

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

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To cite this article: Pfab F, Huss-Marp J, Gatti A, Fuqin J, Athanasiadis GI, Irnich D, Raap U, Schober W, Behrendt H, Ring J, Darsow U. 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* 2009; DOI: 10.1111/j.1398-9995.2009.02284.x.

Key words

acupuncture; allergen; atopic eczema; flare; itch; wheal.

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Accepted for publication 25 October 2009

DOI:10.1111/j.1398-9995.2009.02284.x

Edited by: Thomas Bieber

Abstract

Background: Itch is a major symptom of allergic skin disease. Acupuncture has been shown to exhibit a significant effect on histamine-induced itch in healthy volunteers. We investigated the effect of acupuncture on type I hypersensitivity itch and skin reaction in a double-blind, randomized, placebo-controlled, crossover trial.

Methods: An allergen stimulus (house dust mite or grass pollen skin prick) was applied to 30 patients with atopic eczema before (direct effect) and after (preventive effect) two experimental approaches or control observation: acupuncture at points Quchi and Xuehai [verum acupuncture (VA), dominant side], 'placebo-point' acupuncture (PA, dominant side), no acupuncture (NA). Itch intensity was recorded on a visual analogue scale. After 10 min, wheal and flare size and skin perfusion (via LASER-Doppler) were measured at the stimulus site, and the validated Eppendorf Itch Questionnaire (EIQ) was answered.

Results: Mean itch intensity was significantly lower in VA (35.7 ± 6.4) compared to NA (45.9 ± 7.8) and PA (40.4 ± 5.8) regarding the direct effect; and significantly lower in VA (34.3 ± 7.1) and PA (37.8 ± 5.6) compared to NA (44.6 ± 6.2) regarding the preventive effect. In the preventive approach, mean wheal and flare size were significantly smaller in VA ($0.38 \pm 0.12 \text{ cm}^2/8.1 \pm 2.0 \text{ cm}^2$) compared to PA ($0.54 \pm 0.13 \text{ cm}^2/13.5 \pm 2.8 \text{ cm}^2$) and NA ($0.73 \pm 0.28 \text{ cm}^2/15.1 \pm 4.1 \text{ cm}^2$), and mean perfusion in VA (72.4 ± 10.7) compared to NA (84.1 ± 10.7). Mean EIQ ratings were significantly lower in VA compared to NA and PA in the treatment approach; and significantly lower in VA and PA compared to NA in the preventive approach.

Conclusions: Acupuncture at the correct points showed a significant reduction in type I hypersensitivity itch in patients with atopic eczema. With time the preventive point-specific effect diminished with regard to subjective itch sensation, whereas it increased in suppressing skin-prick reactions.

Abbreviations

EIQ, Eppendorf Itch Questionnaire; NA, no acupuncture; PA, 'Placebo-point' acupuncture; SCORAD, Scoring atopic dermatitis; SP, skin prick; VA, 'Verum-point' acupuncture; VAS, visual analogue scale.

The sensation of itch – defined as ‘unpleasant sensation that provokes the desire to scratch’ (1) – is the most prevalent subjective symptom of inflammatory skin diseases (2–4). It plays a clinical key role in atopic eczema (5–8) and leads to a serious impairment of quality of life of affected patients (3, 9–11). In atopic eczema, itch can be triggered by various allergens including house dust mite and grass pollen (7, 8, 12). Acupuncture has been shown to have antipruritic effects in experimental itch in healthy volunteers showing a significant effect before and after application of histamine as itch stimulus (13–16). In atopic eczema, however, histamine is not the main itch mediator. Furthermore, it is unknown whether acupuncture has an effect on experimental itch in patients with atopic eczema. Therefore, this study aimed to evaluate a possible preventive and therapeutic effect of acupuncture on type I hypersensitivity itch sensation as well as wheal and flare formation in 30 patients with atopic eczema.

Methods

Subjects

Inclusion criteria were patients with atopic eczema (SCORAD (17) > 18) between 18 and 50 years of age with type I sensitivity to grass pollen or *Dermatophagoides pteronyssinus*, respectively.

Patients on systemic or topical treatment with immunosuppressive agents on the nondominant arm were excluded; patients had to stop all these medications at least 10 days prior to the study to avoid treatment effect on itch perception. All patients had given informed consent, had no knowledge on acupuncture, and itch or wheal/flare response to skin-prick testing with grass pollen or *Dermatophagoides pteronyssinus*, respectively. 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 double-blind (patient and observer), randomized, prospective, three-arm crossover trial, in which each patient served as its own control (and was thereby subjected to all three groups). Acupuncturist and observer were different individuals. The study started with positioning the patients comfortably on a treatment couch and fixation of the nondominant subjects arm followed by premeasurements. These included a first temperature and LASER-Doppler measurement (Moor Laser Doppler Imager; Moor Instrument Ltd., Devon, UK) on the left forearm. After the resting period, a first allergen stimulus to induce itch was applied to the volar aspect of the distal nondominant forearm in a clinically nonlesional area using skin prick (SP). According to the patients’ known sensitization, *Dermatophagoides pteronyssinus* (Der p 1; Allergopharma, Reinbek, Germany) or *grass pollen* (timothy grass pollen; Allergopharma) was applied as a single drop in aqueous solution on the skin, followed by a superficial puncture of

this skin region with a skin prick test lancet (18). This model has been validated for studies of experimental histamine itch and results in a deposit of the stimulus at the dermal-epidermal junction, where the terminal endings of itch-related C-fibers are located (19–21). The itch stimulus was followed by continuous measurement of itch intensity, which was quantitatively expressed in percent of a visual analogue scale (VAS) at 20 s intervals over a period of 15 min. At one-third of the scale the intervention point ‘scratch threshold’ was installed; above this threshold each individual felt strongly the desire to scratch (which, however, was not permitted).

The patients were then randomized into one of three groups: ‘verum-point’ acupuncture (VA), ‘placebo-point’ acupuncture (PA) or no acupuncture (NA) (22), which they received 4 min after the first allergen itch stimulus. Ten minutes after the first itch stimulus, wheal and flare reactions (as averages of four perpendicular diameters) as well as regional blood flow and temperature were measured at the stimulus site. Fifteen minutes after the first itch stimulus acupuncture procedures ended, the Eppendorf Itch Questionnaire (EIQ) was completed by the subjects. The latter is a validated instrument for qualitative and quantitative registration of pruritus containing 80 items, including questions concerning painful sensations, which can be rated from 0 (not applicable) to 4 (very applicable) (23).

After a second 15-min resting period with further premeasurements (regional blood flow and temperature), a second allergen stimulus to induce itch was applied to the volar aspect of the proximal nondominant forearm in the same manner as the first stimulus followed by continuous measurement of itch intensity via VAS at 20 s intervals over a period of 15 min. Ten minutes after the second itch stimulus, wheal and flare reactions as well as regional blood flow and temperature were measured at the stimulus site, and 5 min later a second EIQ completed by the subjects. At the end of the study, the patients were asked whether they felt to have received ‘verum-point’ or ‘placebo-point’ acupuncture.

Acupuncture procedures

‘Verum-point’ acupuncture was performed on the arm as well as leg of the subject’s dominant handedness at the points 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; Fig. 1) and Xue Hai (located on the medial thigh two patient’s thumb widths superior to the superomedial angle of the patella, on the vastus medialis muscle; Fig. 1), which are according to a Chinese standard acupuncture textbook important for treating cutaneous pruritus (24). Sterile stainless steel needles (0.25 × 40 mm) were inserted 2–3 cm and manipulated for a 5 s period. After 11 min, the needles were taken out without manipulation.

Placebo acupuncture was performed on the arm (located at the mid point of the acromial part of the deltoid muscle; Fig. 1) as well as leg (located on the frontal thigh four patient’s thumb widths superior to the middle of the upper

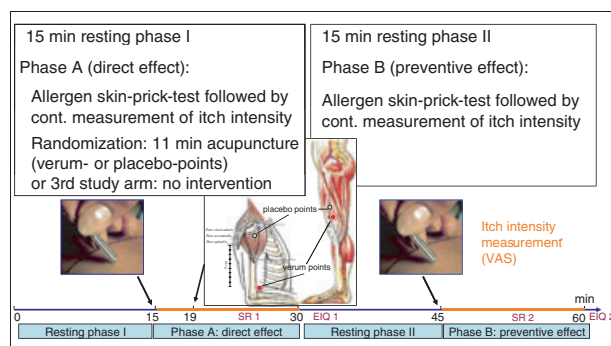


Figure 1 Study design. Abbreviations: EIQ, Eppendorf Itch Questionnaire; SR, Skin Reactions (wheal and flare size).

patella border, on rectus femoris muscle; Fig. 1) of the subject's dominant handedness at two points close to and in the same dermatomes as the 'verum-points', but not belonging to the classic meridian system and so far not acknowledged as acupuncture points (Fig. 1) by traditional Chinese text books. Needling procedures were carried out equally in both acupuncture groups and were carried out at the described location with no regard to whether the site was clinically lesional or nonlesional.

Statistical analysis

If not mentioned otherwise mean values $\pm$ confidence intervals (95%) are given. The main end points of the study were mean itch intensity and wheal and erythema size. Descriptive statistics of wheal and erythema diameters, as well as of the itch parameter maximum ratings, mean and cumulative (area under curve) ratings, and EIQ single and total item scores were calculated. Itch parameters were quantitatively expressed in percent (of 100) of the VAS at the different time points and were also referred to the intervention point (desire to scratch = 33% of VAS). After having checked all parameters as normally distributed by the Kolmogorov–Smirnov one-sample test, differences between treatment groups were evaluated by the paired samples *t*-test. Dichotomous variables for two related results were analyzed using the McNemar test. The Wilcoxon signed rank test was used to compare the frequencies of EIQ item ratings. In case of significance, bivariate post hoc *t*-tests were performed using Bonferroni correction for multiple testing. *P*-values < 0.05 were considered as statistically significant. All tests were performed two-tailed. The analyses were performed using SPSS version 13 (SPSS Inc. Chicago, IL, USA).

Results

Thirty patients (16 female, 14 male) with atopic eczema (SCORAD (17) > 18 ; mean: 39.0 ± 6.3) and a mean age of 28.6 ± 2.1 years with type I sensitivity to grass pollen ($n = 13$) or *Dermatophagoides pteronyssinus* ($n = 17$), respectively, were included in the study.

For both parts of the study (evaluation of the direct as well as preventive effect of acupuncture), 29 of 30 patients reported itch without pain 40 s after histamine application (Fig. 2). One patient showing no itch response was excluded.

Quantitative assessment of itch intensity (VAS)

Before intervention

Before intervention (0–4 min after allergen skin prick), mean itch intensities (in percent of the VAS) were $24.1 \pm 5.4\%$ (NA), $23.5 \pm 4.6\%$ (PA), and $24.9 \pm 5.4\%$ (VA). At time point 4 min – just before intervention – mean itch intensities were $46.6 \pm 8.25\%$ (NA), $43.2 \pm 6.4\%$ (PA), and $46.8 \pm 7.3\%$ (VA).

Direct effect

Regarding the direct effect of acupuncture intervention (4.3–15 min after allergen skin prick), mean VAS-ratings were $45.8 \pm 7.8\%$ (NA), $40.4 \pm 5.8\%$ (PA), and $35.7 \pm 6.4\%$ (VA) with significant differences between VA and NA ($P = 0.009$) as well as VA and PA ($P = 0.022$). With intervention itch intensity decreased in VA, whereas it further increased in NA and PA. Maximum itch intensities and corresponding time points were $51.1 \pm 8.5\%$ (NA) at 6.3 min, $46.0 \pm 5.8\%$ at 5.7 min (PA), and $42.0 \pm 6.1\%$ at 5 min (VA). At 27 of 33 time points mean VAS-ratings were lower ($P < 0.05$) in VA compared to NA; at 13 of 33 time points mean VAS-ratings were lower ($P < 0.05$) in VA compared to PA; and at 4 of 33 time points mean VAS-ratings were lower ($P < 0.05$) in PA compared to NA.

Only, the mean itch intensity of VA fell below scratch threshold level at 33% VAS during the observation period. Measurements above scratch threshold were significantly fewer in VA (22 of 33) compared to PA (33 of 33, $P < 0.0001$) and NA (33 of 33, $P < 0.0001$). Time of itch was thereby reduced by the VA by at least 33% compared to NA and PA.

Preventive effect

Regarding the preventive effect of acupuncture intervention (0–15 min after allergen skin prick; intervention carried out more than 15 min before), mean itch intensities were $44.6 \pm 6.2\%$ (NA), $37.8 \pm 5.6\%$ (PA), and $34.3 \pm 7.1\%$ (VA) with significant differences between VA and NA ($P < 0.001$) as well as PA and NA ($P = 0.002$).

Maximum itch intensities and corresponding time points were $63.0 \pm 8.3\%$ (NA) at 6.3 min, $52.8 \pm 6.6\%$ at 6.0 min (PA), and $49.3 \pm 8.2\%$ at 5.3 min (VA). At 37 of 46 time points mean VAS-ratings were lower ($P < 0.05$) in VA compared to NA; at 4 of 46 time points mean VAS-ratings were lower ($P < 0.05$) in VA compared to PA; and at 26 of 46 time points mean VAS-ratings were lower ($P < 0.05$) in PA compared to NA.

Measurements above scratch threshold were fewer in VA (27 of 46) compared to NA (39 of 46, $P = 0.0003$). Time of itch was thereby reduced by the VA by 26% compared to

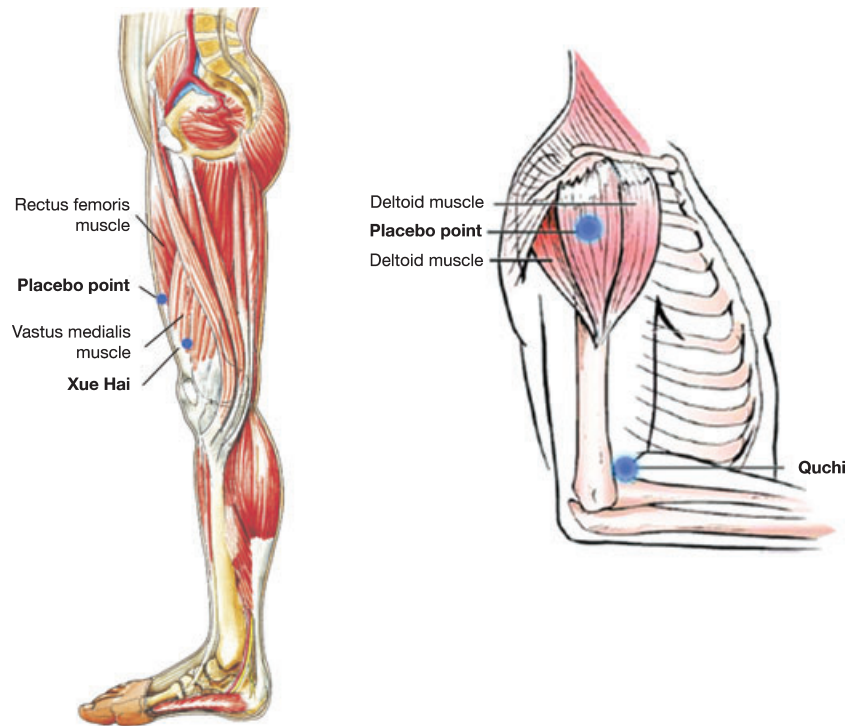


Figure 2 Localization of Quchi, Xue Hai, and placebo-points. Figure from Hecker U, Steveling A, Peuker E, et al. Lehrbuch und Repeti-

torium Akupunktur, Karl F Haug 2002, Stuttgart; modified with permission from Georg Thieme Publisher, Stuttgart, Germany.

NA and 10.9% compared to PA. PA reduced time of itch compared to NA by 15%.

Wheal and flare size, and skin temperature

Direct effect

Regarding the direct effect, mean wheal sizes were $48 \pm 9 \text{ mm}^2$ (NA), $45 \pm 7 \text{ mm}^2$ (PA), and $37 \pm 9 \text{ mm}^2$ (VA) with a significant difference ($P = 0.015$) between VA and NA. Mean flare sizes were $10.1 \pm 2.1 \text{ cm}^2$ (NA), $10.4 \pm 1.8 \text{ cm}^2$ (PA), and $7.79 \pm 1.6 \text{ cm}^2$ (VA) with a significant difference ($P = 0.002$) between VA and PA.

Mean skin temperature differences [t (10 min) – t (before skin prick)] were $0.21 \pm 0.25^\circ\text{C}$ (NA), $0.44 \pm 0.29^\circ\text{C}$ (PA), and $0.36 \pm 0.34^\circ\text{C}$ (VA) with no significant differences between groups.

Preventive effect

Regarding the preventive effect, mean wheal sizes were $73 \pm 28 \text{ mm}^2$ (NA), $54 \pm 13 \text{ mm}^2$ (PA), and $38 \pm 12 \text{ mm}^2$ (VA) with a significant difference ($P = 0.008$) between VA and NA.

Mean flare sizes were $15.1 \pm 4.1 \text{ cm}^2$ (NA), $13.5 \pm 2.8 \text{ cm}^2$ (PA), and $8.1 \pm 2.0 \text{ cm}^2$ (VA) with a significant differences between VA and NA ($P = 0.001$) and VA and PA ($P < 0.001$). Mean skin temperature differences [t (10 min) – t (before skin prick)] were $0.35 \pm 0.32^\circ\text{C}$ (NA), $0.27 \pm 0.33^\circ\text{C}$

(PA), and $0.47 \pm 0.31^\circ\text{C}$ (VA) with no significant differences between groups.

Regional blood flow (LASER-doppler)

Direct effect

Mean perfusion units were 74.8 ± 10.5 (NA), 71.9 ± 8.9 (PA), and 69.8 ± 10.9 (VA). The corresponding median values were 10.8 ± 2.6 (NA), 9.6 ± 2.0 (PA), and 9.0 ± 3.5 (VA) with a significant difference ($P = 0.016$) between VA and NA.

Preventive effect

Mean perfusion units were 84.1 ± 10.7 (NA), 83.1 ± 11.5 (PA), and 72.4 ± 10.7 (VA) with a significant difference ($P = 0.007$) between VA and NA. The corresponding median values were 18.9 ± 5.4 (NA), 18.6 ± 5.9 (PA), and 14.5 ± 4.2 (VA) with a significant difference ($P = 0.02$) between VA and NA.

Qualitative assessment of itch intensity (EIQ)

Direct effect

Mean descriptive ratings of the EIQ were significantly lower in VA (0.99 ± 0.11) compared to NA (1.15 ± 0.10 ; $P < 0.0001$) and PA (1.06 ± 0.09 ; $P = 0.02$) as well as PA compared to NA ($P = 0.01$).

On a single item level, the descriptive items 'less when warm' ($P = 0.016$) and high pitched ($P = 0.012$) were rated significantly lower in VA (0.14 ± 0.13 or 0.55 ± 0.33) compared to NA (0.38 ± 0.26 or 0.97 ± 0.43); the item 'burning' was rated significantly ($P = 0.002$) lower in PA (0.93 ± 0.40) compared to NA (1.66 ± 0.51).

Mean emotional ratings were significantly lower in VA (0.78 ± 0.11) compared to NA (1.06 ± 0.09 ; $P < 0.0001$) and PA (0.92 ± 0.10 ; $P < 0.0001$) as well as PA compared to NA ($P < 0.0001$).

On a single item level, the emotional items 'awful', 'merciless', 'restricting my life', 'no room for other feelings', 'stubborn', and 'frightful' were rated significantly ($P < 0.01$) lower in VA compared to NA with the highest significance level ($P < 0.00001$) for 'no room for other feelings' and 'stubborn'; the emotional items 'stubborn' and 'frightful' were rated significantly ($P < 0.0001$) lower in VA (0.97 ± 0.34 and 0.31 ± 0.20) compared to PA (1.59 ± 0.45 and 0.83 ± 0.32).

Preventive effect

Mean descriptive ratings of the EIQ were significantly lower in VA (1.01 ± 0.10 ; $P < 0.00001$) and PA (1.06 ± 0.10 ; $P = 0.0004$) compared to NA (1.17 ± 0.10).

On a single item level, the descriptive item 'hurting' was rated significantly ($P = 0.007$) lower in VA (0.72 ± 0.32) compared to NA (1.24 ± 0.43); the item 'goes right through me' was rated significantly ($P = 0.005$) lower in PA (0.52 ± 0.33) compared to NA (0.86 ± 0.43).

Mean emotional ratings were significantly lower in VA (0.84 ± 0.09 ; $P < 0.0001$) and PA (0.86 ± 0.09 ; $P < 0.0001$) compared to NA (1.07 ± 0.08).

On a single item level, the emotional items 'unbearable', 'tormenting', 'disturbing my sleep', 'bothering', and 'unmanageable' were rated significantly ($P < 0.01$) lower in VA compared to NA with 'tormenting' and 'bothering' reaching the highest significance levels ($P < 0.001$).

Blinding

At the end of the study, patients were asked, which acupuncture treatment had been rather a classic than a sham acupuncture treatment. Seven of 29 patients responded to have believed that VA had been the classic acupuncture compared to 5 of 29 patients in favor of PA – showing no significant differences between the two intervention groups. Seventeen of 29 patients responded to be ambiguous.

Discussion

This study showed a direct influence of 'verum-point' acupuncture on itch perception and skin reactions. It is the first study on the effect of acupuncture on type I hypersensitivity skin reactions and itch sensation in patients with atopic eczema.

The study was designed to assess the effect of a two-point acupuncture stimulation. To minimize placebo effects, the study was carried out in a crossover design with a placebo-point group, which received acupuncture at nonclassical

acupoints in the same dermatomes and with the same stimulation procedure as the 'verum-point' acupuncture group; the results indicate successful blinding.

Regarding the preventive influence, the specific effect (difference between verum and placebo-point acupuncture) diminished with regard to subjective itch sensation whereas it increased in suppressing skin-prick reactions (wheal and flare size as well as mean LASER-Doppler perfusion units). Placebo-point stimulation showed a significant preventive but no significant direct effect on itch intensity compared to no intervention.

So far three experimental randomized controlled studies have been carried out with acupuncture that investigated the direct effect of acupuncture on histamine-induced itch and skin reactions in healthy volunteers: Belgrade et al. (13) reported reduced itch and flare reduction by electroacupuncture stimulation during intradermal histamine injection. Lundeborg et al. (14) observed reduced itch intensity by intrasegmental electroacupuncture stimulation during intradermal histamine injection, however, no significant reduction in flare size.

Kesting et al. (16) investigated the effect of electrical ear acupuncture on areas of allodynia five minutes after histamine application on both volar forearms in healthy volunteers. Forearms relating to ipsilateral acupuncture showed significantly reduced allodynia areas compared to contralateral and 'nonacupuncture' assessment.

So far only one study investigated the preventive effect of acupuncture on histamine-induced itch showing reduced itch and wheal formation compared to placebo-point acupuncture or no intervention in healthy volunteers (15). It is difficult to explain the mechanisms of the observed effects as acupuncture studies in this field are still rare; further studies will have to specifically focus on the possible pathways of acupuncture action in the pathophysiology of itch or allergic skin reactions.

One could argue that in our study the reduced mean wheal and flare size in the verum-point acupuncture group compared to the control group might be because of a systemic error regarding the allergen skin prick. This, however, seems very unlikely as the study was randomized, and the allergen SPT-mediated itch intensity before intervention (at time point 4 min) was perceived highest in the verum-point acupuncture group (Fig. 3A).

Mean itch intensity was generally perceived slightly higher during the second allergen skin prick than during the first skin prick. This phenomenon has so far not been investigated. A possible explanation for the slightly higher subjective itch sensation after the repeated allergen stimulus could be a neuronal sensitization to the type I hypersensitivity itch stimulus in patients with atopic eczema, which has been shown for neuroselective transcutaneous electrical stimulation (25, 26). This is further supported by the fact that patients with atopic eczema seem to process itch differently compared to healthy volunteers (27).

In comparison with histamine-induced itch (20), allergen-induced itch exceeded the scratch threshold with a slight delay, however, resulted in a more pronounced and longer

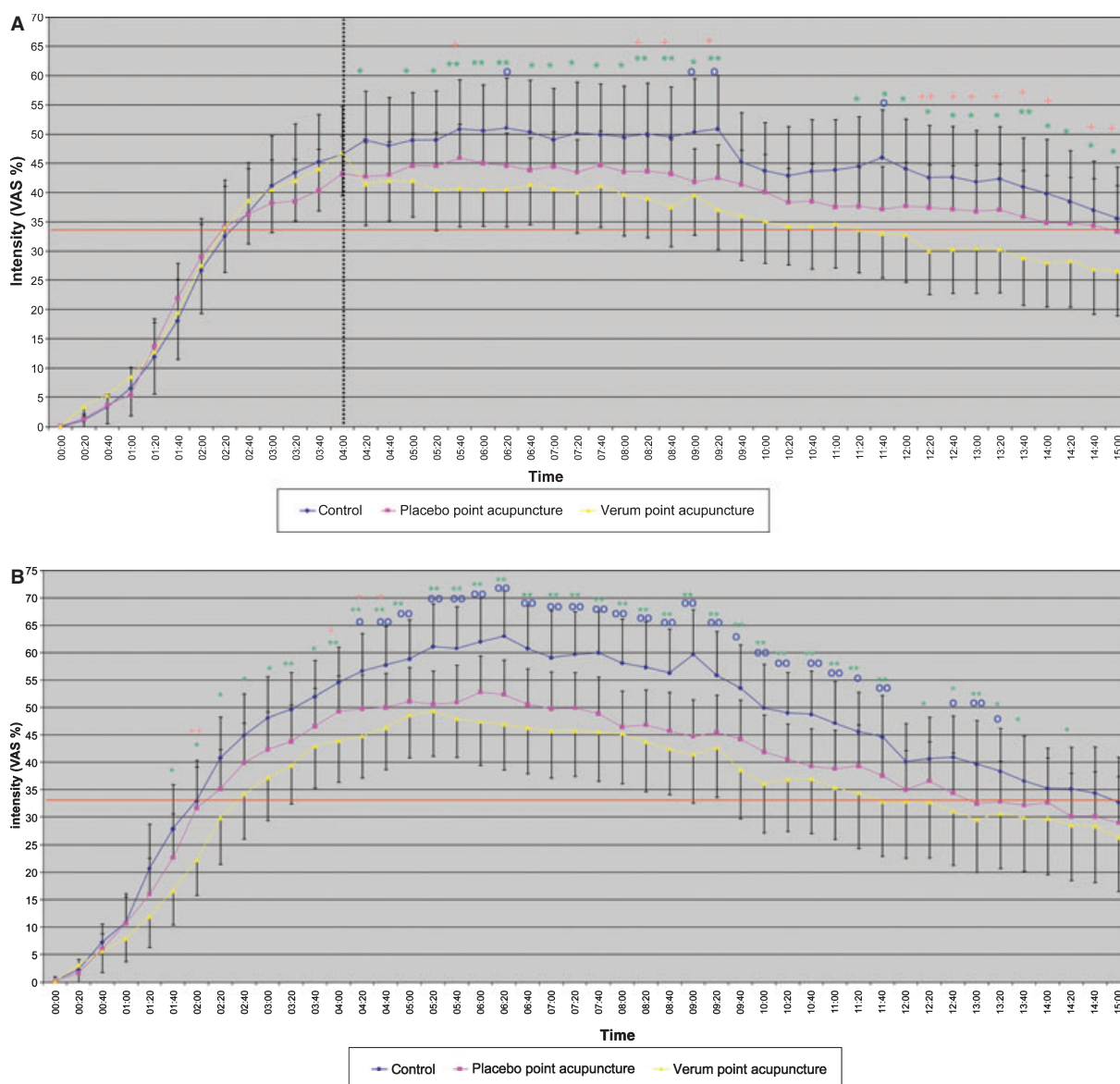


Figure 3 A (direct effect) and B (preventive effect): Mean itch intensity in verum-point acupuncture reaches a lower score and decreases faster below scratch level (represented by the red line at 33% itch intensity) than in control groups. The stars indicate time points of significant differences between verum-point acupuncture

and control, the crosses mark time points of significant differences between verum-point acupuncture and placebo-point acupuncture, the circles show time points of significant differences between placebo-point acupuncture and control (* $+/o$: $P < 0.05$; ** $+/+/oo$: $P < 0.01$).

lasting itch sensation; this can be interpreted as a secondary histamine effect. Leknes et al. (28) reported similar findings.

The fact that in the end of the study the groups could not predict whether they had received verum-point or placebo-point acupuncture can be interpreted as indirectly evaluating the clinical effect. However, the way the question – whether they had received classical acupuncture or not – was asked, the patients focused rather on the procedure of acupuncture itself than on the clinical outcome. A tool used in the study to evaluate the clinical effect is the EIQ, which showed a statisti-

cally significant difference between verum-point and placebo-point acupuncture regarding the direct effect.

The effects on itch are probably because of effects on inflammation (probably neurogenic inflammation) but are not specifically antipruritic. Some data indicate that acupuncture influences mediators that are associated with itch: Endogenous opioid peptides in the central nervous system play an essential role in mediating the analgesic effect of acupuncture (29–34). On a spinal level, acupuncture seems to have a counterirritative effect and reduce prostaglandin E2 levels in both brain and serum in LPS-injected rats (35). Further experiments have

also shown local inhibition of activation and proliferation of mucous mast cells as well as secretion of substance P and vasoactive intestinal peptide (VIP) in the colon of rats (36); and suppression of IgE production and modulation of Th1/Th2 cell response by electroacupuncture in DNP-KLH (2,4-dinitrophenylated keyhole limpet protein) immunized mice (37).

Recent studies point to a central influence of acupuncture stimulation with specific activation of brain regions (30, 38–43) that are involved in the central processing of itch such as the thalamus and the limbic system (43–47). One possible mechanism might be the influence of neuronal structures (perikarya, axons, and/or dendrites) containing enkephalin or beta-endorphin (48).

Conclusion

The study showed a significant reduction in type I hypersensitivity itch sensation after verum acupuncture treatment compared to placebo-point treatment and no treatment in patients with atopic eczema.

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Acknowledgments

The authors thank Hans Jörg Baurecht (Institut für Medizinische Statistik und Epidemiologie, Technische Universität München, Germany) for his support regarding statistical evaluation. The study was supported in part by the Deutsche Ärztesgesellschaft für Akupunktur e.V. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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