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Original Article

Clinical efficacy of CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy in treating periungual and plantar warts

Yuanyuan Li, Qiang Wang, Wenjun Zhong, Xinfeng Pan, Minhong Zhang, Liqiao Chi

Department of Dermatology, Qingpu Branch of Zhongshan Hospital, Fudan University, Shanghai, China

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Abstract: Objective: To analyze the clinical application value of CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy for periungual and plantar warts. Methods: Data from patients with periungual and plantar warts treated at Qingpu branch of Zhongshan Hospital, Fudan University between August 2022 and January 2024 were retrospectively analyzed. After screening based on inclusion and exclusion criteria, 96 patients were included and categorized into two groups according to their treatment regimens: a combination group (n=50, receiving CO_2 laser therapy and 5-aminolevulinic acid photodynamic therapy) and a control group (n=46, undergoing CO_2 laser treatment alone). The two groups were compared in terms of wart scores before and after treatment, clinical efficacy, recurrence rates during follow-up, and incidence of adverse reactions. Results: During the 4th, 6th, and 8th weeks of treatment, the wart scores of patients in the combination group were significantly lower than those of the control group (P<0.05), and at these intervals, the overall treatment efficacy in the combination group was significantly higher than that of the control group (P<0.05). At 3-month follow-up, the recurrence rate in the combination group (2.00%) was lower than that in the control group (10.87%) (P<0.05). At the 2nd, 4th, 6th, and 8th weeks of treatment, the Visual Analog Scale scores in the combination group were significantly reduced compared to the control group (P<0.05). No significant difference was found in the incidence of adverse reactions between the two groups during follow-up (P>0.05). Conclusion: The application of CO_2 laser therapy combined with 5-aminolevulinic acid photodynamic therapy is effective for patients suffering from periungual and plantar warts, and this combination enhances clinical outcome, mitigates pain, and reduces short-term recurrence.

Keywords: CO_2 laser therapy, 5-aminolevulinic acid photodynamic therapy, periungual warts, plantar warts, clinical efficacy, safety

Introduction

Periungual warts are benign verrucous growths that develop around the nail plate due to infection by the human papillomavirus (HPV), which are a specific type of common wart and a frequent dermatologic condition, particularly prevalent among children and young people [1, 2]. Periungual warts may affect both the proximal nail plate and the lateral nail folds. If inadequately managed, the warts may extend beneath the nail plate, leading to lifting or deformation of the nail, a condition known as subungual warts [3, 4]. Plantar warts, also caused by HPV infection, are benign, proliferative skin lesions typically found on the heel, forefoot, or base of the toes. While plantar warts can appear at any age, the incidence is higher among children and young people [5]. Both periungual warts and plantar warts are classified as viral skin warts, with an overall incidence rate of approximately 7% to 12%. Periungual warts can lead to the destruction of the nail plate and nail bed, while plantar warts can cause pain during walking. Both conditions significantly affect the patients' quality of life; therefore, early treatment is recommended [6].

The primary treatments for periungual and plantar warts typically consist of medication and physical interventions, such as cryotherapy, electrocautery, laser therapy, and microwave therapy, all of which have demonstrated proven efficacy [7]. However, clinical observations suggest that these treatments frequently induce trauma, leading to significant postopera-

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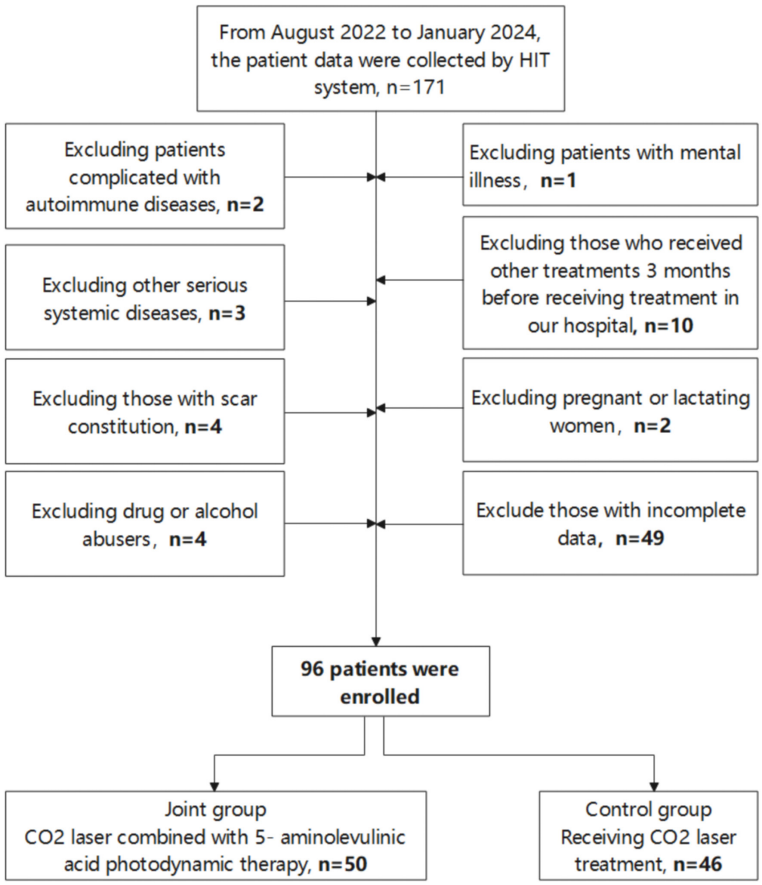

Figure 1. Flow chart of patient inclusion and exclusion.

tive pain. Follow-up results reveal that although the initial clearance rates of these therapies are confirmed, the high rates of recurrence cause substantial distress to patients and hinder the development of a harmonious doctor-patient relationship [8, 9]. CO_2 laser treatment is a commonly used technique for the removal of periungual and plantar warts; however, a single treatment approach often fails to achieve satisfactory results. Photodynamic therapy with aminolevulinic acid, a treatment that integrates pharmaceuticals and medical devices, was first introduced in 1990 for actinic keratosis and basal cell carcinoma. In 2000, it received approval from the U.S. Food and Drug Administration for the treatment of actinic keratosis. In recent years, this therapeutic approach has progressed rapidly in dermatology, demonstrating remarkable effectiveness in treating moderate to severe acne, actinic cheilitis, and squamous cell carcinoma [10, 11]. This study presented an innovative combination of CO_2 laser therapy and 5-aminolevulinic acid photodynamic therapy to explore its clinical efficacy in treating periungual and plantar warts.

Materials and methods

Study design and patients

This is a retrospective analysis. The study was approved by the Ethics Committee of Qingpu branch of Zhongshan Hospital, Fudan University. The study spanned from August 2022 to January 2024, with patient follow-up scheduled every 3 months, concluding in April 2024 based on the enrollment of the final participant. A total of 171 cases of patients diagnosed with periungual and plantar warts at Qingpu branch of Zhongshan Hospital, Fudan University were screened through the hospital's information system. A secondary screening of these 171 patients was then conducted in accordance with the specific inclusion and exclusion criteria (**Figure 1**).

Inclusion criteria: (1) Adherence to the diagnostic standards for periungual warts and plantar warts as specified in Dermatovenereology [12], with corresponding clinical manifestations; (2) Age between 18 and 35 years; (3) Completion of CO_2 therapy or a combination of CO_2 and 5-aminolevulinic acid photodynamic therapy at Qingpu branch of Zhongshan Hospital, Fudan University; (4) Availability of comprehensive results at the 2nd, 4th, 6th, and 8th weeks following treatment; (5) Completion of follow-up data collection at 3 months post-treatment; (6) Completion of Visual Analog Scale (VAS) assessment both prior to treatment and at the 3-month follow-up.

Exclusion criteria: (1) Patients with concurrent autoimmune diseases, mental disorders, or other serious systemic illnesses; (2) Those who had received other treatments within the past 3 months prior to treatment at Qingpu branch of Zhongshan Hospital, Fudan University; (3) Patients with scar constitution; (4) Pregnant or

breastfeeding women; (5) Patients with a history of drug or alcohol abuse.

After screening 171 patients based on the inclusion and exclusion criteria, 96 were ultimately selected and assigned to a combination group (n=50, treated with CO_2 laser therapy or a control group (n=46, receiving CO_2 laser therapy alone).

Data collection

The data of 96 patients were collected through the hospital information system. The collected data included the following aspects: (1) Basic patient information, including gender, age, duration of illness, and whether they had received any prior treatment for over three months before admitting to Qingpu branch of Zhongshan Hospital, Fudan University; (2) The treatment efficacy for patients was assessed by evaluating both the quantity and size of the warts. Each wart was assigned a value of 1 point, with an additional point given for each subsequent wart. The size of each wart was scored based on its diameter: 0 mm scored 0 points, 0-4 mm scored 1 point, >4-8 mm scored 2 points, >8-12 mm scored 3 points, and >12 mm scored 4 points. The patient's overall score was the cumulative total of the points assigned for both the quantity and size of the warts [10]. The time points for assessing treatment efficacy were as follows: prior to treatment, 2 weeks, 4 weeks, 6 weeks, and 8 weeks after the first treatment. The criteria for assessing efficacy were based on the *Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine* [13], with calculations adhering to the Nimodipine method. The specific formula is as follows: Lesion regression rate = [(pre-treatment total score - post-treatment total score)/pre-treatment total score] × 100%. Clinical efficacy was classified into four categories: complete recovery, significant improvement, improvement, and no effect. Complete recovery was defined as a 100% lesion regression rate, significant improvement was defined as a regression rate of 70% to <100%, improvement corresponded to a regression rate of 30% to <70%, and no effect was defined as a regression rate of <30%. The total effective rate included cases with complete recovery, significant improvement, and improvement. (3) The recurrence status of the patients was collected at 3 months after the first treatment. (4) The pain levels of patients were recorded before treatment, and at 2, 4, 6, and 8 weeks after the first treatment using the VAS. (5) The incidence of adverse reactions within the 3 months after the first treatment was recorded.

Outcome measures and statistical analysis

Primary outcomes include clinical efficacy, which evaluated the difference in treatment effectiveness between the two groups of patients, and recurrence, which assessed the recurrence rates at 3-month follow-up after the initial treatment.

Secondary outcomes include pain levels at various time points during treatment and adverse reactions occurring within three months from the initial treatment.

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 24.0. The measured data were confirmed to follow a normal distribution and were expressed as mean ± standard deviation. An independent samples t-test was used for comparisons between groups at the same time points. Counted data were expressed as rates, with intergroup differences evaluated through the chi-square test. $P<0.05$ was regarded as significant.

Results

Comparison of baseline clinical data between the two groups

The clinical data, including age, duration of illness, and gender, were collected from two patient groups via the hospital information system. The results of the comparative analysis revealed no significant differences in baseline clinical data between the two groups ($P>0.05$), thereby indicating comparability between the groups (**Table 1**).

Comparison of pre- and post-treatment scores between the two groups

The quantity and diameter of periungual and plantar warts in the two patient groups were calculated, and the total scores were assessed. A comparative analysis of intergroup differences before treatment revealed no significant differences in these indicators between the two groups ($P=0.226$, $P=0.411$, $P=0.265$) (**Table 2**).

Table 1. Comparison of baseline clinical data between the two groups ($\bar{x}\pm s$)/[n (%)]

General clinical data		Combination group (n=50)	Control group (n=46)	t/χ^2	*P*
Sex	Male	22	23	0.346	0.556
	Female	28	23		
Average age (years)		30.56±8.51	29.69±9.22	0.481	0.632
Average duration of illness (months)		12.01±9.33	11.96±9.51	0.026	0.979
History of treatment	Yes	26	20	0.697	0.404
	No	24	26		
WBC count ($\times10^9$/L)		8.13±1.56	8.09±1.69	0.236	0.625
Fibrinogen content (g/L)		2.01±0.51	1.98±0.62	0.165	0.991
Thrombin time (s)		18.23±1.21	17.98±2.11	0.365	0.711
Prothrombin activity (%)		84.23±10.21	85.62±11.51	0.632	0.416
ALT (U/L)		26.59±5.15	28.56±4.15	0.551	0.416
AST (U/L)		26.35±4.13	25.98±5.06	0.639	0.518

WBC: white blood cells; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 2. Comparison of pre-treatment wart scores between the two groups

Group	Number of cases	Quantity	Diameter	Total score
Combination group	50	17.26±8.01	16.59±8.05	37.97±16.65
Control group	46	16.41±8.21	18.39±8.24	39.32±7.10
t	-	1.236	0.516	0.613
P	-	0.226	0.411	0.265

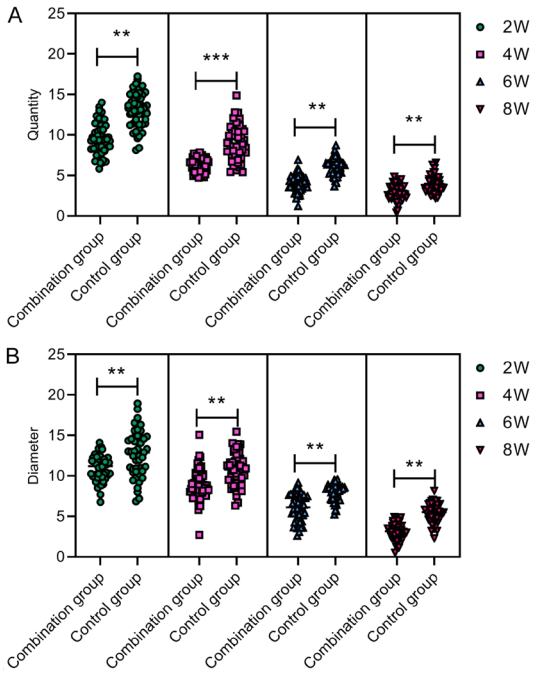

Figure 2. Comparison of post-treatment wart quantity and diameter between the two groups. At 2 weeks, 4 weeks, 6 weeks, and 8 weeks after treatment, the quantity scores (A) and diameter scores (B) in the combination group were lower than those of the control group ($P<0.05$). $^{**}P<0.01$, $^{***}P<0.001$.

At 2 weeks after treatment, the score of quantity in the combination group was lower than that in the control group [(10.01±1.25) vs. (13.56±1.81), $P=0.003$], and it remained significantly lower at 4 weeks [(5.03±0.51) vs. (8.23±0.61), $P<0.001$], 6 weeks [(3.02±0.16) vs. (5.01±0.35), $P=0.012$], and 8 weeks [(2.01±0.11) vs. (4.01±0.32), $P=0.001$] after treatment (**Figure 2A**). The diameter scores of the combination group were also lower than those of the control group at 2 weeks [(11.05±2.31) vs. (14.98±1.98), $P=0.004$], 4 weeks [(8.01±1.21) vs. (11.26±2.01), $P=0.003$], 6 weeks [(5.06±1.21) vs. (9.23±1.59), $P=0.001$], and 8 weeks [(2.03±0.21) vs. (4.06±1.01), $P=0.001$] post-treatment (**Figure 2B**). In terms of total score, both groups showed a marked decrease in total scores at the 2nd week of treatment compared to before treatment but without a significant difference between groups [(25.26±6.23) vs. (27.81±5.98), $P>0.05$] (**Figure 3A**). Significantly lower total scores were observed in combination group than those of the control group at the 4th week of treatment [(20.23±2.16) vs. (26.35±2.69), $P<0.001$] (**Figure 3B**), the 6th week [(12.69±2.13) vs. (18.23±2.95), $P<0.001$] and 8th week

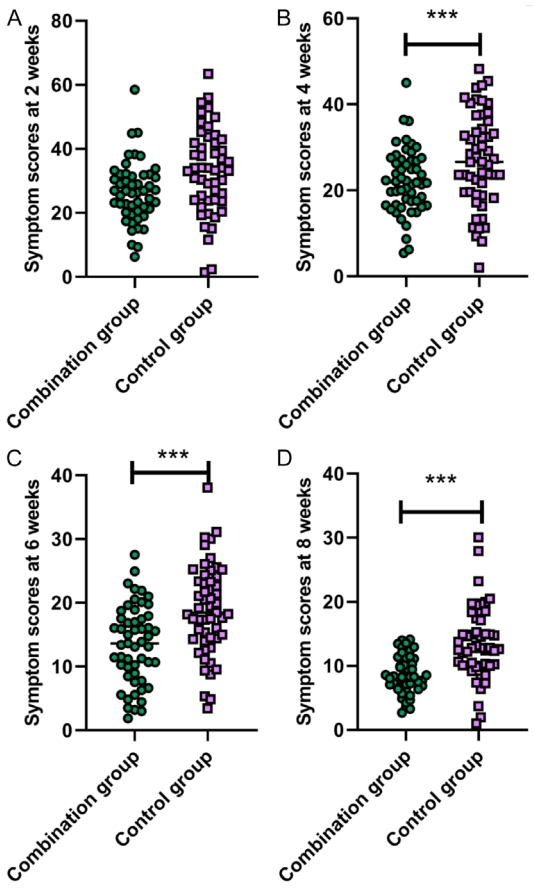

Figure 3. Comparison of post-treatment total wart scores between the two groups. At the 2nd week of treatment, no significant difference was observed in the scores between the two groups (P>0.05) (A). At the 4th (B), 6th (C), and 8th (D) weeks of treatment, the scores of the combination group were significantly lower than those of the control group (P<0.05). ***P<0.001.

[(10.02±1.65) vs. (13.56±1.81), P<0.001] (**Figure 3C**, **3D**).

Comparison of treatment efficacy between the two groups

The treatment efficacy of the two groups was evaluated in accordance with the *Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine*. The results revealed that at 2 weeks of treatment (**Figure 4A**), the overall effective rate in the combination group was 52.00%, not significantly different from 50.00% in the control group (P=0.246). However, at 4 weeks (**Figure 4B**), 6 weeks (**Figure 4C**), and 8 weeks (**Figure 4D**) of treatment, the overall effective rates in the combination group were higher than those of the control group (P=0.038, P=0.005, P=0.038) (**Table 3**).

Comparison of recurrence rate between the two groups

Both patient groups underwent a 3-month follow-up. Results indicated that 1 case of recurrence was observed in the combination group, with a recurrence rate of 2.00%, while 5 cases of recurrence were observed in the control group, resulting in a recurrence rate of 10.87%. The difference in recurrence rate between the two groups was significant (P=0.014) (**Figure 5**).

Comparison of pain levels before and after treatment between the two groups

No significant difference was observed in VAS scores between the two groups before treatment (P>0.05). At the 2nd, 4th, 6th, and 8th weeks of treatment, the VAS scores in the combination group were significantly lower than those of the control group, (P=0.006, P=0.008, P=0.001, P=0.004) (**Figure 6**).

Comparison of incidence of adverse reactions between the two groups

At the 3-month follow-up, there were 2 cases of fever, 1 case of fatigue, 2 cases of myalgia, 1 case of nausea, and 1 case of infection in the combination group, with an incidence of the adverse reactions of 14.00%, which was not statistically different from 6.52% (3/46) observed in the control group (P>0.05) (**Figure 7**).

Discussion

Warts are growths that form on the skin or mucous membranes due to an infection by HPV, which is a relatively common skin condition worldwide. Recent studies suggest that approximately 40% of the global population carries HPV, with an estimated 7% to 12% developing warts, particularly common among children, young people, and individuals with compromised immune systems, the reason for which are related to a more pronounced immune response to HPV in these groups, as well as higher sexual activity rates among young people [14, 15]. Additionally, the frequency of daily activities among young people increases the likelihood of skin injuries, which are significant factors for including patients aged 18-35

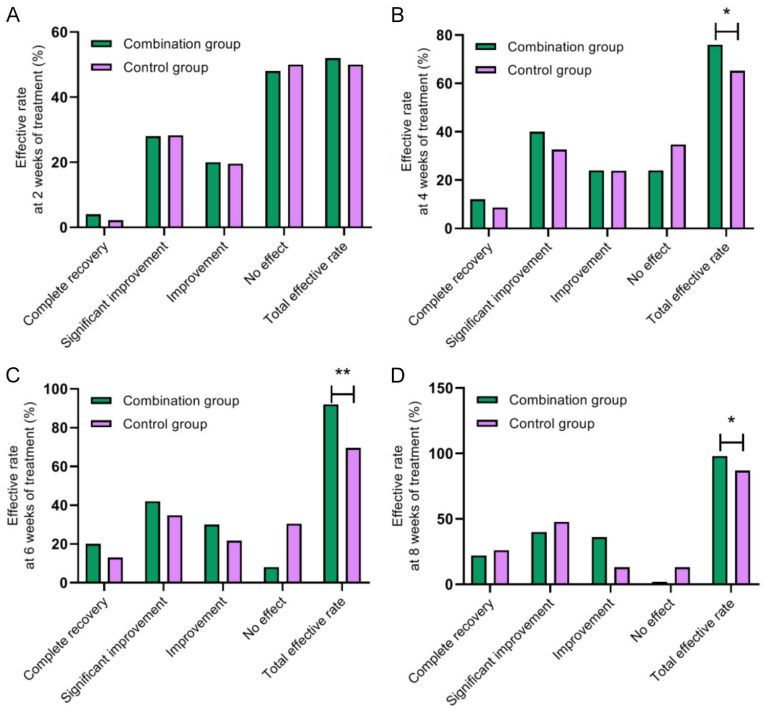

Figure 4. Comparison of treatment efficacy between the two groups. At 2 weeks of treatment (A), the overall effective rate in the combination group was 52.00%, exhibiting no significant difference when compared to 50.00% in the control group ($P>0.05$). At 4 weeks (B), 6 weeks (C), and 8 weeks (D) of treatment, the overall effective rates in the combination group were significantly higher than those of the control group ($P<0.05$). $^{*}P<0.05$, $^{**}P<0.01$.

in this study. The primary source of wart infection is contact with those who are either infected or carriers of the virus. Transmission occurs through both direct or indirect contact, and once infected with HPV, individuals may present a range of manifestations, including clinical types, subtypes, and latent infections [16]. Depending on the location of the wart and its clinical manifestations, it can be classified as common warts, flat warts, plantar warts, periungual warts, and oral warts, among which periungual and plantar warts are characterized by a slow course and pose significant challenges for treatment [17].

CO_2 laser is a widely employed technique in the clinical treatment of periungual and plantar warts. Nevertheless, previous research [18] highlights that plantar warts exhibit a high recurrence rate, with reliance on a single treatment modality identified as an independent risk factor for recurrence. Consequently, combination therapy is recommended in clinical settings to mitigate the likelihood of recurrence. This study explored the clinical efficacy of CO_2 laser therapy in conjunction with 5-aminolevulinic acid photodynamic therapy for the treatment of periungual and plantar warts using a comparative grouping design. The findings revealed that at the 4th, 6th, and 8th weeks after treatment, the total wart scores in the combination group were significantly lower than those in the control group, which received CO_2 laser treatment alone. CO_2 laser therapy is a commonly utilized minimally invasive technique for the removal of warts. CO_2 lasers can effectively vaporize and cauterize wart tissue by emitting a high-energy laser beam, thereby damaging the skin cells infected by the wart virus. The fundamental principle of this method relies on the CO_2 laser's operational wavelength (10.6 micrometers), which falls within the infrared range and exhibits a remarkable absorption by skin moisture. As the moisture in the skin absorbs the energy of the CO_2 laser intensely, the localized tissue rapidly heats up upon exposure to the laser beam, causing the moisture within the wart tissue to evaporate swiftly and resulting in tissue vaporization. Through this precise heating and evaporation process, the affected tissue is gradually eliminated, achieving the desired outcome of wart removal. CO_2 laser therapy demonstrates numerous advantages in clinical application. First, owing to its efficient vaporization characteristics, the laser can precisely target the warty tissue while minimizing damage to the surrounding healthy skin, thus exhibiting minimally invasive qualities. Second, the treatment process is relatively swift, often requiring only local anesthesia, which alleviates discomfort during the procedure. After treatment, the minimal damage to surrounding tissues facilitates rapid wound healing, typically within a few days to weeks, resulting in a short recovery time for patients and generally no noticeable scarring. Furthermore, CO_2 laser therapy proves highly effective for the removal of warts that are diffi-

Table 3. Comparison of treatment efficacy between the two groups (%)

Time point	Group	Complete recovery	Significant improvement	Improvement	No effect	Effective rate	*P*
At 2 weeks	Combination group (n=50)	4.00	28.00	20.00	48.00	52.00	0.246
	Control group (n=46)	2.17	28.26	19.57	50.00	50.00	
At 4 weeks	Combination group (n=50)	12.00	40.00	24.00	24.00	76.00*	0.038
	Control group (n=46)	8.70	32.61	23.91	34.78	65.22	
At 6 weeks	Combination group (n=50)	20.00	42.00	30.00	8.00	92.00**	0.005
	Control group (n=46)	13.04	34.78	21.74	30.43	69.57	
At 8 weeks	Combination group (n=50)	22.00	40.00	36.00	2.00	98.00*	0.038
	Control group (n=46)	26.09	47.83	13.04	13.04	86.96	

Note: Compared to control group at the same time point, *P<0.05, **P<0.01.

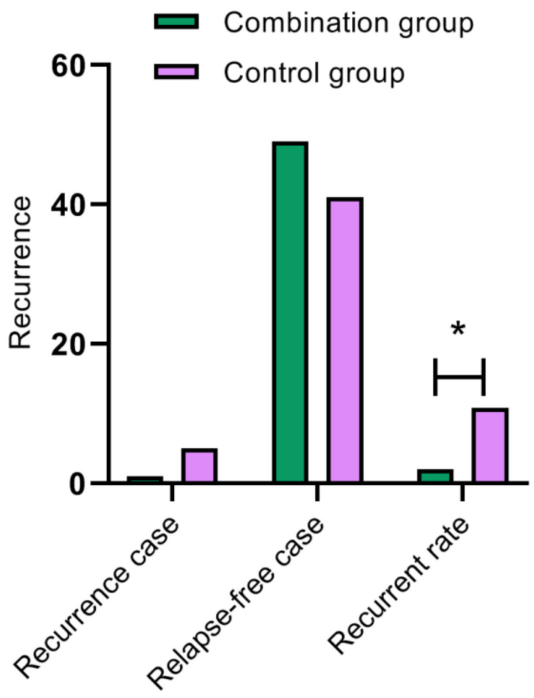

Figure 5. Comparison of recurrence rate between the two groups. At 3-month follow-up, the recurrence rate in the combination group (2.00%) was significantly lower than that of the control group (10.87%) (P<0.05). *P<0.05.

cult to eliminate through conventional methods, such as recurrent and large warts, making it a safe and efficient option for removal of the warts [19, 20]. However, this approach also has certain limitations. After reviewing the literature, the authors summarize the shortcomings of CO_2 laser treatment for warts as follows. (1) Noticeable pain: during the treatment, the laser cauterizes and vaporizes the wart tissue, which may result in significant pain for the patient. Although local anesthesia can alleviate some discomfort, certain patients may still experience varying degrees of discomfort after the procedure, impacting their overall treatment experience [21, 22]. (2) Postoperative discomfort during the recovery period: following the procedure, the skin at the treatment site typically forms scabs, accompanied by redness, swelling, and pain. Patients must pay special attention to keeping the wound clean to prevent infection and promote healing. However, this recovery process may cause inconvenience and impact daily life. (3) Recurrence risk: although the CO_2 laser treatment effectively removes wart tissue from the surface of the skin, it does not entirely eliminate the virus from the skin and therefore cannot completely prevent wart recurrence. Some virus may persist in other areas of the skin, resulting in a heightened risk of recurrence post-treatment. This also elucidates the elevated recurrence rates observed in patients relying on CO_2 laser therapy alone during clinical follow-up [23], and is one of the main reasons for the higher recurrence rate in the control group who received only CO_2 laser treatment.

5-Aminolevulinic acid photodynamic therapy is a treatment method based on photodynamic reactions, primarily aimed at selectively destroying diseased tissue to achieve therapeutic objectives. In this treatment, 5-aminolevulinic acid serves as a photosensitizer that can be transformed into the photosensitizing substance protoporphyrin IX (PpIX) within the affected tissue. When irradiated by light of a specific wavelength, PpIX produces a photodynamic reaction under the excitation of light and the action of oxygen, generating reactive oxygen species that inflict oxidative damage and destruction on cells infected by the wart virus,

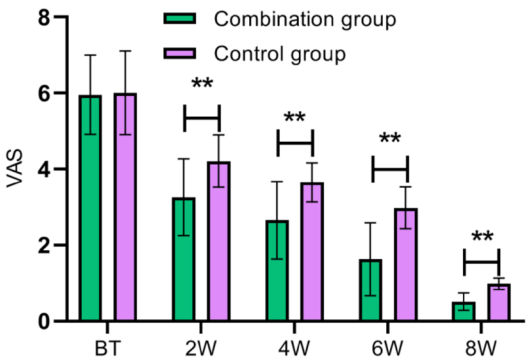

Figure 6. Comparison of pain levels before and after treatment between the two groups. There was no significant difference in VAS scores between the two groups before treatment ($P>0.05$). At the 2nd, 4th, 6th, and 8th weeks of treatment, the VAS scores in the combination group were significantly lower than those of the control group ($P<0.05$). $^{**}P<0.01$. VAS: Visual Analog Scale.

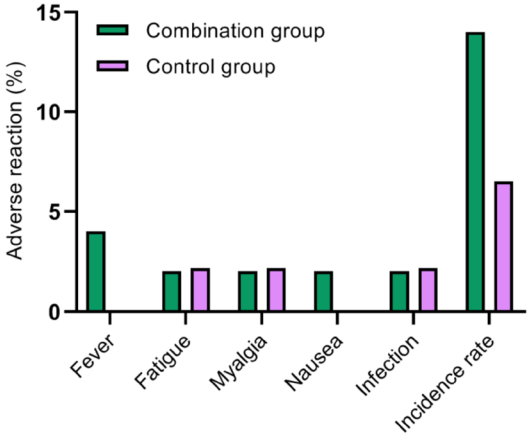

Figure 7. Comparison of incidence of adverse reactions between the two groups. During the 3-month follow-up, there was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$).

thereby achieving therapeutic efficacy. Currently, 5-aminolevulinic acid photodynamic therapy is widely employed in the treatment of common warts, demonstrating high selectivity and good tolerance. A study showed that this therapy is highly effective in treating comon warts and helps reduce recurrence rates. Compared to traditional physical destruction methods, 5-aminolevulinic acid photodynamic therapy not only effectively eliminates wart tissue but also minimizes damage to surrounding healthy tissue, thereby alleviating pain during treatment and discomfort during the postoperative recovery period [24]. The authors of this study found that, in comparison to conventional treatments such as cryotherapy and CO_2 laser therapy, 5-aminolevulinic acid photodynamic therapy has several distinct advantages. (1) The fractional laser delivers concentrated bursts of high-energy light, effectively destroying warts upon impact, leading to their immediate damage, subsequent scabbing, and eventual detachment [25, 26]. (2) The fractional laser can generate vertical perforations that swiftly disrupt lesion tissue, thereby enabling the subsequent absorption of drug into the wart, which significantly enhances the efficacy of the treatment [27]. (3) The fractional laser can directly target localized lesion tissue, using high temperatures to eradicate local viruses, thereby inhibiting their reproduction [28]. (4) The elevated temperature produced by fractional laser treatment, coupled with the residual substances left after the destruction of the virus, can activate the body's immune system, prompting an immune response that ultimately eradicates the HPV virus [29, 30]. (5) Fractional laser treatment requires no anesthesia and is highly safe. The presence of the aforementioned mechanism enhances the efficacy of combined treatment and, by more effectively eliminating HPV, reduces the probability of postoperative recurrence.

However, 5-aminolevulinic acid photodynamic therapy still has certain limitations. For instance, the treatment demonstrates inadequate penetration depth (<6 mm), making it effective for superficial warts but frequently less successful in completely eradicating deeper periungual warts [31]. Furthermore, the expense associated with photodynamic therapy utilizing 5-aminolevulinic acid is relatively high, necessitating a thorough consideration of all these factors in conjunction with the patient's actual condition. Although this study innovatively analyzed the therapeutic efficacy of CO_2 laser therapy combined with 5-aminolevulinic acid photodynamic therapy on periungual and plantar warts, it also has limitations, including a small sample size and a short follow-up period. In future research, we intend to validate the feasibility and safety of this combined treatment through large-scale, multicenter, and long-term follow-up studies.

Conclusion

The application of CO_2 laser therapy combined with 5-aminolevulinic acid photodynamic thera-

py is effective for patients suffering from periungual and plantar warts, and the combination can enhance clinical outcome, mitigate pain, and reduce short-term recurrence.

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Disclosure of conflict of interest

None.

Address correspondence to: Liqiao Chi, Department of Dermatology, Qingpu Branch of Zhongshan Hospital, Fudan University, No. 1158, Gongyuan East Road, Qingpu District, Shanghai, China. Tel: +86-18116015612; E-mail: clq202309@163.com

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