4)	18	30.0 (0.6–69.6)	16
10 month	11.0 (0.8–81.6)	19	10.6 (0.1–88.2)	21	14.2 (0.3–42.5)	17
ECP (μg/L)						
Baseline	344 (30–3222)	19	235 (<2–1325)	19	301 (60–1327)	17
4 month	243 (13–3192)	21	104 (13–1324)	21	282 (8–7189)	17
5 month	198 (5–77636)	20	302 (10–6900)	23	353 (2–3050)	17
10 month	262 (20–3013)	21	176 (67–7978)	23	208 (<2–9209)	19

FEV_1, forced expiratory value in 1 second; PD20, doses of methacholine that provoked a 20% fall in FEV_1, $\log_{10}$-transformed; ECP, eosinophil cationic protein.

variability between the two acupuncture regimens was, however, statistically insignificant. At 5 months, the corresponding decrease of PEF variability was 61%, 52%, and 4% ($p = 0.005$). At 10 months, the PEF variability did not differ significantly among the groups, although the best result (i.e., a decrease of 58%) was seen in patients who received real acupuncture.

Table 4. Asthma Attacks During the Study

Variable	Real acupuncture	n	Sham acupuncture	n	Control group	n
	Asthma attacks per week mean (range)					
Attacks during the day						
Baseline	4.1 (0–14)	23	5.5 (0–38)	22	2.1 (0–12)	20
4 months	1.2 (0–12)	22	1.7 (0–14)	22	1.4 (0–8)	19
5 months	1.2 (0–18)	21	1.8 (0–13)	22	1.7 (0–14)	19
10 months	1.3 (0–15)	21	3.2 (0–27)	20	1.5 (0–11)	20
Attacks at night						
Baseline	1.2 (0–6)	23	2.1 (0–11)	22	2.0 (0–8)	20
4 months	0.3 (0–6)	22	0.3 (0–5)	22	1.1 (0–7)	19
5 months	0.7 (0–10)	21	0.3 (0–2)	22	0.9 (0–7)	19
10 months	0.3 (0–7)	21	0.3 (0–3)	19	0.4 (0–2)	20

The decrease in PEF variability at 4 and 5 months was not accompanied by a similar change of the other spirometric values (Table 5). Correspondingly, asthma attacks during the day and night declined slightly in all three groups (Table 4), the differences among the groups being statistically insignificant, except after 10 months. At this time, the 74% and 67% decrease of asthma attacks in patients receiving real or sham acupuncture differed significantly from the values obtained in controls ($p < 0.05$).

The use of inhaled β-agonists varied slightly during the study in all three groups (Table 6), the mean decrease in the real acupuncture group being more distinct after 10 months. The use of inhaled steroids increased slightly in the patients who received real acupuncture and in the controls, whereas this usage remained almost constant in the sham acupuncture group. None of the changes in asthma drugs were statistically significant.

Scored well-being and physical activities were not significantly affected by real or sham acupuncture.

Airway responsiveness to methacholine improved in the three groups without statistically significant differences between the treatments (Table 5).

Eosinophils in blood and induced sputum decreased during the treatment periods in all three groups. The decrease of eosinophils in blood was greater in the patients receiving real or sham acupuncture. At month 4, only the difference in the group with sham acupuncture was statistically significant in comparison to controls ($p < 0.05$). At month 10, there was a statistically significant difference between patients receiving real and sham acupuncture ($p < 0.05$). Similar but smaller changes were observed when looking at the effects of acupuncture on eosinophils in sputum compared to controls. None of the changes reached statistical significance. This was also the case, when analyzing the effect of the two treatment regimens on ECP concentrations in blood and induced sputum. Although there were some changes after 4 and 5 months favoring patients with real or sham acupuncture, none of them were statistically significant.

No serious adverse effects occurred during the study necessitating the premature termination of the study. Minor side-effects were recorded in only two patients who received real acupuncture. Both complained of prolonged pain at a specific acupuncture point (*Quchi* at right elbow and *Tsusanli* at right knee) after the needles were withdrawn. The painful sensations disappeared without treatment.

DISCUSSION

Among the 66 patients enrolled in this study of the long-term efficacy of acupuncture for bronchial asthma, there was some improvement in pulmonary function, reduction in symptoms, improved physical activities, and a reduction of medication usage. In addition, bronchial hyperresponsiveness decreased as

Table 5. Changes of Primary and Secondary Outcomes

	Changes after 4 months					*Changes after 5 months*					*Changes after 10 months*		
	All patients	n	*Subgroup*	n	*Significance*	*All patients*	n	*Subgroup*	n	*Significance*	*All patients*	n	*Significance*
						PEF Variability, FEV_1 and PD20 (mean ± SD)							
PEF Var. (log_{10} %)													
Real acupuncture	−0.196 ± 0.416	20	−0.299 ± 0.408	10		−0.236 ± 0.383	21	−0.354 ± 0.330	11		−0.372 ± 0.406	20	
Sham acupuncture	−0.203 ± 0.325	23	−0.313 ± 0.332	15	$p = 0.002$*	−0.222 ± 0.385	22	−0.308 ± 0.412	13	$p = 0.005$*	−0.246 ± 0.491	19	n.s.
Control	−0.095 ± 0.306	18	−0.051 ± 0.246	11		−0.121 ± 0.330	19	−0.092 ± 0.262	10		−0.204 ± 0.283	19	
FEV_1 (% pred)													
Real acupuncture	2.88 ± 12.9	23	2.46 ± 10.2	15		1.20 ± 13.6	22	−0.31 ± 5.8	13		0.01 ± 11.0	22	
Sham acupuncture	0.65 ± 8.7	23	−0.55 ± 9.3	17	n.s.	3.35 ± 11.9	23	2.64 ± 10.7	15	n.s.	0.95 ± 15.1	22	n.s.
Control	4.06 ± 14.2	19	−1.61 ± 12.4	12		4.03 ± 12.5	19	0.42 ± 5.9	11		2.02 ± 12.420	20	
PD20 (log μg)													
Real acupuncture	0.70 ± 1.02	23	0.77 ± 1.01	15		0.62 ± 1.29	21	0.42 ± 1.05	12		0.65 ± 0.97	21	
Sham acupuncture	0.04 ± 0.81	21	0.13 ± 0.89	15	n.s.	0.55 ± 1.04	20	0.65 ± 0.98	12	n.s.	0.43 ± 1.13	19	n.s.
Control	0.53 ± 0.72	17	0.23 ± 0.62	11		0.42 ± 0.64	17	0.43 ± 0.78	11		0.60 ± 0.74	19	
						Blood and sputum values (mean ± SD)							
Blood eosinophils ($\sqrt{x}$)													
Real acupuncture	−1.91 ± 5.76	21	−1.33 ± 6.27	13		−1.72 ± 7.13	19	0.42 ± 6.83	10		−4.57 ± 6.56	20	
Sham acupuncture	−1.52 ± 5.24	22	−2.07 ± 4.57	17	$p = 0.10$	−1.64 ± 5.17	22	−2.28 ± 4.81	15	n.s.	−0.82 ± 3.05	21	$p < 0.10$
Control	−0.12 ± 3.54	18	1.19 ± 3.24	12		−1.07 ± 3.85	18	−0.05 ± 2.96	11		−1.32 ± 4.09	19	
Blood ECP (log μg)													
Real acupuncture	−0.14 ± 0.660	23	−0.17 ± 0.532	15		−0.08 ± 0.752	21	0.01 ± 0.404	12		−0.09 ± 0.586	22	
Sham acupuncture	−0.25 ± 0.548	23	−0.32 ± 0.604	17	n.s.	−0.14 ± 0.438	23	−0.07 ± 0.375	15	n.s.	−0.02 ± 0.633	23	n.s.
Control	−0.13 ± 0.706	19	0.23 ± 0.782	12		−0.03 ± 0.647	19	0.08 ± 0.783	11		0.02 ± 0.770	20	
Sputum eosinophils ($\sqrt{x}$)													
Real acupuncture	−0.46 ± 2.07	20	−0.00 ± 2.00	13		−0.70 ± 2.70	19	−0.98 ± 1.78	10		−0.94 ± 2.71	19	
Sham acupuncture	−1.09 ± 2.47	17	−1.29 ± 1.68	13	n.s.	−0.36 ± 2.24	17	−0.32 ± 2.15	13	n.s.	−1.06 ± 3.05	20	n.s.
Control	−0.88 ± 2.60	14	−0.36 ± 2.34	10		−0.72 ± 2.20	13	−0.38 ± 2.26	8		−1.22 ± 2.75	14	
Sputum ECP (log μg)													
Real acupuncture	−0.33 ± 1.12	19	−0.26 ± 1.10	12		−0.63 ± 1.32	17	−0.33 ± 1.51	10		−0.38 ± 0.90	17	
Sham acupuncture	−0.48 ± 1.68	19	−0.53 ± 1.83	14	n.s.	−0.24 ± 1.78	19	−0.02 ± 1.87	12	n.s.	0.28 ± 1.49	19	n.s.
Control	−0.01 ± 1.47	16	0.07 ± 1.53	10		−0.17 ± 2.37	16	0.26 ± 2.11	9		−0.04 ± 2.13	17	

Significance = Kruskal-Wallis test (PEF Var.:ANCOVA, ANOVA) in the groups (after 10 months) and subgroups (after 4 and 5 months); n.s., not significant with $p > 0.10$

*Covariance analysis (baseline values and body weight as covariates; $p < 0.002$). *t*-test (adjusted means):

After 4 months: Real acupuncture (−0.364) vs. control (0.025), $p = 0.003$
Sham acupuncture (−0.324) vs. control (0.025), $p = 0.001$
After 5 months: Real acupuncture (−0.414) vs. control (−0.017), $p = 0.003$
Sham acupuncture (−0.323) vs. control (−0.017) $p = 0.01$

PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 second; ECP, eosinophil cationic protein; ANCOVA, analysis of covariance; ANOVA, analysis of variance.

Table 6. Changes of Asthma Medication

	Changes after 4 months			*Changes after 5 months*					*Changes after 10 months*			
	All patients	n	*Subgroup*	n	*Significance*	*All patients*	n	*Subgroup*	n	*Significance*	*All patients*	n	*Significance*
						Dose of asthma medication-Mean range							
Salbutamol (100 μg puffs/day)													
Real acupuncture	0.0 (−7.5/4.7)	21	−0.6 (−5.0/2.1)	13		−0.1 (−6.1/+4.7)	20	−0.3 (−5.0/+2.6)	11		−1.3 (−8.0/3.2)	20	
Sham acupuncture	−0.2 (−6.9/5.0)	23	+0.1 (−2.0/3.4)	17	n.s.	−0.5 (−6.3/+10)	23	−0.3 (−5.0/+3.4)	15	n.s.	−0.4 (−7.5/11)	20	n.s.
Control	+0.3 (−6.6/7.5)	18	+0.2 (−1.0/2.5)	10		−0.1 (−6.6/+5.8)	19	+0.1 (−1.0/+1.1)	10		+0.1 (−6.6/8.7)	20	
Inhaled beclomethasone (250 μg puffs/day)													
Real acupuncture	+0.6 (−1.3/+4.0)	23	−0.01 (−1.3/+0.6)	15		+0.7 (−0.6/+4.0)	22	0.09 (−0.1/+0.6)	13		+0.9 (−3.1/4.0)	22	
Sham acupuncture	−0.1 (−4.5/+2.0)	23	−0.05 (−0.6/+0.4)	17	n.s.	0.0 (−3.2/+4.0)	23	0.00 (0/0)	15	n.s.	+0.1 (−4.0/4.0)	19	n.s.
Control	+0.7 (−2.0/+6.0)	19	+0.01 (0/+0.1)	12		+0.3 (−2.0/+4.0)	20	+0.01 (0/−0.1)	11		+0.1 (−2.0/6.0)	20	

Significance = Kruskal-Wallis test in the groups (after 10 months) and subgroups (after 4 and 5 months); n.s., not significant with $p > 0.10$.

did eosinophils and ECP in blood and sputum. Most short-term (4 and 5 months) and long-term (10 months) changes were statistically insignificant compared to those in the controls, except for the PEF variability, blood eosinophils, and asthma attacks (during the day) in patients without major changes in the use of asthma drugs.

PEF variability was chosen as the main outcome variable for two reasons: (1) Because our patients had well-treated asthma, only small changes in pulmonary function values were expected to occur after acupuncture; (2) PEF variability is known to be the most sensitive marker for the clinical and functional abnormalities in bronchial asthma. Most patients with asthma, even those with mild disease, show an increased variability compared to healthy subjects (Higgins et al., 1989; Lebowitz and Quanjer, 1997; Quackenboss et al., 1991).

As our results show, PEF variability decreased after both kinds of acupuncture and to a smaller degree also in controls. In the subgroups (i.e., in patients whose asthma medication remained fairly unchanged), the reduction of PEF variability after needling of true points or sham nonpoints differed significantly at month 4 and 5 compared to controls when baseline value and body weight as confounders were taken into consideration.

The question then arises whether a decrease of approximately 50%–60% in PEF variability is clinically relevant. It is if PEF variability is high (Quackenboss et al., 1991) and it is not when PEF variability is already low (9%–11%) as in our patients, whose asthma was pharmacologically well-treated and in a fairly stable state.

Most other functional and clinical variables did not differ significantly from the results obtained in the controls, although a small improvement in those variables was observed. The same was true for the use of asthma drugs: needling of real or sham points was not accompanied by a clinically relevant reduced consumption of inhaled β-agonists and corticosteroids. Moreover, acupuncture had only a small effect on well-being and physical activity. Whereas well-being remained unchanged, there was a slight, however insignificant, improvement in physical activity after acupuncture.

Our clinical and functional results are largely in agreement with the few published controlled long-term trials: Tashkin et al. (1985) failed to demonstrate any short- or long-term benefit of real and sham acupuncture therapy on symptoms, medications use, or lung-function measurements in 25 patients with moderate-to-severe bronchial asthma. In another trial, Tandon et al. (1991) compared the therapeutic effectiveness of classic Chinese acupuncture with sham acupuncture in 15 patients with stable bronchial asthma. Treatment with real acupuncture failed to provide any improvement in asthma symptom scores, number of puffs of β_2-agonist use, and pulmonary function results. Dias et al. (1982), in a controlled trial of 1–4 weeks' duration, concluded that acupuncture has a placebo effect, because all 10 patients in the control group showed significant improvement in their PEF while only 3 of 10 patients in the treated group showed an improvement. The conclusion has been criticized by Jobst (1995) because of significant shortcomings of the study. Mitchell and Wells (1989), in a single-blinded study lasting for 6 months and comprising 29 patients with asthma who received eight treatments of acupuncture at either correct or incorrect points over a 12-week period were also unable to show any statistically significant differences between the groups in regard to symptoms, PEF, medication, and asthma episodes. The controlled study by Christensen et al. (1984) partially contrasts these results. Seventeen (17) patients received 10 treatments either real or sham acupuncture during a 5-week period. A significant improvement was found in symptoms, pulmonary function, and number of puffs of β-agonists after real acupuncture but only and exclusively 2 weeks after beginning therapy.

Bronchial hyperresponsiveness and eosinophilic inflammation are the pathophysiologic hallmarks of bronchial asthma (Boushey et al., 1980; Bousquet et al., 1990). We, therefore, wondered whether needling of the skin influenced these features in our patients, because it has been shown by Tashkin et al. (1977) that acupuncture inhibits methacholine-induced bronchospasm in humans, on the one hand, and the allergic inflammatory process, at least in animals, on the other hand (Xie and Li,1985; Zhang and Gao, 1988). However, only small

and insignificant changes in the degree of hyperresponsiveness were observed. This result is in accordance with two short-term studies reporting no changes of hyperresponsiveness in patients with asthma by acupuncture (Tandon and Soh, 1989); Yu and Lee, 1976).

Regarding eosinophilic inflammation, the eosinophils and ECP in blood and sputum decreased more, even significantly, in patients who received either real or sham acupuncture than in controls, suggesting a possible effect on the inflammatory process as observed in animal experiments (Xie and Lie, 1985; Zhang and Gao, l988). Three pathophysiological mechanisms may be responsible for the changes of blood eosinophils: (1) acupuncture is known to act on the hypothalamic-hypophyseal-adrenocortical system, increasing serum cortisol level (Liao et al., 1979); (2) acupuncture acts on the autonomic nervous system (Ionescu-Tirgoviste, 1991); (3) needling the skin causes pain, which, by itself, produces acute sympathetic reflex responses (Kistler et al., 1996). Both, the stimulation of the hypothalamic–hypophyseal–adrenocortical axis as well as the stimulation of the adrenergic neural system are known to have an effect on the numbers of eosinophils in blood (Beeson and Bass, 1977).

When clinical studies regarding the efficacy of acupuncture are performed, several problems arise that limit the results and conclusions as encountered in our trial. They relate to the characterization and stratification of the patients, the variable course of the bronchial disease itself, the design of the study, the method of randomization, and the sample size. They deal with the technique of acupuncture, the choice of intervention for the controls (i.e. sham or true placebo or no acupuncture), the selection of real "antiasthmatic," sham and placebo true points or placebo nonpoints, the blinding of patients and doctors (de la Torre, 1993; Jobst, 1995; Stux and Pomeranz, 1987; Vincent and Richardson, 1986). Moreover, confounders of different nature may play an important role.

According to Traditional Chinese Medicine, acupuncture therapy should be tailored to each patient`s requirements (de la Torre, 1993; Stux and Pomeranz, 1987). Needling of a series of standard real acupuncture points may mask some of the benefits. We tried to limit this problem by including only patients who met the strict inclusion criteria and who had an excess (*Shi*)-type of asthma based on Traditional Chinese Medicine (Stux and Pomeranz, 1987). In addition, we chose a series of 11 different real acupuncture points that had an inhibitory effect on the main pathophysiological features of asthma, according to traditional Chinese Medicine acupuncture (Yan Jie, 1992). It is possible that despite these precautions the potential benefit of an individually tailored acupuncture was not achieved. In addition, it has to be remembered that sham or placebo acupuncture cannot be administered in the same fashion as placebo medication (de la Torre, 1993; Jobst, 1995). The therapist knows whether he/she is performing real or sham or placebo acupuncture. Because suggestion has been shown to be capable of producing bronchodilation in patients with asthma (Philipp et al., 1972), this has to be considered, when evaluating possible, in this case short-term, effects of acupuncture.

In regard to the many uncontrollable confounders inherent to such a study, the main confounder in our trial was the variable course of the disease itself. It was impossible to keep the asthma medication constant in all patients during the acupuncture treatment periods as provided by the study design. Hence, a beneficial effect of an acupuncture could have been missed by the change of medication. Yet, when examining the effects of acupuncture in patients without a change of their medication, there were only some small, but significant effects on the PEF variability and blood eosinophils, which were not accompanied by significant effects on the other variables, however.

When considering the mostly negative results of our trial as those reported by others (Dias et al., 1982; Christensen et al., 1984; Mitchell and Wells, 1989; Tandon et al., 1991; Tashkin et al., 1985), it has to be kept in mind that a high beta error in the range of 50%–90% in many of the secondary parameters may have masked a beneficial effect of acupuncture. This was the case in regard to the methacholine doses, eosinophils, and ECP. Moreover, baseline values of clinical and functional parameters were only slightly impaired making it difficult to show a clinically relevant change.

In view of these facts and considering that

the effects observed were small, in all likelihood clinically irrelevant, our data do not seem to support the use of acupuncture in the management of pharmacologically well-treated mild-to-moderate persistent bronchial asthma.

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Address reprint requests to:
Tullio C. Medici, M.D.
Lerchenbergstraße 79
CH 8703 Erlenbach
Switzerland

E-mail: media@bluewin.ch