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Original Article

Comparison of the efficacy of ALA and high-frequency electric ion operating on cervical intraepithelial neoplasia grade I

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Abstract: Objectives: To compare the clinical efficacy of topical photodynamic therapy with 5-aminolevulinic acid and high-frequency electric ion operating for cervical intraepithelial neoplasia grade I. Methods: 110 patients with grade I cervical intraepithelial neoplasia treated in our hospital were enrolled. The observational group received topical photodynamic therapy with 5-aminolevulinic acid and the control group received high-frequency electric ion operating. Both groups of patients returned for follow-up examination after 6 and 9 months respectively. Colposcopy, TCT and HPV-DNA were examined and the clinical curative effects were evaluated in follow-up examination after 9 months of treatment. Results: HR-HPV DNA remission rates were 45 of 55 and 6 of 55 cases in the observational group observed in the follow-up examination after 6 and 9 months respectively; on the contrary, 29 and 4 cases in the control group had HR-HPV DNA remission. In the respects of remission rate and total remission rate, the observational group was apparently higher than the control group, with a statistically significant difference. When evaluated at the last follow-up examination, the clinical efficacy of the observational group was significantly better than the control group, with a statistically significant difference. Conclusions: The ALA-PDT is simple in operation, with rapid recovery after treatment, less adverse effects, retainment of the cervical normal tissue structures, without complications such as cervical stenosis. ALA-PDT does not affect the cervical normal reproductive function, and repeat treatments are allowed, with better compliance, and is suitable for widely use in all levels of hospital and outpatient clinic.

Keywords: Cervical intraepithelial neoplasia grade I, ALA, high-frequency electric ion operating

Introduction

Cervical cancer is one common malignant tumor for women, for different classes of CIN, there exist big differences in virological infection and clinical progression, as a consequence, follow-up examination becomes increasingly important when to decide how to carry out effective and correct diagnosis and treatment [1, 2]. 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT) is a relatively updating clinical treatment, the advantages of using it to treat CINI include effective retainment of the cervical normal tissue structures, without the need of anesthetization, less blood lose, less trauma and incidence of complication, in particular the permission of repeat treatments to lesions [3-5]. In this study, 110 patients with grade I cervical intraepithelial neoplasia treated in our hospital from January 2013 to September 2014 were enrolled, randomly divided into two groups to receive ALA-PDT or high-frequency electric ion operating treatment respectively, the clinical efficacies were observed in the processes of follow-up examinations and now it is reported as follows.

Materials and methods

General materials

Accepting criteria: ① All the cases underwent colposcopy and biopsy after admission were diagnosed as grade I cervical intraepithelial neoplasia; ② Diagnosis is based on the CIN classification standard of CINI which the neoplasia cells were confined to the basal 1/3 of the epithelium; ③ The disease course are

Table 1. The demographic information and clinic feature of patients

Features	Observational group (n=55)	Control group (n=55)	*P* values
Age (year)			0.926
<30	14	13	
30-40	21	23	
>40	20	19	
Disease course (months)			0.565
<18	23	26	
≥18	32	29	
Menopausal status			0.848
Premenopausal	31	30	
Postmenopausal	24	25	
HPV high risk test			0.541
Positive	50	48	
Negative	5	7	

12-24 months; ④ HR-HPV examination shows consistent positive results. Excluding criteria: ① Accompanied by disorder of important organs such as heart, liver, lung and kidney; ② Accompanied by nongonococcal urethritis or acute genital tract inflammation during admission; ③ Accompanied by diseases of the immune system or disorder of blood coagulation; ④ Underwent hormones or immunosuppressive medication 2 months before admission; ⑤ With photo-induced, light irritability disease in case history; ⑥ With pregnancy or lactation situation; ⑦ With HIV infection.

110 patients with grade I cervical intraepithelial neoplasia treated in our hospital from January 2013 to September 2014 were enrolled in this study, age 24-46, average 28.01±2.64, with 13-24 months of disease course, average 18.55±1.32 months (**Table 1**); According to the digital meter method, they were randomly divided into observational group and control group. The observational group received topical photodynamic therapy with 5-aminolevulinic acid and the control group received high-frequency electric ion operating treatment. General materials were compared and these are no differences in age or disease course, etc., between observational group and control group ($P>0.05$), two group are comparable. After admission, patients and family members signed informed consent and operation agreement, the study received permission of the Medical Ethics Committee and was supervised by ethics committees during the whole course.

Therapies

The observational group received topical photodynamic therapy with 5-aminolevulinic acid. Operation was underwent in darkroom: 20% 5-aminolevulinic acid solution was prepared with 0.5 ml sterilized Water for injections, sterile cotton or gauze was prepared as well, the He-Ne laser cure instrument generated 632.8 nm red light, with output power <500 VA. The lithotomy position was bladder, Cleaned the vulva, and the vaginal speculum was placed. Benzalkonium chloride solution (1:1000) was used to clean the secretion on the surface of vagina and cervix. Cotton slices immersed with 5-aminolevulinic acid solution (20%) were placed on the surface of the cervical lesion for 3 hours and then the laser fiber of He-Ne laser cure instrument was inserted to the mouse of cervix and fixed, used the red light to cover the lesion of cervical canals and surface. The total Illuminating energy of semiconductor laser was about 100 j/cm^2, the Illuminating time was 40-50 min. The interval between two treatments are 7-10 days and all patients were treated for 4 times.

The control group received high-frequency electric ion operating treatment. After the sterilization of the surface of the cervical, the pattern of therapeutic apparatus was chosen as low-power gear, the power output of therapeutic apparatus was set as intermediate and used to gradually burn the lesions of cervical surface until the no lesions can be seen any more. High-power gear can be chosen temporarily when the blood lose increased. The scope of burn can be expanded to 2 mm length around lesions. The interval between two treatments is one week and all patients were treated for 4 times. In the course of treatment, the patients were asked not to have bath in a tub or sexual life, as for dietary, excitant food should be forbidden. Observations after treatment: Levels of pain, vaginal hemorrhage, the mount of secretions, repair of cervix, with or without cervical stenosis or relapse, etc.

Observational index

Patients returned for follow-up examination after 6 and 9 months respectively. Colposcopy,

Table 2. Comparison of remission rates of HR-HPV DNA in cervical exfoliated cells at 6 or 9 months after treatment

Group	Cases	Infection rate before treatment	Remission rates at 6 months after treatment	Remission rates at 9 months after treatment	Total remission rates
Observational group	55	100%	81.81% (45/55)	10.91% (6/55)	92.73% (51/55)
Control group	55	100%	52.73% (29/55)	7.27% (4/55)	60.0% (33/55)
X^2			4.9381	2.1164	4.2615
P			<0.05	<0.05	<0.05

Table 3. Comparison of clinical efficacy evaluated at the last follow-up examination

group	cases	cure	improvement	invalid	effective rate
observational group	55	51	3	1	98.18%
control group	55	33	6	16	70.91%
X^2					4.0126
P					<0.05

TCT and HPV-DNA were examined and the clinical curative effects were evaluated in follow-up examination after 9 months of treatment.

HPV-DNA was tested by the FDA hybrid capture, all the reagents and instrumental were from DIGENE ltd. The results were defined as relative light unit from biopsy measured by spectrophotometer and compared to positive and fully recorded.

Clinical evaluation and assessment standard: Cure, manifested as negative of TCT, CIN negative when measured by colposcopy or biopsy; Improve, manifested as atypical squamous cells (ASC-US) or sporadic ASC-US in TCT and negative in biopsy examination; Invalid, with no change of CINI or even progress into II-III class measured by colposcopy or biopsy check.

Statistical methods

SPSS 19.0 statistical analysis through count data (%) using X^2 test is applied in this study, *P*<0.05 were considered with statistical significance.

Results

The infection rate in both groups measured by HR-HPV DNA test is 100% before treatment. In the observational group, 45 cases and 6 cases turned into negative, and the remission rates were 45 of 55 (81.81%) and 6 of 55 (10.91%) observed in the follow-up examination after 6 and 9 months respectively, the total remission rate is 51 of 55 (92.73%); on the contrary, 29 cases and 4 cases in the control group turned into negative, 29 (52.73%) and 4 (7.27%) cases had HR-HPV DNA remission, the total remission rate is 33 of 55 (60.0%). In the respects of remission rate and total remission rate, the observational group was apparently higher than the control group (X_2=4.9381, 2.1164, 4.2615), with a statistically significant difference (*P*<0.05), as shown in **Table 2**.

After 4 times of ALA-PDT or high-frequency electric ion operating treatment, in the evaluation of clinical efficacy at 9 months post-treatment, 51 cases were cured with 3 cases improved and one case invalid in observational group, the total effective rate is 98.18%; in control group, 33 cases were cured with 6 cases improved and 16 cases invalid, the total effective rate is 70.91%. The clinical efficacy of the observational group was significantly better than the control group, with a statistically significant difference (*P*<0.05). As shown in **Table 3**.

Discussion

Cervical cancer is one malignant disease with high clinical incidence, which progresses through early CIN to invasive carcinoma and ended as cervical cancer [6]. The early diagnosis and effective treatment of CIN are the important methods to prevent the transition from early CIN to advanced CIN [7]. Some studies indicate that CINI can undergo regression with the incident rate about 25%-45%, 1%-2% of CINI can develop into invasive carcinoma [8]. In our study, we think that it is important to pay great attention to CINI. At present, the main

treatment of CIN is the ablation of the surface of cervical tissue, alternatively, resection operation of cervix is also considered. Some researchers using high-frequency electric ion operating to treat CINI lesion achieved some clinical efficacy.

5-aminolevulinic acid is the second generation of porphyrin class, photosensitive and endogenous matter [9]. 5-aminolevulinic acid is the intermediate products of porphyrin metabolism, which can be used to synthesize heme and without phototoxicity [10]. ALA can be synthesized into protoporphyrin IX with high photosensitiveness in reaction catalyzed by corresponding enzyme, which is very important for heme biosynthesis [11]. Because ALA cannot be reserved in high amount in vivo, so when much ALA appear, some highly proliferative tissue or cancer cells can utilize them to produce high-level of protoporphyrin IX [12]. In cancer cells with advanced malignancy, the activities of bile pigment deaminase is relatively high, together with strong proliferation capacity, the acquirement of protoporphyrin IX is increased, the extraneous ALA is beneficial for cancer cells to synthesize protoporphyrin IX [13].

Photodynamic therapy is a non-invasive new technique based on laser and the interaction of photosensitizer and oxyge. 5-aminolevulinic acid, as one of the second generation of porphyrin class, contains many advantages, such as with high chemical purity, can be eradicated rapidly and is high specific, besides, it can penetrate tissue and can be easily absorbed when used in vitro, which is more suitable for clinical application. Currently, grade I cervical intraepithelial neoplasia is commonly treated with mono-therapy, there is no report on the comparison of the ALA-PDT and high-frequency electric ion operating. In this study, we summarized the previous clinical studies, 110 patients with grade I cervical intraepithelial neoplasia treated in our hospital were enrolled to receive these two different treatment. In follow-up examination, we found that HR-HPV DNA remission rates were 45 of 55 (81.81%) and 6 of 55 (10.91%) cases in the observational group observed in the follow-up examination after 6 and 9 months respectively; on the contrary, 29 (52.73%) and 4 (7.27%) cases in the control group had HR-HPV DNA remission. In the respects of remission rate and total remission rate, the observational group was apparently higher than the control group, with a statistically significant difference ($P<0.05$). When evaluated at the last follow-up examination, the clinical efficacy of the observational group was significantly better than the control group, with a statistically significant difference ($P<0.05$).

However, there were still some limitations in this study. First, all the patients enrolled here were diagnosed as CIN grade 1, and there is chance for spontaneous recovery. Second, the sample size was not big enough. In the following study we will improve our research.

Overall, ALA-PDT is simple in operation, with rapid recovery after treatment, less adverse effects, retainment of the cervical normal tissue structures, without complications such as cervical stenosis. Moreover, ALA-PDT does not affect the cervical normal reproductive function, and repeat treatments are allowed, with better compliance, and is suitable for widely usage in all levels of hospital and outpatient clinic to treat CINI patients.

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Disclosure of conflict of interest

None.

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References

[1] Lees BF, Erickson BK and Huh WK. Cervical cancer screening: evidence behind the guidelines. Am J Obstet Gynecol 2016; 214: 438-43.

[2] Tewari KS and Monk BJ. Development of a platform for systemic antiangiogenesis therapy for advanced cervical cancer. Clin Adv Hematol Oncol 2014; 12: 737-748.

[3] Tetard MC, Vermandel M, Leroy HA, Leroux B, Maurage CA, Lejeune JP, Mordon S and Reyns N. Interstitial 5-ALA photodynamic therapy and glioblastoma: preclinical model development and preliminary results. Photodiagnosis Photodyn Ther 2016; 13: 218-24.

[4] Benito-Miguel M, Blanco MD and Gomez C. Assessment of sequential combination of 5-fluorouracil-loaded-chitosan-nanoparticles

and ALA-photodynamic therapy on HeLa cell line. Photodiagnosis Photodyn Ther 2015; 12: 466-475.

[5] Barnett AA, Haller JC, Cairnduff F, Lane G, Brown SB and Roberts DJ. A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia. Int J Cancer 2003; 103: 829-832.

[6] Dogan NU, Garagozova N, Pfiffer T, Beier A, Kohler C and Favero G. Symptomatic lymphocele formation after sentinel lymph node biopsy for early-stage cervical cancer. J Minim Invasive Gynecol 2016; 23: 442-5.

[7] Ricard-Gauthier D, Wisniak A, Catarino R, van Rossum AF, Meyer-Hamme U, Negulescu R, Scaringella S, Jinoro J, Vassilakos P and Petignat P. Use of smartphones as adjuvant tools for cervical cancer screening in low-resource settings. J Low Genit Tract Dis 2015; 19: 295-300.

[8] Martin CM and O'Leary JJ. Histology of cervical intraepithelial neoplasia and the role of biomarkers. Best Pract Res Clin Obstet Gynaecol 2011; 25: 605-615.

[9] Donnelly RF, Morrow DI, McCarron PA, Woolfson AD, Morrissey A, Juzenas P, Juzeniene A, Iani V, McCarthy HO and Moan J. Microneedle-mediated intradermal delivery of 5-aminolevulinic acid: potential for enhanced topical photodynamic therapy. J Control Release 2008; 129: 154-162.

[10] Gederaas OA, Schonberg SA, Ramstad S, Berg K, Johnsson A and Krokan HE. Cell specific effects of polyunsaturated fatty acids on 5-aminolevulinic acid based photosensitization. Photochem Photobiol Sci 2005; 4: 383-389.

[11] Ma X, Qu Q and Zhao Y. Targeted delivery of 5-aminolevulinic acid by multifunctional hollow mesoporous silica nanoparticles for photodynamic skin cancer therapy. ACS Appl Mater Interfaces 2015; 7: 10671-10676.

[12] Valdes PA, Jacobs V, Harris BT, Wilson BC, Leblond F, Paulsen KD and Roberts DW. Quantitative fluorescence using 5-aminolevulinic acid-induced protoporphyrin IX biomarker as a surgical adjunct in low-grade glioma surgery. J Neurosurg 2015; 123: 771-780.

[13] Ota U, Fukuhara H, Ishizuka M, Abe F, Kawada C, Tamura K, Tanaka T, Inoue K, Ogura SI and Shuin T. Plasma protoporphyrin IX following administration of 5-aminolevulinic acid as a potential tumor marker. Mol Clin Oncol 2015; 3: 797-801.