



# Argon plasma *versus* electrofulguration in the treatment of anal and perianal condylomata acuminata in patients with acquired immunodeficiency virus<sup>1</sup>

Eduardo Angelo Braga<sup>I</sup>, Gaspar de Jesus Lopes Filho<sup>II</sup>, Sarhan Sydney Saad<sup>III</sup>

<sup>I</sup>MSc, Fellow PhD Degree, Postgraduate Program in Interdisciplinary Surgical Science, Division of Surgical Gastroenterology, Department of Surgery, Medical School, Universidade Federal de São Paulo (UNIFESP), Sao Paulo-SP, Brazil. Conception and design of the study, acquisition of data, manuscript writing.

<sup>II</sup>PhD, Chairman Professor, Division of Surgical Gastroenterology, Department of Surgery, Medical School, UNIFESP, Sao Paulo-SP, Brazil. Critical revision, final approval.

<sup>III</sup>PhD, Assistant Professor, Division of Surgical Gastroenterology, Department of Surgery, Medical School, UNIFESP, Sao Paulo-SP, Brazil. Critical revision, final approval.

## Abstract

**Purpose:** To compare the effectiveness of anal and perianal condylomata treatment using argon plasma and electrofulguration.

**Methods:** From January 2013 to April 2014, 37 patients with anal and perianal condylomata, who had been diagnosed through proctological examination, oncotic cytology, polymerase chain reaction (PCR) and histology, underwent treatment with argon plasma and electrofulguration. The perianal and anal regions were divided into two semicircles. Each semicircle was treated using one of the methods by means of simple randomization. Therapeutic sessions were repeated until all clinical signs of infection by HPV were eliminated. The patients were evaluated according to several variables like the genotype of HPV, HIV infection, oncological potential per genotype, oncotic cytology and histology.

**Results:** Among all the variables studied, only immunosuppression due to HIV influenced the results, specifically when the fulguration method was used. There was no significant difference in effectiveness between argon and fulguration based on lesion relapse ( $p > 0.05$ ). However, among HIV-positive patients, fulguration presented worse results, with a significant difference ( $p = 0.01$ ).

**Conclusion:** Regarding treatment of anal and perianal condylomata acuminata, comparison between applying fulguration and argon demonstrated that these methods were equivalent, but use of fulguration presented more relapses among HIV-positive patients.

**Key words:** Condylomata Acuminata. Argon Plasma Coagulation. Electrosurgery. Papillomaviridae. HIV Seropositivity.

## ■ Introduction

Human papillomavirus (HPV) infection is the sexually transmitted disease most frequently diagnosed in both men and women. The incidence of this disease has been increasing over recent years almost everywhere in the world<sup>1-4</sup>. An estimated 10 to 20% of the adult sexually active population is infected by HPV, although only 1% presents classic condyloma and 2% present the subclinical disease, which could be diagnosed by means of high-resolution anoscopy<sup>4-8</sup>. Young adults are the group with the largest number of cases of infection, reaching rates of 46% among people aged between 20 and 30 years<sup>1-4,7,9</sup>.

Coinfection between the papillomavirus and human immunodeficiency virus (HPV-HIV) can reach more than 60% of individuals infected by HIV. This is a concerning situation, given the increasing number of cases of anal squamous cell carcinoma (SCC) among these diseased individuals. Tracking programs among this population have led to a concomitant increase in the number of cases diagnosed with condylomata acuminata<sup>1-4,9-10</sup>.

Anal carcinoma used to be considered infrequent, but its frequency is growing, especially due to an increase in SCC<sup>11</sup>. At the same time, increased numbers of cases of anogenital infections due to the human papillomavirus, which causes condylomata acuminata, have been observed<sup>3,4,12</sup>. Early diagnosis, and correct treatment of the initial lesions are paramount for successful treatment of patients with condylomata acuminata as for anal carcinoma that may arise from such lesions. Diagnosing anal SCC at an early stage is often only possible due to the signs and symptoms caused by the condyloma. It is considered to be a warning sign and brings the opportunity to better investigate this at-risk population<sup>7,13-15</sup>.

Conventional electrofulguration is considered to be one of the methods with lowest relapse rates among the surgical methods available for treating condylomata acuminata<sup>12,16-20</sup>. Proper application causes only a superficial burn, but if

the burn is deep and reaches the dermis or below this and the area treated is large, there is a risk of developing anal stenosis<sup>20-22</sup>.

Another factor that limits use of electrofulguration is the absence of any fine control regarding the depth of the burn and the infecting smoke produced. Care must be taken, particularly to avoid carbonization of tissue and formation of third-degree burns. These could develop as perineal infection, anal stenosis and even as gangrene<sup>4</sup>. Less than half of the patients treated have a complete response after a single session of electrofulguration<sup>16,20,22-26</sup>. Frequent follow-up is needed, to treat recurring lesions as soon as they are diagnosed<sup>20,23</sup>.

Despite the various forms of treatment for condylomata, relapses are frequent and the results are unsatisfactory<sup>7,14-17,20,27</sup>. Use of argon plasma has arisen as an alternative to use of conventional electrofulguration given the promising results presented, although more studies are needed<sup>15,20,24,28</sup>. The present study had the aim of investigating this type of treatment for application among HIV-positive patients<sup>12,24-26,28</sup>.

## ■ Methods

The present study consisted of a prospective investigation carried out among patients with anal condyloma or perianal condyloma, or both of these. The project for this study and the free and informed consent statement for use in this study were approved by the Research Ethics Committee, Universidade Federal de Minas Gerais (COEP-UFMG) 89.531/2012, CAAE 06030112.5.0000.5149, and also by the Research Ethics Committee, Universidade Federal University de São Paulo (UNIFESP), under report number 1.156.495/2015 and CAAE 46010115.3.0000.5505. This study was registered under universal trial number (UTN) U1111-1175-1767 and on the REBEC platform under number RBR-8YTCR4.

Patients over the age of 18 years,

with lesions caused by HPV over the whole circumference of the anal or perianal region, or both, were included in the present study. Patients who presented either unilateral condylomatous lesions or lesions that were too large for treatment at an outpatient service were not included. Patients who did not agree to participate in the study were also excluded.

From January 2013 to April 2014, a total of 93 patients were seen by the researchers at the coloproctology service for sexually transmitted diseases at the public center for specialized consultations of the municipality of Contagem, Minas Gerais. Out of this total, 46 were eligible. However, only 37 participated in the entire study. The patients were studied prospectively for 24 weeks.

The patients underwent a clinical examination, blood count, coagulogram, fasting blood glucose, HIV test, cluster of differentiation count (CD4) (for the HIV-positive patients) and the Venereal Disease Research Laboratory test (VDRL) (Tables 1 and 2). Of these patients, 20 (54.1%) were smokers, 17 (45.9%) were non-smokers, 10 (27%) had undergone some method of treatment previously and 27 (73%) had never been treated.

**Table 1** - Characterization of the laboratory variables (n = 37).

Variables	n (%)
HIV	
Positive	14 (37.8)
Negative	23 (62.2)
CD4	
< 200	1 (7.14)
200 to 399	0 (0.0)
≥ 400	13 (92.86)
Total	14 (100.00)

The condylomatous lesions were diagnosed by means of proctological examinations. These examinations consisted of static and dynamic inspection, rectal touching, anoscopy and high-resolution anoscopy using 3% acetic acid. All the patients underwent specimen collection for histology, oncotic cytology and

polymerase chain reaction (PCR) evaluations.

The results from the cytological analyses were distributed between: negative for intraepithelial lesion (NIL), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). Specific genotypes were identified, risk groups were categorized and the number of genotypes per patient was identified. The histological analyses were categorized regarding the lesions caused by HPV and unspecific lesions. Patients with positive VDRL were also identified<sup>6,8</sup> (Table 2).

**Table 2** - Characterization of the variables from the complementary examinations (n = 37).

Variables	n (%)
VDRL	
Positive	4 (10.8)
Negative	33 (89.2)
PCR	
Positive	36 (97.3)
Negative	1 (2.7)
Genotype	
HPV11	7 (14.0)
HPV16	5 (10.0)
HPV6	18 (36.0)
HPV18	2 (4.0)
HPV31	3 (6.0)
HPV33	3 (6.0)
HPV35	2 (4.0)
HPV56	2 (4.0)
HPV58	2 (4.0)
HPV68	1 (2.0)
HPV70	1 (2.0)
HPV72	1 (2.0)
Undefined type	2 (4.0)
Negative	1 (2.0)
Genotypes categorized as	
High risk	21 (42.0)
Low risk	26 (52.0)
Others (negative or undefined type for the method used)	3 (6.0)
Impairment level per genotype	
1	28 (82.4)
2	2 (5.9)
> 2	4 (11.8)
Total	34 (100.0)
Oncotic cytology	
Negative for intraepithelial lesion	18 (48.6)
Low-grade squamous intraepithelial lesion	18 (48.6)
High-grade squamous intraepithelial lesion	1 (2.7)
Histological result	
Condylomata acuminata	32 (86.5)
Unspecific lesions	5 (13.5)

Condylomata were treated by applying argon plasma and fulguration. To compare these two treatment methods, the anal and perianal region of the same individual was divided into two semicircles, following the model proposed by Billingham<sup>19</sup>. Each treatment method was applied to one semicircle, chosen by simple randomization. Applications were performed until the lesions disappeared, from a macroscopic point of view. The treatment was performed respecting the epithelial planes, with the objectives of improving results and minimizing complications, as described by Reid<sup>29</sup>. During the postoperative period, the patients were evaluated by means of fortnightly proctological examinations during the first month and then monthly examinations until the sixth month of follow-up. If residual lesions were diagnosed, new applications were performed, respecting the type of treatment previously performed on the given semicircle<sup>18,28</sup>.

The results were analyzed statistically. Qualitative variables were described by means of the absolute frequency and percentages. Quantitative variables were assessed using the mean and standard deviation (SD). Pearson's asymptotic and exact chi-square tests were used in the association analyses. The Z-test was initially used to analyze the effectiveness of the methods by comparing proportions. The Kappa test was then used to assess the agreement between the methods. The significance level was set at 0.05. The software used was the Statistical Package for the Social Sciences

(SPSS), version 20.0, and Stata 9.1.

## ■ Results

A total of 119 operations were performed among the 37 patients. Argon plasma was applied on the right side of 22 patients and on the left side of 15. Fulguration was applied on the right side of 15 patients and on the left side of the other 22. Relapses were observed in 16 individuals (43.2%) who were treated with argon and in 19 individuals (51.4%) who were treated with fulguration, with no significant difference ( $p = 0.478$ ). The variables of age group, gender, age when sexual life began, anal coitus, number of partners, smoking, anal manipulation, location of condylomata, previous treatment, cytology and HPV genotype were evaluated regarding their possible influence on relapses, but none of them showed statistically significant values.

Statistical significance was only observed for the fulguration method when applied to seropositive patients, in comparison with seronegative patients (Table 3). The value of the Kappa agreement test regarding comparison of methods was 0.731 ( $p < 0.001$ ).

Since HIV was identified as a determining factor for a higher number of relapses in areas treated with fulguration, the patients were then categorized regarding the virus and CD4 lymphocyte count. Statistical significance was observed for areas of seropositive patients even when the CD4 lymphocyte count was greater than 400 (Table 4).

**Table 3** - Results from analysis on the association between relapse after fulguration or argon treatment and the variables of the study.

Variable	Relapse						Total
	Fulguration		p-Value	Argon		p-value	
	Yes	No		Yes	No		
Age group							
≤ 30 years	9 (52.9)	8 (47.1)	0.858 <sup>1</sup>	9 (52.9)	8 (47.1)	0.272 <sup>1</sup>	17
> 30 years	10 (50.0)	10 (50.0)		7 (35.0)	13 (65.0)		20
Gender							
Female	2 (66.7)	1 (33.3)	>0.999 <sup>2</sup>	3 (100.0)	0 (0.0)	0.072 <sup>2</sup>	3
Male	17 (50.0)	17 (50.0)		13 (38.2)	21 (61.8)		34
Initiated sexual life at							
≤ 20 years	18 (51.4)	17 (48.6)	>0.999 <sup>2</sup>	15 (42.9)	20 (57.1)	0.072 <sup>2</sup>	35
> 20 years	1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)		2
Number of partners							
< 2	5 (31.3)	11 (68.8)	0.077 <sup>2</sup>	5 (31.3)	11 (68.8)	0.227 <sup>1</sup>	16
2 to 5	7 (77.8)	2 (22.2)		6 (66.7)	3 (33.3)		9
≥ 6	7 (58.3)	5 (41.7)		5 (41.7)	7 (58.3)		12
Anal coitus							
Yes	16 (50.0)	16 (50.0)	>0.999 <sup>2</sup>	13 (40.6)	19 (59.4)	0.634 <sup>2</sup>	32
No	3 (60.0)	2 (40.0)		3 (60.0)	2 (40.0)		5
Anal manipulation							
Yes	11 (50.0)	11 (50.0)	0.842 <sup>2</sup>	9 (40.9)	13 (59.1)	0.729 <sup>1</sup>	22
No	8 (53.3)	7 (46.7)		7 (46.7)	8 (53.3)		15
Smoking							
Yes	12 (60.0)	8 (40.0)	0.254 <sup>1</sup>	10 (50.0)	10 (50.0)	0.368 <sup>1</sup>	20
No	7 (41.2)	10 (58.8)		6 (35.3)	11 (64.7)		17
HIV							
Positive	11 (78.6)	3 (21.4)	0.010 <sup>1</sup>	8 (57.1)	6 (42.9)	0.183 <sup>1</sup>	14
Negative	8 (34.8)	15 (65.2)		8 (34.8)	15 (65.2)		23
Location of the condylomata							
Anal	3 (37.5)	5 (62.5)	0.829 <sup>2</sup>	2 (25.0)	6 (75.0)	0.232 <sup>2</sup>	8
Perianal	2 (66.7)	1 (33.3)		2 (66.7)	1 (33.3)		3
Perianal and anal	11 (52.4)	10 (47.6)		8 (38.1)	13 (61.9)		21
Other	3 (60.0)	2 (40.0)	4 (80.0)	1 (20.0)	5		
Previous treatment							
Yes	7 (70.0)	3 (30.0)	0.269 <sup>2</sup>	6 (60.0)	4 (40.0)	0.274 <sup>2</sup>	10
No	12 (44.4)	15 (55.6)		10 (37.0)	17 (63.0)		27
Oncotic cytology							
NIL	8 (44.4)	10 (55.6)	0.625 <sup>2</sup>	7 (38.9)	11 (61.1)	0.611 <sup>2</sup>	18
LSIL	10 (55.6)	8 (44.4)		8 (44.4)	10 (55.6)		18
HSIL	1 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)		1
Genotype categorized as							
High risk	7 (70.0)	3 (30.0)	0.127 <sup>2</sup>	6 (60.0)	4 (40.0)	0.223 <sup>2</sup>	10
Low risk	12 (50.0)	12 (50.0)		10 (41.7)	14 (58.3)		24
Others (negative or undefined type)	0 (0.0)	3 (100.0)		0 (0.0)	3 (100.0)		3

<sup>1</sup>Asymptotic Pearson's chi-square test

<sup>2</sup>Exact Pearson's chi-square test

**Table 4** - Results from analysis on the association between effectiveness variables and CD4.

Variables	HIV	HIV positive		Total	p-Value
	negative	CD4 ≤ 400	CD4 > 400		
Argon relapse					
Yes	8 (34.8)	8 (34.8)	7 (58.3)	9 (75.0)	0.4732
No	15 (65.2)	15 (65.2)	5 (41.7)	3 (25.0)	
Fulguration relapse					
Yes	1 (50.0)	2 (100.0)	16	19	0.0222
No	1 (50.0)	0 (0.0)	21	18	

<sup>2</sup>Exact Pearson's chi-square test.



## ■ Discussion

Operations using ionized argon gas (argon plasma), which is inert and non-toxic, are based on its physicochemical properties. This method allows transference of electrical energy generated by an electrosurgical unit to the target tissue<sup>24,28</sup>. The ionized gas transfers energy without contact between the electrode and the tissue surface, which enables energy distribution according to the impedance of the tissue. This distribution occurs in a predictable manner. As tissue composition changes, tissue conductivity also changes, thus avoiding points at which tissue lesions deepen with formation of eschar<sup>24,25,28</sup>. The ion flow generated and conducted by argon follows the path of least electrical resistance, regardless of the position of the electrode in relation to the tissue, and also regardless of the direction of the flow of the gas<sup>24,25,28</sup>. This phenomenon is advantageous when the treatment is performed in the anal canal, because it improves access to the squamous-columnar transition<sup>28</sup>.

The depth of the burn caused by the method is predictable. It can reach only between 2 and 4 mm in thickness in either skin or mucosa, according to the flow and power used, which stops formation of deep lesions that would increase the chance of postoperative infection and pain<sup>24,25,28</sup>. The depth reached by argon plasma is more than sufficient to eradicate lesions caused by HPV, considering that by reaching depths of 2 mm, more than 90% of lesions are eradicated. In the perianal regions, the recommendation is to reach 1 mm in depth for skin with no hair and up to 2 mm in skin with hair<sup>20,24,25</sup>. Involvement of cutaneous appendices demands greater attention regarding the depth at which argon plasma is applied. Following this criterion, residual lesions are due more to the existence of compromised lateral margins than to insufficient depth of treatment<sup>28,29</sup>.

The sensitivity of the PCR method

in this sample was almost 98%, while other studies in the literature found values close to 75%<sup>5,30</sup>.

Genotypes 6 and 11 were the most common. A substantial number of patients with high-risk genotypes for anal carcinoma were also observed. Moreover, half of the patients presented lesions compatible with LSIL in their cytological evaluations. Regarding division of the genotypes into three categories, the high-risk and low-risk genotypes presented similar occurrence<sup>1,4,6,20</sup>. HPV genotyping, which today is more associated with scientific research than with clinical practice, can individualize patients who might be more susceptible to evolving to carcinoma, due to presence of a high-risk genotype such as types 16 or 18<sup>1,2,4,27</sup>.

All the patients underwent biopsies. Lesions caused by HPV were confirmed in 32 individuals (86.5%), while the histology of the remaining five was unspecific. Oncotic cytological evaluations were performed on all the patients, with sensitivity of 51.3% for detection of cytological lesions caused by HPV, which is in accordance with the literature<sup>7,8</sup>. Through combining evaluations using PCR, histology and cytology, diagnoses of HPV were made in the cases of 100% of the patients. This demonstrated that the methods complemented each other and can be included in systematization of treatments for patients with anal and perianal HPV infections, as proposed by Nadal et al.<sup>30</sup> (Table 2).

The effectiveness of the methods for treating condylomata was measured through the number of sessions needed to eradicate the clinical lesions caused by HPV. The areas treated with fulguration underwent up to three therapeutic sessions, while areas treated with argon required up to four sessions. Although there was no statistical difference in the number of therapeutic sessions, the lower number of applications in the fulguration group may have been due to the aggressiveness of the method. Regarding the argon method,

more areas responded to a single therapeutic session (21 vs. 18), demonstrating, at least in theory, the greatest potential for eliminating subclinical reservoirs around the clinical lesion, although with no statistical difference. Eradication of condylomatous lesions among all the patients was reached after 120 days of treatment, which confirms data from the literature showing that different types of treatment need more than one session to eradicate clinical lesions<sup>20</sup>.

None of the variables studied, with the exception of HIV, was able to influence the response to treatment of either method. The epidemiology and pathogenesis of condylomata caused by different viral genotypes, particularly the most aggressive types, may indicate which patients should be referred for differentiated follow-up because they have greater chances of evolving to carcinoma of anal and perianal squamous cells<sup>2,11,12,20</sup>. Genotypes that were more aggressive from an oncogenic point of view were expected to lead to a greater number of relapses, but there was no difference between treatments<sup>1,13</sup>. The HPV genotype did not influence the number of relapses (Table 3).

The relapse rate was higher among HIV-positive patients when the condylomata was treated using electrofulguration. This was observed through the greater number of sessions needed, in comparison with seronegative even when the CD4 lymphocyte count was greater than 400 (Table 4). This was not seen with use of argon. In this case, the areas treated among HIV-negative and HIV-positive patients did not present any statistical difference regarding the number of relapses (Table 3).

## ■ Conclusions

The application of argon plasma or fulguration to treat anal and perianal condylomata showed similar effectiveness. However, application of argon plasma was not

influenced by serological factors, compared with fulguration, which was statistically less effective in treating HIV-positive patients.

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**Correspondence:**

Eduardo Angelo Braga  
Rua Bernardo Guimarães, 1020  
30140-084 Belo Horizonte – MG Brasil  
Tel.: (55 31)98896-0000  
edubragamd@hotmail.com

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<sup>1</sup>Research performed at Postgraduate Program in Interdisciplinary Surgical Science, Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), Brazil. Part of PhD degree thesis. Tutor: Prof. Gaspar de Jesus Lopes Filho.

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## Erratum

**Manuscript:** Argon plasma versus electrofulguration in the treatment of anal and perianal condylomata acuminata in patients with acquired immunodeficiency virus

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On page 486 of the original publication, instead of this Table 4:

**Table 4** - Results from analysis on the association between effectiveness variables and CD4.

Variables	HIV	HIV positive		Total	p-Value
	negative	CD4 ≤ 400	CD4 > 400		
Argon relapse					
Yes	8 (34.8)	8 (34.8)	7 (58.3)	9 (75.0)	0.4732
No	15 (65.2)	15 (65.2)	5 (41.7)	3 (25.0)	
Fulguration relapse					
Yes	1 (50.0)	2 (100.0)	16	19	0.0222
No	1 (50.0)	0 (0.0)	21	18	

<sup>2</sup>Exact Pearson's chi-square test.

Consider this Table 4:

**Table 4** - Results from analysis on the association between effectiveness variables and CD4.

Variables	HIV	HIV positive		Total	p-Value
	negative	CD4 ≤ 400	CD4 > 400		
Argon relapse					
Yes	8 (34.8)	1 (50.0)	7 (58.3)	16	0.473 <sup>2</sup>
No	15 (65.2)	1 (50.0)	5 (41.7)	21	
Fulguration relapse					
Yes	8 (34.8)	2 (100.0)	9 (75.0)	19	0.022 <sup>2</sup>
No	15 (65.2)	0 (0.0)	3 (25.0)	18	

<sup>2</sup>Exact Pearson's chi-square test.