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#### **Pulsed dye laser versus podophyllin resin in treatment of female genital warts**

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#### **Abstract:**

##### ***Objectives:***

To compare between pulsed dye laser and podophyllin resin in treatment of genital warts regarding pain, number of sessions, clearance rate, and recurrence.

##### ***Methods:***

Thirty-nine female patients were divided into two groups, the first group; 20 patients was treated with podophyllin resin, the second group 19 patients was treated with pulsed dye laser (Candela) 595nm, 1.5 ms pulse duration, 7mm spot size and fluence 12-15 J/cm<sup>2</sup>

##### ***Results:***

Complete cure rate was observed in both groups, but recurrence occurred in only 5 patients treated with podophyllin resin during follow up period.

##### ***Conclusion:***

Both treatments are effective equally regarding the clearance rate but FPDL is superior to podophyllin resin concerning the recurrence.

## Introduction:

The prevalence of genital warts is increasing globally, and is estimated to be about 1% in the sexually active population [1]. It has been estimated that at least half of all sexually active individuals will acquire Human Papilloma Virus (HPV) at some point in their lives, whereas at least 80% of women will acquire an HPV infection by the age of 50 [2].

The HPV viruses are known to invade the squamous epithelium of the entire lower female genital tract, [3]. They usually appear after a latency period of six months or more. The main risk factors for contracting the virus include early beginning of sexual life and multiple sexual partners. Congenital or acquired immunodeficiencies also favor the appearance and persistence of the warts. Vulval HPV warts can cause significant physical discomfort, including inflammation, itching, bleeding and dyspareunia. Although HPV warts are usually benign growth, certain types of HPV pose a potential risk of developing cancer [4].

Many modalities have been used to treat HPV-associated warts such as 5-fluorouracil and interferon that are not recommended because of their low efficacy and toxicity. Trichloroacetic acid is a widely used non-surgical therapy, but little is known about its efficacy, and is associated with unpleasant side-effects. Imiquimod and podophyllotoxin are recommended in both Europe and the US. The wart clearance rates for these two treatments are similar, although imiquimod is associated with lower recurrence rates and is more expensive [5].

Studies suggest that surgical therapies, including cryotherapy, electrotherapy, and surgical excision are largely equivalent to one another with respect to clearance rates. Moreover; these may require anesthesia and have been painful, leading to discomfort among patients. Another major concern, especially with the use of high density CO<sub>2</sub>, is the risk it may have, to the patient and staff, from HPV DNA contamination during the procedure [6].

Podophyllin is a crude extract prepared from the roots of different species of Berberiacae (May apple). It is not a uniform substance and contains a number of active constituents. It has the advantage of being a cost-effective treatment and, accordingly it has been recommended as an appropriate first-line agent. [7]

The Flash lamp Pulsed Dye Laser (FPDL) 595 nm with pulse duration 1.5ms proved to be efficacious and was reported to be successfully used for the treatment of many skin lesions including port wine stains, hemangiomas, telangiectasias and genital warts. This efficacy is based on the principle of selective photothermolysis, which aims to destroy the blood vessels of the vascular lesions. It is the highly selective targeting of the oxyhemoglobin molecule, which absorbs the thermal energy of this wavelength, which is released in this very specific target within the vessel - the red blood cell. The pulse duration of this energy (1.5ms) spares the tissue around from thermal damage [8].

This study adopts to explore further the use of pulsed dye laser and evaluate its impact on vulval HPV treatment in comparison with podophyllin resin regarding four important issues: 1) number of sessions till complete clearance obtained 2) pain associated with treatment, 3) rate of clearance of warts and 4) recurrence of the lesions.

## **Patients and methods:**

Within 12 months, this study was conducted on 39 female patients with external genital warts in the outpatient dermatology clinic, National Institute of Laser Enhanced Sciences Cairo University, Egypt.

Patients were voluntarily included in the study after providing informed consent. Pregnant females and patients who previously had treatment for their warts were excluded from the study.

Inclusions criteria in this study were warts count up to 15 and diameter below 10 cm. The genital warts were divided according to the site into; vulval, anal and anogenital (figure 1). Patients were divided into two randomized groups. The first group (group I) included 20 patients who were treated with podophyllin resin solution 20% dissolved in alcohol that was applied to warts. Areas adjacent to warts were protected and covered by a Vaseline layer. Weekly Sessions were repeated until complete recovery was obtained.

The second group included 19 patients treated with flashlamp pulsed dye laser (FPDL) 595nm (Candela) with a Dynamic Cooling Device (DCD) cryogen spray time 30 ms, delay time 10 ms, pulse duration 1.5 ms, fluence 12-15 J/cm<sup>2</sup>, 7mm spot size and 3-4 sequential pulses were applied till grayish white color of the wart was obtained. Sessions were performed every 2 weeks. We based the joules settings on the standard settings in literature and the subjective opinion of the physician with regard to the size and thickness of the wart. Fucicortâ cream (Fusidic acid 2%+Betamethasone 0.1% preserved with chlorocresol ) manufactured by LEO pharma. Inc. was advised to patients for one week following session.

Pain scoring was measured in two ways: 1) through the use of the visual pain analogue score where the patient gave a score of 0 to 10, where 0 indicates no pain, and 10 indicates excruciating pain; 2) through assessing patients' perception about the pain. During the procedure, patients were asked to indicate whether they perceived the pain as painful or sever pain, hot or moderate pain, warm or mild pain, and no pain.

Each patient was followed up for six months. Visible clearance of warts was assessed using naked eye inspection at 1, 3 and 6 months after the initial treatment.

### ***Statistical methods:***

- Data were collected on special format, verified and then coded when needed prior to analysis.
- All continuous data were expressed as mean±SD; categorical data were expressed as frequency in tables.
- For comparative purposed between groups, in all continuous data independent t-test ANOVA test were performed.
- Chi- square test for testing association in categorical data.

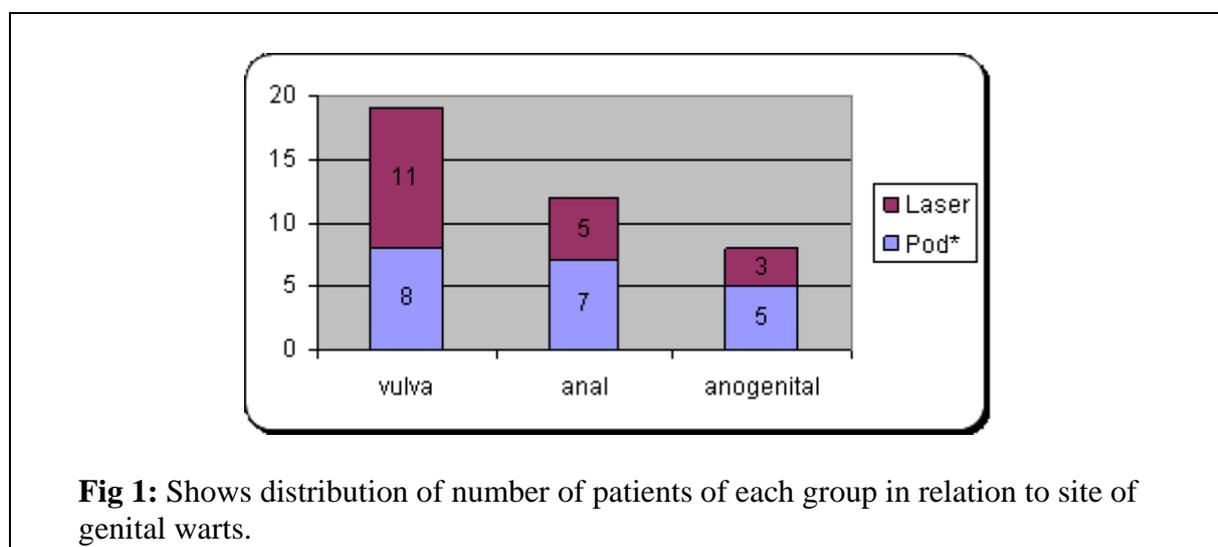
- Value 0.05 was considered significant as Confidence interval 95% was set.
- Analysis has been performed using SPSS12 and graphics by Excel.

**Results:**

The mean age of patients was 35. 9±13.3 years (range 25 to 60)

All patients of both groups show complete remission after an average of

2.6±1.1 sessions, (range 1-4) for Group I and 2.9±1.4 sessions (range 1-5) for group II.



**1. Number of sessions:**

We found that patients with vulval warts needed less number of sessions to have complete cure compared to anal and anogenital types for both groups (table 1, 2). This was statistically significant p=0.0001 for group I and p=0.05 for group II

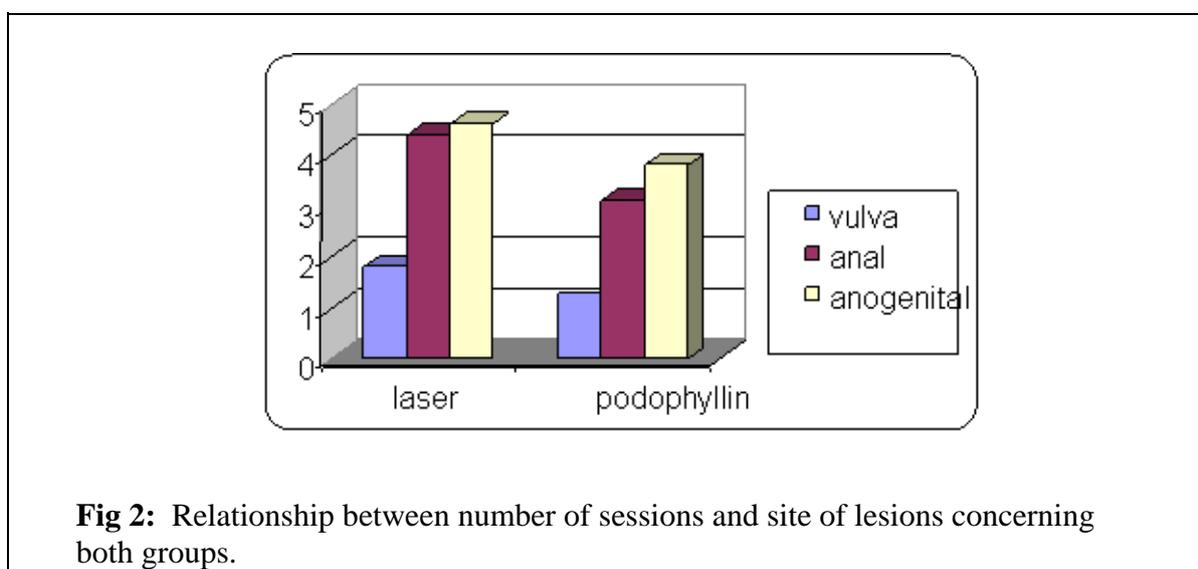
Site	N	Mean of sessions± Std.dev	P value
Vulva	11	1.8±0.6	0.0001
Anal	5	4.4±0.5	
Anogenital	3	4.6±0.5	

**Table (1):** Relation between number of sessions and site of warts in laser treatment group

Site	N	Mean of sessions ± Std.dev	P value
Vulva	8	1.3±0.5	0.05
Anal	7	3.1±0.3	
Anogenital	5	3.8±0.4	

\*N= number of patients

**Table (2):** Relation between number of sessions and site of warts in podophyllin treatment group



**Fig 2:** Relationship between number of sessions and site of lesions concerning both groups.

**2. Pain:**

Assessment of patients' rating of the pain showed that 80% experienced minimal discomfort and were pleased to complete the procedure. The mean visual pain analogue scoring was 4.6 and 2.05 for podophyllin and laser groups respectively, with a range from 1 to 8 and 1 to 7 for podophyllin and laser groups respectively (Table3). It is worthy to mention that ulceration and edema were reported by 2 patients that treated with podophyllin resin in the first 2 days following the session.

	Pain score (0 – 10)			Mean pain score
	1 - 3	4 - 7	8 - 10	
Group I	n=9	n=5	n=6	4.6
Group II	n=16	n=3	n=0	2.05

\*N=number of patients

**Table (3):** Visual Pain Analogue Score by Site of Lesion during and immediately after

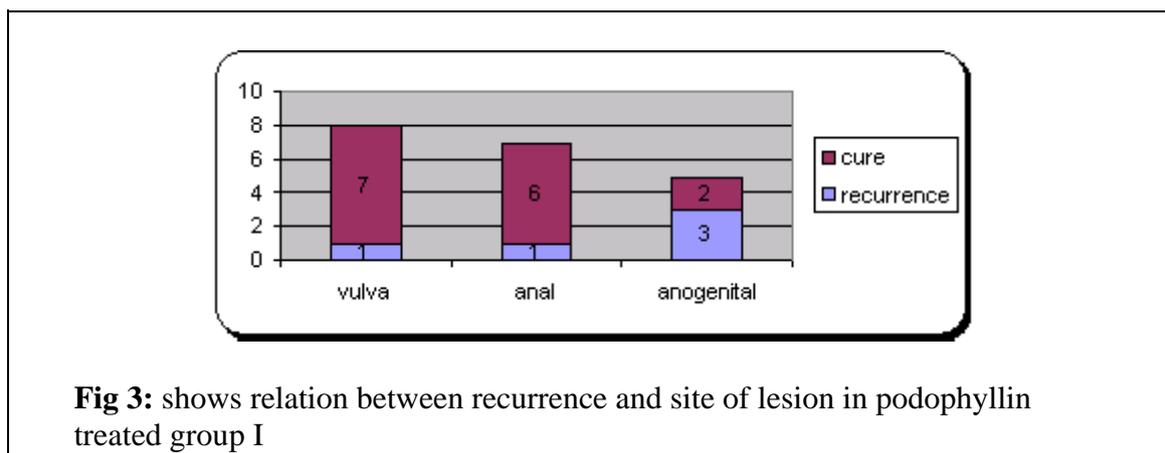
the first session of treatment.

**3. Recurrence:**

Recurrence occurred in 5(25%) patients of group I treated with podophyllin during follow up. The anogenital site was observed to have the highest recurrence yet it didn't match statistical significance level

site	vulva	anal	anogenital	P value
Recurrence	1	1	3	0.448
	20%	20%	60%	
Complete cure	7	6	2	
	46.70%	40%	13.30%	

**Table (4):** Relation between clearance rate and site in podophyllin treated group I



**Fig 3:** shows relation between recurrence and site of lesion in podophyllin treated group I

**Discussion:**

Genital warts represent benign epithelial proliferations induced by human papilloma virus (HPV). Many lines of treatment exist, but the results are not satisfactory because of the high relapse rate (10).

Badawi et al., 2006 found complete resolution of treated warts achieved in 96% of lesions as 174 male patients were treated by using pulsed dye laser (wavelength 585nm, 0.45ms pulse duration Cynosure) with 5- 7mm spot size; fluence 9-10J/cm, recurrence rate was 5%(11). Komericki et al., 2006 treated 22 patients with FPDL that all patients in the study had complete resolution after 1-5 laser sessions with no complication or scarring (12). In study done by Tuncel et al., 2002 both 585nm and 595nm FPDL were used with equal results of success and they claimed achieving complete cure after one session (13). We used FPDL with wavelength 595nm, 1.5 ms pulse duration, fluence 12-15 J/cm<sup>2</sup>. The long wavelength offered

longer depth of penetration (14). DCD cryogen (spray time 30, delay time 10) reduced pain markedly during sessions.

The mechanism of action of FPDL is not fully understood. One histological feature of wart is dilated and congested blood vessels in the dermal papillae. This blood vessel may be responsible for the viability of the wart. The pulsed dye laser destroys vessels by selective photothermolysis of oxyhemoglobin (15). In addition HPV is heat sensitive and lasers may destroy the virus by thermal effect (16). The principle action of Podophyllin is through binding to microtubules sub-units and arresting cell division mitosis. Podophyllin may cause local adverse effects such as inflammation, edema, and ulceration. Teratogenicity and intrauterine fetal death had been described (17). Severe systemic toxicity may arise after topical use of podophyllin, most commonly when used in large volumes (17, 18).

On studying the possible relation between site of warts and number of sessions needed we found that the anogenital warts disappearance "regardless their number" needed more sessions in both types of treatment compared to vulval and anal warts. The difference was statistically significant  $p=0.0001$  for group I and  $p=0.05$  for group II. (table 1, 2).

It was also found that recurrence of the 5 patients treated with podophyllin occurred in 3 patients with anogenital warts.

## Conclusions:

Both treatments are effective equally regarding the clearance rate but FPDL is superior to podophyllin resin concerning the rate of recurrence and post session pain, edema, and ulceration.

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