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# Pain and Cramping Associated with Cryosurgery

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**Background.** Many different cryosurgery methods have been described for the treatment of cervical intraepithelial neoplasia (CIN). The purpose of this study was to evaluate the pain and cramping perceived by patients undergoing four specific cryosurgical methods.

**Methods.** Seventy women consented to the prospective trial and were assigned to one of four cryosurgery techniques: a 2-minute double freeze, a 3-minute double freeze, a 5-minute single freeze, and a 5-minute double freeze. Immediately following the procedure, a trained interviewer recorded each woman's perceptions of pain and cramping. Age, parity, marital status, financial class, race or ethnicity, lesion severity, and pretreatment with a nonsteroidal anti-inflammatory drug (NSAID) were included in the analysis.

**Results.** The median pain scores for the 2-minute double freeze, the 3-minute double freeze, the 5-minute

single freeze, and the 5-minute double freeze were 4, 3, 3, and 7, respectively, on a scale of 0 to 10. The median cramping scores for the procedures were 0, 0, 0, and 7, respectively. The median pain and cramping scores were significantly higher for the 5-minute double freeze than for any of the other procedures ( $P=.012$  and  $P<.001$ , respectively).

**Conclusions.** Pain and cramping are associated with cryosurgery, but the 5-minute double freeze caused the most pain and cramping of all the cryosurgery methods tested. Pretreatment with an NSAID did not lessen the cramping or pain perceived during the 5-minute double freeze.

**Key words.** Cryosurgery; cervical dysplasia; pain; morphometric destruction.

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Cryosurgery has been used for the treatment of benign cervical lesions since 1942<sup>1</sup> and has been advocated since 1967<sup>2</sup> for the treatment of cervical intraepithelial neoplasia (CIN). The freezing technique for treating CIN has varied widely, including a single 3-minute freeze,<sup>2-4</sup> a single 3-minute freeze timed from the lateral spread of the iceball to 4 mm,<sup>5,6</sup> a 3-minute double-freeze method during which the initial freeze was followed by a thaw and an immediate repeat 3-minute freeze,<sup>3,7,8-12</sup> a 2-minute double freeze timed from the lateral spread of the iceball to 4 mm from the probe,<sup>13</sup> a double freeze timed to allow the development of a 4-mm to 5-mm iceball around the probe at each freeze,<sup>14</sup> a single 5-minute freeze,<sup>15,16</sup> a 5-minute double freeze with 5-mm lateral extension of

freeze from the probe,<sup>17,18</sup> and a single 7-minute freeze.<sup>15</sup> A study by Schantz and Thormann,<sup>19</sup> specifically designed to evaluate the efficacy of a single freeze as compared with that of a double freeze, used whatever freeze time was required to achieve a 3-mm lateral freeze spread from the probe surface for both the single and double freezes. They found that these times varied depending on the lesion size, cervix size, and pressure of the cryogenic gas in the tank. The thaw periods (the time required to regain "pinkness") between the above-listed double-freeze processes differed from 2 to 5 minutes.

The pain from cryosurgery has been described quantitatively by only two studies.<sup>20,21</sup> Rodney et al<sup>20</sup> evaluated the pain perceived by women undergoing a cryosurgical procedure. These investigators reported that 13 women, pretreated with a nonsteroidal anti-inflammatory drug (NSAID), had a mean pain score of 2.5 on a scale of 0 (no pain) to 10 (severe pain). These women had significantly less pain than those who were not pretreated with

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an NSAID. The particular cryosurgery method was not described.

Sammarco et al<sup>21</sup> evaluated the pain perceived with the 3-minute double freeze/5-minute thaw cryosurgical procedure. All women in this study were pretreated with an NSAID. The study group had a 2- to 3-mL submucosal injection of 1% lidocaine with 1:100,000 epinephrine at the 2- and 10-o'clock positions on the cervix before cryosurgery. These women experienced significantly less pain than those who were also pretreated with an NSAID but without lidocaine.

If all the above cryosurgical methods produce equivalent cure rates, the method that should be used is the one most acceptable to the patient. One measure of patient acceptance and preference is the intensity of pain and cramping that the woman perceives during the procedure. A MEDLINE search from 1966 to the present produced no reports of studies of the pain and cramping perceived with any of the above-listed cryosurgery methods or any evaluation of the cramping associated with cryosurgery in general.

The purpose of this study was to determine in a prospective manner whether women perceived a difference in intensity of pain when undergoing any of the four cryosurgery methods in standard use in our ambulatory teaching clinics; whether they perceived a difference in the intensity of cramping with any of the four cryosurgery methods; and which discomfort, pain or cramping, was perceived most frequently during the cryosurgical procedures.

## Methods

A prospective clinical study was designed and conducted between October 1992 and March 1994 in the teaching clinics of Truman Medical Center—East hospital in Kansas City, Missouri. Women who were asked to participate in this trial had to meet the following inclusion criteria: (1) willingness and competence to participate; (2) presence of a cervical squamous intraepithelial lesion (cervical intraepithelial neoplasia—carcinoma in situ [CIN 1–CIS]); (3) a cervical transformation zone that could be visualized and appropriately covered by the cryoprobe tip; (4) biopsy results that were concordant with the cytology findings; (5) the entire lesion could be covered by the cryoprobe tip; and (6) fluency in the English language.

Women with any of the following conditions were excluded from participation in the survey: (1) evidence of invasion or microinvasion on the biopsy report; (2) endocervical curettage that was positive for squamous or glandular dysplasia; (3) previous conization, electrosurgical loop excision procedure, laser therapy, or hysterectomy;

(4) presence of any other lower genital tract neoplasia; (5) pregnancy; (6) inadequate colposcopy; (7) allergy to NSAIDs; (8) known drug abuse; or (9) known central or peripheral neurologic deficit.

The study was granted Institutional Review Board approval. Seventy-eight women met the inclusion and exclusion criteria during the study period, eight of whom chose not to participate for personal reasons. The remaining 70 women consented to the study interviews.

Over 90% of the women in the study were white; the others were black, Hispanic, or Asian. Socioeconomic status, based on method of payment, was described as self-pay (57.1%), Medicaid/Medicare (35.7%), or commercial insurance (7.2%). Twenty-four percent of the study participants were nulliparous, and 76% were multiparous. Fifty percent had never been married, 21% were married, 11% were separated, and 17% were divorced.

The cryosurgical methods used in the teaching clinics reflect the opinions of the attending staff regarding the effectiveness of cryosurgery for squamous intraepithelial lesions (SIL). The 2-minute double freeze that is timed from when the lateral spread of freeze is judged to be 4 mm (2-minute double)<sup>13</sup> was used by an attending physician who was in clinic one-half day per week. The 3-minute freeze–thaw–3-minute freeze (3-minute double)<sup>4,12,14,22</sup> was used by an attending physician who precepted in the clinic 1.5 to 2 days a week. The 5-minute single freeze (5-minute single)<sup>15,16</sup> was used by an attending physician who also precepted in the clinic 1.5 to 2 days a week. The 5-minute freeze–5-minute thaw–5-minute freeze (5-minute double)<sup>17,18</sup> was used by an attending physician who precepted in the clinic 1 day a week. A woman was assigned to a particular cryosurgical method based on who was the attending physician in the clinic at the time of her appointment. Therefore, the distribution of women in the four cryosurgery method cohorts was determined by which attending physician was working at the clinic at the time of the procedure. The attending physician also determined the cryoprobe size and shape that would be needed to cover the transformation zone adequately.

Each woman was given either ketoprofen 75 mg or naproxen sodium 550 mg 30 to 60 minutes before the procedure. Age, parity, marital status, financial class, race or ethnicity, lesion severity, and pretreatment with an NSAID were noted for each participant. An intake nurse explained the entire procedure to each patient before the procedure according to a standard format. Even though no patient was informed about which cryosurgery method she would experience, it was self-evident that the freeze was a double or single. Hence, patients were not truly blinded to the treatment type received.

All cryosurgeries were performed with Cryomedics

Table 1. Characteristics of Women Assigned to Four Cryosurgical Method Cohorts in a Study of Pain and Cramping Associated with Cryosurgery (N=70)

Characteristic	2-Minute Double	3-Minute Double	5-Minute Single	5-Minute Double
No. (%) of women assigned to procedure	9 (12.9)	27 (38.6)	23 (32.9)	11 (15.7)
Mean age, y (SD)	22.25 (3.96)	26.78 (8.01)	27.26 (11.07)	28.36 (8.71)
Lesion severity, no.				
LGSIL	9	23	17	8
HGSIL	0	4	6	3
Pretreatment NSAID				
Ketoprofen 75 mg	1	3	4	1
Naproxen sodium 550 mg	8	24	19	10

SD denotes standard deviation; LGSIL, low-grade squamous intraepithelial lesion; HGSIL, high-grade squamous intraepithelial lesion; NSAID, nonsteroidal anti-inflammatory drug.

(Cabot Medical Group, Langhorne, Pa) cryoprobes attached to a large "D" tank of nitrous oxide maintained above 40 kg/cm<sup>2</sup> of pressure. The size and shape of the probes used were determined according to what was most appropriate for the transformation zone and lesion size. Before freezing, a water-soluble lubricant was applied to the probe to improve contact between the probe and the cervical surface. Residents and attending physicians-of-the-day performed the cryosurgeries. None of the physicians mentioned, reaffirmed, or inquired about pain or cramping during the encounter.

Immediately after each procedure, a trained interviewer, blinded to the type of cryosurgical method used, escorted the woman into an interview room to record her perception of pain and cramping associated with the procedure. The intensity of pain and cramping were assessed according to a Likert scale, where on a scale of 0 to 10, 0=no pain/cramping and 10=severe pain/cramping. The questions regarding pain were interspersed with those concerning the ease with which follow-up appointments could be made. The same wording was used for each patient. No reaffirmation or suggestion of pain or cramping was made beyond acknowledgment of these discomforts.

### Statistical Analysis

The descriptive data from each cryosurgical method were tested for differences using the Kruskal-Wallis one-way analysis of variance by ranks for age and parity because these variables were not normally distributed. The chi-square test and Fisher's exact test were used to test for differences in marital status, financial class, race or ethnicity, lesion severity, and pretreatment use of an NSAID among the cryosurgical methods cohorts.

Chi-square was also used to test whether there was a difference in pain and cramping perceived by the women

during the cryosurgical procedure for any of the four methods as well as for all methods combined. The Kruskal-Wallis one-way analysis of variance by ranks was used to determine the differences between the pain scores and the cramping scores for the four cryosurgical methods.

The pain and cramping scores were compared for all methods combined using the Wilcoxon signed-ranks test for matched pairs. The Mann-Whitney *U* test was used to compare the dichotomized pain and cramping scores for each method according to parity (nulliparous vs multiparous), age ( $\leq 26$  vs  $> 26$  years), lesion severity (low-grade SIL vs high-grade SIL), and pretreatment NSAID (ketoprofen vs naproxen sodium).

The level of significance ( $\alpha$ ) was set at .05. All nonparametric tests were one-tailed. The power efficiency of the nonparametric tests was greater than 95%.

### Results

The distribution of women to the cryosurgery method cohorts reflected the assigned time of the physicians to the colposcopy suite. Nine women were assigned to the 2-minute double freeze, 27 to the 3-minute double freeze, 23 to the 5-minute single freeze, and 11 to the 5-minute double freeze cohorts. Even though there were unequal numbers of women assigned to the cohorts, there were no differences among the groups for parity, marital status, financial class, or race or ethnicity. Table 1 shows that age, lesion severity, and pretreatment with NSAIDs also did not differ among the cohorts.

Before taking the pretreatment NSAID, all women stated that they were perceiving no pain or cramping. After the procedure, there was no difference in the number of women who perceived pain among the cryosurgery method cohorts. For the number of women who per-



Table 2. Pain and Cramping As Perceived by Women Assigned to Four Cryosurgical Method Cohorts (N=70)

Discomfort Values	2-Minute Double	3-Minute Double	5-Minute Single	5-Minute Double*	All Methods†
No. (%) of women assigned to procedure	9 (12.9)	27 (38.6)	23 (32.9)	11 (15.7)	70 (100)
Discomfort experienced, %					
Pain	100.0	70.4	69.6	100.0	78.6
Cramping	33.3	25.9	26.1	81.8	35.7
Discomfort scores, median, (25-75th %ile)					
Pain	4 (2-4)	3 (0-5)	3 (0-5)	7 (4-9)	4 (1-5)
Cramping	0 (0-1.5)	0 (0-1)	0 (0-2)	7 (3-10)	0 (0-3)

\*With the 5-minute double as compared with the other three cryosurgical techniques, a significantly greater number of women experienced cramping ( $\chi^2=12.261$ , degree of freedom [df]=3,  $P=.006$ ); the perception of pain was significantly greater (Kruskal-Wallis=11.02,  $P=.012$ ); and the perception of cramping was significantly greater (Kruskal-Wallis=18.15,  $P=.004$ ).  
 †For all cryosurgical methods, significantly more women perceived pain than those who perceived cramping ( $\chi^2=26.45$ ,  $P<.001$ ), and the pain score was significantly higher than the cramping score ( $P<.001$ ).

ceived cramping, there was no difference among the 2-minute double freeze, the 3-minute double freeze, and the 5-minute single freeze methods. For the 5-minute double freeze method, 81.8% of women perceived cramping, compared with 33.3%, 25.9%, and 26.1% for the other three methods, respectively. Significantly more women perceived cramping with the 5-minute double freeze than with the other methods ( $\chi^2=12.261$ , degree of freedom [df]=3,  $P=.007$ ). For all cryosurgery methods, 78.6% of the women had pain and 35.7% of the women had cramping. Significantly more women perceived pain than cramping ( $\chi^2=26.25$ ,  $df=1$ ,  $P<.001$ ) (Table 2).

Pain scores for the 2-minute double, the 3-minute double, and the 5-minute single freeze methods were not significantly different. The median scores were in the lower half of the Likert scale, indicating a small amount of perceived pain. The median pain score for the 5-minute double freeze was 7, with 25th percentile and 75th percentile scores of 4 and 9, respectively. This median pain score was significantly greater than that with any of the other methods (Kruskal-Wallis=11.02,  $P=.012$ ), indicating that the pain perceived with the 5-minute double freeze was severe.

The cramping scores for the 2-minute double, the 3-minute double, and the 5-minute single freezing methods were not significantly different. The median cramping scores were 0 for all three methods. The greatest 75th percentile score was 2, indicating that, taking into consideration that all women were pretreated with an NSAID, cramping associated with these three freezing methods is minimal. The median cramping score for the 5-minute double freeze was 7, with 25th percentile and 75th percentile scores of 3 and 10, respectively. This median cramping score was significantly different from that of the

other three methods (Kruskal-Wallis=18.15,  $P<.001$ ). Women undergoing a 5-minute double freeze perceived severe cramping that differed significantly from the level of cramping experienced by women undergoing any of the other freeze methods. For all cryosurgery methods, women perceived a median pain score of 4 (25th to 75th percentile=1 to 5) as compared with a median cramping score of 0 (25th to 75th percentile=0 to 3). There was significantly more pain than cramping associated with any cryosurgery method ( $P<.001$ ) (Table 2).

Among the women undergoing the 5-minute double freeze, the nulliparous woman perceived significantly more pain (median score of 10) than did the multiparous women (median score of 5) ( $P=.032$ ). Among those undergoing the 3-minute double freeze, the nulliparous women perceived significantly more cramping (median score of 1) than did the multiparous women (median score of 0) ( $P=.039$ ). Parity did not correlate to any other pain or cramping score. Age, lesion severity, and pretreatment NSAID did not affect the pain or cramping perceived during the procedure.

## Discussion

This study did not show any differences in the perception of pain and cramping between women receiving ketoprofen and those given naproxen sodium before cryosurgery. By study design, there was no difference in the timing of the NSAID administered among cohorts; the NSAID was given 30 to 60 minutes before the procedure. Ketoprofen and naproxen sodium reach peak plasma levels in 0.5 to 2 hours and 1 to 2 hours, respectively. Smith<sup>23,24</sup> found that there was a significant decrease in uterine contractility within 30 minutes of ingesting meclufenamate sodium,

which reaches peak plasma levels in 0.5 to 2 hours. He also found that a placebo effect will offer subjective relief for up to 105 minutes post-ingestion.<sup>25</sup> Based on these findings, there was ample time for the pretreatment NSAID therapy to be effective for all cryosurgery cohorts, including the 5-minute double freeze cohort.

In this study, more women experienced pain than cramping, and the intensity of pain was greater than that of cramping for all cryosurgery methods. This difference was also documented for laser vaporization<sup>26</sup> and for the electrosurgical loop excision procedure<sup>27</sup> of the cervical transformation zone. The 5-minute double freeze method caused a higher level of perceived pain and cramping than any other cryosurgery method tested. The innervation of the cervix can account for these differences in pain and cramping perceptions.

The pain pathways of the cervix are adrenergic excitatory nerve fibers derived from Frankenhauser's parasympathetic plexus, S2-4.<sup>28</sup> Intracervical branches terminate at the level of the internal os<sup>29</sup> after traveling through the iliohypogastric, ilioinguinal, uterosacral, and paracervical branches where they can be stimulated by mechanical, chemical, thermal, or electrical stimuli.<sup>30,31</sup> The pain of cryosurgery is mediated through unmyelinated C fibers, which transmit pain in proportion to the temperature gradient and the duration of exposure to the temperature gradient developed at the surface of the cervix.<sup>26,32</sup>

Clinically, a longer freeze to the cervix will produce a greater number of impulses, which, in turn, will deliver a perception of greater pain. In addition, the colder the tissue temperature becomes during the freeze, the greater the pain perception. In this study, the 5-minute double freeze method had the longest time of cervix exposure to cold temperatures, corresponding to the method for which there was also the greatest amount of pain. The nulliparous woman, in particular, felt this pain during the 5-minute double freeze. Rearrangement in the number and location of cervical nerve fibers after the labor and delivery process may have accounted for this difference in multiparous women.

Cramping is independent of the pain perceived<sup>26</sup> and is mediated by an increased local concentration of prostaglandins.<sup>33</sup> Cervical stromal damage, such as that caused by thermonecrosis at  $-20^{\circ}\text{C}$ , stimulates prostaglandin and endoperoxide production, which leads to nerve ending sensitization. When prostaglandin synthesis is inhibited by an NSAID, the afferent nerve endings are not subjected to this stimulation and the cramping should be diminished.

In our study, the perception of cramping was significantly greater with the 5-minute double freeze. The other three methods had a median cramping score of zero, possibly indicating that the plasma levels of the

NSAID inhibited most of the prostaglandin and endoperoxide production. As the time and number of freezes increased, the median pain score increased to 7. Concomitantly, the rate of prostaglandin and endoperoxide production could have also increased sufficiently to overcome the inhibitory effects of the NSAID. This could indirectly indicate that appropriate tissue destruction was occurring with the 5-minute double freeze.

A possible confounding factor in the perception of pain and cramping could be the size and shape of the cryoprobe used. A small flat probe with less tissue contact causes less tissue destruction than a large nipped probe does.<sup>17</sup> The amount of tissue destruction can potentially affect the pain and cramping perceived. In the study reported herein, the number of and time required for freezes affected the difference in pain and cramping perceived during cryosurgery by as much as 7 points on a Likert scale of 0 to 10. It is unknown whether the difference in the probe size and shape influences the intensity of pain and cramping perceived. It may be that the large nipped probe causes more pain and cramping than the small flat or nipped probe, but the difference in units on the Likert scale may be minimal. Because the primary goal is to eradicate disease as efficiently as possible, the size and shape of the cryoprobe must be based only on the transformation zone and lesion size.

Implicit in the design of this study was the assumption that all four cryosurgery methods were equally effective in eradicating squamous intraepithelial lesions. One of the basic tenets of cryosurgery is that the entire transformation zone must be destroyed. The destruction process does not differ depending on the grade of the lesion being treated. The surface transformation zone in each patient could be visualized, but the depth of lesion involvement must be estimated from pathologic studies. To eradicate the entire transformation zone, three standard deviations from the average depth of all lesions must be destroyed. In three different publications, the measured depth of crypt involvement of the most severe CIN 3 lesions were 3.8 mm, 4.8 mm, and 4.6 mm.<sup>34-36</sup> Crisp<sup>22</sup> indicated that with proper tank pressure and cryosurgery technique, tissue thermonecrosis should penetrate to a depth of 5 mm to destroy involved glandular crypts. In only one study by Boonstra and colleagues<sup>17</sup> was the depth of tissue destruction actually measured after cryosurgery. The cryosurgical method was described as follows: the iceball formed to 5 mm lateral to the probe edge, followed by a 5-minute thaw, and an identical repeat freeze. It was estimated that it took at least 5 minutes to achieve a tissue temperature of  $-20^{\circ}\text{C}$  at 5 mm from the probe edge, but that a freeze longer than 5 minutes did not extend the iceball beyond 5 mm from the probe edge. This technique consistently caused tissue destruc-