Local Hyperthermia at 44°C for the Treatment of Plantar Warts: A Randomized, Patient-Blinded, Placebo-Controlled Trial

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There have been anecdotal reports that local hyperthermia was effective in the treatment of viral warts. We conducted a randomized, patient-blinded, placebo-controlled trial to test the effect of local hyperthermia (44°C for 30 min a day for 3 consecutive days plus 2 additional days 2 weeks later) on plantar warts. By the end of 3 months, 53.57% of patients (26/49) in the control group were cured ( ). The effect was (15/28) in the treatment group and 11.54% of patients (3/26) in the control group were cured ( ). The effect was not influenced by patient age, duration of disease, or number or size of lesions.

Plantar warts are a common skin condition caused by human papillomavirus (HPV) infection of the foot. Many treatment options, including destructive therapy, virucidal therapy, antimitototic therapy, and immunotherapy (as well as a combination of these), have been commonly used with varying efficacies [1, 2].

Exogeneous elevation of tissue temperature at 39°C–48°C (hyperthermia) has been successfully used in the treatment of some neoplasms [3]. There have been anecdotal reports that local hyperthermia was effective in the treatment of warts, with cure rates ranging from 41% to 93.5%; these studies used different hyperthermia temperatures (from 40°C to >50°C, which is destructive in nature) and different protocols (successive or intermittent hyperthermia) [4–6]. Our recent open trial of local hyperthermia at a mean temperature of 45.3°C attained a 65.3% cure rate (15/23) among patients with plantar warts [7]. A randomized controlled trial is mandatory to ascertain the effectiveness of local hyperthermia for the treatment of plantar warts, because most have a self-limiting clinical course. It has been estimated that approximately half of such warts resolve within 2 years, although in some patients the warts persist for many years [8].

The biological role hyperthermia plays in skin has not yet been fully understood. We recently noted that local hyperthermia could promote migrational maturation of Langerhans cells (LCs) in both normal and HPV-infected skin and that the effect was stronger at a local hyperthermia temperature of 44°C than at 42°C; the results suggested that hyperthermia might augment the antigen-presenting capability of LCs [9]. We have also observed that hyperthermia at 41°C reduced the numbers of mouse epidermal LCs, which minimized on day 3 and then gradually returned to the original levels on day 7 (authors’ unpublished observation). Yoshioka et al [10] observed that homeostasis of LCs in the epidermis was reached on day 14 after local hyperthermia at 43°C. The cellular immune response is responsible for the elimination of HPV-infected keratinocytes. We thus designed a protocol based on the time frame of the dynamics of epidermal LCs, as reported here.

Methods. This study was conducted at the State Key Department of Dermatology, No. 1 Hospital of China Medical University. Sixty outpatients with plantar warts were consecutively enrolled. The diagnosis of plantar warts was made on the basis of typical clinical manifestations. Inclusion criteria were the presence of plantar warts, lack of prior local or systemic treatment within the past 3 months, and provision of signed informed consent. Patients who reported an immunocompromised condition or severe physical or psychological diseases were excluded from the study. A computer-generated randomization table was used to serially allocate patients to the treatment or control group. Demographic data, such as patient age, duration of disease, previous treatments, and number and size of lesions, were collected. Patients with load-bearing pain (if any) were asked to rate it using a 0–10 ascending visual analog scale (0, no pain; 10, excruciating pain).

A patented hyperthermia device with an infrared emitting source was used in this study (patent no. ZL 2007 2 0185403.3; China Medical University) [7, 9, 11]. The heat generated by the device acted locally on lesional skin without direct contact.
Table 1. Characteristics of Patients Who Completed the Trial

<table>
<thead>
<tr>
<th>Patient cohort</th>
<th>Age, years</th>
<th>Duration of disease, months</th>
<th>Size of target lesion, mm</th>
<th>No. of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n = 28)</td>
<td>9–41 (23.85)</td>
<td>1–36 (11.81)</td>
<td>2–23 (6.42)</td>
<td>1–45 (10.20)</td>
</tr>
<tr>
<td>Control (n = 26)</td>
<td>10–43 (25.71)</td>
<td>1–38 (11.14)</td>
<td>2–25 (7.68)</td>
<td>1–46 (10.80)</td>
</tr>
</tbody>
</table>

NOTE. Data are range (mean).

The heated surface temperature (range, 37°C–48°C) was controlled and stabilized at the desired level (preset temperature, ±0.1°C) by an infrared temperature monitor and a feedback circuit. The infrared temperature monitor shed a red spot (without heat) on the targeted site simultaneously during the power output. Patients in the treatment group received a red spot from the device on the targeted lesion and experienced a heating sensation as well. Patients in the control group received a red spot on the targeted lesion without experiencing a heating sensation. To keep the patients blinded to the treatment received, they were individually informed that a warty lesion would receive a red spot with or without a heating sensation; digital indicators on the panel were concealed from the patients during the procedure.

In our previous trial, we noted that patients could endure a surface hyperthermia temperature of at least 44°C on the foot without experiencing an intolerable burning sensation (except patients with periungual lesions, who could tolerate temperatures <43.5°C) [7]. We accordingly set the surface hyperthermia at 44°C for the treatment group. Patients received hyperthermia treatment or sham treatment once a day for 3 consecutive days, with each treatment session lasting 30 min. Two weeks later, patients received similar treatments for 2 consecutive days. For patients with multiple lesions, we chose only a single target lesion, either the one biggest in size or the one with most prominent load-bearing pain. On completion of treatment, patients were followed up at 1-month intervals for a total of 3 months (the end point chosen to document the effects) through clinical examinations and photography. Evaluation of the primary outcome was dichotomous: the complete disappearance of warty lesions was regarded as cure, whereas the presence of any remaining visible primary lesions was regarded as treatment failure. Patients were further followed up via phone calls or revisitation at the end of 6 months, to document whether there were any further changes or relapse of lesions. The trial was approved by the Ethics Committee of China Medical University and was conducted in accordance with the tenets of the Declaration of Helsinki.

Analysis was conducted using the SPSS software package (version 15.0). The χ² test was used to compare rates between the groups. The effects of age, duration of disease, number of warty lesions per subject, and maximum diameter of warts on the cure rate were tested by the Student t test. Sample size for the study was determined as follows: the natural cure rate was estimated to be 15% at 3 months [8], and we posited a cure rate of 55% [7]. For α = .05 and 1 – β = .90, it was necessary to enroll at least 28 patients in each group to guarantee the above-indicated level of significance and power.

Results. The trial was conducted from September 2007 through February 2009, and 60 patients with planter warts were enrolled. Six patients dropped out of or were excluded from the study, leaving 54 patients for complete analysis. Of the 6 patients, 2 were from the treatment group: 1 received a lesional interferon injection after 3 sessions of local hyperthermia, and 1 lost contact immediately after finishing the last treatment session. Four of the 6 patients were from the control group: 2 dropped out after 1 or 2 treatment sessions, 1 received cryotherapy after 2 months of follow-up visits, and 1 received a lesional interferon injection after 2 treatment sessions. As shown in Table 1, the remaining patients from both groups were well matched for age, sex, duration of disease, size of lesions, and extent of involvement (P > .05 for all, Student t test).

By the end of 3 months, 53.57% of patients (15/28) in the treatment group and 11.54% of patients (3/26) in the control group were evaluated as cured. A statistically significant difference was reached (χ² = 10.718; P = .001). A P value of .001 was again reached by an intent-to-treat analysis (for cure rate of 50% in the treatment group vs 10% in the control group, χ² = 11.429). Figure 1 shows a representative patient with multiple plantar warts.

In the treatment group, 2 patients were cured in 2 weeks, before undergoing the second scheduled treatment session; 2 patients were cured in 1 month; 6 patients were cured in 2 months; and 5 patients were cured in 3 months. In the control group, 2 patients were cured in 1 month, and 1 patient was cured in 2 months. Most of the patients reported that their warts disappeared unnoticed, whereas some patients felt itchy or noticed their lesions “bulging up” or turning “more keratotic” before their clearance. In both the treatment and the control group, the cured patients with multiple warts generally showed concomitant disappearance of target and untreated lesions, a phenomenon suggesting the establishment of a specific immune response against HPV-infected keratinocytes. In the treatment group, those who were cured seemed to have a shorter duration of disease (mean ± standard deviation [SD], 8.0 ± 5.6 months) than did those who were not cured (mean...
Figure 1. Representative patient with multiple plantar warts (circled). Shown are the warts before treatment (A), exaggerated keratotic surface of lesions 1 month after hyperthermia (B), and complete clearance of lesions 2 months after hyperthermia (C). Arrows indicate the targeted lesion.

± SD, 14.8 ± 12.7 months), although a statistical difference was not reached (P = .095, Student t test). Age, maximum diameter of the target lesion, and number of lesions per subject had no statistically significant influence on the cure rate (P > .05 for all, Student t test).

By the end of 3 months, 80% of patients (12/15) in the treatment group who had initial complaints of load-bearing pain reported a decreased sensation of pain; 1 experienced an increased sensation of pain, and 2 remained stable. In the control group, 14.3% of patients (2/14) reported a decreased sensation of pain, 5 experienced an increased sensation of pain, and 3 remained stable. The scoring of load-bearing pain was reduced from a mean ± SD of 6.07 ± 1.49 (range, 4–9) to 1.53 ± 2.45 (range, 0–7) in the treatment group, whereas it was reduced from 5.33 ± 1.72 (range, 3–8) to 5.08 ± 2.64 (range, 0–8) in the control group; there was a statistically significant difference in the improvement of load-bearing pain between the 2 groups (χ² = 9.83; P < .01). With the exception of heating or burning sensation in the treated patients, no adverse events were observed.

By the end of 6 months, 1 more patient was cured in each group. No relapse was observed in the treatment group, whereas a relapsing case occurred in the control group.

Discussion. To date, most reports of the use of local hyperthermia in the treatment of warts have been empirical [4–6]. The present study strongly suggests that local hyperthermia is effective in the treatment of plantar warts, compared with placebo treatment. There was a trend that patients with shorter durations of disease were more responsive to local hyperthermia, although no statistical difference was reached. The cure rate was not affected by patient age, sex, or number or size of plantar warts. Absorption of heat energy by tissue is dependent on temperature and length of time applied (D = tR⁻⁴) [12]. Hyperthermia at 43°C is regarded as the breakpoint above which there are more cells undergoing apoptosis [11, 12], a condition that would facilitate the establishment of a specific immune response [13]. Our previous experience has shown that most patients with plantar warts could endure surface temperatures of at least 44°C without experiencing an intolerable burning sensation. Selection of 44°C would ensure high compliance, especially in young children.

Recent studies have shown that loss of LCs in skin enhances contact dermatitis and prevents chemical-mediated skin cancer [14, 15]. Thus, hyperthermia-mediated LC “loss” may increase the immune response necessary to kill virus-infected keratinocytes. The homeostasis of LCs in the epidermis would be reached in ~1–2 weeks ([10] and authors’ unpublished observation). A 2-week interval in a treatment session would ensure that the second episode of treatment had a sufficient number of epidermal LCs being targeted. Epidermal turnover time in normal skin is 52–75 days; we thus used a 3-month period as the end point, which was long enough for normal epidermal repair provided the patient was cured.

Clearance of warts is dependent on the establishment of a specific immune response against HPV-infected keratinocytes. We noted that patients with multiple warts experienced almost simultaneous clearance of targeted warts as well as the remaining untargeted warts, suggesting that hyperthermia plays an indirect yet facilitating role in the specific immune response against HPV infection. It was interesting to note that local hyperthermia could ameliorate the load-bearing pain in a high proportion of treated patients. Although the reason for this is unknown, the effect was much appreciated by the patients who could not avoid the load-bearing position.
In summary, local hyperthermia was a safe and effective single modality in the treatment of plantar warts. Our findings warrant trials of local hyperthermia for the treatment of other forms of cutaneous warts, such as verrucae plana and genital warts, although conditions might vary.

References