Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

ORIGINAL ARTICLE SKIN AND EYE DISEASES

Acupuncture compared with oral antihistamine for type I hypersensitivity itch and skin response in adults with atopic dermatitis – a patient- and examiner-blinded, randomized, placebo-controlled, crossover trial

F. Pfab[1,2,3,4], M.-T. Kirchner[3], J. Huss-Marp[1,3], T. Schuster[5], P. C. Schalock[6], J. Fuqin[1,3], G. I. Athanasiadis[1], H. Behrendt[3,7], J. Ring[1,7], U. Darsow[1,3] & V. Napadow[2,8]

[1]Department of Dermatology and Allergy, Technische Universität München, Munich, Germany; [2]Department of Radiology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA; [3]Division of Environmental Dermatology and Allergy, Helmholtz Zentrum München/TUM, ZAUM-Center for Allergy and Environment, Munich, Germany; [4]Department of Prevention and Sports Medicine, Klinikum rechts der Isar, Technische Universitaet Muenchen, Munich, Germany; [5]Institute for Medical Statistics and Epidemiology, Technische Universität München, Munich, Germany; [6]Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA; [7]Christine-Kühne Center of Allergy Research and Education (CK-CARE), Munich, Germany; [8]Department of Radiology, Logan College of Chiropractic, Chesterfield, MO, USA

To cite this article: Pfab F, Kirchner M-T, Huss-Marp J, Schuster T, Schalock PC, Fuqin J, Athanasiadis GI, Behrendt H, Ring J, Darsow U, Napadow V. Acupuncture compared with oral antihistamine for type I hypersensitivity itch and skin response in adults with atopic dermatitis – a patient- and examiner-blinded, randomized, placebo-controlled, crossover trial. *Allergy* 2012; **67**: 566–573.

Keywords
acupuncture; allergen; atopic eczema; attention; cetirizine; itch.

Correspondence
Florian Pfab, Department of Radiology, Harvard Medical School, Massachusetts General Hospital, Harvard Medical School CNY 149-2301, 13th St. Charlestown, Boston, MA 02129, USA.
Tel.: +1-617-838-6644
Fax: +1-617-726-7422
E-mail: pfab@nmr.mgh.harvard.edu

Accepted for publication 28 December 2011

DOI:10.1111/j.1398-9995.2012.02789.x

Edited by: Werner Aberer

Abstract

Background: Itch is the major symptom of atopic dermatitis (AD). Acupuncture has been shown to exhibit a significant effect on experimental itch in AD. Our study evaluated acupuncture and antihistamine itch therapy (cetirizine) on type I hypersensitivity itch and skin reaction in AD using a patient and examiner-blinded, randomized, placebo-controlled, crossover trial.

Methods: Allergen-induced itch was evaluated in 20 patients with AD after several interventions in separate sessions: preventive (preceding) and abortive (concurrent) verum acupuncture (VAp and VAa), cetirizine (10 mg, VC), corresponding placebo interventions (preventive, PAp, and abortive, PAa, placebo acupuncture; placebo cetirizine pill, PC) and a no-intervention control (NI). Itch was induced on the forearm and temperature modulated over 20 min, using our validated model. Outcome parameters included itch intensity, wheal and flare size and the D2 attention test.

Results: Mean itch intensity (SE: 0.31 each) was significantly lower following VAa (31.9) compared with all other groups (PAa: 36.5; VC: 36.8; VAp: 37.6; PC: 39.8; PAp: 39.9; NI: 45.7; $P < 0.05$). There was no significant difference between VAp and VC ($P > 0.1$), although both therapies were significantly superior to their respective placebo interventions ($P < 0.05$). Flare size following VAp was significantly smaller ($P = 0.034$) than that following PAp. D2 attention test score was significantly lower following VC compared with all other groups ($P < 0.001$).

Conclusions: Both VA and cetirizine significantly reduced type I hypersensitivity itch in patients with AD, compared with both placebo and NI. Timing of acupuncture application was important, as VAa had the most significant effect on itch, potentially because of counter-irritation and/or distraction. Itch reduction following cetirizine coincided with reduced attention.

Abbreviations:
AD atopic dermatitis; EIQ Eppendorf Itch Questionnaire; NI no-intervention control; PA placebo acupuncture; PAa abortive placebo acupuncture; PAp preventive placebo acupuncture; PC placebo cetirizine; SCORAD scoring atopic dermatitis; SP skin prick; VA verum acupuncture; VAa abortive verum acupuncture; VAp preventive verum acupuncture; VAS visual analogue scale; VC verum cetirizine.

Key messages

- Acupuncture and cetirizine show significant reductions in type I hypersensitivity itch in patients with atopic dermatitis (AD).
- Time of therapy application was an important factor, as abortive acupuncture demonstrated improved itch reduction compared with both preventive acupuncture and cetirizine.
- Cetirizine significantly reduced attention capacity compared with acupuncture and all placebo control therapies.

Introduction

The sensation of itch, defined as 'unpleasant sensation that provokes the desire to scratch', is the most prevalent subjective symptom of inflammatory skin diseases (1–4). For instance, itch plays a key role in atopic dermatitis (AD) (5), leading to significant morbidity (4, 6). Acupuncture reduces both histamine-induced itch in healthy volunteers (7–10) and allergen-induced (type I hypersensitivity) itch in patients with AD (11). However, acupuncture has never been directly compared with current standard systemic (antihistamine) therapy. Furthermore, the temporal relationship between acupuncture administration and efficacy for itch reduction has never been investigated.

Antihistamines are considered the first-line preventive systemic itch therapy for AD (12), although convincing evidence of their effectiveness is still lacking, and mediators other than histamine induce itch in AD (13). Atopic dermatitis itch can be triggered by various allergens including house dust mite, birch pollen and grass pollen (5). While the mechanisms by which antihistamines reduce AD itch are not well understood, this therapy may modulate attentional focus, as drowsiness is a common side-effect (14).

Most acupuncture research has focused on analgesic applications. Pain shows pathophysiological similarities to itch (15), and acupuncture has been shown to reduce itch (7–11,16). Acupuncture has never been compared directly with conventional systemic therapies such as antihistamines, and it is unknown whether acupuncture also modulates attentional focus. Furthermore, acupuncture may have different effects when applied prior to itch induction in a preventive setting compared to application during itch induction, that is, an abortive setting (11).

The aim of our study was to evaluate the effect of different approaches of acupuncture compared with standard systemic antihistamine treatment (cetirizine) on type I hypersensitivity itch sensation and wheal and flare formation. We used our recently developed temperature-modulated itch model (11, 17, 18) and hypothesized that acupuncture would be as effective as antihistamine therapy, without the side-effects of diminished attentional focus. Moreover, acupuncture in an abortive setting would be more efficacious than in a preventive setting.

Methods

Subjects

Patients with AD were recruited from the outpatient clinic of the Department of Dermatology of the Technische Universität München Germany. Inclusion criteria included AD diagnosis [Scoring atopic dermatitis (SCORAD) > 20], age range of 18–50 years and type I sensitivity to any of the following allergens: grass or birch pollen, cat or dog dander, *Dermatophagoides farinae* or *pteronyssinus*. Atopic dermatitis patients on systemic therapy or topical treatment with immunosuppressive agents on the nondominant arm were excluded. Patients had to stop all immunosuppressive medications at least 10 days prior to the study to avoid potential itch suppression. Patients had no prior experience with acupuncture and were not aware of itch or wheal/flare response to skin prick testing. All patients gave informed consent, and the study was approved by the local ethics committee of the Technische Universität München and conducted according to Declaration of Helsinki Principles.

Study design

The study design was a partially double-blinded (patient and observer in regard to verum or placebo acupuncture, and verum or placebo tablet; however, both could differentiate between an acupuncture procedure, tablet and no intervention), randomized, prospective, seven-arm crossover trial. Each patient served as their own control (i.e. randomized to all seven groups in turn). Different intervention sessions were separated by at least 1 week. The acupuncturist and data collection observer were different individuals.

The seven study arms consisted of (1) verum acupuncture performed prior to itch induction (i.e. preventive, VAp), (2) verum acupuncture performed during itch induction (i.e. abortive, VAa), (3,4) placebo acupuncture (both preventive and abortive, PAp and PAa), (5) verum cetirizine, ingested preventively (VC), (6) placebo cetirizine tablet (PC) and (7) a no-intervention control (NI).

Itch experiment protocol

Itch was induced with the validated short-term temperature modulation model, which is capable of increasing and decreasing itch sensation within seconds, as has been previously described (17–20). Allergen solution [house dust mite (Der p1 or De r f1), grass (timothy grass pollen) or birch pollen, cat or dog dander (Allergopharma, Reinbek, Germany)] was applied to the volar aspect of the distal nondominant forearm in a clinically nonlesional area using skin prick. A 30 × 30 mm thermal stimulus probe (Medoc Advanced Medical Systems, Rimat Yishai, Israel) was used to modulate the temperature over the site (Fig. 1), thereby modulating itch – increasing itch during cool cycles and decreasing itch during warm cycles (17, 18, 20, 21). Total experimental time was 20 min, which included 27 warm–cool cycles.

Itch assessment

During temperature modulation, itch intensity was rated on a computerized visual analogue scale (VAS) ranging from 0 to 100, where 0 was defined as 'no itch' and 100 as 'maximum itch'. The scale was also anchored at one-third of the

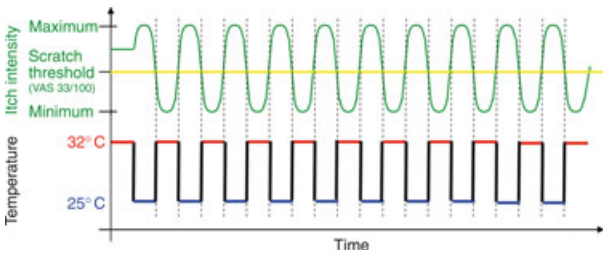

Figure 1 Schematic illustration of the itch stimulation protocol. Temperature is modulated in a block design from 32°C (red) to 25° C (blue) (lower). Idealized time course of the mean itch ratings – increasing itch ratings during cool, 25°C blocks and decreasing ratings during warm, 32°C blocks (upper, in green) (17, 18, 20, 21).

VAS (33/100), defined to patients as the 'scratch threshold' (17, 19, 22). At the end of each session, the Eppendorf Itch Questionnaire (EIQ) (23), a validated instrument, was completed by all subjects, separately for both cool and warm blocks. Descriptive and emotional items were calculated as mean rating loads (23).

Skin reactions

Ten minutes (10) after prick test (and subsequent itch modulation), wheal and flare size were quantified by the average of four perpendicular radii centred at the skin prick site.

d2 Test of attention

Following each session, after the EIQ, patients also completed the German version of the d2 test of attention. This is the standard instrument for measuring concentration speed and attention in both clinical and applied settings (24).

Interventions

Acupuncture procedures

Verum acupuncture (VA) was performed using sterile stainless steel needles (0.25 × 40 mm), inserted 2–3 cm at acupoints on the dominant arm and leg (i.e. opposite to itch provocation). For the preventive VAp arm, acupoints included LI-11 (Quchi, located on the elbow at the midpoint of the line joining the lateral end of the transverse cubital crease and the lateral epicondyle of the humerus) and HT-3 (ShaoHai, between the ulnar end of the cubital crease and medial epicondyle of the humerus). On the leg, acupoints included ST-34 (LiangQiu, 2 cm above the superior lateral border of the patella) and SP-10 (XueHai, 2 cm above the superior medial border of the patella). These acupoints are referenced in standard acupuncture textbooks, as being important for treating cutaneous pruritus (11). For the abortive VAa arm, acupoints included LI-11 and HT-3. Needles were electrically stimulated with high-frequency (100 Hz, 0.2 ms pulse width) electroacupuncture using the constant-current AS Super 4 Han device (Schwa-medico GmbH, Ehringshausen, Germany). Current intensity was set to moderately strong but not painful, that is, innocuous stimulation.

Placebo acupuncture was performed on the dominant arm at nonacupoint locations. In the preventive PAp arm, stimulus locations were along the ulnar aspect of the forearm (SH-1 and SH-2) and shoulder (SH-3 and SH-4). In the abortive PAa arm, SH-1 and SH-2 were used. Stimulation was performed with a validated nonpenetrating placebo needle developed by Streitberger et al. (25). Electrical stimulation was also simulated with the same electrostimulation device as in VA, attaching nonfunctioning electrical leads to the placebo needles and asking subjects to verify that stimulation was in a 'comfortable range.' Subjects were told *a priori* that different forms of acupoint stimulation were being evaluated.

The needling ritual was identical in both the preventive and abortive VA and PA acupuncture groups. Acupuncture was carried out by the same acupuncturist. The needles were inserted, left in place 20 min and removed without manual manipulation.

In the preventive approach (VAp and PAp), acupuncture procedures were completed just prior to itch provocation. In the abortive approach (VAa and PAa), acupuncture was commenced just prior to itch provocation.

Pharmacotherapy (VC and PC)

In the two drug arms, patients preventively received either a cetirizine 5 mg tablet or a placebo tablet of similar appearance, 45 min prior to itch provocation. Patients were told they were receiving current standard medication for itch alleviation. Cetirizine is known to have peak plasma concentration within 1 h postingestion (http://www.drugs.com/pro/cetirizine.html).

Evaluation of blinding

At the end of the study, patients were asked whether they thought they received 'verum-point' or 'placebo-point' acupuncture for each of the acupuncture sessions and 'verum cetirizine' or 'PC' for each of the tablet sessions. Patients were also allowed to answer 'not sure' for each of these questions.

Statistical analysis

The main outcome of the study was mean itch intensity (VAS). Secondary outcome measures were attention, skin responses (wheal and flare size) and EIQ itch questionnaire rating. Descriptive statistics of itch parameter maximum ratings, mean and cumulative (area under curve) ratings, attention scores, EIQ single and total item scores and wheal and erythema diameters were calculated.

To assess differences in itch VAS levels under different treatment conditions (randomized treatment sequences), linear mixed regression models (LMM) were employed. In the LMM analysis (SAS version 9.2; SAS Institute Inc., Cary, NC, USA), contrasts of marginal means were evaluated under simultaneous consideration of measurement time,

temperature (warm/cool) and the interaction between time and temperature. Subjects were considered random effects.

After having checked all parameters as normally distributed by the Kolmogorov–Smirnov test, differences between treatment conditions using data from the EIQ questionnaire were evaluated using multiple paired samples *t*-tests.

Bonferroni adjustment of *P*-values was conducted to correct for multiple comparisons within the primary efficacy analysis. For maximum efficiency (and to not be overly conservative), eight main pairwise group comparisons were chosen prior to data analysis (NI-VAp, NI-VAa, NI-VC, PAp-VAp, PAa-VAa, PC-VC, VAp-VC and VAa-VC).

The global significance level was set to 0.05, and all statistical tests were two-sided. Statistical analyses of secondary endpoints were carried out in an explorative manner considering a local level of significance of 0.05 (two-sided). If not mentioned otherwise, mean values ± confidence intervals are given. Ninety-five per cent confidence intervals are provided for relevant effect sizes.

Results

Twenty (20) patients with AD (14 women and 6 men, SCORAD = 44.5 ± 5.6) with a mean age of 23.3 ± 1.7 years were enrolled. Patients were found to have type I sensitivity to *Dermatophagoides pteronyssinus* ($n = 9$), *Dermatophagoides farinae* ($n = 3$), grass pollen ($n = 4$), birch pollen ($n = 1$), cat dander ($n = 2$) or dog dander ($n = 1$), respectively. Of patients, 95% (19/20) reported itch without pain 40 s after allergen application. One patient showed no itch response and was therefore excluded.

Quantitative assessment of itch intensity (VAS)

Mean itch intensity

The highest mean VAS was found for NI (46 points, VAS = 0–100), and the lowest mean VAS for VAa (32 points) (Table 1, Fig. 2). Visual analogue scale levels were not statistically different for PAp and PC groups (40 points) as well as for PAa (36 points) and VC (37 points). VAp and VC were also not statistically different. Owing to the multiple blocks, 95% confidence intervals were small; hence, all other group contrasts in mean VAS levels were statistically significant at a two-sided 5% level.

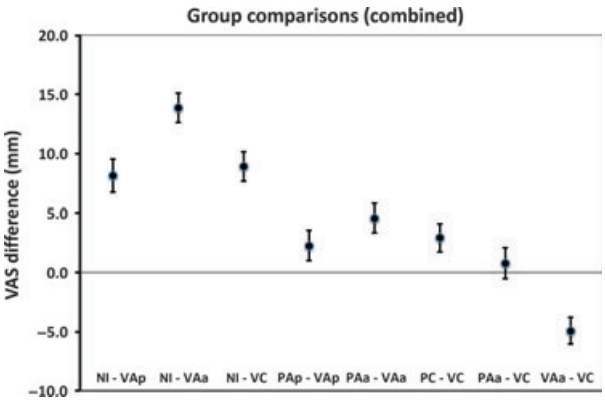

Figure 2 Difference in marginal means based on the linear mixed regression model for visual analogue scale (VAS) response simultaneously considering time, temperature (interaction: time by temp) and treatment condition as explanatory variables. Error bars depict Bonferroni-adjusted confidence intervals for the estimated mean difference (dot in centre of the bars) at a global confidence level of 95%. Confidence intervals above the dotted zero line favour second group as therapeutic option (i.e. significantly lower VAS values compared with the first group). Confidence intervals below the dotted zero line favour the first group as therapeutic option (i.e. significantly lower VAS values compared with the second group).

Mean itch intensity (cool and warm blocks)

In further analyses for both warm and cool blocks, a significant impact of time, treatment condition and interaction was evident ($P < 0.001$ within the multivariable LMM, Table 1, Fig. 3). There was consistent decrease in mean VAS in all

Table 1 Showing mean itch intensity and 95% CI of the different groups

		Temperature setting	
Treatment condition	Entire experiment Marginal mean* (95% CI)	Cool Marginal mean* (95% CI)	Warm Marginal mean* (95% CI)
NI	45.7 (44.9–46.5)	48.7 (47.5–49.8)	42.7 (41.6–43.7)
PAp	39.9 (39.2–40.5)	42.5 (41.4–43.5)	37.1 (36.3–38.0)
Paa	36.4 (35.7–37.2)	38.9 (37.7–40.0)	33.9 (33.0–34.9)
PC	39.7 (39.0–40.5)	41.4 (40.3–42.4)	38 (37.1–39.0)
VAp	37.6 (36.8–38.4)	38.3 (37.1–39.4)	36.8 (35.7–37.9)
VAa	31.9 (31.2–32.6)	34.2 (33.1–35.2)	29.5 (28.6–30.4)
VC	36.8 (36.1–37.5)	38.9 (37.9–40.0)	34.6 (33.7–35.5)

NI, no-intervention control; PAp, Placebo acupuncture preventive; Paa, Placebo acupuncture abortive; PC, placebo cetirizine; VA, verum acupuncture; VC, Verum Cetirizine.

The three columns of the table present results averaged over the entire experimental block design as well as separate results from cool and warm experimental blocks.

*Based on the linear mixed regression model for visual analogue scale response simultaneously considering time, temperature (interaction: time by temp) and treatment condition as explanatory variables.

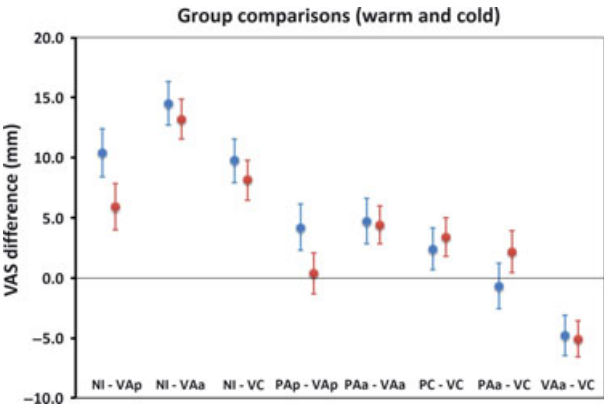

Figure 3 Differences in marginal means based on the linear mixed regression model for visual analogue scale (VAS) response simultaneously considering time, temperature, interaction: time by temp and treatment condition as explanatory variables. Error bars depict Bonferroni-adjusted confidence intervals for the estimated mean difference (dot in centre of the bars) at a global confidence level of 95%. Blue and red error bars represent estimates on mean VAS values from cool and warm phases, respectively. Confidence intervals above dotted line favour second group as therapeutic option (significantly lower VAS values compared with first group). CIs below dotted line favour first group as therapeutic option (significantly lower VAS values compared with second group).

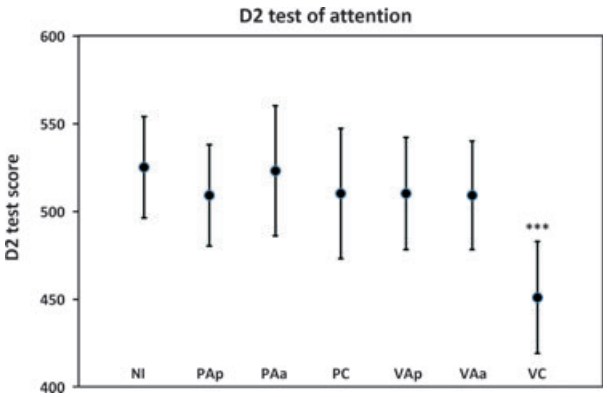

Figure 4 Showing mean total attention scores (correct hits minus errors). The verum cetirizine (VC) group scored significantly lower compared with all other intervention groups.

treatment groups for warm blocks compared with cool blocks ($P < 0.001$). The mean reduction was estimated from 1% to 6% across different study arms. Highest VAS values were found for NI, PAp and PC arms, and lowest values for VAa.

Wheal and flare size

Wheal size at 10 min (Table 2) showed no significant differences between groups ($P = 0.91$) (Wald chi-square test). Flare size at 10 min (Table 2) showed significant differences between groups ($P < 0.001$). Flare size for VAa ($P = 0.003$) and PAa ($P = 0.015$) was significantly smaller than for NI. Flare size for VAp was significantly smaller ($P = 0.034$) than for PAp.

Qualitative assessment of itch intensity (EIQ)

Mean descriptive total ratings were significantly lower for VAa compared to NI (corrected $P = 0.003$); exploratory analyses of individual descriptive EIQ items found that 'itching' (corrected $P = 0.004$) and 'sunburn-like' (corrected $P = 0.003$) were rated significantly lower for VAa compared to NI (Table 2).

Compared to NI, mean emotional total ratings were significantly lower for VAa ($P = 0.003$), PAa ($P = 0.002$) and VAp ($P = 0.003$). Exploratory analyses of individual emotional EIQ items found that 'cruel' ($P = 0.003$) and 'severe' ($P = 0.0001$) were rated significantly lower for VAa compared to NI; 'bothering' ($P = 0.005$) was rated significantly lower for PAa compared to NI; 'severe' was rated significantly lower for VAp ($P = 0.005$) and VC ($P = 0.004$) compared to NI.

Attention evaluation

Mean attention scores (correct hits minus errors) were 525 ± 29 (NI), 509 ± 29 (PAp), 523 ± 37 (PAa), 510 ± 37 (PC), 510 ± 32 (VAp), 509 ± 31 (VAa) and 451 ± 32 (VC). The overall test for group heterogeneity (Wald chi-square test) showed significant differences between groups ($P < 0.001$). The mean attention score following VC was significantly lower compared with all other groups ($P < 0.001$) (Fig. 4).

Evaluation of blinding

For preventive acupuncture, 3 of 19 patients believed that VAp was real acupuncture compared to 6 of 19 patients for

Table 2 Showing wheal and flare size (10 min after allergen skin prick test) as well as mean descriptive and emotional Eppendorf Itch Questionnaire (EIQ) ratings and 95% CI of the different groups

	NI	Pap	Paa	PC	Vap	Vaa	VC
Mean flare size (cm) ± CI	30.5 ± 8.6	25.0 ± 6.4	26.3 ± 6.9	26.5 ± 10.0	27.8 ± 7.8	26.2 ± 7.3	25.6 ± 7.9
Mean wheal size (mm) ± CI	9.0 ± 2.4	8.5 ± 2.5	6.8 ± 1.8	8.5 ± 2.3	6.7 ± 1.9	6.5 ± 2.5	7.3 ± 2.8
Mean EIQ descriptive ± CI	56.2 ± 11.2	49.5 ± 10.6	46.8 ± 13.2	54.6 ± 10.9	49.8 ± 10.3	42.3 ± 11.3	44.4 ± 10.6
Mean EIQ emotional ± CI	48.2 ± 14.4	40.9 ± 12.7	32.9 ± 15.4	39.4 ± 12.8	30.8 ± 12.5	29.1 ± 10.8	31.8 ± 13.0

NI, no-intervention control; Pap, Placebo acupuncture preventive; Paa, Placebo acupuncture abortive; PC, placebo cetirizine; Vap, Verum acupuncture preventive; Vaa, Verum acupuncture abortive; VC, Verum Cetirizine.

PAp – a nonsignificant difference. The majority of patients (10 of 19) answered 'not sure.' For abortive acupuncture, 1 of 19 patients believed that VAa was real acupuncture compared to 5 of 19 patients for PAa – a nonsignificant difference. The majority (13 of 19) again responded they were 'not sure.' Regarding antihistamine therapy, all patients (19 of 19) answered 'not sure.'

Discussion

Our blinded, randomized, placebo-controlled, crossover trial was designed to assess clinically relevant (allergen-induced) itch reduction by two modes of acupuncture stimulation as well as second-generation antihistamine drug, cetirizine. The results demonstrated a specific effect of acupuncture as well as cetirizine on itch perception and skin reactions compared with placebo and NIs. Moreover, the timing of acupuncture interventions played a significant role in itch reduction. While preventive acupuncture and cetirizine showed similar effect sizes, abortive acupuncture was superior to these and all other therapy arms. In fact, abortive acupuncture was the only intervention to reduce itch perception below the clinically meaningful scratch threshold.

In order to control for placebo effects, we used a crossover design with several placebo groups. All verum groups (VAa, VAp, VC) were significantly better at reducing itch compared to respective placebos. For acupuncture, placebo groups were designed with acupuncture-like stimulation at nonclassical acupoints in the same dermatomes and with the same ritual as verum acupuncture groups. Moreover, PA was conducted in both a preventive manner and abortive manner to adequately control for placebo effects for both VAp and VAa, respectively. These results for acupuncture corroborate our previous studies, which demonstrated similar superiority of VA for reducing histamine-induced itch in healthy volunteers (9) as well as allergen itch in patients with AD (11). Importantly, our data confirmed successful blinding.

Several previous studies have also investigated acupuncture for itch reduction, using various methodological approaches. Our previous study evaluated continuous itch response following a skin prick application of allergen in patients with AD (11). Manual acupuncture, at the same acupoints stimulated with electroacupuncture in our current study, was found to reduce itch and skin reaction compared with placebo acupuncture. In this study, itch reduction was also more effective during acupuncture compared with after the acupuncture procedure, suggesting that abortive exceed preventive effects (26). Interestingly, both our previous study and current study found that preventive acupuncture was superior to placebo in suppressing flare skin reaction. Other groups have investigated acupuncture for histamine-induced itch and skin reactions in healthy volunteers. Belgrade et al. (7) found that electroacupuncture reduced itch and flare following intradermal histamine injection. Lundeberg et al. (8) observed reduced itch following intrasegmental electroacupuncture stimulation and subsequent intradermal histamine injection. Our group also investigated preventive acupuncture for histamine-induced itch in healthy adults and demonstrated reduced itch and wheal formation compared with placebo-point acupuncture or no intervention (9).

The mechanisms underlying acupuncture reduction in itch and skin response to allergen are currently not known. Our finding that abortive was superior to preventive acupuncture suggests that counter-irritation and/or distraction (26), which have been better studied for analgesia, may also play a role in antipruritic effects. Also, in comparing preventive acupuncture and cetirizine (a 'preventive' systemic therapy), VAp demonstrated a greater effect during peak itch intensity (cool blocks), while cetirizine had a stronger effect during lower itch intensity (warm blocks) pointing towards different mechanisms of action. Moreover, cetirizine produced a significant reduction of attention compared to both VAa and VAp. These differences hint at potential central mechanisms of action for both acupuncture and cetirizine therapy in reducing itch, which should be further explored with techniques such as neuroimaging.

Other potential mechanisms for antipruritic action of acupuncture include anti-inflammatory effects (27). Inflammation is an important component of AD itch (28). However, acupuncture anti-inflammatory effects probably apply to neurogenic inflammation and would not be specifically antipruritic. Other potential mechanisms might relate to mediators associated with itch, such as endogenous opioid peptides (e.g. beta-endorphin). These neuromodulators have been implicated in acupuncture analgesia (29, 30) and have been shown to influence itch sensation (28). On a spinal level, acupuncture seems to have a counter-irritative effect and reduces prostaglandin E2 levels, a further mediator involved in itch, in both brain and serum in LPS-injected rats (31). While long-term antipruritic acupuncture effects are not well known, our recent study demonstrated that reduced itch was associated with reduction of allergen-induced basophil activation in patients with AD (32).

Previous neuroimaging studies have demonstrated that acupuncture modulates some of the same limbic and paralimbic brain structures (33, 34) known to process itch sensation in both healthy adults (18) and patients with AD (20), such as the amygdala, anterior cingulate and insular cortices. Further studies should apply neuroimaging methods to explore the possible pathways of acupuncture action in the pathophysiology of itch and allergic skin reactions.

Compared to placebo tablet (as well as all acupuncture procedures), cetirizine produced significant reduction of the D2 test of attention score. This result suggests that cetirizine may have affected cognitive function. While the common opinion is that second-generation antihistamines cross the blood–brain barrier to a much lesser extent than first-generation antihistamines, Tashiro et al. found that after a double therapeutic dose of 20 mg, cetirizine occupied 20–50% of the H_1 receptors in the brain (35). Whether the modulation of cognitive processes such as attention is specifically related to itch reduction should be explored in future studies.

Conclusion

Our study showed significant itch reduction after verum acupuncture or cetirizine treatment compared with respective

placebos and no treatment in patients with AD. While preventive acupuncture was similarly effective to cetirizine, abortive acupuncture was significantly more effective than preventive acupuncture or cetirizine. Abortive acupuncture was the only intervention to reduce itch below the clinically relevant scratch urge threshold, while preventive acupuncture was the only therapy to reduce skin reactions (flare size). The results suggest that acupuncture may be a useful complementary therapy to downregulate itch, urticaria or eczema in atopic patients with less cognitive side-effects (specifically regarding attention) compared with cetirizine.

Acknowledgments

This study was partly funded by a grant of the German Acupuncture Society (DÄGfA), German Research Foundation (pf 690/2-1), the Christine Kühne Center of Allergy and Education (CK-Care) and the National Center for Complementary and Alternative Medicine at the National Institutes of Health, USA (VN: R01-AT004714, P01-AT002048).

Conflict of interest

None.

References

1. Charlesworth EN, Beltrani VS. Pruritic dermatoses: overview of etiology and therapy. *Am J Med* 2002;**113**(Suppl 9A):25S–33S.
2. Pfab F, Athanasiadis GI, Kollmar A, Ring J, Ollert M. Lichenoid drug eruption due to an antihypertonic drug containing irbesartan and hydrochlorothiazide. *Allergy* 2006;**61**:786–787.
3. Pfab F, Willi R, Albert A, Huss-Marp J, Athanasiadis GI, Jakob T et al. Anaphylactic reaction to folic acid verified by provocational testing. *Allergy* 2007;**62**:823–824.
4. Misery L, Ständer S. *Pruritus*. London: Springer, 2010.
5. Ring J. *Allergy in practice*. Berlin, Heidelberg, New York: Springer, 2005.
6. Yosipovitch G, Greaves MW, Schmelz M. Itch. *Lancet* 2003;**361**:690–694.
7. Belgrade MJ, Solomon LM, Lichter EA. Effect of acupuncture on experimentally induced itch. *Acta Derm Venereol* 1984;**64**:129–133.
8. Lundeberg T, Bondesson L, Thomas M. Effect of acupuncture on experimentally induced itch. *Br J Dermatol* 1987;**117**:771–777.
9. Pfab F, Hammes M, Backer M, Huss-Marp J, Athanasiadis GI, Tolle TR et al. Preventive effect of acupuncture on histamine-induced itch: a blinded, randomized, placebo-controlled, crossover trial. *J Allergy Clin Immunol* 2005;**116**:1386–1388.
10. Kesting MR, Thurmuller P, Holzle F, Wolff KD, Holland-Letz T, Stucker M. Electrical ear acupuncture reduces histamine-induced itch (alloknesis). *Acta Derm Venereol* 2006;**86**:399–403.
11. Pfab F, Huss-Marp J, Gatti A, Fuqin J, Athanasiadis GI, Irnich D et al. Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema – a blinded, randomized, placebo-controlled, crossover trial. *Allergy* 2010;**65**:903–910.
12. Ikoma A, Steinhoff M, Stander S, Yosipovitch G, Schmelz M. The neurobiology of itch. *Nat Rev Neurosci* 2006;**7**:535–547.
13. Greaves M. Mast cell mediators other than histamine induced pruritus in atopic dermatitis patients – a dermal microdialysis study. *Br J Dermatol* 2000;**142**:1079–1080.
14. Carson S, Lee N, Thakurta S. *Drug class review: newer antihistamines: final report update 2*. Portland, OR: Oregon Health & Science University, 2010.
15. Yosipovitch G, Carstens E, McGlone F. Chronic itch and chronic pain: analogous mechanisms. *Pain* 2007;**131**:4–7.
16. Che-Yi C, Wen CY, Min-Tsung K, Chiu-Ching H. Acupuncture in haemodialysis patients at the Quchi (LI11) acupoint for refractory uraemic pruritus. *Nephrol Dial Transplant* 2005;**20**:1912–1915.
17. Pfab F, Valet M, Sprenger T, Toelle TR, Athanasiadis GI, Behrendt H et al. Short-term alternating temperature enhances histamine-induced itch: a biphasic stimulus model. *J Invest Dermatol* 2006;**126**:2673–2678.
18. Valet M, Pfab F, Sprenger T, Woller A, Zimmer C, Behrendt H et al. Cerebral processing of histamine-induced itch using short-term alternating temperature modulation–an FMRI study. *J Invest Dermatol* 2008;**128**:426–433.
19. Darsow U, Ring J, Scharein E, Bromm B. Correlations between histamine-induced wheal, flare and itch. *Arch Dermatol Res* 1996;**288**:436–441.
20. Pfab F, Valet M, Sprenger T, Huss-Marp J, Athanasiadis GI, Baurecht HJ et al. Temperature modulated histamine-itch in lesional and nonlesional skin in atopic eczema – a combined psychophysical and neuroimaging study. *Allergy* 2010;**65**:84–94.
21. Pfab F, Valet M, Toelle TR, Behrendt H, Ring J, Darsow U. Recent progress in unravelling CNS processing of itch sensation. *World Allergy Organiz J* 2008;**10**:168–173.
22. Darsow U, Drzezga A, Frisch M, Munz F, Weilke F, Bartenstein P et al. Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. *J Invest Dermatol* 2000;**115**:1029–1033.
23. Darsow U, Scharein E, Simon D, Walter G, Bromm B, Ring J. New aspects of itch pathophysiology: component analysis of atopic itch using the 'Eppendorf Itch Questionnaire'. *Int Arch Allergy Immunol* 2001;**124**:326–331.
24. Brickenkamp R. d2 – Aufmerksamkeits-Belastungs-Test. 2002;**9**.
25. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998;**352**:364–365.
26. Moont R, Pud D, Sprecher E, Sharvit G, Yarnitsky D. Pain inhibits pain' mechanisms: is pain modulation simply due to distraction? *Pain* 2010;**150**:113–120.
27. Oke SL, Tracey KJ. The inflammatory reflex and the role of complementary and alternative medical therapies. *Ann N Y Acad Sci* 2009;**1172**:172–180.
28. Darsow U, Pfab F, Valet M, Huss-Marp J, Behrendt H, Ring J et al. Pruritus and atopic dermatitis. *Clin Rev Allergy Immunol* 2011;**41**:237–244.
29. Guo ZL, Moazzami AR, Tjen ALS, Longhurst JC. Responses of opioid and serotonin containing medullary raphe neurons to electroacupuncture. *Brain Res* 2008;**1229**:125–136.
30. Pfab F, Winhard M, Nowak-Machen M, Napadow V, Irnich D, Pawlik M et al. Acupuncture in critically ill patients improves delayed gastric emptying: a randomized controlled trial. *Anesth Analg* 2011;**112**:150–155.
31. Fang JQ, Guo SY, Asano K, Yu Y, Kasahara T, Hisamitsu T. Antipyretic action of peripheral stimulation with electroacupuncture in rats. *In Vivo* 1998;**12**:503–510.
32. Pfab F, Athanasiadis GI, Huss-Marp J, Fuqin J, Heuser B, Cifuentes L et al. Effect of acupuncture on allergen-induced basophil activation in patients with atopic eczema:a pilot trial. *J Altern Complement Med* 2011;**17**:309–314.
33. Napadow V, Dhond RP, Kim J, LaCount L, Vangel M, Harris RE et al. Brain encoding of acupuncture sensation–coupling

on-line rating with fMRI. *Neuroimage* 2009;**47**:1055–1065.

34. Napadow V, Makris N, Liu J, Kettner NW, Kwong KK, Hui KK. Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI. *Hum Brain Mapp* 2005;**24**:193–205.
35. Tashiro M, Mochizuki H, Iwabuchi K, Sakurada Y, Itoh M, Watanabe T et al. Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain. *Life Sci* 2002;**72**:409–414.