

# Therapeutic Effect of Aminolevulinic Acid Photodynamic Two-Step Irradiation on Patients with Condyloma Acuminatum

Wenbin Yang, Li Li\*

Department of Dermatology, Xi'an No.3 Hospital, the Affiliated Hospital of Northwest University, Xi'an 710018, Shaanxi Province, China

\*Corresponding author: Li Li, 570465937@qq.com

**Copyright:** © 2024 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

**Abstract:** *Objective:* To investigate the therapeutic effect of aminolevulinic acid photodynamic two-step irradiation on pain in patients with intraluminal condyloma acuminatum. *Methods:* 60 patients with intraluminal condyloma acuminatum treated with aminolevulinic acid photodynamic therapy (ALA-PDT) in the dermatology department of Xi'an Third Hospital from May 2019 to September 2021 were selected and randomly divided into the experimental group and the control group. The experimental group received aminolevulinic acid photodynamic two-step irradiation treatment while the control group was treated with conventional photodynamic irradiation. The experimental group and the control group were treated once every 7–10 days for four consecutive times. The treatment effect and pain score were recorded. *Results:* The efficacy of aminolevulinic acid photodynamic therapy was observed two weeks after the end of the treatment. The complete response rate of the experimental group was 66.7% (20/30), the partial response rate was 33.3% (10/30), and the ineffective rate was 0. In the control group, the complete response rate was 70% (21/30), the partial response rate was 30% (9/30), and the ineffective rate was 0. There was no significant difference in the complete response rate between the experimental group and the control group ( $\chi^2 = 0.527$ ,  $P = 0.706$ ). Pain scores were evaluated at 5 minutes and 20 minutes during photodynamic therapy, and 30 minutes after photodynamic therapy. The pain scores of patients in the experimental group were lower than those in the control group at 5 minutes, 20 minutes, and 30 minutes after treatment. There was no significant difference in adverse reactions between the experimental group and the control group. *Conclusion:* Aminolevulinic acid photodynamic two-step irradiation can effectively ensure the therapeutic effect of patients with intraluminal condyloma acuminatum, and can significantly reduce patients' pain during and after treatment.

**Keywords:** Aminolevulinic acid; Photodynamic; Two-step irradiation; Condyloma acuminatum; Pain

**Online publication:** March 29, 2024

## 1. Introduction

At present, aminolevulinic acid photodynamic therapy for the treatment of condyloma acuminatum has been a preferred treatment option with evidence-based medical evidence <sup>[1]</sup>, especially for intraluminal (vaginal,

cervical, anal canal, urethral) infections of condyloma acuminatum, which not only reduces the local tissue damage but also effectively lowers the recurrence. However, conventional aminolevulinic acid photodynamic treatment may cause patients to suffer significant pain, or even be unable to tolerate the pain and fail to complete the treatment course, which seriously affects the application of photodynamic therapy in the treatment of condyloma acuminatum. Currently, some studies have found that the two-step method of aminolevulinic acid photodynamic therapy can effectively relieve patients' pain while guaranteeing therapeutic efficacy [2]. In this study, the aminolevulinic acid photodynamic two-step irradiation method is used to treat patients with intraluminal condyloma acuminatum, in order to clarify the relationship between the specific treatment parameters of the aminolevulinic acid photodynamic two-step irradiation method for intraluminal condyloma acuminatum and the clinical effect and pain.

## 2. Subjects and methods

### 2.1. Subjects

60 patients with intraluminal condyloma acuminatum treated in the Department of Dermatology of the Third Hospital of Xi'an City between May 2019 and September 2021 were selected. Inclusion criteria: cases of genital (urethra, cervix, vagina) and intraluminal condyloma acuminatum diagnosed by two dermatologists, and the diagnosis was confirmed by colposcopy, anoscopy, and acetic acid test; detailed records of disease duration, size, number, and distribution of lesions; inability or unwillingness to continue surgical, cryotherapy, laser, and other treatments. Exclusion criteria: patients with severe heart disease, liver disease, kidney disease, and other serious chronic diseases who cannot tolerate treatment; pregnant or breastfeeding women; patients with contraindications to the test drug or drug allergies; patients who have participated in other clinical trials in the last three months; patients who do not have the legal capacity or whose legal capacity is restricted; and any other conditions that are considered by the investigator to be unsuitable for participation in this trial. Patients who participated in this research trial had the right to be informed and were enrolled only after signing a protocol.

The patients were randomly and equally divided into the experimental group and the control group. The experimental group was treated with the aminolevulinic acid photodynamic two-step irradiation method while the control group was treated with the conventional photodynamic injection method. In the experimental group, there were five male patients (3 cases of urethral condyloma acuminatum, 2 cases of condyloma acuminatum in the anal canal) and 25 female patients (8 cases of cervical condyloma acuminatum, 10 cases of vaginal condyloma acuminatum, 4 cases of cervical and vaginal condyloma acuminatum, 2 cases of urethral condyloma acuminatum, and 1 case of condyloma acuminatum in the anal canal), with the age of 19–46 ( $32.45 \pm 4.15$ ) years old. In the control group, there were six male patients (4 cases of urethral condyloma acuminatum, 2 cases of condyloma acuminatum in anal canal) and 24 female patients (6 cases of cervical condyloma acuminatum, 13 cases of vaginal condyloma acuminatum, 3 cases of cervical and vaginal condyloma acuminatum, 2 cases of urethral condyloma acuminatum), with the age of 20–45 ( $31.65 \pm 4.68$ ) years old. There was no statistically significant difference in gender and age between the two groups of patients.

### 2.2. Methods

The vaginal and anal secretions were cleaned, the wart site and the number of warts were accurately determined through colposcopy and anoscopy, and image acquisition of the lesion site and calculation of the area of warts were performed (1 drug for every  $3\text{cm}^2$  lesion range). The topical aminolevulinic acid hydrochloride reagent (Fudan Zhangjiang) was configured into a 20% aminolevulinic acid hydrochloride solution, which was applied

to the warts locally with cotton wool and dressed and fixed. It was left for 3 hours to allow absorption, and the patient was asked to reduce his activity. Subsequently, the treatment site was identified again, the photodynamic therapy instrument fiber optic was used in the irradiation of the warts. The experimental group received aminolevulinic acid photodynamic two-step irradiation treatment: (1) the initial treatment power density was 50 mW/cm<sup>2</sup>, irradiation time was 8 minutes, and the therapeutic energy reached 24 J/cm<sup>2</sup>; (2) after the power density was adjusted to 80–100 mW/cm<sup>2</sup>, irradiation was done for 15 minutes, and the total therapeutic energy reached 100 J/cm<sup>2</sup>. The control group was treated with the conventional photodynamic irradiation treatment: power density 80–100 mW/cm<sup>2</sup>, irradiation for 20 minutes, and total therapeutic energy 100 J/cm<sup>2</sup>. Both the experimental group and the control group were treated once at an interval of 7–10 days, and continuously treated four times.

### 2.3. Observation indexes

- (1) Efficacy indicators: Complete response (CR) is the complete disappearance of skin lesions and negative acetic acid test; partial response (PR) is the disappearance of more than 50% of warts (number or area); null response (NR) is the failure of treatment. Efficacy determination was performed and recorded by a dermatologist who was not involved in the clinical treatment. Patients were rechecked 2 weeks after the four photodynamic treatments for wart resolution.
- (2) Pain score: The numeric rating scale (NRS) pain score was adopted. The specific method is as follows. A straight line was divided into 10 equal parts, each point was labeled with the number 0–10 points to indicate the degree of pain in order to assess the pain; 0 points for no pain, 10 points for severe pain; the patient was instructed to mark the number that best represents the degree of treatment pain. 0: no pain; 1–3: mild pain; 4–6 moderate pain; 7–10 severe pain. The pain scores of the two groups of patients were evaluated during photodynamic therapy for 5 minutes and 20 minutes, and 30 minutes after the end of photodynamic therapy, respectively.
- (3) Observation of adverse reactions at the treatment site: Patients were observed for the presence of blisters, vesicles, exudation, and other adverse reactions at the photodynamic therapy site three days after the end of treatment.

### 2.4. Statistical methods

SPSS20.0 statistical software was applied to analyze the data,  $\chi^2$  test was used to compare the experimental group and the control group; the measurement data conforming to the normal distribution was expressed as mean  $\pm$  standard deviation (SD), and the independent sample *t*-test was used to compare between the groups, and the difference of  $P < 0.05$  was considered to be statistically significant.

## 3. Results

### 3.1. Comparison of the therapeutic efficacy between the two groups

The therapeutic efficacy was observed 2 weeks after the end of photodynamic therapy with aminolevulinic acid. As shown in **Table 1**, the complete response rate of the experimental group was 66.7% (20/30), the partial response rate was 33.3% (10/30), and the null response rate was 0. In the control group, the complete response rate was 70% (21/30), the partial response rate was 30% (9/30), and the null response rate was 0. There was no significant difference in the complete response rate of the experimental group compared with that of the control group ( $\chi^2 = 0.527$ ,  $P = 0.706$ ).

**Table 1.** Comparison of the therapeutic efficacy of aminolevulinic acid photodynamic therapy (cases)

Group	Cases	Complete response (CR)	Partial response (PR)	Null response (NR)
Experimental group	30	20	10	0
Control group	30	21	9	0
$\chi^2$	-	0.527	-	-
<i>P</i>	-	0.706	-	-

### 3.2. Comparison of pain scores between the two groups

Pain scores were assessed during treatment at 5 minutes and 20 minutes, and 30 minutes after the end of photodynamic therapy, respectively. The pain scores of patients in the experimental group at 5 minutes and 20 minutes, and 30 minutes after the end of treatment were lower than those of patients in the control group (**Table 2**).

**Table 2.** Comparison of pain scores in aminolevulinic acid photodynamic therapy

Group	Cases	5 minutes	20 minutes	30 minutes after treatment
Experimental group	30	5.23 ± 0.62	4.03 ± 0.25	1.13 ± 0.16
Control group	30	7.67 ± 2.15	4.53 ± 0.38	2.67 ± 0.19
<i>t</i>	-	6.423	6.135	53.308
<i>P</i>	-	< 0.001	< 0.01	< 0.001

### 3.3. Comparison of adverse reactions between the two groups

The adverse reactions of patients' treatment sites were observed three days after the end of treatment. There was one case of localized erosion (male urethra) in the experimental group and one case of localized erosion and exudation (male urethra) in the control group. There was no significant difference in adverse reactions between the experimental group and the control group.

## 4. Discussion

Condyloma acuminatum has a high incidence rate among clinical sexually transmitted diseases, and the traditional methods of laser, freezing, surgery, and topical medication have a relatively long treatment cycle and a high recurrence rate, which puts great pressure on patients' lives. At present, aminolevulinic acid photodynamic therapy for condyloma acuminatum has become the first-line clinical treatment program <sup>[1]</sup>, offering many advantages for the treatment of condyloma acuminatum in the cavity (vagina, urethra, cervical orifice, and in the anal canal). Photodynamic therapy can not only remove warts with little damage to local tissues, but also has a good therapeutic effect on latent human papillomavirus infections and subclinical infections, and significantly reduces the recurrence rate compared with other treatments <sup>[3]</sup>. However, the conventional photodynamic treatment method causes pain in the local skin and mucous membrane during the treatment and even leads to discontinuation of the photodynamic therapy program for some patients, seriously affecting the therapeutic effect in the patients and limiting the application of aminolevulinic acid photodynamic therapy in the treatment of condyloma acuminatum.

The photodynamic effect is a photochemical reaction that includes photosensitive molecules, light sources with photosensitized wavelengths, and tissue oxygen <sup>[4]</sup>. Tissue hypoxia and singlet oxygen generation are the causes of oxidative damage and cell death due to the photodynamic effect, while its singlet oxygen downstream

products can attack the photosensitizer to make it ineffective (i.e. photobleaching effect). Foreign studies have found that the therapeutic efficacy of aminolevulinic acid photodynamic therapy is mainly related to the total energy of phototherapy [5] and not directly related to the intensity of light [6], and photodynamic such as controlling the total energy of light to reach a certain total amount of treatment can guarantee the therapeutic effect. Some other studies have shown that the pain caused by photodynamic therapy is related to light intensity, and reducing the intensity of phototherapy can significantly reduce the degree of pain in the patients receiving photodynamic therapy [7]. Through this finding, domestic and foreign researchers found that the aminolevulinic acid photodynamic two-step irradiation method can effectively relieve patients' pain in photodynamic therapy [8]. In this study, on the basis of the theory of the two-step photodynamic method of aminolevulinic acid, it was found that the complete response rate of the experimental group was 66.7% (20/30), the partial response rate was 33.3% (10/30), and the null response rate was 0. The complete response rate of the control group was 70% (21/30), the partial response rate was 30% (9/30), and the null response rate was 0. The difference in complete response rate between the experimental and control groups was not statistically significant ( $\chi^2 = 0.527$ ,  $P = 0.706$ ). This suggests that there is no significant difference in the efficacy of the aminolevulinic acid photodynamic two-step irradiation method compared to conventional photodynamic therapy. We maintained the total phototherapy energy at 100 J/cm<sup>2</sup> and reduced the initial phototherapy intensity to 50 mW/cm<sup>2</sup>, which not only effectively relieved patients' pain during treatment at the initial stage of photodynamic therapy, but also significantly relieved pain after increasing the phototherapy intensity in the latter course of treatment and 30 minutes after the end of treatment. It is believed that the slow photobleaching effect of the photosensitizer can reduce the production of singlet oxygen in the tissues and the oxidative damage, thus alleviating the local pain, without significantly aggravating the pain after increasing the intensity of phototherapy in the latter course of the treatment. The specific mechanism of this phenomenon is still to be further investigated.

## 5. Conclusion

In summary, compared with conventional photodynamic therapy, the aminolevulinic acid photodynamic two-step irradiation method can significantly alleviate the patient's pain during and after treatment, and did not have a negative impact on the effect of photodynamic therapy. In the post-treatment observation, it was found that the photodynamic two-step irradiation treatment did not increase the risk of producing erosion, exudation, blisters, and other adverse reactions. Therefore, the aminolevulinic acid photodynamic two-step irradiation method can improve patient compliance and reduce patient pain, which is worth promoting in clinical treatment.

## Disclosure statement

The authors declare no conflict of interest.

## References

- [1] Morton CA, Szeimies RM, Sidoroff A, et al., 2013, European Guidelines for Topical Photodynamic Therapy Part 2: Emerging Indications—Field Cancerization, Photorejuvenation and Inflammatory/Infective Dermatoses. *J Eur Acad Dermatol Venereol*, 27(6): 672–679.
- [2] Yu H, Ma H, 2021, Application of Pain Management in Patients with Condyloma Acuminatum Treated by Aminolevulinic Acid Photodynamic Therapy. *International Journal of Medicine and Health*, 27(15): 2396–2399.

<http://doi.org/10.3760/cma.j.issn.1007-1245.2021.15.047>

- [3] Wang XL, Wang HW, Wang HS, et al., 2004, Topical 5-Aminolaevulinic Acid-Photodynamic Therapy for the Treatment of Urethral Condylomata Acuminata. *Br J Dermatol*, 151(4): 880–885.
- [4] Photodynamic Therapy Research Center of Dermatology and Venereology Branch of Chinese Medical Association, 2015, Expert Consensus on the Clinical Application of Aminolevulinic Acid Photodynamic Therapy. *Chinese Journal of Dermatology*, 48(10): 675–678.
- [5] Novak B, Heesen L, Schary N, et al., 2018, The Influence of Different Illumination Parameters on Protoporphyrin IX Induced Cell Death in Squamous Cell Carcinoma Cells. *Photodiagnosis Photodyn Ther*, 2018(21): 385–392. <http://doi.org/10.1016/j.pdpdt.2018.02.007>
- [6] Chaves YN, Torezan LA, Niwa AB, et al., 2012, Pain in Photodynamic Therapy: Mechanisms of Action and Management Strategies. *An Bras Dermatol*, 87(4): 521–526. <http://doi.org/10.1590/s0365-05962012000400001>
- [7] Apalla Z, Sotiriou E, Panagiotidou D, et al., 2011, Effect of Different Fluences on Pain and Clinical Outcome in Patients with Actinic Keratoses Treated with Photodynamic Therapy. *Photodermatol Photoimmunol Photomed*, 27(4): 181–185. <http://doi.org/10.1111/j.1600-0781.2011.00595.x>
- [8] Chen J, Zhou F, Chen S, et al., 2020, Effect of Two-Step Irradiance Schedule on Pain Control During and Clinical Efficacy of Aminolevulinic Acid-Based Photodynamic Therapy for Moderate-to-Severe Acne. *Chinese Journal of Dermatology*, 53(11): 900–904. <http://doi.org/10.35541/cjd.20200088>

**Publisher's note**

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.