Evaluation of combined treatment with Er:YAG laser and long-pulsed Nd:YAG laser for the treatment of recalcitrant warts: a prospective randomized controlled trial

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ABSTRACT

Background: Viral warts are common infectious skin disease induced by human papillomavirus (HPV). Lasers have been used for warts treatment in recent years with variable success rates.

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Objective: This study aimed to prospectively evaluate combined treatment with Er:YAG laser and long-pulsed Nd:YAG laser compared to Er:YAG laser for the treatment of recalcitrant warts after one session.

Materials and methods: This study included 240 lesions from 24 patients. All the lesions were diagnosed clinically as recalcitrant warts after failure of topical treatment and Cryotherapy. 120 lesions underwent a combined therapy of Er:YAG and long-pulsed (LP) Nd:YAG lasers, and the remaining 120 lesions underwent Er:YAG laser therapy only. The clearance rate was evaluated 5 weeks after and classified by three-graded evaluation: complete response, partial response, and poor response.

Results: The clearance rate in the combined Er:YAG + LP Nd:YAG lasers group was, statistically significant, higher than that of the Er:YAG laser group (p=0.008). The complete response rate was 48% (58 of 120 warts) for the Er:YAG +LP Nd:YAG lasers group and only 29% (35 of 120 warts) for the Er:YAG laser group.

Conclusion: The combination of Er:YAG and long-pulsed Nd:YAG lasers is more effective than Er:YAG laser alone in treating recalcitrant warts after single session.

KEYWORDS: viral warts; treatment; Er:YAG laser; long-pulsed Nd:YAG laser; recalcitrant

Trial registration: ClinicalTrials.gov Identifier: NCT05768893

INTRODUCTION

Viral warts are benign epithelial proliferations, characteristically 1-20 mm in diameter[1], that develop secondary to infection of keratinocytes by human papilloma virus (HPV)[2]. HPV comprises a large group of approximately 120 genotypes that infect the epithelia of the skin or mucosa[3]. Warts are a common dermatological complaint, with an estimated incidence of 5%-20% in children and adults, with peak incidence reported during teenage years[4,5]. Patients often express a significant reduction in quality of life due to this cosmetic nuisance, as well as functional problems and physical discomfort when they occur on the palms of the hands and soles of the feet[6]. Therefore, cutaneous warts are one of the most common pathologies treated by the clinical dermatologist[7].

Although warts may eventually spontaneously disappear once the immune system finds a way to eradicate the virus, the time taken for this to occur varies and can range from months to years[8]. Most of the methods that are used today have their drawbacks and side effects. Topical management requires the application of drugs for long durations and treatment success is, therefore, highly dependent on patient compliance[9,10]. Surgical methods have proven somewhat effective but have their disadvantages of pain and long recovery periods and may offer incomplete and superficial results leading to high recurrence rates [9].

Lasers are new methods of energy-based devices for treating warts[1]. Er:YAG laser (like CO_2 laser) is an ablative laser emitting at a wavelength of 2940 nm and highly absorbed by water. It is considered a safe treatment for viral warts, However, in many patients, mainly those with plantar warts, a significant rate of relapse may occur, requiring additional therapy[11]. Recently, the long-pulsed (LP) 1064 nm Nd:YAG laser has attracted attention in the treatment of palmoplantar warts[12]. The mechanism of the LP Nd:YAG laser is different from the Er:YAG laser. It targets the dermal blood vessels that supply infected cells and destroy them[13] via photothermolysis mechanism. Another effect that the Nd:YAG laser has on the HPV infected cells is an apoptosis effect due to the hyperthermia, hence direct contact of the Nd:YAG laser beam leads to cell death [2]. However, the limitations of this method are that the treatment usually requires several sessions [12,14], and the clearance rate after one session ranges between 14-22% [15,16].

This prospective study evaluates the treatment efficacy of an Er:YAG laser alone compared to a combination of Er:YAG followed by LP Nd:YAG after one session of recalcitrant warts. We hypothesize that combining the two mechanisms of ablating the wart and coagulating the blood supply may lead to a higher wart clearance rate after a sole treatment session.

MATERIALS AND METHODS

Patients

This randomized controlled trial included 240 lesions from 24 patients diagnosed with recalcitrant warts, that were treated from May 2022 to September 2022 after two or more failed treatment lines with Cryotherapy and topical treatments. Patients included 12 males and 12 females, aged 12-72.
Main exclusion criteria included the use of topical treatment for wart lesions in the past month; methods of physical destruction of the lesions in the past month such as surgical excision electrodesiccation, cryosurgery or laser; and anticoagulant drugs administration; patients with single wart lesion; pregnant and breast-feeding patients, and children below the age of 8.
The study was conducted following the approval of the local ethical committee (approval 0141-21-RMB) and was registered at clinicaltrials.gov (MOH_2022-04-12_010737). all patients provided signed informed consent prior to treatment.

Randomization

Each wart of the 240 was given a number and photographed. In cases when the patient had an uneven number of warts, one wart was excluded randomly and was treated it with Erb:YAG laser as a part of the standard management in our clinic regardless of the study. Then, the warts of each patient were randomly divided into two groups using computerized randomization and assigned to group 1 or group 2. Each group consisted of 120 warts. Two copies of the photographs were made; one marked copy that included the wart's number and its assigned group (Figure 1A), and an unmarked copy that included only the wart's number (Figure 1B).

Laser treatment

Treatments were conducted using the *Harmony XL Pro* (Alma Lasers, Caesarea, Israel) platform, which utilizes a 2940 nm Er:YAG laser (*iPixel Pro 2940 module*) and a LP 1064 nm Nd:YAG laser (*Cooled LP Pro* module). The Er:YAG laser parameters used were spot size of 1-4 mm, 2 Hz, 5.5–11.1 J/cm^2 (700-1400mJ/pulse), the treatment endpoint was fulgurating the verruca and 1mm from the surrounding normal skin. The LP Nd:YAG laser parameters used were spot size of 2 or 6mm, a pulse

duration of 15-45 msec, and fluence of 70-350 J/cm^2, Each wart that was treated with Nd:YAG laser received the pulse when the aim was in the center of the wart lesion, covering the whole verruca and at least 1 mm from the surrounding normal skin. Eutectic mixture of local anesthetics (EMLA) was applied, and intralesional injection of lidocaine was injected in each wart lesion prior to the procedure to avoid pain or discomfort during the procedure. The marked photograph copies were used during the procedure to help applying the appropriate laser to the specific lesion according to its respective group. All 240 lesions were treated by the same physician.

Group 1: Combined Er:YAG laser and long-pulsed Nd:YAG laser group

This group included 120 wart lesions, treated with Er:YAG laser followed by LP Nd:YAG laser after 1-2 minutes. Cryo 6 (Zimmer Medizin Systems) was used to cool the lesions before, during and after applying the Nd:YAG laser.

Group 2: Er:YAG laser group.

This group included 120 wart lesions, treated with Er:YAG laser only.

Assessment

Follow up visit to detect warts clearance rate was done 5 weeks after the procedure. At this visit, each wart was photographed again. For each wart, the picture taken prior to the procedure (with no group indication), and the picture taken at the follow-up visit were assessed by a blinded evaluator, who scored them according to their clearance using a three-grade evaluation as follows: Complete response (100% clearance), Partial response (50-99% clearance), and Poor response (less than 50% clearance).

The primary assessor was given two photographs of each lesion, the first is the unmarked photograph copy (doesn't indicate to what group each lesion belongs) that was taken prior to the procedure, the second is the photograph that was taken in the follow up 5 weeks later. Assessments based on the two photographs were conducted by the primary assessor.

The efficacy of the treatment was classified by a three-grade evaluation according to the clearance at the end of therapy.

Statistical analysis

The data were analyzed using R version 4.2.1. The differences in wart outcomes (success/relapse) between the two treatment groups were analyzed using Pearson's chi-squared test. Odds and Risk ratios were calculated from the contingency table of treatment type and success. Statistical significance was defined by a p-value of <0.05.

RESULTS

This study included 240 lesions from 24 patients (12 males, 12 females) aged 12 to 72 years (mean 34.67 years). The number of recalcitrant warts per patient ranged between 2 and 48, the median was 6 and the mean was 10. Patients demographic characteristics are presented in Table 1. On the foot area there were 120 lesions localized on plantar side and 7 lesions localized on the dorsal side. On the hand area there were 26, 44, 19, and 24 on the palms, dorsal side, periungual zone, and arms, respectively. Table 2. shows the basic characteristics of the lesions in the two groups, which were similar.

The clearance rate in the Er:YAG + LP Nd:YAG lasers group was statistically significant higher than that in the Er:YAG laser group (p=0.008). Table 3 presents a cross-tabulation of treatment type and wart outcome. The partial response outcome rate was higher in the Er:YAG laser group 37% (44 out of 120) than in the Er:YAG + LP Nd:YAG lasers group 29% (35 out of 120). The complete response rate was 48% (58 of 120 warts) for the Er:YAG + LP Nd:YAG lasers group and only 29% (35 of 120 warts) for the Er:YAG laser group.

The associations between location of the wart, age of the patient, race, sex, LP Nd:YAG parameters, and success of the treatment were tested using a chi-square test of independence. No association tested was statistically significant.

Adverse effects of both treatment groups are listed in Table 4. Crusts were developed in every lesion in both groups. The difference between both groups regarding pain and other side-effects was not significant (p>.05), except blisters, which were more common among the Er:YAG + LP Nd:YAG lasers group, with a p-value of 0.029.

The photomicrographic documentations are shown in Figures 2, 3 & 4.

DISCUSSION

Viral warts are common benign epithelial proliferations, that are difficult to treat. Topical treatments require the application of drugs for long durations and treatment success is highly dependent on patient compliance[9,10]. The physical destruction treatment methods include surgical excision, electrodesiccation, cryosurgery have variable success rates and may offer incomplete and superficial results leading to high recurrence rates [9].

Laser therapy has recently been used more often and is being studied in recent years. Ablative lasers like Er:YAG and CO_2 lasers, and non-ablative lasers like long-pulsed Nd:YAG laser and PDL laser, are among the laser modalities that have been used to treat recalcitrant viral warts. The CO_2 laser was the first laser used for the treatment of recalcitrant warts [17], it emits high-energy laser light, which results in removing the bulk of the lesion, coagulation of blood vessels and necrosis of the wart [18]. In a review of previous studies, it was found that the success rate of CO_2 lasers against recalcitrant warts ranged between 46.2% and 100% [2], but scarring and pain may occur in about 60% of cases [19–22]. The use of the CO_2 laser was later followed by the Er:YAG laser. The Er:YAG laser beam is absorbed by water, its small penetration depth of few micrometers combined with the high power of the short light pulse enables the Er:YAG laser to ablate and cut soft tissue with surgical precision, similar to that of conventional scalpels [23]. Wollina et al. [11] reported a clearance rate of 72.5% in 69 patients with warts after a single treatment session with Er:YAG laser. Higher clearance rate and more precise ablation of the targeted lesions with fewer damage to the adjacent uninfected epidermal cells leads to fewer scarring and pigmentary changes 27.

Among the non-ablative lasers is the pulse dye laser (PDL) and the long-pulsed (LP) Nd:YAG laser. The mechanism of PDL laser is unclear but it is a result of specific destruction of superficial dilated capillaries in warts by the selective photothermolysis of oxyhemoglobin within the microvasculature. PDL destroys large, dilated blood vessels within the dermal papillae [25]. Complete response rate varies according to different studies, and ranges between 0% and 100% [2].

The mechanism of action of the LP Nd:YAG laser targets the dermal blood vessels that supply infected cells and destroy them [13]. This leads to coagulation (photothermal effect) or blasting (photomechanical effect) of the target tissue depending on the pulse duration and energy density [10]. HPV virus has shown a better response to thermal therapy than cryotherapy, especially at 39–44°C.

So, the laser-induced hyperthermia may induce the clearance of HPV affected keratinocytes and the surrounding ones as well, via apoptosis and immune activation. [7] Lasers may also provoke migrational maturation of epidermal Langerhans cells, leading to the immune response. These Langerhans cells can regenerate every two weeks with epidermal turnover every 52–75 days [26]. That is why laser treatments can be repeated every two weeks with the endpoint after 3 months for an optimal response. Although the exact mechanism of LP Nd:YAG laser in cutaneous warts is not known so far, it is thought that this laser can emit infrared light with a spectrum of 1064 nm which delivers light energy to hyperkeratotic and thickened epidermis related to warts [15]. In addition, it targets dilated blood vessels, which warm and burst rapidly, with purpura formation and subsequence wart destruction. The histopathological findings of this purpura confirm the dermo-epidermal junction separation, epidermal necrosis, and RBC extravasation [10]. However, the limitations of this method are that the treatment usually requires several sessions [12,14], and the clearance rate after one session ranges between 14-22% [15,16].

Being absorbed by the water in the cells, the Er:YAG laser beam causes an ablation to the whole layer of cells that was targeted by the laser. Repeated pulses of Er:YAG laser remove layer after layer of the wart until complete eradication and revealing its base [23]. We hypothesize that hitting the wart base with Nd:YAG laser immediately after revealing it with Er:YAG laser (when it's base blood vessels is the most fragile, prone and sometimes already bleeding) will have the best chances of achieving the most direct contact and coagulation effect of the wart's supplying vessels. It may also help in apoptosing any remained infected cells and elevating the chances of complete eradication of the wart.

To date, numerous studies have reported the use of Er:YAG for the treatment of warts. However, to the best of our knowledge, there is no study reporting the use of Er:YAG in combination with long-pulsed Nd:YAG for the treatment of recalcitrant warts. To fill the gap in the literature, this study combined Er:YAG laser with long-pulsed Nd:YAG laser. We hypothesized that the combined therapy of the two lasers may lead to a higher wart clearance rate after a sole treatment session. The result of the trial supported our hypothesis, in the combined laser group the response rate was 78% (partial and complete) and only 22% had poor response. On the other hand, the response rate was 59% for the Er:YAG laser group and 34% had poor response. The combination therapy in our study yielded better clearance results than the Er:YAG laser alone[11] or LP Nd:YAG laser alone according to the literature[15,16], confirming our hypothesis that adding long-pulsed Nd:YAG laser treatment after Er:YAG laser in the same treatment session yields a synergistic effect.

Our explanation to this synergistic effect is that being absorbed by the water in the cells, the Er:YAG laser beam causes an ablation to the whole layer of cells that was targeted by the laser.

Repeated pulses of Er:YAG laser remove layer after layer of the wart until complete eradication and revealing its base [23]. We hypothesize that hitting the wart base with Nd:YAG laser immediately after revealing it with Er:YAG laser (when it's base blood vessels is the most fragile, prone and sometimes already bleeding) will have the best chances of achieving the most direct contact and coagulation effect of the wart's supplying vessels. It may also help in apoptosing any remained infected cells and elevating the chances of complete eradication of the wart.

No association was found between the location of the wart, age of the patient, race, sex, LP Nd:YAG parameters, and success of the treatment. In addition, the difference between both groups in terms of side-effects was not significant, except for blisters that were more common in the Er:YAG + LP Nd:YAG lasers group, which were transient and didn't leave any more sea quale. The one treatment session and the short period of follow up (5 weeks) may be considered a study limitations.

CONCLUSION

The combination of Er:YAG laser and long-pulsed Nd:YAG laser in the same treatment session for the removal of recalcitrant viral warts leads to higher cure rate than Er:YAG alone rate after 5 weeks of a single treatment session. We, therefore, highly recommend using this combined treatment when these two modalities are available.

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Figure Legends

Figure 1. Pre-treatment photographs. (A) a marked copy that includes the wart's number and to which group it belongs. (B) unmarked copy that includes only the wart's number.

Figure 2. (A) Wart on finger before, and after (B) Er:YAG + LP Nd:YAG lasers therapy with complete response after a single session.

Figure 3. (A) Wart on finger before, and after (B) Er:YAG laser therapy with partial response after a single session.

Figure 4. (A) Wart on palm before and after (B) Er:YAG laser therapy with poor response after a single session.

Table 1.	Basic characteristics of the patients
Characteristic	N = 24[1]
Sex	
Male	12.00 (50 %)
Female	12.00 (50 %)
Race	
Jewish	13.00 (54 %)
Arab	11.00 (46 %)
Number of warts	10.00(9.90) [2.00-48.00]
Age	34.67(12.79) [12.00-72.00]

[1]n (%); Mean (SD)[Minimum-Maximum]

Table 2.	Location of the lesions		
Characteristic	Er:YAG + ND:YAG, N = 120[1]	Er:YAG, N = 120[1]	p-value[2]
Wart location			>0.9
Arm	12 (10%)	12 (10%)	
Dorsal hand	21 (18%)	23 (19%)	
Palmar	12 (10%)	14 (12%)	
Periungual	10 (8.3%)	9 (7.5%)	
Dorsal foot	5 (4.2%)	2 (1.7%)	
Plantar	60 (50%)	60 (50%)	

[1]Median (IQR); n (%)

[2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

Table 3.	Cross-tabulation of treatment type and wart outcome			
	Poor response	Partial response	Complete response	p-value[1]
Treatment				0.008
Er:YAG+LP Nd:YAG	27 (22%)	35 (29%)	58 (48%)	
Er:YAG	41 (34%)	44 (37%)	35 (29%)	

[1]Pearson's Chi-squared test

Table 4. Adverse effects of both treatment groups.

Adverse effect	Er:YAG	Er:YAG + LP Nd:YAG
Blisters	0	6
Crusts	120	120
Scars	0	0
Hyperpigmentation	6	3
Hypopigmentation	4	2
Hypertrophic scar	4	4