Research Snapshots

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THE EFFICACY AND SAFETY OF A CHINESE HERBAL PRODUCT (XIAO-FENG-SAN) FOR THE TREATMENT OF REFRACTORY ATOPIC DERMATITIS: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

OBJECTIVE: To evaluate the efficacy and safety of a Chinese herbal formula, Xiao-Feng-San (XFS), in the treatment of atopic dermatitis (AD) using a randomised, double-blind, placebo-controlled trial.

METHODS: The trial consisted of an eight-week treatment period and a four-week follow-up period. A total of 71 subjects with refractory, extensive and non-exudative AD were enrolled and randomised at a ratio of 2:1, to receive XFS (n = 47) or placebo (n = 24) in powder form. The XFS herbal formula consisted of the herbs Saposhnikovia divaricata (*Fang Feng*), Schizonepeta tenuifolia (*Jing Jie*), Angelica sinensis (*Dang Gui*), Rehmannia glutinosa (*Sheng Di Huang*), Saphora flavescens (*Ku Shen*), Atractylodes lancae (*Cang Zhu*), Cryptotympana pustulata (*Chan Tui*), Linum usitatissimum (*Hu Ma*), Anemarrhena asphodeloides (*Zhi Mu*), Gypsum fibrosum (*Shi Gao*), Clematis armandii (*Chuan Mu Tong*), Glycyrrhiza uralensis (*Gan Cao*) and Articum lappa (*Niu Bang*); while the placebo consisted of caramel, lactose and starch. The powders were to be mixed in 120 ml of warm water, and taken three times a day during the treatment period. The dosages varied according to age group of subjects: 3 g per dose for those aged 3–7 years; 6 g per dose for those aged 8–12; and 9 g per dose for those above 13 years. Subjects were asked to maintain current diet and dermatological treatments during the trial. Assessments were carried out at the beginning of the trial and in weeks four, eight, and 12. The assessments include total lesion score, erythema score, surface damage score, pruritus score and sleep score; blood chemistry/laboratory examinations were done as part of the safety assessment. Subjects were required to keep a daily diary to record treatment compliance and occurrence of side-effects.

RESULTS: Sixty-nine subjects were included in the intention-to-treat analysis. Fifty-six subjects completed the treatment and follow-up period. At the end of the treatment period (week eight), there was a significantly greater improvement in total lesion score, erythema score, surface damage score, pruritus score and sleep score in the XFS group compared to the placebo group. At week 12, after the follow-up period, the XFS group maintained a significant difference in all outcome measures, except in erythema score. There was one case of transient elevation of aminotransferase, which was resolved within eight weeks from the time of cessation of the intervention; and two cases of gastrointestinal upsets were reported.

CONCLUSION: It was concluded that XFS can be an alternative form of therapy for severe, refractory, extensive and non-exudative AD.

COMMENTS: According to the age groups of 3–7 years, 8–12 years and over 13 years, subjects were asked to take 3 g, 6 g, and 9 g of the intervention at each dosing point respectively. However, this will result in a daily dose of 9 g, 18 g and 27 g, which is much higher than the recommended 6–12 g and may be the reason such good results were achieved in this trial. Furthermore, subjects were asked to maintain their dermatological treatments. They applied topical corticosteroids with the same frequency and strength during the trial as they did prior to the study. In previous studies, participants were allowed to reduce the usage of concurrent therapies as their condition improved during the treatment period. The maintenance in concurrent treatment dosage might suggest that XFS is better as an adjunct treatment for AD rather than an alternative treatment. Also, the placebo used in this trial was made of caramel, lactose and starch. In Chinese medicine, sweet foods generate damp and heat which can worsen AD. The presence of sweet substances such as caramel and lactose in the placebo might have prevented a better improvement in the endpoints of the placebo group.

Cheng HM, Chiang LC, Jan YM, Chen GW, & Li TC. The efficacy and safety of a Chinese herbal product (Xiao-Feng-San) for the treatment of refractory atopic dermatitis: A randomised, double-blind, placebo-controlled trial. International Archives of Allergy and Immunology 2010; 155(2):141–148. DOI: 10.1159/000318861

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THE BIOLOGICAL BASIS OF ACUPUNCTURE: A NOVEL MECHANISM

OBJECTIVE: This study tested a novel mechanism for the transmission of the acupuncture signal. Instead of transmission through neural cells, this model proposes that manipulation of acupuncture needles send out acoustic shear waves, which act to stimulate surrounding tissues.

METHODS: The team, led by Geng Li, developed and tested a mechanical needle movement model that is based on the propagation of an acupuncture signal as an acoustic shear wave, which induces measurable changes at the cellular and whole body level. Acoustic shear waves are mechanical vibrations that can be interpreted as sound. When being propagated through a tissue, an acoustic shear wave moves perpendicular to the direction of wave propagation, does not converge and has a degree of continuity. The first set of experiments was performed in 12 human subjects. Needles (0.4 mm silver Hwato needles) were inserted using a piezoelectric drive at a verum acupuncture point (GB 35 *Yangjiao*) or sham acupuncture point 1 cm away, and a shear acoustic wave was generated. Mechanical excitation by the vertical movements of the needle was also used; however, the presence of *deqi* was not determined after manual or piezoelectric stimulation. The propagation of the resulting acoustic shear wave signal was monitored by magnetic resonance elastography (MRE) to determine the spatial and temporal propagation of the wave at the verum and sham acupuncture locations. MRE is a medical imaging technique that images propagating mechanical waves using MRI. Rather than measuring blood flow, MRI measures the stiffness of muscles and tissues. The second set of experiments was performed in a tissue culture dish. These experiments monitored intracellular calcium changes using a Calcium sensitive dye after cultured cells were stimulated with an acoustic wave. There was no verum or sham acupuncture point examined in the tissue culture experiments. Cells derived from different tissue sources were used: cultured fibroblasts, endothelial cells, cardiac myocytes and neural PC 12 cells. Calcium activation, propagation and latency were quantified using a confocal microscope that detected changes in calcium levels associated with changes in fluorescent dye emission. The contribution of calcium channels to the observed result in the cultured cells was tested *in vitro* by blocking or inhibiting the calcium channel. The third set of experiments was performed in a mouse hind limb. These experiments relied on the introduction of a plasmid DNA construct containing the calcium indicator, GCaMP2, which is one of the most robust calcium indicators, into the hind limbs of mice. The introduction of the plasmid by electroporation resulted in the production of transformed cells expressing GCaMP2, an EGFP/calmodulin fusion protein used for studying calcium fluxes *in vivo*. The spatial and temporal changes in intracellular calcium levels were monitored *in vivo* in the mouse hind limb using a two-photon fluorescence microscope after an acoustic shear wave acupuncture stimulus at ST 36 *Zusanli* was applied. The sham acupuncture control for this experiment consisted of inserting a needle into the hind limb without subsequent stimulation. The final sets of experiments, which were performed in mice, measured the activation of beta-endorphins by measuring the blood serum levels of beta-endorphin using a protein based antibody detection kit (ELISA) after acupuncture. The dependence of the beta-endorphin response on calcium was determined by measuring beta endorphin level after acupuncture and the systemic administration of a calcium channel blocker.

OUTCOMES: Shear acoustic waves were propagated at both the verum and the sham acupuncture points; however, there was a statically significant difference in the degree of tissue response and spread of signal in the verum acupuncture point compared to the sham point. The shear wave was propagated more than twice the distance in the longitudinal direction compared with the transverse direction, suggesting a direction of signal flow. In cultured cells, the acoustic shear waves activated intracellular calcium stores and produced calcium response waves. In many cases, the calcium signal was long lasting and a response was detected up to 1.5 hours after stimulation was stopped. Removing calcium from the bath, the application of a calcium channel inhibitor blocked these responses, which suggests that calcium is mediating the shear wave acoustic signal. In the mouse hind limb, *in vivo* acoustic shear wave stimulation showed a significant increase in calcium responses that spread to adjacent muscle fibres compared with a control non-stimulated acupuncture needle. Blocking the effect of the calcium channels also decreased the calcium response in the hind limb. There was an increase in circulating beta-endorphins after the shear wave stimulation *in vivo* at ST36 (*Zusanli*) in mouse hind limb and this increase was blocked when calcium receptors were blocked. The change in beta-endorphins was not tested with a control non-stimulated acupuncture needle insertion.

CONCLUSIONS: The biological basis of acupuncture was well represented using an acoustic shear wave model. Even though activation of calcium at non-acupuncture points was observed, this signal was approximately halved compared to the verum acupuncture signal, thus indicating that the verum response was always stronger and long lasting. This result may explain the observed beneficial result with sham acupuncture points in clinical trials. Even though sham produces a result, verum acupuncture is always better. After stimulation, there was a

measurable change in cytosolic calcium and beta-endorphins. The observed calcium waves were able to spread to adjacent tissue and were long lasting, which supports the observed movement of acupuncture stimulation along meridians and its long lasting effect.

COMMENT: Overall, this was a very well controlled study designed to investigate the biological basis of the acupuncture signal. The identification of dynamic and sustained calcium modulation after acupuncture is exciting because of the multitude of roles that calcium plays in the cell. Calcium is critical for muscle contraction, maintaining osmotic balance and is a common second messenger used to transduce signals within the cell. The calcium changes observed after acupuncture stimulation strongly suggest that the long lasting effects of acupuncture are mediated through calcium signalling causing a sustained change in cell physiology. As with any study, there are a few small experimental issues to keep in mind. There was no stated rationale for the use of GB35 *Yangjiao*. The amount of plasmid DNA introduced *in vivo* can be variable when using electroporation, which may have increased the variability of their result unless the results were standardised. In addition, although they provide statistical analysis of their data, the number of animals and replicates is missing. This study is a necessary first step in testing the acoustic shear wave model. As the authors point out, the article does not investigate analgesia or pain suppression, which is the next step in determining if this model is able support the observed analgesic effects of acupuncture.

Li G, Liang J-M, Li PW, Yao X, Pei PZ, LI W, et al. Physiology and cell biology of acupuncture observed in calcium signaling activated by acoustic shear wave. Eur J Phy. 2011; 462:587-597.

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