

Laser acupuncture and probiotics in school age children with asthma: a randomized, placebo-controlled pilot study of therapy guided by principles of Traditional Chinese Medicine

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Traditional Chinese Medicine (TCM) postulates an interaction between the lung as a Yin-organ and the large intestine as a Yang-organ. The aim of this pilot study was to investigate in asthmatic school age children whether treatment with laser acupuncture and probiotics according to TCM portends a clinical benefit to standard medical treatment performed according to pediatric guidelines. Seventeen children aged 6–12 yr with intermittent or mild persistent asthma were enrolled in this randomized, placebo-controlled, double-blind pilot study. Eight patients received laser acupuncture for 10 wk and probiotic treatment in the form of oral drops (living non-pathogenic *Enterococcus faecalis*) for 7 wk. Nine patients in the control group were treated with a laser pen which did not emit laser light and were given placebo drops. Peak flow variability (PFV) and forced expiratory volume in 1 s (FEV₁) were measured and Quality of Life was assessed by a standardized questionnaire. Laser acupuncture and probiotics significantly decreased mean (standard deviation) weekly PFV as a measurement of bronchial hyperreactivity by –17.4% (14.2) in the TCM group vs. 2.2% (22.5) in the control group ($p = 0.034$). No significant effect was detected for FEV₁, Quality of Life criteria and additional medication. As an exploratory result, patients in the TCM group had fewer days of acute febrile infections when compared with the control group [1.14 (1.4) vs. 2.66 (2.5), $p = 0.18$]. In conclusion, this pilot study generates the hypothesis that the interactive treatment of lung and large intestine according to TCM by laser acupuncture and probiotics has a beneficial clinical effect on bronchial hyperreactivity in school age children with intermittent or mild persistent asthma and might be helpful in the prevention of acute respiratory exacerbations. These results should be confirmed by further studies.

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Traditional Chinese Medicine (TCM) has considered a connection of the lung to the large intestine for 2000 yr. According to the principles of TCM and the theory of the Five Elements

(1, 2) any treatment aimed at the lung, as a Yin-organ, also implicates treatment and regulation of the large intestine, as the linked Yang-organ. For treatment of asthma, TCM relies on

acupuncture in combination with herbal medicine (3) which also includes ingestion of specially prepared feces (Jin zhi) (4) and strict guidelines on diet and lifestyle.

Recently, an interaction between the lung and large intestine was demonstrated by scientific studies focused on the commensal flora of the gut (5–9). The 'Hygiene Hypothesis' provides plausible mechanisms for the increased prevalence of allergies in industrial countries where improvements in public health and hygiene practices result in a reduced exposure to T-helper 1 (Th1)-trophic microbial stimuli both from commensals and pathogens (5). Observations of altered intestinal microflora in allergic children (6) and clinical studies (7–9) elucidated the role of non-pathogenic microbes of the gut as a major factor essential for the maturation of the immune system to a non-atopic mode. Perinatal administration of probiotics halved the development of early atopic disease during the first two years of life in children at high risk (7). This preventive effect extended beyond infancy (8). In addition, probiotics significantly improved the clinical manifestations of atopic eczema in infants compared with a control group (9).

It remains to be determined if probiotics are also able to counteract inflammatory responses in children with pre-existing diseases beyond their first two years, such as clinically relevant relief once asthmatic symptoms have already occurred. Whereas a study using probiotics in teenagers and young adults with birch pollen allergy and asthmatic symptoms demonstrated no beneficial effect (10), another study in adults with moderate asthma reported an increase in interferon-gamma and a decrease in the number of blood eosinophils without change in clinical parameters (11).

Meta-analyses (12, 13) found only poor evidence for efficacy of acupuncture in the treatment of bronchial asthma. Previous studies were criticized for their insufficient scientific quality and for having only studied acupuncture without taking the principles of TCM into account (3).

Thus, in the present double-blind, randomized, placebo-controlled pilot study acupuncture was combined with probiotics to better reflect the treatment strategy of TCM. Laser rather than needle acupuncture was used as a painless technique commonly practiced in the treatment of pediatric patients (14, 15). Probiotic treatment with non-pathogenic *Enterococcus faecalis* was used as substitute for TCM herbs including Jin zhi. To reduce confounding variables, advices on

diet and lifestyle as included in the TCM standard treatment were neglected.

Patients and methods

Patients

Fifty-nine children aged 6–12 yr with longer than 1-yr histories of intermittent or mild persistent asthma were screened. Patients were included in the present study if they had a forced expiratory volume in 1 s (FEV_1) $\leq 85\%$ of the predicted, $\geq 12\%$ reversibility of FEV_1 following 200 μ g of salbutamol during the run-in period and $\geq 15\%$ diurnal variation in peak expiratory flow (PEF) and if informed consent could be obtained. Subjects were excluded if they had received inhaled or systemic corticosteroids within the past 6 months, if laser acupuncture treatment had been performed within the past 6 months and if they had any severe concomitant disease. Based on these inclusion and exclusion criteria, 17 of the 59 patients screened could finally participate. The study protocol was approved by the ethics committee of the Kaiserin Elisabeth Spital, Vienna. The children and their parents were informed of the scope and procedures of the study and they gave written informed consent. This study complies with the Declaration of Helsinki.

Study design

The study was conducted as a placebo-controlled, randomized, double-blind parallel investigation. Primary endpoints were improvement of peak flow variability (PFV) and FEV_1 . Additional endpoints were the reduction of relief medication and improvement of Quality of Life criteria after the 10-wk treatment period and at a follow-up after 3 months. At the initial screening visit, patients were issued a mini Wright peak flow meter and instructed in detail on its use. They were also given daily record cards to record health condition, medications and peak flow values twice daily. During a 2-wk run-in period, asthma medication (inhaled bronchodilators with or without inhaled cromolyne drugs) remained unchanged. Following the 2-wk run-in period, patients were randomized in blocks (computer assisted by the Institute for Medical Statistics of the University of Vienna) to the TCM group ($n = 8$) or the control group ($n = 9$). Four clinical visits were scheduled: before and after the 2-wk run-in period, one immediately after 10 sessions of treatment and a last follow-up visit 3 months later. At each visit, a complete history and physical examination were performed, the

Quality of Life questionnaire (16) was completed and patients underwent pulmonary function testing. The patients measured peak flow twice daily and completed daily record cards during the whole study period of 6 months.

Diagnostic tests

Pulmonary function testing was performed according to standards of the American Thoracic Society (17) at the University Children's hospital, Vienna. Forced vital capacity (FVC) and FEV₁ were recorded as a maximum expiratory flow volume curve (MEFV) (Master lab, E. Jäger, Wuerzburg, Germany). The best of the three efforts was used for calculations. The results were expressed as percent of predicted normal values based on reference measurements (17, 18).

Peak flow was measured daily in the morning using the mini Wright peak flow meter before inhaling a bronchodilator and in the evening preferably not within 4 h of bronchodilator therapy. On each occasion, the highest of the three readings was entered into the daily record card. Patients also recorded the use of asthma medication and symptoms. PFV (in percent) was calculated using the formula:

$$\text{PFV} = 100 \times \frac{(\text{PEF evening} - \text{PEF morning}) \times 100}{(\text{PEF evening} + \text{PEF morning}) \times 0.5}$$

Quality of Life was assessed at clinical visits by the standardized Asthma Quality of Life Questionnaire (16) with 21 questions about asthma events (e.g., symptoms, activities and emotions). These were scored on a seven-point scale ranging from 1 (no limitation/never) to 7 (extremely bothered/always) resulting in a final score between 7 and 147. After 10 treatment sessions, monthly telephone contact with the patients' parents was upheld by a physician until the end of the study, to review compliance with study design, compliance with treatments and to inquire about possible clinical deterioration that might require additional intervention.

TCM treatment

Patients in the TCM treatment group received 10 treatments of laser acupuncture on a once weekly schedule. The laser light was applied for 20 s per point up to 16 points without skin contact, using a Diodes soft laser pen with 670 nm at 10 mW (HELBO-Medizintechnik, Gallsbach, Austria). In addition, probiotic treatment with 20 drops

of Symbioflor I® (Symbio Pharm, Herborn, Germany), a suspension of 6×10^7 living non-pathogenic *E. faecalis*, was administered three times a day for 7 wk. Patients in the control group received 10 placebo laser acupuncture sessions with a specially manufactured laser pen which was identical in appearance to the real pen but did not emit laser light. To avoid any pressure stimulus, no skin contact was made with the acupuncture points. Furthermore, patients received placebo drops of identical appearance based on a starch suspension in saline solution.

Both groups had to wear laser protective glasses to avoid possible damage to the conjunctiva and retina by the laser light and to prevent patients in the control group from becoming aware of the lack of a laser light beam. The parents had to wait outside the treatment room. Laser treatments were carried out by a non-blinded physician but in order to maintain the double-blind study design, history, inspection of the record cards, distribution of and adherence to study medication and any necessary change in the asthma medication were conducted and recorded by a physician who was unaware of the treatment used.

Acupuncture points were chosen according to traditional Chinese diagnostics (questioning, palpitation, tongue diagnostic and pulse diagnostic) in both, the TCM and the control group. The choice of points varied from patient to patient, each individual case was evaluated separately using the system of Chinese Syndromes (2). A maximum of 16 points out of the following were used per treatment: lung 1, 5, 7, 9, 11; large intestine 4, 6, 19, 20; bladder 13, 17, 18, 20, 21, 23; stomach 13, 25, 36, 40, 44; spleen 3, 6, 9, 10; heart 3, 5, 7; small intestine 3; kidney 3, 6, 8, 27; pericardium 6; triple heater 5, 15; gallbladder 3, 34, 40, 41; liver 2, 3, 8, 13; Yin Tang, Ding Chuan; conception vessel 4, 6, 9, 17, 21; governor vessel 4, 13. Points were located according to the Viennese School of Acupuncture's anatomical description (19).

Conventional medical treatment remained unchanged in both groups. Corticosteroids as rescue medication in case of clinical deterioration were allowed only after randomization had occurred and had to be recorded in the diary cards.

Statistical analysis

This pilot study was conducted as an exploratory and hypothesis-generating study. Therefore, no power calculation was carried out. Paired tests

were performed between periods within patients and treatment groups. Differences between treatment groups were analyzed using *t*-test, Wilcoxon 2 sample test and the sign-test, if appropriate. All collected data were represented descriptively for each experimental period as mean value, standard deviation (s.d.), median, quartiles, minimum and maximum. All *p*-values reported have to be interpreted descriptively. The significance level assumed was $\alpha = 0.05$. Data were analyzed using the SAS software package version 6.12 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics and participants

Demographic data of patients are listed in Table 1. There was no statistical difference between the groups for baseline parameters. One child of the TCM group had to be excluded owing to delayed reporting on the inhaling of steroids during the run-in period. Two children of the control group failed to take the final lung function test. All patients' record cards were available until the end of the laser acupuncture period, but the recall rate of record cards in the follow-up period was low. Seven of 16 patients misplaced their diary cards (five of the control group and two of the TCM group). Therefore, PEF, febrile respiratory infections and medication are not presented for the follow-up period.

Lung function

Mean (s.d.) weekly PFV was 25.2% (16.2) and 15.5% (1.8) prior to treatment in the TCM and control group, respectively and changed to 7.9% (2.9) and 17.8% (23.9) after treatment (Fig. 1). The between-group difference was significant (Wilcoxon 2 sample test $p = 0.034$) as was the within-group difference for the TCM group (signed rank test $p = 0.015$). The within-group

difference was not significant for the control group (signed rank test $p = 0.25$).

FEV₁ values increased in both groups after TCM treatment and at follow-up 3 months later without significant difference between the groups (Table 2).

Quality of life

Both groups showed improvements in the Quality of Life scores after treatment but no significant differences were found (Table 2).

Beta mimetics usage

There was no significant difference between both groups regarding the use of beta mimetics when the week prior to treatment was compared with the week after completing treatment (Table 2).

Cortison usage

Two children from each group needed inhaled steroids as rescue medication, but none required systemic steroids.

Cromolyne usage

Five of the nine children of the control group and two of the seven children of the TCM group needed cromolyne drugs. There was no change in the use of cromolyne drugs during the study.

Infections

Days of febrile respiratory infections during the winter months from weeks 3 to 13 of the study were counted (Table 3). Children in the TCM group missed 1.1 (1.4) days [mean (s.d.)] from school owing to febrile respiratory infections compared with 2.7 (2.5) days in the control group. Four of seven (57%) and three of nine (33%) children in the TCM and control group, respectively, had not a single day of febrile infection during these winter months. This difference did not reach statistical significance ($p = 0.18$).

Safety

Laser acupuncture was found to be safe and well tolerated. No adverse events were reported. Adverse events during substitution of *E. faecalis* were few and transient, with no apparent differences between treatment groups. Four patients of the control group and two patients of the TCM group reported mild flatulence and diarrhea for 1 or 2 days. No patient discontinued the study

Table 1. Baseline characteristics of patients

	TCM group, Mean (s.d.)	Control group, Mean (s.d.)	<i>p</i> *
<i>n</i>	7	9	
Age (yr)	9.4 (2.4)	10.0 (1.9)	0.59
Height (cm)	136.5 (13.7)	142.6 (12.3)	0.63
Weight (kg)	32.3 (9.9)	36.5 (8.8)	0.63
Peak flow variability (%)	25.22 (16.17)	15.51 (1.82)	0.39
Beta mimetics (puffs/week)	8.7 (15.41)	3.1 (6.19)	0.72
FEV ₁ (% predicted)	83.9 (5.84)	84.3 (8.35)	0.67

*All *p* values for significance using the Wilcoxon 2 sample test.

Abbreviations: TCM, Traditional Chinese Medicine; s.d., standard deviation; FEV₁, forced expiratory volume in 1 s.

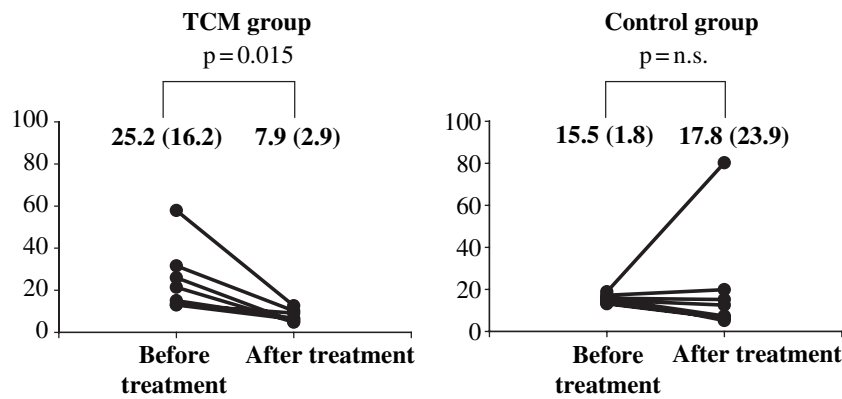


Fig. 1. Mean (s.d.) weekly peak.

Table 2. Outcome variables

	Before treatment, Mean (s.d.)	After treatment, Mean (s.d.)	Follow-up (3 months later), Mean (s.d.)
FEV ₁ (% predicted)			
TCM group	81.8 (8.1)	86.3 (5.7)	85.1 (9.7)
Control group	81.5 (8.0)	88.6 (8.5)	89.1 (5.7)
Quality of Life			
TCM group	62.1 (20)	54.9 (25.4)	49.3 (23.8)
Control group	47.8 (9.5)	34.6 (16.6)	38.7 (17.1)
Beta mimetics (puffs/week)			
TCM group	8.7 (15.4)	9.1 (15.4)	–
Control group	3.1 (6.2)	3.7 (6.7)	–

Abbreviations: TCM, Traditional Chinese Medicine; s.d., standard deviation; FEV₁, forced expiratory volume in 1 s.

Table 3. Days of febrile infections during weeks 3–13

TCM group	Control group
Patient 2: 0	Patient 1: 4
Patient 3: 0	Patient 4: 0
Patient 6: 0	Patient 5: 1
Patient 7: 0	Patient 8: 0
Patient 10: 3	Patient 9: 6
Patient 12: 2	Patient 11: 3
Patient 16: 3	Patient 14: 0
	Patient 15: 6
	Patient 17: 4

because of clinical adverse events and no serious adverse events were noted.

Discussion

This pilot study demonstrates no additional beneficial effects of TCM treatment with laser acupuncture and probiotics on FEV₁, Quality of Life and use of rescue medication in children with intermittent or mild persistent bronchial asthma. However, laser acupuncture in combination with probiotic treatment was able to

significantly improve bronchial hyperreactivity. A second, exploratory finding was that patients treated by TCM had fewer acute respiratory infections during winter months.

As illustrated in Table 1, the TCM group had a statistically non-significant higher baseline PEF variability compared with the control group. It can be argued that a greater reduction was more likely in the TCM group. However, the statistically significant within-group comparison even with the small number of patients studied strengthens the confidence in the validity of the observed findings. It is surprising that the improvement in PEF variability was not accompanied by a change of FEV₁ and Quality of Life criteria. The explanation may be a ceiling effect. All patients included in our study had relatively good FEV₁ values and Quality of Life scores at the beginning of the study, so significant improvements were unlikely. However, PEF variability is an internationally accepted measure for bronchial hyperreactivity (20).

Acupuncture was shown to release endogenous opioids, corticosteroids and adrenocorticotrophic hormone (3), all of which could influence asthma, but has also some immune-modulating effect (21). Acupuncture treatment of patients with allergic asthma resulted in a significant decrease in Th2 derived cytokine serum levels of interleukin (IL)-4, -6 and -10, and a significant increase in IL-8, together with a 32% reduction of blood eosinophils. We speculate that acupuncture might counteract the Th1/Th2 imbalance responsible for chronic airway inflammation in bronchial asthma (5, 22).

Compared with previously published acupuncture studies on patients with bronchial asthma (12, 13, 15) the beneficial effect found in our patient group could have been augmented by the additional administration of non-pathogenic *E. faecalis* according to the TCM relation of lung and large intestine. Gram-positive bacteria

are potent inducers of monocytic IL-12 (23), which is suggested to be a key cytokine involved in regulating the Th1/Th2 balance (24). The presence of IL-12 promotes the differentiation of CD4⁺ precursor T-cells into Th1 subclass, its absence, in contrast, promotes differentiation into the Th2 subclass (25). IL-12 has been demonstrated to suppress antigen-induced airway hyperreactivity and airway eosinophilia in mice when present during initial antigen presentation, but also when present only during subsequent antigen exposure (26). *Enterococcus faecalis*, a gram-positive aerobe used in our study was shown to produce approximately 30% higher amounts of IL-12 than the extensively studied gram-positive probiotic species *Lactobacillus* (23). We therefore hypothesize that stimulation of the gut-associated lymphoid tissue (GALT) via gram-positive probiotics might not only influence atopy acquisition early in life (7), but also immune modulation in patients with existing asthma resulting in a significant improvement of bronchial hyperreactivity as was demonstrated in our patient group.

Probiotics were demonstrated to enhance gut-specific immunoglobulin A (IgA) responses (9, 27). In addition, by stimulating GALT they positively influence other sites of mucosal-associated lymphoid tissue (28), because lymphocytes of enteric, bronchial and nasal mucosa belong to the same recirculating pool (29). The immunostimulatory effect of probiotic bacteria was previously shown to prevent recurrent infections in healthy children attending day-care centers (30) and in adults with recurrent sinusitis (31).

Viral respiratory infections can cause deterioration of pulmonary function in children with bronchial asthma (32). Atopic asthmatic individuals demonstrated a defective Th1 response to rhinovirus (RV) with a shift toward a Th2 phenotype and significantly lower levels of IL-12 and interferon-gamma (33). Therefore, we speculate that the additional probiotic treatment might have been beneficial in our patient group by augmenting secretion of IL-12 and by reducing the susceptibility to respiratory infections resulting in improved bronchial hyperreactivity without any serious adverse events. To reach statistical significance supporting the hypothesis that patients benefit from the TCM-based approach to asthma with respect to acute febrile infections a sample size of about 30 patients per group would be necessary (power: 80%, $\alpha = 0.05$, two-sided).

A major limitation of the present study is the small number of subjects included. To overcome some of the criticisms of previous trials (12, 13), inclusion criteria for the present trial were strict

and only patients with intermittent or mild persistent asthma without steroid treatment in the past 6 months were to be included in order to avoid confounding variables. These strict requirements made the recruiting process difficult. Only 17 children out of 59 screened candidates fulfilled the inclusion criteria.

In conclusion, this pilot study generates the hypothesis that TCM treatment of the lung and large intestine using laser acupuncture combined with probiotics improves bronchial hyperreactivity and might be beneficial in the prevention of acute respiratory exacerbations. These results should promote the design of further studies including larger groups of patients preferably with four study groups (acupuncture, probiotics, combination therapy, control) to confirm and extend the findings reported in the present study.

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