

Ángel García-Iglesias<sup>1\*</sup>, Ángel García-Sánchez<sup>1</sup>, Ima Moslemi<sup>1</sup>, María de la O Rodríguez Martín<sup>1</sup>, David Beltrán-Vaquero<sup>2</sup>, María Paz Alonso-Reyero<sup>3</sup> and Tomás Rodríguez-Bravo<sup>1</sup>

<sup>1</sup>Hospital Universitario. Universidad de Salamanca, Spain

<sup>2</sup>Institute of public Health. Madrid. Spain

<sup>3</sup>Hospital Universitario. León. Spain

**Dates:** Received: 22 February, 2016; Accepted: 17 March, 2016; Published: 18 March, 2016

\*Corresponding author: Garcia-Iglesias, MD. Hospital Universitario de Salamanca. Departamento de Obstetricia y Ginecología. Paseo de San Vicente 58-182. 37007, Salamanca, Spain, E-mail: aiglesias@usal.es

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**Keywords:** Vaginal Neoplasm; Laser vaporization; Recurrences; HPV

## Research Article

# CO<sub>2</sub> Laser Treatment for Vaginal Intraepithelial Neoplasia, Assessment of Recurrence

### Abstract

**Objective:** To assess the response and evolution of vaginal intraepithelial neoplasia (VAIN) after CO<sub>2</sub> laser treatment.

**Material and Methods:** A retrospective study was conducted from a database of 139 women who had VAIN and were referred for treatment with CO<sub>2</sub> laser. The lesions were detected following a hysterectomy. Human papillomavirus (HPV) typification was performed in all cases. The diagnosis of the lesions was performed by liquid based cytology and the location was by colposcopic study. Treatment with CO<sub>2</sub> laser was performed in continuous mode. In the statistical study were assessed: age, diagnosis before hysterectomy, diagnosis before the laser treatment, the characteristics of the lesions and HPV genomic.

**Results:** 131 patients were evaluated after elimination of 8 cases of incomplete data. The age of patients ranged between 35 and 68 years. 68.70% were female aged 45 years and older. The cause of hysterectomy was myoma in 16.3% and the rest for other cervical pathology. 22 patients were diagnosed with VAIN II and 106 (80.91%) of VAIN III. The risk factors for recurrence were age over 45 years, type of VAIN and HPV 16 infection. The lesion with more recurrence was VAIN III, with 15.26%.

**Conclusion:** Laser vaporization can be considered a safe treatment for VAIN.

## Introduction

The diagnosis of vaginal intraepithelial neoplasia (VAIN), has increased in the last decades as a result of the increased number of hysterectomies performed to women of all ages either for benign gynecological processes, cervical intraepithelial neoplasia (CIN) or cervical cancer. It has been noted that 15% of patients who had cervical cancer developed recurrence or vaginal intraepithelial neoplasia after hysterectomy [1].

Cervico-vaginal cytology has been established as a means of singular value, to detect recurrences of preinvasive and invasive disease of the lower genital tract in women both in cervical and vaginal lesions. The sensitivity and specificity of cytology in the prevention and diagnosis of recurrences after hysterectomy or the appearance of new lesions induced by papillomavirus is well documented [2].

The prevalence of VAIN is variable, ranging between 0.3 to 0.5 per 100.000 women, appreciating little variability with other studies [3], occasionally reaching values of 7 per 100.000 women. VAIN may occasionally be multifocal, associating with CIN or vulvar lesions [4], a circumstance that would require performing routine cytological screening.

Cervico-vaginal cytology controls posthysterectomy, detects different types of VAIN of varied locations, frequently in the vaginal vault, forcing, depending on the age, size and location of the lesions to establish conservative treatments that are effective [5], trying to avoid recurrences with the least aggressiveness [6]. This has established several treatment modalities, from medicated, such as topical 5% imiquimod, 5- fluorouracil and trichloroacetic acid to surgical

approaches, such as local excision, vaginectomy, or locally destructive such as criocoagulation, electrocoagulation and laser vaporization. The application of these techniques is determined by the colposcopic lesion, location and size [7]. Nowadays carbon dioxide (CO<sub>2</sub>) laser treatment is valued for its destructive features and few adverse effects of the technique and also less fibrosis that arises in the vaginal walls and vault.

The use CO<sub>2</sub> laser is now widely accepted as one of the most effective forms of treatment of VAIN: although at present, the loop electrosurgical excision procedure has become more popular, there is no evidence to suggest that the results between CO<sub>2</sub> laser and loop excision will vary significantly

Our objective is to determine the response of VAIN lesions detected in women after a hysterectomy, with carbon dioxide laser.

## Material and Methods

### Study design

**Multicenter, retrospective observational study:** Clinical data of this study comes from a database of 139 patients with different types of VAIN, who were referred to the service of Gynecology, of the Hospital of Salamanca (Spain) and also from various hospitals in the Autonomous community for CO<sub>2</sub> laser treatment. The study was conducted between 1997 and 2012. All patients were informed of their diagnosis and the characteristics of the treatment to which they were undergoing, signing the appropriate consent form.

### Inclusion criteria

In the present study, we have included all patients diagnosed of

VAIN, detected after a hysterectomy. All of them had undergone HPV detection. We excluded patients that had previous treatment with CO<sub>2</sub> laser, treatments with radiotherapy and/or chemotherapy, who had records of anal intraepithelial neoplasia or patients hysterectomized for endometrial carcinoma. We also didn't include patients who hadn't free margins in the hysterectomy.

### Diagnostic criteria

Patients, who were referred for treatment with CO<sub>2</sub> laser, had undergone liquid-based cytology, identifying cellular alterations following the Bethesda system. Included patients underwent colposcopic study, applying 5% acetic acid and subsequent application of iodine solution. The affected areas were biopsied using punch or LLETZ, in both single and multiple lesions. The material obtained from the biopsy was processed by the Pathology Department. The detection of HPV was performed by HIBRID Capture II test, a sample was collected with a brush from the vaginal vault and the material obtained was placed in Digene Specimen Transport Medium (STM). The detection of high-risk viruses was carried by CLART HPV 2 detection system, which allows the simultaneous detection of 35 HPV genotypes in a single analysis.

Biopsy in 5% of the cases was done by punch and in the remainder a 10 mm x 10mm LLETZ loop electrode was used. Lesions were previously identified by colposcopy with acetic acid and iodine solution.

### Laser treatment

Ablation of lesions were made with local anesthesia (lidocaine) when single lesions were found and with sedation in cases of multiple lesions. Prior to laser treatment, lugol's iodine solution was applied on the entire vagina. Vaporization was carried out with a Sharplan CO<sub>2</sub> Laser, Model 30 C, in continuous mode with 20 W of power. The lesions were ablated to 2-3mm depth.

Post treatment follow-up was performed by cytological study every 6 months.

### Statistical analysis

Risk factors for recurrence of VAIN in the vaginal vault after laser treatment, was statistically analyzed by assessing the following variables: age, diagnosis before hysterectomy, diagnosis before treatment with laser, the characteristics of lesions and infection by human papillomavirus. Risk factors were determined using logistic regression analysis and 95% confidence interval (CI) for the odds ratio (OR).

SPSS version 18 software was used for statistical analysis. The significance level was set at 0.05.

### Results

Observational study that included 131 patients diagnosed of VAIN referred for treatment with CO<sub>2</sub> Laser. The age of the included patients was between 35 and 68 years old. They were divided into two groups: under 45 years (32.29 %) and over 45 years that were 90 patients (68.70%). The diagnosis of the hysterectomy was symptomatic uterine fibroids in 21 patients (16.3%), CIN I (7.63%),

CIN II in 26 patients (19.84%) and CIN III (41.98%). Hysterectomy was performed for carcinoma in situ in 4 patients and in 11 (8.39%), for invasive squamous cell carcinoma. Three patients (2.29%) had a VAIN I, 22 were diagnosed with VAIN II and 106 (80.91%) VAIN III. The lesions that were identified were single in 43 patients (32.82%) and 88 had multiple lesions (67.17%). 44.27% were smokers. 70.22% were infected with human papillomavirus 16 and the remaining 29.77% with non-16 HPV (Table 1).

In the follow-up, after laser treatment there was no recurrence in VAIN I patients. Of the 22 patients with VAIN II, 4 (3.05%) relapsed, and also 20 patients (15.26%) of VAIN III corresponding to the highest percentage of recurrences (Table 2).

The analysis of significant risk factors was age older than 45 years, previous intraepithelial lesions and human papillomavirus infection, determined by multivariate logistic regression analysis (Table 3).

### Discussion

VAIN 2 and VAIN 3 lesions can be treated with equal success using excision or laser vaporization with success in 69% to 79% of cases following either treatment. Selection of treatment depends on a number of factors. VAIN 3 lesions located at the vaginal apex in women who have had hysterectomy for CIN are more likely to become invasive early. The evolution of VAIN to vaginal carcinoma is not well established [8]. Most women CIN 3 71.2% followed by

**Table 1:** Characteristics of all patients included in the study.

Characteristics	n	%	
Age	<45 years	41	31.29
	≥45 years	90	68.7
Menopause	39	29.77	
Smoker	58	44.27	
<b>Diagnosis prior to hysterectomy</b>			
Fibroids	21	16.03	
CIN I	10	7.63	
CIN II	26	19.84	
CIN III	55	41.98	
Carcinoma in situ	8	6.1	
Cervical cancer	11	8.39	
<b>Diagnosis prior to laser treatment</b>			
VAIN I	3	2.29	
VAIN II	22	16.79	
VAIN III	106	80.91	
<b>Type of lesions</b>			
Single	43	32.82	
Multiple	88	67.17	
HPV 16	92	70.22	
Other HPV	39	29.77	

**Table 2:** Recurrence after laser ablation.

	Laser ablation	Recurrence
VAIN I	3 (2.29%)	0
VAIN II	22 (16.79%)	4 (3.05%)
VAIN III	106 (80.91%)	20 (15.26%)
Total	131	24 (18.33%)

**Table 3:** Risk factors of recurrence of VAIN.

Multivariate analysis				
		Adjusted Odds Ratio	CI 95%	p-value
Age	<45 years	2.18	1.33-5.12	0.72
	≥45 years	2.05	1.15-9.77	0.04*
<b>Diagnosis prior to hysterectomy</b>				
	Fibroids, CIN I, II,III, CIS	1.99	0.99-12.38	0.76
	Cervical cancer	4.33	0.82-17.61	0.31
<b>Diagnosis prior to laser treatment</b>				
	VAIN I, II, III	6.33	1.53-19.21	0.03*
<b>Type of lesions</b>				
	Single	3.71	0.71-13.10	0.81
	Multiple	2.69	0.86-14.21	0.66
	HPV 16	1.66	1.09-11.16	0.05*

\* P<0.05.

cervical cancer stage IaI 20% y CIN 2, 8.8%. We found no cases of adenocarcinoma. For 94 patients 75, 2% postoperativd Papanicolau smears were available with a mean of 5 Papanicolau smear per patient. Among the 94 women with postoperative Papanicolau smear (7.4%) developed a vaginal neoplasia over time. Six (85.7%) of these 7 women had undergone an abdominal hysterectomy (14.3%). This proportion of VAIN after abdominal or vaginal hysterectomy was not statistically significant. Women who developend VAIN 2 after hysterectomy were significantly older than those who did not. The mean interval between hysterectomy and forst biopsy confirmed VAIN 2 diagnosis was 45 months, with a median of 35 months and a range of 5-103 months. The follow-up of hystectomized patients, either by a cervical carcinoma, cervical intraepithelial neoplasia or even benign processes, has shown that increase the risk of VAIN [9] that is detected in up to 15% of these patients. The time interval from diagnosis and hysterectomy is variable, ranging from months to decades [10]. In at least 54.5% of these patients a positive result in the determination of a high risk human papillomavirus was detected. Thus the occurrence of a VAIN after hysterectomy may possibly be influenced by some risk factors that may contribute to its occurrence. Analysis of these can guide us on possible treatments and it may help us to be selective in the treatment of high-grade VAIN [11].

Laser vaporization is the most common treatment used in VAIN and has a low impact in patients [12], although there are no studies comparing laser treatment with other modalities. The procedure is generally well tolerated, heals satisfactorily, and results in minimal sexual dysfunction. A small number of studies have been reported reaching between 69% up to 87.5% clearance after laser ablation [13,14], recurring between 32 to 33% [15,16].

It is recommended to treat with LLETZ in cases with a history of cervical cancer rather than ablation, because the tissue obtained allows a proper histological study of the lesion [17]. Given that the clinical features of VAIN are similar to those of CIN, treatment techniques must be equal [18], given that the main factor in the appearance of VAIN is HPV infection [19]. Also excellent results have been

reported in conservative monitoring, 68% of treated patients went into remission [11].

After treatment, it has been proved that the recurrence of lesions depends on certain epidemiological characteristics of patients. Having said that, after analyzing the response to treatment of 182 patients the recurrence rate after laser treatment was 26.5%, determining laser vaporization as a valid method of the treatment of VAIN in the vaginal vault after hysterectomy. Age over 48 years, increased the risk of recurrence of VAIN. In the group of patients, studied by us, the risk of recurrence is set in 45 years. It is evident that with older age patients the risk of recurrence increases. Other risk factors include a history of CIN and VAIN III that should be considered as factors of recurrence [20].

We must take into account [21], that the incidence of vaginal intraepithelial neoplasia after hysterectomy for CIN, reaches 7.4%, considered high [12]. After 6 months follow-up there is a cure rate of 85.7%. It has also been reported that the prevalence of HPV, specifically genotype 16 favors the recurrence of VAIN.

It is also known that VAIN may recur more quickly when there has been a high-grade dysplasia [22]. One strategy is the removal with loop excision of unifocal or clustered VAIN II-III lesions and laser ablation in multifocal VAIN II-III lesions, producing elimination of the disease in 71% of women [23].

The presence of the genotype of human papillomavirus is another factor to take into account when determining the risk of recurrence. Frega [24] indicates that the incidence of VAIN in women hysterectomized for benign diseases, does not differ from the group of women with malignant disease. HPV testing after 6 months of treatment of VAIN revealed that 80% were carriers of HPV 16 and 20% of HPV 18. It concludes that, follow-up of VAIN should be with cytology and determination of HPV, because it exists a recurrence risk of HPV 16-18 infection. It is known that HPV infection induces diseases of the female genital tract, and therefore vaccination is recommended as a preventive measure [25].

## Conclusion

CO<sub>2</sub> laser vaporization technique is effective in treatment of VAIN but risk factors must be taken into account because they favor recurrence. These risk factors for recurrence of VAIN are age, previous intraepithelial lesions and infection with papillomavirus genotype 16.

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**Citation:** García-Iglesias Á, García-Sánchez Á, Moslemi I, de la O Rodríguez Martín M, Beltrán-Vaquero D, et al. (2016) Co<sub>2</sub> Laser Treatment for Vaginal Intraepithelial Neoplasia, Assessment of Recurrence. *J Gynecol Res Obstet* 2(1): 017-020.