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Comparison of the efficacy of photodynamic therapy and LEEP in the treatment of cervical intraepithelial neoplasia grade 2: Clinical outcomes and considerations for treatment decision-making

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Abstract: Objective: To investigate the therapeutic effect of 5-Aminolevulinic Acid Photodynamic Therapy (ALA-PDT) on cervical intraepithelial neoplasia 2 (CIN2) and the clearance effect of high risk human papiloma virus (HRHPV). **Methods:** Patients treated for high-grade cervical intraepithelial lesions, HSIL/CIN2 from February 2018 to February 2023 in the Department of Obstetrics and Gynecology at the Air Force Specialty Medical Center were collected. Patients with CIN2 who met the eligibility criteria for enrollment were included and divided into a treatment group (ALA-PDT) and a control group (LEEP) in a 1:1 ratio, using a non-inferiority, single-center, open-blind, controlled clinical study method. **Results:** There were 96 people in the treatment group, of whom 91 were treated effectively. In the control group, 107 people were treated, of whom 104 were effective. The effective rate of the control group was 97.20%, and the effective rate of the treatment group was 95.83%, and the difference was not statistically significant ($P > 0.05$). The risk ratio was 0.986 (95%–102%). Difference between the two groups: -1.36% (-5.77% , 3.05%), based on the lower limit of the confidence interval being greater than Δ , i.e., -10% . Therefore, the treatment group was non-inferior to the control group. **Conclusion:** ALA-PDT is an effective and safe noninvasive treatment for patients with cervical HSIL/CIN2. It not only effectively removes diseased tissue and HR-HPV, but also preserves the intact tissue structure of the cervix, and can be used as a therapeutic approach for sick women of reproductive age and patients who wish to observe treatment, which may reduce nonessential surgery. This patient-friendly treatment strategy fully prioritizes patients' physiological needs and long-term health outcomes, avoiding the tissue injury and psychological stress brought by unnecessary invasive surgical procedures.

Keywords: cervical intraepithelial neoplasia grade 2; photodynamic; HPV; cervical LEEP; treatment decision-making

1. Introduction

The treatment modality for high-grade intraepithelial neoplasia of the cervix is surgery, and the main goal of treatment is to prevent cancer by destroying or removing pre-cancerous lesions in order to prevent the development and progression of invasive carcinoma of the cervix [1]. The 2019 American Society for Colposcopy and Cervical Pathology guideline proposes to treat and follow up based on a threshold for treatment [2], as CIN2 can regress naturally [3], which It is clearly stated that for CIN2 part of the population, especially young women with reproductive needs can be observed, indicating that direct surgical treatment for patients with CIN2 may be over-treatment, so how to screen out patients with CIN2 who really need surgical treatment is a

question worth exploring. Photodynamic therapy as a non-invasive modality is being adopted by more and more healthcare institutions, relative to the natural regression of cervical lesions, patients treated with photodynamic therapy have higher HPV clearance and histologic remission rates [4], which can avoid unnecessary surgical treatments, and the emergence of the II-generation photosensitizer, 5-ALA, has been recognized as an advantage due to its flexible mode of administration, the ability to be administered locally, and the lesser number of side effects [5], making it a research hotspot for the treatment of female lower genital tract diseases [6], which is currently used more for the treatment of CIN1 and HR-HPV [7,8], but there is limited data on the treatment of CIN2. 107 patients with CIN2 were enrolled in the present study, using traditional cervical LEEP treatment, 96 cases were treated with the generation II photosensitizer 5-ALA topically, and photodynamic treated CIN2 patients compared to the cervical LEEP group, analyzed the histological remission rate, recurrence rate and HPV clearance rate and adverse effects after photodynamic therapy, and clarified the therapeutic effect of treating CIN2 via a non-invasive modality, with the aim of providing more data to support the choice of treatment options for CIN2, reducing the rate of invasive surgery for CIN2 patients, and preserving the normal structure of their cervix and female fertility.

Main article:

2. Information and methods

2.1. Objects of study

2.1.1. Sources of cases

Recruiting patients receiving treatment for cervical CIN2 from 1 February 2018 to 28 February 2023 in the Department of Obstetrics and Gynecology at the Air Force Specialty Medical Center.

2.1.2. Diagnostic criteria

According to the 2022 Chinese Expert Consensus on the Management of High-Level Intraepithelial Lesions of the Uterine Cervix, categorization of high-level intraepithelial lesions of the uterine cervix: high-level intraepithelial lesions of the uterine cervix include HSIL and adenocarcinomatous carcinoma in situ (AIS), and HSIL, including CIN2 and CIN3, is mainly caused by HR-HPV infection, with cells having the cells have obvious heterogeneity and increased nuclear schizophrania. For patients who took TCT and HPV combined screening in line with colposcopy, patients with HISL/CIN2 were confirmed by perfect colposcopy and cervical biopsy, pathohistology and immunohistochemistry results.

2.1.3. Inclusion criteria

- (1) Pathohistologic and immunohistochemical findings confirmed HISL/CIN2;
- (2) Voluntary participation and signed informed consent;
- (3) Age 18–70;
- (4) Initial consultation, no other treatment used prior to treatment;

2.1.4. Exclusion criteria

- (1) Those with associated light-induced, light-excited disorders;
- (2) Malignant tumors, or those with severe organ function impairment;
- (3) Pregnant or lactating patients;
- (4) Immune dysfunction requiring long-term oral administration of hormonal drugs or immunizing agents;

- (5) Serious systemic diseases (e.g., cardiovascular, respiratory, digestive, endocrine, etc.);
- (6) People with mental illness;
- (7) Subjects with active infections;
- (8) Subjects whose other circumstances the investigator deemed unsuitable for participation.

2.1.5. Experimental stops

The investigator may terminate the trial if the participant experiences a serious adverse event, such as cardiovascular accident, acute or chronic organ failure, severe allergic reactions, and other conditions, poor compliance, loss of visits, and pregnancy of the subject.

2.2. Research design

2.2.1. Test methods

The trial was a noninferiority, single-center, open-blind, case-control clinical study. The trial was approved by the Ethics Committee of the Air Force Specialty Medical Center [2022-86-PJ01].

2.2.2. Non-inferiority threshold Δ sample size calculation

HPV, TCT, and pathology were used as outcomes, and the difference between groups in event rates Δ was 10%. Test level $\alpha = 0.05$, certainty $1 - \beta = 0.8$, and predicted loss to follow-up rate of 20%. Sample size was calculated using the formula: $n = (Z_{1-\alpha} + Z_{1-\beta})^2 \times [p_1(1 - p_{(1)}) + p_2(1 - p_{(2)})] / (\Delta - |p_{(1)} - p_{(2)}|)^2$. n is the sample size required for each group, $Z_{1-\alpha}$ is the number of bits of the unilateral Pisum quasi-normal distribution corresponding to the test level α , $Z_{1-\beta}$ is the number of bits of the unilateral Pisum quasi-normal distribution corresponding to the level of certainty α , and $Z_{1-\beta}$ is the number of bits of the unilateral standard normal distribution corresponding to the level of certainty. degree of unilateral standard normal quantile. p_1 and p_2 are the expected rates for the two groups, respectively, and Δ is the noninferiority cutoff value. The experts of the obstetrics and gynecology team, taking into account the literature reports and clinical experience, unanimously agreed to use a Δ value of 10%, which was calculated to require a sample of 99 cases in each group. Considering a 10% loss to follow-up rate, the final sample size was calculated to be 110 cases in each group.

2.2.3. Randomized grouping

In this trial, the treatment plan was developed with full informed consent from the patients and they were assigned to either the photodynamic group or the LEEP group in a 1:1 ratio. The trial was an open-label design and was not blinded.

2.3. Interventions

2.3.1. Photodynamic therapy

Drug pretreatment: the patient took the truncated position supine on the bed. With 1.5 mL of temperature-sensitive gel, 3 topical dispersions of aminoglutamate hydrochloride (Shanghai Fudan Zhangjiang Biomedical Company, State Pharmaceutical License H20070027, specification 118 mg/branch, trade name 5-ALA) were dissolved into 20% gel mixture, and a tampon was rotationally stuffed into the cervical canal at 1.5–2 cm after being fully dipped in the gel mixture, with the cervical opening retained at the tail end, and a cotton sheet was made according to the actual cervical size as well as the According to the actual size of the cervix and the

condition of the lesion, a cotton pad was made, then the cotton pad was fully dipped in the gel mixture and fully covered the surface of the cervix, and a condom filled with sterile gauze rolls was inserted into the vagina to fix the cotton pads for 3–4 h. The patients were allowed to move around freely during the 4-hour waiting time.

Treatment: 635 nm LED light was used for irradiation, and the output power of the device was set at 90 mW, and the irradiation time was 25 min. the total light dose was 100 J/cm² (LED-IB; Wuhan Ager Photonics Co., Ltd., China). The LED therapeutic instrument was connected to a disposable cannula, inserted into the vagina, and placed about 2 cm away from the surface of the cervix, in addition to a semiconductor laser therapy machine (LD600-C; Wuhan Yage Photoelectric Co., Ltd., Wuhan, China) with a laser wavelength of 635 nm, an output power of 90 mW, and an irradiation time of 25 min. the laser intensity was 100 J/cm². During treatment, a disposable fiber optic sleeve was placed outside the columnar fiber, and the fiber optic was inserted into the endocervix at 2 cm to fix the fiber. Cervical irradiation was performed simultaneously with cervical surface irradiation. The treatment was performed once every 7–14 d, avoiding the menstrual period, and at least 8 times.

2.3.2. LEEP treatment

The patient took the cystotomy position, routinely disinfected and laid aseptic towel, placed the speculum, disinfected the cervix and vagina, fully exposed the cervix, and used Luger's iodine solution to conduct iodine test on the cervix, to clarify the scope of cervical lesions. LEEP resection of lesions, the resection scope should include the lesion outside the edge of the margins of the lesion of 0.5~1 cm, the height of the cone of 1~2 cm, and routinely haemostasis, and observe whether there is any bleeding. The excised cervical tissue was labeled and fixed with 10% formaldehyde for pathological examination.

2.4. Determination of treatment effect and follow up

Photodynamic therapy group: the first follow-up: 3–6 months after the last treatment, the second follow-up: 9–12 months after the last treatment, each follow-up will be rechecked for HPV, TCT, colposcopy according to the TCT and HPV results, and cervical biopsy if necessary. The third follow-up: 18–24 months after the last treatment, focusing on those with escalating disease. The primary evaluation criterion of the study is disease regression and the secondary endpoint is HPV clearance. During the follow-up process, if HPV and TCT results were negative, colposcopy was performed according to the patient's wishes or follow-up continued on schedule; if HPV types 16 and 18 were positive and TCT was negative, or other high-risk types of HPV were positive and TCT results were in the ASC-US and above, further colposcopic pathological biopsy was performed, and the results were suggestive of normal, chronic cervicitis, visible dug-out cells, or LISL/CIN1 If the treatment effect is recognized as regression of pathology, i.e., the treatment is effective, continue to follow up, if the pathology result suggests CIN2, the treatment effect is recognized as persistence of pathology, according to the patient's wish to continue to follow up closely or perform cervical LEEP surgery, if the pathology result suggests that the pathology type is unclear or CIN3 is the progression of the pathology, perform cervical conization surgery.

LEEP treatment group: complete cervical TCT + HPV examination within six months after surgery, and the follow-up content is the same as treatment group (photodynamic group).

2.5. Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Count data were expressed as the number of cases (percentage). Independent samples t-test was used for comparison of components of normally distributed measures, and Mann-Whitney U test was used for comparison between groups of non-normally distributed measures. Comparisons between groups of count data were performed using the rank sum test. And the test of K related samples (Friedman Test) was used, and the comparison between groups was performed by chi-square test and Fisher's exact probability method; in the non-inferiority test, R4.3.1 software was used, which was judged by calculating the difference in the effective rate of the two groups and their confidence intervals. In this study, except for the non-inferiority test for the primary outcome, all statistical tests were two-sided, and $P < 0.05$ was considered a statistically significant difference.

3. Results

3.1. Inclusion of cases

In this study, from 1 February 2018 to 28 February 2023, 220 people were recruited, of which 218 were eligible for enrollment. 3 people did not agree to sign the informed consent. According to the inclusion exclusion criteria, finally 211 people were grouped into photodynamic group and LEEP group respectively after informed consent. Among them, 101 were in the photodynamic group and 110 in the LEEP group. In the photodynamic group, all patients had no combined intracervical canal lesions and refused surgery in the hope of preserving the intact cervical structure, out of these 101 patients, there were 5 cases of lost visits, which were excluded from the data analysis, and the clinical data of 96 patients were actually analyzed. In the control group, i.e., the cervical LEEP group, out of 110 patients, 3 were lost to visit, and 107 patients were actually analyzed in the end. The enrollment process is detailed in **Figure 1**.

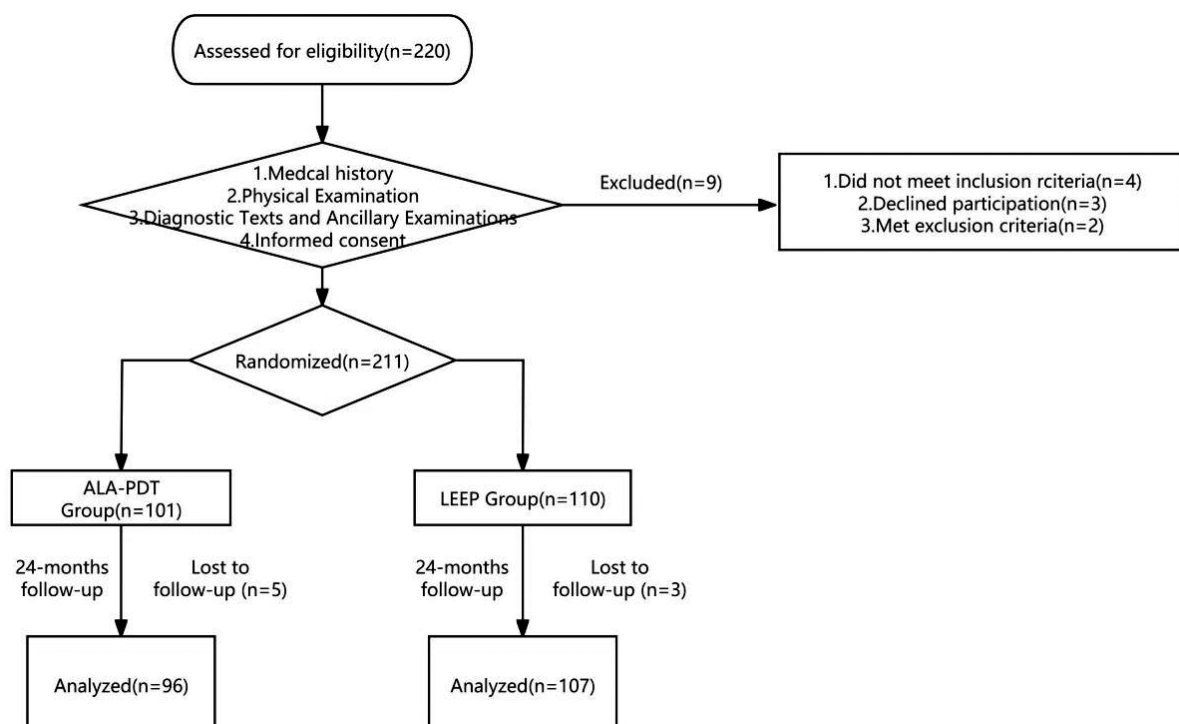


Figure 1. Flowchart of experimental design.

3.2. Clinical characteristics of the case

The mean age was 32.25 (years) in the photodynamic therapy group and 39.65 (years) in the LEEP group. HPV typing in the photodynamic therapy group, 49 (51.04%) were 16/18 and 47 (48.96%) were positive for other high-risk types. Analysis of TCT results in the photodynamic group: NILM 17 (17.02%), AS-CUS and LISL 64 (65.96%), HISL and ASC-H 15 (17.02%). HPV typing in the LEEP treatment group, 16/18 type 47 (43.92%), other high-risk types positive 60 (56.07%). Analysis of TCT results: NILM 28 (26.17%), AS-CUS and LISL 59 (55.14%), HISL and ASC-H 20 (18.69%). See **Table 1** for details.

Table 1. Baseline characteristics of participants.

	Hallmark	Number of cases (%)	
		Photodynamic group	LEEP group
(A person's) age	< 30 years old	30 (31.25%)	16 (14.95%)
	≥ 30 years old	66 (68.75%)	91 (85.05%)
HPV subtype	16/18	49 (51.04%)	47 (43.92%)
	Other high-risk types	47 (48.96%)	60 (56.07%)
	Single subtype	47 (48.96%)	71 (66.36%)
	Many subtypes	49 (51.04%)	36 (33.64%)
	NILM	17 (17.71%)	28 (26.17%)
TCT results	AS-CUS, LISL	64 (66.67%)	59 (55.14%)
	HISL, ASC-H	15 (15.63%)	20 (18.69%)

NILM: negative for intraepithelial lesion or malignancy; ASC: atypical squamous cells; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells. squamous intraepithelial lesion); HSIL: High-grade Squamous Intraepithelial Lesion; ASC-H: Atypical Squamous Cells, cannot exclude High-grade Squamous Intraepithelial Lesion (Atypical). Squamous Cells, cannot exclude High-grade squamous intraepithelial lesion).

3.3. Analysis of pathological findings at 3–6 and 9–12 months follow-up after photodynamic therapy

After 3–6 months of follow-up, the cervical photodynamic therapy group, after TCT + HPV review, details are shown in **Table 2**. It can be seen that the initial TCT results of the patients were mostly suggestive of AS-CUS or LISL (66.67%), after photodynamic therapy, 74 cases (77.08%) of patients had normal TCT results at the 6-month follow-up, and the number of patients with normal TCT results reached 92 cases (97.87%) at 12-month follow-up, and the number of patients with abnormal TCT results was also only AS-CUS. At the 12-month follow-up, the number of patients with normal TCT results reached 92 (97.87%), and those with abnormal results showed only AS-CUS. In order to further clarify the histological changes in the cervix of the patients, we performed colposcopy on some of the patients (both those with TCT results suggestive of lesions of ASC-US and above, and those with no abnormal TCT results but were positive for HPV16 or 18), and targeted retention of Cervical histopathology was performed. The data were further consolidated to observe the regression and progression of specific subtypes, as detailed in **Table 3**.

3–6 months after the end of photodynamic therapy, cervical histopathology showed regression in 91 patients (94.79%), persistence of pathology in 4 patients, and progression to CIN grade 3 in 1 patient. 1 patient with persistent and 1 patient with progression of pathology underwent surgical intervention after the 6-month follow-up. Ninety-four patients continued with 9–12 months post-treatment follow-up, of which 92 patients showed regression of cervical histopathology, with a cumulative pathological regression rate of 95.83%, with a p -value of <0.01 compared with pre-treatment. There was one case of recurrence, and one case of cervix was vaginally complicate with VAIN2 although suggestive of a low-grade lesion. The results showed that photodynamic therapy well reversed cervical tissue status of high-grade lesions. According to Logistic regression results, the main effect of time point (March-June vs. September-December) was not significant ($OR = 1.23$, $P = 0.65$), and the overall rate of regression did not significantly increase over time. The interaction between initial status and time point was not significant ($P = 0.90$), with consistent time trends across initial status groups. Therefore, considering the initial status regarding TCT: normal, AS-CUS and LSIL, HSIL and ASC-H sensitivity to photodynamic therapy did not differ between groups.

Table 2. TCT results at 3–6 and 9–12 months after ALA-PDT treatment.

TCT	Pretreatment	6-month follow-up ($n = 96$)	12-month follow-up ($n = 94$)
NILM	17 (17.71%)	74 (77.08%)	92 (97.87%)
AS-CUS, LISL	64 (66.67%)	21 (21.88%)	2 (2.13%)
HISL, ASC-H	15 (15.63%)	1 (1.04%)	0
Aggregate	96	96	94

Table 3. regression and progression of cervical lesions at 3–6 and 9–12 months after ALA-PDT treatment.

TCT	Pre-treatment	3–6 months follow-up			9–12 months follow-up			3–6 months cumulative subsidence rate	9–12 months cumulative abatement rate	P -value
		Subside $\leq cin1$	Preservation cin2	Make headway cin3	Subside $\leq cin1$	Preservation cin2	Progress cin3			
NILM	17	17	0	0	16	0	1	100%	94.12%	0.09
AS-CUS										
LSIL	64	60	3	1	61	1	0	93.75%	95.31%	
HSIL										
ASC-H	15	14	1	0	15	0	0	93.33%	100%	
Add up the total	96	91	4	1	92	1	1	94.79%	95.83%	

3.4. Analysis of HPV clearance rates 3–6 and 9–12 months after photodynamic therapy

As shown in **Table 4**, the overall HPV clearance rate after photodynamic therapy could reach 71.88% at 6 months and 88.54% at 12 months, and further analysis showed that the clearance rates of patients infected with only 1 HR-HPV subtype, after photodynamic therapy, 16/18-positive or other subtypes-positive, at 6 months

after treatment were 81.81% and 80.00%, respectively ($P > 0.05$), the clearance rates of patients infected with a single HR-HPV subtype, whether it was 16/18-positive or other subtypes-positive, were 81.81% and 80.00%, respectively ($P > 0.05$). The clearance rates at 12 months after treatment were 95.45% and 88.00%, respectively ($P > 0.05$), and the clearance rates of single HPV subtype infections, whether 16/18 or other subtypes, improved at 12 months after treatment compared with 6-month follow-up.

Table 4. Clearance of HPV infection at 3–6 and 9–12 months after ALA-PDT treatment.

HPV subtype		Pre-treatment	3–6 months		P-value	9–12 months		P-value
			HPV negative(a)	Clearance%		HPV negative(a)	Clearance%	
Single subtype	16/18	23	18	78.3%	$P = 0.47$	22	100.0%	$P = 0.13$
	Other than	24	20	83.3%		21	87.5%	
Many subtypes	16/18	27	18	66.67%	$P = 0.144$	23	85.19%	$P = 0.266$
	Other than	22	13	59.09%		18	81.82%	
Add up the total	Single subtype	47	38	80.9%		43	93.5%	
	Many subtypes	49	34	69.4%		42	87.5%	
Total		96	69	71.88%		85	88.54%	

The clearance rates of patients with multiple HPV subtypes infections after photodynamic therapy, including and without subtypes 16/18, were 66.67% and 59.09% at 6 months after treatment ($P > 0.05$), and 85.19% and 81.82% at 12 months after treatment ($P > 0.05$), respectively, and from the table, it is clear that the multiple HPV subtypes infections whose HPV clearance rate also increased gradually over a 1-year period, and it took longer to clear multiple subtypes of HPV infections compared with single HPV subtype infections followed up during the same period. (6 months: 16/18 vs. 16/18+: 81.81% vs. 66.67% ($P < 0.01$); other vs. other+: 80.00% vs. 59.09% ($P < 0.01$); 12 months: 16/18 vs. 16/18+: 95.45% vs. 85.19% ($P > 0.05$); other vs. other+: 88.00% vs. 81.82% ($P > 0.05$)).

Finally, we compared the distribution of the 4 HPV subtypes 16, 52, 58, and 33, which persisted at 9–12 months of post-treatment follow-up, with the distribution of HPV subtypes prior to photodynamic therapy, as detailed in **Table 5**. It was found that these 4 subtypes were also the top 5 types in terms of the number of subtypes of HPV infected prior to treatment, and of these types, HPV 16 was the subtype with the highest number of infections and the subtype with the highest clearance rate (95.45%) was the highest subtype, and the other 3 HPV subtypes had decreasing clearance rates in that order.

Table 5. Clearance of different HPV infection subtypes.

Arrange in order	HPV subtype	Number of positives (persons)			
		Pretreatment	Post-treatment		Clearance
			3–6 months	9–12 months	
1	Type 16	47	7	3	91.49%

Continuation Table:

Arrange in order	HPV subtype	Number of positives (persons)			
		Pretreatment	Post-treatment		Clearance
			3–6 months	9–12 months	
2	Type 52	21	5	3	85.71%
3	Type 58	19	5	3	84.21%
4	Type 51	11	0	0	100%
5	Type 33	10	2	2	80%

3.5. Comparison of treatment efficiency between the two groups

As can be seen from Table 6, according to the TCT and HPV results suggesting normal, chronic cervicitis, visible scooped cells or LISL/CIN grade 1 after treatment, the treatment effect was judged to be pathological regression, i.e., the treatment was effective. There were 96 people in the photodynamic therapy group (treatment group), of whom 91 were treated effectively and 5 were ineffective. 107 people in the LEEP group (control group), of whom 104 were treated effectively and 3 were ineffective. The control group had an effective rate of 97.20% and the treatment group had an effective rate of 94.79%. *p*-value (0.45) was greater than the level of significance (0.05) indicating that there was no significant difference in the effective rate between the two groups. The risk ratio was 0.986, indicating that the photodynamic therapy group was 98.6% as effective as the LEEP group. Since the confidence interval contains 1, it indicates that the difference in the effective rate between the treatment and control groups is not statistically significant.

Table 6. Outcome of photodynamic therapy group and LEEP treatment group.

Groups	Validity	Null	Efficient	<i>p</i>	RR (95% CI)
Photodynamic group	92	4	95.83%	0.45	0.986 (0.95–1.02)
LEEP group	104	3	97.20%		
(Grand) total	196	7	96.55%		

RR: Risk Ratio.

3.6. Comparison of non-inferiority between the two groups

After treatment according to the two treatment programs, 107 people in the LEEP group and 96 people in the photodynamic group. Calculations using R showed that the treatment group had an efficiency rate of 95.83%, and the control group had an efficiency rate of 97.20%. Difference between the two groups: −1.36% (1.36% lower in the treatment group than in the control group), 95% confidence interval: [−5.77%, 3.05%]. The non-inferiority cutoff (*Δ*) was therefore set previously at 10%. Based on the lower limit of the confidence interval of −5.77%, it is greater than −10%. Therefore, the treatment group was non-inferior to the control group. That is, the test group is considered non-inferior to the control group at the pre-set non-inferiority cut-off value.

3.7. Characterization of patients with no HPV conversion at 12 months after ALA-PDT treatment.

We continued to follow the 9 patients who were persistently HPV positive at 12-month follow-up for a maximum of 39 months, of the 9, 1 was lost to follow-up, 2 were HPV negative at 36–39 months post-treatment respectively, 2 recurred, and 1 progressed to CIN3 at 18–27 months after photodynamic therapy, all 3 were treated with cervical excision and were retested at 6 months after treatment TCT, HPV were negative, 1 person's cervical pathology was maintained at low-grade lesions, but complicated with vaginal intraepithelial neoplasia grade 2, which is now being treated with laser therapy, and the remaining 2 people were followed up with regular colposcopies, and the pathology results were suggestive of low-grade lesions.

3.8. Adverse reactions

All patients had no adverse reactions during drug pretreatment, and after treatment with ALA-PDT, the patients' adverse reactions mainly consisted of mild to moderate lower abdominal cramps, increased secretions, and vulvar itching, which naturally resolved 1–3 days after treatment, and there were no drug allergies, LED light allergies, infections, ruptures, and other adverse reactions, and there was no cervical scar formation after the lesions subsided.

4. Discussion and conclusion

The latest American Society for Colposcopy and Cervical Pathology guidelines for cervical pre-cancer state that the treatment of choice for HSIL (CIN2 and CIN3) is excisional therapy, which includes loop electrosurgical excision, cold-knife LEEP, and laser cone biopsy, with reported cure rates of 90%–98% for each method. Despite the high cure rate, disruption of the physiologic structure of the cervix is a common problem with excisional treatments, which can lead to infertility, miscarriage, or preterm delivery, resulting in reduced female fertility. Another problem with excisional treatments is that they do not eradicate HPV, and persistent HPV infections play an important role in cervical cancer development. Considering the side effects of excision treatment and the fact that CIN2 can regress naturally, the guideline also suggests that “some people with CIN2, especially young women with reproductive needs, can be observed” [2,9], after the implementation of the new guideline, the number of people who chose conservative treatment has gradually increased, and the data from several studies show that the natural regression rate of CIN2 is in the range of 35% to 35%. The natural regression rate is between 35% and 73.1%, the progression rate is 14.2%–17.1%, and the natural regression rate is higher in young women younger than 25 years old [10], The psychological burden associated with a CIN2 diagnosis and the subsequent treatment decision-making process is substantial. Patients who opt for conservative observation, particularly young women with reproductive needs, frequently experience considerable anxiety and fear during the monitoring period. This emotional distress stems from the uncertainty surrounding disease progression and the potential risk of developing invasive cervical cancer, despite the relatively favorable natural regression rates reported in the literature [11]. The psychological toll of “watchful waiting” should not be underestimated, as sustained anxiety can adversely affect patients' quality of life, treatment adherence, and overall mental well-being. Fertility concerns represent another critical psycho-oncological dimension. The ASCCP guidelines emphasize excisional therapy as the treatment of choice for HSIL, yet these procedures inevitably disrupt the physiologic architecture of the cervix, with well-documented risks of subsequent infertility,

miscarriage, and preterm delivery. For young women desiring future pregnancy, the prospect of fertility compromise introduces psychological conflict.[12]. Therefore, there is a desire to find a treatment that does not over-treat without missing patients who really need surgery. Photodynamic therapy (PDT) emerges as a promising psycho-oncologically favorable alternative. By offering a minimally invasive, highly selective, and fertility-preserving therapeutic option, PDT may substantially alleviate the psychological burden associated with traditional treatment paradigms. The reduced trauma and preservation of cervical anatomy address the fertility-related anxieties that plague reproductive-aged women, while the effective treatment of superficial lesions provides psychological reassurance against disease progression. The ease of operation and minimal toxic side effects further contribute to reduced treatment-related stress.[5].

From the results of this study, it can be seen that the cumulative pathological regression rate reached 95.83% at the follow-up of 9–12 months after the end of photodynamic therapy, which approximates the sum of the results of lesion disappearance and regression of 92.59% in the study of Wu et al. This result shows that photodynamic therapy can well reverse the status of high-grade lesions in cervical tissues [13]. We further divided patients into 3 groups according to their initial TCT status: normal group, AS-CUS and LSIL group, HSIL and ASC-H group, and found that the therapeutic efficacy of photodynamic therapy was not related to the results of initial TCT. With photodynamic therapy proven to be effective in treating CIN2, the main concerns physicians currently have about non-surgical treatment of high-grade cervical lesions are recurrence and failure to detect lesions in a timely manner. In the present study, four patients with pathology downgraded to CIN1 after treatment recurred 12–27 months after treatment with a recurrence rate of 4.17%, whereas another study on the use of photodynamic therapy for the treatment of CIN2 did not have a single case of recurrence at follow-up up to 12 months, as can be seen from the study on the follow up of surgical treatment, Bogani et al. conducted a study on 200 patients who underwent LEEP for CIN 2–3 patients were followed up for at least 5 years with a postoperative recurrence rate of 5.5 [14], while another Maita analysis that included 15 studies showed that the rate of residual or recurrent high-grade CIN assessed at 2 years or less ranged from 4%–18%, with a mean of 8% [15]. Of course, the low recurrence rate after photodynamic therapy in this study may be related to the small amount of data, the short follow-up period, and the fact that the initial cases did not include CIN grade 3. But compared to the 17.1%–19% progression rate with conservative treatment [10,16], more people can avoid surgery with photodynamic therapy. We know that patients who have undergone circular electrosurgical excision, cold knife LEEP, and laser cone biopsy have no choice but to opt for hysterectomy in case of recurrence if the residual cervix is small in size, whereas patients who have recurred after photodynamic therapy can be preferred to cervical resection treatment as the cervix is intact, reducing the huge trauma and psychological stress associated with hysterectomy[17]. According to the 2019 American Society for Colposcopy and Cervical Pathology follow-up opinion, patients with a history of high-grade lesions can safely return to low-intensity routine screening after opting for observational therapy as long as they have had two consecutive negative HPV and TCT combined screens, and then three more combined screens spaced 1 year apart, all with negative results. With the accumulation of data on photodynamic therapy for CIN2, at low recurrence rates, patients with CIN2 who are monitored for precancerous lesions with photodynamic therapy and repeat colposcopy can avoid excisional therapy while minimizing treatment-related adverse effects, including possible preterm labor [17].

Persistent HRHPV infection is thought to be responsible for the development of cervical lesions [18]. It is also a prerequisite for CIN recurrence after treatment [20,21]. In our study during the first year of follow-up after the use of photodynamic therapy, the overall HPV clearance rate after photodynamic therapy was up to 71.88% at 6 months and 88.54% at 12 months, with a higher clearance rate for single HPV subtype infections compared to multiple subtypes of infections, and previous studies have found that HPV types 16 and 18 are the HPV types most likely to lead to invasive cervical cancers, accounting for 70% of all HPV positive cervical cancers [22], but from the data of our study, it is known that these two types of HPV are not the most difficult HPV types to be cleared after photodynamic therapy, after 12 months after photodynamic therapy, all (100%) of the HPV18 infections were cleared, and the clearance rate of HPV16 was 95.45%, and the study suggests that HPV16 and HPV18 are prone to cause cervical cancer. It was shown that HPV16 and HPV18 are prone to cause cervical cancer because the E6 and E7 genes in the viruses are easily integrated into human keratinocytes, which leads to the progression of the lesions to invasive cervical cancer, and the integration of the genes is related to the duration of the infection [23,24]. If the duration of infection is shortened through photodynamic therapy, integration of the HPV genes with human genes can be avoided, and thus preventing the occurrence of cervical lesions or invasive cervical cancer. This suggests that the reversal of cervical cytopathy in HSIL/CIN2 patients benefits from the clearance of HPV infection after PDT treatment. Our study also identified four HPV subtypes 16, 52, 58, and 33 that persisted at 9–12 months of post-treatment follow-up, a finding that approximates the results of a retrospective study involving more than 310,000 individuals by Li et al. which noted that HPV 16, 33, 39, 52, and 58 are the hr-HPVs that are more likely to persist, and therefore, the HPV types that are more difficult to clear [25].

In this study, we compared the efficacy rate of photodynamic therapy and cervical LEEP treatment, and the results showed that the efficacy rate of the photodynamic therapy group was 94.79%, and the efficacy rate of the control group was 97.20%. The difference in the efficiency between the two groups was not statistically significant ($p = 0.45$), and the risk ratio was 0.986 (95% CI: 0.936–1.039), suggesting that the photodynamic therapy group's efficiency was close to that of the control group, and that the difference was within the clinically acceptable range. This result is consistent with some of the available studies and supports photodynamic therapy as a viable alternative. There was no statistically significant difference in treatment outcomes between the two groups, and the photodynamic group was noninferior to the LEEP group. Combining photodynamic therapy offers its own unique clinical advantages such as minimally invasiveness, preservation of fertility and reduced risk of complications. These advantages are particularly prominent in young women or those with reproductive needs. In addition, in the enrolled population, most women who chose photodynamic therapy were young women who had not completed childbearing, and most women in the LEEP group were women who had completed childbearing. There was a difference in the mean age of the two groups. The photodynamic group was young and sexually active, with a high relative risk of HPV infection. The photodynamic group can eliminate cervical HPV by directly destroying the cells at the lesion area through photochemical reaction and increasing the local and systemic immunity. For women with reproductive requirements, ALA-PDT has the advantages of significant efficacy, non-invasive, simple operation, etc. It can block the cervical HPV in time. It can promptly block the persistent infection of cervical HRHPV and reduce the risk of progression of this

disease, while also preserving the integrity of the cervix, which has clear clinical application value.

However, the relatively small sample size of this study may have limited the ability to detect smaller differences. In addition, the overall follow-up period was 12 months, and individual patients with abnormal results were followed up for up to 24 months, failing to assess longer-term efficacy and recurrence rates. Future studies should further expand the sample size and conduct long-term follow-up to verify the efficacy and safety of photodynamic therapy. Meanwhile, subgroup analyses may help identify the advantages of photodynamic therapy in specific patient groups. Overall, Clinicians should recognize that treatment recommendations for CIN2 extend beyond purely biological considerations. A patient-centered approach that integrates psycho-oncological support—including counseling regarding fertility preservation, anxiety management during observation periods, and shared decision-making that acknowledges patients' values and reproductive goals is essential. The results of this study provide clinicians with more treatment options to choose either photodynamic therapy or LEEP therapy based on patient-specific conditions and preferences.

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