

Cryotherapy of the Uterine Cervix

E.J. Mayeaux, Jr, MD; Shannon D. Spigener, MD; and Jeffrey A. German, MD
Shreveport, Louisiana

Cryotherapy is a time-proven ablative method of treating lower grades of dysplasia of the uterine cervix. Women who need cryotherapy typically have had an abnormal Papanicolaou smear that has led to colposcopy, biopsy, and a diagnosis of cervical dysplasia. The basic procedure, indications, and outcomes of cryotherapy are reviewed. The procedure is easy to learn and perform, and can easily be applied in outpatient settings.

KEY WORDS. Cryotherapy; cervix dysplasia; cervical intraepithelial neoplasia. (*J Fam Pract* 1998; 47:99-102)

Cryotherapy involves the rapid removal of heat from tissue with a cryoprobe to produce a controlled destruction of premalignant epithelial lesions. The cryoprobe is cooled by the Joule-Thompson effect: Refrigerant gas is fed into the hollow cryoprobe under pressure, where it rapidly expands and absorbs heat in the process. This reduces the temperature of the probe to -65 to -85°C when using nitrous oxide as the refrigerant. The cryoprobe then acts as a heat sink and removes heat from the cervical tissue.^{1,2} Theories concerning the mechanisms of cellular destruction include physical destruction by formation of intracellular ice, change in intracellular ionic milieu, or denaturation of cell membrane components.¹

Cervices treated with cryotherapy usually heal quickly and completely. No anesthesia is required since freezing the tissue in itself provides anesthesia. Some authors recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or a paracervical block to decrease the cramping often associated with the procedure.³⁻⁵ Subepithelial injection of 1% lidocaine with 1:100,000 epinephrine may be used to decrease any possible local pain.^{4,6}

After the cryoprobe is placed in contact with the cervix and activated, a ring of frozen tissue (also called an "iceball") rapidly moves outward. The depth of the freeze approximates the lateral spread of the freeze. Most of the tissue in this zone will become necrotic. However, there is a ring of tissue (the thermal injury or recovery zone) that freezes but does not reach the -20°C necessary for cell death.² Since dysplastic cells in this area may not be destroyed, it is necessary to freeze well beyond the margins of any lesions.

Studies have demonstrated that endocervical crypt (gland) involvement of cervical intraepithelial neoplasia (CIN) may penetrate from 3.6 mm to 3.8 mm into the cervix.^{7,8} Therefore, a freeze that causes cell death to 4 mm will effectively eradicate 99.7% of lesions with gland involvement. To accomplish this goal, current recommendations are to produce an iceball with a 5 mm lateral spread using a double freeze. The older time-based

method of using a 3-minute freeze followed by a 5-minute thaw, then another 3-minute freeze may also be used but may produce a less reliable freeze because of variations in cervical bloodflow in different areas of the cervix.^{9,10}

A water-soluble lubricant is applied to the probe to act as a thermocouple with the irregular surface of the cervix.¹⁰ This produces a more uniform freeze. A rapid freeze followed by a slow thaw maximizes cryonecrosis.² A freeze-thaw-refreeze cycle is also more effective than a single freeze and is currently recommended for all cervical cryotherapy.^{2,10,11-14} The cure rates* for a nitrous-oxide unit using a double-freeze technique range from 76% to 96.7%.^{15,16}

EQUIPMENT

The cryotherapy device consists of a gas tank containing nonexplosive, nontoxic gases (usually nitrous oxide, but occasionally carbon dioxide is used).^{2,10} A 20-lb gas cylinder (the "short, fat tank") is preferable to the 6-lb "E"-type tank, since the former has a more efficient pressure release curve.² Liquid nitrogen has been used in the past, but is difficult to control and is not currently recommended.⁹ The regulator usually contains a gas cut-off valve and a pressure gauge. The refrigerant is delivered by flexible tubing through a gun-type unit to a silver or copper cryoprobe tip.¹ The cryoprobe is disinfected between uses, usually by chemical methods.

OFFICE MANAGEMENT

Cryotherapy units may be obtained from equipment supply houses or directly from the manufacturers. The procedure is billed under evaluation and management code (CPT) 57511. In 1997, a typical charge for an obstetrician/gynecologist or family physician was approximately \$200. The Medicare national allowable amount was approximately \$118.

INDICATIONS

Cervical cryotherapy is only indicated for the treatment of biopsy-confirmed squamous dysplasia after an adequate colposcopic examination. It may be used to treat human

* A summary of cure rates listed by refrigerant source and freeze type may be found at <http://lib-sh.lsumc.edu/fammed/default.html>

Submitted, revised, May 27, 1998.

From Louisiana State University Medical Center, Shreveport, Louisiana. Requests for reprints should be addressed to E. J. Mayeaux, Jr, MD, Department of Family Medicine, LSU Medical Center, 1501 Kings Highway, Shreveport, LA 71130-3932. E-mail: emayea@lsumc.edu

TABLE

Advantages and Disadvantages of Cryotherapy for the Treatment of Cervical Dysplasia**Advantages**

- Serious injuries or complications are rare.
- It is quick and easy to learn and perform.
- It can be done easily in the outpatient setting with relatively simple and inexpensive equipment.
- No anesthetic is required. The procedure is relatively painless, though cramping may occur.
- It can be performed in a short time and does not interfere with other activities such as work or school later in the day.
- There is minimal chance of heavy bleeding during or after the procedure.
- It is the least expensive widely available form of treatment for cervical intraepithelial neoplasia.
- It has apparently little effect on fertility or labor.

Disadvantages

- Women will experience a heavy discharge for several weeks after cryotherapy.
- Uterine cramping often occurs during therapy but rapidly subsides after treatment.
- Bleeding and infection during the reparative period are rare occurrences.
- Cervical stenosis is a slight possibility following cryotherapy.
- Some patients may experience vasomotor reactions, such as flushing or orthostatic hypotension immediately after the procedure.
- Unlike excision therapies, there can be no histologic examination of the entire lesion. However, the cost of histologic examination is saved.
- Future Papanicolaou smears and colposcopies may be more difficult after cryotherapy. The squamocolumnar junction has a tendency to migrate deeper into the cervical os making it difficult to visualize and sample the cervical canal. This is especially problematic with older nipple-tipped probes, which are not currently recommended.
- Therapy may fail.

papillomavirus on the external genitalia for cosmetic purposes (using different freezing protocols than those for treating the uterine cervix).^{1,10} It is often reserved for CIN 1 and 2 level lesions, although it is routinely used for CIN 3 in some centers. There may be a higher recurrence rate compared with loop electrosurgical excision procedure (LEEP) for CIN 3 level lesions, possibly because of the greater depth of glandular involvement with CIN 3.^{9,13,17-19}

Cryotherapy is primarily used for cervical disease limited to a small area of cervix that is easily visible in its entirety. The cryotherapy probe must be able to cover the entire transformation zone and the entire lesion for the therapy to be most effective.^{1,20}

CONTRAINDICATIONS

Cervical cryotherapy is contraindicated when lesions extend into the endocervical canal more than a few mil-

limeters since the area of destruction may not reliably penetrate beyond this level.¹⁷ A positive result from an endocervical curettage is also a contraindication. Another modality of treatment should be considered in these situations.^{9,10,20-23}

The patient's cytologic, histologic, and colposcopic findings should be consistent within two histologic grades.^{1,27} Although case reports indicate no associated complications, cervical cryotherapy should be avoided in pregnancy.¹³ There is apparently little effect, however, on fertility or labor.^{9,16,24} Similarly, most cervical therapies are avoided in the presence of active cervicitis.

LEEP is usually used for CIN 3 or carcinoma in situ lesions because of the lower cure rates with cryotherapy compared with CIN 1 and 2 lesions.^{1,12,13,20,25} This allows for histologic examination of the treatment specimen to rule out unexpected invasive disease. Some authors recommend using an excisional therapy such as LEEP for recurrent dysplasia after ablative therapy.⁹ Patients with large lesions that cannot be covered with the cryoprobe tip are not candidates for cryotherapy.^{1,10,20} Invasive lesions and adenocarcinoma in situ should be treated only with cold knife conization or hysterectomy.²⁰

HOW TO PERFORM CRYOTHERAPY

1. The appointment should be scheduled when the patient is not experiencing heavy menstrual flow.
2. The patient may take an NSAID, such as ibuprofen, ketoprofen, or naproxen sodium, before cryotherapy to decrease cramping.
3. Inform the patient of the risks and benefits of cryotherapy and obtain informed consent.
4. If there is any doubt regarding the patient's pregnancy status, a pregnancy test should be performed.
5. Make sure that there is adequate pressure in the gas tank (on most tanks the needle will be in the "green zone" on the pressure gauge).
6. Place the patient in the dorsal lithotomy position. Select the largest speculum that the patient can comfortably tolerate, and open the blades and the front end of the speculum as widely as possible without causing the patient discomfort. If collapsing sidewalls are a problem, place either a condom with the tip cut off, the thumb from a very large rubber glove with the tip cut off, or half of a Penrose drain over the speculum. Alternatively, tongue blades or sidewall retractors may be placed to improve exposure.
7. Select a probe that adequately covers the entire lesion and the entire transformation zone. Use only flat-ended probes, not probes with long endocervical extensions or nipple-tipped probes. These are more likely to cause cervical stenosis. Apply a water-soluble lubricant to the probe.
8. Apply the probe firmly to the cervix and make sure that it is not touching the sidewalls of the vagina. Start

the freeze by pulling the trigger (if using a green gun) or pressing the freeze button (if using a black gun). Within a few seconds the probe will be frozen to the cervix, and the cervix can then be gently drawn forward a few millimeters into the vagina where probe contact with the sidewalls is less likely. A rim of ice should form and grow to a width of at least 5 mm in all quadrants.

9. Discontinue the freeze. On the single-trigger guns, release the trigger; on the double-trigger guns, press the defrost button. Wait until the probe visibly defrosts before disengaging it. The cervix should be allowed to regain its pink color, which usually takes approximately 5 minutes.
10. Repeat the freeze sequence. The second freeze sequence usually requires less time to complete. After the freeze is complete, disengage the probe and remove the speculum. The patient may get up, get dressed, and leave as soon as she feels ready.

COMPLICATIONS

The most common minor complication during the procedure occurs if the probe touches the vaginal sidewall and adheres to it. The operator may quickly push the vaginal mucosa off the probe with a tongue blade. If this is not done quickly, it will become more difficult as the freeze deepens, and more vaginal mucosa will be destroyed. The operator should defrost the probe just enough to release the sidewall and then continue the freeze. Slight bleeding may occur from the injured vaginal mucosa. Occasionally, a tongue blade placed along each sidewall as a barrier is the only way to prevent unwanted contact between the probe and the vagina. An asymmetric freeze on the face of the cervix is another possible problem. Changing probes or freezing in segments will usually solve this problem.

Occasionally, a patient may experience an undue amount of pain and cramping, usually associated with a high level of anxiety. If this can be anticipated, a paracervical block prior to cryotherapy, benzodiazepines (ie, 1-mg lorazepam intramuscularly or 5-mg diazepam orally), or intravenous sedation may be chosen for relief. These measures are seldom required. Rarely does a patient may have a vasovagal reaction.^{17,26} Allowing the patient to rest on the examination table after the procedure and to get up slowly is usually sufficient to overcome this problem. Other rare complications include cervical stenosis, delayed healing of the cervix, and severe dysmenorrhea during the first period following the procedure.²⁶

AFTERCARE AND FOLLOW-UP

Most patients experience a heavy and often odorous discharge for the first month after cryotherapy.²⁷ This discharge results from the sloughing of dead tissue and exu-

date from the treatment site. Some physicians recommend debridement of the eschar 48 hours after therapy to decrease the discharge and odor, but this has not been proved effective. Amino-Cerv cream (Milex, Chicago, Ill) (1 applicator high in the vagina at bedtime for 10 days) may be used after therapy in an attempt to decrease the discharge.

The patient should refrain from sexual intercourse, douching, and tampon use for 2 to 3 weeks after cryotherapy to allow the area to reepithelialize.¹⁹ Excessive exercise should also be discouraged to lessen the chance of post-therapy bleeding.^{9,28}

The first follow-up Papanicolaou (Pap) smear should be done in 3 to 6 months. A Pap smear is of no value during the sloughing or regenerative phases, which take at least 3 months to complete. If this and the following smears are normal, Pap smears should be repeated every 6 months for 2 years after treatment. Most recurrences will occur within 1 year of treatment.^{9,15,24,29,30} Yearly smears may be recommended after that. An alternative method involves replacing the initial and each yearly Pap smear with a colposcopic examination. With either method, special care must be taken to adequately sample the endocervical canal to rule out hidden dysplasia. If any of the follow-up test results are positive, restart the workup as if for newly discovered dysplasia.

If a follow-up Pap smear result is abnormal, a colposcopy with directed biopsy is usually performed. Unfortunately, colposcopy may be more difficult because of migration of the squamocolumnar junction deeper into the cervical os. Other treatment methods (usually LEEP) are preferred if persistent disease is discovered.

CONCLUSIONS

Cryotherapy is a safe and effective method for treating lower grades of cervical dysplasia. It is easy to learn and can be performed in an outpatient setting. It is cost effective and is well tolerated by patients.

REFERENCES

1. Charles EH, Savage EW. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstet Gynecol Surv* 1980; 35:539-48.
2. Ferris DG, Ho JJ. Cryosurgical equipment: a critical review. *J Fam Pract* 1992; 35:185-93.
3. Rodney WM, Huff M, Euans D, Hutchins C, Clement K, MaCall JW. Colposcopy in family practice: pilot of pain prophylaxis and patient volume. *Fam Pract Res J* 1992; 12:91-8.
4. Sammarco MJ, Hartenbach EM, Hunter VJ. Local anesthesia for cryosurgery of the cervix. *J Reprod Med* 1993; 38:170-2.
5. Harper DM. Paracervical block diminishes cramping associated with cryosurgery. *J Fam Pract* 1997; 44:71-5.
6. Rogstad KE, White DJ, Ahmed-Jushuf. Efficacy of lidocaine analgesia during treatment of the cervix. *Lancet* 1992; 340:942.
7. Anderson MC, Hartley RB. Cervical crypt involvement by intraepithelial neoplasia. *Obstet Gynecol* 1990; 55:546-50.
8. Boonstra H, Aalders JG, Koudstall J, Oosterhuis JW, Janssens J. Minimum extension and appropriate topographic position of tissue destruction for treatment of cervical intraepithelial neoplasia. *Obstet Gynecol* 1990; 75:227-31.

9. Krumholz BA. The treatment of premalignant lesions of the uterine cervix. *J Lower Genital Tract Dis* 1997; 1:82-94.
10. Creaseman WT, Henshaw WM, Clarke-Pearson DL. Cryosurgery in the management of cervical intraepithelial neoplasia. *Obstet Gynecol* 1984; 63:145-9.
11. Creaseman WT, Weed JC Jr, Curry SL, Johnston WW, Parker RT. Efficacy of cryosurgical treatment of severe cervical intraepithelial neoplasia. *Obstet Gynecol* 1973; 4:501-6.
12. Kaufman RH, Conner JS. Cryosurgical treatment of cervical dysplasia. *Am J Obstet Gynecol* 1971; 109:1167-74.
13. Bryson SCP, Lenehan P, Lickrish GM. The treatment of grade 3 cervical intraepithelial neoplasia with cryotherapy: an 11-year experience. *Am J Obstet Gynecol* 1985; 151:201-6.
14. Kaufman RH, Acosta AA. Cryosurgery in the treatment of abnormal cervical lesions. *J Reprod Med* 1971; 7:163-6.
15. Schantz A, Thormann L. Cryosurgery for dysplasia of the uterine ectocervix. A randomized study of the efficacy of the single- and double-freeze techniques. *Acta Obstet Gynecol Scand* 1984; 63:417-20.
16. Elmfors B, Stormby N. A study of cryosurgery for dysplasia and carcinoma in situ of the uterine cervix. *Br J Obstet Gynaecol* 1979; 86:917-21.
17. Ostergard DR. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstet Gynecol* 1980; 56:231-3.
18. Tredway DR, Townsend DE, Hovland DN, Upton RT. Colposcopy and cryosurgery in cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 1972; 114:1020-4.
19. Tavaheri G, Balin M, Meltzer RM. Role of cryosurgery in the treatment of cervical intraepithelial neoplasia. *Obstet Gynecol* 1981; 58:83-7.
20. Townsend DE, Richart M, Marks E, et al. Invasive cancer following outpatient evaluation and therapy for cervical disease. *Obstet Gynecol* 1981; 57:145.
21. Kaufman RH, Strama T, Norton PK, Conner JS. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstet Gynecol* 1973; 42:881-6.
22. Draeby-Kristiansen J, Grasaee M, Bruun M, Hansen K. Ten years after cryosurgical treatment of cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 1991; 165:43-5.
23. Anderson ES, Husth M. Cryosurgery for cervical intraepithelial neoplasia: 10-year follow-up. *Gynecol Oncol* 1992; 45:240-2.
24. Monaghan JM, Kirkup W, Davis JA, Edington PT. Treatment of cervical intraepithelial neoplasia by colposcopically directed cryosurgery and subsequent pregnancy experience. *Br J Obstet Gynaecol* 1982; 89:387-92.
25. Hatch KD, Shingleton HM, Austin Jr JM, Soong SJ, Bradley DH. Cryosurgery of cervical intraepithelial neoplasia. *Obstet Gynecol* 1981; 57:692-8.
26. Walton LA, Edelman DA, Fowler WC Jr, Photopoulos GJ. Cryosurgery for the treatment of cervical intraepithelial neoplasia during the reproductive years. *Obstet Gynecol* 1980; 55:353.
27. Townsend DE, Richart M. Cryotherapy and carbon dioxide laser management of cervical intraepithelial neoplasia: controlled comparison. *Obstet Gynecol* 1983; 61:75-8.
28. Crisp WE. Cryosurgical treatment of neoplasia of the uterine cervix. *Obstet Gynecol* 1972; 39:495-9.
29. Hemmingsson E, Stendahl U, Stenson S. Cryosurgical treatment of cervical intraepithelial neoplasia with follow-up of five to eight years. *Am J Obstet Gynecol* 1981; 139:144.
30. Wright BC, Davies EM. The conservative management of cervical intraepithelial neoplasia: The use of cryosurgery and the carbon-dioxide laser. *Br J Obstet Gynaecol* 1981; 88:663-8.