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## Acupuncture compared to 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

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### 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 anti-histamine 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 AD patients after several interventions in separate sessions: preventive (preceding) and abortive (concurrent) verum acupuncture (VAp and VAa), cetirizine (10mg, 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 minutes, 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 to 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 ( $p > 0.1$ ), though both therapies were significantly superior to their respective placebo interventions ( $p < 0.05$ ). Flare size following VAp was significantly smaller ( $p = 0.034$ ) than PAp. D2 attention test score was significantly lower following VC compared to all other groups ( $p < 0.001$ ).

**Conclusions**—Both VA and cetirizine significantly reduced type-I-hypersensitivity itch in AD patients, compared to both placebo and NI. Timing of acupuncture application was important, as

VAA had the most significant effect on itch, potentially due to counter-irritation and/or distraction. Itch reduction following cetirizine coincided with reduced attention.

## Keywords

Itch; allergen; acupuncture; atopic eczema; cetirizine; attention

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## 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 AD patients (11). However, acupuncture has never been directly compared to current standard systemic (anti-histamine) 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). AD 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 (7–10)(11, 16). Acupuncture has never been compared directly to conventional systemic therapies such as anti-histamines 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, i.e. an abortive setting (11).

The aim of our study was to evaluate the effect of different approaches of acupuncture compared to standard systemic anti-histamine 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 anti-histamine therapy, without the side effects of diminished attentional focus. Moreover, acupuncture in an abortive setting would be more efficacious than a preventive setting.

## Methods

### Subjects

AD patients were recruited from the outpatient clinic of the Department of Dermatology of the Technische Universität München Germany. Inclusion criteria included AD diagnosis (SCORAD > 20), 18–50 years old, type-I-sensitivity to any of the following allergens: grass or birch pollen, cat or dog dander, *Dermatophagoides farinae* or *pteronyssinus*. AD patients on systemic therapy or topical treatment with immunosuppressive agents on the non-dominant 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 or tablet or 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 one 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 Der f1), grass (timothy grass pollen) or birch pollen, cat or dog dander (Allergopharma, Reinbek, Germany)) was applied to the volar aspect of the distal non-dominant forearm in a clinically non-lesional area using skin prick. A 30 × 30 mm thermal stimulus probe (Medoc Advanced Medical Systems, Rimat Yishai, Israel) was used to modulate temperature over the site (Figure 1), thereby modulating itch – increasing itch during cool cycles, decreasing itch during warm cycles (17, 18, 20, 21). Total experimental time was 20 minutes, 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 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 (10) minutes after prick test (and subsequent itch modulation), wheal and flare size were quantified by the average of 4 perpendicular radii centered 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 with sterile stainless steel needles (0.25 × 40mm), inserted 2–3cm 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, 0.2ms pulse width) electro-acupuncture using the constant-current AS Super 4 Han device (Schwa-medico GmbH, Ehringshausen, Germany). Current intensity was set to moderately strong but not painful, i.e. innocuous stimulation.

Placebo acupuncture (PA) was performed on the dominant arm at non-acupoint 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 non-penetrating placebo needle developed by Streitberger et. al (25). Electrical stimulation was also simulated with the same electro-stimulation device as in VA, attaching non-functioning 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 minutes, 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 5mg tablet or a placebo tablet of similar appearance, 45 minutes 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 hour post-ingestion (<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 “placebo cetirizine” 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, Eppendorf itch questionnaire 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 of time and temperature. Subjects were considered random effects.

After having checked all parameters as normally distributed by the Kolmogorow-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, 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  $\pm$  confidence intervals are given. Ninety-five percent confidence intervals are provided for relevant effect sizes.

## Results

Twenty (20) AD patients (14 female, 6 male, SCORAD=44.5  $\pm$  5.6) with a mean age of 23.3  $\pm$  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. 95% of patients (19/20) reported itch without pain 40 seconds 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, Figure 2). VAS 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. Due 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.

**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, Figure 3). There was consistent decrease in mean VAS in all treatment groups for warm blocks compared to 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 minutes (Table 2) showed no significant differences between groups ( $p = 0.91$ ) (Wald chi-square Test).

Flare size at 10 minutes (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 PAp.

### Qualitative assessment of itch intensity (EIQ) (Table 2)

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  $p = 0.004$ ) as well as “sunburn-like” (corrected  $p = 0.003$ ) were rated significantly lower for VAa compared to NI.

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” ( $p=0.003$ ) as well as “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  $525\pm 29$  (NI),  $509\pm 29$  (PAp),  $523\pm 37$  (PAa),  $510\pm 37$  (PC),  $510\pm 32$  (VAp),  $509\pm 31$  (VAa) and  $451\pm 32$  (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 to all other groups ( $p<0.001$ ) (Figure 4).

### Evaluation of Blinding

For preventive acupuncture, 3 of 19 patients believed that VAp was real acupuncture compared to 6 of 19 patients for PAp - a non-significant 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 non-significant 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 a second generation antihistamine drug, cetirizine. The results demonstrated a specific effect of acupuncture as well as cetirizine on itch perception and skin reactions compared to placebo and no intervention controls. 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 cross-over 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 non-classical acupoints in the same dermatomes and with the same ritual as verum acupuncture groups. Moreover, PA was conducted in both a preventive 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 AD patients (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 AD patients (11). Manual acupuncture, at the same acupoints stimulated with electro-acupuncture in our current study, was found to reduce itch and skin reaction compared to placebo acupuncture. In this study, itch reduction was also more effective during acupuncture compared to 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 (8) et al. 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 to placebo point acupuncture or no intervention (9).

The mechanisms underlying acupuncture reduction of 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 anti-pruritic 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 anti-pruritic 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 anti-pruritic. 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 anti-pruritic acupuncture effects are not well known, our recent study demonstrated that reduced itch was associated with reduction of allergen-induced basophil activation in AD patients (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 AD patients (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 20mg, cetirizine occupied 20% to 50% of the H<sub>1</sub>-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 to respective placebos and no treatment in AD patients. 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 down-regulate itch, urticaria or eczema in atopic patients with less cognitive side effects (specifically regarding attention) compared to cetirizine.

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## Abbreviations

<b>AD</b>	Atopic dermatitis
<b>VAS</b>	Visual analogue scale
<b>EIQ</b>	Eppendorf Itch Questionnaire
<b>min</b>	minute(s)
<b>s</b>	second(s)
<b>mm</b>	millimetre(s)
<b>cm</b>	centimetre(s)
<b>SCORAD</b>	Scoring atopic dermatitis
<b>SP</b>	skin prick
<b>VA</b>	Verum acupuncture
<b>PA</b>	Placebo acupuncture
<b>NI</b>	No intervention control
<b>VAp</b>	preventive verum acupuncture
<b>Pap</b>	preventive placebo acupuncture
<b>VAA</b>	abortive verum acupuncture
<b>PAa</b>	abortive placebo acupuncture
<b>VC</b>	Verum Cetirizine
<b>PC</b>	Placebo Cetirizine

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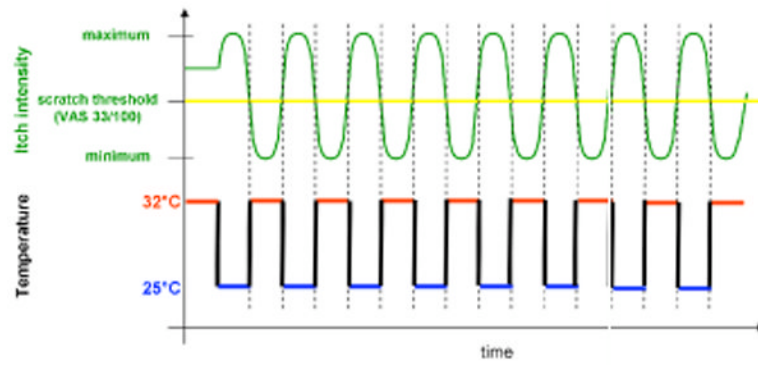


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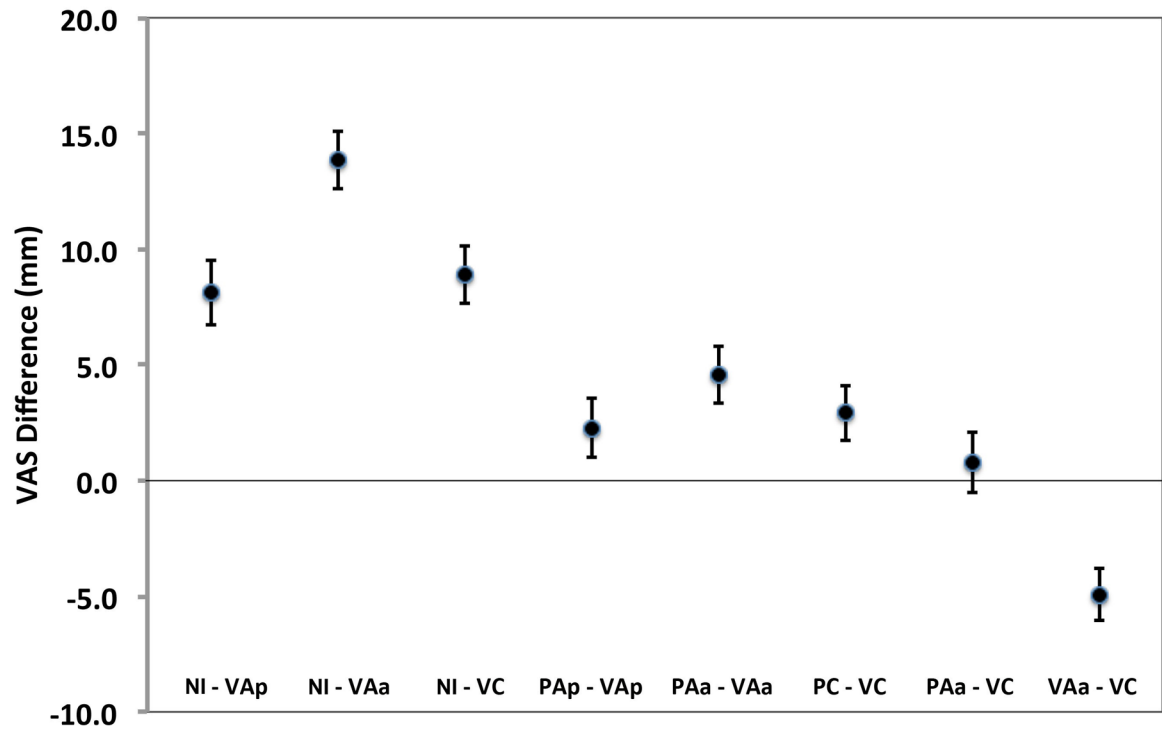
**Key messages**

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



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

## Group Comparisons (Combined)



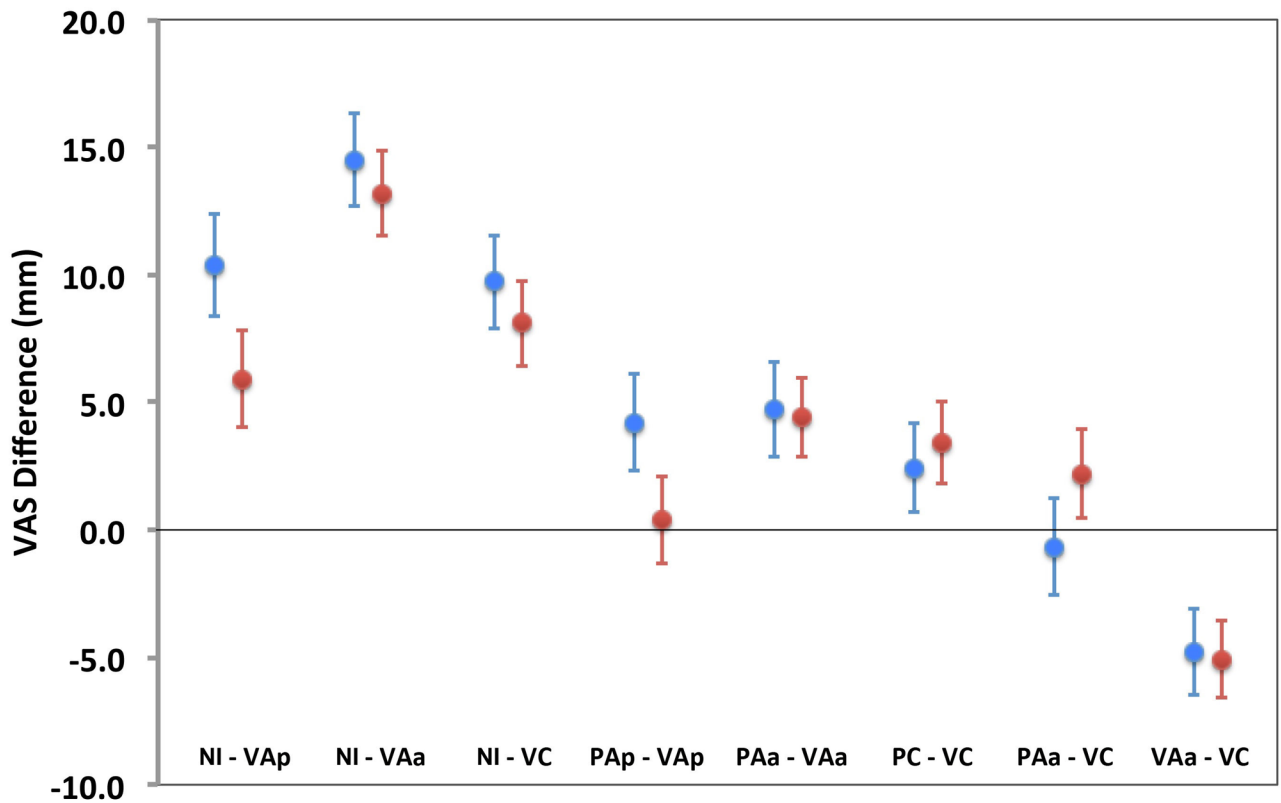
**Figure 2.**

Difference in marginal means based on the linear mixed regression model for 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 to the first group). CIs below the dotted zero line favour the first group as therapeutic option (i.e. significantly lower VAS values compared to the second group).

## Group Comparisons (Warm and Cold)

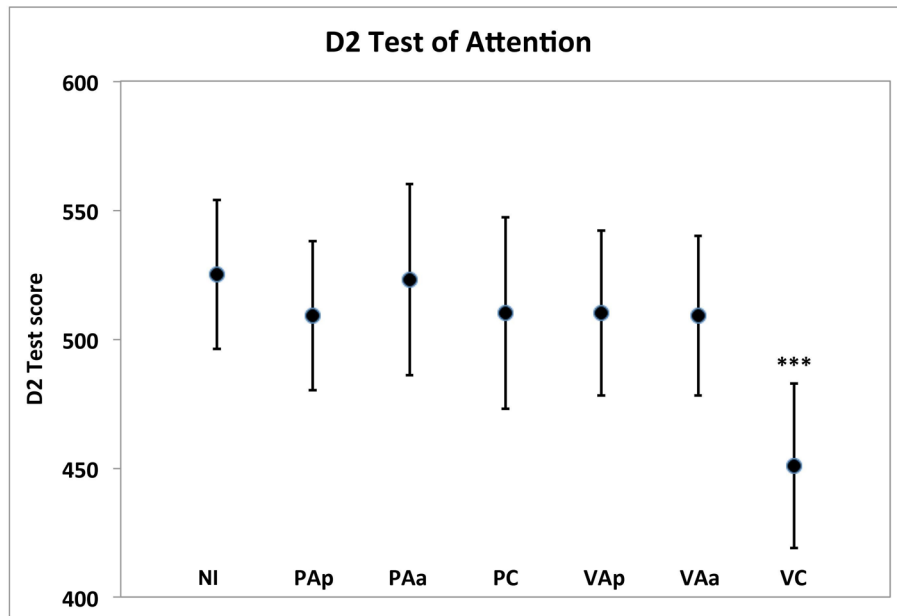


**Figure 3.**

Differences in marginal means based on the linear mixed regression model for 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 to first group). CIs below dotted line favour first group as therapeutic option (significantly lower VAS values compared to second group).



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

Showing mean itch intensity and 95% CI of the different groups (\*based on the linear mixed regression model for VAS response simultaneously considering time, temperature (interaction: time by temp) and treatment condition as explanatory variables.) 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.

**Table 1**

treatment condition	entire experiment			temperature setting		
	marginal mean*	95% CI		cool	warm	
				marginal mean*	marginal mean*	95% CI
<b>1- NI</b>	45.7	(44.9 – 46.5)	48.7	(47.5 – 49.8)	42.7	(41.6 – 43.7)
<b>2- PAp</b>	39.9	(39.2 – 40.5)	42.5	(41.4 – 43.5)	37.1	(36.3 – 38.0)
<b>3- Paa</b>	36.4	(35.7 – 37.2)	38.9	(37.7 – 40.0)	33.9	(33.0 – 34.9)
<b>4- PC</b>	39.7	(39.0 – 40.5)	41.4	(40.3 – 42.4)	38	(37.1 – 39.0)
<b>5- VAp</b>	37.6	(36.8 – 38.4)	38.3	(37.1 – 39.4)	36.8	(35.7 – 37.9)
<b>6- VAa</b>	31.9	(31.2 – 32.6)	34.2	(33.1 – 35.2)	29.5	(28.6 – 30.4)
<b>7- VC</b>	36.8	(36.1 – 37.5)	38.9	(37.9 – 40.0)	34.6	(33.7 – 35.5)



**Table 2**

Showing wheal and flare size (10 minutes after allergen skin prick test) as well as mean descriptive and emotional Eppendorf Itch Questionnaire 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