Journal of the Institute of Medicine 1999; **21**: 1 –45 Original Article

Carbon dioxide laser therapy of cervical intraepithelial neoplasia

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ABSTRACT

We present a prospective study of cytology, colposcopy and histology reports of the first 70 women treated with CO_2 laser for CIN lesions in East Surrey Hospital, Redhill (U.K) from 1st Sep 1984 to 30th July 1986.

Follow-up evaluation consisted mainly of cytology sampling and colposcopy if needed. Initial follow-up was at 6 weeks after laser therapy, then 3 monthly for the first year, 6th monthly interval for the second year, and yearly thereafter for the rest of life. Out of 70, 68 patients were regularly seen at the gynaecological clinic. Two patients left the country to live aboard, and advice being given to follow the above schedule and to send us the copy of the smear reports (were reported Normal up to 2 years). Nine out of 70 patients (12.8%) demonstrated abnormal cytology indicating the presence of CIN following laser therapy. All these cases were recolposcoped and rebiopsied for accurate diagnosis. Two out of 20 patients CIN grade II recolposcoped (10%) demonstrated persistent disease following primary laser therapy. Seven out of 42 patients in CIN grade III (16.6%) demonstrated persistent disease. Over 97% of the patients were cytologically free of CIN at the end of the study.

CO_2 laser is an effective form of treatment of CIN leisons. Failure rate was just under 3%. We recommend that any follow-up protocol should include 3 monthly interval for the first year, then 6 monthly interval for the 2nd year and then yearly thereafter for the rest of the life.

Keywords: CIN; cytology; CO_2 Laser.

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INTRODUCTION

CIN is a broad term covering all the precursors (dysplasia and carcinoma-in-situ) of squamous cancer. CIN can be graded as CIN I, CIN II, CIN III. CIN I corresponds to mild dysplasia. CIN II to moderate dysplasia and CIN III to severe dysplasia and carcinoma-in-situ (CIS) lesion. With the use of papanicolaou smear, it is possible to detect these intraepithelial lesions and to treat them early, thereby obtaining a high cure rate. At present, conization of the cervix and hysterectomy are considered to be over treatment for CIN. With the rising frequency of the diagnosis of early CIN in younger women and with increased knowledge of cellular biology and pathology, there has been a marked trend towards conservatism. The CO_2 laser ablation is a recent modality of the treatment of such lesions. Our own experience with laser treatment of CIN is presented. This is followed by a discussion on the other forms of conservative treatment for CIN.

OBJECTIVE

To study the long-term efficacy of CO_2 laser therapy of cervical intraepithelial Neoplasia (CIN) and to evaluate the Diagnostic merits of colposcopy and cytology in the follow-up of these women.

PATIENTS AND METHOD

A total number of 70 patients were diagnosed as having CIN lesions and treated. most patients were referred to by general practitioners because of abnormal smear they found and some were referred to by colleague gynaecologist consultants from other hospitals for laser treatment of CIN lesion. The finding of an abnormal smear prior to treatment varied from 3-31 months. The youngest patient was 21 years and the oldest was 49. The majority of the patients (60.5%) were of parity one or two, and (38.5%) were multiparous and only 1 was grand multiparous (P5+1). 90% of the patients presented with symptomless abnormal smears, the rest presented in addition a variety of symptoms such as heavy periods, intermenstrual or post-coital bleeding, with or without vaginal discharge. 80% of the patients had macroscopically normal cervix and the rest had varying degrees of erythroplakia.

Clinical Staging

The clinical staging proposed by Richart (1967)[1] was used. The staging is based on cytology, colposcopy and histological evaluation. Infection was excluded by high vaginal swab culture. The distribution of the various grades of CIN in this series is shown in Table I.

Table I: Distribution of patients into various grades of CIN

No.	*Disease Stages*	*No. of patients*	*Percentage of patients*
1	CIN I	8	11.5
2	CIN II	20	28.5
3	CIN III	42	60.00
Total		70	100.00

Colposcopy

Colposcopic evaluation of the patients with an abnormal smear is essential before

treating them with CO_2 laser. The use of colposcopy helps to evaluate the changes in the terminal network of the vessels of the cervix, pinpoints the area of neoplastic change, the extent of the lesion, differentiates from other infective and invasive malignant lesions of the cervix, and it also helps to obtain a directed biopsy for histological diagnosis. Colposcopic examination was carried out mostly without anaesthesia, except in a few apprehensive patients. The colposcopic examination included a brush smear, a repeat pap smear (when necessary), application of normal saline and 3% acetic acid to the cervix, the use of green filter for optimal contrast of the vessels, and the colposcopic magnifications of 6-16x or more, and finally the use of Schiller's Iodine test.

After inspection of the saline moistened cervix, a generous amount of 3% acetic acid is applied which makes areas of columnar epithelium stand out as a typical grape-like structure, while areas of higher density of nucleoproteins (immature metaplasia, dysplasia and CIS lesions) assume a whitish appearance, over a fairly well demarcated area. Table II shows the different stages of the lesions as diagnosed by colposcopy.

Table II: Different stages of disease diagnosed by colposcopy

No.	*Disease Stages*	*No. of patients*	*Percentage of patients*
1	CIN I	7	10.00
2	CIN II	20	28.5
3	CIN III	43	61.50
Total		70	100.00

Colposcopic impression

Eighty-six per cent of the patients had white epithelium, 96.5% had punctation, 88.20% had mosaicism, and markedly abnormal vessels were seen in 8.5% of the patients, with suspicion of micro-invasion in 2 patients. The transformation zone varies from 1-3 cms in diameter and the upper margin of this zone was seen in all these patients.

Brush Smear

The cervical brush smear was designed to study cells and tissue changes including those of the endocervix and add more information to that provided by initial cervical smear. The brush smear is separated in the arbitrary grouping of B1/B2/B3.

B1 corresponds to I and II Papanicolaou smear

B2 corresponds to I, III & IV Papanicolaou smear

B3 corresponds to I, IV & V Papanicolaou smear

Microdensitometry on shed cells from positive cervical brush smear was studied by staining with a controlled technique as reviewed in detail by Levene (1979).[2] From this study, three patterns of histogram emerged and were classified as D1/D2/D3 which correlate well with other cytological and histological findings.

Histology

The final diagnosis was reached by a colposcopically directed biopsy. In the majority of patients, the colposcopic impression agreed precisely with the histology. 2 patients were overdiagnosed and 1 patient was underdiagnosed at colposcopic

examination. 31 patients had carcinoma-in-situ, 11 patients had severe dysplasia and 6 patients had mild dysplasia. 2 patients showed only basal cell hyperplasia. Table III shows the various stages of disease diagnosed by tissue biopsy.

Table III: Histological staging of the disease

No.	*Disease stages*	*No. of patients*	*Percentage of patients*
1	Basal cell hyperplasia	2	2.85
2	Mild dysplasia	6	8.5
3	Moderate dysplasia	20	28.55
4	Severe dysplasia	11	15.75
5	Carcinoma-in-situ	31	44.28
Total		70	100.00

Treatment

The term laser is used for "Light amplification by simulated emmision of radiation". Laser therapy was first proposed in 1958 by Schwawhow and Townes.[3] Since then various other laser works have been advanced. The carbondioxide laser was developed in 1965 and Yahr and Struly (1966)[3] described the cutting and the haemostatic properties of this new laser. Various experiments indicated that the energy of this laser was strongly absorbed by all biological tissue and that a focused beam could vaporize and incise skin, muscles and bone. The American Optical Company later on devised a micromanipulator which allows microsurgery to be performed with definite accuracy.

The Principle of Action of Laser

Laser energy is the consequence of an atomic process. It produces spontaneous emission when the atom is in the excited energy level system, creating a laser effect. All atoms - solid, liquid and gas, can be excited, so solid, liquid and gas laser exist.

The CO_2 laser used in this study (American Optical Corporation Model 350) was described in detail by Polanyi and Tabias (1967).[4] Briefly, a standard 3-feet electronic cabinet contains the gas supply for the laser, a vacuum pump, a power pack, operating controls, and safely interlocks. A cooling system is self contained, only a connection for the electric power is needed. The energy is supplied by passing an electrical current through a gas mixture of Helium (82.0%), Nitrogen (13.5%) and Carbon Dioxide (4.5%) contained in a cylinder called an optical cavity. An electrical discharge from a mixture of the above gives rise to an infra-red invisible beam, which when strikes a mirror, is reflected to a second mirror and returned in similar fashion. If a small opening is created in the middle of one mirror, a stream of laser light egresses. This stream has the unique property of having a parallel beam of uniform wave length of 10.6 micron of the same frequency. If this energy is passed through a lens system, the laser beam can be focused to an area of small dimension producing a power density of unprecedented magnitude. The laser beam is coupled to an operating colposcope by means of a micromanipulator attachment. This arrangement allows positioning of the laser beam with great precision in the visual field of the colposcope.

The power can be varied from zero to 100 watts by turning on a knob on the control panel. Continuous exposure is used and the final output of the laser beam is opened by a foot pedal switch. For documentation of laser procedure, a TV camera is attached to the beam splitter of the colposcope and the findings was recorded on a videotape.

Biological effect of Laser

Hall and Co-workers[4] studies showed that all incident radiation is absorbed as heat by the first 100u of tissue. The microscopic changes of the tissue following laser treatment shows that the most superficial layers of the cervical mucosa is vaporized by the CO_2 laser as a result of boiling and evaporation of extra and intra-cellular water. The volume of this vaporized tissue is directly related to the power output and the exposure time of the laser. By utilizing high power density, the time of exposure could be shortened and thermal damage to adjoining tissue margins reduced. For the treatment of CIN, stormal destruction greater than 4.0 mm depth was required to eliminate involved endocervical glands. The pain in the region is minimal because of the limited tissue injury.

Pre-requisites for Laser Therapy

1. The cervix must be assessed by an expert colposcopist.
2. The entire lesion should be located on the visible portion of the cervix and not extended into the endocervical canal beyond the field of view.
3. The squamous-columnar junction must be fully visible.
4. There should be no evidence of invasion colposcopically and histologically.

Subsequently, 70 patients who fulfilled the above requisites underwent laser treatment. It was performed without anesthesia in most of the patients and they tolerated the procedure well. The power output was maintained at 25-30 watts and the whole of the transformation zone was destroyed. The depth of tissue destruction was 5-7 mm and the time exposure for this destruction varied from 4 minutes to 15 minutes. The water vapour (smoke) was removed by a continuous suction which was attached to the speculum. After the procedure, the patients were given Betadine pessary, to be used vaginally once daily for 2 weeks and asked to abstain from intercourse for 6 weeks and then have only protected intercourse for another 6 weeks.

These patients were seen 6 weeks later following laser treatment. The cervix was so completely healed that it was difficult to identify the treatment site. Baggish (1980)[5] described the complete healing of the cervix in 50 cases following laser treatment. During the first 48 hours, maximal sloughing of the necrotic tissue occurred. 10% of the patients had spotty bleeding with sloughing. The discharge peaked by the third day and stopped by the first week. By the end of the first week, the treated zone was a sharply circumscribed shallow red depression. By the fourteenth day this entire depression was fully

covered with young squamous cells. By the fourth week the cervix was completely healed.

Complications

1. Bleeding: Moderate bleeding occurred in 5 patients during the procedure. The bleeding was controlled by laser and silver nitrate sticks. Only 1 patients needed a stitch to control bleeding. One patient developed delayed haemorrhage 48 hours after laser therapy who required suturing of the bleeding point under general anaesthesia.

   Four patients (5.17%) complained of having secondary haemorrhage two weeks following laser therapy, the amount was less than a period and required no treatment.

2. Pain: All patients perceived heat sensations as the laser therapy progressed. Only one patient found it intolerable and required general anaesthesia to complete the therapy. The major discomfort was described as cramping, similar to menstrual cramp. The pain diminished once the therapy stopped and there was no evidence of persistent pain.

3. Infection: No infection occurred in this series.

4. Cervical Stenosis: To date, laser therapy has been carried out without any evidence of stenosis. The endocervical epithelium seems occasionally to

   overheal with a resultant rosette at the squamocolumnar junction. Therefore, the squamo-columnar junction is readily apparent for subsequent screening.

5. Scar Information: Connective tissue proliferation following laser surgery appears to be minimal. Nevertheless, some scarring does form in the small zone of stormal necrosis.

6. Delayed Healing: No delayed wound healing was observed in this study.

RESULT

Follow-up evaluation consisted of cytological sampling and colposcopy where needed. Initial follow-up was at 6 weeks following laser therapy and further follow-up was at 3 monthly intervals for the first year, 6 monthly intervals for the second year and yearly thereafter.

Out of 70, 68 patients were regularly seen at the gynaecological clinic. 2 patients left the country to live abroad, advice being given to follow the above follow-up schedule and to send us the copy of smear reports. 9 out of 70 patients (12.8%) demonstrated abnormal cytology indicating the presence of CIN following laser therapy. All these cases were re-colposcoped and rebiopsied for accurate diagnosis. Two out of 20 CIN Grade II (10.0%) demonstrated persistent disease following primary laser therapy. 7 out of 42 patients in CIN Grade III (16.6%) demonstrated persistent disease. Those data are shown in Table IV.

Table IV: Persistent disease following 1st laser therapy

No.	*Disease*	*No.*	*Persistent Disease*

	Stage	*treated*	*No.*	*%*
1	CIN I	8	0	0.0
2	CIN II	20	2	10.0
3	CIN III	42	7	16.66
Total		70	9	0

Patients who were free of disease and presumed cured by 1st laser therapy have been followed-up between 6 months to 24 months (Table V).

Table V: Follow-up of patients cured 1st laser therapy

Disease Stage	*Total Cases*	*Follow-up in months*				*Total*
		1-6	*7-12*	*13-18*	*19-24*	
CIN I	8	1	1	3	3	8
CIN II	18	3	5	7	3	18
CIN III	35	4	15	10	6	35
Total	61	8	21	20	12	61

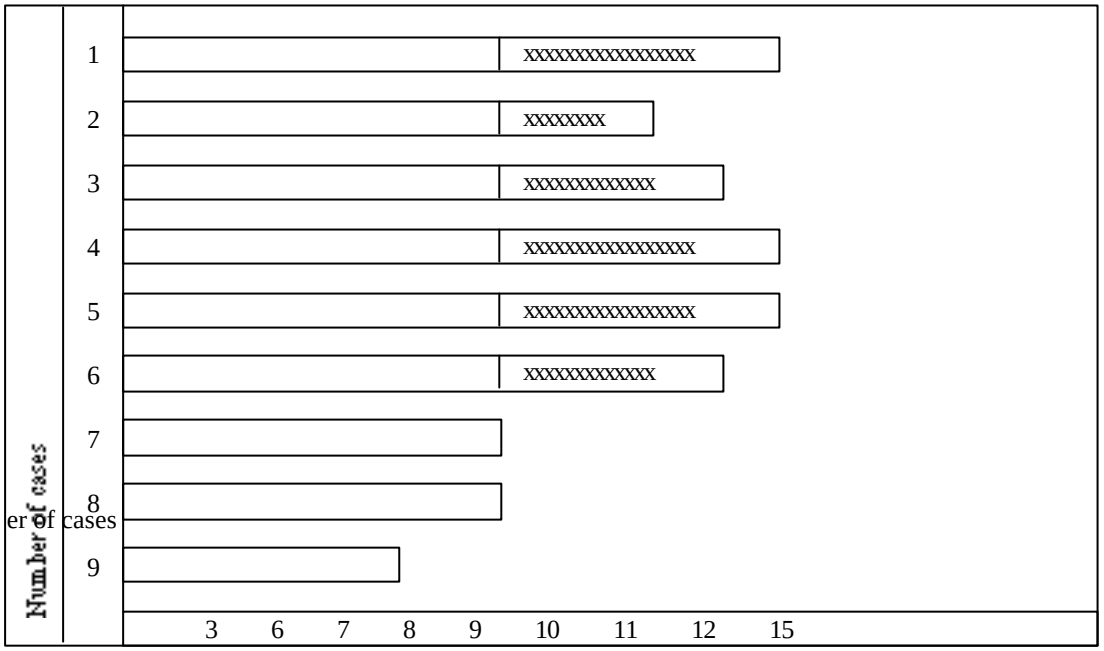
About 89% of patients were seen beyond 6 months, 36 between 7-12 months and 52.2% have had follow-up more than two years. 86.9% of patients had normal smears beyond 18 months. All persistent disease was identified within 6 months of follow-up of 1st laser therapy. More than half of the cases were detected within 3 months and the remainder at 6 months. Table VI showed the lesion detected by cytology.

Out of these 9 persistent cases, 7 patients (77.7%) were successfully treated by a 2nd therapy. 2 patients had conization of the cervix after finding suspicion of an invasive lesion on colposcope. The histology reports showed extensive CIS lesion but no evidence of invasion. 1 of them showed abnormal smears at 6 weeks following cone biopsy and underwent hysterectomy 4 weeks later at the patient's request. Table VII shows the management of the persistent lesions after 1st laser therapy.

Table VI: Identification of persistent lesion by cervical Cytology during follow-up

Disease Stage	*Follow-up period in months*								*Total*
	1-3		*4-6*		*7-12*		*12-24*		
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	
CIN I	0	0.0	0	-	0	-	0	-	0
CIN II	2	10.0	0	-	0	-	0	-	2
CIN III	4	0.51	3	7.10	0	-	0	-	-
Total	6		3						9

Table VII: Management of persistent lesions and duration of negative smear reports following 2nd laser treatment (confidence level of cure at 8 months of persisting negative cytology)



The overall success rate of laser therapy (one or two application) in this study was 97.3%.

Table VIII:

Disease Stage	*No. of patients treated*	*Success rate after 1st laser*		*Success rate after 2nd laser*		*Overall success*	
		No.	*%*	*No.*	*%*	*No.*	*%*
CIN I	8	8	100	-	-	8	100
CIN II	20	17	85	2	10	19	95
CIN III	42	34	83.1	5	11.9	39	93
Total	70			7		66	

Two patients left the country to live abroad, but their smear reports were reported negative.

DISCUSSION

CIN is a continuum and that any grade of CIN has an unpredictable possibility of invasion is well established[1,6] and should be treated.[7] The development of the colposcopic technique and greater understanding of the CIN lesion, have allowed for greater conservatism in the management of the women with abnormal cervical cytology. In this study, the colposcopic impression agreed

with the histological diagnosis in more than 95% of the cases. However, there was a total error of 15% reported in a large study.[8]

An ideal form of therapy should accomplish precise and complete destruction of the lesion with no scattering of neoplastic tissue. There should be minimal damage to the adjacent normal tissue and sealing of the lymphatic channels to inhibit metastatic spread; bleeding and scarring should be minimal since quick healing and patient acceptability are of major importance. The CO_2 laser meets all these criteria.[9] Bellina in 1974 in New Orleans[10], was the first to attempt to eradicate CIN lesion with CO_2 laser and the earliest report on the success of treatment came from the United States of America.[5,6,11] Considerable experience has been gained over the last 12 years with satisfactory results. An early appraisal of laser treatment for CIN was disappointing because of low power density resulting in inadequate destruction of the neoplastic lesion and resultant regrowth.[8]

Recently, high-power density with continuous time mode usage has produced greater than 90% cure rate.[11,12] With this modality, rates of persistent disease following primary laser therapy are most satisfactory. Follow-up of the treated women is the most important part of any kind of treatment, specially true, in conservative method of treatment. Strict follow-up evaluation as recommended-cytology and colposcopy is necessary. The role of colposcopy in the follow-up of women who have been treated for CIN remains controversial. Recent guidelines from the United Kingdom National Screening Program suggest that a follow-up colposcope examination is not essential.[13]

However there are a few drawbacks to laser therapy. Firstly, the exposure of the whole of the transformation zone by colposcope is particularly difficult in nulliparous patients with a tightly closed os or following surgical procedures such as cone biopsy, diathermy, cryo-surgery or Tracholoraphy. Atrophic effects of age in the post-menopausal woman may also make colposcopy indecisive. This problem could be solved by the following methods: differentials curettage, endocervical aspiration, kevorican currette[14] and cone biopsy. These methods are not devoid of significant difficulty and 7 patients were not incorporated in our series for these reasons and were treated by cone biopsy.

Stafly and Wilknson[8] reviewing the present status of CIN, believe that there is growing evidence that endocervical cytology sampling will decrease the false negative result of cervical vaginal cytology. However, the methods of achieving this by endocervical curettage are not devoid of significant difficulty and Urcuyo *et al* [15] comments that in their series of 259 patients the procedure was associated with a significant amount of pain which sometimes thwarted the attempt. We believe that an endocervical brush designed by M. Levene[2] provides the clinician with an early, painless method of sampling such cellular material from the cervix and reduces the false negative rate. A second criticism is that the local destructive method of treatment is the depth of crypts and glands involvement

and those who advocate routine cone biopsy or hysterectomy claim that the destructive method will frequently leave residual tissue in the tips of the crypts and glands. This problem has been clarified by Anderson[16] who showed that 99% of the lesions do not extend any more than 3 mm below the surface and one can therefore predict that if the depth of the destruction is more than 5 mm then this will eradicate almost all epithelial abnormality. This destruction must include the entire transformation zone which is the site of neoplastic potentials.[16,17] A third criticism is its high cost and the immobility of the instrument which limits its practical use and efficiency. With the development of smaller, more mobile machines, a more versatile and less expensive laser model, the noted advantages of this modality of therapy, may become of more practical value for the treatment of CIN and vaginal intraepithelial neoplastic lesions.

The question that arises is how does laser therapy compare with other current conservative therapeutic measures ?

Cone Biopsy

Conization of cervix requires removal of a large amount of both normal and abnormal tissue. Although this procedure offers advantages of copious tissue for diagnosis and the best method for orientation of sections, it has several disadvantages. For example, it requires hospitalization and general anaesthesia. The risk of haemorrhage, infection and the effect on future fertility, are serious drawbacks.[18] An excellent long term study by Kolstad 1976[19] has shown that 2.3% of recurrences of CIS following cone biopsy and an invasive carcinoma may still occur in small number of women after therapeutic conization.

Cryosurgery

Crysurgery has been extensively used for the treatment of CIN with varying degree of success.[20,21,22] A source of concern about cryosurgery is that it does not usually destroy tissue beyond the depth of 3 mm. Therefore, there is a theoretical possibility that such residual tissue maybe covered by regenerating squamous epithelium and remain in this state undetected by cytology and colposcopy until such time as it becomes invasive. Frequently the squamo-columnar junction is relocated into the endocervial canal. The failure rate or persistent disease, is exceptionally high, ranging from 18-30%.[21] However, the advantages over the laser is its easy portability and low cost.

Electro-diathermy

This technique leads to massive destruction of normal and abnormal tissue. Necrosis is extensive with great sloughing of tissue and extensive vascular injury and general anaesthesia is needed. General anaesthesia alone carries a mortality rate of 1:1000 women. Further haemorrhagic complication requiring blood transfusion exceed the mortality and morbidity rate of disease under treatment. Using this technique 90% cure rate for CIN disease was reported.[23,24,25] The cervical physiology is adversely affected by deep electro-diathermy, particularly if the lesion was extensive, but it does not appear to affect subsequent fertility.

Large loop excision of the transformation zone (LLETZ)

Since it was first reported in 1981[27] primarily as an alternative to laser vaporization, the technique of large loop excision of the transformation zone (LLETZ) has rapidly proved a popular method for treating CIN. LLETZ is performed easily as an out-patient procedure and both costs and short-term outcome compare favourably with local destructive and other excisional technique.[28,29,30] Follow-up protocols have been based on those following more established treatment as laser vaporization. With this method the recurrence of CIN was significantly more frequent in women in whom the lesion was thought to have been incompletely excised (x2p=0.01); women younger than 21 age and those older than 40 years had a higher prevalence of subsequent CIN than women of 26-45 (x2p=0.02).[28] Failure rate of 4.4% in 12 months have been reported[28] which is slightly higher than over laser ablation therapy. A possible advantage of treatment with LLETZ is the opportunity for the entire transformation zone to be subjected to histological examination.

In considering the above methods, laser therapy definitely has some advantages over the conservative methods of treatment of CIN lesion of the cervix. The precise tissue removal without post operative pain, bleeding, stenosis or synechial and decreasing the cost by eliminating unnecessary conization and patient acceptability is now a reality.

CONCLUSION

This study is to be viewed as a preliminary report since the number of patients is small and the follow-up period is short. The cure rate after the first laser treatment is 88% and after the second is over 95%. Failure rate was just under 3%. Persistent lesions detected within the first six months after treatment were not classified as recurrence but considered as persistent disease. If the cervical smear remains normal up to 8 months of laser therapy, they have been taken as a cure from the disease.[8] We could concur with other authors in the observation that the current treatment result of CIN with cryosurgery, electrodiathermy, large loop excision of transformation Zone (LLETZ) and laser therapy similar. In my opinion, with above mentioned advantages of laser therapy, the CO_2 laser may find a special place as a treatment modality in future.

ACKNOWLEDGEMENTS

I am very grateful to my consultant Dr. J.D. Andrew, senior consultant obstetrician/ gynaecologist, East Surrey Hospital, Redhill U.K. for his kind permission to examine and treat his patient along with him and teaching me the use of colposcope and CO_2 laser machine manipulation during my three years of working with him. I am deeply abliged to him for his kind consideration and continuous inspiration till I passed my MROCG examination. My special thanks are to gyanecological secretary in the U.K. and in Nepal for helping in computer typing.

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