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Acupuncture, an Adjunct Therapy for Asthma: a Pilot Study Protocol of Randomized Controlled Trial

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본 임상시험을 대비한 천식 침치료 무작위 대조군 예비 임상시험 프로토콜

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Abstract

배경 : 최근까지 이루어진 천식의 침치료 무작위 대조군 연구들에 의한 결과는 뚜렷한 효과를 보여주지 못하고 있다. 이러한 요인의 하나로 적절한 피험자 수를 정하기 위한 예비 임상시험의 부재가 거론되고 있다. 따라서 천식에 대한 침치료의 본 임상시험에 앞서 이의 실행 가능성 및 규모를 예측하는 예비임상시험이 필요한 상황이다.

목적 : 예비임상시험을 통해 서양의학적 치료를 받고 있는 천식환자들에 대한 침치료의 부가적 효과를 검증하기 위한 본 임상시험의 실현 가능성을 예측하기 위함.

방법 : 본 시험은 무작위 단일 맹검 대조군 평행 설계 예비 임상시험이다. 1차 평가변수는 최대 호기량 검사기로 집에서 아침, 저녁으로 매일 측정한 수치로 구해진 최대 호기 유속 일중 변동률의 1주간 평균치 변화이며 2차 평가변수는 의료기관에서 시행하는 폐기능 검사, 기준시점 호흡곤란 지수, 호흡곤란 변화에 대한 지수, 천식환자들의 삶의 질 평가를 위한 설문 등이다. 피험자 수는 총 45명으로 선정 및 제외기준을 통해서 참여하게 되며 1주간의 최대 호기 유속 기저치 평가 기간을 거친 후 진짜침 처치 군, 가짜침 처치 군, 대기군 세 군에 각각 무작위로 15명씩 할당된다. 모든 피험자에게 기존의 천식관련 약물의 사용을 허용하며, 진짜침 처치군 및 가짜침 처치군은 주 3회 4주간 해당 처치를 받고 2주 후에 각 평가 항목에 대하여 추적, 관찰하게 된다. 대기군은 기존의 천식관리를 유지하면서 2주마다 방문하여 총 6주간 평가를 받고 진짜침 처치를 4주간 받게 된다.

고찰 : 본 연구는 국내에서 최초로 이루어지는 천식에 대한 침 무작위 대조군 예비 임상시험으로 향후 적절한 피험자 수와 실행가능성을 예측할 수 있으리라 기대된다.

Key words : asthma, acupuncture, Randomized Controlled Trial, Pilot Study

Ⅰ. Introduction

Recently, 3.9% of Koreans are reported to be suffering from asthma, and its severeness is often undervalued by both doctors and patients. In addition, death rate prevalence of chronic lower respiratory diseases increased from 12.9 deaths

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per 100,000 cases in 1992 to 22.6 deaths per 100,000 cases in 2002. According to the data from the pharmaceutical industry, from 2001 to 2004 the annual gross value of drugs sold in Korea increased by nearly 50% (from U$3.48 to U$5.21 billion), and the proportion shared by drugs for asthma treatment in the respiratory drug market increased by approximately 36% (from U$51.8 to U$70.6 million)[1]. Furthermore, a recent cross-sectional study showed that the prevalence of wheeze and waking in the night because of cough or shortness of breath in the preceding 12 months was 12.9% and 13.5%, respectively in 5,048 Korean male and female adults aged 20 to 44 years or older[2].

With the increasing morbidity and mortality of asthma and the tremendous cost of conventional anti-asthmatic medicine, various traditional medical approaches, including acupuncture, that have shown some efficiency and safety for treating asthma in clinical situations should be tested for evidence and should contribute to public health more widely.

Recent systematic reviews, however, showed that the efficacy of traditional acupuncture treatment on asthma is not so clear[3,4]. The results of these systematic reviews and meta-analysis is limited by several problems in the individual studies including sample size, placebo treatment, missing information, etc. In recent clinical studies of acupuncture on asthma, there were some meaningful positive results regarding long-term immunological biomarker improvement[5] and short-term immediate bronchodilating effect[6]. The long-term effects (more than 4 weeks) of acupuncture on pulmonary function and quality of life, which would be the main surrogates of asthmatic patients' state, have either not been shown or have not been appropriately evaluated, probably due to the lack of appropriate sample size[5]. It is still too early to conclude that traditional acupuncture is ineffective in asthma, and more well-designed and full-scale clinical trials testing the effects of acupuncture on asthma need to be conducted.

Since there has been no pilot study of randomized controlled trial (RCT) of acupuncture on asthma, it is reasonable to proceed with a pilot study of acupuncture on asthma to conduct feasibility testing and appropriate sample size calculation before the later main clinical trial. Besides, there is a recommendation of setting up the waiting list group into the clinical trial to evaluate the appropriate efficacy of acupuncture on asthma[4]. Therefore, a pilot study with three arms (active acupuncture group, sham acupuncture group and waiting list group) has been planned for evaluating acupuncture's effect on asthmatic patients' pulmonary function and quality of life (QOL), and is in progress.

II. Method

1. Research Aims

The aim of this pilot study is to evaluate the feasibility of an RCT exploring additional anti-asthmatic effectiveness of acupuncture treatment on patients who are using routine conventional medicine, such as inhaled steroids or beta agonists. For this purpose, we will perform crude power analysis over three kinds of treatments and estimate participants' drop out and adherence to provide optimal design of the main RCT.

Research questions are as follows:

a. What is the trend of changes in asthmatic patients' daily peak expiratory flow (PEF) variability, pulmonary function, and QOL with acupuncture treatment on specific acupoints (CV22 and bilateral LU5, ST40, BL13, EXB1) compared with minimal acupuncture treatment (sham control group) on non-acupoints, and no acupuncture treatment (waiting list control group)?

b. How safe is the treatment of acupuncture on asthmatic patients?

2. Study Period

September 2008 - March 2009

3. Participants

Asthmatic patients aged 19-70 years will be included initially. All subjects will be confirmed as asthmatic by bronchodilator response tests that should show at least 12% improvement in forced expiratory volume in one second (FEV1) after the administration of short acting beta2 agonist. All of the participants' FEV1 values should be more than 60% of the predicted value and should have at least one typical asthmatic symptom (ex. intermittent dyspnea, cough, sputum, wheezing, chest tightness). All patients should have been using more than one routine anti-asthmatic medicine such as inhaled corticosteroids, inhaled bronchodilator, or oral anti-asthmatic agents for more than 4 weeks. During the study period, all patients will be allowed to use their medications.

Patients will be excluded if: (1) they have been treated by acupuncture for asthma within 12 months of the study (2) they have been treated for asthma in an emergency department within one month of the study (3) they have been hospitalized for asthma within three months of the study (4) they have had upper respiratory tract infections within six weeks of the study (5) they have had systemic infections, cancers, autoimmune disorders, cardiac failures, myofacial infarcts, angina pectorises, renal failures or hepato-biliary diseases (6) they smoke more than ten cigarettes per day (7) they have blood clotting disorders (8) they are using more than 500 μg per day of inhaled fluticasone or other inhaled corticosteroids

more than the doses equivalent to 500 μg of fluticasone daily (9) they are pregnant or planning to become pregnant or are breast-feeding or taking oral contraceptives or (10) they are unable to be compliant to the study.

The ethical validity of this study has been assessed and approved by the Institutional Review Board (IRB) of the Oriental Medical Hospital in the Kyunghee Medical Center (KOMC IRB 2008-08). All patients will be notified about the procedures of the study and will be asked to sign a form verifying informed consent. They will also be informed of the associated risks of acupuncture treatment (cough, bleeding, bruise, fainting, itching, chilling, urticaria), and they will be told that they can quit participating in the study at any time with no type of penalty or loss of benefits they would otherwise be entitled to.

4. Randomization and Treatment Allocation

The patients will be recruited by consecutive selection via inclusion-exclusion criteria. Allocation of treatment will be held by computer-aided randomization to three arms which are Group A (active acupuncture group), Group B (sham acupuncture group) and Group C (waiting list group). The distribution between groups will be 1:1:1, with blocks of 3. After each patient meets inclusion-exclusion criteria, he/she will go for his/her baseline assessment and will sign the informed consent form. After that, he/she will be allocated to one of the three treatment groups and the acupuncture practitioners will be told the patient's allocated group. The random allocation sequence will be generated by the statistician who is irrelevant to treatment or outcome collection. To keep the same expectation of effectiveness with all participants, every kind of treatment will be initially considered effective to asthma.

5. Sample Size

Since this study is to determine preliminary feasibility, there will be no sample size calculation. Aimed sample size is 45 and predicted drop-out rate is 20%. 36 patients are predicted to complete the study. This sample size is considered to be sufficient to provide power analysis and sample size calculation for the main RCT.

6. Interventions

After a run-in period, a total 12 sessions of active or sham acupuncture treatment will be performed three times a week for 4 weeks in group A and group B patients. In group C patients, no acupuncture treatment will be done for 6 weeks after randomization. After that

period, patients in group C will receive active acupuncture treatment as in group A patients (Fig. 1). Acupuncture performance will be done by a licensed oriental medical doctor with disposable stainless steel acupuncture (0.25㎜x40㎜, Dongbang Acupuncture Inc., Korea).

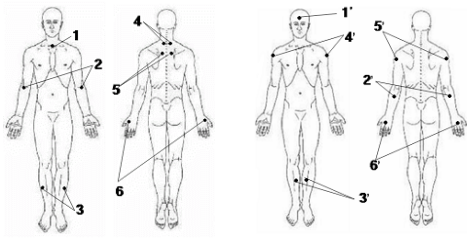
Nine acupoints (CV22 and bilateral LU5, ST40, BL13, EXB1) will be treated in group A subjects in a sitting position at each session (Figure 2). In treating CV22, the needle will be inserted perpendicularly in 0.2-0.3 cun then the direction of needle will be changed approximately 40 degrees downward and inserted in 0.7-1 cun parallel to the posterior surface of the sternum. In treating LU5, EXB1, and LI4 the needle will be inserted perpendicularly by inducer in about 0.3-0.5 cun, 1-1.5 cun, and 0.5-1 cun, respectively. For ST40, the needle will be slightly directed into the medial side with 1-1.5 cun in depth. In treating BL13, the needle will be inserted approximately 30 degrees oblique to the vertebrae. For all treatments of group A patients, the needling will be manipulated by the lifting-thrusting method for Deqi sensation.

Nine non-acupoints corresponded with each active acupoint will be treated with minimal stimulation in group B patients (Figure. 2).

Every insertion of a needle on non-acupoints will be done by an inducer, and the skin will be penetrated minimally about 0.2-0.3 cun in depth without any manipulation.

Figure. 1. Trial Work Plan of a Randomized Clinical Trial of Acupuncture Therapy on Asthmatic Patients.

* PEF: Peak Expiratory Flow
† PFT: Pulmonary Function Test
‡ BDI: Baseline Dyspnea Index
§ TDI: Transition Dyspnea Index
‖ QLQAKA: Quality of Life Questionnaire for Adult Korean Asthmatics



(A) (B)

Figure. 2. (A) Acupoints in Active Acupuncture Group (Group A) and (B) non-acupoints in Sham Acupuncture Group (Group B)

1. CV22
2. LU5
3. ST40
4. EXB1
5. BL13
6. LI4

7. Outcome Measures

a. Diary Recordings

Portable peak flow meters (MPE7200 Micropeak, Micro Medical Ltd., UK) and asthma diaries will be given to all subjects. PEF tests will be performed twice a day (one in the morning before using any asthma medication and one in the evening) at home and the results will also be recorded in the diaries. Daily PEF variability will be calculated from daily results of the PEF, and the average of each week's daily PEF variability will be analyzed as the primary outcome measure. After patients have been recruited, they will write in their asthma diaries for one week prior to treatment allocation (run-in period) for the baseline evaluation. Diary recordings will be continued for six weeks after the run-in period.

The daily PEF variability equation is as follows:

$$Daily\ PEF\ variability(\%) = \frac{evening\ PEF - morning\ PEF}{1/2(evening\ PEF + morning\ PEF)} \times 100$$

Daily asthma symptoms, frequencies, and doses of daily consumed asthma medications will be also recorded on their diaries during the study period.

b. FEV1

FEV1 of predicted value (%) will be performed using the office spirometer (Vmax, SensorMedics Corporation, USA) at the pulmonary function test room in the Kyunghee Medical Center. This office pulmonary function test of all patients will be done first as the baseline evaluation after the one week run-in period and will be followed by a test every two weeks during the six-week study period.

c. Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI)[7)]

BDI and TDI have been developed and validated to measure the severity of dyspnea in three different categories: functional impairment, magnitude of task, and magnitude of effort. These quantitative scales have been shown to have a high correlation with lung function in asthmatic patients and can give us complementary information to the pulmonary function test[8)]. BDI is a scoring system of dyspnea at a single state (baseline), and TDI is for evaluating changes of dyspnea from baseline. Therefore BDI will be checked at baseline, and TDI will be checked at two, four, and six weeks after the BDI evaluation.

d. Quality of Life Questionnaire for Adult Korean Asthmatics (QLQAKA)[9)]

QLQAKA is a questionnaire for scoring adult asthmatic patients' quality of life, consisting of 4 domains with a total of 17 questions. It has been validated by 15 multi-center studies. This questionnaire reflects the patients' cultural and behavioral characteristics and is therefore suitable for evaluating Korean asthmatic patients' quality of life. QLQAKA will be performed at baseline, two weeks after baseline and four weeks after baseline.

8. Statistical Analysis

Because this study is to determine feasibility, the main focus is catching the trend of outcome variable changes rather than testing the statistical significance. So the point estimates and confidence intervals will be represented for the changes of outcome variables associated with the three groups. An ANCOVA will additionally be performed for adjusting baseline outcome values and a repeated measures ANOVA will be used for the trends of outcome value changes over time elapsing and for the interactions associated with different interventions on. If parameters are non-normally distributed, non-parametric statistical analysis will be performed. The power analysis and sample size calculation for a later large RCT will also be conducted. The waiting list control group (group C) will be included in the main analysis only until week 6 after randomization.

III. Discussion

Since this is the first RCT of acupuncture planned for asthmatic patients in Korea, a careful preliminary study considering the feasibility is needed. The treatment acupoints in group A are commonly used in traditional Korean medical clinical situation and were selected from the Korean acupuncture textbook[10)] and several foreign reviews[11-13)] combined with the clinical experience of the allergy-respiratory clinic of the Oriental Medical Hospital in the Kyunghee Medical Center. Because minimal acupuncture treatment in the control group could have some real effects on treating asthma, a no-treatment group must be added in acupuncture clinical trials, as recommended by Cochrane review[4)]. Because of this, the current trial has three arms: the active group (group A), the sham group (group B), and the waiting list group (group C). Until now, only one acupuncture RCT on asthma adopted this three-armed design[14)]. In this study, Medici et al.[14)] reported that PEF variability in active acupuncture group and sham acupuncture group was decreased significantly compared to the no treatment group after four and five months. There was no statistical difference, however,

between the active group and sham group in the decrease of PEF variability. There might be two reasons for the non-difference between active and sham acupuncture treatment. First, there was no consideration of proper sample size sufficient to make a statistically significant difference. Secondly, there may have been problems with the treatment point selection in the sham acupuncture group. Because points on the body trunk were used in the sham acupuncture group, it might have resulted in somatovisceral reflexes, thus resulting in some effects on the asthma. For this reason, Joos et al.[5] avoided using points located on the trunk in the sham acupuncture group.

In the current study, the point estimates with confidence intervals of (not significant test of) each groups' outcome variable changes will be represented and will be used in sample size calculation for the future main RCT. Also, points on the body trunk have been avoided in the group B sham acupuncture treatment group and non-acupoints that are thought to be relatively irrelevant to asthma have been selected by an experienced Korean traditional medical doctor (S.K. Jung).

This pilot study, the first trial of acupuncture treatment on asthma in Korea, is expected to provide the potentialities of a future main RCT and its appropriate sample size.

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