Treating intraepithelial lesions of the uterine cervix by laser CO_2. Evaluation of the past, appraisal for the future

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Summary

Background and Objective: Carbon dioxide laser (CO_2) has been widely used in the past for the treatment of squamous intraepithelial lesions (SIL) of the uterine cervix. We present our 10-year experience of using this modality while evaluating its current and future use.

Materials and Methods: From 1988 to 1998, 3,078 women were treated for an intraepithelial lesion of the uterine cervix (SIL) by laser CO_2 either by vaporization or conization. The procedure was performed on an outpatient basis and was well tolerated by the great majority of patients. The mean age of the women treated by vaporization was 27.5 years whereas of those managed by conization, 34.8 years.

Results: From the 3,078 women, 750 (24.4%) underwent laser vaporization and the remaining 2,328 (75.6%), conization of the cervix. Complications were minimal and consisted of intraoperative and postoperative bleeding (0.56%), pelvic infections (0.04%) and cervical stenosis (1.1%). Mean follow-up time was 83 months (range 24-142). Relapsing disease (either persistent or recurrent) was detected in 5.6% of the vaporization and 3.9% of the conization group.

Conclusions: The management of SIL of the uterine cervix by laser CO_2 offers excellent success rates with minor complications. The preservation of the anatomical integrity of the cervical tissue offers a better follow-up of these patients and the potential for repeat treatment. Although other treatment modalities are available, we believe that laser CO_2 represents an excellent surgical tool for the management of intraepithelial lesions of the uterine cervix.

Key words: CO_2 laser; Squamous intraepithelial lesions (SIL); Cervix.

Introduction

During the last 25 years, a notable increase in the number of women with squamous intraepithelial lesions (SIL) of the uterine cervix has been observed [1]. The fact that the majority of these women are young is probably related to the spread of the infection of the lower genital tract by the human papilloma virus (HPV) in younger ages. On the other hand, better detection of these precancerous lesions of the cervix, mainly due to the propagation of colposcopy, has caused a dramatic increase of the disease incidence. Human papilloma virus infection is the most common sexually transmitted disease of the lower genital tract of women. Multiple sexual partners, low socioeconomic status, smoking, diet, oral contraception and early first coitus were also implicated as having a causal relationship with pre-invasive and invasive cervical neoplasia. However, during the last ten years, there is universal agreement that HPV infection is the only confirmed factor associated with this disease [2, 3, 4]. Since 1988, the Bethesda System has essentially abolished the term CIN (cervical intraepithelial neoplasia) and included HPV infection and CIN I in the same category of low grade squamous intraepithelial lesions (LGSIL), whereas CIN II and CIN III formed the high grade lesions (HGSIL) [5]. Currently, international colposcopic guidelines suggest that HGSIL must be treated even though the majority of these women will not develop invasive disease [6]. On the other hand, management of LGSIL remains controversial. Some authors believe that follow-up of these lesions is the best approach since almost 60% of them will regress [7], whereas others believe that they should be treated either destructively or excisionally, especially in women in whom surveillance is not possible. The treatment for CIN during the first half of the century was Wertheim's hysterectomy. In 1952, Graham and Meigs proposed simple hysterectomy as a more conservative way to treat these lesions [8]. It was not until 1963 that cold knife conization of the cervix was introduced by Krieger and McCormack. In the years that followed, even more conservative methods such as cryotherapy and electrocautery were applied [9, 10]. They were all focused on the destruction of the transformation zone since it was already speculated that almost all of the premalignant lesions of the cervix were detected a in that area. The CO_2 laser was first introduced as a method for local destruction in 1977 by Belina. Two years later (1979) Dorsey and Diggs proposed conization of the cervix with the CO_2 laser [11]. Later on, large loop excision of the transformation zone (LLETZ) by Prendiville and more recently, needle excision of the transformation zone (NETZ) were described as alternative methods [12, 13].

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The aim of this retrospective study is to present our 10-year experience in using the CO_2 laser for the treatment of a large number of patients with SIL with a long follow-up. The aim was also to optimize the current use of laser CO_2 and other modalities for treating cervical intraepithelial neoplasia which have evolved.

Materials and Methods

From February 1988 to March 1998, 3,078 women underwent laser CO_2 treatment in terms of vaporization or conization of the uterine cervix due to cervical intraepithelial neoplasia (CIN). All women were evaluated preoperatively in the Colposcopy Unit of our Department, with cytology and colposcopy followed by histological confirmation of the lesions by directed biopsies. Cytology smears consisted of sampling of the ectocervix with an Ayron spatula, and of the endocervix with a cytobrush, were assessed by consultants or senior staff at the Department of Cytology. Colposcopy was performed with the Zeiss OPMI-1 colposcope at a focal length of approximately 300 mm and 6-12X magnification. The laser CO_2 instrument used was a 1040 Sharplan with maximum power output of 40 watts, continuous wave generation, coupled to the colposcope. The beam spot diameter ranged from 0.5-1mm with an irradiance ranging from 2500-3500 Watts/cm, guided by a micromanipulator. All but five treatments were performed in the Colposcopy Unit under local anesthesia. Five women from the conization group had treatment under general anesthesia. In two cases there was severe narrowing of the vagina and the operation was impossible due to severe pain after the insertion of the speculum. In three cases the patients requested it.

After a preoperative colposcopic examination using 5% acetic acid and Lugol's solution, the outer ectocervical lesion borders were delineated by laser spots. A 30-gauge needle was used to insert 8 ml of a 2% lidocaine solution with or without adrenaline at the 3, 6, 9 and 12 o'clock positions of the cervix.

Out of the 3,078 treated women, 750 (24.4%) underwent laser vaporization. Indications for vaporization are shown in Table 1. The laser beam was guided by manipulating the joystick and starting from the lower part of the cervix. The lesions were destructed in a clockwise and counter-clockwise motion leaving a circular defect on the cervix to a depth of 6-8 mm into the endocervical canal and 5-6 mm on the periphery. The width of destruction was approximately 4-5 mm beyond any visible lesion. Coagulation was achieved by running the laser beam defocused over the bleeding points and the vessels.

Table 1. — *Indications for laser vaporization treatment.*

Laser vaporization
– Low-grade SIL (histologically confirmed)
– Ectocervical lesions
– Fully visible T-zone
– No suspicion of microinvasion or glandular disease
– Young (less than 35 years old), nulliparous women
– Large ectocervical lesions extending to the vaginal fornices

Table 2. — *Indications for laser conization treatment.*

Laser conization
– High-grade SIL (histologically confirmed)
– Any grade of endocervical lesion
– Suspicion of microinvasion or glandular disease
– Older (more than 35 years old) women
– Discrepancy between cytology, colposcopy and/or histology

In the remaining 2,328 (75.6%) patients laser conization was the modality used. Indications for conization are shown in Table 2. The transformation zone (T-Zone) was always removed along with the lesion in situ, being the cervical area at risk of developing cervical neoplasia. The beam was guided through the micromanipulator parallel to the elongated axis of the endocervical canal, to a depth of at least 1.5 cm and width of 2.0 cm. The excisional technique applied for each cone depended on the colposcopic assessment of the lesion and the involvement of the canal. Thus, large lesions in women with a wide transformation zone who had already completed their families were excised to a large extent providing a "large" and shallow cone. Lesions that were located around the cervical os in younger women or abnormalities that involved the endocervical canal in pre- or postmenopausal patients were excised to a lesser extent at the ectocervix but to an increased depth, thus providing a "narrow" and long cone. In this way it was possible to tailor the treatment, serving the needs of any particular patient. All cones had a cylindrical shape and bent top, leaving a circular crater on the cervix. They were further vaporized to a depth of 1-3 mm providing coagulation and anatomic integrity of the crater. In case a lesion extended into the endocervical canal, it was excised at a greater depth in the center (Cowboy hat technique). Whenever the lesions were large or extending to the vaginal fornices, a "combination" technique was performed, consisting of removal of the central, high-risk part of the lesion while destroying by vaporization the peripheral area. At the end of the procedure, Ferrus Subsulfate solution (Monsell's) was applied into the cervical crater in all cases. All specimens were kept in formaline and were sent to the Pathology Department of our Institution. Sectioning and examination of the cones was performed by consultants or senior staff of the department. If disease was observed on the ecto- or endocervical margins of a cone, they were considered involved. Uncertain margins were considered involved. Thermal artifacts prevented the estimation of the margins in 17 cases. Notably, all these women were treated in the first two years of the initiation of laser application as a method of treating CIN in our unit. Postoperatively, women were advised to abstain from sexual intercourse for four weeks and to use an antibiotic vaginal cream for five days.

All treated women entered the same follow-up protocol which included a pap smear and colposcopy at three, six and 12 months for the first year, every six months for the second, and yearly thereafter.

Statistical analysis was performed using the chi-square test and when applicable the Fisher's exact test. Differences in the mean values were examined for statistical significance by the Student's t-test. A p value less than 0.05 denoted a statistically significant difference.

Results

The mean age of the women treated by laser vaporization was 27.5 years (median: 28, range: 21-34) and of those who underwent laser conization, 34.8 years (median: 35, range: 21-53). The difference between the two groups was found to be statistically significant ($p = 0.0001$).

Intraoperative bleeding occurred in eight women (0.26%). In three patients from the vaporization group (0.4%) and five of the conization group (0.21%) the laser beam failed to control bleeding so hemostatic sutures and tamponade were placed for 24 hours. There was no statistically significant difference between the two groups ($p = 0.41$).

Postoperative bleeding was observed in nine patients (0.3%). The occurrence of postoperative bleeding was approximately the same between the two groups, 0.3% (7 patients) for the conization group and 0.26% (2 patients) for the vaporization group ($p = 0.99$). In all these cases, bleeding was minor and occurred between days 8-12 after treatment. Management consisted of application of Monsell's solution and tamponade for 12 hours.

One woman from the conization group (0.04%), presented with pelvic infection 24 hours after treatment. She was febrile (38.8°C), complaining of abdominal tenderness and minor vaginal discharge. She was admitted to the hospital, and was treated with intravenous antibiotics (Cefoxitin and Metronidazole). By day 1 she became afebrile. She was released on day 3 with oral antibiotics.

The most common complication among our patients was cervical stenosis. Thus, 34 women (1.1%) presented with cervical stenosis during follow-up. Women treated with vaporization presented stenosis less frequently ($n = 5$; 0.66%) compared to women that underwent conization ($n = 29$; 1.24%), however this difference was not statistically significant ($p = 0.23$). Patients that presented with scarring of the canal (opening of the canal < 2.5 mm) were diagnosed by symptoms of secondary dysmenorrhea, hematometra or, most frequently, with unsuccessfully attempted cytological sampling of the endocervix. The majority of these women ($n = 24$) were treated by opening of the cervical os using the laser CO_2 while the remaining ($n = 10$), were managed by conventional dilatation. The age of the patients that experienced post-laser cervical stenosis ranged from 33 to 52 years (mean: 45 years ± 0.9), while patients that did not present cervical stenosis as a complication were significantly younger (mean: 32.9 years ± 0.08) ($p = 0.0001$). Six patients (17.6%) presenting postsurgical stenosis were younger than 40 years whereas 28 (82.4%) were more than 40 years old.

Histology of the cone specimen is shown in Table 3. The majority of the histological results of the cones (94.4%) matched the preoperative diagnosis (HGSIL). In the remaining 59 (2.5%), histology showed LGSIL and in 71 (3.1%) invasive carcinoma of the cervix. From these, 49 (2.1%) had microinvasive carcinoma (SGO definition: depth of invasion less than 3 mm and no lymph-vascular space involvement), and the rest of the 22 women (1%) had a > 3 mm depth invasive carcinoma. All the patients in whom an invasive cancer was found were excluded from the study. Forty-one of 2,257 women (1.8%) had involved margins of the cone. In detail, involved cone margins were found in 38 patients with HGSIL (1.7%) and in three patients with LGSIL (5.1%). The difference between the two groups was not statistically significant ($p = 0.09$). Patients with involved margins were followed-up with the standard protocol of the unit. From the 49 patients with microinvasive disease, in 43 with clear margins the treatment was considered adequate and the patients entered the follow-up protocol. The remaining had a second laser cone. The margins of all second cones were clear so these women entered the same follow-up protocol.

The mean time of follow-up was 83 months (range 24-142). Approximately 7% (215 women) were lost during follow-up. Detection of disease during the first year of follow-up was considered as residual disease, and after the first year as recurrent disease. Persistent or recurrent disease was confirmed in all cases by colposcopically directed cervical biopsies and was considered as such by the presence of squamous intraepithelial lesions of any grade but not by the simple presence of HPV compatible changes.

Overall recurrence rate in the vaporization group was 5.6% (42 patients) (Table 3). Twenty-seven women (3.6%) presented with residual and 15 (2%) with recurrent disease. Nineteen out of the 27 patients (70.3%) with residual disease and 11 out of the 15 (73.3%) with recurrent disease were treated in the first four years (1988-1992) of practicing the method, when depth of destruction was 5 mm. Low grade lesions (24 in the residual and 12 in the recurrent group) constituted the vast majority, but also, one case of invasive disease was detected. This was the case of a 29-year-old woman that was originally treated with vaporization for LGSIL. She was lost after 18 months of negative follow-up. She presented 36 months later with invasive disease, stage 1B1. She had a radical hysterectomy with dissection of the pelvic lymph nodes, and remains free of disease up to now. Treatment of the other patients depended on the grade of the lesion, age of the patient, time passed since first treatment and desire of the woman to maintain her fertility. Young women, with low-grade lesions who had not completed their families, were either followed or had a second cone. Older patients, who did not desire to maintain their fertility, with difficulty in follow-up due to scarring of the canal or inadequate follow-up, were treated by simple hysterectomy. Thus, 20 women (47.6%) had a second laser cone, 15 (35.7%) were followed and seven (16.6%) had a simple hysterectomy.

Overall recurrence in the conization group was 3.98% (90 patients). Fifty-nine women (2.61%) presented with residual, and 31 (1.37%) with recurrent disease. Thirty-eight patients (64.4%) of those with persistent disease had HGSIL whereas LGSIL was found in 22 (70.9%) of the women with recurrent disease. From the 41 women with positive margins on the cone, only four (9.7%) pre-

Table 3. — *Histological findings of cone specimens.*

Neoplasm	Percent (%)
HGSIL	94.4%
LGSIL	2.6%
Microinvasive Ca	2.1%
Invasive Ca	0.9%

sented with persistent or recurrent disease. Three with LGSIL and one with HGSIL. Respectively, in the group with negative margins on the cone, 86 of 2,216 women (3.8%) presented with persistence or recurrence. No statistically significant difference in recurrence rate was found between patients with negative or positive cone margins (p = 0.16). From those with negative margins, 51 (59.3%) had LGSIL and 35 (40.6%) HGSIL. During follow-up, one case of invasive carcinoma was detected. This 34-year-old woman had had a laser cone for HGSIL in 1993. She returned only once in the next 12 months of follow-up, which was negative. She presented in 1998, without having been followed elsewhere, with invasive disease, stage 1B2. She had a radical hysterectomy with pelvic lymph node dissection and is currently free of disease. All other women were managed like those in the vaporization group. Thus, 56 patients (62.2%) had a second laser cone, 25 (27.7%) had a simple hysterectomy and eight (8.8%) were followed-up. Comparison of disease outcome between patients who underwent vaporization or conization is demonstrated in Table 4.

Table 4. — *Persistence and recurrence rates according to the type of treatment.*

Treatment	Vaporization	Conization	P value
Overall relapses	42 (5.6%)	90 (3.9%)	0.05
Residual	27 (3.6%)	59 (2.6%)	0.16
Recurrence	15 (2%)	31 (1.3%)	0.22

Discussion

Carbon dioxide laser offers an experienced gynecologist a variety of treatment options for squamous intraepithelial neoplasia such as vaporization, conization or combined procedures.

In the Colposcopy and Laser Surgery Unit of Alexandra Hospital, laser vaporization was performed to treat low grade, large, ectocervical lesions, with a fully visible transformation zone in young women. The cure rates of laser vaporization vary in the literature between 71% and 96% [14, 15]. Our results were similar (94.4%) although none of these women was diagnosed with a high-grade lesion preoperatively. All women treated by this method on an outpatient basis under local anesthesia had minimal blood loss, and tolerated the procedure very well. Complications were minor, consisting of intraoperative bleeding in 0.4% of the women treated, postoperative bleeding in 0.26%, and cervical stenosis in 0.66%. Residual or recurrent disease in this series was detected in 5.6%, which is comparable to other series [16, 17]. Notably, the majority of these cases (n = 28; 67%), occurred in the years that the depth of destruction was less than 5 mm. Approximately the same results were reported by Jordan *et al.*, showing recurrence in 63% of the women when depth of destruction was 4 mm, compared to 10% when destruction reached 7-8 mm. Again, the treatment applied by that team concerned all grades of CIN [17]. The case of invasive disease reported in our series was originally treated by a destructive method, recurred after an interval and became invasive. This finding is consistent with others reported in the literature [18].

The fact that colposcopically directed biopsies preceding treatment of SIL cannot exclude invasive disease or adenocarcinoma in situ, has led several authors to believe that treatment of all grades of CIN should provide a specimen [19]. The possible pitfall of misleading colposcopy and biopsy in relation to the recognition of invasive disease, convinced us that small cones providing a specimen should be performed even in low grade lesions [20]. In addition to that, conization is very well tolerated by the patients, time of treatment is shorter and complications are similar to those of vaporization [16]. Thus, from 1995 up to now, in our department most of the low-grade lesions if treated, have been managed either by laser conization or by other excisional methods such as LLETZ.

The cure rate by laser conization varies in the literature between 90-97% [21, 22]. Successful 1st treatment in our series was 96.1%. These data are similar to success rates reported by others using the cold-knife technique for conization [23], but the complication rates are extremely high with the latter method consisting of intraoperative and postoperative bleeding (15 to 50%), infections (1 to 25%), and cervical stenosis (5 to 20%) [24, 25, 26, 27]. Our results for the same complications were 0.51, 0.04 and 1.24%, respectively. These rates highlight the hemostatic properties of laser in relation to bleeding, the sterilizing effect provided due to the high temperature in the area of conization in relation to infections, and better follow-up of women since it offers anatomic integrity of the endocervical canal. It is the authors' belief that cervical stenosis occurs more frequently in patients older than 40 years, in cases where the size of the cervical tissue excised is large enough to reach the endocervical os or where an excessive thermal effect has been produced. Overall recurrence rate in our series was 3.9%, a rate similar to that of other reports studying laser or LLETZ as excisional modalities [28, 29]. During the past decade, LLETZ has been widely used for the treatment of CIN. The advantages of this technique are mainly its low cost, that it is easily learned, and most important, that it provides a specimen for histology. The main disadvantages are over-treatment, morcellation of the specimen when performed incorrectly and possible thermal injury to the vagina and the site where the ground pad is applied. The depth of loop excision cannot always be safely predicted possibly leaving residual disease in cases where the lesions are large or upper in the endocervical canal. Additionally, some authors have reported increased recurrence rates following LLETZ procedures when the glandular component is involved, and especially in cases of adenocarcinoma in situ [30, 31]. We suggest that these lesions are best treated with laser conization.

The case of invasive disease encountered in the conization group could be attributed to possible failure to recognize the lesion the only time that this woman came to follow-up, or to progression of the disease in the years that the patient defaulted from follow-up.

There are no data today relating laser conization with possible infertility, pregnancy loss or preterm labor [32, 33]. The depth of the cones is usually shallow enough to prevent incompetence of the endocervix (exceptions are the narrow, long cones for adenocarcinoma in situ or large deep cones for microinvasion). A major concern stated by other authors was that of the thermal artifacts produced on the specimen by the laser, and consequently the potential misinterpretation of the histology by the pathologist [34]. We did not confront this problem in our series. This is probably due to the fact that only four very experienced physicians performed the procedures. Thus, most of the thermal damage to the specimen occurred in the first period of application of the method.

We agree with Baggish and believe that CO_2 laser is a superior modality in the treatment of cervical intraepithelial neoplasias in comparison with cold coagulation, radical electrodiathermy and cryosurgery [35]. Cold coagulation has not been widely accepted and few papers have been published regarding its efficacy. Radical electrodiathermy has proven to be a very effective method with first-time treatment, but it requires general anesthesia. Cryotherapy is as effective as any other method for only treating CIN 1 and 2 but it cannot be sufficiently tailored to the extent of the lesion.

Patients with large abnormal transformation zones (> 2.5-3 cm) where combination of an ablative and excisional method is particularly helpful, may be better treated with laser. Similarly, low-grade lesions that extend from the ectocervix onto the adjacent vagina can be treated by vaporization [36]. Finally, satellite HPV lesions are thought to be one of the reasons of residual disease after treatment of CIN with LLETZ [37]. These lesions, when visible, can be very well treated with laser vaporization following conization, thus extending the treatment zone.

It is a fact that there is a long learning curve in using lasers and that results improve with experience. Nevertheless, it is our point of view that laser surgery, when performed by experienced physicians under hospital settings, provides excellent results. Individualization of management according to the extent, the topography and the severity of the lesion as well as the age of the patient should always be taken under consideration, aiming thus to the best outcome achievable.

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