#4815

THERAPEUTICS

RCT asthma cross-over acupuncture

Acupuncture for bronchial asthma?

A double-blind crossover study

Maharaj K Tandon, Phillip F T Soh and Andrew T Wood

The therapeutic effectiveness of classic Chinese acupuncture was compared with "placebo" acupuncture in 15 patients with stable bronchial asthma. The patients received treatments with real and placebo acupuncture in a randomly ordered, subject and evaluator-blind crossover fashion twice weekly for five weeks. Both real and placebo treatment periods were preceded by three week periods when no acupuncture was administered. Five patients felt better on real treatment, five patients preferred placebo and five did not feel any improvement on either of the two treatments. Treatment with real acupuncture when compared with no treatment and placebo treatment failed to provide any improvement in daily peak flow rates, asthma symptom scores, number of puffs of β_2-agonist aerosol use, and pulmonary function results.

(Med J Aust 1991; 154: 409-412)

Acupuncture has been used in China for treatment of a number of diseases, including bronchial asthma, since 400 BC,[1] but very few properly controlled trials of its efficacy have been carried out. A review of the literature revealed only eight studies in which the effect of acupuncture on bronchial asthma had been investigated by means of a controlled trial methodology with a "placebo" or no treatment group.[2-9] Of these, five studies investigated only the acute effects of acupuncture on bronchial asthma.[2-6] Three looked at the longer term effects of acupuncture on bronchial asthma,[7-9], but results of these studies are conflicting. Dias et al. observed only a placebo effect.[8] Christensen et al. observed improvement with acupuncture but the beneficial effect was only evident two weeks after the beginning of therapy.[9] Tashkin et al. in a double-blind crossover trial failed to demonstrate any short-term or long-term benefit from acupuncture therapy in the management of patients with moderate to severe asthma.[5]

In clinical practice, patients with chronic bronchial asthma not uncommonly resort to alternative medicine for symptom control.[10] In view of the paucity and conflicting nature of evidence relating to the effect of acupuncture on bronchial asthma, we designed a double-blind crossover study to test whether treatment with acupuncture would improve the condition of patients with moderately severe asthma requiring regular bronchodilator therapy.

Patients and methods

Fifteen patients, nine men and six women, aged 19 to 57 years (mean, 40.5 years) with chronic stable asthma were enrolled in the study. All had typical bronchial asthma according to the American Thoracic Society Criteria.[11] Two subjects were ex-smokers, the others had never smoked. The observed resting values for forced expiratory volume in one second (FEV_1), expressed as a percentage of the predicted normal value, ranged from 31% to 81% with a mean of 61%. After administration of a bronchodilator aerosol the FEV_1 values of all patients with an FEV_1 less than 80% of the predicted normal value rose by a mean of 29% (range, 18%–52%). Two patients with an FEV_1 greater than 80% of the predicted normal value had evidence of bronchial hyperresponsiveness to histamine with a fall in FEV_1 of 20% at a histamine concentration of 0.0625 and 0.5 mg/mL respectively, when tested by the method described by Cockcroft et al.[12]

All patients had had asthma for more than five years (range, 5–34 years). All had a history of atopy producing exacerbation of bronchial asthma. None had a history of chronic productive cough suggesting associated chronic bronchitis. In addition to regular inhaled β_2-agonist bronchodilators, all required treatment with inhaled beclomethasone and all except one were taking theophylline by mouth for optimal control of symptoms.

Because of the severity and chronicity of their asthma and the number of drugs required for its control, all the patients were anxious to receive additional non-medical treatment.

We obtained their informed consent in writing before including them in the study. The study was approved by the bioethics committee of the

Study design

Period 1: Baseline control — three weeks without treatment. Patients keep a daily record of symptoms, medication use and peak flow readings. *Evaluation* of daily diary cards and pulmonary function tests at the end of the period.

Period 2: Real or placebo acupuncture administered twice weekly for five weeks. *Evaluation* of daily diary cards and pulmonary function tests at the end of the period.

Period 3: "Wash out" control — no acupuncture for three weeks. *Evaluation* of daily diary cards and pulmonary function tests at the end of the period.

Period 4: Patients cross over to alternative acupuncture treatment, administered twice weekly for five weeks. *Evaluation* of daily diary cards, pulmonary function tests at the end of the period and treatment preference (ask patients if treatment (2) or (4) was better or no different). *Statistical comparison* of real and placebo acupuncture with control periods of no treatment, and of real acupuncture with placebo acupuncture.

Thoracic Division, Repatriation General Hospital, Hollywood, WA 6009.
Maharaj K Tandon, MD, FRCP, FRACP, Consultant Thoracic Physician
Andrew T Wood, BA, DipMathStat, PhD, Biostatistician. Currently Biostatistician, Department of Statistics, School of Mathematics and Statistics, Australian National University, Canberra, ACT 2601
142 Cambridge Street, Leederville, WA 6007.
Phillip F T Soh, MB BS, General Practitioner.
No reprints will be available. Correspondence: Dr M K Tandon.

Repatriation General Hospital, Hollywood, Western Australia.

The study was carried out according to the protocol outlined in the box, "Study design." Patients included in the study were followed up for three weeks (period 1) before any treatment with acupuncture was given. During this time they kept a daily diary of symptoms (coded to produce "symptom scores") and medication use, and recorded their peak flow readings (PFRs) morning and night, using a Mini Wright peak flow meter (Airmed, Clement Clarke Ltd, England).

All patients were advised to take their β-agonist bronchodilator aerosol only when required for symptom control, while their regular treatment with theophylline and inhaled beclomethasone remained unchanged.

The frequency of use of β-agonist bronchodilator aerosol was one of the important parameters used for evaluation of the treatment effect. No patient received treatment with sodium cromoglycate or orally administered steroids for one month prior to, and for the duration of, the study.

At the end of the three week control period the diary cards were collected and (after a 30 minute rest in the laboratory) the patients underwent routine spirometry. We calculated FEV_1, forced vital capacity (FVC), forced expiratory flow after 50% of vital capacity was exhaled (FEF_{50}) and forced expiratory flow after 75% of vital capacity was exhaled (FEF_{75}). We repeated spirometry to yield at least three satisfactory tracings of each patient and the highest FEV_1 value was used to calculate spirometric indices. For all lung function studies the patients were requested not to take their β-agonist bronchodilator for at least six hours before attending the clinic.

After the resting pulmonary function data had been obtained and there was evidence of airflow obstruction, a bronchodilator aerosol was administered and lung function tests were repeated 30 minutes later.

The two patients with no evidence of airflow obstruction at rest were given bronchial provocation with histamine to determine their bronchial hyperresponsive status, by the method described by Cockcroft et al.[12]

We allocated patients to receive either real or placebo acupuncture according to a computer generated randomisation chart which was given to the acupuncturist by an independent person. Real or placebo acupuncture was given twice weekly for five weeks in an identical manner using laser acupuncture. Only the acupuncturist was aware of the nature of treatment given, and he had no other contact with the patients or the physician evaluator.

The real acupuncture loci were selected according to classic Chinese acupuncture and the treatment was given by a physician (P F T S) who was also a trained acupuncturist. The "placebo" acupuncture was given at sites which are not supposed to affect lung function. Both the patients and the observer (M K T) remained unaware of the nature of treatment given. None of the patients had previously received treatment with acupuncture. During this treatment period the patients continued to keep a daily record of symptom scores, frequency of β-agonist inhaler use and morning and evening PFRs. At the end of five weeks (period 2) the patients were seen at the chest clinic for collection of diary cards and pulmonary function testing.

During period 3 no acupuncture was given. The patients continued to fill in their daily diary cards. At the end of three weeks pulmonary function tests were repeated and diary cards were collected.

Period 3 served to "wash out" any residual effects of the previous treatment as well as being a control for period 4 when the patients crossed over to receive the alternative acupuncture treatment. At the end of period 4 the observer asked the patients whether they had noticed any difference between the two periods of therapy and, if so, which they believed resulted in greater improvement in their asthma symptom control.

Laser acupuncture

In this study acupuncture treatment was given with a helium-neon laser which had a wavelength of 632.8 nm and emitted a beam of 5.6 mW at the tip of the probe. It stimulated a square millimetre of skin area. The treatment times were 20 seconds for each body point and 10 seconds for each ear point. The power density delivered at each point was 0.56 J/cm² per second. For real acupuncture the points chosen were Sp 6, S 36, L 9, Li 11, CV 17, CV 22, Ding Chaun, B 13, and the ear points for asthma, lung and internal secretions.

The points selected for placebo acupuncture were G 34, Liv 8, Liv 14, Si 3, Si 6, B 18, B 25, and the ear points for uterus and bladder.

Statistical methods

We analysed pulmonary function results and diary card data using the two-tailed *t*-test. Since changes within individuals were of interest, paired *t*-tests were used throughout to test for any difference: (a) between control periods and placebo acupuncture, (b) between control and real acupuncture, and (c) between real and placebo acupuncture.

Results

Analysis of patient preference for the two treatments showed that five patients did not perceive any difference in their asthma during the two interventions. Of the remaining 10 patients, five felt better when they received real acupuncture and the other five felt better with placebo acupuncture.

As acupuncture therapy may have had a slow onset of action and there may have been a carry-over effect into control periods, we analysed the diary card data for only the last week of each of the four study periods. Morning and evening peak flows, symptom scores and β-agonist inhaler use recorded during the last week of each treatment period were compared with the last week's recordings of their respective control periods (Table 1). Both real acupuncture and placebo acupuncture produced, relative to their standard errors, small (statistically insignificant) differences in the diary data.

Similarly, comparison of real and placebo acupuncture showed that the differences in diary data were small, relative to their standard errors (Table 2). To be significant at $P = 0.05$, the differences for morning peak flow and symptom scores had to be greater than 47 and 3 respectively. Differences for diary card data detectable with a probability of 0.75 were not achieved in this study.

Analysis of pulmonary function data for FEV_1, FVC, FEF_{50} and FEV_{75} at the end of treatment with real and placebo acupuncture showed small (statistically insignificant) differences relative to their standard errors (Table 3). Differences in pulmonary function data detectable with a probability of 0.75 were not observed.

TABLE 1: Patients' responses to real and "placebo" acupuncture compared with no-treatment control periods*

Patient diary parameters	Real acupuncture v. control		Placebo acupuncture v. control	
	Mean difference (SE)†	95% CI‡	Mean difference (SE)†	95% CI‡
Morning peak flow rates (L/min)	−5.2(27.3)	(−63.9–53.4)	−8.9(14.0)	(−39.0–21.2)
Symptom score	−2.7(1.5)	(−6.0–0.6)	1.0(1.3)	(−1.8–3.8)
β-agonist inhaler use (uses/day)	0.3(0.5)	(−0.8–1.4)	−0.0(0.4)	(−1.0–0.9)
Evening peak flow rates (L/min)	−3.2(27.6)	(−62.4–56.0)	−32.6(22.9)	(−81.8–16.6)

*$n = 15$.
†SE = standard error.
‡CI = confidence interval. The 95% confidence interval is for the mean difference, and was derived using the paired *t*-statistic with 14 degrees of freedom. Mean difference = score for acupuncture − score for control.

TABLE 2: Patients' responses to real acupuncture compared with responses to "placebo" acupuncture*

Patient diary parameters	Mean difference (SE)†	95% confidence interval‡	Difference detectable with probability 0.75§
Morning peak flow rates (L/min)	−23.7(23.2)	(−73.5–26.0)	61.1
Symptom score	−1.7(1.5)	(−4.9–1.5)	4.0
β-agonist inhaler use (uses/day)	0.1(0.5)	(−0.9–1.2)	1.3
Evening peak flow rates (L/min)	−1.0(26.7)	(−58.3–56.3)	70.4

*$n = 15$.
†Mean difference = score for real acupuncture − score for placebo acupuncture. SE = standard error.
‡The 95% confidence interval is for the mean difference, and was derived using the paired *t*-statistic with 14 degrees of freedom.
§The "difference detectable" is that for which the Type II error probability is approximately 0.25 (1 − 0.75). The calculation assumes that the true standard error equals the estimated standard error.

TABLE 3: Comparison of lung function results for real and "placebo" acupuncture*

Lung function parameters†	Mean difference (SE)‡	95% confidence interval§	Difference detectable with probability 0.75‖
FEV_1 (L)	0.024 (0.06)	(−0.11–0.16)	0.16
FVC (L)	0.063 (0.11)	(−0.16–0.29)	0.29
FEF_{50} (L)	−0.035 (0.06)	(−0.17–0.10)	0.16
FEF_{75} (L)	0.025 (0.05)	(−0.08–0.13)	0.13

*$n = 15$.
†FEV_1 = forced expiratory volume in one second (litres); FVC = forced vital capacity (litres); FEV_{50} = forced expiratory flow after 50% of vital capacity was exhaled (litres); and FEF_{75} = forced expiratory flow after 75% of vital capacity was exhaled.
‡Mean difference = score for real acupuncture − score for placebo acupuncture. SE = standard error.
§The 95% confidence interval is for the mean difference, and was derived using the paired *t*-statistic with 14 degrees of freedom.
‖The "difference detectable" is that for which the Type II error probability is approximately 0.25 (1 − 0.75). The calculation assumes that the true standard error equals the estimated standard error.

Indications of the statistical power achieved in the study are given in the final column of Tables 2 and 3. The "detectable differences" are the true differences in the means that would be detectable with a probability of approximately 0.75, with the given sample size ($n = 15$). For the diary parameters, the "detectable differences" in Table 2 are substantial in clinical terms, which indicates low statistical power; for the lung function data, the "detectable differences" in Table 3 are small in clinical terms, indicating that satisfactory power has been achieved.

Discussion

In this double-blind placebo controlled crossover study in patients with chronic moderately severe asthma, treatment with real laser acupuncture for a five week period did not produce any improvement in symptoms and PFRs or any reduction in β-agonist inhaler usage when compared with five weeks of placebo laser acupuncture. As well, the majority of the patients either did not feel any difference between real and placebo acupuncture or reported feeling better when they received placebo acupuncture. Only five out of the 15 patients reported an improvement during real acupuncture.

The failure of acupuncture to provide an improvement in the control of asthma is in keeping with the observations of Tashkin et al.[6] The improvement felt by some patients after receiving placebo acupuncture suggests that any benefit reported from acupuncture may be psychogenic, as reported by Sovijarvi and Poppius.[13] The failure of laser acupuncture over a five week period to improve asthma in this study is in keeping with our earlier observation that prior treatment with needle acupuncture failed to attenuate bronchial hyperreactivity to histamine.[14]

The patients included in this study had long-standing asthma of moderate severity. It appears that acupuncture is unlikely to provide any significant benefit in this group of patients because of the severe chronic nature of the disease. However, it is patients of this type who are most likely to seek additional therapy such as acupuncture.

According to traditional Chinese medicine acupuncture therapy should be tailored to each patient's requirements. Using standard "loci" may mask some of the benefit. We tried to overcome this problem by including patients who had similar asthma, so that the treatment loci could be standardised. It is possible that this was not achieved.

The fact that the acupuncturist was the only person unblinded should have produced a more favourable result. As this did not occur it appears that the acupuncturist showed no bias in the administration of real and placebo acupuncture.

Additional treatment with inhaled beclomethasone and theophylline remained unchanged during the course of the study. Hence, changes in medications should not have masked any benefit.

Whilst classical needle acupuncture is the most widely used method of acupuncture, laser acupuncture has been shown to be effective in the treatment of various disorders which respond to classical needle acupuncture.[15,16] Laser acupuncture, rather than classical needle acupuncture, was used in this study because it is painless, has no danger of crossinfection with hepatitis B or human immunodeficiency viruses and has no harmful effects such as causing pneumothorax.

In view of the small number of patients included in this study, and the relatively large standard errors observed in the results presented, it is important that further studies with a larger number of patients should be conducted to find if acupuncture has any place in the management of patients with bronchial asthma.

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(Received Oct 3, 1989; accepted Nov 12, 1990)

CASE REPORTS

Cholesterol atheroembolism: an increasingly frequent complication of cardiac catheterisation

Hean T Ong, Wayne G Elmsly and Denis H Friedlander

Cholesterol atheroembolisation is increasingly encountered as a complication of cardiac catheterisation. We report three cases seen recently in our unit. Autopsy and histological evidence confirmed cholesterol atheroembolism in one case, while the other two patients presented with classical clinical features of this condition. All three patients were elderly with extensive atheromatous disease. No excessive difficulty was encountered at catheterisation. Embolisation involved the gastrointestinal tract, the skin and extremities, and the kidneys. Despite anticoagulation, dialysis and surgical intervention all our patients died. With investigative and therapeutic catheterisation being increasingly performed in the setting of severe atherosclerosis, the need for continued scrutiny for catheter-induced complications is emphasised.

(Med J Aust 1991; 154: 412-414)

Cholesterol embolisation from disrupted atheromatous plaques was thought to be a rare complication of cardiac and vascular catheterisation.[1,2] Recently, more clinical cases have been reported.[3-5] Amongst patients dying within six months of vascular catheterisation, autopsy evidence suggests that the incidence of subclinical cholesterol atheroembolisation is between 25% and 30%.[6] We report three cases seen recently in our catheterisation laboratory. The diagnosis was confirmed at autopsy in one patient, while the other two had classical clinical features of atheroembolism. All eventually died of complications arising from atheroembolism.

Clinical records

Case 1

A 72-year-old man presented with a two-month history of unstable angina. He was hypertensive and had a history of transient cerebral ischaemia, renal impairment, organic impotence and chronic obstructive airway disease. An exercise tolerance test was stopped after 4 min 6 s in stage two of the Bruce Protocol with marked ST segment changes in his electrocardiogram (ECG). His total serum cholesterol value was 7.2 mmol/L.

Catheterisation was initially unremarkable; 2500 IU of heparin were given and a left ventriculogram was performed. Eighteen minutes into the procedure, the patient complained of severe left hypochondrial pain and a red-blue mottling appeared on his abdomen and lower limbs. Computed tomography excluded an aortic dissection or puncture. His white cell count rose to 23.4 × 10^9/L with a 90% neutrophilia. Marked hypertension developed and was resistant to therapy. A laparotomy was performed because of clinical peritonitis and showed occlusion of the ileocolic artery and gangrene of the terminal ileum and proximal colon. An extended right hemicolectomy was performed with an ileocolic anastomosis; the rest of the bowel appeared viable and the mesenteric vessels were pulsating.

Renal function deteriorated after operation with his serum creatinine level rising from 0.164 mmol/L to 0.568 mmol/L over two days. Hemodialysis was started. However, the patient could not be weaned off the ventilator and *Pseudomonas aeruginosa* was cultured from tracheal aspirates. A white cell scan with technetium-labelled monoclonal antibody suggested ongoing bowel sepsis and at repeat laparotomy gangrene was found in the descending colon. The patient had a cardiac arrest shortly afterwards, 10 days after catheterisation.

Results of autopsy, showed left ventricular hypertrophy with an old anterior infarction. Atheromatous stenosis was noted in both branches of the left coronary artery. The aorta showed severe ulcerative atheroma, with large masses of porridge-like material which on microscopy showed multiple cholesterol clefts (Figure 1). The spleen, the pancreas, both kidneys and the right lobe of the liver had extensive areas of infarction. Results of histological tests showed that numerous vessels of these organs were occluded by emboli containing prominent cholesterol clefts (Figure 2). The superior mesenteric artery was occluded and microemboli were noted in the intestinal submucosa.

Case 2

A 66-year-old man had had an inferior myocardial infarction in 1977. He also had a history of angina (which had worsened recently), hypertension and intermittent claudication.

Waikato Hospital, Hamilton, New Zealand.
Hean T Ong, MRCP, MMed, Registrar, Department of Cardiology. Currently Cardiologist, Penang Adventist Hospital.
Wayne G Elmsly, FRCPA, Pathologist, Department of Pathology.
Denis H Friedlander, MRCP, FRCP, FRACP, Cardiologist, Department of Cardiology.
Reprints: Dr H T Ong, Cardiologist, Penang Adventist Hospital, 465 Burmah Road, 10350 Penang, Malaysia.