Effectiveness of HERPIGEN in the treatment of external anogenital warts

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City of Havana
2008
Effectiveness of HERPIGEN in the treatment of external anogenital warts

Experimental Phase III Clinical Trial, prospective aimed to the following objectives:

General:
- Assessing the effectiveness of the combination HERPIGEN - VIUSID in the treatment of external genital warts.

Specific
- Describing the population under study according to clinical and socio-demographic variables.
- Identifying the results obtained with HERPIGEN - VIUSID and Podophyllin.
- Describing any adverse reactions and discomforts reported by patients during the treatment.

Patients’ Number: 100 divided in two groups of 50

Treatment Duration: 6 weeks

1. Inclusion criteria:
- Male and female patients aged 17 and over
- Signed informed consent
- Affected area size up to 10 sq cm
- Not having previously undergone any treatment
- Serology and HIV tests completed

2. Exclusion criteria
- Unwilling to participate in the research
- No signed consent informed provided
- Patients aged under 17
- Having received previous treatment
- Pregnancy
- Patients currently taking systemic and local antivirals, steroids, immunomodulators and immunodepressants
For HERPIGEN, 3 - 5 applications were indicated in writing (one nebulization corresponded to two short strokes) to be applied at home, depending on the area size, up to a maximum 10 sq cm:

- 1 - 3.9 sq cm ____________3 daily applications
- 4 - 6.9 sq cm ____________4 daily applications
- 7 - 10 sq cm ____________5 daily applications

The period for application of HERPIGEN ranged between 5 days and 8 weeks depending on the evolution and clinical improvement of patients. Beyond this period, the treatment was reassessed to decide whether to combine or replace it with conventional treatments depending on each specific case and, as with Podophyllin, they were recorded as discontinuance.

VIUSID (mixture) was administered in 30 ml doses every 8 hours daily throughout the treatment, after each meal, dissolved in drinking water, fruit juice or milk.

**CONCLUSIONS**

1. The use of HERPIGEN combined with VIUSID was effective in the treatment of external anogenital warts.
2. The research feature a predominance of males.
3. The most numerous age group in both treatments was the 15 - 24 age group.
4. Injuries were found most frequently on the penis (including body, foreskin, balanopreputial groove, frenulum and glans).
5. Most patients’ affected skin surface area was under five centimetres and evolution time is between one and four months.
6. Good clinical response predominated in both treatments.
7. The combined treatment HERPIGEN-VIUSID performed better than the Podophyllin treatment,
8. Over half of the sample did not report any side effects.

**Recommendations**

1. Assess the level of recurrence of post-treatment injuries.
2. Increase the concentration of the active ingredient to find out if the time of treatment can be shortened.
3. Include a third group to assess the combined use of both treatments (HERPIGEN/VIUSID plus Podophyllin).
Final Report of Research

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2008
“True writers never include everything in their books. The most essential part of their work springs from the spirit of their readers”.

A. F. Rendelet.
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Abstract

Experimental research was conducted for the purpose of demonstrating the effectiveness of a drug undergoing clinical assay stage III (Herpigen) combined with a nutritional supplement prepared for boosting the immune system (VIUSID) in the treatment of one of the most common sexually transmitted infections of both Cuba’s and the world’s sexually active population: external anogenital warts. The research universe included patients clinically diagnose to have anogenital injuries by Dermatology specialists from the Manuel Fajardo Hospital. The sample involved 2 groups of 50 patients each selected by simple random sampling and meeting all inclusion criteria. One group was treated with Herpigen + VIUSID (HV) and the second group with 25%-alcohol Podophyllin, to compare both results. It was found that the combined Herpigen-Viusid treatment was effective for 87.5% of patients —a slightly higher percentage than reached with the podophyllin treatment—and that hardly any adverse reactions were detected during the treatment.
Introduction

Background and current state of the subject

Warts have been known for thousands of years. The term *verruca* is Latin for “a steep place”, and thus was adopted because warts were alike “small hills on the skin”. Ancient Greeks and Romans noted that anogenital warts (Condyloma Acuminatum or “cockscomb papilloma”) were sexually transmitted, but it was not until the 19th century that they were regarded as a form of syphilis or gonorrhoea.

Warts are benign skin and mucosa proliferations caused by a papillomavirus infection (hereinafter referred to as PVs). This virus does not show acute symptoms or signs but induce slow growth of injuries that may remain sub-clinical for long periods of time. ¹

Human Papillomavirus (hereinafter referred to as HPVs) is a group of DNA virus that belongs to the Papovaviridae family, which have no coating, that cause all types of warts with a high level of tropism in different body regions ². Up to 100 types have been identified, of which around 40 infect the anogenital tract in both men and women ³. Classified as either monogenic high-risk (PHI hr) or low-risk —the latter including types 6 and 11, which are directly responsible for the occurrence of condylomas in over 90% of cases ⁴. HPV type 16, 18, 31, 33 and 35 present oncogenic high-risk and are found occasionally in visible genital warts (GW), and are associated to the squamous intraepithelial neoplasia (in-situ squamous cell carcinoma, Bowenoid Papulosis, Erythroplasia of Queyrat or Bowen Disease) in external genital areas; intraepithelial dysplasia and cervical, anal and vaginal squamous cell carcinoma. Patients with visible GW may also be infected simultaneously with multiple types of HPV VG ⁵, ⁶, ⁷, ⁸, ⁹. The virus was isolated in Darier Disease virus ¹⁰, Focal Epithelial Hyperplasia (HPV-13 and 32) ¹¹, associated to Netherton Syndrome ¹², in Epidermodysplasia Verruciformis (HPV-20) ¹³.
**Table 224-1 - Clinical associations of HPV types**

<table>
<thead>
<tr>
<th>HPV type</th>
<th>Most common clinical injuries</th>
<th>Less common injuries</th>
<th>Oncogenic potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Deep palmar/plantar warts</td>
<td>Common warts</td>
<td></td>
</tr>
<tr>
<td>2, 4, 27, 29</td>
<td>Common warts</td>
<td>Plantar, palmar, mosaic, oral and anogenital warts</td>
<td></td>
</tr>
<tr>
<td>3, 10, 28, 49</td>
<td>Flat warts</td>
<td>Flat warts in EV</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Butcher’s warts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13, 32</td>
<td>Oral focal epithelial hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5, 8, 9, 12, 14, 15, 17, 19–26, 36, 47, 50</td>
<td>Epidermodysplasia verruciformis (EV); Warts in immunosuppression</td>
<td>Normal skin (?)</td>
<td>HPV-5, -8, -9 isolated from SCCs</td>
</tr>
<tr>
<td>6, 11</td>
<td>Anogenital warts, cervical condyloma</td>
<td>Bowenoid Papulosis; common warts; respiratory papillomatosis</td>
<td></td>
</tr>
<tr>
<td>16, 18, 31, 33–35, 39–40, 51–60</td>
<td>Cervical condyloma; anogenital wart; Bowenoid papulosis</td>
<td>Common warts</td>
<td>Genital y cervical carcinoma and dysplasias; rare in skin SCC; “high risk”</td>
</tr>
</tbody>
</table>

Note: SCC, squamous cell carcinoma

**Epidemiology**

GWs are one of the world’s most common sexually transmitted infections, and have been in the increase in the last three decades: estimates show that around 600 million people are infected and 190 million suffer clinical infection son. No statistics are available in Latin
America that shed light on the real incidence of HPV infections. In Cuba, 83,521 cases were reported in 1990-2003.

HPV contagion depends on several factors: location of injuries, virus concentration, degree and nature of contact, and immunological condition of the affected individual.

Adults are most commonly infected via sexual transmission, although transmission can also be occasionally caused by traumatism with contaminated material or contact with surfaces containing the virus. Sexually-transmitted HPV hr include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69 and possibly other types. These types cause generally flat, almost invisible formations, compared with warts triggered by HPV-6 and HPV-11. In children, transmission may also be vertical (transplacentally) or perinatal (contact with the birth canal). Infectivity levels are high (90%-100% of infected women are infected, and 50%-60% of contacts are infected after a single exposure). Epidemiology research show that up to 50% of women get infected and 80% may develop an infection within the first two years of initial sexual activity. The occurrence of anogenital warts has been reported in children of an average age ranging from 10 months to 2 years of age whose mothers were HPV carriers during pregnancy or birth. A high spectrum of HPV was detected in 35% of normal skin biopsy samples and up to 90% via scraping sampling of normal skin surfaces.

No clear understanding of the natural history of HPV infection has yet been acquired. It is accepted that the virus penetrates through micro abrasions on the epithelium and infects basal layers, where it takes advantage of cell division to launch its own breeding cycle, replicating itself specifically inside the nucleus of squamous epithelial cells.

The incubation period lasts 2 to 9 months, yet the incidence of the latent or sub-clinical disease can be as much as a hundred times as great as the clinical disease, therefore the right moment of the contagion is practically impossible to ascertain. Infectivity levels appear to be higher soon after the outbreak of the disease.
External GWs are found on the penis, vulva, scrotum, perineum and perianal region; uterine neck, urethra, anus, mouth, as well as on conjunctiva, nose and larynx. Injuries range from punctiform papules to cauliflower-shaped masses, and can be pinkish, red or skin-coloured. Depending of their size and location, GWs can either be painful, friable or itching, but normally asymptomatic yet triggering major psychological problems.

The diagnosis is based on the clinical examination and can be confirmed via biopsy. The application of acetic acid (3%-5%), improves the chances of discovering these injuries. Most infected patients develop low serum-antibody thresholds, which persist for many years even if the individual becomes viral DNA-negative and past and present infection is discovered. The immunohistochemical discovery of PV structural proteins confirms the presence of the virus. The DNA hybridization technique, currently limited to laboratory research activities, may be more widely available in the short term. A final diagnosis of HPV infection is based on the discovery of viral nucleic acid (DNA or RNA) or protein in the capsid.

GWs can rarely disappear spontaneously, remain unaltered or increase in number and size. Determining whether the treatment can reduce transmission is difficult, for there are no laboratory markers of infectivity available and also because clinical studies for evaluation of the persistence of HPV’s DNA in genital tissue following treatment have provided variable results. The impact of future post-treatment transmission remains uncertain.

Treatment

Current treatments involve the physical destruction of infected cells. The existence of multiple forms of treatment proves that none is uniformly effective or directly antiviral. The treatment option depends on the situation, size, number and type of warts, as well as on the patient’s age and cooperation. Pain, discomfort, risk of scarring and the physician’s experience are a priori considerations for evaluation of the treatment. Currently available surgery and non-surgery therapies involve a number of downsides ranging from pain and discomfort to risk of scarring and recurrence. As the selected treatment involves the removal of the visible wart, there is no evidence available to show whether the currently available treatment eradicates the HPV infection, decreases infectivity or alters the natural development of the infection.
Among non-surgery therapies, Interferon (topical, intralesional or systemic); Podofilox and Imiquimod topical (both of which can be self-applied by the patient at home) have been randomly compared with placebos in a limited number of clinical trials, which provided variable improvement results: 45%-77% for Podofilox, 17%-63% for Interferon intralesional, 6%-90% for Interferon topical, 17%-67% for Interferon systemic and 37%-50% for Imiquimod 5%. Other destructive treatments used such as cryotherapy, surgical scission and laser cryosurgery were compared with other treatments, but there is by and large no clear evidence of one being more effective than the others, and simple treatments are not ideal for all patients or all warts. Therefore, the current prevention guide issued by the Disease Control Centre (CDC) for treatment of sexually transmitted diseases recommend that the treatment must be based on the patient’s preference, availability of resources and experience of the health professional in charge. Rosa María Corona, Moore et al. recommend Imiquimod 5% cream as the best option for patients willing to self-medicate at home and able to afford a non-expensive treatment. 24

Among the numerous types of treatments, the most widely used (more experience) are Podophyllin, Trichloroacetic Acid, and Cryosurgery. Other treatments are available including Podophyllotoxin (Podophyllin’s active ingredient), Imiquimod (cream 5%), Bleomycin intralesional, Retinoic Acid, Cantharidin (extracted from green blister beetles)1, 5-Fluorouracil (cream) and Interferon α-2b. Other conventional treatments include standard surgery, CO2 laser and electrofulguration1, 3, 4, 5. Currently, Cidofovir 1% once a day for 5 days during two weeks (originally developed to fight cytomegalovirus [CMV]) has proven useful for treatment of HPV, as did HspE7, a brand new drug that has provided benefits in preliminary research studies 25. Treatment with HPMPC, acyclic nucleoside phosphonate analogues featuring high-spectrum antiviral activity (HSV, VZV, CMV, EBV, adenovirus, poxvirus and HPV), must be used either alone or in combination with other drugs designed for severe HPV injuries, as gel 1% once a day for 6 months 15, 23. Yuan Hong li et al. provided evidence that Aratinoid ethyl ester (third generation polyaromatic retinoid 0.03 mg 1 or 2 times a day during 2 months and maintenance dose of 0.03 mg once or twice a week) has an anti-papillomavirus effect 8,000
stronger than trans-retinoic acid, and 16,000 stronger than 13-cis-retinoic acid in Darier disease\textsuperscript{10}. In a placebo-controlled clinical assay, Zinc Sulphate (10 mg/kg/day) provided high level of effectiveness in the treatment of stubborn viral warts, proven safety levels and minimal adverse reactions\textsuperscript{27}.

Speculation has fuelled the idea that both Dinitrochlorobenzene (DNCB) and Diphenylcyclopropenone boost local immunity. Cimetidine has recently gained ground in the treatment of skin warts, particularly in children. A double-blind test did not give any effects whatsoever.

Cytokines were used successfully for the treatment of warts in a patient with neutropenia\textsuperscript{1}. Immunotherapy involving intralesional candida antigen injection was also tried\textsuperscript{28}.

Prophylactic and therapeutic HPV vaccine testing are currently either planned or in progress\textsuperscript{1}. Recently (June 2006) the FDA (Food Drugs Administration) approved the vaccine marketed by drug company Merck under the name GARDASIL (which blocks infection caused by 4 HPV strands) for its use with young girls and women aged 9-26.\textsuperscript{35}

**Current Situation in Cuba**

The infection shows in Cuba the same behaviour as elsewhere in the world (HPV types causing anogenital and cervical injuries\textsuperscript{30}, identical appearance and treatment). The most widely used specific treatments include the following: Podophyllin (10%-25%) in alcohol solution or Benzoin tincture, Bi / Trichloroacetic acid (80%-90%) in alcohol solution, Electrofulguration (for isolated injuries), Cryotherapy and surgical Exeresis\textsuperscript{31,32,33}. A clinical assay conducted in 2005, which enabled to determine the level of effectiveness of podophyllin, trichloroacetic acid and cryosurgery, did not provide any significant differences between said substances when used for the treatment of external anogenital warts\textsuperscript{34}.

Alternative therapy is a part of the armamentarium available for the treatment of many diseases we deal with on a daily basis. On the basis of the aforementioned data plus other knowledge gathered from current research, Laboratorios Catálisis have developed a product
called Herpigen which features as main active ingredient Glycyrrhizinic Acid (GA), a
substance sourced from the plant Glycyrrhiza Glabra, widely called “sweet root” and already
known in Ancient Egypt and China, where it was used for treatment of respiratory infections
and anti-inflammatory. Evidence was recently provided of its anti-inflammatory power, as
well as anti-ulcer and antiviral properties. The ingredient (0.1 g in 100 mg of the vehicle)
interacts with virus proteins and, depending on the affected viral phase, lead to the following:

- Extra-cellular deactivation of free virus particles.
- Prevention of intracell decapsulation of infecting particles.
- Deterioration of the capacity of assemblage of structural viral components.

The advantage of its action is based on a Molecular Activation procedure, which greatly
improves the biological activity of anti-oxidant molecules and all other molecules containing
carboxyl groups in their structure —and antiviral activity can be boosted up to 10,000 times.

In vitro testing provided evidence of its inhibitory activity, featuring zero mortality and
minimal eye and skin irritation in animals. Clinical assays for treatment of VA at
dermatovenerology and gynaecology clinics in the last ten years have provided evidence of its
effectiveness. No complications were reported in pregnant women. It is 100% effective,
specifically during the first stages of the disease, and 90% in cases or relapse. It is perfectly
tolerated, does not cause irritation and is fairly innocuous. The product, easy to apply, does
not cause discomfort. Both forms (cream and spray) provided identical results, but researchers
prefer the spray for the treatment of mucosas and hard-to-reach areas. 35 It did not present any
interactions when combined with other physical or mechanical products. VIUSID, a
nutritional product specifically designed for balancing and boosting immunological system
functions, is one of these products.

The activation of VIUSID’s ingredients succeeded in boosting greatly the biological functions
without altering or modifying molecular structures. The Antiviral Agents, Antioxidants and
Anti-Free Radicals contained in its formula are key body health elements, as they reinforce
immunological system defences and strengthen the entire organism.
All compounds that integrate the VIUSID formulation are naturally found in the human organism and, therefore, no side effects or toxicity were detected following the application of the product. This product’s antioxidant substances cancel all the negative effects that may be caused by free radicals present in all infection processes. The essential amino acids contained in the product enable the appropriate nutritional development required for boosting immunological defences. It can activate the induction of Interferon.

The product is presented in sachets (Boxes with 21 and 90 4g sachets) and mixture (100 ml bottle) both forms with identical composition, except that sachets contain Guar Gum, and the mixture, water. According to producers, VIUSID ® includes the following ingredients:

<table>
<thead>
<tr>
<th>Ingredients:</th>
<th>Daily dose</th>
<th>Ingredients:</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malic Acid</td>
<td>0.666g</td>
<td>Pyridoxal</td>
<td>0.0006g</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>0.080g</td>
<td>Folic acid</td>
<td>0.0070g</td>
</tr>
<tr>
<td>Arginine</td>
<td>0.666g</td>
<td>Cyanocobalamin</td>
<td>0.0003 mg</td>
</tr>
<tr>
<td>Glycine</td>
<td>0.333g</td>
<td>Sodium Methylparaben</td>
<td>0.003g</td>
</tr>
<tr>
<td>Glycyrrhizinic Acid</td>
<td>0.333g</td>
<td>Neohesperidin</td>
<td>0.005g</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>0.020g</td>
<td>Lemon</td>
<td>0.666g</td>
</tr>
<tr>
<td>Zinc Sulphate</td>
<td>0.005g</td>
<td>Peppermint</td>
<td>0.033g</td>
</tr>
<tr>
<td>Calcium Panthotenate</td>
<td>0.002g</td>
<td>Guar Gum</td>
<td>0.833g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Honey</td>
<td>0.650g</td>
</tr>
</tbody>
</table>

Goals

General:
- *Assessing the effectiveness of the combination Herpigen - VIUSID in the treatment of external genital warts.*

Specific
- *Describing the population under study according to clinical and socio-demographic variables.*
- *Identifying the results obtained with Herpigen - VIUSID and Podophyllin.*
• Describing any adverse reactions and discomforts reported by patients during the treatment.

Materials and Method

Design

- Type of Research: Experimental
- Specification: Clinical Assay
- Time: Prospective

This research was conducted in coordination with Laboratorios Catalysis, Madrid, Spain.

The research was started upon approval granted by the Ethics Committee for the corresponding Clinical Research.

Type of assay: Stage III Clinical Trial conducted at a National Reference Centre that provides services to patients from all provinces of the country. The research involved two groups to assess the effectiveness of the product in the treatment of external anogenital warts.

Universe: Patients clinically diagnosed to have external anogenital warts by dermatologists at outpatient appointments carried out at the “Manuel Piti Fajardo” Hospital or Policlinics in Plaza de la Revolucion district, City of Havana. These patients were referred to our service’s ITS Department.

Sample: formed by 100 patients split into two groups of 50 patients each, which were selected by simple random sampling according to the following:

1. Inclusion criteria:
   - Male and female patients aged 17 and over
   - Signed informed consent
   - Affected area size up to 10 sq cm
• Not having previously undergone any treatment
• Serology and HIV tests completed

2. Exclusion criteria
• Unwilling to participate in the research
• No signed consent informed provided
• Patients aged under 17
• Having received previous treatment
• Pregnancy
• Patients currently taking systemic and local antivirals, steroids, immunomodulators and immunodepressants.

3. Discontinuance criteria (if any of the following occur during treatment):
• Pregnancy
• Failure to show up during two consecutive weeks
• Patient willing to discontinue participation in the research
• No improvement following 8 weeks of treatment with both products
• Deterioration of symptoms
• Hypersensitivity to any or both products
• Patients associating other drugs
• Discontinuance of treatment due to other reasons

Method for use of the drug

All patients had their injuries measured with a ruler to determine the surface area of skin affected.

Podophyllin, one touch was applied weekly during 6 weeks. An area of up to 10 sq cm was treated. Once this term was completed and injuries remained, the treatment was changed and further results and monitoring data were not included in the study, and were only recorded as discontinuance of treatment.
For Herpigen, 3-5 applications were indicated in writing (one nebulization corresponded to two short strokes) to be applied at home, depending on the area size, up to a maximum 10 sq cm:

- 1 - 3.9 sq cm ______________ 3 daily applications
- 4 - 6.9 sq cm ______________ 4 daily applications
- 7 - 10 sq cm ______________ 5 daily applications

The period for application of Herpigen ranged between 5 days and 8 weeks depending on the evolution and clinical improvement of patients. Beyond this period, the treatment was reassessed to decide whether to combine or replace it with conventional treatments depending on each specific case and, as with Podophyllin, they were recorded as discontinuance.

Viusid (mixture) was administered in 30 ml doses every 8 hours daily throughout the treatment, after each meal, dissolved in drinking water, fruit juice or milk.

Photodocumentation was included weekly in the patient’s diagnosis to record the progress, and stored on CD (compact disc). Three photos were selected, which are attached to the final report of research (taken at diagnosis and during progress).

Each patient was provided comprehensive information of their condition, the best treatment options including possible advantages and side effects. Cases treated with Herpigen were also provided product information. Questionnaires including general data of patients and diseases were used (see annexe). Both samples were broken down into 5 age groups, classified by gender and occurrence of side effects. All results were stored in an Excel database and statistically processed. The number of percentage of qualitative variables was calculated as well as the arithmetic mean and standard deviation of quantitative variables. Analyses were conducted for the purpose of finding out whether there were significant differences between the results obtained from both treatments.
Patients were required to express their willingness to participate in writing (see annexe). Patients were informed that rejection to participate in the research would not undermine the doctor-patient relationship.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type</th>
<th>Operationalization</th>
<th>Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>15 - 24 year old 25 - 34 &quot;&quot; 35 - 44 &quot;&quot; 45 - 54 &quot;&quot; ≥ 55 year old</td>
<td>Time passed since birth to the first medical appointment</td>
</tr>
<tr>
<td>Gender</td>
<td>Nominal-</td>
<td>Female Male</td>
<td>Biological sex of the individual</td>
</tr>
<tr>
<td></td>
<td>qualitative</td>
<td></td>
<td>No, %</td>
</tr>
<tr>
<td>Skin phototype</td>
<td>Nominal-</td>
<td>I-VI**</td>
<td>Skin reactivity to light</td>
</tr>
<tr>
<td></td>
<td>qualitative</td>
<td></td>
<td>No, %</td>
</tr>
<tr>
<td>Type of treatment</td>
<td>Nominal-</td>
<td>-Podophyllin (25%) en alcohol or Benzoin tincture -Herpigen (0.1g in 100 ml) gel or cream</td>
<td>Topical substance or method of application to be used</td>
</tr>
<tr>
<td></td>
<td>qualitative</td>
<td></td>
<td>No, %</td>
</tr>
<tr>
<td>Location of injuries</td>
<td>Nominal-</td>
<td>Penis, scrotum, vulva, pubis, perineal and inguinal region</td>
<td>Place where warts are located</td>
</tr>
<tr>
<td></td>
<td>qualitative</td>
<td></td>
<td>No, %</td>
</tr>
<tr>
<td>Injury size</td>
<td>Continuous</td>
<td>Total size ≤ 10 sq cm</td>
<td>Size of area invaded by warts</td>
</tr>
<tr>
<td></td>
<td>Quantitative</td>
<td></td>
<td>No, %</td>
</tr>
<tr>
<td>Reaction to treatment</td>
<td>Ordinal-</td>
<td>Podophyllin: Outstanding (A): Fully healed after ≤ 2 sessions Excellent (B): Fully healed after 3 - 4 sessions Average: (C): Fully healed after 5 - 6 sessions Poor (D): No improvement after 6 sessions Herpigen: A: Fully healed after ≤</td>
<td>Level of improvement of injuries according to the number of sessions (Podophyllin) and weeks of treatment (Herpigen) required</td>
</tr>
<tr>
<td></td>
<td>qualitative</td>
<td></td>
<td>No, %</td>
</tr>
</tbody>
</table>
### Injury evolution time

- **Number of seasons per treatment**
  - Discontinuous quantitative: 1 session/week (Podophyllin) 3 - 5 daily sessions (Herpigen) Viusid (mixture)  
   - Time passed since first occurrence of warts to start of treatment: No, %

### Side effects

- **Ordinal-quantitative**
  - Ulceration, infection, balanoposthitis, necrosis, scarring, hypochromia, systemic toxicity, none  
   - Undesired effect that occurs to doses normally used with men for treatment of their condition either referred by patient or physician: No, %

### Discomfort referred

- **Ordinal-quantitative**
  - Burning, pain, pruritus, other, none  
   - Unpleasant sensation reported by the patient: No, %

### Fitzpatrick skin phototype classification

<table>
<thead>
<tr>
<th>Phototype</th>
<th>Skin colour</th>
<th>Tanning ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pale white</td>
<td>Always burns, does not tan</td>
</tr>
<tr>
<td>II</td>
<td>Fair</td>
<td>Burns easily, tans poorly</td>
</tr>
<tr>
<td>III</td>
<td>Darker white</td>
<td>Gradual and uniform tan after initial light burn</td>
</tr>
<tr>
<td>IV</td>
<td>Light brown</td>
<td>Burns minimally, tans easily</td>
</tr>
<tr>
<td>V</td>
<td>Brown</td>
<td>Rarely burns, tans darkly</td>
</tr>
<tr>
<td>VI</td>
<td>Dark brown or black</td>
<td>Never burns, always tans darkly</td>
</tr>
</tbody>
</table>
Results and Discussion

A total of 100 patients was selected, which were classified in two groups. One was treated with Herpigen spray, and the other with Podophyllin 25% alcohol. Two patients of the first group decided unilaterally to discontinue the treatment, and 48 completed it. All members of the second group completed the treatment. The results of the analysed variables were the following:

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Herpigen</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>15 - 24</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>25 - 34</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>35 - 44</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>45 - 54</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>≥ 55</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>50</td>
</tr>
</tbody>
</table>

On table 1 we can note that the disease is more widespread in youth, specifically youth aged 15 to 24. This is justified as this is a highly sexually active age group, even though there may be other factors in connection with lack of awareness of this disease, but this was not the goal of this research. *Marcos A. Munguía* (35) obtained identical results in his research conducted in 2006 for his Dermatology Specialist degree, which is included in the bibliography section herein (36).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Herpigen</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>50</td>
</tr>
</tbody>
</table>
Our sample featured a two-to-one predominance of males over females, that is, two men per each woman, which coincides with M. Mungía’s results, even though other works have reported a higher frequency of females over males in their research (5).

<table>
<thead>
<tr>
<th>Skin phototypes</th>
<th>Herpigen</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>IV</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>V</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injury size</th>
<th>Herpigen</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 sq cm</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>≥ 5 sq cm</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>50</td>
</tr>
</tbody>
</table>

The predominance of skin phototypes II and III, as shown on table 3, is a small-scale reflection of the skin types that predominate in our country, as a result of both the mixed-race population and tropical climate of the island most of the year.
Over 84% of our sample presented under five sq. cm. of affected body area at the time of the clinical diagnosis. Even though the measurement unit for this variable used in our research is different to the units used in other published works, some connection is found between them, as most series analyzed have reported fewer than 10 injuries (essentially small) in most patients. These may infer an analogy between said injuries (1, 5, 8, 34, 35), but this must yet be researched. This may be justified by easy access to qualified staff, patients’ medical culture and the fact of infections being found on “significant” body areas for sexually active people, which prevents them to show up with extended areas of affected skin.

<table>
<thead>
<tr>
<th>Injury location</th>
<th>Herpigen No</th>
<th>Herpigen %</th>
<th>Podophyllin No</th>
<th>Podophyllin %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penis</td>
<td>29</td>
<td>60</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Perianal region</td>
<td>9</td>
<td>19</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Pubis</td>
<td>6</td>
<td>13</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Lips</td>
<td>6</td>
<td>13</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Perineum</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Inguinal region</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Clitoris</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fourchette</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Anus</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Scrotum</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Crena ani</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
<td><strong>100</strong></td>
<td><strong>50</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

It was reasonable to find that the penis was the most affected genital location due the predominance of males in our sample, representing in all varieties 60% of the total for Herpigen and 28% for Podophyllin. Some works (35, 37) describe that the disease is more common on the genital area, mostly in places where coital friction is more intense.

<table>
<thead>
<tr>
<th>Injury evolution time</th>
<th>Herpigen No</th>
<th>Herpigen %</th>
<th>Podophyllin No</th>
<th>Podophyllin %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td>3</td>
<td>6.3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>1 y 4 months</td>
<td>23</td>
<td>47.9</td>
<td>26</td>
<td>52</td>
</tr>
<tr>
<td>5 - 8 months</td>
<td>9</td>
<td>18.8</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>9 - 12 months</td>
<td>8</td>
<td>16.6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>5</td>
<td>10.4</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
<td><strong>100</strong></td>
<td><strong>50</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

At the time of the interview, we recorded the time passed since the patient felt his or her injuries to the time of diagnosis, finding, as shown on table 6, that about half of the patients
had already had their injuries for 1 to 4 months, a result that coincides with several international studies. (8, 34, 35, 37). I believe that this is due to the same reasons explained for results shown on table 4.

<table>
<thead>
<tr>
<th>Table #7. Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpigen</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Generally, the response to both treatments was good, with a slightly better response to Herpigen over Podophyllin. It was analysed whether this difference was statistically significant for a 95% interval of confidence, and the opposite result was found. International works provide variable effectiveness responses to Podophyllin ranging between 44% and 76% (1, 4, 5, 9, 34, 35) and good results featuring high healing rates with Herpigen, but which do not state the percentage of effectiveness (38, 39, 40, 41, 42)

![Grafico # 2. Respuesta al tratamiento. Hospital Manuel Fajardo, Cuba. 2008](image)

Table #8. Treatment response frequency-based patient distribution

<table>
<thead>
<tr>
<th>Response to treatment (weeks)</th>
<th>Herpigen</th>
<th>Response to treatment (weeks)</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>On</td>
<td>%</td>
<td>On</td>
<td>%</td>
</tr>
</tbody>
</table>
Table #10. Discomfort referred during treatment

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Herpigen</th>
<th>Podophyllin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
</tbody>
</table>

Taking into account the maximum time in weeks of the application of both products (8 for Herpigen and 6 for Podophyllin), it was found that the higher percentage of patients cured within the previously established time occurred during the last two weeks for both treatments.
Table 10 shows that the fact that 82% of patients did not report any discomfort during the treatment with Herpigen is evidence of its innocuousness. With Podophyllin, even though over half of patients did not report any discomfort, 30% reported burning, independently of the care taken at the time of applying the drug, due to its caustic properties, which justifies these results. Other authors have found similar results for Herpigen (35, 36…42).

We analysed the likelihood of any connection between injury evolution time and treatment response, finding that these variables behaved independently, as shown on table 11, for both treatments.

Likewise, we also analysed if the size of affected area would be connected with treatment response. Evidence suggests that these variables were also independent, as shown on table 12.
Conclusions

1. The use of Herpigen n combined with Viusid was effective in the treatment of external anogenital warts.
2. The research feature a predominance of males
3. The most numerous age group in both treatments was the 15-24 age group
4. Injuries were found most frequently on the penis, (including body, foreskin, balano-preputial groove, frenulum and glans).
5. Most patients’ affected skin surface area was under five centimetres and evolution time is between one and four months.
6. Good clinical response predominated in both treatments.
7. The combined treatment Herpigen-Viusid performed better than the Podophyllin treatment,
8. Over half of the sample did not report any side effects.

Recommendations

1. Assess the level of recurrence of post-treatment injuries.
2. Increase the concentration of the active ingredient to find out if the time of treatment can be shortened.
3. Include a third group to assess the combined use of both treatments (VIUSID/Viusid plus Podophyllin)
Bibliographic References


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Annexe 1: Informed Consent

Mr / Mrs:____________________________________
Identity Card Number:____________________________

Being of sound mind, I hereby declare on my own free will that I have been duly informed and that, accordingly, I give my consent to my participation in the medical procedure for treatment of external genital warts using either Podophyllin or Herpigen, taking into account that:

1. I have understood the nature and purpose of the procedure
2. I have been given the opportunity to clear my doubts
3. I am satisfied with the information provided
4. I understand that my consent can be revoked any time prior to the start of the procedure
5. I hereby declare that all my medical history data I have provided are true and that I have not omitted any information that may jeopardise the treatment in any way.

Therefore, I hereby declare that I have been duly informed and give my consent to my participation in the proposed treatment.

Patient’s signature_________________                   Doctor’s signature_______________
Name and surnames: __________________________________________ -

Gender: M____ F___

Age: ___

Skin phototype: I__ II__ III__ IV__ V__ VI__

Occurrence of first injuries (month / year): ________________

Discomfort reported during treatment:
- Burning__
- Pain__
- Pruritus__
- Other__
- None__

Physical examination:
1. Location and number of injuries:
   - **Vulva**: clitoris__ Minor lips__ Major lips__
   - **Penis**: glans__ body__ balano-preputial groove__ foreskin__ base__ frenulum__
   - Scrotum__
   - Perineum__
   - Perianal region__
   - Pubis__
   - Inguinal region__

2. Area (sq cm):

Treatment: Podophyllin___ Herpigen___

Number of sessions___

Evolution:
Satisfactory___ Unsatisfactory___ Moved to different treatment___
Annexe 3. Presentation of Herpigen cases

Time of diagnosis
After 6 weeks
Time of diagnosis

After 8 weeks
Time of diagnosis

After 8 weeks
Time of diagnosis

After 7 weeks
Time of diagnosis

After 8 weeks
Time of diagnosis

After 6 weeks
After 8 weeks. Not healed, but improved.
Time of diagnosis

After 8 weeks
Chart #1. Gender-based patient distribution. Hospital Manuel Fajardo, Cuba. 2008

Source: Table 2
Chart # 2. Response to treatment. Hospital Manuel Fajardo, Cuba. 2008

Good

Herpigen  Podophyllin

Source: Table 7
Chart # 8. Treatment response frequency-based patient distribution

> 6  
btw 5 - 6  
btw 3 - 4  
≤ 2

Podophyllin %

Source: Table 8

Chart # 4. Treatment response frequency-based patient distribution

> 8  
btw 6 - 8  
btw 3 - 5  
≤ 2

Herpigen %

Source: Table 8