Decrease Recurrence Rate of Condylomata Acuminata by Photodynamic Therapy Combined with CO₂ Laser in Mainland China: A Meta-Analysis

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Key Words

Photodynamic therapy · CO₂ laser · Condylomata acuminata · Recurrence

Abstract

Background: Condylomata acuminata (CA) are caused by human papillomavirus. Most conventional therapies for CA have high recurrence rate. **Objectives:** To compare the recurrence rate of 5-aminolaevulinic acid photodynamic therapy (ALA-PDT) combined with CO₂ laser and CO₂ laser alone for CA treatment in mainland China. **Methods:** In this meta-analysis, 2,048 cases of CA from 22 articles were divided into two groups. The treatment group was treated by using ALA-PDT combined with CO₂ laser, and CO₂ laser alone was applied in the control group. The recurrence rate of the two groups was calculated and compared. **Results:** The recurrence rate was 42.67% (451/1,057) in the control group and 10.29% (102/991) in the treatment group, with a significant statistical difference between the two groups ($\chi^2 = 271.98$, $p < 0.0001$). **Conclusion:** ALA-PDT combined with CO₂ laser was more effective in decreasing the recurrence rate of CA compared with CO₂ laser alone. It might offer a wide clinical application for CA treatment.

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Introduction

Condylomata acuminata (CA) are a common sexually transmitted disease (STD) [1], which has been ranked as the third most prevalent STD in China. Human papillomavirus (HPV), typically HPV 6 and 11, is the main etiological agent of CA [2]. HPV 6 and 11 have been detected in up to 95% of CA cases [3], and HPV 6 has been detected approximately 3 times more often than HPV 11 in these lesions. CA usually manifest proliferative exophytic papillomatous lesions, which more commonly affect the anogenital area [4]. In men, CA more commonly involve the coronal sulcus, glans penis and penile shaft, and are more frequent in uncircumcised men [5]. However in women, lesions are commonly found in external genitalia such as the vulvar vestibulum, and it can also affect the cervix.

The prevalence of CA has increased by approximately 25% from 1996 to 2005 [6]. Multiple therapies had been applied in the treatment of CA, including cryotherapy, surgical excision, electrocautery, laser therapy and drugs [7]; there was still a high recurrence rate in patients with CA after various therapies [8]. The relapse of CA may be closely related to many factors such as subclinical infection of harboring HPV, abnormal function of individual

Fig. 1. Flow diagram of article selection. A total of 22 articles were finally selected for the meta-analysis.

local immunity, insufficient and inefficient treatment, and so on. Topical photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) is a promising attractive technique for local treatment of HPV-related diseases, and promising results have been reported for CA treatment in recent years, especially for urethral CA. PDT has been shown to augment antitumor immunity in lots of research studies [9]. The decreased recurrence rate of CA treated with ALA-PDT may be related to simultaneous treatments of microscale and subclinical lesion, which improves the current situation of CA treatment. However, the expensive medical cost of PDT and its recurrent use on lesions led to the limitation of PDT application in China because the costs need be paid by the patients alone. Therefore, PDT combined with CO₂ laser was frequently recommended to clear larger warts and to reduce the number of PDT applications and its medical cost. The purpose of the present meta-analysis was to discuss the application of ALA-PDT combined with CO₂ laser and to compare the recurrence rate of ALA-PDT combined with CO₂ laser with that of CO₂ laser alone for CA treatment in mainland China.

Materials and Methods

Study Selection Criteria

Published material was extracted from the citations listed in the China National Knowledge Infrastructure. Key search terms included: condylomata acuminata/genital warts, photodynamic therapy, CO₂ laser, recurrence rate and China. In this meta-analysis,

Fig. 2. No publication biases were observed in funnel plots.

we searched for articles published in the China National Knowledge Infrastructure from October 2006 to December 2011. All the studies included in this meta-analysis were limited to the following inclusion criteria: (1) Study subjects were from mainland China. (2) CA cases were diagnosed by histology, clinical results or cytology. (3) Lesions in the glans, prepuce, penile shaft, scrotal, suprapubic, inguinal or perineal areas, and urethral orifice were included in this study for males. Lesions commonly affected external genitalia in females, such as the vulvar vestibulum and labium, and could also be found in the cervix. However, the following situations were excluded from this study: pregnant women, immunodeficient patients (such as AIDS), severe systemic diseases, malignant tumors, other STDs (such as syphilis and gonorrhea) and patients accepting immunosuppressant treatment up to 1 month before. Size and number of lesions were not exclusion criteria. (4) The cases were taken from outpatients in the Dermatology Clinic. (5) Informed written consent for treating CA was obtained from every subject. (6) The patients were divided into two groups: treatment group and control group. Most patients in both groups experienced the initial treatment. The treatment group was treated with ALA-PDT combined with CO₂ laser. The lesions (more than 2 mm in diameter) were firstly removed by CO₂ laser, and then ALA-PDT was applied. The procedures of ALA-PDT were included as follows: a gel containing 10–20% 5-ALA (Fudan Zhang Jiang Biomedical Corp., Shanghai, China) was applied topically and covered with a polyethylene dressing. After at least 3 h incubation, the application sites were irradiated for 40 min with 120 mJ/cm²/s of red light at a peak emission of 635 nm delivered using an XD-635AB (Xingda Photoelectricity Medical Equipment Corp., Guilin, China). ALA-PDT was applied to treat CA once a week for 3 consecutive weeks. The control group was treated with CO₂ laser alone. (7) All patients were followed up for 3 months. During the follow-up period, the patients with repeated emergence lesions were defined as relapsed cases. (8) Publication with the largest sample size was selected if the data or data subset was published in more than 1 article.

Data Extraction and Quality Assessment

After the overlap studies were excluded, this meta-analysis covered a total of 22 articles on ALA-PDT combined with CO₂ laser and CO₂ laser alone for CA treatment [10–31]. Two reviewers independently extracted and assessed the data using a standard data extraction form designed for this review. We resolved differences in data extraction by consensus, with reference to the original article. If necessary, we sought information from the authors of the primary studies.

Statistical Analysis

When the outcome was reported in more than 1 paper, these results were combined in meta-analysis using Review Manager 5.0 which was developed by the Cochrane Collaboration [32]. The adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated. Heterogeneity among studies was examined with the I² test interpreted as the proportion of total variation contributed by between-study variation. If there was a statistical difference in terms of heterogeneity (I² < 50%, p > 0.05), a fixed-effect model was selected to combine the data. Otherwise, a random-effect model was employed. The significance of pooled OR was determined by the Z test, and two-tailed p < 0.05 was considered as statistically significant. p values for the comparison of recurrence rate between the two groups were calculated using the χ^2 test. Evidence of publication bias was determined by visual inspection of the funnel plot [33].

Results

Eligible Studies

In this article, the recurrence rates of CA were investigated by way of ALA-PDT combined with CO₂ laser and CO₂ laser alone using meta-analysis in a wide range of populations. As shown in figure 1, 22 articles were finally selected and investigated in this meta-analysis. The detailed characteristics of these studies were presented in table 1. A review of funnel plots did not demonstrate a strongly suggestive pattern of publication bias (fig. 2).

Meta-Analysis for the Recurrence Rate of CA

A total of 2,048 CA cases from 22 identified studies were included. All the cases were divided into two groups: control group (1,057 cases) and treatment group (991 cases). The control group and the treatment group were treated with CO₂ laser alone and ALA-PDT combined with CO₂ laser, respectively.

Heterogeneity among 22 articles was firstly examined. According to χ^2 and I² tests shown in figure 3, the results revealed a low statistical heterogeneity among studies ($\chi^2 = 31.57$, d.f. = 21, p = 0.06, I² = 33%). Then we used a fixed-effect model for meta-analysis. The fixed-effect model was explored in relation to the summary effect size to estimate the mean distribution of effect. The heteroge-

Table 1. Main characteristics of the 22 selected studies for meta-analysis

First author	Year	Total cases	Control group	Treatment group	Recurrent cases	
					control	treatment
Liu [11]	2011	73	31	42	18	4
Shi [14]	2011	60	30	30	17	4
Wang [26]	2011	85	42	43	16	2
Chen [23]	2011	78	36	42	15	5
Zhong [17]	2011	70	35	35	13	2
Li [25]	2011	78	39	39	15	4
Huang [21]	2011	170	85	85	16	3
Wang [16]	2010	128	62	66	25	18
Liu [30]	2010	148	118	30	43	4
Yang [18]	2010	80	40	40	25	4
Hu [24]	2010	104	52	52	21	5
Hu [29]	2010	61	30	31	14	2
Lv [20]	2010	78	38	40	5	2
Chen [13]	2009	107	52	55	35	4
Ge [15]	2009	120	55	65	26	7
Yang [31]	2009	65	37	28	9	2
Xu [19]	2009	104	54	50	34	6
Chen [22]	2009	60	30	30	12	5
Hu [28]	2009	105	52	53	20	4
Li [10]	2009	78	41	37	16	6
Xiang [27]	2008	136	68	68	38	6
Wang [12]	2006	60	30	30	18	3

Table 2. Comparison between recurrence and cure rate between the two groups (n = 2,048)

Group	Total cases	Recurrent cases (%)	Cure cases (%)	χ^2	p
Control group	1,057	451 (42.67)	606 (57.33)	271.98	<0.0001
Treatment group	991	102 (10.29)	889 (89.71)		

neity statistic (Q) was calculated to determine whether the studies shared a common effect size. Q represents the observed weighted sum of squares and d.f. is the expected weighted sum of squares [34]. After the results included in these articles were synthesized, it was shown in figure 3 that a significant difference in the recurrence rate of the two groups was observed (OR = 0.15, 95% CI: 0.10–0.20, Z = 15.41, p < 0.00001).

A χ^2 test was also used to evaluate the recurrence rate between the two groups. As shown in table 2, the recurrence rate was 42.67% (451/1,057) in the control group and 10.29% (102/991) in the treatment group. There was a significant statistical difference in the recurrence rate between the two groups ($\chi^2 = 271.98$, p < 0.0001).

Fig. 3. Analysis of the recurrence rate of ALA-PDT combined with CO₂ laser and CO₂ laser alone for treating patients with CA. A low statistical heterogeneity among 22 studies was observed ($\chi^2 = 31.57$, d.f. = 21, $p = 0.06$, $I^2 = 33\%$). A significant difference in the recurrence rate of the two groups was observed (OR = 0.15, 95% CI: 0.10–0.20, $Z = 15.41$, $p < 0.00001$).

Fig. 4. Publication bias was analyzed in the Begg and Egger funnel plot. There was no publication bias for the main summary estimate for the recurrence rate (Begg: $p = 0.735$, Egger: $p = 0.089$).

Sensitivity Analysis

We did not perform any planned sensitivity analysis as no unpublished articles were found.

Publication Bias

As shown in figure 2, no evidence of publication bias was observed in funnel plots (available upon request). The Egger test and the Begg test were used to assess the possibility of publication bias [35]. The results in figure 4 show that there was no publication bias for main summary estimate for the recurrence rate (Begg: $p = 0.735$, Egger: $p = 0.089$) with STATA11.0 software (StataCorp LP, College Station, Tex., USA).

Adverse Events

No severe adverse effects were reported, but a few of the patients noticed an intense sensation of burning during and immediately after light exposure. Application site reactions such as itching and pain occurred in parts of patients treated with ALA-PDT combined with CO₂ laser. In addition, different degrees of edema and erythema occurred around the treatment areas in some patients during laser irradiation.

Discussion

CA are one of the most common STDs caused by different types of HPV. The incidence of CA in the European and American population is around 1–2% [36]. At present, conventional therapeutic modalities for CA include cryotherapy with liquid nitrogen, cytostatic agents (20–25% podophyllin and 0.15–1% podophyllotoxin), keratolytic agents (20–50% trichloroacetic acid), surgical methods, curettage, electrosurgery, laser therapy, and immunotherapy (5% imiquimod) [37]. These therapies are likely to be painful and lead to a high recurrence rate, because HPV may persist in normal-appearing epithelium adjacent to treated lesions [38]. CA and the high relapse rate thereof seriously affect the quality of life and treatment confidence of patients, as well as their family stability and welfare [39].

Relapse is a major problem in the clinical treatment of CA. One of the reasons for relapse is remnant occult lesions after the removal of visible warts by a certain treatment. For example, CO₂ laser effectively removes visible lesions, but may leave invisible lesions. In addition, CO₂ laser can artificially disseminate virions to skin folds in the surrounding area, leading to relapse [40]. It can also result in ulcers if the depth of the radiation site is not well

controlled. Scarring after healing can provide shelter for viruses to grow and cause relapse [41]. The modality of CA is usually associated with unsatisfactory treatment outcomes and serious structural and functional complications such as scar formation, depigmentation and relapse of lesions.

Nowadays, an increasing body of evidence supports the utilization of PDT in the treatment of cancerous and infectious diseases [42]. In particular, topical ALA-mediated PDT has been demonstrated to have had good clinical outcomes in the treatment of genital warts [43]. ALA-PDT could trigger apoptosis and necrosis of HPV-infected keratinocytes in CA [44]. One of major mechanisms is the production of a photosensitizer, protoporphyrin IX (PpIX), from the precursor (ALA). The external addition of ALA or its derivatives results in enhanced synthesis of porphyrin by rapidly proliferating cells [45]. PpIX generates a large number of singlet oxygen and some reactive oxygen species under light irradiation at a certain wavelength, and then causes the desired damage to overly proliferative cells [46, 47]. The PpIX is activated by red light in ALA-PDT, which tends to be helpful in eradicating HPV in perilesional skin and reduces the recurrence rate. Recently, some researchers demonstrated that ALA-PDT can induce a favorable infiltration of immune cells (e.g. CD4+ T cells and dendritic cells) in CA, which can be responsible for healing and long-term efficacy [48].

ALA-PDT was thought to be an ideal therapy for CA. However, penetration of ALA-PDT may not be enough and often showed poor efficacy for thick warts which needed further applications of PDT; thus ALA-PDT combined with CO₂ laser was recommended for CA treatment. Larger warts were removed by CO₂ laser and then ALA-PDT was applied. It was thought to achieve good clinical efficacy.

In this meta-analysis, 22 articles were included to compare the recurrence rate of systemically used ALA-PDT combined with CO₂ laser and CO₂ laser alone for CA treatment. In most articles 20% of ALA concentration was used and 10% was used in a few of the articles. The results from the studies with 10 and 20% of ALA concentration had no significant differences. It was observed from this meta-analysis that the recurrence rate of the treatment group was lower than that of the control group. There was a significant statistical discrepancy in the recurrence rate between the two groups (as shown in fig. 3 and table 2). The patients treated with ALA-PDT combined with CO₂ laser obtained better clinical efficacy than those with CO₂ laser alone. Furthermore, ALA-PDT combined with CO₂ laser was well tolerated, with a rela-

tively low incidence of systemic adverse events. Consequently, it should be proposed to patients with CA to select and adopt ALA-PDT combined with CO₂ laser in order to reduce the recurrence rate.

Limitations

The meta-analysis included a large number of articles from China. We should carry out a comprehensive evaluation for the recurrence rate of two kinds of different treatment methods for CA in China. Of course, relapse of CA is associated with lots of factors such as sex and age. However, primary articles included in the meta-analysis did not sufficiently report the corresponding number of cases by sex and age, so we were not able to assess the association between them and the recurrence rate of CA.

Conclusion

Overall, the meta-analysis demonstrated that ALA-PDT combined with CO₂ laser is effective in decreasing the recurrence rate of CA. It might offer a wide clinical application for CA treatment.

Although the number of articles studied is limited, it implicated that ALA-PDT combined with CO₂ laser could powerfully treat CA. The combination of these two kinds of therapies should be of interest to clinicians. Future research should focus on various factors, including sex, age and HPV subtypes, which can influence the relapse of CA. The combined use of the two kinds of different treatment methods for CA should be recommended to reduce the pain of patients considerably.

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Disclosure Statement

The authors have no conflicts of interest.

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