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Original Article

Cervical vaporization in LSIL and persistent HPV infection

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ABSTRACT

Objective: To assess rates of negative cytology and high-risk HPV testing after CO_2 laser treatment for low-grade lesions and persistent infection with high-risk HPV as well as factors that can influence these rates.

Material and methods: Between February 2011 and January 2015, 124 cervical vaporizations were performed with a CO_2 laser in patients presenting persistent infection with high-risk HPV or LSIL of CIN I that had persisted for more than 2 years. Data on parity, condom use, oral contraceptive use, smoking, vaccination against HPV, and immune status were collected and the relationship with rates of negative cytology and high-risk HPV testing was studied.

Results: We performed cytology, colposcopic and high-risk HPV detection 6 months after treatment in 116 patients (93%). Seventy-nine percent of patients had benign cytology in this control and 60% had negative results for HPV. Both parameters were normalized in 54% of patients. Mean follow-up was 22.35 months. Rates of negative cytology testing showed no significant relationship with any of the variables studied. Regarding rates of negative high-risk HPV testing, there is a statistically significant relationship with age younger than 45 years; type of high-risk HPV other than 16 and 18; and nulliparity and condom use. Among patients with persistent HPV infection and abnormal cytology at 6 months of vaporization, 55% had normalized cytology results but only 14.7% had negative results for high-risk HPV at the end of follow-up.

Conclusions: CO_2 laser vaporization is a simple, safe, and successful outpatient treatment that can be performed without anesthesia.

Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignant condition of cervix. The term CIN refers to squamous abnormalities. Cervical glandular neoplasia refers to adenocarcinoma in situ and adenocarcinoma. CIN can be of a low or high grade. Low-grade lesions have low rates of progression to carcinoma [1]. The terminology used to describe cervical lesions has varied over the years. Until recently it was based on the Bethesda system [2–4] with different names for the findings obtained using cytology and biopsy. Thus, the findings in cytology were appointed as SIL (squamous intraepithelial lesion) and biopsy findings were called CIN and assigned to one of 3 different degrees of severity. In 2012, the LAST system (Lower Anogenital Squamous Terminology) used the same terminology to report citologic and histologic findings [5]. The annual incidence of CIN in the USA is 4% for CIN 1 and 5% for CIN 2–3 [6].

The only known etiologic factor in cervical intraepithelial lesions is infection with human papilloma virus (HPV). Treatment of HPV infection is based on the results of a colposcopy-guided cervical biopsy. This may be excisional (cone biopsy) or ablative (cervical laser vaporization, cryocoagulation, electrocoagulation, or cryotherapy). Excisional treatments have a diagnostic and therapeutic aim and are usually reserved for high-grade lesions with histologic confirmation or for histologic diagnosis in cases of discrepancy. Ablative treatments do not allow histologic study of the specimen and are reserved for patients with persistent low-grade lesions or high-grade lesions when the patient has satisfactory colposcopy findings and there is a possibility of adequate monitoring. Laser treatment was associated with fewer vasomotor symptoms, less malodorous discharge and less unsatisfactory colposcopy than cryotherapy.

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Objectives

The aim of the study was to evaluate rates of negative cytohistological testing and detection of high-risk HPV after CO_2 laser vaporization in patients with persistent low-grade lesions and/or persistent high-risk HPV infections. As opposed to ablative techniques such as cryotherapy, scarce data exist on outcomes of CO_2 laser vaporization in the literature. Factors influencing the success rate of treatment are also analyzed.

Material and methods

Between February 2011 and January 2015, 124 CO_2-laser vaporizations were performed in patients infected with high-risk HPV or LSIL (CIN category I) persisting for more than 2 years. Patient data including age, parity, type of HPV, condom use, oral contraceptive use, smoking, vaccination against HPV, and immune status were collected retrospectively.

Inclusion criteria consisted of the following: a) age at least 18 years; b) negative pregnancy test; c) satisfactory Papincolaou (Pap) test rated as LSIL/ASCUS; d) agreement between cytology and endo- or exocervical biopsy if required; 3) Persistent low-grade citologic lesions or high-risk HPV infection and normal cytology. Persistent LSIL and persistent HPV infection were defined as a positive cytology for LSIL and a positive high-risk HPV test during two years or more.

Exclusion criteria included a) known or suspected invasive or high-grade lesions as revealed by cytology, colposcopy, or biopsy; b) positive pregnancy test; c) current pelvic disease, cervicitis, or other gynecologic infection; d) impossibility of patient follow-up.

Laser vaporizations were performed by up to 5 different gynecologists working in the Unit for Diseases of the Lower Genital Tract in our hospital and with the same level of training. Vaporization was carried under colposcopic vision; a Sharplan® 1030 (Laser-CO_2) generator with a power of 30 W was used in pulsed or continuous mode, without any general or regional anesthesia or patient admission.

The first post-treatment control was performed in all patients at 6 months and consisted of cytology, testing for high-risk HPV infection and, if required, colposcopy-guided cervical biopsy. In each patient, we performed a liquid Pap test with the Thin Prep® system and DNA capture via hybridization for 13 types of high-risk HPV detection (Qiagen HC2 High-Risk HPV DNA Test® technology Hybrid Capture 2®) taking 2 independent samples for cytology and HPV detection (DNA Pap cervical sampler®).

Thus, this is an observational retrospective study and for statistical analysis, R version 3.1.2® was used. To evaluate the association between post-treatment results for high-risk HPV and cytology testing and the different variables collected Odds ratio with 95% confidence interval was calculated and the *P* value was obtained from the Chi-square or Fisher test. All the patients signed the corresponding informed consent.

Results

The median duration of follow up was sixteen months. The mean age was 37 years (range 21–65 years), and 89% were younger than 45 years. Of all patients included, 80.2% were nulliparous. Twenty-one percent used hormonal contraception and 57.8% usually used only barrier methods. Sixty-four percent of the patients had completed HPV vaccination with 3 doses at 6 months after treatment, 4% had started vaccination, and 32% were not vaccinated. Forty-two percent of patients were smokers. Four percent (n = 5) were immunosuppressed (HIV-positive status or receiving chronic treatment with immunosuppressants).

As for the indication of vaporization, 32% (39/122) of patients had LSIL/CIN I persisting over 2 years, 42.6% (52/122) presented persistent high-risk HPV infection without cyto-histologic lesions for more than 2 years and by 25% (31/122) cases, low-grade lesion or persistent HPV after cone biopsy.

The distribution of HPV genotypes pretreatment was as follows: 56% were found to be serotypes 16 and 18, while 43% were had different serotypes and 6.7% were positive for both types.

No complications were recorded in any of the reviewed cases (i.e., vaginal bleeding, infection, and cervical stenosis).

Cytology, colposcopy and high-risk HPV testing 6 months following vaporization was accomplished in 116 patients (93%). Seventy-nine percent of the patients had benign cytology in this control and 60% had become negative for HPV infection. Fifty-four percent had normalized results for both parameters. The average follow-up time was 22 months.

Cytology results 6 months after treatment showed no statistically significant relationship with any of the variables studied. Although not statistically significant, patients with positive results for HPV types 16 and 18 had a risk of abnormal cytology findings after treatment that was 1.2 higher than that of patients who were positive for other serotypes. In addition, patients aged above 45 had the same increased risk of developing persistent cytological alteration than younger patients. Risk of cytologic alteration at 6 months was 2.9 times higher in multiparous patients than in nulliparous women (Table 1).

As for the HPV test results 6 months after treatment with CO_2 laser vaporization, the variables age, parity, HPV type, and use of barrier contraception showed a statistically significant relationship: patients older than 45 years had a 4-fold higher risk of persistent HPV infection after treatment, while the risk in

Table 1
Rates of negative cytology testing 6 months after treatment.

	Negative		Positive		OR	p
	N	%	N	%		
Age						
≤45 years	81	80,2	20	19,8	1,21	NS
>45 years	10	76,9	3	23,1		
HPV type						
No 16, 18	39	81,2	9	18,8	1,17	NS
16,18	52	78,8	14	21,2		
Parity						
Nulliparous	76	84,4	14	15,6	2,9	NS
Multiparous	15	65,2	8	34,8		
Condom use						
No	35	81,4	8	18,6	1,02	NS
Yes	47	81	11	19		
Hormonal contraception						
No	64	81	15	19	0,75	NS
Yes	17	85	3	15		
Vaccination						
No	20	83.3	4	16,7		NS
Incomplete	2	66,7	1	33,3	2,5	
Complete	39	79,6	10	20,4	1,28	
Indication for vaporization						
LSIL/CIN I	25	71,4	10	28,6		NS
HPV+	42	85,7	7	14,3	0,42	
LSIL/CIN I + HPV+	24	80	6	20	0,62,	
Inmunosupression						
No	86	78,9	23	21,1		NS
Yes	5	100	0	0		
Previous conization						
No	67	79,8	17	20,2	0,98	NS
Yes	24	80	6	20		

multiparous patients was 6 times higher than in nulliparous and carriers of HPV types 16 and 18, and had a 3-fold higher risk than carriers of other types. A greater percentage of patients who used barrier contraception showed regression at 6 months (OR 0.4) (Table 2).

Among the patients with persistent HPV infection and/or cytological abnormalities 6 months after treatment, 55% had negative cytology results at the end of follow-up, but only 14.7% had a negative high-risk HPV test.

Discussion

CIN is a premalignant condition of the cervix and the most common disease affecting the female genital tract. HPV is the only necessary factor for the development of CIN, although not a sufficient condition to cause the disease [7]. The 2 main factors associated with the development of high-grade CIN are virus subtype and persistence: HPV 16 and 18 are most frequently associated with CIN 2+, disease persistence, and progression to invasive cancer. HPV serotypes 16 and 18 cause 25% of CIN I, 50–60% of CIN 2–3, and 70% of cervical cancers [8]. In addition, over 50% of HPV infections resolve within 6–12 months and 80% are resolved within 2–5 years [9]. Therefore, only patients with low-grade lesions or HPV infections that persist for more than 2 years were treated. Other factors that seem to play a role in the persistence of the infection are the age of the patient, immune status, smoking, use of hormonal contraceptives, and co-infection with other sexually transmitted diseases.

In our study, patients with age above 45 years, HPV serotypes 16 and 18, and lack of use of barrier contraceptive methods showed significantly lower rates of disappearance of the virus after treatment with CO_2 laser vaporization. A negative result following high-risk HPV testing after treatment of CIN is the most important independent risk factor for the development of persistence and recurrence of cervical lesions and outcome, thus indicating that this test can optimize patient monitoring [10,11]. Regarding treatment for CIN, excisional or ablative techniques can be performed depending on the degree and extent of the injury, age, and genesic desire to become pregnant and potential patient monitoring. Excisional treatments have diagnostic and therapeutic aims and are usually reserved for high-grade lesions with histological confirmation or for histological diagnosis in cases of discrepancy. Ablative treatments do not allow histologic study of the specimen and are reserved for patients with persistent low-grade lesions or high-grade lesions in young patients with satisfactory colposcopy and no evidence of injury in the endocervix and the possibility of adequate monitoring [12,13]. Ablative treatments can be performed with cryotherapy, CO_2 laser ablation, cold coagulation, and electrocoagulation, of which cryotherapy and laser vaporization are the most common.

Ablative techniques are minimally invasive and safe and can be performed on an outpatient basis and without anesthesia. Their main drawback is the inability to histologically evaluate biopsy samples, therefore introducing risk of inadvertent destruction of areas with invasion or microinvasion in the case of CIN 2+ [12].

Cryotherapy is a simple, affordable, and accessible technique in settings with low resources. Despite the existence of probes with different sizes and shapes, the procedure is not a very selective treatment. Colposcopy-guided procedures, like laser ablation, allow selective destruction of tissue and adequate control of the depth of the destroyed tissue [12]. Laser ablation is based on the fact that water in the tissue absorbs the energy emitted by the laser and destroys the tissue by vaporization. The technique is optimal when the power used is between 20 and 50 W, an average of 750–2000 W/cm^2, with a depth of 7 mm in exocervix and 12 mm in endocervix [14]. It is estimated that the success rate of laser ablation is 95%–96% [15].

Most ablative techniques have similar cure rates (80–90%) and similar rates of complications (bleeding 1–5%, 1–3% cervical stenosis, and infection 1–9%) [16]. Yliskoski et al. concluded that the cure rates with cervical cryotherapy and laser were significantly higher than the rates of spontaneous regression ($P < 0.001$), suggesting that treatment with both changes the natural history of HPV [17]. Few published studies on the effectiveness of laser vaporization have focused exclusively on low-grade lesions and have included treatment of persistent HPV infection. Most of studies usually include only high-grade lesions or a mixture of both high- and low-grade disease.

A meta-analysis published in 2013 on CIN treatment concluded that none of the existing surgical techniques are better than the rest for the treatment of CIN in terms of treatment failure or associated morbidity. No significant differences in residual disease (RR 1.13, 95% CI 0.73–1.76), perioperative bleeding (RR 5.83, 95% CI 0.71–47.96), postoperative pain (RR 2.00, 95% CI 0.64–6.27), and cervical stenosis (RR 5.83, 95% CI 0.71–47.96). In the 2013 study, laser treatment was associated with fewer vasomotor symptoms (RR 0.02, 95% CI 0.00–0.40), less malodorous discharge (RR 0.30, 95% CI 0.12–0.77), and less unsatisfactory colposcopy (RR 0.38, 95% CI 0.26–0.56) [18].

Cervical stenosis is increased in women who have been exposed to diethylstilbestrol (DES) in the intrauterine stage and who have been treated with cryotherapy, cold knife conization and electrocautery, likely due to an alteration in connective tissue [19]. Cervical stenosis is lower in laser treatment because tissue vaporization preserves the fibromuscular tissue, with less risk of deformity and stenosis [14].

Table 2
Rates of negative PAP test, 6 months after treatment.

	Negative		Positive		OR	p
	N	%	N	%		
Age						
≤45 years	66	64,1	37	35,9	4,01	0,02
>45 years	4	30,8	9	69,2		
HPV type						
No 16, 18,	37	74	13	26	2,84	0,009
16,18	33	50	33	50		
Parity						
Nulliparous	64	69,6	28	30,4	6,47	0,0001
Multiparous	6	26,1	17	73,9		
Condom use						
No	22	51,2	21	48,8	0.41	0,03
Yes	43	71,7	17	28,3		
Hormonal contraception						
No	52	64,2	29	35,8	1,47	NS
Yes	11	55	9	45		
Vaccination						
No	12	50	12	50		NS
Incomplete	1	33,3	2	66,7	2,0	
Complete	32	62,7	19	37,3	0,59	
Indication for vaporization						
LSIL/CIN I	24	64,9	13	35,1		NS
HPV+	29	59,2	20	40,8	1,27	
LSIL/CIN I + HPV+	17	56,7	13	43,3	1,41	
Inmunosupression						
No	67	60,4	44	39,6	1,01	NS
Yes	3	60	2	40		
Previous conization						
No	53	61,1	33	38,4	1,23	NS
Yes	17	56,7	13	43,3		

In 1998, Mitchell et al. analyzed 498 patients with LSIL who were assigned to treatment with cryotherapy, laser ablation, and loop excision. In this study, no significant differences in complications, persistence, or recurrence of virus infection were found. However, the authors did observe that the risk of persistence was greater in women with extensive lesions, age over 30 years, carriers of serotypes 16 and 18, and those with previous cervical treatments [16].

Conclusions

There is a scarcity of published data on the effectiveness of laser vaporization exclusively on low-grade lesions and for the treatment of persistent HPV infection, as studies usually include only high-grade lesions or a mixture of both.

The results obtained with CO_2 laser vaporization for low-grade lesions and persistent high-risk HPV infection are: Seventy-nine percent of patients had benign cytology and 60% had negative results for HPV six months after treatment. Those results are above the rate of spontaneous regression of lesions after 2 years. Age over 45 years, positive status for HPV serotypes 16 and 18 and lack of barrier-contraceptive use were correlated with significantly lower rates of disappearance of the virus after treatment. CO_2 laser vaporization can be performed on an outpatient basis, without anesthesia and without major complications.

Conflicts of interest

There is no conflict of interest.

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