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RESEARCH ARTICLE

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Cantharidin (1%), podophyllin (5%), and salicylic acid (30%) formulation in recalcitrant plantar warts: Analysis of 48 patients

Jéssica Amo-Navarrete[1] | Sara García-Oreja[1] | Diego León-Herce[1] | David Navarro-Pérez[1] | José Luís Lázaro-Martínez[2] | Francisco Javier Álvaro-Afonso[2]

[1]University Podiatric Clinic, Complutense University of Madrid, Madrid, Spain

[2]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), University Podiatric Clinic, Complutense University of Madrid, Madrid, Spain

Correspondence

Sara García-Oreja, University Podiatric Clinic, Complutense University of Madrid, Edificio Facultad de Medicina, Pabellón 1, Avda, Complutense s/n, 28040, Madrid, Spain.
Email: sagarc14@ucm.es

Abstract

A plantar wart is a benign hyperplasia that appears on the feet due to the human papillomavirus (HPV). One method used for the treatment of recalcitrant plantar warts, those lasting over 2 years or persisting after at least two treatment attempts, is the cantharidin (1%), podophyllin (5%), and salicylic acid (30%) formulation, also known as the CPS formulation. Although this method is in use, there are few studies on it. This study's objective was to ascertain its cure rate. For this retrospective observational study, we reviewed the medical records of patients treated with the CPS formulation at a podiatric clinic specializing in plantar wart treatment. Our sample size was 48 subjects. The CPS formulation had a cure rate of 62.5%. Out of the cured patients, 86.67% (26/30) required one or two applications. There was no observable correlation ($p > 0.05$) between wart resolution and virus biotype, evolution time, patient's morphological and clinical attributes, location, number of warts, or preceding treatments. The CPS formulation presents a relatively high efficacy rate for treating recalcitrant HPV plantar warts. Still, additional studies are necessary to evaluate its safety and efficiency.

KEYWORDS

cantharidin, HPV, human papillomavirus, plantar warts, recalcitrant

1 | INTRODUCTION

A plantar wart is a benign hyperplasia occurring on the plantar aspect of the foot, resulting from an infection of the epidermal cells or keratinocytes by human papillomavirus (HPV).[1–3] There are over 200 types, distinguished by their DNA sequences.[1] HPV 1, 2, 4, 10, 27, and 57 are the most prevalent types detected in plantar warts.[3]

Although plantar warts can sometimes resolve spontaneously within the first 2 years of their appearance, they are generally resistant to various forms of treatment, and their duration can span several years.[2,4] Recalcitrant or recurrent warts, defined as those enduring more than 2 years or persisting after at least two treatment strategies, often make a resurgence.[2]

Plantar warts are among the most prevalent skin conditions seen by podiatrists and other health professionals responsible for managing skin diseases. They have a global annual incidence of 14% and 2% of the world's population seeks treatment each year. Concern for aesthetic appearance, along with pain and

functional limitations caused by these warts, prompt this need for treatment.[2,5]

Currently, there is a wide variety of treatments for plantar warts, each with different success rates.[5] However, none of them has demonstrated clear efficacy in all patients.[1,2,4] In a recent systematic review, first-line treatments such as cryotherapy and salicylic acid had very low cure rates (45.61% and 13.6%, respectively).[5]

A formulation comprised of 1% cantharidin, 5% podophyllin, and 30% salicylic acid, or CPS, is a widely used topical therapy for HPV plantar warts.[5] This combination includes 1% cantharidin, known for its vesicant properties which, when applied, yields a vesicle encompassing the papilloma and adjoining wart tissue. Salicylic acid (30%), a strong keratolytic with mild caustic capabilities, is also included. The active principle of the podophyllin resin, podophyllotoxin, provides antibiotic and antiviral protection and adds slight caustic irritation. Last, the formulation contains elastic collodion, purposed as an excipient. This blend is usually recommended for treating persistent warts.[6–8]

The CPS formulation is usually employed as a second or third line of treatment.[5] The latest systematic review indicates a mean cure rate of 97.82% (range: 93.3%–100%); however, included studies exhibit substantial heterogeneity.[5] Moreover, very few concentrate on the treatment of recalcitrant plantar lesions. All these factors highlight the necessity of the current study to ascertain its efficacy.

Thus, the primary aim of this study was to establish the cure rate of the CPS formulation for treating stubborn HPV plantar warts. The secondary aims included determining the required treatment applications of the CPS formulation to achieve full plantar wart healing, establishing the average number of weeks needed to completely heal the plantar wart with the CPS formulation, and exploring whether other factors, such as the virus's biotype, duration of evolution, patient's morphological and clinical characteristics, location, number of warts, and prior treatments impacted the resolution of the plantar warts with the CPS formulation.

2 | MATERIAL AND METHODS

2.1 | Participants and sample

A retrospective observational study was conducted, which received approval from a local ethics committee (Hospital Clínico San Carlos, Madrid, Spain) with the code number 23/689-E. This study adhered to the principles of the Declaration of Helsinki as well as the current national legislation relating to research involving patients.[9] Due to the retrospective nature of the study, informed consent was not required.

A review of the medical records of all patients attending a specialized podiatric clinic for treatment of plantar warts between January 2019 and January 2024 was performed, including by consecutive sampling only those patients who had been treated with the CPS formulation. For this purpose, records were documented in an Excel spreadsheet (Microsoft® Excel® 365 MSO version 2309).

All patients older than 12 years with one or more recalcitrant plantar warts (warts persisting for more than 2 years or not cured after two or more treatment modalities) were included.[2] Conversely, patients with no prior treatment, who were pregnant or breast-feeding, diagnosed with Diabetes Mellitus, suffering from peripheral vascular disease, any form of peripheral or central neuropathy, scarring changes, a coagulation disorder, Raynaud's disease, or any other alteration in the perception of cold or heat were excluded.

In patients diagnosed with multiple plantar warts, only the first wart treated with the CPS formulation was included in the study.

All patients included in the study had a previous diagnosis of a plantar wart, confirmed by polymerase chain reaction (PCR) testing. Moreover, as these were recalcitrant lesions, they had received prior treatment with other first-line treatments typically used in the clinic's protocol, as indicated in the study by López López et al.[8]

To apply this formulation, the area should first be washed and disinfected. Next, the hyperkeratotic layer that covers the wart is removed with a scalpel handle and a no. 15 blade. The preparation must then be carefully applied with a swab to the plantar wart, ensuring not to exceed the lesion's margins by more than 3 mm. After application, it should be left to dry for a few seconds. Subsequently, the lesion should be covered with a nonabsorbent dressing.[7] The patient is advised to return within 24–48 h for draining of the blistering lesion and further debridement of the area. Follow-up treatment includes a topical application of antiseptics, healing agents or antibiotic ointments as per professional discretion, alongside covering the lesion to prevent potential infection.[7]

After 15 to 20 days, if the area is completely epithelialized and no signs related to HPV are observed (such as hyperkeratosis, loss of dermatoglyph visibility, hemorrhagic stippling, pain upon lateral-medial pressure of the lesion, or a positive ringing sign), the patient is discharged.[6–8] However, if signs are still present, a second application can be performed post the same duration to allow the skin to epithelialize.[7] The application can be repeated one or two more times to obtain desired results. However, it is not recommended to perform more than three applications.[6–8]

A cure was considered in cases where following one or more treatment sessions, there were no clinical signs of a wart.

In instances where the maximum indicated number of product applications (three times) did not eradicate clinical signs, it was classified as non-healing.[6,7]

2.2 | Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 22.0 (SPSS, Inc.). Tables and graphs were utilized to describe the sample.

The Shapiro-Wilk test was conducted to assess whether the variables adhered to a normal distribution ($p > 0.05$). This helped to determine the application of parametric tests and subsequently to select parametric or nonparametric tests for statistical analysis. Based on the Shapiro-Wilk test results, none of the examined variables presented a normal distribution ($p < 0.01$), so nonparametric tests were utilized for further analysis.

The analysis of the correlation between the principal variable and the remaining qualitative and quantitative variables in the study was performed using a logistic regression model. This model incorporated only those variables that exhibited significant differences in the univariate analysis. The covariates of the multivariate model were selected by focusing on both quantitative and categorical variables with a p value of less than 0.05.

Pearson's chi-square test was utilized for qualitative variables. The Mann–Whitney U test was employed when one variable was qualitative and the other was quantitative. Conversely, Spearman's test was used to compare two quantitative variables.

The Kaplan–Meier method was used to describe the time required to complete a cure, comparing this survival by virus biotype with the use of the log-rank test. A statistical significance was set at $p < 0.05$ with a 95% confidence level. The estimated sample size needed for this analysis was 46 samples, which is based on a statistical power of 0.80 and an alpha level of 0.05, using the GRANMO sample size calculator version 7.12 online (Institut Municipal d'Investigació Mèdica).

3 | RESULTS

Finally, a sample of 48 patients from the Podiatry Clinic of the Complutense University of Madrid, who were treated with the CPS formulation, was selected for this study. Of the sample, 32 out of 48 patients (66.7%) were women. The mean age of the participants was 51.15 ± 17.40 years (Table 1). The number of warts for each patient can also be found in Table 1.

The most common location for plantar warts was on the 2nd to 5th metatarsal head (23 out of 48 patients, 47.9%), and the most prevalent HPV biotype was 1 (14 out of 48 patients, 29.2%) (Table 2).

The duration of evolution before treatment initiation, the type of prior treatment, and the average number of CPS formulation applications can be found in Table 1. Forty-one out of 48 (85.4%) of the patients had undergone previous treatment.

A complete cure of warts was observed in 30 out of 48 (62.5%) patients, and 3 out of 48 (6.3%) patients there was a loss to follow-up.

The average number of CPS formulation applications in cured patients was 1.83 ± 1.02. Of those clinically discharged, 26 of the 30 patients (86.7%) required one or two CPS applications to achieve complete recovery. However, the remaining four patients (13.3%) required between three and five applications to attain healing.

The CPS formulation demonstrated a median cure time of 5.47 weeks, with interquartile ranges of 4 weeks (Table 1).

To perform the linear regression model, the primary variable was individually analyzed with each of the secondary variables, excluding the 'weeks to cure' variable due to the loss of follow-up of 18 out of 48 patients (37.5%) in the sample.

In the univariate model, no statistically significant association ($p > 0.05$) was discovered between the cure rate and factors such as age, sex, patient's medication, number of plantar warts, location, HPV biotype, period before treatment initiation, pretreatment application, type of pretreatment, number of CPS formulation applications, and weeks needed to cure the plantar lesion. Hence, the multivariate model could not be executed.

Using the Kaplan–Meier method for time to healing, and performing the log-rank test ($p = 0.869$), Figure 1 shows that there is no significant difference in the probability of healing among the different HPV biotypes.

TABLE 1 Baseline characteristics and treatment details.

			N	Range	Minimum	Maximum	Mean	Standard deviation
Age			48	59	16	75	51.15	17.407
Number of warts			48	4	1	5	1.58	0.801
Evolution time (months)			18	959	1	960	92.44	231.827
Number of CPS applications			48	8	1	9	2.17	1.506
Curing time (weeks)			30	25	0	25	5.47	5.87
						Frequency		Percentage (%)
Type of previous treatment	Valid	Nitric acid				4		8.3
		Salicylic acid				13		27.1
		Cryotherapy				8		16.7
		Nitric acid-zinc complex				8		16.7
		Multiple treatments				8		16.7
		Total				41		85.4
	Lost data	System				7		14.6
	Total					48		100.00

4 | DISCUSSION

In the current study involving 48 patients with resistant plantar warts, complete cure was achieved in almost two-thirds of patients treated with the CPS formulation. Furthermore, most of the successfully treated patients, only one to two applications of the CPS formulation were required.

TABLE 2 Location and biotype of plantar warts included in the study.

		Frequency	Percentage (%)
Location of plantar wart	2nd–5th metatarsal heads	23	47.9
	1st metatarsal head	1	2.1
	1st finger pad	4	8.3
	Heel	5	10.4
	Multiple locations	15	31.3
	Total	48	100.00
VPH biotype	1	14	29.2
	2	13	27.1
	5	2	4.2
	14	2	4.2
	27	6	12.5
	57	4	8.3
	Multiples biotypes	7	14.6
	Total	48	100.00

Previous studies have reported higher cure rates of the CPS formulation than those found in our study.[6–8] A systematic review published in 2020 showed an efficacy of 97.82%. The authors believe that this might be due to the treatment producing more extensive injury to the wart and perilesional skin than other treatments, thereby generating a stronger immune response.[5] Similarly, in a systematic review by Vakharia,[10] studies exhibited an efficacy of the CPS formulation for both pediatric and adult common and plantar warts ranging from 81% to 100%. Moreover, the majority of these warts were remitted after the first application.

A retrospective case series (144 patients) by Becerro de Bengoa Vallejo et al.[7] demonstrated similar cure rates (95.8%). In this study, 86.8% of patients received a single application of the solution, while the remaining 9% required two or more applications. Becerro et al.[7] reported no significant adverse effects or complications from the use of the CPS formulation. Additionally, López López et al.,[8] in a 2016 case series involving 65 patients, indicated a complete cure rate of 72% after a single application of the CPS formulation. The cure rate increased to 100% after a second application, with no significant adverse effects observed.

To our knowledge, few clinical trials have compared the efficacy of the CPS formula with other treatments commonly used for plantar warts. A clinical trial conducted by Ghonemy [11] reported a cure rate of 93% for recalcitrant plantar warts using the CPS formulation, compared to 73% for the long-pulse Nd:YAG laser. Conversely, the randomized controlled trial (RCT) led by Kaçar et al.[12] demonstrated a

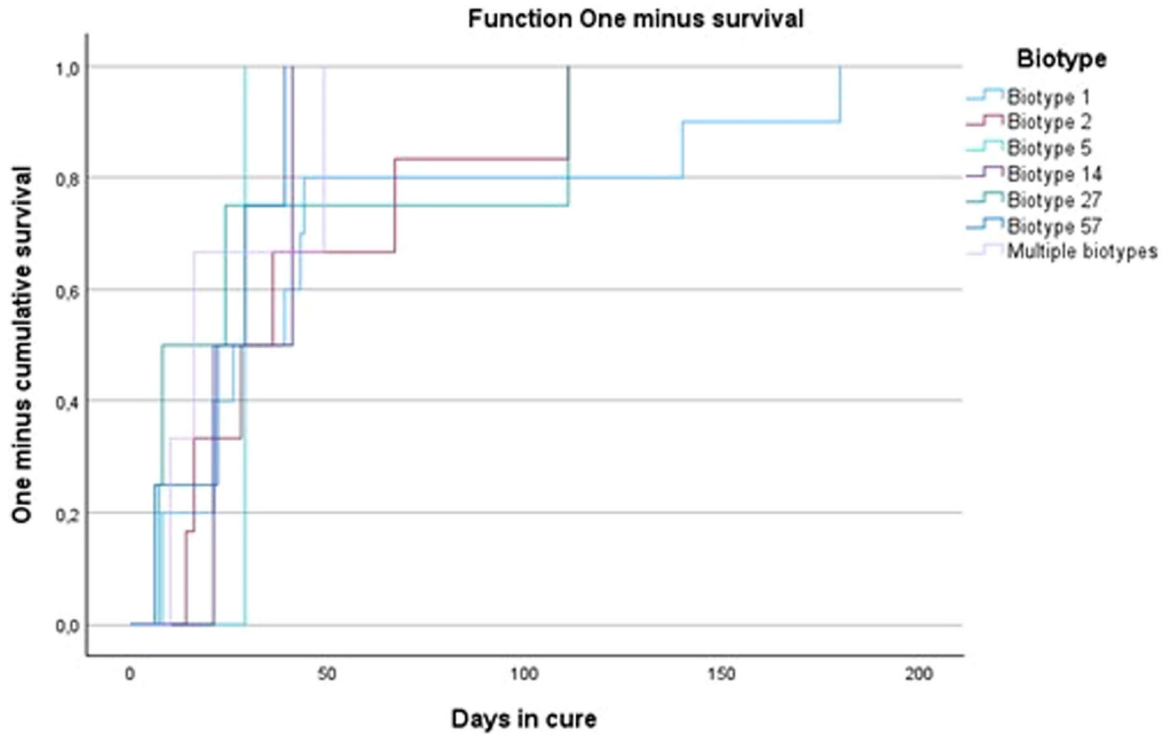

FIGURE 1 Survival graph using Kaplan-Meier method of HPV biotype variable.

100% complete cure rate for all patients with plantar warts treated with the CPS formula; in contrast, among the patients treated with cryotherapy, only 41.7% were entirely cured.

Hence, our study reported lower cure rates of the magistral formulation CPS in patients with HPV plantar warts, in comparison to prior studies, marking the first time a cure rate for the CPS formulation fell below 80%. The reason for these results could be that our patient pool was comprised of those treated with the CPS formulation only after the failure of other first-choice treatments, such as salicylic acid or cryotherapy. This followed the protocol of the Podiatry Clinic, which was established based on the recommendations from the technical data sheet of the CPS formulation, where the product's indication is specifically for recalcitrant plantar warts.[6]

Only the studies by López López et al.,[8] Navarro Pérez et al.,[6] and Ghonemy [11] used patients with recalcitrant plantar warts as a sample. This condition has a higher risk of local adverse effects, such as blisters, burning, and ulcers compared to other first-line treatments, like cryotherapy or salicylic acid.[5] The most frequent local adverse effects of cryotherapy treatment include painful symptoms, depigmentation, scar formation, delayed healing, and/or recurrence of plantar warts.[13,14] Salicylic acid can lead to contact dermatitis, pain, erythema, skin irritation, a stinging sensation, and burns.[2,15]

No significant differences were found between the healing variable and the rest of the secondary variables: age, sex, medication taken by the patient, number of plantar warts, location, HPV biotype, evolution time before starting treatment, application of previous treatment, type of previous treatment, number of CPS formulation applications, and weeks required for the plantar lesion to heal. Previous studies have not reported an association of any of these variables with the healing of plantar warts after the application of the CPS formulation. Some studies have reported an association between wart healing after the application of different topical treatments and the virus biotype. In a study by Garcia Oreja et al.[16] involving 372 patients with plantar warts, they observed a statistical association between HPV biotype and healing after applying different treatments. Bruggink et al.[17] in another clinical trial, observed that cure rates were higher in plantar warts with HPV biotype 1 compared to HPV biotypes 2, 27, and 57 after treatment with salicylic acid, cryotherapy, or no treatment (natural response).

The strengths of this study include achieving the estimated sample size and being one of the few studies to analyze the influence of variables such as age, sex, medication taken by the patient, number of plantar warts, location, HPV biotype, the time of evolution before initiating any treatment, prior treatment, type of prior treatment, the number of applications of the CPS formulation, and the weeks it took to heal the plantar lesion on the cure rate with the CPS formulation.

The primary limitations of this study include its observational and retrospective nature. Consequently, not all data were available for analysis since they were not consistently recorded in the medical records. This inconsistency may have introduced bias into the results. Additionally, being a single-center study, the possibility that the results might differ in other populations was not evaluated.

In conclusion, the CPS formulation is moderately effective, boasting a cure rate of 62.5% for stubborn warts. Although remarkably high cure rates have been documented in past studies when used on plantar warts—whether they be intractable and/or recurrent or not—where success can reach 100% in some instances, it remains unclear if it can function as a primary treatment due to the discomfort and blister formation it may cause. Future randomized controlled clinical trials focusing on different types of plantar warts, such as those of recent onset or recurrent and/or stubborn ones, would be beneficial to evaluate the efficacy and safety of this treatment.

AUTHOR CONTRIBUTIONS

Jéssica Amo-Navarrete, Sara García-Oreja, Francisco Javier Álvaro-AfonsoA, and José Luís Lázaro-Martínez had full access to all data in the study and were responsible for their integrity. Sara García-Oreja provided the study concept and design. Jéssica Amo-Navarrete obtained the data. Diego León-Herce and David Navarro-Pérez statistically analyzed the data. All authors interpreted the data, drafted the manuscript, and critically revised the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The protocol was approved by the medical ethics committee of the Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC) (protocol number 23/689-E).

ORCID

Jéssica Amo-Navarrete https://orcid.org/0009-0002-3135-1068
Sara García-Oreja http://orcid.org/0000-0002-2937-7122
Diego León-Herce https://orcid.org/0009-0009-7973-9652
David Navarro-Pérez https://orcid.org/0000-0003-3588-0557
José Luís Lázaro-Martínez https://orcid.org/0000-0001-6110-0265
Francisco Javier Álvaro-Afonso http://orcid.org/0000-0003-4674-3822

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