

Combination Therapy with Intralesional Interferon α -2b and Pulsed Dye Laser for the Treatment of Periungual Warts

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Background : Periungual warts are a therapeutic challenge. Many studies have revealed that intralesional interferon α -2b therapy and pulsed dye laser therapy have numerous advantages over other modalities of treatment.

Objective : The purpose of this study was to determine if combination therapy with intralesional interferon α -2b and pulsed dye laser might offer an effective treatment for periungual warts.

Methods : Thirty-three patients were randomly assigned to one of three study groups. In group A, the patients received both intralesional interferon α -2b treatment and pulsed dye laser (PDL) therapy (n=13). Group B patients were treated with intralesional interferon α -2b alone (n=10) and group C was done with PDL therapy only (n=10).

Results : The clearance rate was 92.3% for the patients treated with the combination therapy of intralesional interferon α -2b treatment and pulsed dye laser (PDL) therapy. It was 50% for the patients with the intralesional interferon α -2b treatment alone, and 0% for the group with the PDL therapy only. No significant side effects were observed. At 6 months after cessation of the therapy, total 2 cases (one from group A and the other from group B) were recurred.

Conclusion : The combination therapy with intralesional interferon α -2b treatment and pulsed dye laser therapy was highly effective for the treatment of recalcitrant periungual warts. (*Ann Dermatol* 14(2) 82-87, 2002).

Key Words : Combination therapy, Interferon α -2b, Periungual warts, Pulsed dye laser

Warts, or verrucae are benign tumor of the skin caused by human papilloma virus (HPV) coming from the papova family. They are a common dermatologic complaint, with an estimated incidence of 10% in children and young adults¹. Commonly warts occur at the periungual areas and pose a problem in the management².

Interferons have been used for the treatment of vi-

ral disease, cutaneous tumors, HIV-associated Kaposi's sarcoma and other inflammatory diseases. Besides, interferons have been administered by different routes to patients with refractory warts³. Previous studies suggested the pulsed dye laser (PDL) therapy might be highly effective for the treatment of warts. The mechanism of PDL may be a result of intense heating of dermal vessels with collateral damage of virally infected keratinocytes⁴.

Despite the numerous advantages of intralesional interferon α -2b treatment and pulsed dye laser therapy, there have been few studies for periungual warts. The main purpose of this study is to evaluate the effect of combination therapy with intralesional interferon α -2b and pulsed dye laser on periungual warts.

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MATERIALS AND METHODS

Thirty-three patients with periungual wart were enrolled for this study (between November 1999 and October 2000). In this study, single periungual warts were restricted to the finger, not toe, affecting nail folds as well as the surrounding tissues. A single, experienced dermatologist diagnosed all 33 cases based on clinical characteristics. All of the patients were judged to have recalcitrant warts because they had a failure of at least one type of conventional treatment modalities. All patients filled out an informed consent form after the procedure and alternative methods were explained. They were in good general health, and anyone with a history of significant medical diseases were excluded. Also, patients on a regimen of immunosuppressive or cytotoxic therapy were excluded.

Before treatment, the patients were randomly assigned to one of the three study groups. In group A, the patients received both intralesional interferon α -2b treatment and pulsed dye laser (PDL) therapy (n=13). Group B patients were treated with intralesional interferon α -2b alone (n=10) and group C was done with PDL therapy only (n=10). All of the patients were not treated for three months in order to avoid the residual effect of previous treatment.

Interferon α -2b : A wart was injected three times a week for 3 weeks with 1×10^6 IU of human recombinant interferon α -2b (Intron A[®], Schering-Plough, Ireland) in a volume of 0.1mL, using a syringe with a 30 gauge needle. The planned schedule of injection was Monday, Wednesday, and Friday for three consecutive weeks.

Pulsed dye laser : All patients were treated once a week for three weeks. A SPTL-1 flashlamp-pumped pulsed dye laser (Candela Laser Corp., Wayland, USA) was used in patients emitting 585nm yellow light, with a pulse duration of 450 microseconds. The patients were treated with the 5-7mm spot size and fluence was 8 J/cm². Each location received 2 pulses with 1 to 2mm overlap. A surrounding 2 mm rim of normal-appearing tissue was treated as well.

Combination therapy : PDL laser therapy was performed first and the intralesional Interferon α -2b was injected. The patients in group A were treated with the combined therapy for three consecutive weeks.

Prior to all types of treatment, the keratotic component or debris of the warts, if present, was pared with a #15 scalpel blade, while taking care to avoid bleeding. The involved nail plate was trimmed if necessary, especially in case warts were beneath the nail. Local anesthetic cream, EMLA[®] (Astra Pharmaceutical Products Inc., Westborough, USA) was applied to the persons who required it. Patients were instructed to treat the area with topical antibiotics twice daily.

At the initial visit, a photograph of the wart was taken, and each wart was measured and subsequently tracked individually throughout the study with successive photographs. For patients whose lesions cleared completely before they received the full(3 weeks) treatment, the rest of the therapy was stopped. Clinical efficacy was determined by quantitative assessment of the treated warts. The patients in whom no visible evidence of warts remained on review(100% clearance of lesion) were translated into 'complete response'. Warts that failed to respond to the treatment (0-99% reduction in size) were classified into 'no response'. The patients were also monitored for the adverse effects of scarring, hypo- or hyperpigmentation. After treatment, the warts were evaluated at 2 and 6 months posttreatment to assess clearance rate and recurrence of the lesion, respectively.

For statistical analysis, chi-square test and Fisher's exact test were used to compare the differences in clearance rates between groups. The influence of the sex, age of patients, and duration of the disease on the clearance rates were evaluated by ANOVA test.

RESULTS

All of the patients entered completed the study. The demographic characteristics of the patients are listed in Table 1. The subjects ranged in age from 5 to 62 years and included 20 males and 13 females. Mean duration of illness was 1.75 years. Sixteen(48.5%) of the patients had a lesion on their thumbs(Group A:9, Group B: 3, Group C:4). All patients had a failure of at least one type of treatment for their warts. Previous treatments included cryosurgery (25 cases), CO2 laser (6 cases), DPCP immunotherapy (1 case), combined treatment with cryosurgery and CO2 laser (1 case).

We found that lesions completely cleared in two

Table 1. Demographic characteristics of patients with periungual warts

No. of enrolled patients	Group A	Group B	Group C	Total
Male	8	6	6	20
Female	5	4	4	13
Age (Y) Mean	20.08	18.60	21.00	19.90
Range	(7-62)	(5-37)	(11-55)	(5-62)
Mean duration of illness(Y)	2.11	1.50	1.55	1.75
Clearance rate(%)	92.3 (12/13)	50 (5/10)	0 (0/10)	
Recurrence rate(%)	8.3 (1/12)	20 (1/5)	-	

Group A : Combination therapy with intralesional interferon alpha-2b and pulsed dye laser

Group B : Intralesional interferon alpha-2b, only

Group C : Pulsed dye laser, only



Fig. 1. An 8-year-old female with recalcitrant periungual warts on her thumb which were resistant to cryotherapy and causing cosmetic alteration. The lesion was treated by combination therapy with intralesional interferon α -2b and pulsed dye laser.



Fig. 2. Result. Complete healing with good cosmetic result at 12 weeks of posttreatment.

patients (2nd patient of group A and 6th patient of group B) before they received the full(3weeks) treatment. In these cases, we stopped the rest of the treatment when the warts cleared.

The clinical features and responses to the treatment of groups A, B and C are as follows. After treatment, 'complete response' was noted in 12 out of 13 patients in group A (clearance rate: 92.3%, Figure 1, 2), 5 of 10 patients in group B (clearance rate:50%), and none in group C patients (clearance rate:0%). Group A had a statistically significant higher value of clearance rate than group B or C ($p=0.0325$ and < 0.0001 , re-

spectively). Also the clearance rate of group B is higher than that of group C ($p=0.0163$). The sex, age of patients, and duration of the warts did not have any apparent influence on the clearance rate($p>0.05$, ANOVA test).

All patients of groups A and B found the intralesional injections to be painful, but no local necrosis occurred. However the general consensus was that this method was less painful compared to cryotherapy. Eight patients (61.5%) of group A and five patients (50%) of group B experienced some flu-like symptoms in the form of fever, chill, or myalgia. But these problems occurred within the day of the injection, usually only after the first two to three injections and were usually relieved by taking

acetaminophen and rest. In groups A and C, immediately following laser exposure, the warts developed gray-black discoloration that persisted for about 1 week. The general opinion of patients was that the procedure did not produce intolerable pain during the laser pulse. There were no episode of scarring and hypo- or hyperpigmentation. All patients of groups A, B and C were able to resume the normal activities following the treatment.

In two patients (one in group A and the other in group B), recurrences were noted between 2 and 6 months after cessation of the therapy.

DISCUSSION

Warts commonly occur at the periungual areas. Periungual warts can extend around or beneath the nail, causing discomfort and an embarrassingly poor cosmetic appearance. Several different modalities of treatments have been noted in the literature, no single therapy has been established as the best. In addition periungual warts have proven to be difficult to eradicate because of their location, the high recurrence rate and the need to avoid disfiguration. During the therapy there may be many problems including damaging the nail matrix, and nail plate. And they cannot be left alone as they are disfiguring and if the warts involved the nail matrix cause the permanent nail dystrophy, too. However, there has been no report for the effective treatment of only the periungual warts. Therefore, it is important to seek an effective and safe method^{5,6,7}.

Interferons have been used for the treatment of hairy cell leukemia, multiple myeloma, HIV-associated Kaposi's sarcoma, viral hepatitis, and other cutaneous tumors and vascular tumors. Recently recombinant interferons were noted for their role in the treatment of a variety of HPV infections, such as, condyloma acuminata and refractory warts³. Intralesional therapy of condyloma acuminata with recombinant alpha interferon have shown efficacy ranging up to 69% in some studies^{8,9,10}. Similar studies using natural alpha interferon, beta interferon has proven effective^{11,12,13}. In addition to these studies, interferons were also shown to be effective in common warts on the extremities, including some palmar and plantar wart^{14,15}. But no study has been shown to be effective in the treatment of periungual warts with interferon.

A possible mechanism of interferon as a treatment modality for warts is antiviral effects on HPV-infected cells. Additionally antiproliferative, immunomodulatory and antitumor activities may also play a role in clearing the warts virus. The immunomodulatory activity is made by inducing afferent antigen presentation, as well as efferent, cytotoxic, immune mechanisms^{3,16}. Furthermore interferon downregulates oncogenes, upregulates tumor suppressor genes, and affects cellular differentiation¹⁷.

A common side effect of interferon therapy is flu-like symptoms in the form of myalgia, fever, headache. But these symptoms are usually relieved by taking acetaminophen and tolerance is quickly developed. They can occur with intralesional as well as subcutaneous or intramuscular delivery, indicating that systemic absorption may take place with either route. Less common adverse reactions include GI upset, somnolence, emotional lability, laboratory abnormalities, such as, transient hepatic enzyme elevation, and mild cytopenia. Most adverse effects of interferons are rapidly and fully reversible following discontinuation of the therapy¹⁸.

The PDL is usually used in the treatment of port-wine stain, telangiectasia, and other small, flat, or minimally elevated vascular lesions¹⁹. PDL has been tested in the treatment of viral warts, too. There have been conflicting results in the treatment of warts with the PDL, with reported efficacy rates ranging from 21% to 95%⁴. Tan et al in a preliminary report, showed 72% of patients were cleared of their recalcitrant warts after an average of 1.68 treatments²⁰. Webster et al studied 54 patients with warts, finding clearance in 71% of flat warts, 44% of common warts and 33% of periungual warts²¹. Other recent studies reported lower response rates. Huilgol et al found 0% clearance for recalcitrant warts²².

The mechanism of action is not fully understood. But it is likely that the intense damaging of dermal vessels causes a collateral damage of virally infected keratinocytes. Oxyhemoglobin within the RBC in the dermal capillaries of warts preferentially absorbs yellow light (585nm) leading to selective microvascular destruction. Removal of blood supply to the wart, and the heat generated by laser, may lead to the destruction of the virus-infected cells in the basal layer of the dermis²³.

The combination of various modalities is theo-

retically very attractive in the case of recalcitrant warts. There were many reports using combination therapy, resulting in diverse outcomes. But most studies of the combination therapy were focused on anogenital warts, and there have been few studies for periungual warts. Furthermore, main arm of combination therapy was the ablative therapy such as CO₂, cryotherapy, etc.^{24,25}. In periungual warts, not only are we concerned about the effectiveness, but we also try to avoid the disfigurement or dystrophy of the nail and the surrounding structure. Hence, it is absolutely necessary to obtain a safe, effective and non-destructive modality to treat periungual warts.

In our study the clearance rate of PDL therapy (0%) was inferior to the response rates of monotherapy of interferon (50%) or combination therapy (92.3%). It is noteworthy that clearance rate of PDL is different from those of the previous reports, which showed good response rates of PDL therapy. It is uncertain why this result had occurred. But the overlying nail of periungual or subungual warts maybe diminished the laser light exposure. However it can be stated with certainty that the interferon treatment was more responsible for this effect. One possible mechanism for the synergistic effects of the combination therapy is as follows: the first exposure of laser light causes local dermal vessel destruction and damage of virally infected keratinocytes. The damaged keratinocytes are exposed to the immune system. The subsequent injection of interferon boosts cell-mediated immunity causing the eradication of viral warts. Although our study did not have large numbers of patients, the results were very encouraging. Furthermore only the periungual warts that is usually resistant to other therapy were entered into this study, so the combination therapy should be considered as a cause of high clearance rate and a valuable treatment option for curing the periungual warts. Moreover this method has a profile of low side effects, limited to the transient pain and flu-like symptoms.

In summary, the results of the present study strongly suggest that the combination therapy with intralesional interferon α -2b treatment and pulsed dye laser therapy was highly effective for the treatment of recalcitrant periungual warts.

Since the number of patients in our study was small and there was no other controlled study, a long-term case-controlled study would be required to determine the optimal dose and treatment schedule that will maximize the convenience and effectiveness.

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