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Treatment of cervical intraepithelial lesions

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Abstract

Precancerous cervical lesions precede the development of invasive cervical cancer by 10–20 years, making cervical cancer preventable if these lesions are detected and effectively treated. Treatment has evolved in the last few decades and now includes ablative options that can be performed in lower-resource settings where surgical excision is not feasible or routinely available. Gas-based cryotherapy, which freezes cervical tissue to induce localized necrosis, is the most commonly used ablative treatment. However, its implementation in low-resource settings is difficult because the refrigerant gas can be difficult to procure and transport, and is expensive. New cryotherapy devices that do not require an external supply of gas appear promising. Thermal coagulation, which burns cervical tissue to induce necrosis, has become more widely available in the last few years owing to its portability and the feasibility of using battery-powered devices. These two ablative treatments successfully eradicate 75%–85% of high-grade cervical lesions and have minor adverse effects.

KEYWORDS

Cervical precancer; Cryotherapy; Low- and middle-income country; Thermal coagulation; Treatment

1 | INTRODUCTION

Although cervical cancer is preventable, more than half a million women around the world develop this disease every year, and around 270 000 die.[1] The main reasons for these unnecessary deaths are the lack of screening, management, and treatment for women at the target age for secondary prevention in many low- and middle-income countries (LMICs). In high-income countries, effective screening programs based on cervical cytology (Pap smear) resulted in a dramatic decrease in cases of cervical cancer, but these have not been established in low-resource areas because of inadequate infrastructure and insufficient numbers of skilled providers. Currently, there are several newer screening options for detecting precancerous lesions of the cervix.[2] However, there will be no impact on the burden of disease if screen-positive women do not receive care, including effective treatment for precancerous cervical lesions.[3]

Today there is a better understanding of the natural history of human papillomavirus (HPV) infection and cervical cancer. Virtually all cases of cervical cancer are associated with chronic infection by carcinogenic HPV genotypes, which leads to the development of precancer in the epithelium of the cervix.[4] Lesions designated as cervical intraepithelial neoplasia (CIN) grade 3 (CIN 3) (formerly termed carcinoma in situ) and adenocarcinoma in situ (AIS) precede the development of invasive cervical cancer by 10–20 years and are the best proxies for cancer risk. CIN 3 lesions span at least two-thirds of the thickness of the epithelium, which is approximately 0.2 mm thick,[5] although involutions forming the cervical glands cause the tissue to be much thicker. Invasive cervical cancer develops as the result of the intrusion of abnormal cells through the basement membrane of the epithelium into the underlying stroma. Approximately one-third of CIN 3, if left untreated, will become invasive cervical cancer over a 30-year period.[6] The risk of invasive

TABLE 1 Published studies reporting the depth of CIN 3 lesions.

	Abdul-Karim et al.[8] (n=319)	Anderson and Hartley[9] (n=343)
Mean depth of CIN 3, mm	1.35±1.15	1.24±0.87
Depth of 95% of all CIN 3, mm	3.60	2.92
Depth of 99.7% of all CIN 3, mm	4.80	3.80

cervical cancer following failed treatment of CIN 3 remains very high compared with the risk from lower-grade abnormalities.[7]

The average depth of CIN 3 lesions has been reported to be 1.2 mm and 1.4 mm in the USA,[8,9] and 2.0 mm in Peru (Dr Jose Jeronimo, personal communication, February 21, 2017) (Table 1). It is unclear whether these differences are real, or are due to differences in screening methods, size of the lesions, or differences/errors in measurements. An analysis of these reports indicates that in order to eliminate close to 100% of CIN 3 lesions, the treatment should destroy or remove the epithelium up to 5 mm or 6 mm in depth. The depth of CIN 3 lesions, and therefore the depth of necrosis that should be achieved by treatment, is much greater than the thickness of the epithelium itself owing to involutions forming the cervical glands.

Treatment for CIN 3 may be excisional or ablative. Excisional treatments remove all or part of the cervix; pathologists can evaluate the excised tissue and render final histological diagnosis. Ablative procedures do not remove the tissue, but instead destroy it in situ; therefore, no histological specimen is available for definitive diagnosis nor to reveal a cancer that needs additional follow-up and care.

2 | EVOLUTION IN THE TREATMENT OF PRECANCEROUS LESIONS

Treatment options for CIN 3 have changed over the last several decades, but some in the medical community have been unwilling to alter their practices and adopt the more conservative approach that ablative techniques provide. Hysterectomy was the treatment recommended for most CIN 3 lesions until the 1970s. This surgery requires general anesthesia and hospitalization for several days and is associated with significant morbidity. Cold-knife conization (CKC) is the surgical removal of the transformation zone of the cervix—the site of most precancerous lesions. Originally, this procedure was used for diagnosis prior to hysterectomy, but later was accepted as a definitive treatment if histological analysis of the specimen showed complete excision of the CIN 3 lesions.[7] Later, large loop excision of the transformation zone (LLETZ or loop electrosurgical excision procedure [LEEP] in the USA) was introduced for performing cone excision of the cervix, and it was rapidly adopted because it can be done using local anesthesia in outpatient clinics.[10] Both CKC and LEEP/LLETZ procedures provide tissue specimens for histological evaluation.

In the 1980s and 1990s, use of ablative treatments changed the prevailing belief that a surgical specimen and pathology evaluation were always required for appropriate care. It is now generally accepted that only a small percentage of women with precancerous lesions of the cervix need excisional procedures and the associated specimen for diagnosis, as reflected in WHO recommendations for ablation as the first option for treatment.[2]

In the 1990s, the ablative technique of cryotherapy was introduced in a number of LMICs. This treatment uses a refrigerant gas (nitrous oxide or carbon dioxide) to cool a probe to very cold temperatures (−90°C). The cold probe is applied to the cervical tissue, freezing the cervical epithelium and inducing necrosis of the cells, thereby destroying the abnormal (HPV-infected) cells.

Another ablative technique, cold coagulation—now termed thermal coagulation—has been used for several decades in the UK but has not gained wide acceptance elsewhere, presumably because of the predominance of cryotherapy in low-resource settings. This treatment uses a heated probe applied in a manner similar to the cold probe used for cryotherapy, but instead burning the cervical epithelium to induce tissue necrosis.[11]

3 | EFFECTIVENESS OF TREATMENTS FOR CIN 3

The main determinant for cure of CIN 3 is complete excision or destruction of the lesion. The mean depth of CIN 3 is between 1.2 and 1.4 mm,[8,9] but as noted above, the treatment should destroy tissue approximately 5–6 mm deep to eradicate these lesions. However, there could be other factors at work in the successful treatment of the CIN 3, such as the lateral size of the lesion that influences whether the margins of the lesion are clear (negative).[12,13]

A randomized study in the USA reported a success rate of 84% when lesions were excised using LEEP, compared with 76% if the tissue was destroyed with cryotherapy.[14] The severity of the lesion (CIN 1–3) was not the main factor for a successful treatment; rather, the proper selection of treatment based on the size of the lesion appeared to be the key determinant. A study from a population-based program in a low-resource setting found a cure rate of 70% for CIN 3 lesions treated with cryotherapy at 1-year follow-up.[15] CIN 3 cases were selected for cryotherapy based on the size and location of the lesions, and large lesions were referred for excision with LEEP. A recent meta-analysis reported that cryotherapy cures 85%–92% of CIN 2 or CIN 3 (CIN 2–3) lesions.[16]

A recent meta-analysis reported that thermal coagulation cures 85%–95% of CIN 2–3 lesions.[17] The studies in the meta-analysis used a range of temperatures and durations for application of the probe: some used 100°C, and others used temperatures up to 120°C. Some reported applications of 30 seconds and others up to 40 seconds. Most reports used only one application of the probe. A recent retrospective analysis of observational data reported that effectiveness of thermal coagulation and LLETZ were similar at 12-month follow-up.[18]

Despite the limited number of controlled studies evaluating cure efficacy for CIN 3 using cryotherapy or thermal coagulation, with

TABLE 2 Comparison of features of cryotherapy and thermal coagulation as ablative treatments for precancer of the cervix.

Cryotherapy	Thermal coagulation
Meta-analysis level evidence of efficacy: 85%–92% cure rates for CIN 2–3 lesions[16]	Meta-analysis level evidence of efficacy: 85%–95% cure rates for CIN 2–3 lesions[17]
Treatment requires 3-min freeze, 5-min thaw, 3-min freeze cycle or a single 5-min application	Treatment requires single 30–45-s application
Cleaning and sterilizing procedures are straightforward	Cleaning and sterilizing procedures are straightforward
Appropriate for nonphysician provider (ongoing continuing professional development and competency assessment should be built into VIA "screen and treat" program)	Appropriate for nonphysician provider (ongoing continuing professional development and competency assessment should be built into VIA "screen and treat" programs)
Weight of full gas cylinder 15–20 kg	Weight of thermo-coagulator 3.6 kg (first generation)
Requires regular purchase of compressed gas, supply of which is expensive and often erratic in many LMICs	Initial cost outlay for machine plus probes but ongoing maintenance costs are low (in one Malawian setting, cost savings compared with cryotherapy were realized after 50 treatments)
Electricity is not required	Requires electricity (grid or battery-powered)
Few reports of adverse events[16]	Few reports of adverse events[17,25,27]; reports of only minor adverse effects[26]
No requirement for anesthesia	No requirement for anesthesia (studies of patient experience are ongoing)
New models of delivery of cryotherapy (CryoPen and CryoPop) are under development and evaluation; these are robust, portable, and battery-operated	New models recently on the market are lightweight, battery-operated, and/or solar powered (Liger Thermo-coagulator [Lehi, UT, USA] and WISAP C3 Thermo-coagulator [Brunnthal, Germany])

prospective follow-up of just 1–2 years, the information available shows that thermal coagulation is a very promising treatment. Thermal coagulation appears to cure most CIN 3 cases, and the time needed for the treatment is a fraction of that required for cryotherapy. The remainder of this review focuses on cryotherapy and thermal coagulation, whose features are presented in Table 2 and discussed below.

4 | EXPERIENCE WITH CRYOTHERAPY

Cryotherapy has several advantages that make it attractive in areas with limited resources. This treatment does not require anesthesia and can be done in outpatient clinics or in campaigns at the community level. Complications are typically minor ones such as vaginal discharge or spot bleeding, with major complications such as pelvic inflammatory disease or severe bleeding mentioned as rare complications. The authors of this paper have not observed or read of major complications after the treatment of thousands of women in different countries and environments.

WHO specifies that cryotherapy should not be used if the lesion involves more than 75% of the cervix, extends more than 5 mm beyond the border of the tip of the cryotherapy probe, or if cancer is suspected or diagnosed.[19] Experience from multiple countries shows that 70%–80% of women requiring treatment are eligible for ablation with cryotherapy, and 20%–30% of women should be referred to a health facility because there is suspicion of cancer, or the lesions are too large for cryotherapy and require LEEP, or the location of the lesion makes it unreachable with cryotherapy (Dr Jose Jeronimo, personal communication, February 21, 2017).

Two decades of experience with cryotherapy in low-resource settings have revealed several logistical challenges that make it difficult to implement in LMICs. The refrigerant gas is often expensive and its quality is unreliable.[20] Filling a 60-pound tank with nitrous oxide, enough to treat up to 30–40 patients, can cost from US $200–$400. Even if there are resources to purchase gas, shipping the tanks to gas plants for refilling creates logistical problems because in most LMICs there are limited gas production facilities in metropolitan areas, and none in remote locations. An evaluation in Uganda showed that there were 25 health facilities with cryotherapy devices in the country but almost half of them were not operational owing to the lack of gas.[21] Over a 5-year period in Malawi, only 43.3% of women with visual inspection with acetic acid (VIA)-positive, cryotherapy-eligible lesions received cryotherapy owing to challenges in delivering cryotherapy.[22]

New cryotherapy methods that do not rely on large tanks of gas are now under development. For example, CryoPen (Southlake, TX, USA) uses electricity to cool the cryoprobe. A second-generation CryoPen for LMICs, designed to be more robust, portable, and to work using a battery, is under development and its therapeutic effectiveness is being evaluated (ClinicalTrials.gov identifier: NCT03084081). Another device is CryoPop (Jhpiego, Baltimore, MD, USA), which is also under evaluation (ClinicalTrials.gov identifier: NCT02367625).

5 | EXPERIENCE WITH THERMAL COAGULATION

Thermal coagulation has been in use for treating CIN 3 for the last 3–4 decades but, as noted above, most of the experience has been in the UK.[17,23] However, in the last 5 years, several LMICs have reported promising results with this method. Nessa et al.[24] implemented thermal coagulation in a study in Bangladesh for treatment of CIN 1–2

lesions, but most cases treated with ablation were CIN 1, and LEEP was offered to most women with high-grade lesions. The authors reported that 95% of patients treated with either LEEP or thermal coagulation cleared the virus and were without evidence of CIN during follow-up.

Naud et al.[25] reported that in a group of 52 women, 84% with CIN 2–3 lesions were cured using thermal coagulation, and no serious adverse effects or complications were observed. Patients were selected for thermal coagulation if the WHO criteria for cryotherapy treatment were met.[19] Most women reported only mild pain. A study in Cameroon aimed to determine the percentage of screen-positive patients who met the criteria to undergo thermal coagulation, but did not evaluate cure rate. Among 121 screen-positive women, 91% were eligible for this treatment, and 99% received their treatment 1 month after screening.[26] Nearly all treated women reported vaginal discharge for up to 1 month after thermal coagulation and three women required antibiotics for vaginal infections, but there were no hospitalizations.

Campbell et al.[27] reported on thermal coagulation in a VIA screen-and-treat approach in Malawi. Although there was no histological confirmation of cervical abnormalities, 85% of treated women had a negative VIA result after 1-year follow-up, but just 61 women of the original 381 treated returned at 1 year. Later analysis of a larger dataset from the same service after it had more experience showed over 90% VIA-negative at 1-year follow-up (CC, unpublished data). The authors reported no serious adverse effects, and pain was reported as minor by most women—a single woman reported significant pain. Oga et al.[28] reviewed studies that had used thermal coagulation in VIA-based screen-and-treat programs at six sites in Nigeria, which included both HIV-positive and HIV-negative women. Again, no histological confirmation of diagnosis was available in these reports. Over a 4-year period, 177 screen-positive women were treated and had a follow-up visit at 6 months. Treatment failure occurred in 18.3% of HIV-positive women and 12.3% in HIV-negative women. Persistence of disease was determined using evaluation by VIA or visual inspection after application of Lugol iodine. These studies did not measure pain among women treated with thermal coagulation.

While studies to date have used a countertop thermal coagulation unit weighing 3.6 kg and requiring electrical power, there are now second-generation, battery-powered, hand-held thermal coagulation devices in development and under evaluation (Liger Medical, LLC, Lehi, UT, USA; ClinicalTrials.gov identifier: NCT02956239; and WISAP Medical Technology GmbH, Brunnthal, Germany). These devices are light and portable, and can treat around 20–30 women per battery life (or more if extra charged batteries or a larger battery are available), overcoming the need for an external electricity supply.

While reports of the use of thermal coagulation in low-resource settings are encouraging, research is needed to address a number of questions. First, it is important to determine the cure rates for CIN 3 when thermal coagulation is used in population-based programs in such settings and the treatment is delivered by trained healthcare workers. Next, there are some reports of pain from women receiving treatment, but detailed quantification is required to determine if local anesthesia should be recommended for some or all women. It is also important to evaluate cultural differences in the reporting of pain.

6 | VISUALIZING LESIONS FOR ABLATIVE TREATMENT

For the successful use of ablative techniques, the cervix must be visualized to determine which lesions can be successfully treated by ablation and which need LEEP/LLETZ or cancer management.[19] The recommended visualization technique, like VIA, requires applying dilute acetic acid to the cervix to reveal lesions as acetowhite areas. However, the goal of this visualization is only to determine what treatment/management is needed—that is, whether there are contraindications for ablation—not to identify acetowhite lesions among screen-positive women (i.e. HPV-positive women), which is the goal of screening with VIA. To avoid confusion, we propose a new term, visual assessment for treatment (VAT), to differentiate it from VIA. In a screening program using VIA, ablative treatment eligibility by VAT is assessed concurrently with screening (rather than requiring a second pelvic exam). However, in a screen-and-treat program using HPV testing in which all HPV-positive women will undergo some type of treatment, a VAT exam is done only to determine whether the cervix can be treated by an ablative method. Hence, in this example, an HPV-positive woman could be VIA negative (no visible lesions) but still get treatment as determined by VAT (no contraindications for ablation). Like VIA, VAT requires training and quality control measures to ensure the correct use of ablative techniques.

7 | FUTURE RESEARCH ON TREATMENT METHODS

While all currently used ablative techniques appear effective, there are limited data on the effectiveness of thermal coagulation in low-resource settings and long-term effectiveness of any ablative method to reduce cancer risk. In addition, rigorously conducted trials with head-to-head comparisons would be useful to determine best treatment methods, reasons for treatment failures, short- and long-term harms, and cost-effectiveness. Clinical protocols and training for treatment are needed to ensure reliable, high-quality care.

Key remaining questions include the following:

1. Do any ablative or excisional cervical treatments increase the risk of HIV transmission by compromising the protective cervical epithelium? There are limited data on the risk of HIV acquisition following cervical treatments.[29]
2. Is the effectiveness of treatments the same in HIV-infected as in HIV-uninfected women and, if not, what factors (e.g. lesion size) explain these differences? A recent systematic review,[30] and subsequent publications,[28,31–33] suggest that HIV-infected women are more likely to have treatment failures/recurrent disease, but the

evidence for each treatment modality is very limited. The most likely explanation is that HIV-infected women have larger lesions due to immune suppression[28] and therefore the lesion margins are not clear,[32] leading to failure/recurrence.

3. Does the healed epithelium following ablation allow for effective monitoring and diagnosis of recurrent (untreated) disease? Placed into context, if a treatment is 90% effective in treating CIN 2–3, the treated cohort has a prevalence of 10% CIN 2–3, which is several fold higher risk than the general population from which they were screened. Therefore, these women warrant follow-up to ensure that their lesions have been effectively treated.
4. Does ablation destroy the squamocolumnar junction sufficiently to reduce future cancer risk, as has been hypothesized[34]?
5. Is the pain/discomfort from thermal coagulation greater than from cryotherapy? If so, can a local anesthetic be cheaply and effectively applied prior to treatment? One clinical trial addressed the question of using anesthesia prior to thermal coagulation and reported a significant reduction in pain.[35] However, the practicality (cost, procurement, and logistics) of using such an approach, especially in an LMIC setting, should be evaluated and may vary by location.

8 | SUMMARY AND NEXT STEPS

Treatment of cervical precancer is often the weakest component in cervical cancer screening and treatment programs in LMICs. Newer ablative treatments are promising because of their low rate of complications and simplicity of use. These factors allow the possibility for delivery of treatment even at lower levels of health systems, including local health centers in remote areas. Ultimately, the choice of treatment modality(s) will depend on capacities, logistics, and costs required to deliver care.

However, even if a simple and affordable treatment such as cryotherapy or thermal coagulation is available, it may be challenging to have treatment devices and trained personnel in all basic health facilities. Thus, it may be important to consider having health facilities organized in clusters, with a group of three or four centers offering screening, and one having the equipment and trained personnel to provide treatment. This approach must be weighed against having all facilities fully equipped, permitting screening and treatment at the same facility and perhaps on the same day, thereby reducing loss to follow-up of screen-positive women.

Thermal coagulation has been used successfully for several decades in the UK, but experiences outside of high-income regions, especially in LMICs, are needed. Thermal coagulation is an attractive option because it requires minimal supplies, and because there are very low rates of complications. While it appears that sufficient evidence is available to deploy thermal coagulation for treatment, especially in LMIC settings with limited alternative therapeutic options, it will be important to conduct concurrent research studies and gather additional information on its effectiveness, safety, and acceptability, and on causes of treatment failures. Finally, even if the newer ablative treatments are available, many countries and health workers will not incorporate these options into their practices until recommendations are issued by international agencies—a process that is already underway—and national guidelines are updated.

AUTHOR CONTRIBUTIONS

All authors contributed to the development, drafting, and editing of this manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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