

Cryotherapy versus CO₂ laser in the treatment of plantar warts: a randomized controlled trial

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ABSTRACT **Background:** Warts are one of the most common infections in humans. Plantar warts are a subtype of non-genital warts, and several procedures and topical treatments have been used in its treatment. Cryotherapy is one of the most popular modalities, but it is time-consuming and remission rates vary in different studies. CO₂ laser was the first laser used for treating warts. To date, no clinical trial has been done to compare CO₂ laser with cryotherapy in the treatment of plantar warts.

Patients and Methods: This randomized controlled trial was performed in order to compare the efficacy and number of sessions needed to treat plantar warts in 60 patients who had received no previous treatment in the previous 3 months. They were randomly allocated to the cryotherapy or CO₂ laser group. The number of sessions needed for response and the recurrence rate after a 3-month follow-up was compared in the 2 groups.

Results: Sixty patients with plantar warts were randomly allocated to either the CO₂ laser or cryotherapy groups. Median age was 25 (range=18-53) and 27 (range= 18-75) years in the cryotherapy group and CO₂ laser groups, respectively. Both groups were matched for age and sex (56% male and 44% female in the cryotherapy group and 34% male and 66% female in the CO₂ laser group). The median number of sessions needed for complete resolution of the warts in the CO₂ laser and cryotherapy groups were 1 (range=1-2) and 3 (range=1-12), respectively. The difference in the number of sessions was statistically significant between the 2 groups (P-value≤0.001). Recurrence rates after a 3-month follow-up was not statistically significant (P-value= 0.069).

Conclusion: The number of sessions needed to treat plantar warts was less using CO₂ laser than cryotherapy; therefore, this modality can be a good addition to the already existing anti-wart armamentarium.

Introduction

Warts are one of the most common benign neoplasms. It is the third most common skin disease in childhood and is probably even more common in adulthood [1]. Warts are induced by over 100 types of human papillomavirus (HPVs) and can affect any race [2]. They are subdivided into genital and non-genital types. In a study from India in 2016, the ratio of non-genital warts to the genital forms was 9 to 1 [3]. Non-genital warts are subsequently subdivided into common, plane, palmoplantar, mosaic, filiform or digitate types [4]. Palmoplantar warts are one of the most common types of non-genital warts [5]. Following discovery of HPVs as the causative agent of warts, several treatment methods have been introduced. Currently, there is no specific antiviral agent against HPVs. Systemic cidofovir affects DNA viruses such as HPV, but renal toxicity limits its use [6]. No curative standard definitive oral or topical treatment exists for warts [7]. Current treatments are based on 2 mechanisms: destruction of the bulk of the neoplasm or stimulation of cellular immunity against HPVs [8,9]. Topical immunomodulators (imiquimod [10]), topical and intralesional cytotoxic agents (5-FU, podophyllin [11]), immunotherapy (diphenylcyclopropenone [12]), topical and oral retinoids [13], and systemic immunomodifiers (cimetidine, interferons [14]) have been used with some success. Local destructive methods are used more often than immunomodifiers. They include cryotherapy [15], trichloroacetic acid [16], lactic acid, salicylic acid, electrosurgery, curettage, surgery with scalpel or scissors [17], photodynamic therapy [18], and various types of lasers [17]. In a Cochrane review done in 2003 by Gibbs et al [19], cryotherapy was reported to be the most commonly used therapy for warts. However, the treatment outcome with cryotherapy as compared to topical salicylic acid was not significant, and a higher morbidity was reported for cryotherapy. For bleomycin, 5FU, and intralesional interferon and photodynamic therapy, data was limited. This clinical trial challenges the use of cryotherapy in the treatment of warts. Patients treated with cryotherapy face a higher cost, as stated by Stamuli et al [20]. Ablative and non-ablative lasers have been used in order to decrease the duration of the treatment course and recurrence of warts. The first laser that was used for warts was CO₂ laser [21], followed by pulsed dye laser and Er: YAG laser [22,23]. CO₂ laser has been used for recalcitrant warts with remission rates ranging from 50% to 100%, in only a few studies [24,25].

To our knowledge, no clinical trial in the English literature has compared cryotherapy with CO₂ laser in the treatment of plantar warts [26]; hence, this study was designed to compare the efficacy of these 2 modalities in the treatment of plantar warts.

Patients and Methods

This study was designed as a randomized controlled clinical trial (RCT), and its protocol was approved by the ethics committee of Shiraz University of Medical Sciences with reference number IR.SUMS.MED.REC.1396.08. The RCT was registered on the Iranian Registry of Clinical Trials website with code number 24482, and the study was done at the Department of Dermatology at Faghihi Hospital, Shiraz, Iran.

Inclusion criteria were: men and women aged 18 years or older with clinically diagnosed plantar warts who had not received any treatment in the previous 3 months prior to referral. Pregnant and lactating woman and those with a history of keloid formation were excluded from the trial.

Sixty patients who fulfilled the above criteria were enrolled in the study after signing the written informed consent. The patients were randomly allocated into the cryotherapy or CO₂ laser groups using computer-generated block randomization. During the first visit, complete medical history was taken and the number of lesions (on the plantar area and any other body site) as well as evidence of any concomitant systemic disease were documented, and photography was taken on each visit.

The cryotherapy group received treatment weekly until clinical resolution of the lesions. In each session, 2 freeze-and-thaw cycles of a 15-second duration was performed. Patients were visited weekly for evaluation of response and any possible complications.

The CO₂ laser group received therapy weekly until clinical resolution of the lesions. CO₂ laser (SmartXide DOT; DEKA, Italy) was used as the modality of treatment for the plantar warts. Each session consisted of 1 to 2 passes of CO₂ laser on continuous mode with a power of 15-25 watts according to the depth of the lesion, estimated on physical examination. Each pass had 2 components. First, the focused mode with a spot size of 1 mm, and second, the unfocused mode that was induced with a 5 cm distance between the laser probe and the lesion(s).

Mupirocin ointment was prescribed for all the patients 2 times a day for 3 days.

Resolution of the lesions was considered as clearance of the lesion(s) on inspection and palpation and was documented by photography. Persistence of the lesion(s) after 12 weeks of treatment with cryotherapy or 3 sessions of CO₂ laser was considered as failure.

Three months after resolution of the lesions, the patients were re-evaluated for possible recurrence.

Results

Sixty patients were enrolled in the trial. Twenty-seven in the cryotherapy group and 29 in the CO₂ laser group completed

TABLE 1. Characteristics of the patients

Parameter	Cryotherapy	CO ₂ laser
Age (years), Median	25 (range=18-53)	27 (range= 18-75)
Sex, Number (Percentage)	Male: 15 (56%) Female: 12 (44%)	Male: 10 (34%) Female: 19 (66%)
Number of warts in each group, Median	1 (range= 1-20)	5 (range= 1-20)

the trial. Three patients in the cryotherapy group were lost to follow-up, and a patient in the laser group was withdrawn from the trial and had to be referred for skin biopsy because of a suspicious lesion on the plantar surface of his opposite foot that appeared to be melanoma.

Demographic characteristics of the patients are summarized in Table 1. The 2 groups were matched according to sex and age. Five patients in the laser group and 2 in the cryotherapy group had coexistent warts on their hands. Two patients in the laser group and 3 in the cryotherapy group had diabetes mellitus type 2, and a patient in the laser group had hypothyroidism.

The CO₂ laser power used was 21±4 watts, both for focused and unfocused mode. The median number of sessions needed for complete treatment with CO₂ laser was 1 (range= 1-2) while in the cryotherapy group, it was 3 (range=1-12). The number of required sessions for the 2 groups was compared by Mann-Whitney test, and the difference was statistically significant (P-values ≤ 0.001) (Figures 1-3). One patient

in the laser group and one in the cryotherapy group failed treatment (Figure 4).

After 3 months of treatment completion, 3 patients in the laser group and 8 patients in the cryotherapy group developed a recurrence. In other words, remission rate was 89.7% in the laser group and 70.4% in the cryotherapy group. The difference was evaluated by chi-square test and was not statistically significant (p-value=0.069).

No clinical infection was detected in any of the patients. Two episodes of moderate bleeding occurred during laser therapy, which was managed by coagulation with the CO₂ laser unfocused mode.

Discussion

There are several treatment options for treating plantar warts ranging from office-based therapy (such as cryotherapy) to treatments applied by the patient (such as salicylic acid) [27]. Various lasers have been used for this purpose with different



Figure 1. Phases of treatment in one patient who underwent CO₂ laser therapy (a) before laser therapy; (b) immediately after therapy; (c) 1 week after therapy. [Copyright: ©2018 Hemmatian Boroujeni et al.]



Figure 2. Phases of treatment in another patient in the CO₂ laser group (a) before laser therapy; (b) immediately after therapy; (c) 3 months after therapy). [Copyright: ©2018 Hemmatian Boroujeni et al.]



Figure 3. Phases of treatment in a patient who underwent cryotherapy (a) before cryotherapy; (b) cryotherapy after 6 sessions; (c) cryotherapy after 11 sessions. [Copyright: ©2018 Hemmatian Boroujeni et al.]



Figure 4. Phases of treatment in another patient in the cryotherapy group (a) before cryotherapy; (b) cryotherapy after 6 sessions; (c) cryotherapy after 12 sessions; failure of treatment. [Copyright: ©2018 Hemmatian Boroujeni et al.]

success rates. In this study, we compared CO₂ laser and cryotherapy in order to determine their efficacy. Our remission rate in the CO₂ laser group was 89%. This is very similar to the result that Mitsuishi found in his study [28]. Mitsuishi et al reported the only prospective non-blinded, non-randomized study on plantar warts to date. They included 31 patients with a remission rate of 89%, after 3-12 months of follow-up. However, in other studies using lasers for plantar warts, the results were not as promising. In a retrospective survey by Landsman et al, in 166 patients with plantar warts treated by CO₂ laser, the remission rate was 75%, after a 3-72 month follow-up [29]. In another retrospective survey by Sloan et al, in 92 patients with recalcitrant warts, remission rate was 64% at 12-month follow-up [30]. The difference in the remission rate between our study and the other studies cited above can be attributed to the different duration of follow-ups used and inclusion of recalcitrant cases. When recalcitrant cases are included in a study, the remission rate is usually lower.

In the other arm of our study we used cryotherapy. There are several studies on the efficacy of cryotherapy and the adverse effects attributed to this method, although there is limited data comparing this method with other methods in the treatment of plantar warts [31]. Liquid nitrogen with a temperature of -196° C was used for cryotherapy and was applied with spray gun, probe, or cotton swab. For choosing the best interval for applying cryotherapy, we did not find any difference between 1-week, 2-week, or 3-week intervals. It seems that the number of sessions determine efficacy of

treatment, not the time interval between each session [32]. In some studies, 2 cycles of freeze-and-thaw had a better result than only 1 cycle in plantar warts, while this was not the case for warts on other parts of the body such as the hands [33]. We chose the 2-cycle freeze-and-thaw method using the spray gun with an interval of 1 week between each session. Cryotherapy can destroy the bulk of the wart and induce inflammation and immune response but cannot kill HPVs. Liquid nitrogen might become contaminated if direct contact devices are used; not so with spray guns [34]. The remission rate with this method in our study was 70%. In a study by Ahmed et al, the authors noted a 44% and 47% cure rate with cryotherapy using the spray gun and cotton swab, respectively [35]. This difference between our results and the aforementioned article may be due to the difference in disease chronicity and follow up.

To our knowledge, there is no study comparing CO₂ laser with cryotherapy in the English literature, although comparisons of other lasers have been undertaken. In a study by Akhyani et al, no superiority in remission rate for PDL laser was found when compared with cryotherapy. However, patients in the PDL group achieved remission sooner in the course of treatment [36]. In our study, we did not find a statistically significant difference in the recurrence rate between our 2 groups, and the P-value was 0.069.

One main concern in this study was the issue of possible transmission of warts with CO₂ laser plume to the dermatologist or patient and contamination of the laser device that could be a cause of transmission of the virus to other

patients who later undergo aesthetic procedures using the same device. It seems that the risk of viral transmission from CO₂ laser plume after procedures on non-genital warts is not higher than the general population [37]. In our study, we did not see any clinically apparent warts in our cosmetic patients that used the same device and no warts were observed in the dermatologist performing the laser treatment in our cases.

The absence of any clinical infection in both groups can be attributed to the topical application of mupirocin ointment. Therefore, administering a topical ointment might help to reduce post-procedural infections.

Conclusion

Overall, CO₂ laser can be an effective and timesaving treatment modality for plantar warts. However, studies with larger sample sizes and longer follow-up periods are advised in order to confirm the results of this study.

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