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Treatment of condyloma acuminatum using the combination of laser ablation and ALA-PDT

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ABSTRACT

Background: Human papilloma virus (HPV) infection and condyloma acuminatum (CA) in the genital area often exist in extensive and multi-point fashion. Laser ablation combined with topical photodynamic therapy (PDT) is a feasible approach for genital CA but its effectiveness and limitations need to be evaluated.
Methods: This single-arm prospective study consisted of 100 newly diagnosed CA cases of both sexes. All patients underwent laser ablation and then three times aminolaevulinic acid-based photodynamic therapy (ALA-PDT). The outcomes were evaluated and analyzed 3 months after the treatment.
Results: A total of 98 patients completed the study. Except for 6 patients (4 males and 2 females) showed some residual lesions other 92 patients (93.8%) showed complete cure. However, there were 18 patients (10 males and 8 females) showed new lesions near the treated areas. Although the HPV types of 18 patients before and after treatment were not completely consistent, 94.4% percent of patients (17/18) had the same HPV type as the primary lesion, which suggested that these late-onset CA might have latent infection or subclinical infection in the early stage of the disease but the length of the incubation period was longer.
Conclusion: Combination approach is effective in treating genital CA and preventing CA recurrence. But its limitations need to be recognized as the late-onset CA might occur near the treated area. The treatment plan needs to be optimized for multiple genital CA lesions.

1. Introduction

Papilloma viridae is an ancient and ubiquitous virus. More than 200 species of human papilloma virus (HPV) are identified and divided into 16 genera. The differentiated human squamous epithelium is susceptible to Papilloma viridae and almost anybody's skin can be infected [1]. Risk factors include sex, public bathrooms and immune suppression [2].

The traditional treatment methods of genital warts or condyloma acuminatum (CA) include: topical medications (trichloroacetic acid and imiquimod), and surgical therapy (cryotherapy, carbon dioxide (CO_2) laser, surgical excision, foreskin removal) [3]. However, the recurrence rate of CA remains very high [4]. Each method has some limitations and no single therapy can achieve complete cure and prevent relapse [5]. HPV latent and subclinical infections continue to exist, which is a major factor of recurrence in CA [6,7]. There is a need to develop more effective approach to treat CA.

Ross et al. demonstrated in 1997 that CA could selectively accumulate protoporphyrin IX (PpIX) after topical application of prodrug 5-aminolaevulinic acid (ALA) [8]. This implicates a potential of ALA/PpIX-based photodynamic therapy (ALA-PDT) for the treatment of CA. Topical ALA-PDT has been approved for the treatment urethral CA in China in 2007. As recommended in the Chinese Guideline of condyloma acuminata treatment (2014), ALA-PDT should be used in conjunction with laser ablation [9]. In general, ALA-PDT is applied after the removal of visible warty lesions using laser [10].

In this study, the combination of CO_2 laser and ALA-PDT was used to treat CA of adult patients of both sexes. Treatment outcomes were

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evaluated 3-month after the treatment. Our data suggest that the combination of laser ablation and ALA-PDT is feasible and effective in the treatment of CA.

2. Materials and methods

2.1. Study design

This was a randomized single-arm prospective single-hospital study of newly diagnose CA of both sexes. The primary goal of the study was to evaluate the clinical outcomes of combining laser ablation and ALA-PDT treatment.

2.2. Patient collection

A total of 100 consecutive patients from the First Affiliated Hospital of Harbin Medical University participated in this study between January 2014 and January 2016. All patients were diagnosed with CA with the confirmation from pathological biopsy or typical clinical manifestations. All patients were newly diagnosed cases without receiving any treatment. Before treatment, lesion counting and HPV typing were performed. Inclusion criteria: warts located in the perianal area, distal urethra and external genitalia. The maximal diameter of a single lesion was < 3 cm with a thickness < 3 mm. Exclusion criteria: those suffered from other sexually transmitted diseases, cervicitis, autoimmune disease or other serious chronic systemic diseases, used corticosteroids and immunosuppressive agents within the past three months, used antiviral drugs within the past two weeks, pregnancy and lactation, CA in the anal, vaginal and cervical area. All patients signed the informed consent. This research program was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University.

2.3. Equipments and reagents

CO_2 laser was obtained from Jilin KeYing Laser Technology Co., Ltd. (Jilin, China). Diode laser of 633 ± 10 nm was obtained from Wuhan Yage Optical Technology Co. (Wuhan, China). ALA solution of 20% was freshly prepared by dissolving ALA powder (Fudan Zhangjiang Bio-Pharmaceutical Co., Ltd., Shanghai, China) in saline.

2.4. Treatment protocol

The first step was to remove the visible CA lesions by the CO_2 laser. Care was taken to look for and remove all visible warts. The second step, i.e. ALA-PDT, was carried out immediately after the laser treatment. Pending on the wart size and location, cotton balls/cotton sheets/gauze soaked with ALA solution was used to cover the lesion area (i.e. the site already treated by the laser) plus 1-cm margin. The ALA applied surface was covered with clean film and occulated for 3 h. Light irradiation of 100–150 J/cm^2 was carried out at the power density of 60–100 mW/cm^2 [10]. The light spot should cover the lesion and margin. PDT was performed once a week for a total of three times.

2.5. Follow-up

All patients were followed up at 3 months after the treatment. Cure was defined as no any remaining visible wart on the perianal and genital area and HPV typing test results were negative at least once.

2.6. Statistical analysis

SPSS software (version 17.0) was used for statistical analysis. *t*-test was used for patient demographic data assay. The cure rate was presented as a percentage. $P < 0.05$ was considered statistically significant.

Table 1
Patient demographic data.

Patient No.	98
Male	63 (64%)
Female	35 (36%)
Mean age	34.4
(range)	(19 – 50)
Course of disease	28 days to 1 year
Average No. of warts	9.28
Male	8.59 (2 - 21)
Female	9.97 (2 - 22)
HPV typing	
High risk	37 cases
Low risk	24 cases
Mixed	37 cases

3. Results

3.1. Patient demographic data

Amongst 100 selected patients 98 of them completed the study. Their demographic data are listed in Table 1. Lesions mainly located in the urethra orifice, underneath pubic hair and around the anus in male patients and in both the inner and outer labia and around the anus in female patients.

3.2. Clinical outcomes

Laser ablation and ALA-PDT were well tolerated. Mild burning and/or pain could occur in the illuminated area. At day one and day two after treatment, mild swelling might occur at the treated area, which was allowed to relieve by itself without intervention. There were 2 cases of wound infection and cured by topical anti-inflammatory cream.

After three consecutive ALA-PDT sessions at one week intervals, all patients were followed up at 3 months after the last treatment. Two male patients lost during follow-up. Based on lesion counting and HPV typing, a complete cure rate of 93.8% (92/98), i.e. elimination of warts and HPV typing test results are negative at least once, was achieved after three-course of ALA-PDT. Figs. 1 and 2 show the complete cure of warty lesions in two male patients.

For those 6 patients (4 males and 2 females), residual lesions were visible at the treated areas and HPV typing was positive (Table 2).

During follow-up, there were total of 18 patients (10 males and 8 females) showed new lesions in un-treated areas (Table 2). All lesions were confirmed HPV positive. Although HPV typing was inconsistent to that obtained at the original lesion site, except one male patient showed totally different types (type 11 and 35 in original site vs type 6 and 52 in new site) all other 17 patients with newly developed CA had at least one same type of HPV as before.

3.3. Discussion

HPV infection was considered as STDs, but it is now known that the sexual penetration is not necessary for HPV infection. Skin-to-skin and mucosa-to-mucosa contact can be a potential transmit route for HPV, which presents a high risk of recurrence tropism for those tissues [11]. Since sexual contact or indirect contact is often associated with HPV infection the locations of CA are often multi-point. In which it may be located around the wart or distant sites from the visible wart [12,13]. Furthermore, it can also become latent and subclinical infections which are often untreated and therefore become the source of recurrence over time.

In the treatment of CA, warty lesion removal is an important step. The recurrence of CA and HPV infection are more frequent in patients with a larger number of CA rashes. Several chemical and physical methods can be chosen. Among them, CO_2 laser is an effective conventional means for this purpose. It uses the pooled energy of the

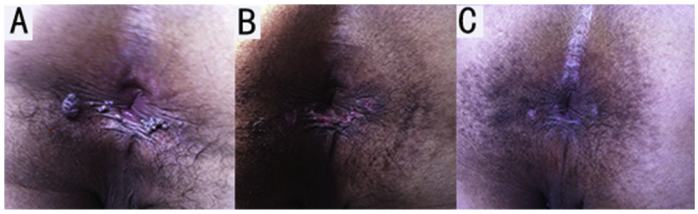

Fig. 1. A male 45-year-old patient with CA around the anus and a disease course of two months. A comparison of the pre- and post-treatment of the genital warts around the anus is shown. (A: Before treatment B: After 2 weeks of treatment C: After 3 months of treatment).

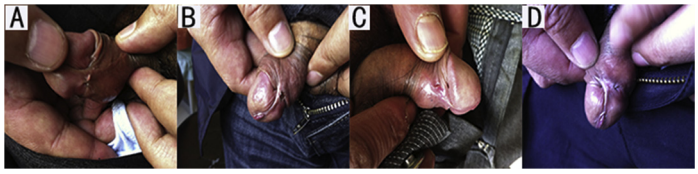

Fig. 2. A male 33-year-old patient with CA on the penis and a disease course of 20 days. A comparison of the pre- and post-treatment of the genital warts at the penis is shown. (A: Before treatment B: 1 week after treatment C: After 2 weeks of treatment D: After 3 months of treatment).

Table 2
Characteristics of visible lesions at three months after treatment.

	Remaining lesions	New lesions
No. of Patients	6	18
Male	4	10
Female	2	8
Average No. of warts		
Male	7.21 (2 - 20)	9.51 (2 - 21)
Female	9.09 (7 - 22)	8.97 (4 - 21)
HPV typing		
High risk	1 cases	9 cases
Low risk	1 cases	4 cases
Mixed	4 cases	5 cases

infrared beam to quickly and accurately vaporize warty lesion. But it neither completely cure CA lesions nor necessarily eliminate latent and subclinical infections around the visible lesions. Relapse rate is high after laser treatment [14]. Moreover, in laser treatment the smoke might contain active HPV virus and therefore poses a risk of relapse of local CA [15]. There is a need to develop the treatment that can cure CA and prevent its relapse.

In recent years, ALA-PDT has been used for the treatment of CA and HPV infection in addition to non-melanoma skin cancers [16,17]. In ALA-PDT the precursor ALA is converted to potent photosensitizer protoporphyrin IX in HPV infected cells [18]. Under the light irradiation of certain wavelengths (e.g. 630 nm), the interaction of protoporphyrin IX and light can generate singlet oxygen that can cause cell damage and cell death [19,20]. Clinical data suggest that ALA-PDT is effective in the treatment of latent and subclinical infection of CA, hence prevent the recurrence of CA [21,22]. Studies showed that indeed in comparison to laser alone ALA-PDT had benefit of the reduction of the recurrence rate of CA. A recent meta-analysis of Chinese data showed that the recurrence rate of laser alone was 42.67% (451/1,057) and that of CO_2 and ALA-PDT combination was 10.29% (102/991), clearly indicating that the combination therapy was significantly better than laser alone [23]. Another meta-analysis of 20 randomized controlled trials of 1903 patients (ALA-PDT = 1106, no ALA-PDT = 797) also showed that ALA-PDT significantly reduced the recurrence rate within 12 weeks after treatment and ALA-PDT should be considered as a viable treatment for CA [10].

In our study, although the high cure rate (93.8%) without relapse was achieved for original visible lesions after laser ablation and repeated sessions of ALA-PDT, which is higher than that reported by Szeimies et al. (50% for external genital CA achieved by the combination of laser and PDT) [24], close to that reported by Chen et al. (92.%) [25]. Huang et al. reported a recurrence rate of 7.1% [26].

However, there was 18.3% (18/98) patients showed the new CA at new area during the time of follow-up (see Table 2). Based on the HPV typing which indicated that patients with newly developed wart had at least one same type of HPV as the original lesion, it suggested that these new lesions might be from latent and subclinical infections that had longer latency in this group of patients. Some concerns are raised from this finding. On one hand, if lack the doctors careful registering the locations of treated lesions, such new lesions might be mistaken as the relapse. Meanwhile, the patients can be frustrated and unsatisfactory on the occurrence of new lesions. On the other hand, fail to treat such latent and subclinical infections can indeed lead to treatment failure. Need to get the attention of the doctor. This manuscript objectively evaluates the efficacy and limitations of laser combined with photodynamics. Thus, to overcome this problem the entire vulva and perianal area should be treated. However, due to the concerns on the high price of PDT treatment and patient compliance, it is not feasible to apply ALA to the large area. Other possible solutions, such as the local and systemic use of antivirus drug and remedy to enhance antivirus immune responses, might be considered in conjunction with ALA-PDT [27,28].

4. Conclusion

The combination of laser ablation and ALA-PDT is feasible and effective in the treatment of CA. Although a high cure rate can be obtained, it should be recognized that certain longer latency infections around the treated area might develop into warty lesions and their treatment warrants further improvement.

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