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Systematic Review

Efficacy and Safety of Thermocoagulation *vs.* Cryotherapy for Cervical Precancerous Lesions: A Systematic Review and Meta-Analysis

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Abstract

Background: The World Health Organization (WHO) has recently endorsed thermal coagulation as an alternative to cryotherapy for cervical precancerous lesions. However, the comparative efficacy and safety of these two treatments lack robust support from large-sample data. This systematic review and meta-analysis aim to evaluate the effectiveness and safety of thermocoagulation compared to cryotherapy in the treatment of cervical precancerous lesions. **Methods**: A comprehensive search of PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov was conducted from inception. Additional trials were identified through the reference lists of published reviews. Inclusion criteria encompassed original data studies with colposcopically, biopsied, cytologically, or visually inspected (VIA/VILI) identified patients. Studies were required to have a follow-up duration of at least 6 months, a sample size exceeding 20 patients, a follow-up attendance rate exceeding 50%, and involve cryotherapy or thermocoagulation treatments. **Results**: Inclusive of all patients, thermocoagulation demonstrated a significantly higher pooled cure proportion compared to cryotherapy (85% *vs.* 81%, z = 2.245, $p = 0.025$). However, for VIA-positive patients alone, the difference was not statistically significant (80.0% *vs.* 79%, z = 1.932, $p = 0.053$). The incidence of pain was comparable between the two treatment arms, while both exhibited a high incidence of vaginal discharge. Thermocoagulation displayed a lower complication rate for intraoperative pain and postoperative vaginal discharge than cryotherapy, providing a higher level of patient comfort. **Conclusions**: Thermal coagulation proves to be more effective for patients with cervical precancerous lesions, but the effectiveness of the two regimens is similar if only for VIA-positive patients. In terms of complications, thermocoagulation exhibits a similar rate of intraoperative pain and a lower rate of postoperative vaginal discharge than cryotherapy, enhancing patient comfort.

Keywords: cervical precancerous lesions; thermocoagulation; cryotherapy; cervical lesions; thermal ablation

1. Introduction

Cervical cancer ranks as the fourth most common cancer globally, both in terms of incidence and mortality among women, and ranks the eighth most common cancer among all cancers. In the Global Cancer Data Statistics 2020, the number of new cases of cervical cancer was 604,127 and the number of new deaths was 341,831. Cervical cancer is the most commonly diagnosed cancer in 23 countries and the leading cause of cancer deaths in 36 countries [1]. Although the incidence of cancer is gradually decreasing in developed Western countries, the incidence of many cancers (e.g., cervical cancer) is still on the rise in low-and middle-income countries (LMICs). In resource-constrained settings, the World Health Organization (WHO) has recommended the implementation of "see-and-treat" screening programs, and cryotherapy has been suggested as an alternative ablation technique for cervical precancerous lesions, but the implementation of cryotherapy in LMICs has been limited by a number of factors, and the WHO has recently recommended the use of thermal ablation as an alternative to cryotherapy [2], the comparative efficacy and safety of these two treatments lack robust support from large-sample data.

This study systematically reviews and meta-analyzes the efficacy and safety of thermocoagulation compared to cryotherapy in the treatment of cervical precancerous lesions.

2. Materials and Methods

A thorough search of PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), ICTRP, and ClinicalTrials.gov from inception to 1 May 2023, was conducted. Inclusion criteria encompassed original data studies with colposcopically, biopsied, cytologically, or visually inspected (VIA/VILI) identified patients, a follow-up duration of at least 6 months, a sample size exceeding 20 patients, and a follow-up attendance rate exceeding 50%. Studies involved cryotherapy or thermocoagulation treatments. The risk of bias was assessed using the Newcastle-Ottawa Scale for retrospective studies and Cochrane Handbook guidelines for randomized controlled trials (RCTs).

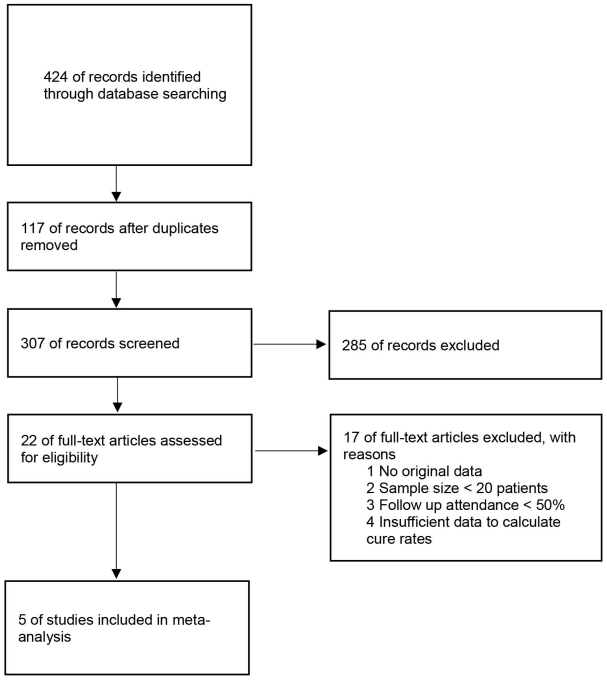

Fig. 1. Study flow diagram.

This study was previously registered with PROSPERO (CRD42023485006) and followed PRISMA guidelines.

2.1 Data Extraction

For all relevant papers identified for inclusion, the following items were collected separately using a data extraction form: author information, publication year, patient age, case definition, human immunodeficiency virus (HIV) status, treatment procedures, number of patients treated, attendance, follow-up, cured patients, follow-up duration, cure definition, and complications.

2.2 Statistical Analysis

STATA/SE 16.0 (Stata Corp, College Station, TX, USA) will be used for meta-analysis. Whenever appropriate, we will calculate odds ratios (OR), risk ratios (RR), or effect label together with 95% confidence intervals (95% CIs). p values of <0.05 will be considered statistically significant for the meta-analysis. The heterogeneity between studies will be assessed using I^2 test: $I^2 < 30\%$ will be considered low heterogeneity, $30\% < I^2 < 50\%$ will be considered moderate heterogeneity, and $I^2 \geq 50\%$ will be considered high heterogeneity. When there is substantial heterogeneity, we will use random-effects model to combine data. Instead, fix-effects model will be used. Publication bias will be evaluated using the Begg's funnel plot and statistical assessment using the Egger test. If meta-analysis cannot be conducted for some outcomes, we will report the results in a narrative manner.

3. Results

3.1 Search Results

Following an exhaustive search across various platforms, a total of 307 articles were identified. Subsequent screening based on titles, abstracts, etc., led to the exclusion of 285 articles. The remaining 22 underwent detailed review, with 5 articles excluded due to a lack of original data, 6 for having a sample size below 20 patients, 3 for attendance below 50%, and 3 for insufficient data to calculate cure rates. Ultimately, 5 articles were included in this review (Fig. 1). And Table 1 (Ref. [3–7]) provides the details of the included papers.

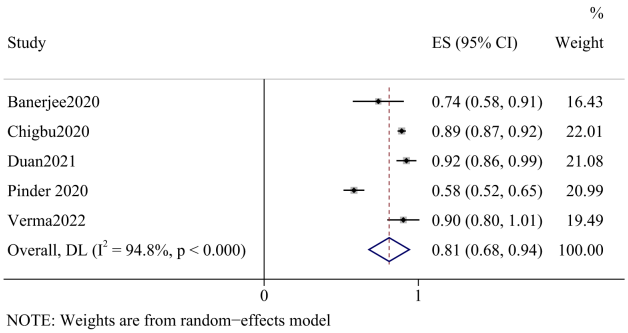

Fig. 2. The pooled cure proportions of cryotherapy. 95% CI, 95% confidence interval.

3.2 Effectiveness

Addressing the question of treatment effectiveness between cryotherapy and thermo-coagulation for patients with precancerous cervical lesions, a meta-analysis was conducted on the five included papers. "Cure rate" served as the outcome indicator, revealing a combined sample size of 1663 cases. The pooled cure proportion for cryotherapy was 81% (Fig. 2, Ref. [3–7]), while for thermo-coagulation, it was 85% (Fig. 3, Ref. [3–7]). Statistical heterogeneity was minimal ($I^2 = 0.0\%$, $p = 0.732$) (Fig. 4, Ref. [3–7]), with acceptable clinical heterogeneity. Meta-analysis using a fixed-effects model indicated a significantly higher cure rate in the thermal coagulation group [OR = 1.35, 95% CI (1.04, 1.75)], with a statistically significant difference ($z = 2.245$, $p = 0.025$).

In the subset analysis of VIA-positive patients, three papers were considered, revealing pooled cure proportions of 80.0% (thermocoagulation (TA) arm) *vs*. 79% (cryotherapy arm), demonstrating mild statistical heterogeneity ($p = 0.830$, $I^2 = 0.0\%$). Meta-analysis using a fixed-effects model indicated a similar cure rate in both arms [OR = 1.30, 95% CI (1.00, 1.71)] ($z = 1.932$, $p = 0.053$). Thus, this study concludes that the effectiveness of cryotherapy and thermo-coagulation treatments is comparable in the treatment of VIA-positive patients.

Table 1. The studies included in this Meta-analysis.

Study	Study type	Case definition	Treatment providers	Cure definition	Cryotherapy					TA				
					N	Age	Cure rates	Satisfaction	HIV (N)	N	Age	Cure rates	Satisfaction	HIV (N)
Banerjee 2020 [3]	RCT	VIA/HPV positive	Trained female health workers	No CIN	150	36.1	74.10%	98%	/	136	36.7	81%	99.30%	/
Chigbu 2020 [5]	RCT	VIA positive	Trained medical personnel	VIA negative	512	47.3	85.50%	80.5	/	511	47.1	89.20%	93.20%	/
Duan 2021 [4]	RCT	CIN2/3	Staff gynecologic colposcopy specialist	HPV and cytology negative, CIN2–	71	31.2	92.30%	/	0	74	31.5	98.50%	/	0
Pinder 2020 [7]	RCT	VIA positive	Trained nurses at the clinic	HPV negative (positive for the same HPV type at baseline), negative VIA (baseline HPV negative)	250	25–49	60%	100%	40%	250	25–49	64%	100%	45%
Verma 2022 [6]	RCT	VIA positive	Not mentioned	VIA negative	34	34.35	90.32%	/	/	34	36.82	93.54%	/	/

RCT, randomized controlled trial; VIA, visual inspection with acetic acid; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; HIV, human immunodeficiency virus; TA, thermocoagulation.

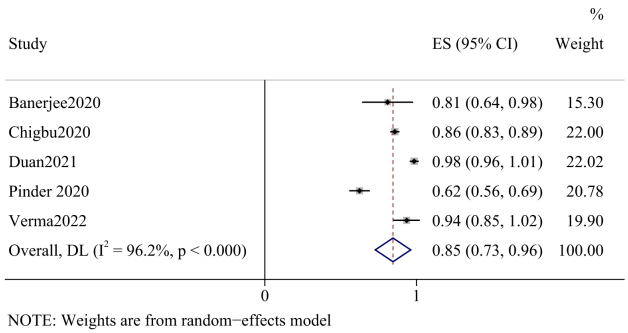

Fig. 3. The pooled cure proportions of TA.

Additionally, Banerjee *et al.*'s study [3] focused on women with cervical intraepithelial neoplasia (CIN) 1 or worse lesions, reporting cure rates of 74.1% (cryotherapy arm) and 81% (TA arm) (p = 0.57). Meanwhile, Duan *et al.*'s study [4] included patients with CIN grades 2–3, with cure rates of 92.3% (cryotherapy arm) and 98.5% (TA arm), respectively ($p > 0.05$).

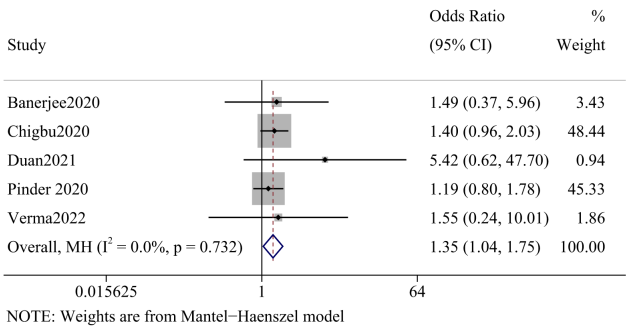

Fig. 4. Cure rates of TA arm and cryotherapy arm of all patients in the included studies.

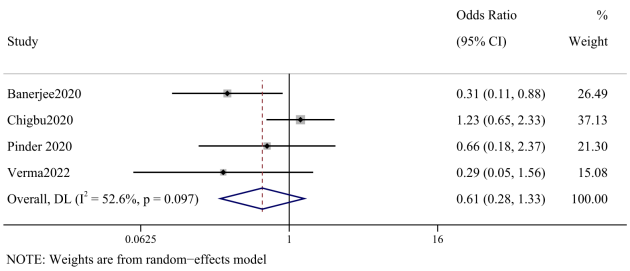

Fig. 5. Moderate or higher pain of TA arm and cryotherapy arm of all patients in the included studies.

3.3 Complications: Pain, Vaginal Discharge

A total of five papers in this study [3–7] focusing on the occurrence of pain during treatment, results from the analysis of pain levels across these studies revealed that the incidence of moderate or higher pain during cryotherapy ranged from 2.4% to 17.6%, whereas for thermal coagulation, it ranged from 1.6% to 5.9%. Meta-analysis of four of these papers, utilizing a random-effects model, demonstrated a similar level of pain between the two treatment arms (test for heterogeneity: I^2 = 52.6%, p = 0.097; OR = 0.61, 95% CI [0.28, 1.33]) (Fig. 5, Ref. [3–7]). However, Duan *et al.*'s study [4] reported significantly higher pain scores in the thermal coagulation arm compared to the cryotherapy arm (visual analog scores 2.2 $\pm$ 1.3 *vs.* 3.0 $\pm$ 2.4, $p < 0.05$). In addition to pain, three of the reviewed papers [4–6] investigated the occurrence of vaginal discharge. These studies revealed a high incidence of vaginal discharge in both treatment arms, ranging from 29% to 100% in cryotherapy and 51.6% to 100% in thermal coagulation. Notably, Duan *et al.*'s study [4] reported a 100% incidence of vaginal discharge in both arms, while Verma *et al.*'s study [6] noted a lower incidence of vaginal discharge in the thermal coagulation group compared to the cryotherapy arm, though the difference was not statistically significant (28.13% *vs.* 51.61%, $p > 0.05$). Conversely, Chigbu *et al.*'s study [5] demonstrated a significantly lower incidence of vaginal discharge in patients treated with thermal coagulation compared to the cryotherapy group (82.2% *vs.* 38.0%, $p < 0.0001$).

4. Discussion

Studies have confirmed that cervical cancer is considered to be almost entirely preventable if highly effective primary (human papillomavirus (HPV) vaccine) and secondary (screening) preventive measures are taken; however, these measures have not been equitably implemented between and within countries, and as of May 2020, <30% of LMICs have implemented a national HPV vaccination program, compared to >80% of high-income countries [8], so that although the incidence of cancer is gradually decreasing in developed Western countries, the incidence of many cancers (e.g., cervical cancer) is still on the rise in LMICs. Because thermal coagulation therapy has the advantage of being portable, transportable and storable, which greatly reduces costs and is very much in line with the concept of "see-and-treat" advocated by the World Health Organization, it makes more sense to promote it in LMICs.

According to the findings of this review, both thermal coagulation and cryotherapy are effective methods for treating precancerous cervical lesions in terms of cure rates, and in the combined analysis of CIN and VIA-positive patients, the cure rate was higher in the thermal coagulation group, whereas the cure rates of the two arms were similar in the inclusion of VIA-positive patients only. Already in 2014, in a Meta-analysis by Dolman *et al.* [9] it was suggested that thermocoagulation was comparable to other therapies (freezing, excision, etc.) in terms of effectiveness for the treatment of CIN; additionally, de Fouw *et al.* [10] in a review published in 2019 included eleven papers on cryotherapy and seven on thermocoagulation and showed

that, both cryotherapy and thermal coagulation were effective treatments for CIN lesions, with cure rates ranging from 90.1%–92.8% for VIA-positive lesions, 91.4%–93.8% for CIN1, and 82.6%–91.6% for CIN2/3, the difference in cure rates between the two regimens in VIA-positive patients and CIN1 grade was not statistically significant, the difference between the treatment effectiveness for CIN2/3 lesions was statistically significant, but when comparing the effectiveness of both treatment modalities in LMICs only, the proportion of cure was similar. Notably, our study's focus on LMICs revealed similar cure proportions for both treatment modalities, with lower overall pooled cure rates, possibly influenced by the inclusion of middle/low-income countries and a significant number of HIV-positive patients in certain studies. These results align with previous research, emphasizing the need for targeted interventions in LMICs.

Regarding intraoperative pain levels, both regimens demonstrated low incidence rates of moderate and higher pain levels, with high patient satisfaction and willingness to recommend the treatment. A randomized non-inferiority clinical trial by Soler *et al*. [11] supported the safety and acceptability of both ablative treatments. In addition, the incidence of postoperative vaginal fluid was high in both arms, but more studies have concluded that the rate of postoperative vaginal fluid is lower with thermal coagulation than with cryotherapy.

In addition, only Pinder *et al*.'s study [7] in the review counted the HIV status of the patients, and in that study, the HIV-positive rate of the patients in both arms was high (49% in the TA arm and 54% in cryotherapy arm). Importantly, despite lower cure rates for HIV-positive patients, the regimens proved safe and equally effective. However, due to the small sample size, further research is warranted to explore the efficacy and safety of thermal coagulation in HIV-positive patients.

While our study adhered to a review protocol, several limitations need acknowledgment. The small number and size of included studies, along with heterogeneity in sample sizes, follow-up duration, inclusion criteria, and "cure rate" definition, necessitate cautious interpretation. On the other hand, the treatment providers in the studies were professionally trained physicians or clinical nurses, and the institutions ranged from rural clinics to teaching hospitals, the experience of treatment providers and the medical level of each institution may have a certain impact on the research results. Future research, incorporating more extensive studies and larger sample sizes, is vital to validate our conclusions.

5. Conclusions

In summary, thermal coagulation proves to be more effective for patients with cervical precancerous lesions, with comparable effectiveness to cryotherapy in the subset of VIA-positive patients. In terms of complications, thermocoagulation exhibits a similar rate of intraoperative pain and a lower rate of postoperative vaginal discharge than cryotherapy, enhancing patient comfort. Moreover, the cost-effectiveness of transportation and storage further positions thermal coagulation as a promising solution. This study underscores the potential suitability and merits of thermal coagulation in the management of cervical precancer, particularly in middle/low-income countries. Its attributes advocate for further promotion and integration into clinical applications.

Availability of Data and Materials

All data points generated or analyzed during this study are included in this article and there are no further underlying data necessary to reproduce the results.

Author Contributions

JL and XP designed the research study. JL, XP and HC performed the research. JL and XP analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5103072.

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