Brief report

Non-ablative controlled local hyperthermia for common warts

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Cutaneous warts are common skin diseases caused by human papillomavirus (HPV) infection. The prevalence of cutaneous warts varied from 2.4%–12.9%, with common warts, planta warts and genital warts being the most common ones.[1-4] About 67% of patients with warts might resolve spontaneously within 2 years,[4] while in some patients warts persist for years.[5] A cellular immune response is essential for the clearance of HPV.[6,7] Treatment modalities are usually ablative.

Local hyperthermia had been successfully tried in the treatment of a variety of neoplasms.[8,9] There have been anecdotal reports that local hyperthermia was effective in the treatment of warts with cure rates from 41.0%–93.5%. These studies used different devices such as microwave, radiofrequency or thermal patch as the source of hyperthermia, different hyperthermia temperatures (from 40°C to more than 50°C) and different protocols (successive or intermittent hyperthermia lasting from seconds to 50 minutes).[10-13] To further define the effect of local hyperthermia in the treatment of viral warts, we set up an open trial in which the local hyperthermia temperatures were controlled with the ranges in which a patient could well tolerate (in a fixed time) without anesthesia. We also analyzed the factors that might influence the effect of hyperthermia in the treatment of warts.

METHODS

Hyperthermia device

We designed and produced a patented hyperthermia device for the study (patent No.: ZL 2007 2 0185403.3, Patent holder: The First Hospital of China Medical University, China). This device has an infrared emitting source. The heat generated by the device acted locally on skin surface without direct contact. The heated surface temperature was controlled and stabilized at the desired level (pre-setup temperature±0.1°C) by an infrared temperature monitor and a feedback circuit.

Patients

The diagnosis of warts was made by typical clinical manifestations. Inclusion criteria were the presence of warts on hands or/and feet, no prior local or systemic treatments within the last 3 months. Exclusion criteria were patients who were in an immune-compromised condition; patients with severe psychological or physical diseases.

Forty-four patients were enrolled into the study, while five patients (two with warts on hands and three on feet) dropped during the follow-up. Thirty-nine patients (19 male and 20 female, 6–59 years of age) with common warts on hands (16 cases) or feet (23 cases) completed the trial. Duration of the disease ranged from 1–90 months, average 16.3 months (warts on hands were 23.7 months; warts on feet were 11.1 months). There were 8 patients with a single lesion and 8 patients with multiple lesions on hands; 9 patients with a single lesion and 14 cases with multiple lesions on feet, 3 patients with multiple lesions afflicting both hands and feet, respectively.

Treatment protocol

This open trial was designed to be non-ablative and well tolerated, as the temperatures of local hyperthermia were adjusted at ranges within which a subject had tolerable sensation of burning or pain without anesthesia. Patients were asked to receive local hyperthermia once a day for 5 consecutive days. Each treatment lasted 30 minutes. For patients with multiple lesions, only one target lesion was chosen to receive local hyperthermia.

Upon completion of the treatment, patients were followed up at intervals of a month for 3 months (endpoint to document the effects) through clinical examinations and photography. Patients were further interviewed by phone calls or revisiting 6 months after treatment, to document if there were any further changes or relapse of their lesions.

The evaluation of effects was simply put into two categories. Complete disappearance of warty lesions was

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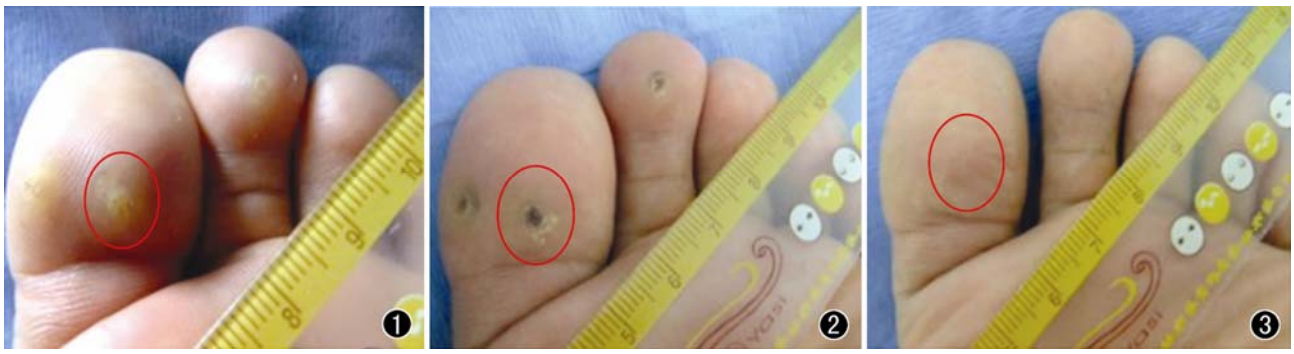

Figure 1. A patient with mutiple warts on his feet before treatment. The circled lesion served as the target lesion that received local hyperthermia.
Figure 2. One month after local hyperthermia, the targeted as well as the remaining lesions showed remarkable shrinkage and desquamation.
Figure 3. Complete resolusion of all the warty lesions two months after local hyperthermia.

regarded as cured, while those with any lesions left were regarded as treatment failure. This clinical trial was approved by the Ethnics Committee of The First Hospital of China Medical University. Informed consent was obtained from each patient.

Statistical analysis

Data were analyzed with SPSS 13.0 software (SPSS Inc., USA). A Fisher′s Exact test was used to compare the cure rates in regard to sex, age, site of lesions, duration of the disease, local hyperthermia temperatures applied. A two-tailed *P* value of less than 0.05 was regarded as statistically significant.

RESULTS

Lesions on hand and foot had different ranges of tolerability to local hyperthermia

Local hyperthermia temperature was careful adjusted for each subject. Patients with targeted lesions on hands could tolerate local hyperthermia temperature between 40.6°C–46.0°C (average 43.5°C), that on feet 43.5°C–47.5°C (average 45.3°C). Patients with warts on feet could tolerate higher local hyperthermia temperature that those warts on hands (P <0.01).

Clinical response of warts to local hyperthermia

By the end of three months after local hyperthermia, 21 out of 39 (53.8%) cases were cured. Among them, 6 out of 16 (37.5%) cases of warts were on hands and, 15 out of 23 (65.2%) cases of warts on feet. Although there was a higher cure rate for warts on feet than those on hands, the difference did not reach statistical significance (P >0.05). Of the six cases of hand warts that were cured, two cases healed within a month, one case within two months and three cases within three months, respectively. Of the fifteen cases of warts on feet that were cured, two cases healed within a month, four cases within two months and nine cases within three months, respectively.

Treatment response was not affected by number of warts, sex, age and temperatures applied

Among the patients who were cured, there were 12 cases (12/17) with single lesion and 9 (9/22) cases with multiple lesions, while there was no statistical difference of cure rates between them (P >0.05). Of patients with multiple warts who were cured, they generally showed simultaneous clearance of targeted lesion and the remaining lesions. A typical response case with multiple planta warts in a time series was shown in Figures 1–3. Of the three cases that had warts on both hands and feet, only one case healed within three month. Interestingly, it was the warts on hands that first disappeared (within two months), though the targeted lesion was on her foot.

The cure rate was not affected by sex, age (childhood vs adulthood) and duration of the disease (shorter vs longer than 2 years) (all P >0.05). Hyperthermia temperature at 43°C is regarded as the breakpoint above which there are more cells undergoing apoptosis,[8] however, there was no statistical difference of cure rates between patients who received local hyperthermia treatment below and equal/above 43°C (P >0.05).

By the end of six months after hyperthermia treatment, one additional case of wart on hand and two cases of warts on feet disappeared. There was no report or sign of recurrence. All the patients felt slight burning sensation during hyperthermia treatment. One patient had a heat induced painful bullae soon after hyperthermia.

DISCUSSION

There have been anecdotal reports that local hyperthermia was effective in treating the recalcitrant warts.[10-13] Local heating with a bundle of smoldering dried moxa leaf has been practiced ages in the treatment of warts in traditional Chinese medicine. There has been no consensus reached as what might be the best protocol in carrying out a hyperthermia treatment. The hyperthermia device we produced was able to stabilize, monitor and record the surface temperature of the heated skin during the trial. Patients could tolerate, depending on individual′s sensitivity, local hyperthermia at ranges of 40.7°C–47.5°C without obvious side effects. In general, warts on feet are more tolerable to higher local heating.

Though there were more cured patients with warts on feet than on hands, a statistical difference was not reached in this small scale trial. A larger cohort study is necessary to further prove this point. Though there was a tendency of self-healing of warts, in this study, the cure rates by local hyperthermia were not affected by the duration of the disease, suggesting local hyperthermia could promote the clearance of warts.

Tissue temperature of deep skin could be higher than the surface temperature, due to transmission and accumulation of heat energy.[10] Precautions should be taken to avoid deep skin damage when choosing a local hyperthermia condition. Except the tolerable burning sensation felt by all the patients and a heat induced bullae in a patient, there was no other adverse effect observed in this study. Weather hyperthermia could promote the integration of HPV DNA into genome is not known. We had detected HPV specific DNA from scrapes of warty lesions in 26 (out of 27) volunteers by PCR (data not shown). These types of HPV have low risk of oncogenicity when integrated into the genome. Thus a long-term safety of local hyperthermia in these patients is expected.

Local hyperthermia above certain thresholds could induce cell death.[8] Direct heat induced death of HPV infected keratinocytes might be one of the reasons for the effect of local hyperthermia.[14] In this trial, we noted that the resolving target lesions were often accompanied by clearance of the remaining lesions, in the case of multiple warts. Some of the patients experienced an episode of "bulging up" of the warts before their clearance, a phenomenon most probably caused by infiltrating inflammatory cells. We recently observed that local hyperthermia could promote migratory maturation of Langerhans cells in both normal and HPV infected skin.[15] This scenario suggested that local hyperthermia might function by an array of mechanisms, such as local destruction of infected tissue, promotion of specific immune response against HPV infected keratinocytes. In addition, the direct effect of local hyperthermia on HPV replication is an interesting field of study.

In summary, this open trial suggested that local hyperthermia might be an effective and safe alternate for the treatment of warts. A randomized controlled trial is required to prove its efficacy and an optimized protocol of treatment is needed based upon its mechanism of actions.

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