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Original Article

Evaluation of photodynamic therapy using topical aminolevulinic acid hydrochloride in the treatment of condylomata acuminate

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Abstract: Objectives: To investigate the efficacy and safety of topical application of 5-aminolaevulinic acid (ALA) photodynamic therapy (PDT) for the treatment of condylomata acuminata (CA) in larger population. Methods: Patients with CA were given a treatment of ALA-PDT once a week for 3 weeks and followed up at 4, 8, 12 and 24 weeks after the treatment finished. Results: In 531 patients, a clearance rate was observed 95.27%. The rates rouse with PDT cycles. The clearance rate of three PDT cycles was significant higher than one PDT cycles ($P < 0.001$) and two PDT cycles ($P < 0.001$). The clearance rate (88.73%) of small lesions (diameter small than 5mm) was significant higher than that (97.74%) of larger lesions ($P < 0.001$). The clearance rate varied with the location of the lesions. The clearance rate of urethral meatus was highest and that of perianal was lowest. Follow-up for patients with complete response lasted for 24 weeks. The recurrence rate was 5.65%, 11.30%, 15.07%, 15.44% and 16.20% after 1, 4, 8, 12 and 24 weeks. The recurrence rate varied with the location of the lesions. The recurrence rate of perianal was highest and that of labium was lowest. The side effects mainly included flare, pain, erosion, ulcer, and hyperpigmentation. The adverse reaction rate was 7.72%, 8.10%, 2.26%, 0.94% and 0.19%. Sexual dysfunction and urethral malformations were not observed during the 24 weeds visit. Conclusion: Topical application of ALA-PDT is a simple and as effective therapy with a lower incidence of adverse effects in the treatment of condylomata acuminata.

Keywords: Clearance rate, condylomata acuminate, photodynamic therapy

Introduction

Porphyrin-mediated photodynamic therapy (PDT) is a modern and effective therapeutic method. The principle of PDT is to induce phototoxic reactions by synergy of photosensitizer and light [1, 2]. Topical Photodynamic therapy (PDT) using 5-aminolaevulinic acid has been shown to be effective for the treatment of non-melanoma skin cancers (NMSC), such as Bowen's Disease (BD), Basal cell carcinoma (BCCs) Squamous cell carcinoma (SCCs) and nevus flammeus [3], and to heal with less scarring and improved cosmetic outcome. Recently, studies have showed that ALA-PDT is an attractive technique of inflammatory and non- inflammatory skin diseases other than non-melanoma skin cancer, especially in the treatment of condylomata acuminate (CA) [4-7].

CA is a highly contagious sexually transmitted disease caused by some sub-types of human papillomavirus (HPV). It occurs in clusters and can be very tiny or can spread into large masses in the genital or penis area. More and more attention has been paid to this medical condition mainly because it has been believed to be related to genital carcinogenesis. Our previous study shows that topical application of ALA-PDT is a simpler, more effective and safer therapy with a lower recurrence for treatment of CA compared with conventional CO_2 laser therapy [8]. The aim of this multicentre study was to investigate the efficacy and safety of topical application of 5-aminolaevulinic acid (ALA) photodynamic therapy (PDT) for the treatment of CA in larger population. This was a retrospective multicenter study was organized by Huashan Hospital affiliated Fudan University and per-

Table 1. General characteristic of 531 patients

Locations	The incidence of the patients		Total
	Primary (%)	Recurrence (%)	
Urethral meatus	110 (53.40)	96 (46.60)	206
Coronal	27 (39.71)	41 (60.29)	68
Foreskin	24 (48.98)	25 (51.02)	49
Perianal	15 (34.88)	28 (65.12)	43
Penis	12 (44.44)	15 (55.56)	27
Labia	15 (57.69)	11 (42.31)	26
Glans	11 (45.83)	13 (54.17)	24
Others	57 (64.77)	31 (35.23)	88
Total	271 (51.04)	260 (48.96)	531

formed at 18 centers from December 2009 to December 2010.

Material and methods

Subjects

Men and women aged 18 years and older who were clinically diagnosed with genital warts but were otherwise healthy participated in this multicentre trial. All of the wart lesions were located on the external genitals or distal urethra and the number of the lesions of each patient was less than three. Pregnant or breastfeeding patients were excluded. Additional criteria for exclusion included evidence of infection in patients in the targeted genital zones, patients who were treated with HPV therapies during the 3-month period prior to participation, and patients with contraindications to any of the ingredients in the preparation. All patients underwent a physical examination prior to being accepted to participate in the study. All patients gave written informed consent before participation.

5-aminolaevulinic acid-photodynamic therapy

A 20% ALA (Fudan Zhangjiang Bio-Pharm Co. Ltd, Shanghai, China) solution (w/v) was prepared by dissolving ALA in sterile 0.9% NaCl immediately prior to its application. The external genital skin around the lesions was washed with an aqueous 0.4% chlorhexidine solution. A thin cotton swab or an absorbent ball was soaked in the solution and was gently inserted into the distal urethra or put on the external genitals, to be in contact with and cover the warts and the adjacent normal skin (5-mm border). Then small amounts of 20% ALA were dropped on to the surface of the absorbent ball every 30 min. The lesions were occluded with food-grade cling film and covered with thick gauze for light protection. Patients were asked to lie still until illumination was performed. The time interval between drug application and illumination was 3 h. Light irradiation of 100 J cm^2 at 100 mW was applied to the lesion and the adjacent normal skin (5-mm border) using a cylindrical helium-neon laser fibre (Yage Laser Apparatus Co. Ltd, Wuhan, China) emitting a 635-nm laser light. In patients with multiple lesions, the warts were irradiated one by one. Each lesion was given a treatment once a week for 3 weeks. The lesions were evaluated after each treatment session. The follow-up was conducted at 4, 8, 12 and 24 weeks after the treatment finished. The number, location and area of the warts and the adverse effects were evaluated for each patient at each follow-up.

Statistical analysis

The indicators of efficacy were the clearance rate of wart lesions and the recurrence rate in those patients whose lesions had completely cleared. Lesions were designated 'complete response' if all (100%) of the lesions disappeared. A recurrence was defined as occurrence of the lesions after a complete response. The clearance rate = (the number of the warts which had been cleared completely/the number of the warts) ×100%. The recurrence rate = (the number of the recurrence/the number of the warts) ×100%. The number of the warts after treatment and the adverse The number of the warts in the two groups before treatment was evaluated with the Wilcoxon matched pairs test. The number of the warts after treatment and the adverse effects were evaluated with the χ^2 test or Fish exact test.

Results

General characteristics

A total of 618 patients were enrolled into the study and 531 patients were allocated into the final result. Twenty-one patients discontinued treatment and 66 were withdrawn from the study. Of these 531 patients completed the trial, 385 were males and 146 were females. 271 lesions were primary and 260 lesions were recurrence. Lesions were located on the external genitals, such as Urethral meatus, Coronal,

Table 2. The clearance rate after different PDT cycles

	Before PDT		One PDT cycles		Two PDT cycles		Three PDT cycles	
	Cases	Warts numbers	Clearance number	Rate (%)	Clearance number	Rate (%)	Clearance number	Rate (%)
Locations								
Urethral meatus	206	397	297	74.81	349	87.91	391	98.49
Coronal	68	127	84	66.14	97	76.38	114	89.76
Foreskin	49	99	67	67.68	81	81.82	97	97.98
Perianal	43	93	56	60.22	65	69.89	82	88.17
Penis	27	65	41	63.08	48	73.85	60	92.31
Labia	26	51	31	60.78	41	80.39	49	96.08
Glans	24	31	21	67.74	25	80.64	30	96.77
Others	88	172	108	62.79	134	77.91	163	94.77
Total	531	1035	705	68.12	840	81.16	986	95.27
Lesions (diameter)								
0-5 mm	357	751	524	69.77	629	83.75	734	97.74
5-10 mm	174	284	181	63.73	211	74.30	252	88.73
Total	531	1035	705	68.12	840	81.16	986	95.27

Table 3. The recurrence rate with different visit

Locations	The recurrence rate after PDT treatment				
	One week (%)	Four weeks (%)	Eight weeks (%)	Twelve weeks (%)	Twenty-four weeks (%)
Urethral meatus	9 (4.37)	18 (8.74)	30 (14.56)	31 (15.05)	31 (15.05)
Coronal	5 (7.35)	9 (13.23)	9 (13.23)	9 (13.23)	9 (13.23)
Foreskin	5 (10.21)	8 (16.33)	8 (16.33)	8 (16.33)	8 (16.33)
Perianal	2 (4.65)	6 (13.95)	10 (23.25)	10 (23.25)	13 (30.23)
Penis	2 (7.41)	3 (11.11)	4 (14.81)	4 (14.81)	4 (14.81)
Labia	1 (3.85)	1 (3.85)	2 (7.69)	2 (7.69)	3 (11.54)
Glans	2 (8.33)	3 (12.50)	3 (12.50)	3 (12.50)	3 (12.50)
Others	4 (4.54)	12 (13.64)	14 (15.91)	15 (17.04)	15 (17.04)
Total	30 (5.65)	60 (11.30)	80 (15.07)	82 (15.44)	86 (16.20)

foreskin, perianal, penis, labia and glans. The diameter of 357 lesions were small than 5 mm and 174 lesions were large than 5 mm (**Table 1**).

Clinical efficacy

In 531 patients, a clearance rate was observed 95.27%. The rates rouse with PDT cycles. Clearance rate was 68.12% after one PDT cycles, 81.16% after two PDT cycles and 95.27% after three PDT cycles. The clearance rate of three PDT cycles was significant higher than one PDT cycles ($\chi^2 = 255$, $P < 0.001$) and two PDT cycles ($\chi^2 = 99$, $P < 0.001$). The clearance rate (88.73%) of small lesions (diameter small than 5 mm) was significant higher than that (97.74%) of larger lesions ($\chi^2 = 37$, $P < 0.001$). The clearance rate varied with the location of the lesions. The clearance rate of urethral meatus was highest and that of perianal was lowest (**Table 2**).

Follow-up for patients with complete response lasted for 24 weeks. The recurrence rate was 5.65%, 11.30%, 15.07%, 15.44% and 16.20% after 1, 4, 8, 12 and 24 weeks. The recurrence rate varied with the location of the lesions. The recurrence rate of perianal was highest and that of labium was lowest (**Table 3**).

Safety evaluation

The side effects mainly included flare, pain, erosion, ulcer, and hyperpigmentation. The adverse reaction rate was 7.72%, 8.10%,

2.26%, 0.94% and 0.19%. Sexual dysfunction and urethral malformations were not observed during the 24 weeds visit.

Discussion

ALA-PDT is a new technique based on the interaction of light, photosensitizer and oxygen. ALA is a newly invented topical used photosensitizer with few side effects. It is the first compound in the porphyrin synthesis pathway. ALA is selectively absorbed by tumour cells and rapidly proliferating cells, and transformed to endogenous protoporphyrin IX (PpIX) after the exogenous application of ALA. The PpIX is then activated by red light, leading to the formation of singlet oxygen, which leads to the killing or destruction of tumour cells and proliferative cells. Cells infected by human papillomavirus are proliferative cells; ALA is selectively absorbed by these cells and can be killed by the radiation of red light [7, 9]. Stefanaki et al. [10] reported that the PpIX transformed from the ALA was accumulated in the warts, subclinical lesions and virus-shedding areas. This means ALA-PDT treatment can destroy visible and invisible infected tissues reduce the number of the viral load and the recurrence rate.

ALA-PDT treatment has been widely used in the treatment of CA. A previous study enrolled 91 patients showed that a clearance rate was observed 95.93% of the total warts after one cycle PDT treatment. The recurrence rates of ALA-PDT group and CO_2 group are 9.38% and 17.39%. The adverse reaction rates of ALA-PDT group and CO_2 group are 8.82% and 100% [8].

In this multicenter study, a total of 531 patients finished three PDT cycle treatments and six months visits. A clearance rate was observed 95.27% of the total warts. The rates rouse with PDT cycles. The clearance rate of three PDT cycles was significant higher than one PDT cycles and two PDT cycles. The clearance rate varied with the size and the location of the lesions. The clearance rate of small lesions (diameter small than 5 mm) was significant higher than that of larger lesions. The clearance rate of urethral meatus was highest and that of perianal was lowest. The recurrence rate was 16.20% after 24 weeks follow-up. The recurrence rate after 8 weeks was 15.07% and was not significant higher than 24 weeks (16.20%). The recurrence rate varied with the location of the lesions. The recurrence rate of perianal was highest and that of labium was lowest.

The high recurrence rate of CA is a big challenge in the treatment. The sub-clinical lesions and virus-shedding areas cannot be treated effectively and caused the high recurrence rate [11]. The application of topical ALA-PDT treatment could destroy the warts and cause selective and specific destruction of subclinical virus-shedding areas [12]. However, the recurrence rate of some lesions, for example the lesions around the perianal, was still high. In these cases, a therapeutic alliance such as ALA-PDT combined with the imiquimod can be considered.

The side effects mainly included flare, pain, erosion, ulcer, and hyperpigmentation. The most frequent side-effect is pain (8.10%) and flare (7.72%) and could be tolerated. The erosion, ulcer, and hyperpigmentation were of low frequent. Sexual dysfunction and urethral malformations were not observed during the 24 weeks visit.

We conclude that topical ALA-PDT is a simple and as effective therapy with a lower incidence of adverse effects in the treatment of condylomata acuminate.

Disclosure of conflict of interest

None.

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