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Cantharidin is superior to trichloroacetic acid for the treatment of non-mucosal genital warts: a pilot randomized controlled trial

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Summary

Condyloma acuminatum is a sexually transmitted viral disease caused by the human papillomavirus (HPV). It is the most common viral sexually transmitted disease. In this randomized controlled trial, cantharidin was found to be more effective and better tolerated than trichloro-acetic acid (TCA) for the treatment of these lesions. Patients treated with cantharidin healed with less scarring than those treated with TCA ($p < 0.034$), had less pain during treatment ($p < 0.01$), and required fewer treatments to eradicate warts ($p < 0.01$) when compared to trichloroacetic acid.

Key words: Condyloma acuminatum; Human papillomavirus; Cantharidin; Trichloroacetic acid.

Introduction

Condyloma acuminatum is a sexually transmitted viral disease caused by the human papillomavirus (HPV). This double-stranded DNA virus affects the epidermis, the vulva, the vagina, the cervix, and the rectum. Genital warts are the most common viral sexually transmitted disease [1] and in the past few years has reached epidemic levels [2]. In the past quarter century, the number of infected individuals has risen 700% according to the Center for Disease Control's 2011 Sexually Transmitted Disease Surveillance Data Sources. The prevalence of HPV is especially high among sexually active teenagers with multiple partners.

There are four morphologic types of genital warts: cauliflower-shaped, smooth papular, keratotic, and flat.

Conditions known to predispose women to infection with HPV include local trauma, diabetes, and immunosuppression. Management depends on the location, size and extent of disease, and pregnancy status, with the goal of eliminating macroscopic lesions. Current treatments include podophyllin, imiquimod, trichloro-acetic acid (TCA), cryotherapy [3], laser, or surgical and electrocautery [4]. Each of these modalities present some drawbacks. While TCA treatment is somewhat effective and relatively cheap, its side effects include irritation, pain, and peeling. Podophyllotoxin, which disrupts microtubules during cell cycle replication, is relatively expensive. Imiquimod, which upregulates immune mediators such as tumor necrosis factor and interferon is expensive, requires multiple applications, and may lead to erosions and erythema [5, 6]. Procedural therapies such as cautery, laser, and cryotherapy, require expensive instrumentation, are time consuming, may cause scaring, and frequently require multiple treatments.

An alternative treatment modality involves the use of cantharidin, a terpenoid secreted by blister beetles and isolated in 1810 by Pierre Robiquet. This acantholytic vesicant creates a blister between the epidermis and the dermis and has been used to treat warts, molluscum contagiosum, calluses, and acquired perforating dermatoses [7]. To date, there have been no studies published on the use of cantharidin for peri-genital warts [8]. The authors conducted a randomized controlled study comparing cantharidin to TCA with the hypothesis that this mode of therapy might be superior to TCA in terms of efficacy and adverse effects in the treatment of genital warts.

Materials and Methods

Patients who attended the St. Vincent's Gynecology Clinic in New York for the treatment of newly diagnosed external genital warts were invited to participate. Following informed consent, they were randomly assigned to either the TCA group or to the cantharidin group based on previously prepared cards placed in opaque sealed envelopes. Women who were pregnant or under 18 years old, lesions that were larger than 4 mm across, unclear diagnoses of condyloma, and women with internal warts (cervical, vaginal, clitoral) were excluded from the study, as cantharidin application on mucosal surfaces is contraindicated due to increased propensity to blister [9, 10]. Women with a known history of diabetes, HIV or immunocompromise were also excluded. Warts on or within 2 cm of mucosal areas (perianal, perivaginal, labial) were excluded from this study as were warts in intertriginous areas. However, warts on the mons pubis were included in the study. Pap smears were performed as clinically indicated, and in all cases birth control and condom use was advised.

Cantharone (cantharidin collodion) 0.7% was and applied directly onto the wart without curettage using a wooden applicator

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Table 1. — *Cosmetic, pain, and satisfaction grading system.*

Cosmesis	
Skin grows back perfectly	5
Slight discoloration	4
Discoloration	3
Thickened skin	2
Slight scarring	1
Scarring	0
Pain	
Extreme	5
Severe	4
Moderate	3
Mild	2
Slight	1
None	0
Subjective satisfaction	
Excellent	5
Very good	4
Good	3
Moderate	2
Dissatisfied	1
Very dissatisfied	0

stick in a thin layer and extending about 2 mm from the margin of the wart. After air drying, the wart was covered with a transparent adhesive waterproof film dressing. Patients were told to keep the plastic on for about 4-6 hours and to gently rinse the treated area with soap and water in the shower. A questionnaire inquiring about pain was given shortly after treatment. Patients were counseled about the pain that may occur after the skin blisters on the day following treatment and were given a prescription for ibuprofen to use as needed for analgesia.

TCA was used in the control group and applied after a protective layer of petroleum jelly was placed 2 mm circumferentially from the wart's margin.

Patients were asked to return two weeks after the procedure for clinical evaluation and, possibly, for repeat application. At this subsequent visit, patients were asked to rate the pain they recall having from the last treatment over the course of the two weeks. Patients remained in the study for up to four visits or until the wart was no longer visible. At their final visit, they were asked to rate their overall satisfaction with their experience. Rating scales are presented in Table 1.

An unpaired two-tailed student *t*-test, assuming unequal variances, was used to compare cosmesis, number of treatments required to eradicate the wart, number of warts not eradicated by the end of the study (four treatments), the pain during and after treatment, and the subjective satisfaction of the patient during treatment. This study was conducted under IRB approval (reference 2012092).

Results

Twelve patients were enrolled in the study, six of which were treated with cantharone, and all patients completed the study. The results of this trial are summarized in Table 2. A total of 15 warts were treated in the cantharidin group while 14 warts were treated in the control group. One hundred percent of patients treated with cantharone had complete clearance of their warts compared to 66% of patients treated with TCA ($p = 0.45$). Although this result was not statistically significant, this may be due to the small size of our study. In the TCA group, 86% of the lesions were eradicated.

An evaluation of the skin's cosmesis two weeks after the eradication of the wart, or at the conclusion of the study, was conducted as described in Table 1. Patients treated with cantharone healed with less scarring than those treated with TCA ($p < 0.034$). Cantharone required significantly fewer treatments (2.21 *vs.* 3.07) to eradicate warts ($p = 0.012$). The number of warts that remained at the conclusion of the study was higher in the TCA group than in the cantharone group (2 *vs.* 0). This data supports the possibility that cantharidin requires less treatments to eradicate warts.

During cantharone application, none of the patients complained of pain and several patients commented that treatment was completely painless. About four hours after application, some mild discomfort may be felt by the patient at the treatment site. Blisters, which usually form the day after application are fairly tender but tend to respond to tylenol or ibuprofen. The pain subsides and occasionally patients report an itching sensation during days 3-5 when the crusted blisters fall off leaving an erythematous superficial skin erosion. The present study showed that the overall amount of pain experienced by patients in the cantharidin group was significantly less than those in the control group both at the time of treatment ($p < 0.01$) and as they reported at the two-week follow up visit ($p < 0.02$).

At the conclusion of the trial, the overall patient satisfaction with cantharone was significantly higher than those in the TCA group ($p < 0.01$).

Discussion

Most modalities for the treatment of warts focus on destruction of the lesion through electrocautery, chemical burning, cryotherapy or immune mediators [11]. Cantharidin, in contrast, works as a vesicant. Ideal therapy should be effective, efficient in terms of the number of necessary treatment visits, painless, and yield superior cosmesis post therapy.

Cantharidin, which was used medicinally for the past 2000 years [12], and since the 1950s for the treatment of warts [10], lost U.S. Food and Drug Administration (FDA) approval in 1962 after manufacturers failed to produce mandatory efficacy data. In 1998, President Clinton signed into law an amendment to the FDA, adding section 503A which allows for certain drugs to be compounded by pharmacists for individual patients. Cantharidin was placed on this "Bulk Substance List" which restricts the drug to in-office use and to be applied only by a physician [13]. The limited availability of the drug and the paucity of suppliers,

Table 2. — *Treatment outcomes.*

Patient-level analyses (mean ± SEM)			
	Cantharidin	Trichloro-acetic acid	*p* value
Number of warts	2.80 ± 0.66	2.33 ± 0.42	0.829
Pain during treatment	0.40 ± 0.24	3.17 ± 0.31	<0.0001*
Pain after treatment	2.60 ± 0.24	3.50 ± 0.22	0.022*
Satisfaction	4.60 ± 0.24	3.17 ± 0.31	0.006*

Lesion-level analyses (mean ± SEM)			
	Cantharidin	Trichloroacetic Acid	p value
Percent not eradicated	0.00	14.29	0.165
Cosmesis	4.64 ± 0.13	4.07 ± 0.20	0.034*
Number of treatments	2.21 ± 0.24	3.07 ± 0.20	0.012*

* *Indicates statistical significance.*

has limited its general adoption. Cantharidin, which is absorbed by lipids in keratinocytes, activates serine proteases and leads to acantholysis [14, 15]. Depending on the amount, concentration, duration of exposure and occlusion, an intraepidermal blister will form and resolve, without formation of a scar, within a week [7]. Subsequent studies may seek to optimize these factors to further maximize treatment effectiveness.

The current price of cantharone is 93 USD for a 7.5-mL vial which allows for about 60 applications [16]. The cost per application is approximately 1.55 USD. TCA retails for around 50 USD for a 15-mL vial or 42 cents per application. While each cantharone treatment costs about three times as much, canthridine required significantly fewer treatments (2.26 *vs.* 3.07) to eradicate warts. It is likely that, as cantharidin's use becomes more widespread, production prices may further decrease. When taking into account the cost of extra provider visits, cantharidin is a more efficient and more cost effective treatment modality.

Cantharidine, according to the manufacturer's indication for use, contraindicates the product on eyes, mucous membranes, in ano-genital, intertriginous or axilla areas. Mucosal limitation is primarily related to the difficulty of controlling the application of the liquid on mucosa, as the topical treatment of wet mucosal tissues has been problematic [17]. This randomized control trial shows that cantharidin is effective, safe, yields better cosmesis, and requires fewer applications than TCA for the treatment of warts when used sufficiently far from mucosal and intertriginous areas as described in this paper. In the present study it was also shown to be well-tolerated and that patients being treated with cantherone were significantly more satisfied than those treated with TCA. This may be attributed to less pain during application and during the entire treatment, better cosmetic results, and perhaps fewer visits. Although more studies are required to evaluate safety and efficacy, this pilot study suggests that cantharidin may be another valuable method in the treatment of genital warts. This modality may be particularly of value in populations, such as pediatric and adolescent gynecologic patients, where cosmesis and pain during application of treatment are of great importance.

Although rare side effects such as ring warts, lymphangitis, infection and varicelliform [18] vesicular dermatitis have been reported, none were encountered in these studies [19, 20].

While this randomized control pilot study was small, it demonstrates the potential benefits of cantharidin in gynecologic settings. Further work and higher power studies, are necessary to compare this modality to others as well as to determine if this treatment modality can be safely adapted for use on larger warts, warts closer to mucosal surfaces, and on internal warts as these are more difficult to treat with conventional modalities.

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