Topical Calcipotriol for the Treatment of Cutaneous Warts: An Assessor-Blind Randomized Placebo-Controlled Trial

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Received 11 November 2022; Revised 15 January 2023; Accepted 7 February 2023; Published 16 February 2023

1. Introduction

Cutaneous warts are benign epidermal proliferations caused by human papillomavirus (HPV) and can be categorized into different types, including common (verruca vulgaris), plantar (verruca plantaris), and flat (verruca plana) warts [1]. Although approximately 75% of warts can resolve spontaneously within 2 years, patients often seek treatment for cosmetic reasons and pain [2]. The common treatment methods include electrocoagulation, laser, and cryotherapy; however, they are expensive and require a long treatment period with multiple sessions, and lesions can recur [3]. Therefore, intralesional immunotherapy has been introduced over the last few years, which is believed to enhance cell-mediated immunity [4, 5].

It has been suggested that vitamin D can modulate the immune system by inhibiting the expression of cytokines [6]. The expression of vitamin D receptors and vitamin D
1-hydroxylase genes is upregulated when human macrophages are activated by toll-like receptors. This leads to the modulation of innate immunity [7]. Intrallesional vitamin D has been shown to be safe and effective for the treatment of warts [8–11]. Very few studies have also demonstrated the efficacy of topical vitamin D derivatives in this regard, including a case report and a study on 17 patients [12, 13]. We aimed to evaluate the safety and efficacy of topical calcipotriol for the treatment of cutaneous warts.

2. Methods

2.1. Participants and Study Design. This assessor-blind randomized placebo-controlled trial included patients with cutaneous warts referred to the dermatology clinic of BouAli Hospital, Sari, Iran, from January 21 to March 20, 2020. The inclusion criteria were the clinical or pathological diagnosis (only for suspicious lesions to confirm diagnosis) of cutaneous warts by an expert dermatologist, age >2 years, and a maximum of 20 warts. The exclusion criteria were pregnancy and lactation, facial, inguinal, and genital warts, hypersensitivity to topical vitamin D derivatives, extensive warts requiring other treatments, and receiving any treatments in the past two months. Based on the study by Kareem et al. [14], in which complete improvement occurred in 40% of the intervention and 5% of the control groups, as well as α = 0.05 and β = 0.1, the sample size was calculated as at least 28 in each group.

The study received ethical approval and complies with the statements of the Declaration of Helsinki. Written informed consent was obtained from the patients or their parents/guardians. The trial has also been registered at the Iranian Registry of Clinical Trials (IRCT).

First, the general characteristics including age, sex, underlying disease, previous treatments (i.e. cryotherapy, topical salicylic acid preparations, and laser), sites of lesions, disease duration, and severity (based on the number of lesions (<5 mild, 5–10 moderate, and >10 severe) were recorded. Then, patients were randomized into two groups using block randomization by using the Random Allocation software, with a block size of four. Patients in the calcipotriol group received calcipotriol 0.05% ointment (Caspian Tamin Pharmaceutical Co., Iran) twice a day on the lesions with cutaneous warts referred to the dermatology clinic of BouAli Hospital, Sari, Iran, from January 21 to March 20, 2020. The inclusion criteria were the clinical or pathological diagnosis (only for suspicious lesions to confirm diagnosis) of cutaneous warts by an expert dermatologist, age >2 years, and a maximum of 20 warts. The exclusion criteria were pregnancy and lactation, facial, inguinal, and genital warts, hypersensitivity to topical vitamin D derivatives, extensive warts requiring other treatments, and receiving any treatments in the past two months. Based on the study by Kareem et al. [14], in which complete improvement occurred in 40% of the intervention and 5% of the control groups, as well as α = 0.05 and β = 0.1, the sample size was calculated as at least 28 in each group.

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The primary outcome was complete response to treatment evaluated four months after the initiation of therapy. Secondary outcomes were the number and size of the warts assessed at 1, 2, and 4 months and adverse events, including erythema, pruritus, burning sensation, and scaling. The outcomes were evaluated by the same physician blinded to the patient groupings at each visit.

2.2. Data Analysis. We used the Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp., USA) for data analysis. Continuous variables were described using means and standard deviations. Categorical variables were described using frequencies and percentages. Fisher’s exact test was used to compare categorical variables, and the independent t-test was used to compare continuous variables between groups. P values <0.05 were regarded as statistically significant.

3. Results

Initially, 65 patients were assessed for eligibility, of whom three did not meet the inclusion criteria and two declined to participate. The remaining patients were randomized into two equal groups (n = 30). Thereafter, two patients from the calcipotriol group and one from the control group were lost to follow-up. In addition, one patient in the control group discontinued intervention (Figure 1), leaving 28 patients in each group for the final analysis.

Patients in both groups were comparable regarding previous treatment, underlying disease, and disease duration (Table 1). However, patients in the control group were older. Also, a higher proportion of patients in the calcipotriol group were male and had warts on their palms and toes. Moreover, a higher percentage of controls had moderate disease.

The mean number and the size of lesions did not differ between groups before intervention; however, both were significantly lower in the calcipotriol group than in controls at 1st, 2nd, and 4th months (Table 2). In addition, complete response to treatment was significantly higher in the calcipotriol group (85.7% vs. 16%; P < 0.001). On the other hand, the frequency of adverse events was not different between groups (P = 0.352) (Table 3). Figure 2 shows images of patients before and after treatment.

4. Discussion

In the current study, we found that calcipotriol was effective for the treatment of cutaneous warts in terms of the number and size of lesions as well as the overall response to treatment. Moreover, the frequency of adverse events was comparable between the calcipotriol and control groups. Calcipotriol is a vitamin D3 analogue, assumed to have immunomodulatory effects [6]. On the other hand, lower serum vitamin D levels have been reported in patients with viral warts [15, 16].

Intrallesional vitamin D derivatives have been evaluated for the treatment of warts. Amin et al. compared cryotherapy with intrallesional vitamin D3 (5 mg/ml) for warts on the hands and feet and showed similar efficacy for both modalities [10]. In another study, Ihsan Mahmoud and Ayyash used 60,000 and 120,000 IU of intrallesional vitamin D3 for common warts and found both effective without any significant difference [11]. Additionally, Kumar and Brar demonstrated that 600,000 IU intrallesional vitamin D3 was safe and effective for the treatment of palmoplantar warts [17]. Similarly, Kavya et al. showed the safety and efficacy of intrallesional vitamin D for multiple cutaneous warts [8]. Consistently, Aktas et al. treated single or multiple plantar warts with intrallesional vitamin D3 in 20 patients, of whom...
80% showed complete resolution [9]. Nevertheless, intralesional vitamin D appears not to be as effective for anogenital warts [18].

Topical vitamin D3 (maxacalcitol) was first successfully used by Imagawa and Suzuki for the treatment of refractory warts in 17 patients, including four adults and 13 pediatric patients. Warts disappeared in all of the patients [13]. This is in agreement with our results; nonetheless, the resolution of warts in their study occurred after 6 months of treatment, while the maximum treatment duration in our study was four months. Moreover, Rind et al. reported the successful treatment of anogenital warts in an infant [12].
Table 2: Comparison of the number and size of lesions between groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Calcipotriol (n = 28)</th>
<th>Control (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lesions, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before intervention</td>
<td>5.54 (5.09)</td>
<td>5.11 (3.75)</td>
<td>0.927</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; month</td>
<td>2.89 (5.09)</td>
<td>4.50 (3.92)</td>
<td>0.009</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; month</td>
<td>1.61 (3.79)</td>
<td>3.96 (3.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; month</td>
<td>0.68 (3.02)</td>
<td>3.72 (3.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Size of lesions (cm&lt;sup&gt;2&lt;/sup&gt;), mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before intervention</td>
<td>0.44 (0.19)</td>
<td>0.45 (0.15)</td>
<td>0.699</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; month</td>
<td>0.22 (0.21)</td>
<td>0.41 (0.19)</td>
<td>0.001</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; month</td>
<td>0.13 (0.19)</td>
<td>0.37 (0.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; month</td>
<td>0.06 (0.18)</td>
<td>0.37 (0.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: N, number; SD, standard deviation. *Analyzed by the independent t-test.

Table 3: Comparison of adverse events and response to treatment after 4 months between groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Calcipotriol (n = 28)</th>
<th>Control (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to treatment, N (%)</td>
<td>24 (85.7)</td>
<td>4 (16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adverse events, N (%)</td>
<td>4 (14.3)</td>
<td>1 (3.6)</td>
<td>0.352</td>
</tr>
</tbody>
</table>

Abbreviations: N, number. *Analyzed by Fisher’s exact test.

Figure 2: Two warts on the palm of a patient (a) before and (b) after treatment with calcipotriol and a wart on the sole of a patient in the placebo group (c) before and (d) after receiving a placebo.
The major strength of the current study was its superiority to previous studies regarding the sample size. Nevertheless, this study was not without limitations. First, the effects of interventions on the number and size of lesions should have been adjusted for age, sex, site, and severity of lesions as well as preintervention values. Second, although our sample size was higher than that of previous studies, it was still relatively small, which limits the generalizability of our findings. Finally, the patients were not evaluated after four months; therefore, the long-term effects and the relapse rate could not be assessed.

5. Conclusions
Response to treatment was significantly better with calcipotriol in this study, with comparable adverse events compared to the control group. Therefore, calcipotriol can be considered a safe and effective treatment option for cutaneous warts. However, larger double-blind randomized placebo-controlled trials, potentially including another arm for intralesional vitamin D, are required to confirm these findings.

Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval
The study received ethical approval from the Ethics Committee of the Mazandaran University of Medical Sciences under the ethics code: IR.MAZUMS.REC.1398.1259 and complied with the statements of the Declaration of Helsinki. The trial has also been registered while recruiting at the Iranian Registry of Clinical Trials (IRCT), IRCT20170818035762N2, available at https://www.irct.ir/trial/45716.

Consent
Written informed consent was obtained from the patients or their parents/guardians.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
AK was responsible for conceptualization and study validation. AB and MM were responsible for implementation and supervision. ZH and MR were responsible for data analysis and interpretation. NG was responsible for writing and reviewing the manuscript. All the authors have read and approved the final version of the manuscript.

Acknowledgments
The authors sincerely appreciate the dedicated efforts of the investigators, the coordinators, the volunteer patients and their parents, and the laboratory personnel of BouAli Hospital, Mazandaran, Iran. This study was funded by the Mazandaran University of Medical Sciences.

References


