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Clinical efficacy of thermocoagulation in women with biopsy-confirmed cervical low-grade squamous intraepithelial lesions (LSILs) or less after colposcopy referral

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ABSTRACT

Objectives: To evaluate the clinical efficacy of thermocoagulation in women with biopsy-confirmed cervical low-grade squamous intraepithelial lesions (LSIL) or less after colposcopy referral.

Material and methods: A longitudinal study was performed. Women who were diagnosed with cervical LSIL or chronic cervicitis underwent scheduled follow-up examinations with cytology and human papilloma virus (HPV) genotyping for two years after the initial management with thermocoagulation or observation without treatment. All women underwent scheduled follow-up with combined cytology and HPV test at 6th months, 12th months, and 24th months after the initial management. Both HPV clearance and cytological regression were included in the analysis, with clinical cure defined as normal cytology and negative HPV results.

Results: A total of 221 women were included. The histopathological results identified 136 (61.54%) patients with LSIL and 85 (38.46%) with chronic cervicitis. Of these, 113 (51.13%) received thermocoagulation therapy, and 108 (48.87%) chose observation. The 2-year follow-up rate was 91.40%. Women who received thermocoagulation presented a significantly higher probability of cure for two years than those who chose observation (62.86% vs 39.18%, $p < 0.001$). This preponderance was not observed in the subgroup analysis regarding women with cervical cervicitis (54.17% vs 41.38%, $p = 0.277$) but was observed in women with LSILs (70.18% vs 38.24%, $p < 0.001$).

Conclusions: Thermocoagulation may be indicated for patients with cervical LSILs as an effective outpatient procedure in clinical practice.

Key words: ablative techniques; cervical intraepithelial neoplasia; cytological regression; HPV clearance; outpatient

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INTRODUCTION

Cervical low-grade squamous intraepithelial lesions (LSILs) (CIN1) are considered transient indicators of human papilloma virus (HPV) infection. Considering the high rate of spontaneous regression and low rate of progression, guidelines recommend a conservative approach with follow-up in women with CIN1[1, 2]. However, studies have reported that 20–40% of low-grade lesions will progress to high-grade squamous intraepithelial lesions (HSILs) [3–5]. Additionally, a recent study revealed that doctors were not satisfied with the current treatment options [6]. Therefore, more active treatments are warranted on account of the stressful experience and negative impact on the patient's daily life caused by repeated follow-up tests without treatment [7].

Local ablative techniques such as thermocoagulation have been used to treat cervical premalignant lesions for decades [8, 9] and proven effective [10]. This method uses electricity to generate temperatures of 100–120°C for ablation of cervical lesions and was introduced by Kurt Semm in 1966 [11]. Thermocoagulation has various attractive features, making it suitable for use in treating CIN1, especially in low- and middle-income countries (LMICs). The procedure

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is easy and fast, anesthesia is not needed in most patients (practicable in the clinic), and complications and side effects are minimal.

However, few currently available studies regarding thermocoagulation have focused on the specific population with pathologically confirmed low-grade cervical lesions or chronic cervicitis (HPV infected but no cervical squamous intraepithelial lesions were confirmed) after colposcopy referral. Also, no WHO guidelines exist regarding thermocoagulation [12]. Thus, the objective of this study was to compare the clinical efficacy of thermocoagulation with that of untreated controls in the management of biopsy-confirmed LSILs or chronic cervicitis. Findings from this study are expected to provide useful information for clinical practice.

MATERIAL AND METHODS

Participants

All the patients with a histopathological diagnosis of cervical LSIL and chronic cervicitis, between January 2018 and December 2019 in Fujian Maternal and Child health hospital, were recruited consecutively. All patients underwent colposcopy-guided biopsy of suspicious areas of the uterine cervix after an abnormal referral cervical cytology/HPV finding, according to 2012 ASCCP guidelines [1].

Only women who had the referral cytology (Thinprep cytology test, TCT) and HPV test performed in our institutions were included in the present analysis. The eligibility criteria for the present study were adequate colposcopy examination, type 1 transformation zone of the cervix, no evidence of endocervical canal involvement. Women with previous diagnosis or treatment for cervical dysplasia or invasive cervical cancer were excluded, as well as women with synchronous intraepithelial lesions (vulva, vaginal, anal) and women with HIV infection or other type of immunodepression.

At baseline, we classified patients into the thermo-coagulation arm if they received thermo-coagulation treatment and into the observation arm otherwise. Participants gave written consent according to guidelines approved by the Committee for Human Research, Fujian Maternal and Child health hospital (approval No. 2019-033). The clinical data of all patients were collected, including patient age, gravidity and parity, cytology, HPV test results.

Procedures

Cytological findings were classified by expert cytopathologists in our center according to the Bethesda system terminology. The polymerase chain reaction reverse dot blot HPV genotyping kit (Yaneng® Limited Corporation, Shenzhen, China) , which has been demonstrated that displayed good agreement with the internationally recognized Cobas 4800 test [13, 14], was used to detect 18 high-risk HPV types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -53, -56, -58, -59, -66, -68, -73, -82, and -83) and 5 low-risk HPV types (HPV-6, -11, -42, -43, and -81). Colposcopy and colposcopy-guided punch biopsy were performed by expert colposcopists in our center. Histopathological diagnoses of LSIL (on colposcopy-guided biopsy) were made by pathologists with expertise in the field of cervical intraepithelial lesions.

After the initial diagnosis of cervical LSIL and chronic cervicitis (HPV infected only), patients were offered treatment with thermocoagulation or conservative follow-up without treatment according to their willingness following consultation. For thermocoagulation, procedures were performed under colposcopic guidance. The probe was applied to the cervix at 100 for 45 s without anesthesia. In situations where the transformation zone was larger than the thermocoagulation probe, the probe was applied for another 45 s to the untreated area overlapping the treated area [15].

Sample size calculation

Based on the reported articles [16, 17], in the sample size calculation we hypothesize the cure rate in the observed group was about 60% and in treated group was about 80%. A minimal total sample size of 158 patients (79 in each group) was needed to detect a 20% increase in cure rate for thermo-coagulation over observation, at 80% Power, significance level of 5%, and 1:1 ratio. Allowance was made for a loss to follow-up rate of 20%, hence at least 198 patients (99 in each group) was needed for the study.

Follow up

All women underwent scheduled follow-up examinations with combines cytology and HPV-genotyping test at 6^{th} months, 12^{th} months, and 24^{th} months after the initial management and diagnosis of cervical LSIL or chronic cervicitis. The primary end point was "clinical cure", defined as the detection of normal cytology and negative HPV tests in a single visit during the scheduled follow-up, with censoring at the last date of follow-up. Colposcopy referrals during follow-up were also defined as censored events. The HPV clearance rate and cytological regression (negative cytology tests following an abnormal cytological finding on referral) rate were also measured.

Statistical analyses

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, New York, USA). $\chi 2$ testing and Fisher's exact test were used, as appropriate, to evaluate associations. A Kaplan-Meier survival curve was constructed to determine the time-based rate of regression to cure. The curves of the two groups (thermocoagulation group and observation group) were tested by using the log-rank test. A $p < 0.05$ was considered statistically significant.

Table 1. Baseline and follow-up characteristics of the study cohort

Characteristics	Observation (108)	Thermocoagulation (113)	p
Baseline			
Age, year	37.00 (11.00)	40.00 (14.00)	0.345
Gravidity ≥ 3	50/108 (46.30)	48/113 (42.48)	0.568
Parity ≥ 2	47/108 (43.52)	44/113 (38.94)	0.187
HPV infection			
HR-HPV	104/107 (97.20)	101/112 (90.18)	/
Multiple	45/107 (42.06)	34/112 (3036)	
16, 18 genotype	24/107 (22.43)	15/112 (13.39)	
TCT			
NILM	36/108 (33.33)	56/113 (49.56)	/
ASC-US	46/108 (42.59)	28/113 (24.78)	
LSIL	25/108 (23.15)	28/113 (24.78)	
ASC-H	0/108 (0.00)	0/113 (0.00)	
HSIL	1/108 (0.93)	1/113 (0.88)	
Biopsy			
LSIL (CIN1)	76/108 (70.37)	60/113 (53.10)	**0.008**
Chronic cervicitis	32/108 (29.63)	53/113 (46.90)	
Follow-up			
HPV clearance			
Yes	42/96 (43.75)	66/103 (64.08)	**0.004**
No	54/96 (56.25)	37/103 (35.92)	
Cytology			
NILM	72/97 (74.23)	90/105 (85.71)	
Regression (baseline cytology > NILM)			
Yes	48/68 (70.59)	46/54 (85.19)	0.057
No	20/68 (29.41)	8/54 (14.81)	
Cure			
Yes	38/97 (39.18)	66/105 (62.86)	**< 0.001**
No	61/97 (60.82)	39/105 (37.14)	

HR-HPV — high-risk human papillomavirus; TCT — Thinprep cytology test; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesion; ASC-H — atypical squamous cells — cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; CIN — cervical intraepithelial neoplasia; Bold indicate $p < 0.05$

RESULTS

During the study period, a total of 221 women were included. A total of 219 (99.09%) had positive results on HPV testing, and 129 (58.37%) had abnormal cytological findings on referral. The histopathological results identified 136 (61.54%) patients with LSILs and 85 (38.46%) with chronic cervicitis. Of these, 113 (51.13%) received thermocoagulation therapy, and 108 (48.87%) chose observation. The general clinical features of 221 patients in the two groups were all comparable and are shown in Table 1.

After two years, 19 (8.60%) patients were lost to follow-up, and the follow-up rate was 91.40%. In the thermocoagulation group, 66 out of 103 (64.08%) HPV-infected women showed HPV clearance, and 46 out of 54 (85.19%) women with abnormal TCT results showed cytological regression. In the observation group, 42 out of 96 (43.75%) HPV-infected women showed HPV clearance, and 48 out of 68 (70.59%) women with abnormal TCT results showed cytological regression. The HPV clearance and cure rate for thermocoagulation were significantly higher than that for observation (HPV clearance: 64.08% vs 43.75%, $p = 0.004$; cure: 62.86% vs 39.18%, $p < 0.001$). Figure 1 represents the Kaplan-Meier curves for the 2-year probability of cure according to different management strategies after the initial histopathological diagnosis of LSIL (CIN1) or chronic cervicitis. The women who received thermocoagulation presented a significantly higher probability of cure for two years than those who chose observation ($p < 0.001$).

To control potential bias in our results due to the different cervical lesion compositions of the two groups, we per-

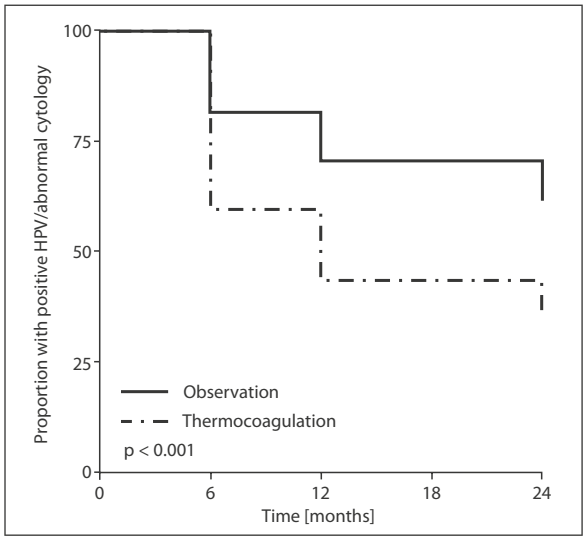

Figure 1. Kaplan-Meier analysis of time-based proportion of patients with positive HPV/abnormal cytology

formed subgroup analyses in the LSIL and chronic cervicitis subgroups. Notably, the HPV clearance rate for thermocoagulation was significantly higher than that for observation (73.21% vs 41.79%, $p < 0.001$) in the LSIL subgroup, whereas no significant difference in the HPV clearance rate between the women who received thermocoagulation and the women who were followed without treatment was observed in the chronic cervicitis subgroup. Differences regarding cytological regression between the thermocoagulation and observation groups were not significant in any subgroup analysis. Furthermore, for the cure rate, the women who received thermocoagulation presented a higher probability than those in the observation group in the LSIL subgroup (70.18%vs 38.24%, $p < 0.001$). However, the results from analyses including the chronic cervicitis subgroup did not show a higher cure rate in the women who received thermocoagulation ($p = 0.277$) (Tab. 2, 3). Kaplan-Meier analysis also confirm our results above. (Fig. 2, 3).

Table 2. Baseline and follow-up characteristics of women with biopsy-confirmed LSIL (CIN1)

Characteristics	Observation (76)	Thermocoagulation (60)	p
Baseline			
Age, year	35.00 (10.00)	38.00 (12.75)	0.122
Gravidity ≥ 3	36/76 (47.37)	25/60 (41.67)	0.507
Parity ≥ 2	33/76 (43.42)	25/60 (41.67)	0.837
HPV infection			
HR-HPV	74/75 (98.67)	57/59 (96.61)	/
Multiple	34/75 (45.33)	22/59 (37.29)	
16, 18 genotype	17/75 (22.67)	9/59 (15.25)	
TCT			
NILM	20/76 (26.32)	17/60 (28.33)	/
ASC-US	33/76 (43.42)	19/60 (31.67)	
LSIL	22/76 (28.95)	23/60 (38.33)	
ASC-H	0/76 (0.00)	0/60 (0.00)	
HSIL	1/76 (1.32)	1/60 (1.67)	
Follow-up			
HPV clearance			
Yes	28/67 (41.79)	41/56 (73.21)	< 0.001
No	39/67 (58.21)	15/56 (26.79)	
Cytology			
NILM	48/68 (70.59)	46/57 (80.70)	
Regression (baseline cytology > NILM)			
Yes	35/52 (67.31)	34/42 (80.95)	0.137
No	17/52 (32.69)	8/42 (19.05)	
Cure			
Yes	26/68 (38.24)	40/57 (70.18)	< 0.001
No	42/68 (61.76)	17/57 (29.82)	

HR-HPV — high-risk human papillomavirus; TCT — Thinprep cytology test; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesion; ASC-H — atypical squamous cells — cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion; Bold indicate $p < 0.05$

Table 3. Baseline and follow-up characteristics of women with biopsy-confirmed chronic cervicitis

Characteristics	Observation (32)	Thermocoagulation (53)	p
Baseline			
Age, year	43.50 (15.50)	41.00 (14.50)	0.261
Gravidity ≥ 3	14/32 (43.75)	23/53 (43.40)	0.975
Parity ≥ 2	14/32 (43.75)	19/53 (35.85)	0.469
HPV infection			
HR-HPV	30/32 (93.75)	44/53 (83.02)	/
Multiple	11/32 (34.38)	12/53 (22.64)	
16, 18 genotype	7/32 (21.88)	6/53 (11.32)	
TCT			
NILM	16/32 (50.00)	39/53 (73.58)	/
ASC-US	13/32 (40.63)	9/53 (16.98)	
LSIL	3/32 (9.38)	5/53 (9.43)	
ASC-H	0/32 (0.00)	0/53 (0.00)	
HSIL	0/32 (0.00)	0/53 (0.00)	
Follow-up			
HPV clearance			
Yes	14/29 (48.28)	25/47 (53.19)	0.677
No	15/29 (51.72)	22/47 (46.81)	
Cytology			
NILM	24/29 (82.76)	44/48 (91.67)	
Regression (baseline cytology > NILM)			
Yes	13/16 (81.25)	12/12 (100.00)	0.238
No	3/16 (18.75)	0/12 (0.00)	
Cure			
Yes	12/29 (41.38)	26/48 (54.17)	0.277
No	17/29 (58.62)	22/48 (45.83)	

HR-HPV — high-risk human papillomavirus; TCT — Thinprep cytology test; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesion; ASC-H — atypical squamous cells — cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion

DISCUSSION

The present 2019 ASCCP recommendations prefer continued observation of patients with histologic LSIL (CIN1) diagnosed on consecutive visits for at least two years [18]. However, some studies reported the increased rate of histologic HSIL (CIN 2+) at among women who underwent LEEP for CIN 1 diagnosed [19]. Thus, treatment is an acceptable option and cannot be ignored in clinical practice. There is now a growing, solid evidence supporting the use of thermocoagulation in the treatment of cervical lesions, but most of the studies were within screen-and-treat programmes [20, 21]. The findings of our study demonstrate that thermocoagulation can serve as an efficacious management strategy in women with a biopsy diagnosis of LSIL. The easy, fast, and anesthesia-free features of these techniques, which have further reduced the operational challenges, add to the clinical importance of this finding.

The effectiveness of thermocoagulation in the treatment of LSILs derived from this study are in accordance with published studies. A meta-analysis of 13 studies on thermocoagulation up to 2014 reported a cure rate of 95% for cervical precancers [22]. Additionally, our results (24 months post-treatment) corresponds well with the preliminary cure rate reported previously, with a thermocoagulation cure rate of > 80% (at 6 months to 1 year) in HIV-positive women in India [23] and 89.2% at 6 months in Nigeria [15]. However, it is intriguing to note that thermocoagulation may not improve the cure rate or, in other words, the HPV clearance rate in women with a biopsy diagnosis of chronic cervicitis. One explanation might be that HPV infection is transient and has

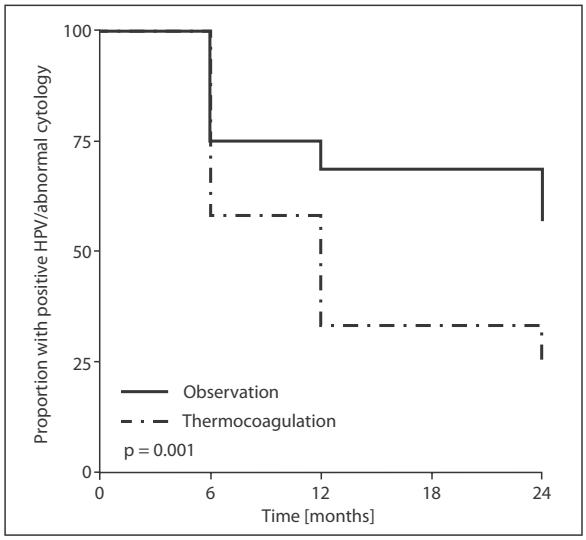

Figure 2. Kaplan-Meier analysis of time-based proportion of positive HPV/abnormal cytology in patients with biopsy-confirmed LSIL (CIN1)

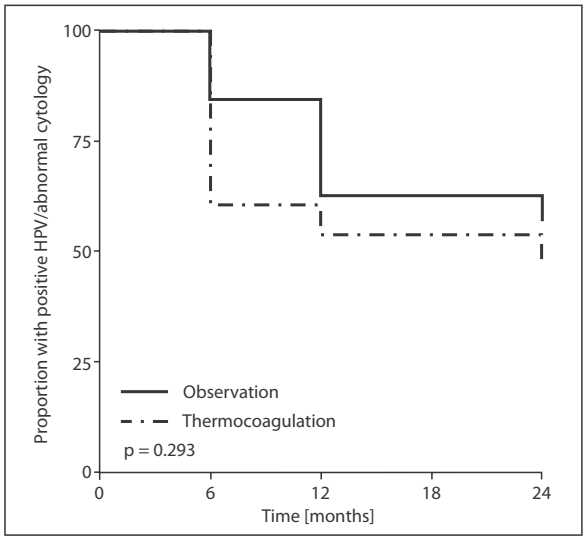

Figure 3. Kaplan-Meier analysis of time-based proportion of positive HPV/abnormal cytology in patients with biopsy-confirmed chronic cervicitis

not elicited lesions in this population and could be cleared out naturally without intervention in most cases.

In our series, thermocoagulation was restricted to patients with a biopsy for diagnosis of LSIL and chronic cervicitis with histopathological assessment after colposcopy. Furthermore, we did not include patients whose colposcopic examination showed a cervical transformation zone that was not completely visible or invisible. These factors would be considerable strengths of our study, given that inappropriate treatments, such as nonexcisional procedures for high-grade lesions and missed application for endocervical lesions, could be avoided in the included study population. However, the modest sample size from a single hospital is the main limitation and potentially limits the generalizability of the results. According to previously published results [7, 24, 25], the regression rate of LSIL appeared to be linked to the referral cytology and HPV infection status, but the small numbers of patients prevented us from conducting a subgroup analysis.

CONCLUSIONS

In conclusion, thermocoagulation may be indicated for patients with cervical LSILs as an effective outpatient procedure. Further studies including larger populations to confirm our findings regarding their clinical utility are, however, recommended.

Article informations and declarations

Conflict of interest

The authors declare no conflicts of interest.

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