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Cold Coagulation Versus Cryotherapy for Treatment of Cervical Intraepithelial Neoplasia: Results of a Prospective Randomized Trial

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ABSTRACT

A prospective randomized study is presented of 161 patients with cervical intraepithelial neoplasia (CIN) comparing treatment either by "cold" coagulation or cryotherapy. Following colposcopy with directed biopsy confirmation of CIN, patients were randomized on the basis of their medical record numbers and received outpatient therapy. Seven patients were excluded from analysis of final cure rates. The follow-up period ranged from 3 months to 4 years, with 81% of subjects being followed for longer than 1 year. Of 154 patients assessable for cure following single or repeat treatment using the same modality, 89 had received cold coagulation and 65 cryotherapy. Final cure rates using cold coagulation were for CIN I 95.3%, CIN II 100%, and CIN III 92.6%; the overall cure rate for the three grades combined was 95.5%. In the 65 patients treated with cryotherapy, the final cure rates for CIN I, II, and III were 96.7%, 100%, and 84.2%, respectively, and overall, for the three grades combined, it was 93.8%. There was no statistically significant difference in these cure rates between the two modalities either for each grade of CIN or for all three grades combined. All patients tolerated treatment without discomfort but 2 (1 after each treatment) developed local cervical infection which was cured with outpatient medication.

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Although both modalities were equally effective, cold coagulation offers several advantages over cryotherapy: easy portability, no gas requirement, it is electrically operated, and it incorporates automatic self-sterilization. Cold coagulation also requires a far shorter treatment time compared to cryotherapy, making it the destructive modality of choice for outpatient CIN therapy.

INTRODUCTION

IN RECENT YEARS COLPOSCOPY has occupied a central role in the management of patients with abnormal cervical cytology and it has enabled the application of a variety of destructive therapies for treatment of cervical intraepithelial neoplasia (CIN). Destructive therapies for CIN have become of even greater importance because of the increasing numbers of young nulliparous women presenting with premalignant conditions of the cervix, for whom cone biopsy or hysterectomy would not only be overtreatment, but could seriously impair their fertility. For safe application of destructive therapies expert colposcopic assessment is essential, because it allows study of the topography and morphology of CIN lesions and facilitates selection of those patients who fulfill the accepted criteria for locally ablative therapy and identification of others in whom cone biopsy is indicated for diagnostic and/or therapeutic purposes. The role of locally destructive therapies has been well defined, and in expert hands cure rates in excess of 90% can be achieved.[1] However, the existence of several different modalities of local tissue ablation, each with its proponents, suggests that none fulfills all the criteria of being the ideal method of tissue destruction. Electrocoagulation diathermy[2] requires hospital admission and regional or general anesthesia while the carbon dioxide laser,[3] which involves a heavy outlay of capital expenditure, may be used with local anesthetic infiltration of the cervix in an outpatient clinic setting. Cryotherapy[4] instrumentation involves relatively low costs compared with the carbon dioxide laser and requires no anesthesia; it is thus suitable for outpatient or colposcopy clinic use.

Cold coagulation achieves tissue destruction by application of 100–110°C of heat through a Teflon-coated thermosound. In contrast, cryotherapy utilizes tissue freezing to −75°C to achieve tissue destruction. Cold coagulation was initially used to treat benign cervical erosions,[5] but early reports of cold coagulation as an effective destructive therapy for CIN have been encouraging;[6,7] further evaluation is necessary, however, to validate its efficacy, and particularly, to compare it with other modalities already available for treatment of CIN. Particularly, it needs to be evaluated in comparison with cryotherapy since both are ideal for use without anesthesia in an outpatient clinic setting and do not involve the outlay of a heavy capital expenditure. To our knowledge, no controlled studies have so far been reported which compare the efficacy of cold coagulation with any of the other locally ablative modalities for treatment of CIN; we therefore decided to compare its efficacy with cryotherapy in a prospective randomized study. This is a report of our findings.

PATIENTS AND METHODS

Patient selection and treatment criteria

Patients with either two atypical or a single abnormal cervical smear showing dyskaryotic cells are referred to our colposcopy clinic where they have colposcopy performed by or under the supervision of an experienced colposcopist. In patients in whom the neosquamocolumnar junction cannot be identified or in whom any lesion extends into the endocervical canal beyond the visual range of the colposcope (unsatisfactory colposcopy) and those with microinvasion in directed biopsies are considered for diagnostic conization and are excluded from the study. Only patients with satisfactory colposcopy and directed biopsies histologically confirming CIN I, II, or III and suitable for locally ablative therapy by generally accepted criteria[8] are included in the study. Patients with colposcopic features of subclinical papillomavirus infection (SPVI) or in whom cervical cytology or directed biopsy revealed only koilocytotic atypia (KA) are not included unless there were also histologic changes regarded as CIN by the participating pathologist. Patients were advised of the need for therapy and informed consent was obtained for recruitment into the study.

Using the above criteria during the period from September 1983 to February 1988, 161 patients had treatment allocated on a randomized basis according to the last digit of the 7-digit hospital registration number. Those having even numbers being treated with cold coagulation and those with odd numbers with cryotherapy. Ninety-two patients were randomized to cold coagulation and 69 to cryotherapy. Neither the severity (grade of CIN) nor the extent (number of cervical quadrants involved) of disease were taken into consideration during randomization. Three patients were excluded from the study because two with CIN III had been previously treated with cold coagulation, the case records for one of these patients could not be found and the other did not return for the first follow-up visit following initial treatment; another patient with CIN I treated with cryotherapy was excluded because she did not return following initial treatment and could not be contacted despite attempts to trace her. This left 90 patients in the cold coagulation group and 68 in the cryotherapy group, for a total of 158 patients who comprise the study group. Four patients from the study group could not be assessed for final cure for a variety of reasons and are excluded from cure rate analysis (vide infra), which is therefore based on 154 patients.

Clinical characteristics of patients

The clinical characteristics of the 158 patients who were randomized to either cold coagulation (90 patients) or to cryotherapy (68 patients) are shown in Table 1. The age range of the patients was 20 to 53 years for those treated with cold coagulation and 20 to 50 years for the cryotherapy group; the mean age of the former group being 35.2 years and of the latter 34.5 years. The parity of the cold coagulation-treated patients ranged from 0 to 9 and 0 to 6 for the cryotherapy group, but the majority in each group (76%) had two to three previous viable pregnancies. The

TABLE 1. CLINICAL CHARACTERISTICS AND FOLLOW-UP OF 158 PATIENTS TREATED WITH EITHER COLD COAGULATION OR CRYOTHERAPY

Clinical characteristics	*Cold coagulation*	*Cryotherapy*
Age (years)	35.2 ± 7.20	34.5 ± 6.29
Parity (no.)	2.64 ± 1.42	2.46 ± 1.27
CIN I (no.)	43 (55.8%)[a]	30 (54.8%)
CIN II (no.)	19 (47.4%)[a]	17 (47.1%)
CIN III (no.)	28 (28.6%)[a]	21 (33.3%)
Follow-up periods		
<1 year	16 (17.8%)	14 (20.6%)
>1 <2 years	46 (57.1%)	26 (38.2%)
2 years or >	28 (31.1%)	28 (41.2%)

[a]% with koilocytotic atypia either in cervical cytology or in directed biopsy.

mean parity was 2.6 in the cold coagulation group and 2.5 in the cryotherapy group, with the proportion of nulliparas being 4.3% and 5.7%, respectively. The number of patients with each grade of CIN in the two treatment groups and the number with KA or wart virus infection changes in the biopsies are also shown in Table 1. The proportion of patients within each grade of CIN found to have features of KA were well balanced between the two treatment groups, with approximately 55% of patients with CIN I, 47% with CIN II, and 30% with CIN III in either group having changes of KA in directed biopsies.

Colposcopy and treatment procedure

Colposcopy was performed with a Zeiss colposcope using a standard technique of normal saline to cleanse the cervix, inspection under green filter, followed by application of 3% acetic acid. Directed biopsies were taken from the most abnormal appearing areas (often two to three specimens in each patient) and treatment was performed at a second visit 2 to 4 weeks later after careful review of the histologic report. Routine endocervical curettage was not performed, because if the entire transformation could not be visualized or atypical epithelium extended into the endocervical canal out of colposcopic view, then the case was considered to require a cone biopsy. Both cold coagulation and cryotherapy were performed on an outpatient basis at the colposcopic clinic only after repeat colposcopic examination. A full explanation was given to all patients prior to therapy, and they were told that menstrual-like cramps might be experienced during therapy, but that these would subside promptly if they requested interruption of therapy. No oral analgesics were routinely used and no patient required local anesthetic infiltration into the cervix or

paracervical block to complete treatment. For cold coagulation, a Semm cold coagulator (Wisap) was routinely set at a temperature of 100 to 110°C, and when the most appropriately shaped selected thermosound reached this temperature (within 10 to 20 s), it was applied against the cervix to destroy the entire transformation zone and all atypical epithelium within a 4 to 5 mm margin of normal epithelium. The Teflon coating on the thermosound prevented it from adhering to the coagulated tissue and no smoke or odor occurred during treatment. Each application lasted for 20 seconds and the cervical epithelium could be seen to coagulate to a white appearance. Treatment time usually ranged from 40 to 60 seconds. The procedure was repeated for two to three applications, with appropriately selected thermosounds until all typical epithelium including the entire transformation zone was destroyed. The cryotherapy group was treated with a Spembly cryotherapy unit (which uses nitrous oxide as the refrigerant) using the double-freeze technique with the appropriate cryoprobe promoistened with a water-soluble gel and the cervix moistened with saline. A 3- to 5-minute freeze period was followed by a 5-minute thaw period and then freezing was repeated to ensure that the ice ball had extended 4 to 5 mm beyond the edge of all atypical epithelium and the entire transformation zone.

Posttherapy follow-up and retreatment

Following the procedure, patients were advised to abstain from coitus and to avoid using tampons or douches for 2 weeks. They were told to expect a heavy watery vaginal discharge for 2 to 3 weeks and instructed to return if this was malodorous or if there was any associated bleeding or febrile episode associated with pelvic or lower abdominal discomfort. All patients were asked to return for the first posttherapy check at 3 months for repeat cervical cytology and colposcopy; if persistent atypical epithelium or suspected CIN were identified these areas were again biopsied and treatment repeated with the same modality only after review of histology. A second posttherapy visit was scheduled 3 months later; subsequently follow-up continued at 6-month intervals. At each visit repeat colposcopy and cervical cytology were done and only patients with persistent histologically confirmed CIN had repeat treatment. All patients were followed up for at least 2 years, after which they were advised to return to their referring physicians for continued annual cervical cytologic examinations, some, however, preferred to continue follow-up at our clinic.

Patients who had normal cytology and colposcopic examination either following a single or repeat treatment and no evidence of CIN in any repeat biopsies of suspect areas were considered cured. Only patients who were not cured after a second treatment with the same modality were considered as treatment failures in our calculation of final cure rates, whereas those who failed single treatment and did not have repeat therapy were analyzed separately (single treatment cures) but excluded from the final cure rate calculation. Treatment failures were managed either by carbon dioxide laser vaporization conizations or, if indicated, by laser excisional conizations to enable full histogical assessment.

RESULTS

Cold coagulation treatment cure rates and management of failures

Of 90 patients treated with cold coagulation (Table 2), the cure rate for CIN I was 88.4% with a single treatment, and with repeat therapy 95.3% were finally cured, whereas for CIN II the corresponding cure rates were 84.2% and 100%. There was a 78.6% cure rate with a single treatment and a 92.6% final cure rate for those with CIN III. Of this latter subset with CIN III, a single patient who failed initial treatment requested carbon dioxide laser therapy in an attempt to achieve a quicker return to normal cytology so that she could attempt to conceive without delay and is excluded from final cure rate calculation (see Table 4). The overall cure rates for all grades of CIN combined in those treated with cold coagulation was 95.5%. In 4 patients who failed cold coagulation therapy, 2 with CIN I had laser vaporization of the cervix while 2 with CIN III had laser excisional conizations. There were no defaulters from follow-up in this group treated with cold coagulation.

Cryotherapy treatment cure rates and management of failures

The cure rates with cryotherapy in 68 patients are shown in Table 3; following single and repeat treatment for those with CIN I, the cure rates were 86.7% and 96.7%, respectively. In this subset 1 patient had spontaneous resolution of a CIN I lesion persisting after single treatment before treatment could be repeated. For CIN II the cure rates were 64.7% and 100%, respectively, for single and repeat treatments; a single patient who was rescheduled for repeat treatment requested laser therapy and she is regarded as a failure in initial cure rate calculation but excluded from the final cure rate calculation of this subset. Of 21 patients with CIN III treated with cryotherapy, 20 were assessable for cure by a single treatment, of whom 80% were cured (Table 3); but of 3 patients who had repeat cryotherapy, in none did it lead to complete resolution of the CIN, resulting in a final cure rate of 84.2%. Two patients with CIN III are excluded from cure rates calculation (see footnotes to Table 3); in one patient, a careful review of the initial histology raised

TABLE 2. COLD COAGULATION THERAPY RESULTS

Histology	*Number*	*Single treatment number (%) cured*	*Repeat treatment number treated*	*Final cured number (%)*
CIN I	43	38 (88.4)	5	41 (95.3)
CIN II	19	16 (84.2)	3	19 (100)
CIN III	28	22 (78.6)	5	25[a] (92.6)

[a]Repeat treatment was not performed in 1 patient because she requested laser treatment as she was anxious to conceive quickly and she is excluded from denominator in final cure rate calculation.

TABLE 3. CRYOTHERAPY TREATMENT RESULTS

Histology	*Number*	*Single treatment number (%) cured*	*Repeat treatment number treated*	*Final cured number (%)*
CIN I	30	26[a] (86.7)	4	29 (96.7)
CIN II	17	11 (64.7)	5	16[b] (100)
CIN III	21	16[c] (80.0)	3	16[d] (84.2)

[a]Includes 1 patient who initially failed single treatment but then had spontaneous resolution of CIN I.

[b]One patient requested treatment with laser after failure of single treatment and is excluded from final cure rate calculation.

[c]One patient on review of directed biopsy histology was thought to have early stromal invasion, laser excisional conization confirmed < 1-mm invasion and she is excluded from calculation of both single treatment and final cure rate calculation.

[d]One patient who defaulted after failing single treatment is excluded from final cure rate calculation.

the prospect of early stromal invasion in the directed biopsy and a laser excisional cone biopsy confirmed invasion into the stroma less than 1 mm from surface epithelium showing CIN III. Therefore, she is excluded from both single therapy and final cure rate calculation while the other patient defaulted after failing a single treatment and is excluded from calculation of final cure rate only. The overall cure rate for all grades of CIN combined treated with cryotherapy was 93.8% (Table 4). Four patients failed cryotherapy despite repeat treatment; 1 with CIN I is awaiting laser therapy; in 3 others with CIN III, 2 underwent laser vaporization and the other was successfully treated with cold coagulation.

Comparison of cure rates with cold coagulation and cryotherapy

Of the 90 patients treated with cold coagulation, a single patient with CIN III is excluded from the calculation of final cure rate (see footnote to Table 2). Thus only 89 patients could be analyzed for final cure following cold coagulation (Table 4). Of 68 patients treated with cryotherapy, 3 were excluded from final cure rate calculation (see footnotes to Table 3), leaving 65 assessable patients. Therefore, a total of 154 patients including those cured by single treatment and those who received repeat therapy are analyzed for final cure rates (Table 4). Statistical analysis using Fisher's exact test showed no statistically significant difference in the final cure rates for the two therapies either for each grade of CIN or for all grades of CIN combined, being 95.5% for cold coagulation and 93.8% for cryotherapy ($P > 0.05$).

Follow-up of patients and complications of therapy

Because this was a prospective study, every attempt was made to contact all defaulters who failed to reattend. This was successful in all except three instances

TABLE 4. COMPARISON OF FINAL CURE RATES OF CIN WITH COLD COAGULATION AND CRYOTHERAPY USING FISHER'S EXACT TEST

	Cold coagulation		*Cryotherapy*		
	Number cured/ number treated (%)		*Number cured/ number treated (%)*		*P value*
CIN I	41/43	(95.3)	29/30	(96.7)	0.63
CIN II	19/19	(100)	16/16	(100)	1.0
CIN III	25/27	(92.6)	16/19	(84.2)	0.33
All grades	85/89	(95.5)	61/65	(93.8)	0.46

which included the single patient whose case records could not be found and two others who could not be contacted to reattend after initial treatment and therefore could not be assessed for cure. These were the only 3 patients excluded from the study, leaving 158 who could be assessed following single or repeat treatment and analyzed for cure rates. The period of follow-up ranged from 3 months to 4 years but most patients were discharged to their own physicians for regular smears after normal cytology was present beyond 2 years following initial therapy. The details of follow-up are shown in Table 1, but essentially 17.8% of the cold coagulation group were followed up for less than 1 year and 88.2% for more than 1 year, whereas of the cryotherapy group the corresponding figures were 20.6% and 79.4%. Of the entire study group 19% were followed up from 3 months to less than 1 year, 46% for 1 to less than 2 years, and 35% for at least 2 years or longer. Complications of therapy developed in 2 patients (1 from each group), who developed a local cervical infection with malodorous blood-stained discharge from necrotic sloughing of tissue. Both were treated with antiseptic cleansing in the clinic followed by self-application of a triple sulfonamide vaginal cream and oral broad-spectrum antibiotics and promptly resolved without further sequelae.

DISCUSSION

The rationale to treat all grades of CIN is the increasingly greater acceptance that CIN is a continuum of change along a spectrum of preinvasive disease that precedes invasive cancer. The need to treat is all the more urgent considering the reported increased mortality among younger women from cervical carcinoma.[9] Destructive therapies which include cryotherapy, electrocoagulation diathermy, carbon dioxide laser, and recently cold coagulation for CIN following expert colposcopic assessment are safe with cure rates in the region of 90-95%,[1,8] but personal preference, local availability, and familiarity with each technique has prompted various proponents to expouse the superiority or advantages of their favored modality. Although

extensive experience has been reported with each modality in numerical terms of patients treated, seldom have these modalities been compared with others in randomized studies.

Cryotherapy has produced cure rates for CIN I of 95%, CIN II of 93%, and for CIN III of 88% with an overall cure rate of 92% being reported for all grades of CIN combined,[4] which is in close agreement with our 94% cure rate for all grades of CIN combined using cryotherapy. These overall cure rates for all CIN grades combined using cryotherapy are comparable to those reported with the carbon dioxide laser of 87%[10] and with electrocoagulation diathermy of 97%.[2] More recently, cold coagulation for CIN treatment during preliminary evaluation in 71 patients[7] produced overall cure rates comparable to those obtained with cryotherapy or the carbon dioxide laser, with 97% of patients reverting to normal cytology, and these cure rates were confirmed in a subsequent report of a much larger study comprising 598 patients by Duncan[6]; in the latter study all patients had been followed up for at least 6 months and three quarters had been followed up for 1 year or longer. The results in the present report of a 96% cure rate with cold coagulation for all grades of CIN combined are directly comparable to those of earlier studies[6,7] using this modality and extends the published experience with cold coagulation for CIN treatment.

Moreover, we believe the present study is the first randomized evaluation of these two modalities and confirms that both cryotherapy and cold coagulation are equally effective treatment for CIN. Lack of such randomized studies has had its drawbacks; it has hindered objective evaluation of the therapeutic efficacy of each newly introduced destructive modality directly against other older modalities when tested under uniform conditions of a single clinic patient population during similar time periods. Our study does not suffer from these disadvantages since those treated were from a single clinic of similarly evaluated patients treated during parallel time periods.

Treatment of CIN using destructive modalities has gained in popularity primarily because widespread use of colposcopy for evaluation of patients with abnormal cervical cytology enables precisely tailored destructive therapy to treat completely the abnormal area of the cervix under direct visual control. All destructive modalities in current use are safe and effective when patients receive careful pretherapy evaluation by expert colposcopists, but deficient evaluation is fraught with risk of treating unrecognized invasive cervical cancer.[11] Adverse effects on the fertility of the increasingly greater proportion of younger women desiring further child bearing who undergo such destructive therapies for CIN is rare.[1,6,12] In this respect too, cold coagulation has no disadvantage compared with cryotherapy and electrocoagulation diathery because it does not impair fertility as shown in a subsequent 94% conception rate[6] in those desiring to conceive. Neither is the performance of the cervix adversely affected during pregnancy or labor since scarring is minimal, unlike that which might possibly occur when other modalities utilizing more intense heat such as electrocautery or electrocoagulation diathermy are used.

We learned from the present study that, of the two modalities we evaluated, cold coagulation offers several distinct advantages over cryotherapy. Mainly, although the costs of the two devices may be comparable, the cold coagulator works conveni-

ently and inexpensively on readily available simple main electrical power and obviates the need for gas and gas cylinders which, in addition to being costly, are inconvenient and difficult to handle. The portability of the small cold coagulator device is especially convenient; it can be transported to almost any location where electricity is available; between procedures the thermosound is simply washed under the tap water and the automatic self-sterilization is activated simply by turning on the switch again before its next use. Moreover, its mode of operation is silent, and it requires a much shorter treatment time, seldom exceeding 80 seconds for three applications per patient compared to the 20–30 minutes required for three applications of a freeze-thaw-freeze cycle of cryotherapy. The thermosounds do not stick to the tissue during treatment, whereas cryotherapy requires defrosting of the cryoprobe before it can be removed from the cervix, which is another time-saving feature. The very short treatment time (less than 2 minutes per patient) with cold coagulation makes for a very significant time saving and also a greater acceptance by patients. Both of these factors make for smooth and efficient operation of an outpatient clinic and a satisfied clientele.

Even though both cold coagulation and cryotherapy are highly effective and equally efficient in terms of cure rates for CIN treatment, these modalities are, however, not applicable for treatment of intraepithelial neoplasia or human papilloma viral infections affecting the vagina, vulva, and perineum. Human papilloma viral infections are an increasingly common clinical problem. In this respect, the carbon dioxide laser has far greater versatility because it allows performance of a variety of procedures consisting of vaporization or incision or a combination of both in the cervix[13] and vaporization of affected epithelium to precisely controlled dermal levels in the vagina and vulva,[14] a feature which is unmatched by any of the other currently available destructive modalities. Furthermore, when performed by competent and experienced individuals, healing of the treated areas following carbon dioxide laser therapy is excellent. The carbon dioxide laser, however, involves heavy initial expenditure. Therefore when costs are a consideration, it would seem that cold coagulation would be the preferred modality for use in an outpatient clinic setting for therapy of CIN or benign cervical lesions in view of its many practical advantages and lower operating costs. The carbon dioxide laser we feel, is ideal for management of outpatient clinic therapy failures, cervical conizations, and therapy of vaginal and vulvar disease, the latter especially, generally require either regional or general anesthesia and are therefore best done in an operating theatre setting on a day surgery basis.

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