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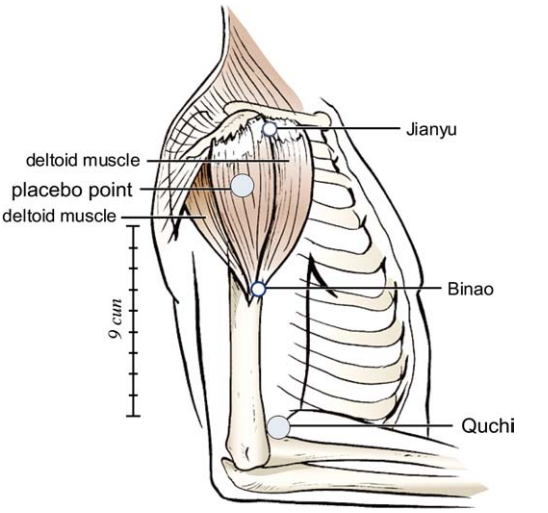

FIG 1. Localization of Quchi (located on the elbow at the midpoint of the line joining the lateral end of the transverse cubital crease and the lateral epicondyle of the humerus) and placebo point (located at the midpoint of the acromial part of the deltoid muscle and therefore being at least 2 cm apart from classical acupuncture points). Reprinted with permission from Hecker U, Steveling A, Peuker E, et al. *Lehrbuch und Repetitorium Akupunktur.* Stuttgart: Karl F. Haug; 2002. Modified with permission from Georg Thieme Verlag, Stuttgart, Germany.

Preventive effect of acupuncture on histamine-induced itch: A blinded, randomized, placebo-controlled, crossover trial

To the Editor:

The sensation of itch is the most common symptom and cause of suffering in many dermatologic and some allergic conditions.[1,2] In its subjective characteristics, it has some psychophysiologic similarity to pain, but recent neurophysiologic research has confirmed the distinctiveness of itch and pain pathways.[3] Clinically, itch can be classified by distinguishing on the basis of the peripheral and central origins: pruritoceptive, neuropathic, neurogenic, and psychogenic itch. Pruritoceptive itch plays the greatest role in skin diseases and can be triggered by various itch mediators; it can be elicited experimentally most effectively through a histamine prick test.[4] Acupuncture was shown to have antipruritic effects in early studies with healthy volunteers in the 1980s.[5,6] It is unknown, however, whether acupuncture has a preventive effect on itch. Therefore this study aimed to evaluate a possible preventive effect of acupuncture on skin prick test histamine-induced itch and flare and wheal formation in 10 healthy volunteers.

The study design was a blinded, randomized, prospective, 3-arm crossover trial. The acupuncturist and the observer were different individuals. All volunteers provided informed consent, had no acupuncture knowledge, and did not use medication with the potential to influence histamine reactions and normal itch or flare/wheal response to intraepidermal histamine injection.

After a 15-minute resting period, the volunteers were randomized into one of 3 groups: ''verum-point'' acupuncture (A1), ''placebo-point'' acupuncture (A2) or no acupuncture (NA).[7] After acupuncture procedures (lasting 15 minutes) or after a corresponding resting period, an evaluated 1% histamine dihydrochloride stimulus was applied on the dorsum of the forearm of the subject's dominant hand. The technique was performed by the same investigator using conventional blood lancets for skin prick testing as in routine allergy diagnosis. Itch intensity was rated on a computerized visual analog scale (VAS) at 20-second intervals over a period of 10 minutes. At one third of the scale, the intervention point scratch threshold was installed; above this threshold, each individual strongly felt the desire to scratch, which was not permitted.

Itch parameters were quantitatively expressed in percentages of the VAS at 30 different time points. The area under the curve was calculated as VAS (in percentages) multiplied by time (in seconds). After 10 minutes, wheal-and-flare reactions were measured at the stimulus site as averages of 4 perpendicular diameters, and the Eppendorf Itch Questionnaire (EIQ),[8] a validated instrument for qualitative and quantitative registration of pruritus, was presented to the volunteers. It contains 80 items, including questions concerning painful sensations. Each item was rated from 0 (not applicable) to 4 (very applicable).

Verum-point acupuncture was performed on the arm of the subject's dominant hand at the point Quchi (Fig 1), which is, according to a Chinese standard acupuncture textbook, most important for treating cutaneous pruritus.[9]

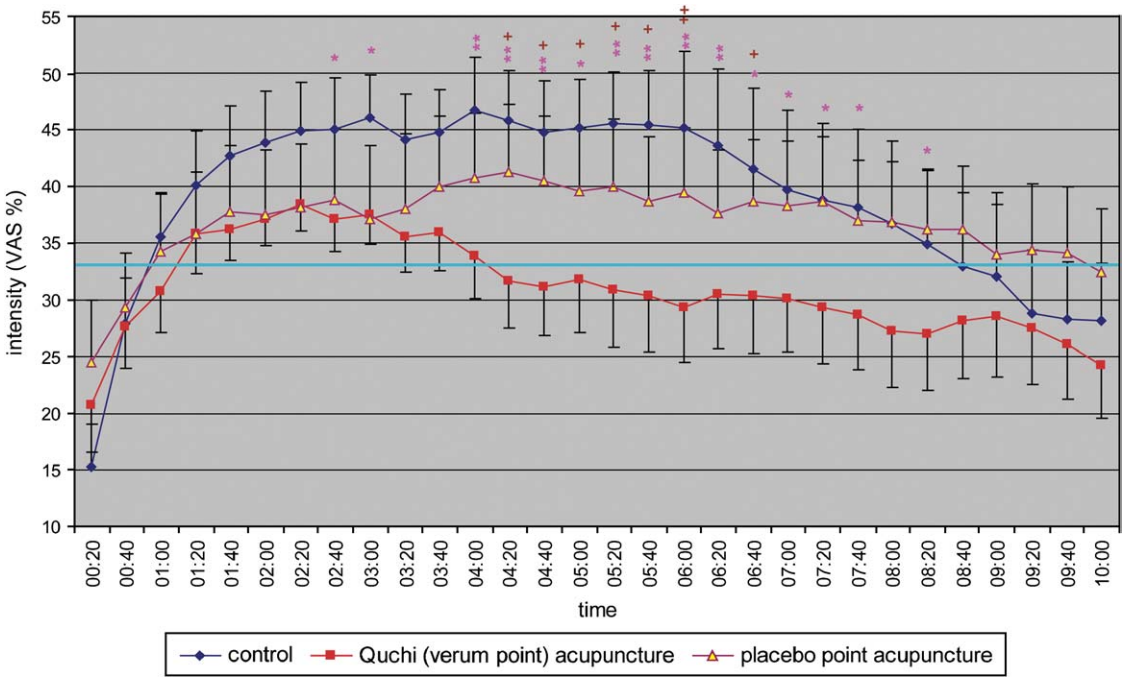

FIG 2. Mean itch intensity in verum-point acupuncture reaches a lower score and decreases faster below scratch level (represented by the turquoise line at 33% itch intensity) than in control groups. *Asterisks* indicate time points of significant differences between Quchi acupuncture and control, and *crosses* indicate time points of significant difference between Quchi acupuncture and placebo-point acupuncture. */+$P < .05$, **/++$P < .01$.

A stainless-steel needle (0.25 × 40 mm) was inserted 2 to 3 cm and manipulated for a 15-second period. After 15 minutes, the needle was taken out without manipulation. Placebo acupuncture was performed on the dominant arm at a point in the same dermatome (C6) as Quchi but not belonging to the classic meridian system and thus far not acknowledged as an acupuncture point (Fig 1). Needling procedures were carried out equally in both acupuncture groups.

All subjects reported itch without pain 40 seconds after histamine application (Fig 2). Maximum itch intensity and corresponding time were 46.7% at 4 minutes (NA group), 38.4% at 2.3 minutes (A1 group), and 41.2% at 4.3 minutes (A2 group). The mean VAS ratings for the entire 10-minute measurement period were significantly lower in the A1 group (31% ± 13%) compared with those in the A2 group (37% ± 17%, $P < .001$) and the NA group (39% ± 19%, $P < .001$). The area under the curve for itch intensity was significantly lower in the A1 group (18,600%s ± 6900%s) compared with that in the NA group (23,500%s ± 9500%s, $P = .02$) and the A2 group (22,100%s ± 9400%s, $P = .05$). At 15 of 30 time points, mean VAS ratings were significantly lower in the A1 group compared with that in the NA group; at 7 of 30 time points, mean VAS ratings were significantly lower in the A1 group compared with those in the A2 group. Measurements above the scratch threshold were significantly lower in the A1 group (9/30) compared with those in the A2 group (27/30, $P < .0001$) and the NA group (23/30, $P = .001$). The area above the scratch threshold was significantly ($P = .05$) lower in the A1 group (2600%s ± 2500%s) compared with that in the NA group (6500%s ± 6900%s). Corresponding mean flare/wheal sizes were 36.7/5.8 mm (NA group), 33.9/4.7 mm (A1 group), and 37.2/5.2 mm (A2 group), with a significant difference in mean wheal size between the A1 and NA groups ($P = .03$, see Table E1 in the Online Repository in the online version of this article at www.jacionline.org). In the EIQ (n = 9) descriptive ratings showed no significant difference between groups. The frequency of high emotional EIQ item ratings was significantly less in the A1 group compared with that in the NA group ($P = .001$) and the A2 group ($P = .018$). On a single-item level, the item ''bothering'' was rated significantly higher in the NA group compared with in the A1 group ($P = .045$).

The study showed a significant reduction of experimentally induced itch and wheal formation after acupuncture point pretreatment compared with placebo-point pretreatment and no pretreatment.

Thus far, no controlled study has investigated the preventive effect of acupuncture on histamine-induced itch. We observed an influence of verum-point acupuncture on emotional EIQ ratings without changes in descriptive ratings. A similar effect has been noted in patients with chronic pain, in whom acupuncture influences

affective rather than sensory experience. It is as yet difficult to explain the pathophysiology of the observed effects because acupuncture studies in this field are still rare. Some data indicate that acupuncture might influence itch-associated mediator effects[10]: in the central nervous system opioids and serotonin, on the spinal level prostaglandin E2, and in the periphery substance P, calcitonin gene–related peptide, vasoactive intestinal peptide, neuropeptide Y, TNF-α, IgE, IL-1, IL-6, IL-8, and IL-10.

Further studies are needed to specifically evaluate a possible role of these mediators in acupuncture prophylaxis or treatment of itch and to evaluate the clinical effect in histamine-mediated diseases. We conclude that prophylactic acupuncture at point Quchi can significantly reduce histamine-induced itch and wheal formation compared with placebo-point acupuncture and no intervention, showing the relevance of point specificity for both procedure and underlying condition.

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Conjugation of 3′ hexameric deoxyriboguanosine run to phosphodiester CpG oligodeoxynucleotides can inhibit allergen-specific IgE synthesis with less risk of splenomegaly

To the Editor:

CpG oligodeoxynucleotides (ODNs) have the CpG motif, which displays a 5′-purine-purine-unmethylated cytosine-guanine-pyrimidine-pyrimidine-3′ base sequence and enhances T_H1 response and regulatory immune response through a pattern recognition receptor, Toll-like receptor 9.[1] CpG-ODNs are expected to be a new therapeutic modality for allergic diseases, cancer, and infectious diseases.[1] CpG-ODNs have 2 different kinds of backbone structure.[2,3] One is the natural phosphodiester backbone (PE), which is very susceptible to exonuclease. PE CpG-ODNs have very low immunostimulatory effect *in vivo* because of their susceptibility to exonuclease. The other is the synthetic phosphorothioate backbone (PS) structure, which is resistant to exonuclease and has a high immunostimulatory effect *in vivo*. We reported that the conjugation of a hexameric deoxyriboguanosine run (dG_6 run) to CpG-ODNs enhanced the protective effect against allergic asthma in mice. The protective effect of 3′ dG_6 run–conjugated PE CpG-ODNs was almost equivalent to that of PS CpG-ODNs.[2]

Possible side effects of CpG-ODNs were suggested to be as follows: CpG-ODNs might cause local inflammation (eg, arthritis after intra-articular injection), can promote autoimmune disease as an adjuvant, and can trigger systemic inflammatory response syndrome on endotoxin exposure or after TNF-α exposure.[4] PS CpG-ODNs induce massive splenomegaly in mice[5] and other toxicities related to excessive immune stimulation, including the death of the immunized hosts, when used in large amounts.[2]

We evaluated the effect of 3′ dG_6 run conjugation to PS or PE CpG-ODNs on splenomegaly in mice. Ten BALB/c mice for each group were sensitized with 20 μg of ovalbumin and 2 mg of alum by means of intraperitoneal injection on days 1 and 14. The mice were challenged with 1% ovalbumin on days 21, 22, and 23. CpG-ODNs or PBS was injected at the time of sensitization with the allergen. CpG-ODNs used were as follows: PS-CpG (tccatgacgttcctgacgtt), PE-CpG (TCCATGACGTTCCTGACGTT), PS-CpG-dG_6 (tccatgacgttcctgacgttgggggg), PE-CpG-dG_6 (TCCATGACGTTCCTGACGTTGGGGGG), and PE*-CpG-dG_6 (ie, PE-CpG-dG_6 with 2 phosphorothioate backbone at the 5′ terminus [tccATGACGTTCCTGACGTTGGGGGG]). On day 25, body weight and weight of the spleen, which was cautiously separated without bleeding, were measured. Serum ovalbumin-specific antibodies and cytokine production from the spleen were evaluated as