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ORIGINAL ARTICLE

Topical Immunotherapy with Diphenylcyclopropenone Is Effective and Preferred in the Treatment of Periungual Warts

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Background: There exists a treatment challenge with periungual warts. Topical immunotherapy with diphenylcyclopropenone (DPCP) has recently been reported to be an effective treatment for recalcitrant warts, including periungual types. **Objective:** We aimed to evaluate the effectiveness and preference of topical immunotherapy with DPCP in treating periungual warts. **Methods:** Twenty-seven patients with periungual warts who were treated with DPCP immunotherapy (2007 through 2010; Dongguk University Ilsan Hospital, Goyang, Korea) were retrospectively recruited. Other treatment modalities were also used in some patients. Lesions were grouped into the types according to the following locations: proximal nail fold, lateral nail fold and hyponychium. Total and group clearance rates as well as treatment periods according to location and disease duration were evaluated. A patient questionnaire was performed to assess the satisfaction for the treatments in those who received multiple therapies. **Results:** Total success rates were 85% (by subjects) and 91% (by individual lesions). Success rate and treatment period for proximal nail fold type seemed more desirable than other locations. Success rate decreased and treatment period increased as disease duration increased. The questionnaire revealed a significantly higher satisfaction rate for DPCP immunotherapy than for cryotherapy and pulsed-dye laser. **Conclusion:** Topical immunotherapy with DPCP is an effective and preferred method in the treatment of periungual warts. **(Ann Dermatol 25(4) 434~439, 2013)**

-Keywords-
Diphenylcyclopropenone, Immunotherapy, Periungual wart, Therapy

INTRODUCTION

Warts are common benign tumors of the skin caused by the infection of human papillomavirus. Most of the lesions show spontaneous regression, but some may increase in number and size, which may interfere with daily activities of the infected individuals. Periungual warts, in particular, are known for the high recurrence rate and recalcitrance and thus present a treatment challenge. A wide range of treatment modalities have been used for warts including cryotherapy[1], laser therapy[2-4], immunotherapy[5,6] and intralesional bleomycin[7], among many others. While many of the treatments have limitations in practice due to pain and scarring, especially for those of periungual locations, recent reports have demonstrated that topical immunotherapy with diphenylcyclopropenone (DPCP) is a safe and effective treatment modality of recalcitrant warts, which includes the periungual types for its painless application and absence of scarring[8-10]. We evaluated the clearance rate of DPCP immunotherapy (DPCPi) and performed a patient questionnaire to assess the preference level of DPCPi in those who received multiple therapies.

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MATERIALS AND METHODS

Subjects

Twenty-seven patients with periungual warts, who were treated from 2007 through 2010 in Dongguk University Ilsan Hospital, were included in this study. Some lesions were treated with DPCPi alone, while others employed multiple therapies with DPCPi after cryotherapy and/or pulsed-dye laser were initially performed.

Diphenylcyclopropenone immunotherapy

All recruited subjects were treated with DPCPi. While other treatment modalities including cryotherapy and/or pulsed-dye laser were employed initially in some cases, DPCPi was the last method used to complete the treatment. The DPCP solution of concentration 0.1% (for adults) and 0.05% (for pediatric patients) were applied on the upper inner arm to induce sensitization. It was confirmed to have occurred on the week following when the application site showed eczematous conditions, which were represented by an itch, erythema and/or mild oozing. Once a patient was sensitized, DPCP of an appropriate concentration starting from 0.1%, which was gradually increased up to 2% until a mild eczematous reaction was noticed, was applied onto the lesions weekly until all lesions cleared. The concentration of DPCP was adjusted depending on the severity of the inflammatory reaction from the previous application. If the reactions were severe enough to have bullae or severe oozing, the concentration was lowered. The concentration was elevated when the reaction from the previous application was too weak to produce desired results. The desired target concentration was the initial point when erythema, mild itch and/or mild oozing was observed.

Assessment of clinical outcome

We assessed the results of the treatment as 'success' or 'failure.' A 'success' was clinically defined as when all lesions were completely cleared, and 'failure' was considered in one of the following four conditions: (i) if a patient had not been sensitized; (ii) if a proper reaction had not occurred on the wart lesions that were treated with DPCPi for 3 consecutive weeks in a sensitized patient; (iii) if clinical improvement had not been observed for 3 consecutive weeks, although a proper reaction of DPCP application had occurred; and (iv) if there were severe adverse reactions, including generalized eruptions and intolerable itch.

We grouped the lesions into three different types, according to the location: proximal nail fold, lateral nail fold and hyponychium types (Fig. 1A, C, E). Total success rate was assessed, both by the subject and individual wart lesion. In addition, group success rate and treatment period were investigated to compare inter-group differences. Success rate and treatment period according to disease duration were also investigated. Adverse side-effects including generalized itch and/or eczematous eruptions during the treatment period and the recurrence rate after six months of successful treatment were monitored.

Questionnaire

We conducted a telephone questionnaire for those who received multiple therapies. Pain and satisfaction of each treatment were evaluated in the questionnaire, which used the visual analogue scale (VAS) score. We also investigated the preferred treatment with the question, 'What would be your choice of treatment be if you had a newly occurred wart lesion and why?'

Statistical analysis

Statistical analysis was performed to compare success rates between locations and disease duration, utilizing Fisher's exact test. Mann-Whitney U test was utilized to analyze the questionnaire results and to compare treatment periods between the location and disease duration. $p < 0.05$ was considered to be significant.

RESULTS

Demographic data

Of the 27 patients, 14 were male and 13 were female. The mean age was 10.9 years (ranging from 1 to 38). The total number of individual lesions was 66, with 37 proximal-nail-fold lesions, 15 lateral-nail-fold lesions and 14 hyponychium lesions. Mean number of lesions per subject was 2.44 (varying from 1 to 6).

Clinical outcome

Total success rate, assessed by each subject, was 85% (23/27 subjects), and it was 91% (60/66 lesions) when evaluated by individual lesions (Fig. 1). Among the 23 patients who were treated successfully, 11 were treated with DPCPi only and the others with multiple therapies (Fig. 2). The success rate for proximal nail fold type (95%) was higher than those of other locations: 87% for lateral nail fold and 86% for hyponychium (Fig. 3A). Success rates decreased as the disease duration increased: 100% (5/5, less than 6 months), 89.5% (17/19, 6 to 12 months) and 33.3% (1/3, older than 12 months) (Fig. 3B). Statistical significance was not noted when comparing the success rates of different locations and disease durations. Treatment periods, according to the location, were 12.8, 21.7

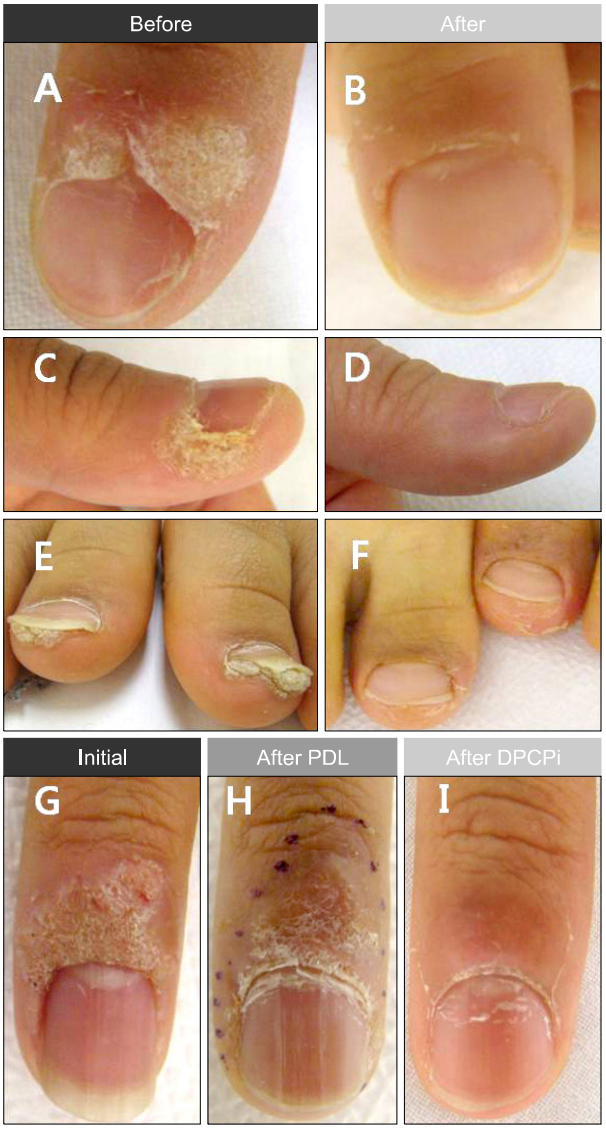

Fig. 1. Periungual warts completely cleared with DPCPi. (A, B) Proximal nail fold type treated with DPCPi alone. (C, D) Lateral nail fold type treated with DPCPi following pulsed-dye laser. (E, F) Hyponychium type treated with DPCPi following cryotherapy. (G) Initial untreated periungual wart. (H) 'After PDL' in the middle, showing the remaining lesion with an ill-defined margin. (I) Lesion was completely cleared after DPCPi. PDL: pulsed-dye laser, DPCPi: diphenylcyclopropenone immunotherapy.

and 23.7 weeks for proximal nail fold, lateral nail fold and hyponychium lesions, respectively (Fig. 3C). There were no statistically significant differences in the treatment periods for the different locations. Treatment periods according to disease duration were 7.8, 17.7 and 54 weeks for less than 6 months, 6 to 12 months and over 12 months, respectively. The treatment period increased as the disease duration increased with statistical significance (Fig. 3D). There were 4 treatment failures for the following reasons: two were not sensitized and the other two did not show proper reactions on the wart lesions that were treated with DPCPi, although sensitization was achieved (Fig. 2). We had an aggravated itch that was relieved by systemic antihistamine in 17% (4/23 patients). Significant adverse reactions such as severe widespread eczematous eruption or intolerable urticaria were not observed. Recurrence was observed in one of the 23 patients, with a successful treatment 6 months after the clearance.

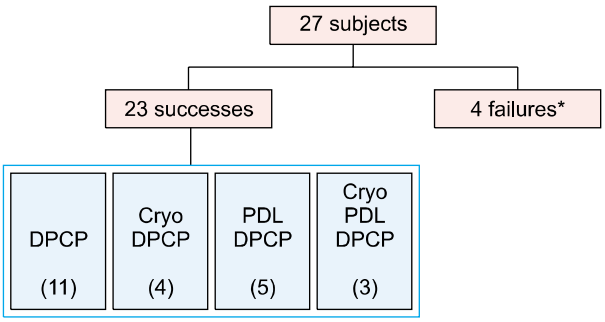

Fig. 2. Flow diagram of the study. Within parenthesis is the number of subjects. DPCP: diphenylcyclopropenone, Cryo: cryotherapy, PDL: pulsed-dye laser. *Two patients were not sensitized and the other two did not show proper reactions on wart lesions treated with DPCP immunotherapy.

Questionnaire

Among the 27 patients, a questionnaire was performed for 12 subjects who received multiple therapies. Number of patients treated with other therapies, in addition to DPCPi, was 4 for cryotherapy, 5 for pulsed-dye laser and 3 for both cryotherapy and pulsed-dye laser (Fig. 2). Mean VAS of pain for DPCPi was 0, whereas cryotherapy and pulsed-dye laser showed 8.57 and 8.87, respectively (Fig. 4A). Mean VAS score of satisfaction for DPCPi (8.3) was significantly higher than that for cryotherapy (5.6) and pulsed-dye laser (4.3) (Fig. 4A). There were 11 of 12 patients who chose DPCPi as the treatment of choice if a newly occurred wart lesion (Fig. 4B). Of these 11, 10 patients preferred DPCPi for the painless application and 1 for the satisfactory improvement.

DISCUSSION

Viral warts are benign tumors caused by human papillomavirus infection, and its prevalence among general population is reported to be 7% to 10%[11,12]. Although spontaneous resolution is observed in most cases, treatments are required in some cases with increasing size and number. Periungual warts, particularly, behave recalcitrant to treatments and become cosmetic problems and distress to daily life in many cases.

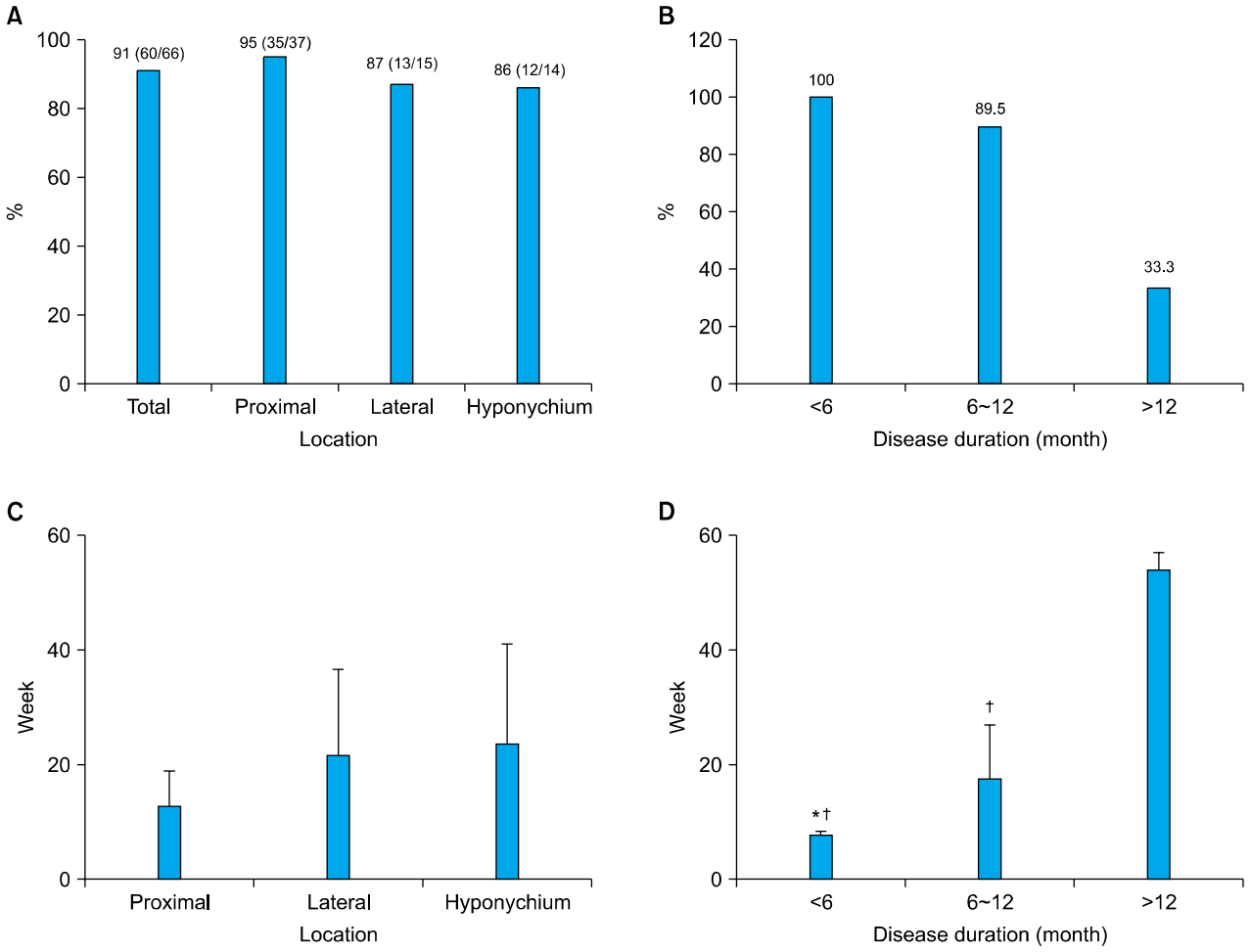

Fig. 3. (A) Success rate by individual lesions (total and subgroups according to locations). Within parenthesis is the number of lesions. (B) Success rate according to disease duration. (C) Treatment period for each location. (D) Treatment period according to disease duration. *$p<0.05$ when compared to 6 to 12 months; †$p<0.05$ when compared to over 12 months.

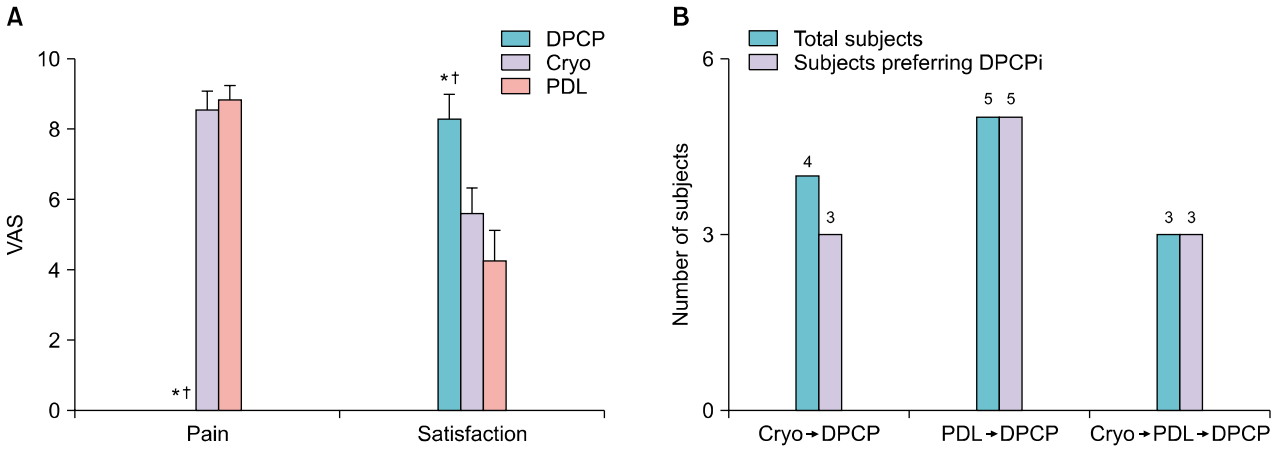

Fig. 4. (A) VAS score of pain and satisfaction for each treatment modality. (B) DPCP is preferred to other methods. Eleven out of twelve subjects who experienced multiple therapies chose DPCP for a new wart. VAS: visual analogue scale, DPCP: diphenylcyclopropenone, Cryo: cryotherapy, PDL: pulsed-dye laser, DPCPi: diphenylcyclopropenone immunotherapy. *$p<0.05$ when compared to cryo; †$p<0.05$ when compared to PDL.

There is a wide variety of treatment modalities in the management of viral warts, which includes cryotherapy, chemical therapies, laser therapies, intralesional bleomycin and immunotherapy. As stated earlier, a treatment of periungual warts has proven to be difficult, and recurrence is commonly observed. Involvement of the nail fold and/or nail bed increases the possibility of damaging or deforming the nail apparatus, including matrix, bed or underlying bone, which highlights the importance of choosing a proper treatment plan[13]. None of the above, however, has been shown to be a perfectly suitable solution for periungual warts.

Topical immunotherapy for warts was first described by Lewis[14] in 1973, when warts cleared after the application of a universal allergic contact sensitizer dinitrochlorobenzene in previously sensitized subjects. DPCP was first reported to successfully treat patients with resistant plantar warts in 1984[15] and since then, there have been several other reports of recalcitrant warts, including periungual warts, which were successfully treated with DPCPi[8-10,16,17]. It has been reported to have a high response rate, absence of scarring and painless application[8,9].

Our cure rate of 85% (by subject) is comparable to that of other treatment modalities for periungual warts reported in the literature: 60% for DPCPi[9], 90% for cryotherapy[13], and 51.1% for pulsed-dye laser[18]. It was even higher (91%) when evaluated by the individual lesions. Cryotherpy has been reported to have a high cure rate of up to 90% and is shown to be a safe modality in pregnant women and children, but it may have undesirable side effects which include mild to moderate pain, infection, nail plate damage and the discomfort produced by postoperative bullae[13]. Pulsed-dye laser in the literature has been reported to have a success rate of 51.1%[18]. However, its high cost, uncomfortable pain and the relative lack of research makes it a difficult method to choose as the first-line treatment for periungual warts. Our results show the effectiveness of DPCPi for treating periungual warts. Moreover we noticed that DPCPi completely cleared the lesions, even when the border became extensively ill-defined after the destructive methods, including cryotherapy and pulsed-dye laser (Fig. 1G～I). This shows usefulness of DPCPi when deciding the extent of area to treat with the more destructive modalities.

As disease duration increased, the success rate decreased and treatment period increased. Treatment period of the lesions of less than 6 months was significantly lower than those of 6 months and over. Further studies are needed to strengthen our statistical weaknesses due to the small number of subjects in our study. However, our data indicate that better results should be expected from early treatments with DPCPi.

Although there was no statistical significance, the treatment period and success rate according to the location appeared to be the most desirable in the proximal nail fold type. It may be associated with the anatomic features of each location. The epidermis of lateral nail fold and hyponychium is directly connected to the epithelium of the nail bed. Therefore, warts of these locations tend to involve the nail bed. However, in the case of proximal nail fold, eponychium may serve as a structural barrier preventing warts on this location from involving the nail matrix and the bed of the nail.

Potential side-effects of topical immunotherapy are not significant, most of involve blistering at the sensitization and application site. Distant or more widespread eczematous eruptions also occur, but such reactions usually disappear with topical steroid[9,16,19,20]. More rarely, contact urticaria[16], erythema multiforme-like reactions[21], influenza-like symptoms[10,22] and vitiligo[23] have been reported as well. We only experienced one patient which complained of aggravated itch that responded to systemic antihistamine.

As our questionnaire results indicate, DPCPi shows substantial benefits of not causing pain. Mean VAS for pain was 0 for DPCPi, which is substantially low compared to that of cryotherapy (8.57) and pulsed-dye laser (8.87). High satisfaction with DPCPi was shown in the questionnaire results, where DPCPi was preferred to other treatment methods in 11 of 12 subjects who experienced multiple therapies. The fact that most patients preferred DPCPi for its painless application shows that pain greatly influences the satisfaction level for a treatment, which ultimately leads to the choice of treatment.

The results of our study indicate that DPCPi is an effective and preferred treatment option for periungual warts. We recommend that DPCPi be first considered and initiated at the earliest possible point in treating periungual warts, especially for children, to whom pain is a big consideration factor in choosing a treatment modality.

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