Comparison of Real and Placebo Acupuncture in Histamine-Induced Asthma*

A Double-Blind Crossover Study

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A double-blind crossover study of the effects of real and placebo acupuncture on bronchial reactivity to histamine was carried out on 16 patients with moderately severe asthma. Treatment with real or placebo acupuncture failed to modulate the bronchial hyperreactivity to histamine. These results suggest that a single treatment with acupuncture is unlikely to provide improvement in the management of acute bronchial asthma. *(Chest 1989; 96:102-05)*

HAP = histamine acid phosphate; PC20 = concentration of histamine producing 20 percent fall in FEV_1

Although acupuncture has been used for thousands of years for many diseases, reports in the literature on beneficial effects of acupuncture on asthma are conflicting. While a number of workers[1-3] have reported a significant benefit in the control of asthma following acupuncture, almost an equal number of workers[4-6] failed to show any significant improvement in the control of asthma following acupuncture. Experimentally, in a controlled double-blind crossover study, Tashkin et al[7] showed that acupuncture improved methacholine-induced bronchospasm to some extent. Fung et al[8] showed that both real and placebo acupuncture, applied 20 min before exercise, attenuated exercise-induced asthma but that the benefit from real acupuncture was greater than that produced by placebo acupuncture. Increased bronchial reactivity to inhaled histamine is one of the characteristic features of asthma.[9] Makino[10] showed that the level of bronchial reactivity to histamine has a relationship to the symptoms and severity of asthma.

Although for treatment of bronchial asthma, the acupuncture is commonly given as chronic therapy, it is also given as single treatment for acute asthma.[11] We undertook a double-blind crossover study in order to determine if prior treatment with acupuncture, as given for acute asthma, would attenuate bronchial hyperreactivity to histamine in a group of patients with moderately severe asthma.

Material and Methods

Patients

Sixteen patients, ten male and six female, with moderately severe asthma requiring regular treatment with bronchodilators, were included in the study. Their ages ranged from 11 to 60 years, with a mean of 39 years (Table 1). No patient was a current smoker. Four patients were ex-smokers who had ceased smoking 5 to 15 years prior to the study. Except for one patient, all had a history of atopy. No patient had a history of chronic productive cough suggestive of associated chronic bronchitis. The clinical history was typical of bronchial asthma as defined by the American Thoracic Society Criteria.[12] The chest x-ray films were normal and FEV_1-values had been shown during an unstable phase to improve by at least 20 percent after inhalation of a bronchodilator aerosol. At the time of the study, the measured FEV_1 value had to be greater than 75 percent of the predicted normal.

All subjects were taking regular inhaled $beta_2$ sympathomimetic bronchodilators for control of asthma. With one exception, all were taking inhaled beclomethasone dipropionate. Thirteen patients required additional treatment with oral theophylline. Five patients were also receiving treatment with sodium cromoglycate. No patient had received treatment with oral corticosteroids for at least one month. Based on the medication requirements and symptoms, asthma of all patients was in a stable phase at the time of the study. No patient had had any respiratory tract infection in the preceding month.

Treatment with oral theophylline, inhaled corticosteroids and sodium cromoglycate was ceased for at least 12 hs prior to the study. Treatment with these agents could not be withheld for any longer period for fear of making the patients susceptible to severe asthma and impairing the stability of asthma, which was an essential prerequisite for the study. Inhaled bronchodilators were withheld for at least 6 hs prior to each experimental session. All patients were advised not to take any antihistamines for at least one week prior to and for the duration of the study. Written consent from each patient or guardian was obtained prior to the study. All patients were studied on three separate days at one-week intervals and at the same time of the day. At the first study, a detailed history of atopy, seasonal variation and any variation in severity of asthma symptoms were taken.

Pulmonary Function Testing

After 30 min of rest, baseline pulmonary function assessment with measurements of FVC and FEV_1, using the best of the three vital capacity efforts, was done on a water-filled spirometer of 10-L capacity (Goddard Expirograph, Gould Instruments, Cleveland).

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Transfer factor for Dco was measured, using Morgan transfer test system (P.K. Morgan Ltd., Chatham, Kent, United Kingdom), in the past three months during a routine pulmonary physiologic evaluation of the patients. After baseline FEV_1 and FVC was recorded, an aerosol of phosphate-buffered saline solution via a Wright nebulizer with oxygen at a flow rate of 7 L/min, was given for two minutes with the nose clipped. Subjects were requested to inhale the aerosol through the mouth using tidal breathing for two minutes. Measurements of FEV_1 and FVC were made at 30 and 90 s after inhalation of the aerosol. Thereafter, bronchial provocation with an aerosol of HAP in a similar manner as just noted was given at five-min intervals in doubling concentrations from 0.0325mg/ml to 8mg/ml. Spirometry was repeated at 30 and 90 s following each inhalation. The inhalations were discontinued when a fall of 20 percent in FEV_1 was achieved. This was calculated from the lowest post-saline FEV_1 (FEV*A*) and the lowest post-HAP FEV_1 (FEV*B*) as follows:

$$\frac{100 \times (\text{FEV}A - \text{FEV}B)}{\text{FEV}A}$$

The method described here is that reported by Cockroft et al.[13] The dose of HAP producing a 20 percent fall was designated as the PC20. This dose of HAP was calculated from a dose-response curve, or if only one concentration had been given, from the formula:

$$\frac{\text{HAP concentration} \times 20}{\%\ \text{fall FEV}_1}$$

On the second and third study days after baseline FEV_1 and FVC values were measured in order to ensure a stable condition of the patients, the subjects were then randomly administered either real or placebo acupuncture in another room by the acupuncturist. The order of real or placebo acupuncture treatment was predetermined by a computer-generated randomization table. The observer and the patients were unaware of the nature of the acupuncture treatment given. No patient had previously received treatment with acupuncture. Immediately after acupuncture, FEV_1 and FVC were again measured, and then a histamine inhalation test was performed to obtain the HAP concentration required for PC20 in the manner described above.

After histamine inhalation test, all subjects were given treatment with nebulized salbutamol aerosol for two minutes to reverse the histamine-induced bronchospasm. No patient left the laboratory until his FEV_1 and FVC values had returned to the baseline values measured at the onset of the study.

Acupuncture

Real and placebo acupuncture was given by a physician who was also a trained acupuncturist in the Chinese method of acupuncture. The acupuncture points used for real acupuncture were Dingchuan, Ren 17 (Shanzhong), lung 6 and lung 7.[14] Dingchuan, used for the treatment of acute asthma, is located 0.5 cun from the midline between C7 and T1 spinous processes. A "cun" is the distance between the creases of the two interphalangeal joints when the middle finger is fully flexed. Ren 17 (Shanzhong) regulates lung function and is located on the front of the chest between the nipples. In females, the 4th intercostal space is used. Lung 6 (Kongzui) is located on the anterior aspect of the forearm, 7 cun above the wrist crease. Lung 6 is used for treating acute lung conditions. Lung 7 (lieque), located 1.5 cuns above the radial stylod process, is supposed to relieve airflow obstruction in the lung.

Placebo acupuncture points used were triple energy 5, stomach 25 and gallbladder 34. Triple energy 5 is on the back of the wrist, stomach 25 is on the anterior abdominal wall next to the umbilicus; and gallbladder 34 is on the front of the head of the fibula. These three points are believed to have no effect on the treatment of asthma and were therefore used as placebo points. Autoclaved stainless steel needles (25 cm long, 0.32 mm in diameter) were inserted aseptically without local anesthesia. In order to achieve the desired acupuncture effect on insertion of the needles, the acupuncturist tried to achieve a maximum local sensation of numbness with a systemic feeling of distension or heaviness. The needles were manually rotated clockwise and anticlockwise every 5 min during the 20-min treatment period and were subsequently removed. The same technique was used for both real and placebo acupuncture. The acupuncturist only gave the acupuncture and did not divulge the nature of treatment given to the observer performing histamine challenge studies in another part of the clinic to maintain the double-blind nature of the study.

Statistical Method

Newman-Keuls method[15] was used for multiple paired comparison of the mean values of the baseline FEV_1 values on the three study days. The same method was used for comparison of HAP concentration required for PC20 on the control, real and placebo acupuncture days and against each other.

Results

All patients included in the study were considered to have moderately severe asthma because they required regular bronchodilator therapy together with

Table 1—*Anthropometric, Historical and Pulmonary Function Data*

Subject	Age Years	Sex	Smoking History	Height (cm)	Age Onset Asthma	History of Atopy	FEV_1, % Predicted	FVC, % Predicted	Dco, % Predicted	Control Day PC20 (mg/ml)
1	11	M	Nonsmoker	156	25	Yes	95	97	105	0.89
2	51	F	Nonsmoker	168	19	Yes	75	80	95	0.72
3	47	F	Nonsmoker	152	30	Yes	90	95	98	1.117
4	12	M	Nonsmoker	160	Birth	Yes	98	95	105	2.215
5	15	M	Nonsmoker	170	4	Yes	105	98	98	0.0335
6	46	F	Ex-smoker, 5 yr	165	19	Yes	80	75	95	0.073
7	60	F	Nonsmoker	158	55	No	80	85	90	0.79
8	35	M	Ex-smoker, 15 yr	180	5	Yes	100	100	105	0.062
9	42	M	Nonsmoker	165	Birth	Yes	80	85	95	0.454
10	36	M	Nonsmoker	170	Birth	Yes	95	100	105	0.68
11	39	F	Nonsmoker	160	24	Yes	85	90	95	0.1625
12	48	M	Nonsmoker	170	34	Yes	95	100	100	0.104
13	56	M	Ex-smoker, 15 yr	172	54	Yes	100	100	105	0.352
14	57	M	Nonsmoker	175	55	Yes	95	100	110	0.114
15	19	F	Nonsmoker	160	5	Yes	100	100	105	0.185
16	52	M	Ex-smoker, 8 yr	175	3	Yes	75	80	90	0.202
Mean	39.13			166	19.84		89.87	92.62	99.75	0.382

Table 2—*Basal Lung Function Results of Three Study Days*

		Mean Difference	SD	p Value
Control day FEV_1 2.15* (1.14-3.4)†	Real Acupuncture day FEV_1 2.23* (1.1-3.3)†	0.0737	0.245	>0.05
Control day FEV_1	Placebo Acupuncture day 2.27* (1.19-3.76)†	0.113	0.352	>0.05

*Mean values of FEV_1 (liters)
†Range of FEV_1 values.

inhaled beclomethasone or sodium cromoglycate to remain symptom-free. Except for one, PC20 of all patients on the control day was less than 1.0 mg (Table 1). No patient prior to the study had evidence of airflow obstruction and Dco measurements of all patients were normal. The age of onset of asthma ranged from birth to 55 years of age.

Comparison of basal FEV_1 values on the three study days showed no significant differences and the basal pulmonary function status of patients was similar on the three study days (Table 2). Comparison of PC20 on the control day with those seen after real and placebo acupuncture were also not statistically different (Table 3). There was no significant difference in the PC20 following real acupuncture and that following placebo acupuncture.

All patients tolerated acupuncture well, apart from one child who developed a transient fainting sensation.

Discussion

Inhalation tests with histamine give a sensitive indication of bronchial hyperreactivity.[16] Increased bronchial reactivity to histamine is an abnormality seen in active asthmatic subjects, and Charpin et al[9] have indicated that in France it is included as a part of the definition of asthma. Increased bronchial reactivity to histamine has been shown to have a close parallel with the overall severity of asthma as indicated by the usual drug requirements for optimum symptom control.[13] Patients with PC20 under 1 mg are classed as having moderately severe asthma, as included in this study, and have been shown to require treatment with bronchodilators on a regular basis with or without additional corticosteroids.[13]

Table 3—*Comparison PC20 Histamine Doses*

		Mean Difference	SD	p Value
Control 0.382*	Real Acupuncture 0.273*	0.11	+0.262	>0.05
Control 0.382*	Placebo 0.369*	0.0122	+0.243	>0.05
Placebo Acupuncture—Real Acupuncture		0.0963	+0.268	>0.05

*Geometric mean values on the study days.

Bronchial hyperreactivity to histamine was used in this study to evaluate the effectiveness of acupuncture on modulating the underlying asthma status because this approach was considered to be a reliable method of determining whether or not the acupuncture would affect the underlying asthma. Any changes in bronchial hyperreactivity to histamine would have to be due to a change in the bronchial smooth muscle reactivity rather than due to any environmental changes because all patients were studied during a stable phase and within a short period of time with stable lung function. This method of studying the effect of a controversial modality of treatment, such as acupuncture, has significant advantages over clinical studies. In the latter, varying environmental conditions may influence the severity of bronchial asthma and thereby, influence the results to some extent. At the same time, this method has the disadvantage that it investigates only the bronchial smooth muscle reactivity to a chemical mediator without studying the part played by neural reflex or inflammatory changes in bronchial mucosa. Notwithstanding these disadvantages, acute acupuncture therapy as given in this study, is unlikely to help in the management of acute asthma because it does not attenuate bronchial smooth muscle reactivity. This failure to attenuate bronchial hyperreactivity to histamine following acupuncture was not due to any change in the basal lung function because the basal lung functions on the three study days were not significantly different.

This study was conducted strictly according to double-blind principles because both the patients and observer were unaware of the nature of treatment given by the acupuncturist on the two study days according to predetermined randomization protocol. Failure of acupuncture to attenuate severity of bronchial asthma in this study is at variance with results of previous similarly conducted studies.[7,8]

The acupuncture loci used in this study were those used for protection against acute asthma as recommended by the theory of traditional Chinese medicine[14] which is said to be a prerequisite for optimum protection. In clinical practice, acupuncture is given prophylactically long-term for a number of treatments or short-term by a single treatment for management of acute asthma. Our study was done to find if prior treatment with acupuncture, as used for acute asthma, would attenuate bronchial hyperreactivity to histamine and thereby improve the underlying asthmatic state. The failure of real and placebo acupuncture to attenuate bronchial hyperreactivity to histamine in this study suggests that a single treatment as used in this study is unlikely to be of any clinical benefit in

this type of management of acute asthma.

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