

A three-year review of treatment of cervical intraepithelial neoplasia with large loop excision of the transformation zone

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One hundred and eighty-five patients were treated with large loop excision of the transformation zone for cervical intraepithelial neoplasia from October 1992 through September 1994. All patients were followed up regularly until September 1995 to review the outcome and morbidity. Cure rates of 97.2% in the first six months and 95.4% at the end of the first 12 months were obtained. Thirteen patients (7.0%) were admitted as emergency cases for post-operative haemorrhage, which required suturing, cauterisation with silver nitrate or electrocoagulation, vaginal douching, or antibiotic treatment. One patient developed cervical stenosis and incomplete excisions were noted in 46 (24.9%) patients. Eleven (6.0%) patients had cervical carcinomas detected. Our findings further confirm that this method is a reliable and safe way to treat cervical intraepithelial neoplasia with an acceptable rate of morbidity.

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Introduction

Cervical intraepithelial neoplasia (CIN) is a pre-malignant condition that requires appropriate treatment and regular follow up to prevent and detect any progression of disease. Treatment modalities employing local destruction methods such as cryotherapy, electrocautery diathermy, cold-coagulation diathermy, or laser vaporization do not provide tissue specimens for histological confirmation. Cases of microinvasive and invasive carcinoma of the cervix have been reported after local destruction methods.¹⁻³ Alternatively, local excisional treatment such as cold knife cone biopsy or laser cone biopsy can be used. However, the traditional cold knife cone biopsy usually requires general anaesthesia and laser cone biopsy involves special training and a high capital cost.⁴

Since large diameter wire loop electrodes were introduced by Prendiville in 1989 for the excision of CIN,⁵ large loop excision of the transformation zone (LLETZ) has become the treatment of choice in many colposcopy clinics in Hong Kong. It involves the excision of cervical tissue by a thermal effect produced by passing high frequency alternating current through a thin wire loop that is used for cutting. Blended currents of spark gap type wave forms and continuous sine wave forms are employed to combine good electrosurgical cutting effect with a moderate degree of coagulating effect. The equipment is much less expensive than laser equipment. It is a simple procedure that can easily be learned and carried out at the outpatient clinic using local anaesthesia.

To the best of our knowledge, only two reports have been published documenting local experience with this treatment method. One report describes preliminary experience with 72 patients with a 12-month follow up,⁶ while another report documents the histological findings.⁷ The present report is a retrospective study attempting to review the long term outcome and morbidity in this group of patient for a follow up period of three years.

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Subjects and methods

One hundred and eighty-five patients with CIN grade II (CIN II) or above were treated with LLETZ from October 1992 through September 1994 (24 months). A total of 190 procedures were performed. Prior to the procedure, all patients underwent a colposcopic examination and the diagnoses were confirmed with guided biopsy. All cases had satisfactory colposcopic findings in which the upper margins of the lesion or the whole transformation zone were clearly visualised through the colposcope.

The procedure

All patients were put in the lithotomy position and grounded via a diathermy pad attached to the thigh. A bivalve speculum was inserted into the vagina to expose the cervix. After the application of Lugol's iodine solution to the cervix, the transformation zone could be delineated. Local infiltration of about 10 to 20 mL 1:200 000 adrenaline (with 1% lignocaine) was given to the 2, 5, 7, and 11 o'clock positions of the cervix. Various sizes of loop diathermy (2 cm x 2.5 cm or 2 cm x 1.5 cm) were used and placed about 5 mm lateral to the margin of the lesion. This was excised together with the entire transformation zone by pushing the wire loop perpendicularly into the cervical tissue to a depth of 5 to 7 mm. The loop was then slowly drawn across the transformation zone parallel to the surface. It was then withdrawn out of the cervix perpendicular to the opposite side of the transformation zone. A button-shaped piece of tissue was obtained. The endocervical canal was inspected with the colposcope after staining the tissue using 5% acetic acid. If abnormal areas were identified, multiple cutting of the endocervical lesions could be performed using wire loops of smaller sizes. Haemostasis was achieved by electrocoagulation using ball diathermy or the application of Monsel's solution.

Anaesthesia

One hundred and seventy-four (91.6%) procedures were performed using local anaesthesia with 1% lignocaine and 1:200 000 adrenaline solution, 15 (7.9%) procedures were performed under general anaesthesia, and one (0.5%) procedure was conducted under spinal anaesthesia. The choice of anaesthesia was mainly according to the patient's wishes. However, seven patients required another procedure in the same setting (five had termination of pregnancy by suction evacuation, one had excision of labial cyst, one had hysteroscopy pus dilatation and curettage for dysfunctional uterine bleeding).

Prophylactic antibiotics

Doxycycline 100 mg twice daily for seven days was given to all patients after the procedure.

First follow up after the procedure

All patients had their first follow up visit at two to seven weeks after the procedure. Cervical smears were taken during this and all subsequent visits that were arranged at three- to four-monthly intervals.

Duration of follow up

All patients were followed up until 16 September 1995. The mean duration was 18.3 months (range, 1.5-35 months). Apart from cervical smears, endocervical cytobrush (Cytobrush Plus cell collector, Medscand AB, Sweden) was also used in the patients whose endocervical margins were involved.

Results

The mean age was 30.3 years (range, 19-62 years; median, 35 years). Twenty-seven patients (14.6%) had been previously treated with cryotherapy. Nineteen had persistent CIN and eight had recurrent CIN after cryotherapy. Five patients had termination of pregnancy, one patient had a labial cyst excised, and another had hysteroscopy pus dilatation and curettage.

No pathology was detected in 13 specimens. Twenty-three per cent were grade CIN III and 77% were CIN II in pre-LLETZ colposcopic-guided biopsy (Table 1). Only one specimen was found to be unsatisfactory for histological diagnosis by the pathologist. Eleven patients (6.0%) were found to have cervical carcinoma. One hundred and forty-six patients (78.9%) had specimens that confirmed the diagnoses given by their colposcopically-directed cervical biopsies. Nearly 25% (45/185) of patients had incomplete excision according to the histopathological finding (Table 2).

One patient had excessive bleeding of approximately 500 mL while undergoing termination of a 12-week pregnancy by suction evacuation at the same time (Table 3). There were no reports of abdominal cramps except for mild discomfort; no analgesics were required. There were no cases of electric shock but one patient had a mild vaginal burn due to accidental contact between the charged wire loop and the vaginal mucosa. Twenty-six patients (14.1%) were admitted as emergencies. For the nine patients admitted because of persistent vaginal discharge, positive cultures were obtained in four cases: *Bacteroides fragilis*, *Peptostreptococcus* spp., *Streptococcus* spp. group D, *Streptococcus* spp. group B, and *Enterococcus* spp. were identified.

Table 1. Results of histopathology of the loop specimens (n=185)

Histology	No. of patients (%)
Unsatisfactory specimen	1 (0.5)
Normal cervix	13 (7.0)
CIN II	37 (20.0)
CIN III	123 (66.5)
Cervical carcinoma:	
Microinvasion	2 (1.1)
Invasive carcinoma	9 (4.9)

Two patients (1.1%) were admitted within 24 hours after the operation because of haemorrhage. One was examined under general anaesthesia and needed electrocautery and suturing of the cervix. The other required chemical cauterisation with silver nitrate solution only. Eleven patients (6.0%) were admitted and the time interval from the day of operation ranged from two to 24 days (mean, 9.6 days). The duration of hospitalisation varied from one to 10 days (mean, 3.2 days). Only one patient required suturing under general anaesthesia for haemostasis. The others were treated either by cauterisation using silver nitrate solution and/or electrocoagulation or Monsel's solution or vaginal douching using 1% povidine. Antibiotics (doxycycline, doxycycline + Flagyl or Amoxil + Flagyl) were prescribed in most of the cases.

One patient developed severe cervical stenosis and presented with secondary amenorrhoea and cyclical abdominal pain. She was found to have haematometra and haematosalpinx on ultrasound scanning. Cervical dilatation under general anaesthesia was required.

Fertility

Eleven patients had been pregnant after the operation and five requested termination of their pregnancy. One patient had a missed abortion requiring suction evacuation while three patients had term delivery (two patients had normal vaginal delivery, one had Caesarean section). Two patients are attending our antenatal clinic.

Outcome at three-year follow up

A total of 174 records were reviewed. These included two patients with final diagnoses of microinvasive squamous cell carcinoma, which were treated conservatively.

Nine patients with microinvasive squamous cell carcinoma (two patients with the depth of invasion > 2 mm

were treated by Wertheim's hysterectomy, seven patients with the depth of invasion < 2 mm were treated by simple abdominal hysterectomy) were excluded. One patient, who had endometrial carcinoma eight months after the procedure, had a total hysterectomy and bilateral salpingo-oophorectomy performed and was also excluded.

Cure rate

A cure rate of 97.2% in the first six months was obtained and maintained at 95.4% at the end of the first 12 months.

Failure rate

This was most commonly seen within the first 12 months of treatment (88.9% of total failure cases, Table 4). The failure rate within the first 12 months was 4.6% (8/174). Three patients (n=24, 12.5%) belonged to the group of incomplete endocervical excision margin, two patients (n=9, 22.2%) were in the group of incomplete ectocervical and endocervical excision margins, three patients (n=11, 27.3%) had complete excision but the lesions were very close to the margins. One patient (0.5%), who had incomplete excision of the ectocervix, had persistent disease detected 15 months after the operation.

Table 2. Types of cervical intraepithelial neoplasia involvement found in surgical margins

Types of margin involvement	No. of patients (%)
Endocervical margin	25 (55.6)
Ectocervical margin	8 (17.8)
Both margins	12 (26.6)

Management of persistent disease

Five patients had repeat LLETZ while the transformation zones and lesions could be seen completely. Three did not show residual disease. One patient with complete excision has been followed up for 25 months since the second LLETZ and has no evidence of recurrence. Another had incomplete excision on second LLETZ and has been followed up closely with cervical smears being taken and endocervical cytobrush being used.

Two patients had cone biopsies and one did not have any signs of residual disease on the specimen. One patient had CIN grade I. This patient was observed and monitored with regular cervical smears and cytobrush. One patient had total abdominal hysterectomy in a private hospital.

Recurrence

There was no recurrence after 18 months of follow up.

Discussion

Several studies have reviewed the usefulness of (LLETZ) in the treatment of CIN.^{6,8-12} When compared with either the cold knife conization¹³ or carbon dioxide laser treatment,¹⁴ this procedure has been found to produce similar cure rates with fewer complications or morbidity.

Prendiville reports a 'success' rate after a single treatment of 98% in his series.⁵ Gunasekera noted a 5.1% recurrence rate in patients treated with LLETZ versus 6.9% in patients treated with laser ablation.¹⁴ In our study, a cure rate of 97.2% in the first six months and 95.4% at the end of the first 12 months was obtained. The incidence of persistent disease or failure rate, being defined as the presence of CIN within one year of treatment, is 4.6%. All cases of persistent disease occurred in patients with incomplete excisional margins or with lesions close to the excisional margins. The incidence of involvement of surgical margins of the LLETZ specimens in our series is 24.9%. Others have reported rates of 5.3% to 27.0% of cases.^{15,16} A pathological report of incomplete excision or marginal involvement may give rise to concerns of inadequate treatment. The available evidence suggests that only a minority of these cases harbour a residual lesion¹⁰ and the presence of incomplete excisional margins does not adversely affect the long term outcome in terms of treatment failure.^{15,16} Such observations are explained by the fact that the thermal cutting effect and the post-LLETZ coagulation diathermy to the cervical craters may help destroy small lesions at the surgical margins or on the tissue surface.

Too much concern with completely clear surgical margins may lead to larger and larger loops or cones being performed. This may increase the incidence of bleeding, infection, and cervical stenosis. A margin of 2 mm of normal tissue around the colposcopically-defined lesion will be optimal.¹⁷ Apart from the surgical technique, the key to avoiding treatment failure is the proper selection of patients. Risk factors associated with higher treatment failure include a large CIN lesion, lesions with a squamo-columnar junction within the endocervix, and anxious or restless patients who may not co-operate during the outpatient procedure under local anaesthesia. The use of appropriately smaller diathermy loops to excise the endocervical lesion guided by colposcopy following the initial

LLETZ may help overcome the topographic problems with CIN lesions.

Table 3. Morbidity associated with large loop excision of transformation zone (n=185)

Types of morbidity	No. of patients (%)
Intraoperative haemorrhage	1 (0.5)
Emergency admissions:	
Primary haemorrhage	2 (1.1)
Secondary haemorrhage	11 (6.0)
Persistent vaginal discharge	9 (4.9)
Return of menstruation	1 (0.5)
Cervical stenosis	1 (0.5)
Total	25 (13.5)

The two major short term complications of LLETZ are haemorrhage and infection. In our experience, intraoperative haemorrhage has not been a problem and the only patient who bled excessively was having a concurrent termination of pregnancy. The incidence of primary haemorrhage within 24 hours of the operative procedure is 1.1%, which compares favourably with the reported 0.5% to 2.0% cited in other studies.^{5,18} It has been suggested that primary haemorrhage may be related to the amount of cervical tissue excised and, therefore, only the minimum amount of tissue compatible with successful treatment should be excised.¹⁹ Secondary haemorrhage appears to be a more common problem, with reported incidence ranging from 0.6% to 5.5%.^{5,6,16,19-21} In our series, the incidence is 6.0%, which is much higher than the other series. However, the cases reported in these series represent those patients who had sufficiently severe bleeding to require hospitalisation with suturing or vaginal packing of the bleeding points. This may underestimate the true incidence. Most of our patients were admitted via the accident and emergency department and did not have severe enough bleeding to warrant hospital treatment. This assumption is apparently supported by the median blood loss of only 100 mL and the median haemoglobin count of 12.5 g/dL. Five patients did not require any treatment after admission. Hence, the majority of patients were well and would have been treated on an outpatient basis.

In the present series, oral or vaginal antibiotics were given to all patients after LLETZ with the aim of re-

ducing post-operative haemorrhage and infection. However, there have been no randomised controlled trials to document a beneficial effect. It has also been suggested that the use of Monsel's solution (Ferric subsulphate solution) to achieve haemostasis instead of using diathermy may cause less necrotic slough and have less potential for superinfection. Infection following LLETZ is reported to be quite common, with an incidence of 1.4% to 8.0%.^{5,6} *Bacteroides fragilis* and *Gardnerella vaginalis* are the most frequently responsible organisms. Those patients with colposcopic evidence of cervico-vaginitis and those with a recent history of lower or upper genital tract infection have a higher risk of infection and secondary haemorrhage. To minimise the incidence of infection, it is better to start appropriate treatment for the pre-existing infection and to postpone LLETZ in these patients. Although two of our patients were admitted because of heavy menses, overall, no significant difference was observed in terms of amount of menstrual loss, dysmenorrhoea, intermittent vaginal bleeding, or postcoital bleeding compared with other series.¹⁵

One patient in our series (0.5%) had cervical stenosis and presented with haematometra. The incidence of cervical stenosis in other series has been reported to be between 1.3% and 10%,^{16,19,21} which is much lower than the 17% incidence found with cold knife cone biopsy. The occurrence of cervical stenosis has been reported to be related to a depth of excision greater than 14 mm.¹⁸

The incidence of infertility is difficult to assess because of limited data available for analysis. Potential mechanisms causing infertility include cervical stenosis, ascending infection leading to tubal damage,

and changes in the physical characteristics of cervical mucous affecting sperm transport. In our series, no patient has complained of infertility and 11 patients have conceived after the treatment. It has been reported that the pregnancy outcome is similar to that achieved in those treated with laser vaporisation or electrocoagulation rather than those who have had cold knife conization.¹⁰ Except for a significantly lower birth weight, there was no evidence of a worse pregnancy outcome in terms of preterm labour or Caesarean section.²² A recent report even questions this observation and suggests that when socio-epidemiological factors associated with the development of CIN are controlled for, LLETZ does not appear to exert an independent adverse effect on subsequent pregnancy outcome.²³ Even when LLETZ is performed in patients in early pregnancy, a normal spontaneous vaginal delivery at term is reported.⁵ Although it would be premature to draw any firm conclusion, the observations so far are reassuring, especially for young women who may require this form of treatment.

In the present series, 11 patients (6.0%) were found to have unexpected microinvasive carcinoma. Two were thought to have invasive disease and one was thought to have microinvasive disease on colposcopic examination, however, only CIN III was reported pathologically. One patient was treated with cryotherapy three times before this procedure. One patient had incomplete endocervical excision margin on first LLETZ with residual disease on follow up cervical smear and the second LLETZ revealed a microinvasive lesion. Such findings confirm that LLETZ is effective in discovering unexpected cervical carcinoma that may be missed if destructive therapy is employed.

Table 4. Persistence or recurrence of cervical intraepithelial neoplasia at 18-month follow up (n=174)

Site of involvement	Length of follow up (mo)			
	<6	6-12	12-18	>18
Endocervix	1 (3)	2 (8)	0 (4)	0 (9)
Ectocervix	0 (0)	0 (0)	1 (4)	0 (2)
Endo- & Ectocervix	1 (1)	1 (2)	0 (4)	0 (2)
Clear but close to endocervix	2 (3)	0 (0)	0 (2)	0 (4)
Clear but close to ectocervix	1 (1)	0 (0)	0 (0)	0 (1)
Clear margin	0 (9)	0 (19)	0 (38)	0 (58)
Total (Study total)	5 (17)	3 (29)	1 (52)	0 (76)
%	0.29	1.7	0.6	0

The present series follows the traditional approach of management for abnormal smears i.e. confirmation of CIN lesions with a colposcopically-guided biopsy followed by LLETZ. There are colposcopists who advocate the use of LLETZ for both diagnosis and treatment in a single visit as a pathological specimen suitable for excluding the presence of microinvasive or invasive carcinoma of the cervix is obtained.^{20,24,25} Further evaluation of this approach is required because of the possibility of overtreatment in those patients with only a mild degree of CIN and the possible, albeit small, risk of complications associated with LLETZ. For patients with high grade CIN in cervical smears or those with a clear-cut colposcopic appearance of high grade CIN, the "see and loop" approach certainly has its attractions both in terms of convenience and cost-effectiveness.

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