Safety and Efficacy of 0.5% Podofilox Gel in the Treatment of Anogenital Warts

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Objective: To determine the safety and efficacy of a new gel formulation of podofilox in the treatment of anogenital warts.

Design: Double-blind, randomized, multicenter, vehicle-controlled investigation.

Setting: Private dermatology practices, university clinics (dermatology, gynecology, and infectious diseases), and contract research organizations.

Patients: Three hundred twenty-six patients with anogenital warts.

Main Outcome Measure: Number of patients with clearing of all treated warts (treatment success).

Results: The 0.5% podofilox gel was significantly better than vehicle gel for successfully eliminating and reducing the number and size of anogenital warts. In the intent-to-treat population, 62 (37.1%) of 167 patients treated with 0.5% podofilox gel had complete clearing of the treated areas (treatment successes) compared with 2 (2.3%) of 86 patients who had clearing of warts with the vehicle gel ($P<.001$) after 4 weeks. Nineteen additional patients treated with 0.5% podofilox gel and 2 patients treated with vehicle gel had clearing of warts with continued treatment up to 8 weeks. After 8 weeks, 35.9% of the baseline anogenital warts treated with 0.5% podofilox gel remained; this was significantly fewer than in the vehicle-treated group (88.4% of the baseline number) ($P=.001$). The 0.5% podofilox gel was generally well tolerated, with predominantly mild or moderate local adverse reactions occurring in the majority of patients. Only 7 patients (3.2%), all receiving 0.5% podofilox gel, discontinued study treatment because of drug-related local reactions.

Conclusions: The results demonstrated that 0.5% podofilox gel is safe and significantly more effective than vehicle gel in the treatment of anogenital warts.

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EXTERNAL GENITAL and perianal warts (anogenital warts) are caused by human papillomaviruses. Human papillomaviruses are highly prevalent in sexually active men and women, although only a minority of these infections result in overt wart disease. Visible warts of the genital tract and anus are commonly called condylomata acuminata. It has been estimated that in 1987 approximately 1% of the population in the United States had genital warts. Because it is believed that the presence of anogenital warts facilitates the sexual transmission of the virus, it is important that the warts be treated.

Anogenital warts can be difficult to treat successfully, particularly because they frequently recur. The Centers for Disease Control and Prevention state in its guidelines that treatment of genital warts should be guided by the preference of the patient. Expensive therapies, toxic therapies, and procedures that result in scarring, should be avoided. The goal of treatment is the removal of exophytic warts and amelioration of signs and symptoms—not the eradication of HPV [human papillomavirus].

Treatment options currently available include podophyllin resin, podophlox, trichloroacetic acid, cryotherapy, interferon, and laser and conventional surgery, with clearance rates ranging from 60% to 90%.

Podofilox (podophyllotoxin) is a biologically active component in podophyllin resin, a crude extract from the roots and rhizomes of the May apple or podophyllin plant (either the North American Podo-
PATIENTS, MATERIALS, AND METHODS

STUDY POPULATION

Immunocompetent patients older than 18 years, with at least 2 distinct external anogenital (genital and/or perianal) warts, were enrolled into this multicenter, double-blind controlled study between December 1992 and March 1994. Women of child-bearing potential had negative results of a pregnancy test prior to enrollment, were not breastfeeding, and used an approved method of birth control for the duration of the study. Patients were excluded if they had received treatment for their anogenital warts within the last month. All patients gave written informed consent to participate in the study, and the study was approved by the institutional or ethical review boards of all participating institutions.

STUDY DESIGN

This was a randomized, double-blind, multicenter, vehicle-controlled study. Blood and urinary samples were collected before entry into the study, after 2 weeks of treatment, and at termination of treatment. Evaluations at baseline included a general medical history, physical examination, concomitant use of medication, examination for upper genital tract infection, wart history, wart treatment history, and clinical assessment of the anogenital warts to be treated. The location, number, dimensions, and clinical type of each wart selected for treatment and the total area to be treated were recorded on standardized case report forms.

Patients were randomized 2:1 to receive 0.5% podofilox gel or vehicle gel. Patients applied the topical medication twice daily for 3 consecutive days followed by a 4-day treatment-free period (1 treatment cycle). At the baseline visit, patients received instructions on proper application of the assigned medication to warts selected for treatment. Treatment was repeated by the patient until all study warts had cleared, for a minimum of 2 and a maximum of 8 treatment cycles. Gel applications could be postponed for up to 1 week if a local reaction occurred.

Patients were evaluated for the treatment’s efficacy and safety weekly for 4 weeks, then every other week for an additional 4 weeks. Treated areas were assessed for an additional 8 weeks after completion of treatment to quantitate the recurrence rate of the treated warts and to ensure resolution of any adverse events. Thus, total patient study time varied from 9 to 16 weeks depending on the number of treatment cycles and timing of follow-up visits. Patients could be discontinued from the study if no effect was seen after 4 weeks of treatment.

At each visit the investigator recorded objective findings, including the dimensions of each treated wart, the total wart area being treated, and an assessment of the patient’s overall response to treatment using the following 7-point scale: 0, exacerbation; 1, no change; 2, slight improvement; 3, moderate improvement; 4, marked improvement; 5, clear (no evidence of remaining wart tissue); and 6, normal skin (no residual erythema and return of skin lines). Separate assessments of response to treatment were made for the genital and perianal warts. At each visit, the severity of any local adverse reactions in the treated areas (including pain, burning, itching, inflammation, erosion, and bleeding) were assessed as mild, moderate, or severe. Any other adverse reactions and changes in concomitant use of medications that occurred during the study were also recorded on the appropriate case report forms.

STUDY POPULATION

The treatment groups were compared for primary and secondary efficacy variables according to the patients’ original treatment assignment (intent-to-treat analysis). The intent-to-treat analysis covered 2 populations: safety populations for all patients who returned after the baseline visit (316 patients) and efficacy for all patients with evaluable data (292 patients). An efficacy-evaluable analysis was also conducted—this excluded 32 patients who were noncompliant with the protocol.

For the purpose of data analysis, patients were classified according to wart location. The external genital subgroup included all patients with external anogenital warts; the perianal subgroup included patients with perianal warts. The combined population was referred to as the anogenital subgroup. Some patients had both external genital and perianal warts; these patients contributed data to both subgroups but were only counted once in the anogenital group.

The primary efficacy variable was the total disappearance of all treated warts (termed treatment success), while secondary variables were the number of warts, wart surface area, individual wart assessment scores, physician assessment of overall response (based on total area of treated warts remaining and overall severity of disease signs compared with baseline visit), patient discontinuation of treatment because of insufficient response, and recurrence rate of treated warts.

All efficacy evaluations used a Last-Observation-Carried-Forward data analysis because the number of visits was so varied between patients. The Fisher exact test was used to compare differences in treatment success rates between treatment groups, while differences in success rates between study sites were tested using the Cochran-Mantel-Haenszel test. Secondary efficacy variables were compared between treatment groups using a 2-tailed Student t test (wart number and wart surface area), Wilcoxon rank sum test (physicians’ overall assessment of response), and a χ² test (analysis of patient discontinuations).

phyllum peltatum or the Indian Podophyllum emodi). This antimitotic agent has been used extensively to treat genital warts and is a recommended topical treatment for this disease. Unlike podophyllum, 0.5% podofilox solution contains 4 to 16 times less podofilox than podophyllum extracts and does not contain either quercetin or kaempherol, thereby eliminating the possible toxic effects from these known mutagens. The 0.5% podofilox solution is approved for patient self-use and when used in 3-day treatment cycles, topically applied podofilox is far less toxic than podophyllum resin and has been shown to be more efficacious. Currently, clinical trials data have limited its approved use in the United States to a treatment period of only 4 weeks and excluded patients with perianal warts.
Podofilox gel was formulated as an easier-to-apply alternative to the solution that requires application via a cotton swab. In this study, the safety and efficacy of the gel formulation was determined in the patient-applied treatment of perianal, as well as external, genital warts for a maximum of 8 weeks. The gel was applied to wart tissue by finger or applicator tip.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

A total of 326 patients (194 men and 132 women) were enrolled in the study, with 219 randomized to receive 0.5% podofilox gel and 107 randomized to receive vehicle gel. Eighty percent of the patients were white and 12% were black. The number of patients enrolled at the investigational sites ranged from 15 to 54. Ten patients failed to return after the first visit, leaving 316 patients (213 receiving 0.5% podofilox gel and 103 receiving vehicle gel) for safety analysis. An additional 24 patients were not compliant with the protocol and were excluded from the efficacy analysis, resulting in 292 patients (197 treated with 0.5% podofilox gel and 95 treated with vehicle gel). Of these 292 patients, 237 patients (73 women and 164 men) only had external genital warts; 79 patients were treated with vehicle gel and 158 with podofilox gel. Twenty-three patients (12 women and 11 men) only had perianal warts; 11 were treated with vehicle gel and 12 with podofilox gel. Thirty-two patients (26 women and 6 men) had both genital and perianal warts; 5 were treated with vehicle gel and 27 were treated with podofilox gel.

Within the total patient (anogenital) population and among patients with external genital warts, there were no statistically significant differences between treatment groups with respect to age, height, weight, sex, race, duration of current wart infection, baseline number of warts, and surface area of warts (Table 1). For patients presenting with only perianal warts, those receiving 0.5% podofilox gel were significantly older (34.1 vs 28.8 years; P<.04) than those receiving vehicle gel and tended to have a greater total wart surface area.

There were no significant differences between treatment groups in the distribution of wart locations, wart morphological classification, previous wart therapy, or vital sign measurements at baseline or in the frequency of concomitant use of medication at any time during the study. The majority of warts were located on the penile shaft in men (66.8% in both treatment groups) and on the labia in women (60.1% treated with vehicle gel; 55.2% treated with 0.5% podofilox gel). Approximately 20% of the patients had received previous treatment for their current wart infection; the most frequent previous wart therapies in each treatment group were podophyllum resin (10%-12%) and cryotherapy (9%-10%).

TREATMENT SUCCESS

Intent-to-treat analysis of the patients whose warts cleared completely demonstrated that 0.5% podofilox gel was significantly more effective at clearing anogenital and external genital warts than vehicle gel after both 4 and 8 weeks of treatment (P<.001). The data for perianal warts also showed a trend in favor of 0.5% podofilox gel. In the anogenital wart population, the increase in treatment success from 62 to 81 patients (an increase of 31%) with additional podofilox gel therapy (4-8 weeks) was also significant (P<.001) (Table 2). Similar treatment successes were noted in the efficacy-evaluable popula-

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**Table 1. Comparison of Select Demographic and Clinical Characteristics Between Patient Groups by Wart Location**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>External Genital Warts</th>
<th>Perianal Warts</th>
<th>Anogenital Warts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
</tr>
<tr>
<td>No. of patients</td>
<td>91 201</td>
<td>17 40</td>
<td>103 213</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>30.8 31.2</td>
<td>28.8 34.1*</td>
<td>30.6 31.5</td>
</tr>
<tr>
<td>Sex</td>
<td>F 33 82</td>
<td>12 26</td>
<td>41 86</td>
</tr>
<tr>
<td></td>
<td>M 58 119</td>
<td>5 14</td>
<td>62 127</td>
</tr>
<tr>
<td>Duration of present infection, mo</td>
<td>25.9 26.0</td>
<td>13.2 30.7</td>
<td>24.0 27.3</td>
</tr>
<tr>
<td>Mean No. of warts to be treated</td>
<td>5.4 5.2</td>
<td>3.6 3.3</td>
<td>5.4 5.5</td>
</tr>
<tr>
<td>Mean total wart surface area, mm²</td>
<td>145.4 124.9</td>
<td>185.6 369.4</td>
<td>141.8 159.2</td>
</tr>
</tbody>
</table>

*P=.04.

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**Table 2. Treatment Success at 4 and 8 Weeks (Intention-to-Treat Efficacy Population) by Wart Location**

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>External Genital Warts</th>
<th>Perianal Warts</th>
<th>Anogenital Warts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
</tr>
<tr>
<td>4</td>
<td>0/75 (0.0)</td>
<td>2/15 (13.3)</td>
<td>2/86 (2.3)</td>
</tr>
<tr>
<td>8</td>
<td>1/82 (1.2)</td>
<td>3/16 (18.8)</td>
<td>4/93 (4.3)</td>
</tr>
</tbody>
</table>

*P<.001.

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tion with 58 (38.4%) of 151 and 74 (44.6%) of 166 of the patients treated with podofilox gel in the anogenital group having complete clearing after 4 and 8 weeks of treatment, respectively. There were no substantial differences between men and women in the response to treatment with 0.5% podofilox gel, with similar numbers of each sex achieving complete clearing of wart tissue. After 4 weeks, 38 (38%) of 100 men and 24 (35.8%) of 67 women in the anogenital group were considered treatment successes; after 8 weeks, 47 (43.1%) of 109 men and 34 (47.2%) of 72 women were considered treatment successes. There was a significant interaction (P<.05) across sites for this primary efficacy parameter. However, the results for all centers were unidirectional in favor of 0.5% podofilox gel and the significant finding related to the degree of positive effect between centers.

SECONDARY EFFICACY VARIABLES

Absolute changes in the mean wart surface areas were obscured somewhat by the total mean values, particularly in the perianal group where baseline data for 0.5% podofilox gel were higher than for vehicle gel. By calculating changes in terms of percentage of baseline wart areas, the data showed a statistically significant effect of 0.5% podofilox gel at 4 and 8 weeks in the external genital warts and total anogenital warts populations (P=.001), and at 8 weeks in patients with perianal warts (P=.03) (Figure).

Warts remaining at each week (expressed as a percentage of the number of warts at baseline) decreased during the study period. After 4 weeks, only 41.5% of the baseline number of anogenital warts treated with podofilox gel remained; this was significantly fewer than in the group treated with vehicle gel (89.5% of the baseline number of warts) (P=.001). After 8 weeks, 35.9% of the baseline anogenital warts treated with 0.5% podofilox gel remained; this was significantly fewer than in the group treated with vehicle gel (88.4% of the baseline number) (P=.001).

Physician assessment of response to treatment demonstrated that 73.8% of the patients treated with 0.5% podofilox gel had either moderate or marked improvement or complete clearing of their warts after 4 weeks. This was significantly better (P=.001) than the percentage of patients treated with vehicle gel (15.1%) who had moderate or marked improvement or complete clearing. At 8 weeks, 81.1% of the patients treated with 0.5% podofilox gel in the anogenital group had either moderate or marked improvement or complete clearing of their warts compared with 17.2% of the patients treated with vehicle gel (P=.001).

Because insufficient treatment response is an indirect proxy for treatment failure, an analysis of patient discontinuations due to insufficient response was considered a secondary efficacy parameter. Fifty-eight patients (61.1%) in the group treated with vehicle gel discontinued participation in the study because of insufficient treatment response, compared with 17 patients (8.6%) in the group treated with 0.5% podofilox gel (P=.002). Within the first 4 weeks of treatment, 35 patients (37%) treated with the vehicle gel and 3 patients (1.5%) treated with 0.5% podofilox gel discontinued study participation because of insufficient response.

Following the completion of treatment, 25 (30.9%) of 81 patients successfully treated with 0.5% podofilox gel had a recurrence of at least 1 wart within 12 weeks. The majority of these recurrences occurred within the first 4 weeks after treatment was stopped. Recurrence data in the patients successfully treated with vehicle gel could not be meaningfully measured because only 4 patients had their warts cleared completely during the treatment period.

SAFETY

The frequency of adverse events was significantly greater during treatment with 0.5% podofilox gel than with vehicle gel (P<.001). The most common local adverse events reported during the study by patients treated with 0.5% podofilox gel and vehicle gel were, respectively, as follows: burning (76.1% vs 45.6%); inflammation (71.4% vs 11.7%); itching (58.7% vs 25.2%); erosion (54.0% vs 2.9%); pain (54.0% vs 5.8%); and bleeding (29.1% vs 1.9%). The incidence of these local adverse events was similar during the first 4 weeks of treatment. Other local adverse reactions that occurred in less than 7% of the patients included stinging, erythema, and scabbing.

The frequency or severity of most local adverse events decreased during the treatment period in both treatment groups. Of the percentage of patients treated with 0.5% podofilox gel (anogenital population) with local adverse reactions during the treatment period, burning was the most frequent local adverse reaction reported during the first 6 weeks (59.1% [week 1] to 44.6% [week 6] of the patients) while the percentage of patients who reported itching increased from 29.1% to 42.9% during the treatment period. In the patients treated with vehicle gel, mild or moderate burning was observed in up to 32% of the patients and itching was noted in up to 14% of the patients. Almost all local adverse events were resolved within the 4 weeks following cessation of treatment, with only 1 recipient of 0.5% podofilox gel still experiencing
some burning and 6 continuing to experience itching. Seven patients (3.2%), all receiving 0.5% podofilox gel, discontinued study treatment because of drug-related reactions.

The incidence of inflammation and erosion was significantly greater in men than in women ($P < .05$). In the group with external genital warts, of those women treated with 0.5% podofilox gel, the most prevalent local adverse event was burning (75.3%), followed by itching (59.3%), pain (54.3%), and inflammation (49.4%) (Table 3). In men with external genital warts, the most prevalent local event was inflammation (83.2%), followed by burning (72.3%) and erosion (63%). In the patients with perianal warts treated with 0.5% podofilox gel, the most prevalent local adverse event in women was burning (91.7%), while inflammation (71.4%) and pain (71.4%) were the most prevalent local reactions reported in men.

A total of 38% of patients receiving 0.5% podofilox gel reported a nonlocal adverse event, compared with 24% of the patients treated with vehicle gel ($P = .02$). The most common nonlocal adverse event was headache (5.8% of the patients treated with vehicle gel vs 9.4% of the patients treated with 0.5% podofilox gel), followed by cold and sinus symptoms.

There were no clinically significant changes or trends in laboratory test results between baseline and end-of-treatment blood and urinary samples.

**Table 3. Patients With Local Adverse Events (Intention-to-Treat Safety Population): Effect of Wart Location and Sex**

<table>
<thead>
<tr>
<th>Local Adverse Event</th>
<th>Sex</th>
<th>External Genital Warts</th>
<th>Perianal Warts</th>
<th>Anogenital Warts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
<td>Vehicle Gel 0.5% Podofilox Gel</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td>F: 9.1 49.4</td>
<td>16.7 79.2</td>
<td>12.2 52.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: 10.3 83.2</td>
<td>0 71.4</td>
<td>9.7 81.9</td>
</tr>
<tr>
<td>Erosion</td>
<td></td>
<td>F: 0 38.3</td>
<td>0 58.3</td>
<td>0 40.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: 5.2 63.0</td>
<td>0 50.0</td>
<td>4.8 61.4</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>F: 9.1 54.3</td>
<td>8.3 79.2</td>
<td>9.8 55.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: 3.4 49.6</td>
<td>0 71.4</td>
<td>3.2 50.4</td>
</tr>
<tr>
<td>Burning</td>
<td></td>
<td>F: 57.6 75.3</td>
<td>83.3 91.7</td>
<td>63.4 76.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: 32.8 72.3</td>
<td>60 64.3</td>
<td>32.9 70.9</td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td>F: 27.3 59.3</td>
<td>50 83.3</td>
<td>36.6 60.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: 15.5 52.9</td>
<td>20 57.1</td>
<td>16.1 52.8</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td>F: 0 29.6</td>
<td>8.3 45.8</td>
<td>2.4 32.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M: 1.7 28.6</td>
<td>0 40.7</td>
<td>1.6 26.8</td>
</tr>
</tbody>
</table>

Although well tolerated and effective for the treatment of external genital warts, 0.5% podofilox solution has not been previously evaluated in a controlled study in perianal warts or for a longer duration of treatment than 4 weeks. This study was undertaken to evaluate a new formulation, 0.5% podofilox gel, in the treatment of perianal warts as well as external genital warts for a period of up to 8 weeks.

This study shows that 0.5% podofilox gel was significantly more effective than the vehicle gel for all parameters examined. The efficacy of the 0.5% podofilox gel appears similar to that reported for the solution. For example, after 4 weeks of therapy, the mean wart area was reduced by 4.2% or 7.1% in the vehicle solution groups and 82.3% or 94.9% in active drug recipients. These figures compare with 4-week data from the current gel study that showed a mean wart surface area increase of 1.3% in the vehicle group and a wart surface area decrease of 73.7% in the 0.5% podofilox gel recipients. This study also demonstrated the benefits of continued therapy, with 19 patients treated with 0.5% podofilox gel having their warts cleared with treatment beyond 4 weeks.

Despite the low numbers of patients with perianal warts, statistical significance was achieved for both external genital and perianal wart subgroups for changes in wart surface area and physician assessment of positive response to therapy after 8 weeks. The 0.5% podofilox gel also had a significant effect on reducing the number of warts in all study patients. The 0.5% podofilox gel was generally well tolerated in this study. The majority of adverse events were local effects at the site of application; there were no apparent drug-related systemic adverse events. Although patients receiving 0.5% podofilox gel experienced local adverse events at a significantly higher frequency than those receiving the vehicle gel, the majority of these reactions were mild or moderate in severity and transient in nature. This is similar to local adverse reactions reported with 0.5% podofilox solution. These local reactions are not unexpected and are related to the destruction of the wart tissue.

**COMMENT**

With the exception of injectable interferon, podofilox topical solution, and imiquimod cream, most therapies for genital warts have not been extensively or formally studied. Following its introduction in the United States, a large, postapproval study of 0.5% podofilox topical solution in more than 1300 patients further demonstrated its efficacy and safety in the real-life clinical setting. This study also demonstrated a patient preference for self-treatment with 0.5% podofilox solution over other treatments, primarily because of the added convenience to the patient.
In conclusion, 0.5% podofilox gel was found to be effective and generally well tolerated and well suited for outpatient treatment of anogenital warts.

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18. Syed TA, Lundin S, Ahmad SA. Topical 0.3% and 0.5% podophyllotoxin cream for the self-treatment of condylomata acuminata in women. Dermatology. 1994;189:142-145.


Correction

Error in Number. In the review titled “Photoaging and Topical Tretinoin: Therapy, Pathogenesis, and Prevention,” published in the October issue of the ARCHIVES (1997;133:1280-1284), the number 72 was inadvertently replaced with the number 92 on the bottom of page 1283. The sentence should have read: “The specificity of AP-1 in these MMP inductions was supported by a lack of messenger RNA, protein, or enzyme activity elevations of non–AP-1 regulated 72-kDa gelatinase.”