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ARTICLE

Experience using cryotherapy for treatment of cervical precancerous lesions in low-resource settings

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Abstract Cervical cancer can be successfully prevented if timely identification of precancerous lesions is followed by effective treatment. In many developing countries, treatment of precancer is neglected because therapeutic services are unavailable, inaccessible, inappropriate, or inadequately linked to screening services. One of the main focuses of the Alliance for Cervical Cancer Prevention (ACCP) has been to ensure that safe and effective methods of treatment for precancer are both available and accessible to women who need them. Cryotherapy, in use for the past 40 years, is a relatively simple, safe, effective, acceptable, and appropriate outpatient procedure for the treatment of precancer. ACCP studies conducted in more than a dozen developing countries show that cryotherapy for precancer can be performed safely and effectively as an outpatient procedure at all levels of health facilities by trained and competent midlevel providers, thus increasing availability and accessibility to precancer treatment services.

1. Introduction

Cervical cancer can be prevented if timely identification of precancerous lesions is followed by effective treatment. In many developing countries, treatment of precancer is neglected because therapeutic services are unavailable, inaccessible, or inadequately linked to screening services. To add to this, the conventional approach of screening, diagnosis, and treatment requires multiple visits to health facilities. Women in many developing countries—and particularly women in rural areas—have limited access to health services due to living long distances from health centers, transportation costs, family and work responsibilities, and other barriers. In developing countries, the proportion of women who do not return for treatment after screening can be as high as 80%, severely jeopard-

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izing the effectiveness of a cervical cancer prevention program [1,2]. Programs that bring treatment and follow-up closer to where women live make it easier for women to receive the care they need, which increases the effectiveness of the program.

Safe and effective outpatient methods are preferred for management of precancerous lesions. However, in many developing countries, clinicians lack training and experience and/or the essential equipment and supplies required for simple outpatient procedures to treat precancerous lesions, so they rely on inpatient methods, such as cold-knife conization and hysterectomy. Although invasive procedures such as hysterectomy might be appropriate in special circumstances—for example, for a woman with a coexisting symptomatic uterine fibroid—invasive procedures should be used judiciously, because they can be associated with significant complications, including bleeding, pelvic infection, and injury to adjacent pelvic organs. Additionally, these inpatient procedures require regional or general anesthesia and skilled and experienced gynecologists. These resource barriers are potential impediments to the implementation of safe and effective treatment services in low-resource settings.

Thus, it is crucial that health care providers in low-resource settings give special consideration to safety, cost, and availability of skilled providers when selecting treatment interventions. They should use an effective treatment method with minimal morbidity risks, because support for managing complications is limited. Using techniques that require relatively simple and inexpensive equipment and supplies and limited training reduces costs. Relying on midlevel providers (nurses, midwives, and general practitioners) rather than specialists increases availability and accessibility at primary- and secondary-care facilities. This article reviews the experience of the Alliance for Cervical Cancer Prevention (ACCP) experience with the use of cryotherapy in low-resource settings: the outcomes, programmatic implications, and conclusions.

2. Outpatient methods for treatment of precancer

The ability to offer women appropriate, effective, and efficient treatment for precancerous lesions is a critical component of an effective cervical cancer prevention program. Treatment for precancer can be provided by ablative or excisional methods, as has been described in detail elsewhere [3—5]. The major practical difference between the two methods is that in ablative procedures, the abnormal tissue is destroyed (although a biopsy sample can be obtained before the procedure), whereas excised tissue can be used to verify the diagnosis and to confirm treatment effectiveness.

Ablative methods include cryotherapy, cold coagulation, and laser vaporization. Cryotherapy involves freezing abnormal areas on the cervix, using compressed carbon dioxide (CO_2) or nitrous oxide (N_2O) as refrigerant. Cold coagulation involves the destruction of tissue using heat energy and is performed with special equipment currently available primarily in Europe. The limited data available on the effectiveness of this procedure indicate that it is similar to other ablative methods [5].

Excisional methods, which are performed as outpatient procedures, include loop electrosurgical excision procedure (LEEP) and laser conization. LEEP is usually performed with colposcopic guidance by gynecologists in secondary- or tertiary-care facilities. LEEP utilizes a high-voltage, high-frequency alternating current that is passed through a thin electric wire loop electrode to excise the abnormal area of the cervix. LEEP provides a reliable tissue specimen for histological confirmation and ascertaining the adequacy of treatment with the least associated morbidity [6]. Because of the shortage of skilled providers, sophisticated equipment and supplies, and a continuous power supply in some places, LEEP is more difficult to provide in developing countries. Additionally, histological confirmation is problematic in many developing countries because of the scarcity and cost of histology services. Laser conization can also be used to excise or ablate a lesion but is rarely used to treat precancer, because it requires costly equipment and because effective, simpler, and less-expensive methods, such as cryotherapy and LEEP, are available. A recent Cochrane review concluded that no one surgical technique is superior for the treatment of cervical intraepithelial neoplasia (CIN) [6].

3. Safety and effectiveness of cryotherapy as a treatment for cervical precancer: summary of a literature review

Cryotherapy, an outpatient procedure for treating precancerous lesions in women who test positive for cervical precancer, has been in use for more than 40 years. The ACCP systematically reviewed the literature on the safety, effectiveness, and acceptability of cryotherapy as a treatment option

for women with precancerous lesions [7]. The majority of the studies that met the inclusion criteria were conducted in developed countries, and high-level providers performed the cryotherapy under colposcopic guidance. In this review, 38 studies assessed or discussed complications, and half of these reported no complications at all. Severe bleeding, during or after cryotherapy, requiring further medical attention is a very rare occurrence, and no cases were identified in the systematic review. Nineteen studies reported at least one complication occurring within 1 month of treatment. The main reported complications were pelvic inflammatory disease (PID), and severe pain and cramping related to the treatment, occasionally referred to as "necrotic plug syndrome." PID was reported in fewer than 1% of study subjects. Necrotic plug syndrome was reported as a problem in only four studies, in which approximately 3% of study participants returned complaining of severe pain and cramping. Necrotic plug syndrome is probably related to an unusually high extension of the freeze in the endocervical canal produced by cryoprobes with long nipples. Studies show that the severe pain and cramping subside immediately after the removal of the necrotic tissue blocking the cervix or soon after cervical dilatation to facilitate drainage.

Data from seven randomized clinical trials (RCTs) and 25 follow-up studies (case series) indicate that the overall cure rates for any degree of CIN are 89.5% (summary statistic mean; 95% CI, 87.3—91.7%) and 91.9% (95% CI, 91.0—92.8%), respectively. Among the seven RCTs, there is a trend toward a decrease in cure rates as lesion grade increases. The one RCT that controlled for size and lesion grade found a statistically significant lower cure rate for large lesions, but that trial included only three lesions larger than 75% of the cervix [8]. Of the other six studies, two found a statistically significant association between positive endocervical curettage and decreased effectiveness of cryotherapy [9,10]. Although cryotherapy is commonly performed with the double-freeze technique, it is not clear if there are significant differences in efficacy and complications between single- and double-freeze techniques [7,11,12].

Studies related to acceptability are few, and most report provider perceptions of women's experience with the treatment and the occurrence of side effects. The main negative experience reported by patients is the pain and discomfort experienced during and after cryotherapy. However, this discomfort is brief and generally acceptable to women. Profuse watery vaginal discharge for a few weeks is a universal consequence of cryotherapy and accepted by most patients with proper counseling.

Long-term sequelae such as cervical stenosis and infertility are not evident in the literature reviewed. The available data provided no evidence that cryotherapy is associated with other obstetrical problems, such as precipitate or preterm labor, increased cesarean section rates, or higher spontaneous abortion rates.

Cryotherapy has the added advantage of being a simple outpatient procedure that can be performed by trained nonphysicians. The advantages and disadvantages of using cryotherapy are summarized in Table 1.

Table 1 Strengths and limitations of cryotherapy compared to other outpatient methods of treating precancerous cervical lesions

Strengths	Limitations
Overall cure rate of 89—91% at 1-year follow-up.	May be slightly less effective for treating CIN3.
Uses simple and inexpensive equipment, compared with other methods, and requires only few consumable supplies.	Should not be used for lesions extending into the endocervical canal.
Can be performed by a trained and competent nonphysician as an outpatient procedure in a primary care setting.	Because it is an ablative procedure, no tissue sample is available for histological examination to confirm the diagnosis, the grade of the lesion, or the adequacy of treatment. However, a punch biopsy specimen can be taken before the procedure.
Requires approximately 11 min if double-freeze method is used.	Requires access to a supply of carbon dioxide or nitrous oxide.
Anesthesia is not required.	In some cryotherapy instruments, especially with carbon dioxide, problems with the flow of refrigerant may occur, interfering with freeze adequacy and/or requiring technique modification.
Electricity is not required for equipment functioning.	Profuse watery discharge is usual, persisting for up to 6 weeks.
Few complications/side effects are related to the procedure.	
Equipment is easy to decontaminate with high-level disinfection methods.	

4. Providing cryotherapy in ACCP projects

One of the ACCP's main focuses has been to ensure that safe and effective methods of treatment for precancer are both available and accessible to women who need to be treated. ACCP experience confirms that a range of trained and competent health care providers, such as nurses, auxiliary nurses, nurse assistants, public health workers, nurse midwives, clinical officers, general practitioners, and gynecologists, can successfully select appropriate clients and perform cryotherapy.

4.1. Selecting clients for cryotherapy

In ACCP studies, all clients diagnosed with precancerous lesions were assessed to ensure that the lesions were suitable for cryotherapy. Suspicion of cancer was an absolute contraindication for cryotherapy, and women with such lesions were referred to an appropriate center for further evaluation with colposcopy and biopsy.

There are several selection criteria for cryotherapy. The full extent of the cervical lesion, as outlined by visual methods such as visual inspection with acetic acid (VIA) or visual inspection with Lugol's iodine (VILI), should be fully covered by the cryoprobe; therefore, cryotherapy cannot be used to treat lesions that extend into the endocervical canal or onto the vaginal wall. Menstruation was not considered a contraindication to performing cryotherapy in ACCP studies unless menstrual flow was heavy and interfered with visualization of the lesion. In some projects, women were treated during early pregnancy, with no reported problems [13]. In general, the ACCP recommends that treatment be delayed if women are known or suspected to be pregnant (according to specific World Health Organization criteria) [14]; these women should be advised to return for treatment 12 weeks after delivery. Difficulties visualizing the cervix because of redundant vaginal walls were resolved by using a condom over the blade of the speculum or a lateral wall retractor. However, when these methods were not sufficient, women were referred to a higher-level facility (e.g., to a hospital, as opposed to an outpatient center) for further management. The ACCP's experience shows that the majority (85—90%) of clients with positive screening test results can be managed using cryotherapy immediately after the screening (i.e., at the same visit) [15].

All women for whom cryotherapy was judged to be unsuitable because of lesion size or location were referred for further evaluation by a gynecologist or medical officer or other health personnel (according to local standards). Such cases were managed either by LEEP or cold-knife conization. It is important that management decisions be consistent with local, program—specific criteria and available resources and expertise.

4.2. Cryotherapy procedure

All clients in ACCP projects were counseled, and informed consent was obtained before cryotherapy was performed. Cryotherapy was done using compressed CO_2 or N_2O refrigerant with the aim of creating an ice ball with a depth of freeze denoted by a peripheral margin of 4—5 mm of frost. The hypothermia produced by the ice ball results in ice crystal formation within cervical tissue, leading to tissue destruction (Fig. 1). To freeze the lesion, the cryoprobe is placed on the cervix, covering the entire lesion but not touching the vaginal wall. The coolant gas is allowed to flow through the channels in the metal tip of the cryoprobe.

Cryotherapy treatment is performed using a double-freeze or single-freeze technique. The double-freeze technique involves applying the coolant continuously for a 3-min freeze, followed immediately by a 5-min thaw, followed by another 3-min freeze. The single-freeze technique consists of continuously freezing for 5 min. Results from an ACCP randomized, controlled study comparing single- and double-freeze techniques will be available in 2005.

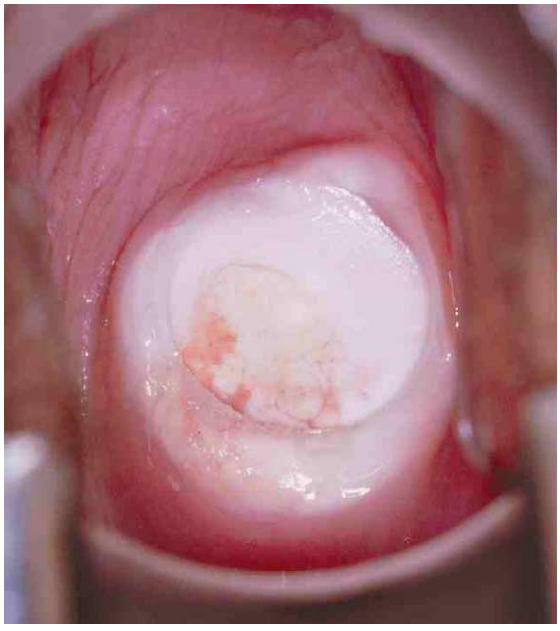

Figure 1 Cervix immediately after cryotherapy. (Reprinted with permission from JHPIEGO).

Pain relief, in the form of local anesthesia or oral analgesics (acetaminophen or a nonsteroidal anti-inflammatory drug) and/or sedation, is not required during cryotherapy. In ACCP studies, oral nonnarcotic analgesics were provided only to women experiencing bothersome cramping after cryotherapy. ACCP studies confirm that women experience some level of discomfort during and immediately after cryotherapy, and approximately 6% require nonnarcotic analgesics [13]. There is a clear need for counseling and supportive care for women undergoing this procedure, given the associated pain and possibility of dizziness, fainting, or flushing. These physical sensations can cause fear and anxiety that could be eased with appropriate pretreatment counseling and support.

ACCP experience also shows that the routine use of antibiotics to prevent reproductive tract infection is not mandatory for cryotherapy. If country guidelines indicate that antibiotics are required for similar gynecological procedures or to presumptively treat undiagnosed sexually transmitted infections, however, women may be treated with the locally recommended antibiotics and counseled to complete the full course of medication.

4.3. Posttreatment counseling

The ACCP's experience emphasizes the need to reinforce key messages after cryotherapy. Women tend to be more relaxed and to internalize messages better after the procedure is completed. Both verbal and written instructions in the clients' own languages were provided to all clients. Wherever necessary, instruction sheets were enhanced using culturally appropriate illustrations (see http://www.alliance-cxca.org/ for examples).

Because a large area of the cervix is denuded after ablative or excisional cervical procedures, there is an increased potential for transmitting or acquiring HIV infection while healing is taking place [16,17]. Therefore, it is important to provide extensive posttreatment counseling about temporary abstinence from sexual intercourse for at least 4 weeks after treatment, and about safe sex practices and use of male or female condoms if abstinence is not feasible. In the ACCP projects, counseling included demonstration of condom use. In addition, all clients were provided with an adequate supply of condoms.

In ACCP studies, approximately 5—31% of treated women reported having sexual intercourse within 4 weeks after treatment [13,15,18,19]. A postcryotherapy survey shows that among the women who were unable to adhere to 4-weeks of abstinence, more than 85% reported consistent condom use during the 4 weeks after cryotherapy [13].

It is also important to advise clients about what to expect after treatment, including information on self-care, warning signs of complications, and the relevant information for a follow-up schedule (i.e., dates, times, and venue). Tables 2 and 3 summarize the key messages that were provided to clients after cryotherapy.

Table 2 Counseling messages about what to expect and what to do after cryotherapy

Expect some degree of cramping during and after the procedure, which usually stops shortly after the procedure. For occasional mild cramping after treatment, use the same medications or other remedies used for menstrual cramps.
Expect vaginal spotting and/or light bleeding for 1—2 weeks.
Expect watery vaginal discharge lasting up to 6 weeks, which may necessitate using feminine sanitary pads or towels. (Color of vaginal discharge usually changes from pink tint to clear white or a yellow tint occasionally streaked with blood.)
Avoid intercourse and putting anything in the vagina, such as vaginal douche or tampons, for 4 weeks.

Table 3 Counseling messages about warning signs that indicate complications

Fever for more than 1 day.
Severe lower abdominal pain, especially with fever.
Foul-smelling or pus-colored vaginal discharge.
Bleeding heavier than the heaviest day of menstrual bleeding for more than 2 days and/or bleeding with clots.
Clients are advised to go to the nearest facility as soon as possible if they have any of the above warning signs.

4.4. Follow-up care after cryotherapy

Routine follow-up to ascertain treatment success is advisable. Based on the ACCP's experience and on safety and effectiveness data in the literature, the ACCP recommends the following for routine posttreatment follow-up: all women should be followed up at 1 year. The total duration of follow-up should be a minimum of 1 year and, if possible, should include annual follow-up visits for up to 5 years. Most recurrences occur within this time period. At each annual follow-up visit, it is recommended that the primary or confirmatory test (whichever is being advocated, singly or in combination) should be performed to determine whether the treatment was successful. If treatment failure is diagnosed at the first posttreatment follow-up appointment, and if it is appropriate for the identified lesion, cryotherapy can be used for repeat treatment. Women who experience further treatment failures

should be referred for evaluation and additional management.

4.5. Cryotherapy equipment and supplies

The equipment and supplies needed to perform cryotherapy are an examining table, an adequate light source, a vaginal speculum, a cryotherapy unit (Fig. 2), an adequate supply of refrigerant gas, and new disposable gloves or gloves that have been subject to high-level disinfection. It is preferable to have various sizes of cryoprobe tips available so that treatment can be tailored to the lesion size. However, if it is only possible to have one or two cryoprobe sizes, 20- and 25-mm diameter probes are recommended. The availability of adequate supplies of consumables such as cotton wool, vinegar, bleach, alcohol, and gluteraldehyde should be ensured by using an inventory control system that includes timely reordering [20]. To ensure uninterrupted services, it is important that health care systems should have access to personnel with expertise in repair and maintenance in case equipment breaks or malfunctions.

ACCP providers reported encountering technical issues such as frequent blockage of the tubes due to ice formation or foreign material. Such blockages can lead to an interruption in the cryotherapy procedure and failure to accomplish an adequate treatment. One of the techniques used in some ACCP projects is the "cough" technique ("freeze, flush, freeze" technique), which consists of pressing the defrost button (only possible if an active defrost function is available on the cryotherapy unit) for approximately 1 s every 20 s during the 3 min of freezing. The cough technique should be done during both freeze sessions when using the double-freeze method (freeze/thaw/freeze). However, blockage may occur despite the use of the cough technique. A device that conditions the gas and appears to prevent blockage has been developed by PATH (Seattle, WA) and is currently undergoing field evaluations in Peru, Kenya, and Ghana. The design of the device will be described in a publication after evaluation is completed in late 2004.

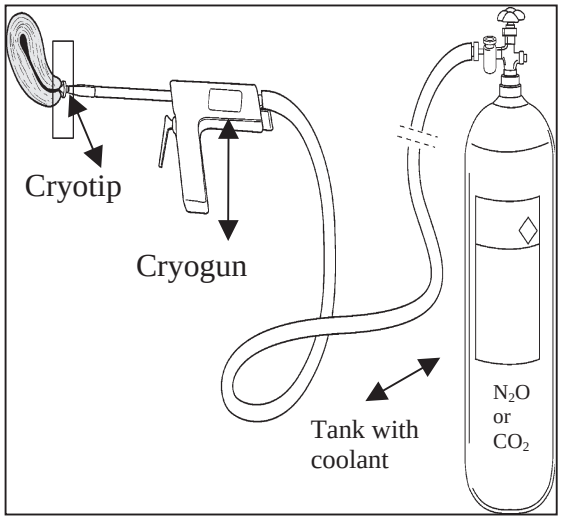

Figure 2 Cryotherapy equipment. (Adapted with permission from JHPIEGO).

5. ACCP cryotherapy outcomes: safety, effectiveness, and acceptability

Preliminary results from ACCP projects confirm that cryotherapy is safe and effective when used appropriately in the treatment of cervical precancerous lesions. The results of more than 6000 cryotherapies performed by midlevel clinicians in ACCP projects in developing countries worldwide show that major complications, such as PID or bleeding, that require hospital admission with or without surgical intervention are extremely rare (occurred in 0.03% of cases). Unscheduled visits for minor complications needing simple outpatient management ranged from 1% to 4% [13,15,18,19,21]. ACCP data from South Africa on HIV transmission after screen-and-treat approaches using cryotherapy will be available in 2005.

Final results on 1-year effectiveness are not available, because many ACCP activities are still ongoing or still completing data processing. Preliminary results for 1-year cure rates from an ongoing ACCP project for biopsy-confirmed low-grade (CIN 1) and high-grade (CIN 2—3) lesions are 86% and 77%, respectively [22]. The ACCP's demonstration project in Thailand, where more than 700 women underwent cryotherapy as part of the screen-and-treat approach (VIA followed by cryotherapy), shows that at the 1-year posttreatment follow-up visit, 94% of women were VIA negative [13,18]. Preliminary results from the ACCP's studies show that cervical cancer, indicating either treatment failure with progression to cancer or else incorrect initial diagnosis, was diagnosed in only two of a total of approximately 4000 women who completed their 1-year postcryotherapy follow-up [13,18].

Data from ACCP studies using cryotherapy show that the transformation zone is fully visible at 1 year in more than 95% of women treated with cryotherapy [15,18]. Data from an ACCP study in Thailand indicate that in women between the ages

of 35 and 45 years who have been pregnant one or more times, the movement of the squamocolumnar junction is minimal, and follow up by a visual method of testing such as VIA or using colposcopy is possible.

Data on acceptability of cryotherapy from ACCP projects in Thailand and South Africa and preliminary results from Ghana and Kenya indicate that more than 95% of women are totally satisfied with their cryotherapy treatment and would recommend cryotherapy to other women needing treatment. Nearly all women said they found the experience with cryotherapy either equal to or better than expected [13,15,19,23].

6. Feasibility of using cryotherapy in low-resource settings

Simpler, less invasive, safe, and effective outpatient treatment methods can minimize women's health risks, help increase program effectiveness, and reduce strain on scarce health care resources. ACCP's experience in low-resource settings affirms that midlevel providers can be trained to competently perform cryotherapy [24] in both static primary care facilities and outreach clinical services (mobile units), thereby increasing the availability and accessibility of precancer treatment services. The ACCP's experience also shows that a reliable source of gas supply is possible in many low-resource settings and that it is logistically feasible to refill gas tanks and transport cryotherapy equipment for use in outreach clinical facilities. Hence, the safety profile of cryotherapy and the feasibility of using it in low-resource settings make it a suitable treatment option for the screen-and-treat approach, even with the inherent potential for overtreatment such an approach poses.

However as discussed earlier, cryotherapy will not be appropriate for the treatment of precancer in some women. These women will need excisional treatment. Accordingly, outpatient excisional procedures should be made available in referral centers, such as secondary- and tertiary-level facilities.

7. Conclusions

Evidence from published literature and ACCP studies supports the conclusion that cryotherapy is safe and, when used appropriately, results in cure rates similar to those of other outpatient procedures, such as laser ablation and LEEP. ACCP studies conducted in more than a dozen developing countries show that cryotherapy for precancer can be performed safely and effectively as an outpatient procedure at health facilities of all levels by trained and competent midlevel providers, thus increasing the availability and accessibility of precancer treatment services. Additionally, by combining cryotherapy with screening tests that provide immediate results, the majority of clients (85—95%) with positive results of tests for precancer can be managed at the same visit, so that more women receive treatment, increasing the effectiveness of the cervical cancer prevention program.

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