




Cryotherapy versus topical nitric-zinc complex solution for the treatment of plantar warts: A randomized controlled trial

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Funding information

Universidad Complutense de Madrid y Banco Santander

Abstract

Cryotherapy is commonly regarded as the primary treatment method for plantar warts. A new medical device called nitric-zinc complex solution (NZCS) has also emerged as a potential alternative for wart treatment. The main aim of this study was to analyze and compare the effectiveness of cryotherapy using liquid nitrogen and NZCS in treating plantar warts. We conducted a randomized and controlled clinical trial involving patients with plantar warts. A total of 62 patients were enrolled in the study and monitored for 12 weeks or until their warts were completely resolved. The patients received either cryotherapy or NZCS, with a maximum of six treatment applications. The cure rate was 65.5% in the group treated with cryotherapy and 56.6% in the group treated with NZCS. The average number of treatment applications required for curing warts was significantly lower in the cured group (3.28 ± 1.63) than in the group with unresolved warts (5.5 ± 1.27) ($p < 0.01$). Moreover, the average number of applications was lower in the cryotherapy group (3.6 ± 1.8) than in the NZCS group (4.8 ± 1.8) ($p < 0.01$). Based on the findings, NZCS could be considered a favorable first-line treatment option for plantar warts.

KEYWORDS

cryotherapy, cutaneous warts, human papillomavirus, nitric-zinc complex solution, plantar warts, RCT

1 | INTRODUCTION

Plantar warts are prevalent viral skin lesions caused by human papillomavirus (HPV) infection.¹ There are over 200 identified types of the virus, categorized into five genera: alpha, beta, gamma, mu, and nupapillomavirus.² Among these, HPV biotypes 1, 2, 4, 10, 27, and 57 are the most commonly detected in foot warts.^{3,4} The estimated overall prevalence of HPV is

40%, and the annual incidence of plantar warts is approximately 14%.⁵

Various treatment options are available for plantar warts, including cryotherapy, salicylic acid, cantharidin in a magistral formulation, bleomycin, intralesional immunotherapy, and laser therapy. However, it is important to note that none of these treatments have demonstrated universal effectiveness in all patients.⁶

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Topical treatments involving physical or chemical products are designed to destroy the affected epidermal cells by damaging the targeted tissue. However, these treatments can also lead to injury in the surrounding healthy skin, causing discomfort and pain.^{2,6,7} In some cases, these treatments may not fully eliminate the latent virus in nearby cells, leading to the persistence and recurrence of warts, making them difficult to treat.^{6,7} As a result, approximately 2% of the general population seeks medical treatment for warts annually.⁵

Cryotherapy is considered the primary treatment method for warts.^{6–8} It involves the application of liquid nitrogen to the wart tissue, leading to localized freezing followed by gradual thawing.^{7,9,10} Cryotherapy and salicylic acid remain the preferred treatments for plantar warts.^{6,11} However, recent systematic reviews have revealed that these treatments exhibit relatively low cure rates (45.61%) compared to alternative approaches like laser therapy, the magistral formulation cantharidin-podophyllin-salicylic acid (97.81%), or topical antivirals (72.45%).^{6,7} A 2022 systematic review with meta-analysis on the efficacy of cryotherapy for plantar warts suggested that cryotherapy tends to yield lower cure rates than other treatments in most published randomized clinical trials.⁷ Nevertheless, the authors concluded that due to significant heterogeneity among the various studies, there is insufficient evidence to support the superiority or inferiority of cryotherapy compared to other treatments.⁷

The limited availability of treatments with higher cure rates and the absence of studies with robust evidence on the efficacy of various treatments for plantar warts^{6,7} have prompted healthcare professionals to explore new therapeutic alternatives.

Nitric-zinc complex solution (NZCS) is a novel medical device—a topical solution containing organic acids, nitric acid, zinc, and copper salts—that is applied to warts, inducing a painless caustic effect and leading to mummification of the affected tissue.^{12,13} The efficacy of NZCS has been highlighted in the guideline for managing anogenital warts (AGW) in daily practice, demonstrating a high effectiveness rate (89.7%) and a lower recurrence rate (18.4%) compared to cryotherapy for this type of warts.¹² A case series by Cusini et al.¹⁴ reported a 90% complete wart cure rate after four sessions of zinc nitric complex, but it is important to note that only 2 out of 37 selected patients had plantar warts. In another case series by Giacaman et al.,¹⁵ which focused on a pediatric population (children aged 4–16 years) with periungual and palmoplantar warts, the total cure rate was 87.5% for periungual warts and 71% for palmoplantar warts. The study involved 24 periungual warts (77.4%), 2 palmar warts (6.45%), and 5 plantar warts (16.12%), with an average of six treatment sessions. Additionally, Puviani et al.¹⁶ conducted a multicenter study, collecting questionnaires from dermatologists in 14 Italian medical centers, which concluded that NZCS exhibited superior efficacy and tolerability compared to previous wart treatments. They further noted it to be an effective and less invasive treatment option for both children and adults, offering reduced

pain, lower cost, easier application, and requiring fewer sessions for difficult-to-treat warts such as periungual, facial, and external genital warts, without any significant adverse effects.¹⁶

Thus, the primary objective of this study was to conduct an intention-to-treat analysis to assess the clinical efficacy of cryotherapy with liquid nitrogen and NZCS in treating plantar warts caused by HPV.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design

We conducted a randomized and controlled parallel (1:1) clinical trial on patients with plantar warts. The current study is registered on [ClinicalTrials.gov](https://clinicaltrials.gov) under Registration number: NCT04654091.

2.2 | Study population

Participants were eligible for the study if they were 12 years of age or older and had an HPV-associated plantar wart that had been previously confirmed through a polymerase chain reaction test. Samples of the warts were obtained using a scalpel to scrape the hyperkeratotic surface of the lesion and collected in an Eppendorf tube, following the same method as described in our 2022 publication.¹⁷ For patients with multiple warts (two or more), only the largest wart was considered for inclusion in the study. The remaining warts were treated with the same product as the main study wart but were not included in the main study outcome.

Participants were excluded from the study if they were diagnosed with diabetes or vascular disease, an immune system disorder, were immunosuppressed, or were taking immunosuppressive drugs. Additionally, individuals with central or peripheral neuropathy, coagulation problems, Raynaud's syndrome, impaired cold perception, and those with impaired healing or collagen synthesis were also excluded from the study.

2.3 | Recruitment and randomization of participants

Participants were recruited between February 2020 and March 2022. This study received approval from a local ethics committee (Hospital Clínico San Carlos, Madrid, Spain) in October 2019 (approval no.: 19/471-R_X_Tesis). Each patient provided written informed consent before being included in the study.

All patients included in the study were followed for 12 weeks, with one visit per week, or until their warts were completely resolved.

Patients were randomly assigned to receive either cryotherapy or nitric zinc complex treatment. The randomization process was conducted using Epidat version 4.1 (Consellería de Sanidade, Xunta de Galicia, Spain).

2.4 | Intervention

Patient follow-up and all interventions performed during the study were carried out by the same podiatrist and researcher (study's responsible podiatrist).

Weekly, at each visit, before initiating the treatment, the study's responsible podiatrist conducted debridement of the hyperkeratotic tissue covering the wart using a no. 3 scalpel handle and a no. 15 scalpel blade, following the procedure described by Becerro de Bengoa Vallejo et al.¹⁸ During the initial visit, all participants received their randomized treatment. Subsequent weekly visits involved the podiatrist deciding whether to administer another treatment application, wait until the next weekly visit for a new application, or determine the wart as cured.

Additionally, all patients were requested to assess their satisfaction with the treatment at Weeks 1, 3, and 12 of follow-up.

2.4.1 | Cryotherapy

Liquid nitrogen was applied using CryoPen b[®] (HO Equipments). CryoPen[®] is an instrument designed to directly apply N₂ in its liquid phase, capable of reaching temperatures as low as -89°C.¹⁹ Following the removal of hyperkeratotic tissue, the gas was evaporated directly onto the treatment area, maintaining a distance of 0.5–4 mm from the wart and applying it at a 45° angle for 15 s. After 30 s, the gas was further applied to the wart's surface for an additional 15 s. Subsequently, the lesion was covered with a nonadherent dressing, and patients were instructed to keep it on for 24 h.

2.4.2 | NZCS

The NZCS was applied using Verrutop[®] (Isdin). Verrutop[®] is an aqueous solution containing organic acids (lactic, oxalic, and acetic acid), nitric acid, zinc, and copper salts.¹⁹ Following scalpel debridement of the keratinized surface of the wart, the product was applied as follows: first, the ampoule (0.1 mL) of Verrutop[®] was broken, and the solution was loaded into one of the applicators provided with the product. It was then applied by direct contact with small touches over the entire surface of the lesion. Finally, the treated area was covered with a nonadherent dressing, and patients were instructed to clean the area daily with 70° alcohol to reactivate the product until the next weekly check-up.

2.5 | Outcome measurements

2.5.1 | Primary outcome

The primary outcome was the complete clearance of the plantar wart at 12 weeks after randomization. Clearance

of the plantar wart was defined as the absence of clinical signs of the wart and the restoration of normal skin upon close inspection.

Persistence of lesions after 12 weeks of follow-up or after six treatment sessions was considered not cured.

2.5.2 | Secondary outcomes

Secondary outcomes included (a) a search for an association between plantar wart clearance and age, sex, history of plantar warts, number of warts at baseline, wart location, HPV biotype, time of evolution, whether it was a recalcitrant wart (more than 6 months of evolution and/or previously treated), whether it had been previously treated and the type of previous treatment, and with the healing of other warts (b) analyze the influence of the number of treatment applications, (c) time to clearance of wart, and (d) patient satisfaction with the treatment.

2.6 | Statistical analysis

All analyses were conducted on an intention-to-treat basis, incorporating all patients in the groups to which they were randomized. Statistical analysis was performed using SPSS v.22 (IBM Corp.). Frequency and descriptive analyses were conducted as part of the study.

The Kolmogorov–Smirnov test was conducted to assess whether the variables followed a normal distribution ($p > 0.05$) for applying parametric tests or exhibited a non-normal distribution ($p < 0.05$) for applying nonparametric tests. Based on the results of the Kolmogorov–Smirnov test, all quantitative variables analyzed demonstrated a non-normal distribution ($p < 0.05$). As a result, we employed nonparametric tests for their analysis.

The primary analysis involved comparing the cure rate of plantar warts at 12 weeks between the two randomized groups using a χ^2 test. To analyze qualitative and quantitative variables, a logistic regression model was employed. For comparing other variables, the χ^2 test was used when they were qualitative variables, and the Mann–Whitney U test was used when one variable was qualitative and the other was quantitative. The time to complete the cure was described using the Kaplan–Meier method, with the log-rank test utilized to compare this survival between treatments. Statistical significance was set at $p < 0.05$, with a confidence level of 95%.

The sample size was calculated to be 27 patients per treatment group, with a statistical power of 0.80 and a significance level (α) of 0.05, using the GRANMO Sample Size Calculator version 7.12 Online (Institut Municipal d'Investigació Mèdica, Barcelona, Spain).

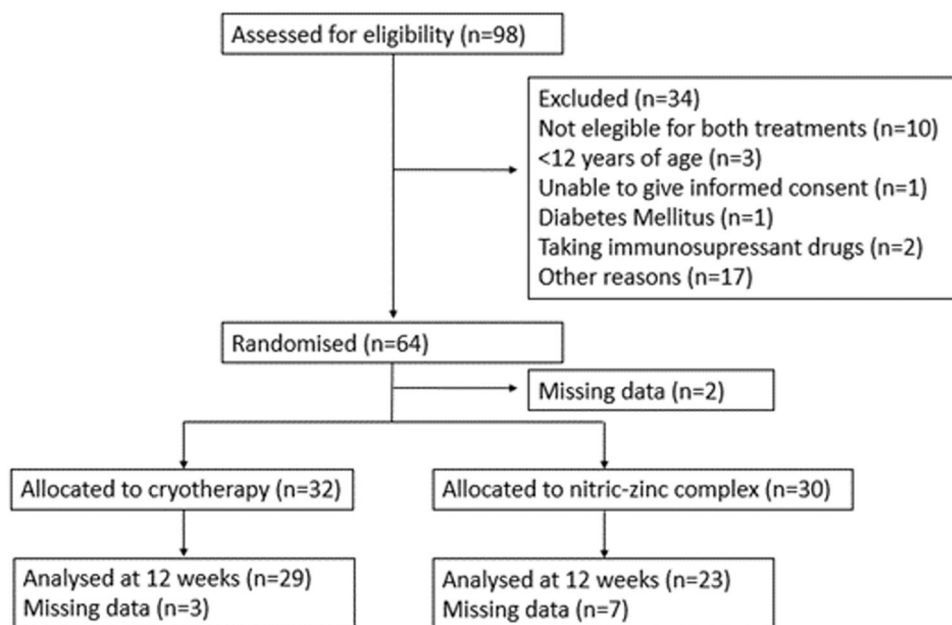


FIGURE 1 Study flow diagram.

3 | RESULTS

Ninety-eight people were selected as potential participants, of whom 62 (60.8%) were randomized: 32 to the cryotherapy treatment group and 30 to the nitric–zinc complex treatment group. A flowchart of the study is shown in Figure 1. Table 1 summarizes the baseline characteristics of the participants included in the study, and Table 2 outlines the characteristics of their plantar warts. Additionally, Table 3 summarizes the biotypes detected in the study warts.

A total of 52 participants remained in the follow-up 12 weeks after randomization. Overall, 32 out of the 52 (61.5%) patients had healed their study plantar wart at the 12-week mark, comprising 19 out of 29 (65.5%) patients in the cryotherapy group and 13 out of 23 (56.6%) patients in the nitric–zinc complex group. No significant difference was observed between the two groups (difference 8.9%, $p = 0.508$). Logistic regression analysis indicated no evidence of differences between the cryotherapy and nitric–zinc complex groups (odds ratio: 1.47 [95% confidence interval: 0.47–4.5], $p = 0.509$).

Table 4 presents the results of the univariate analysis. We identified a statistical association between the healing of plantar warts at 12 weeks and the following variables: previous plantar warts, the number of warts at the start of the study, time of evolution, previous treatment of warts, and the number of applications. Subsequently, we performed a multivariate model with the significant variables from the univariate analysis ($p < 0.05$). The analysis revealed an association of healing at 12 weeks only with the variable “number of applications” ($p < 0.01$). It is worth noting that the mean number of treatment applications was lower in the patients who were cured (3.28 ± 1.63 applications) at 12 weeks compared to those who were not cured (5.5 ± 1.27 applications).

TABLE 1 Baseline characteristics of participants.

Characteristics	Cryotherapy (32)	Nitric–zinc complex (30)
No. (%) of each sex		
Female	19 (59.4)	22 (73.3)
Male	13 (40.6)	8 (26.7)
Age (years)		
Mean (SD)	50.3 (22.4)	51.5 (17.7)
Median (range)	52.5 (8.0–86.0)	55.0 (14.0–78.0)

Table 2 provides a summary of the treatment details for each group. The mean number of applications was lower in the cryotherapy group (3.6 ± 1.8) than in the nitric–zinc complex group (4.8 ± 1.8) (odds ratio: 1.48 [95% confidence interval: 1.04–2.12], $p = 0.03$). However, there was no significant association between the number of applications and treatment in cured patients (odds ratio: 1.58 [95% confidence interval: 0.96–2.58], $p = 0.07$). Furthermore, the mean number of weeks to healing was lower in the cryotherapy group (5.6 ± 3.2 weeks) than in the zinc–nitric complex group (7.1 ± 3.5 weeks) (odds ratio: 1.15 [95% confidence interval: 0.92–1.44], $p = 0.22$). By using the Kaplan–Meier method for time to cure and performing the log-rank test ($p = 0.194$), it is evident from Figure 2 that there are no significant differences in the probability of cure between the different treatment groups.

The percentage of patients who presented an isolated wart was 59.6% (31/52 patients). Twelve patients with multiple warts were treated with cryotherapy and 9 patients with the nitric–zinc complex. The cure rate of the remaining warts 12 weeks after the start of

TABLE 2 Characteristics of plantar warts and summarizes the treatment details for each group.

Characteristics	Cryotherapy (32)	Nitric-zinc complex (30)	p Value
No. of plantar warts per participant			0.19
Mean (SD)	2 (1.2)	1.6 (1.1)	
Median (range)	1.5 (1.0–5.0)	1.0 (1.0–6.0)	
No. (%) of participants with a history of plantar warts	10 (31.3)	8 (26.7)	0.69
Duration of warts	No. of plantar warts (%)	No. of plantar warts (%)	p Value
1–6 months	10 (31.3)	10 (33.3)	0.65
7–12 months	4 (12.5)	6 (20.0)	
>12 months	171 (53.1)	14 (46.7)	
The patient does not remember	1 (3.1)	0 (0.0)	
No. (%) of warts previously treated	5 (15.6)	6 (20.0)	0.65
No. of recalcitrant warts	13 (40.6)	11 (36.7)	0.75
Type of previous treatment	No. of plantar warts (%)	No. of plantar warts (%)	p Value
Cryotherapy	1 (3.1)	3 (10.0)	0.46
Cryotherapy	3 (9.4)	4 (13.3)	
Combination of treatments	1 (3.1)	0 (0.0)	
None	27 (84.4)	22 (73.3)	
The patient does not remember	0 (0.0)	1 (3.3)	
Location	No. of plantar warts (%)	No. of plantar warts (%)	p Value
Plantar forefoot	24 (75.0)	24 (80.0)	0.74
Plantar heel	2 (6.3)	2 (6.7)	
Fingertips	4 (12.5)	4 (13.3)	
Back of midfoot	1 (3.1)	0 (0.0)	
Interdigital	1 (3.1)	0 (0.0)	
Clinical signs	No. of plantar warts (%)	No. of plantar warts (%)	p Value
Hyperkeratosis	31 (96.9)	27 (90.0)	0.27
Disruption of normal dermatoglyphics	32 (100.0)	29 (96.7)	0.29
Pinpoint bleeding	19 (59.4)	14 (46.7)	0.32
Pain on lateral compression of the wart	26 (81.3)	23 (76.7)	0.66
No. of treatment applications			0.03
Mean (SD)	3.6 (1.8)	4.8 (1.8)	
Median (range)	4.0 (0.0–6.0)	5.0 (1.0–6.0)	
Time to clearance of wart			p Value
Mean (SD)	5.6 (3.2)	7.1 (3.5)	0.22
Median (range)	5.0 (1.0–12.0)	7.0 (2.0–12.0)	

Note: Bold value statistically significant $p < 0.05$.

TABLE 3 Summarizes the biotypes detected in the PCR samples.

HPV biotype	Total, N (%)	Cryotherapy (32), N (%)	Nitric-zinc complex (30), N (%)
1	11 (17.5)	7 (21.9)	4 (13.3)
2	15 (23.8)	8 (25.0)	6 (20.0)
5	5 (7.9)	1 (3.1)	4 (13.3)
19	3 (4.8)	1 (3.1)	2 (6.7)
27	9 (14.3)	6 (18.8)	3 (10.0)
57	6 (9.5)	4 (12.5)	2 (6.7)
65	5 (7.9)	3 (9.4)	2 (6.7)
14	8 (12.7)	2 (6.3)	6 (20.0)
Nontypable	1 (1.6)	0 (0.0)	1 (3.3)

Abbreviations: HPV, human papillomavirus; PCR, polymerase chain reaction.

TABLE 4 Results univariate model.

Variables	Cured Frequency (%)	Uncured Frequency (%)	All participants		
			OR	95% CI	p Value
Sex			1.82	0.55–5.93	0.32
Female	18 (56.3)	14 (43.8)			
Male	14 (70.0)	6 (30.0)			
Previous warts	7 (41.2)	10 (58.8)	3.57	1.06–12.01	0.04
Wart location			–	–	0.9
Plantar forefoot	27 (64.3)	15 (35.7)			
Plantar heel	1 (33.3)	2 (66.7)			
Fingertips	3 (60.0)	2 (40.0)			
Back of midfoot	1 (100.0)	0 (0.0)			
Interdigital	1 (100.0)	0 (0.0)			
HPV biotype			–	–	0.8
1	8 (72.7)	3 (27.3)			
2	9 (64.3)	5 (35.7)			
5	0 (0.0)	0 (0.0)			
19	2 (100.0)	0 (0.0)			
27	3 (37.5)	5 (62.5)			
57	3 (50.0)	3 (50.0)			
65	1 (33.3)	2 (66.7)			
14	5 (71.4)	2 (28.6)			
Nontypable	1 (100.0)	0 (0.0)			
Time of evolution			–	–	0.02
>12 months	10 (38.5)	16 (61.5)			
1–6 months	15 (88.2)	2 (11.8)			
7–12 months	6 (75.0)	2 (25.0)			

TABLE 4 (Continued)

Variables	Cured Frequency (%)	Uncured Frequency (%)	All participants		
			OR	95% CI	p Value
The patient does not remember	1 (100.0)	0.0			
Recalcitrant wart	15 (78.9)	4 (21.1)	3.52	0.97–12.91	0.57
Previous treatment	1 (10.0)	9 (90.0)	25.36	2.87–223.81	<0.01
Type of previous treatment			–	–	0.3
Chemical	0 (0.0)	3 (100.0)			
Cryotherapy	2 (28.6)	5 (71.4)			
Combination of treatments	0 (0.0)	1 (100.0)			
None	30 (75.0)	10 (25.0)			
The patient does not remember	0 (0.0)	1 (100.0)			
Healing other warts			–	–	0.45
Yes	10 (90.9)	1 (9.1)			
No	0 (0.0)	10 (100.0)			
	Mean (SD)	Mean (SD)	p Value		
Age	51.66 (20.7)	44.1 (18.1)	0.18		
No. of applications	3.28 (1.63)	5.5 (1.27)	<0.01		
No. of warts	1.6 (0.94)	2.4 (1.5)	0.04		

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: CI, confidence interval; HPV, human papillomavirus; OR, odds ratio.

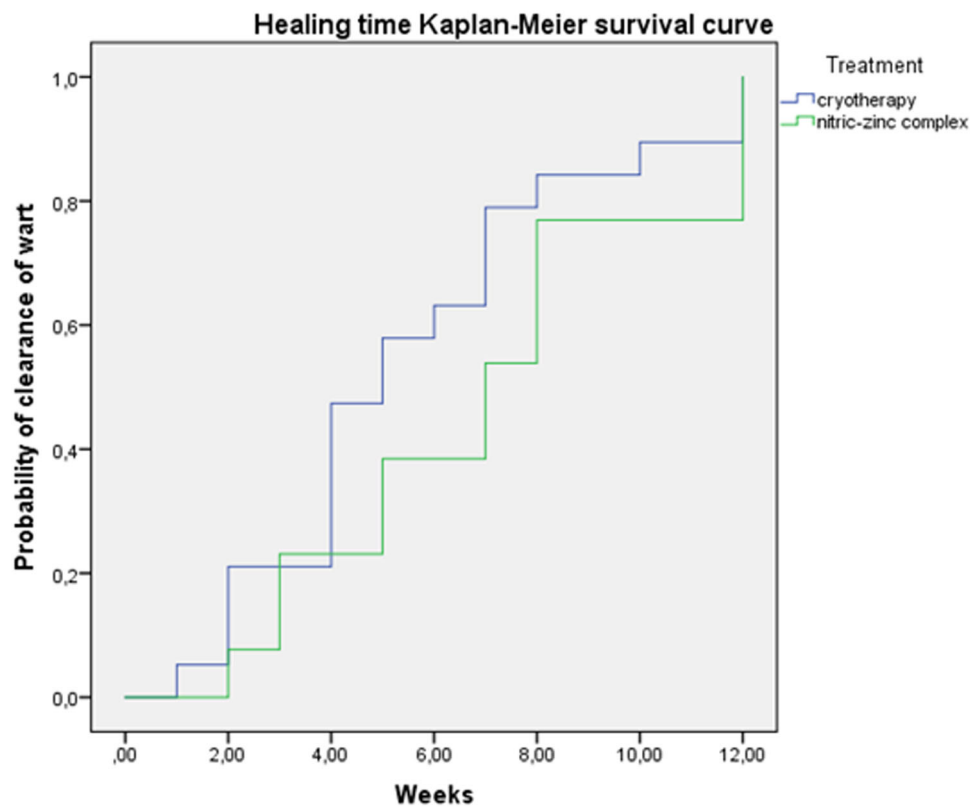


FIGURE 2 Kaplan-Meier survival curve. Healing time (weeks) of plantar warts by treatment group.

Satisfaction with treatment					
Time and treatment	Very unhappy	Unhappy	Indifferent	Happy	Very happy
Week 1					
Cryotherapy (N = 29)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (100.0)
Nitric-zinc complex (N = 23)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	23 (100.0)
Week 2					
Cryotherapy (N = 29)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (100.0)
Nitric-zinc complex (N = 23)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	22 (95.7)
Week 3					
Cryotherapy (N = 29)	0 (0.0)	2 (6.9)	4 (13.8)	1 (3.4)	22 (75.9)
Nitric-zinc complex (N = 23)	0 (0.0)	3 (13.0)	4 (17.4)	0 (0.0)	16 (69.6)

Note: Values are numbers (percentages) of patients.

treatment was 50% in the cryotherapy group and 55.5% in the nitric-zinc complex group ($p = 0.96$).

Table 5 presents the results of patient satisfaction with treating plantar warts using cryotherapy or the nitric-zinc complex at 1, 3, and 12 weeks after randomization. Using a 5-point scale ranging from “very happy” to “very unhappy,” patients rated their treatment satisfaction during the specified time points. Using a 5-point scale ranging from “very happy” to “very unhappy,” patients rated their treatment satisfaction during the specified time points. A score of 5 signified a patient status of “very happy” (patient satisfied with the treatment received and the results), and a score of 1 signified a status of “very dissatisfied” (patient dissatisfied with the treatment received and the results) with the treatment received. At Week 1, the percentage of “very happy” patients was similar in both treatment groups. At Week 3, the percentage of “very happy” patients was remarkably high in both groups (100% in the cryotherapy-treated group and 95.7% in the nitric-zinc complex-treated group), and there was only one patient who expressed feeling “indifferent” in the nitric complex-treated group. The cryotherapy group showed a higher percentage of patients who were “happy” or “very happy” at week 3 (79.4%) compared to the nitric-zinc complex group (69.6%). On the other hand, the percentage of patients who were “indifferent” was higher in the nitric-zinc complex group (17.4% vs. 13.8% in the cryotherapy group), and the percentage of “unhappy” patients was also higher in the nitric-zinc complex treatment group (13% vs. 6.9% with cryotherapy). However, no significant association was found between patient satisfaction with treatment and the treatment group at both Week 3 and Week 12 (χ^2 test $p = 0.26$ for Week 3, $p = 0.68$ for Week 12). Calculating between-treatment statistics for satisfaction at Week 1 was impossible because the variable is a constant. Additionally, when analyzing whether there were intragroup differences by week, we only found significant differences between Weeks 3 and 12 in the nitric-zinc complex treatment group ($p = 0.03$).

TABLE 5 Patient satisfaction with cryotherapy or nitric-zinc complex treatment for plantar warts at 1, 3, and 12 weeks after randomization.

4 | DISCUSSION

This study aimed to compare the clinical efficacy of cryotherapy with the nitric acid-zinc complex for treating plantar warts and found no significant difference in efficacy between the two treatments. Similarly, Pontini et al.¹² conducted a multicenter randomized clinical trial on 120 patients in 2020 and also reported no difference in cure ratio between cryotherapy (75.4%) and the zinc-nitric complex (89.7%) for the treatment of AGW.

The complete cure rates observed with cryotherapy (65.5%) and the zinc-nitric complex (56.6%) in this study were higher than those reported for most conservative treatments in the literature. A recent systematic review investigating the efficacy of various topical treatments for plantar warts showed complete cure rates of 45.61% with cryotherapy and 13.6% with salicylic acid, commonly considered the first-choice treatment for these lesions.⁶ Among the more aggressive treatments used in compassionate cases after the failure of initial treatments, cantharidin-podophyllin, salicylic acid, intralesional bleomycin, and immunotherapy demonstrated higher cure rates (97.82%, 83.37%, and 68.14%, respectively).⁶

The complete cure rate of plantar warts with cryotherapy (65.5%) observed in this study surpassed the rate reported in the aforementioned systematic review (45.61%), as well as the rates reported in other randomized clinical trials conducted by Cockayne et al.²⁰ (14.3%) and Kaçar et al.²¹ (41.7%). This could suggest that our study's higher cryotherapy cure rates were potentially influenced by the debridement of hyperkeratosis covering the wart before treatment. However, it is worth noting that other clinical trials have also shown higher cure rates without prior debridement of hyperkeratosis, as indicated in a recent meta-analysis⁷ on cryotherapy for plantar warts. This meta-analysis revealed highly variable cure rates among the different included studies, ranging from 0% to 96%.

As found in this study, the complete cure rate of plantar warts with the nitric-zinc complex was 56.6%. To the best of our knowledge, only one randomized clinical trial has been published to date on treating AGW with the nitric-zinc complex,¹² making the

present study the first clinical trial to evaluate its efficacy in plantar warts. Notably, case series examining the treatment of palmoplantar warts with the zinc–nitric complex have reported very high cure rates, with Cusini et al.¹⁴ observing a 100% cure rate and Giacaman et al.¹⁵ reporting a cure rate of 71%. Furthermore, Giacaman et al. observed an 87.5% cure rate for periungual warts.¹⁵ In the study by Puviani et al.,¹⁶ the efficacy of the zinc–nitric complex for recalcitrant warts was analyzed through questionnaires conducted at 14 dermatology centers. A total of 83 questionnaires were analyzed, revealing that the zinc–nitric complex was more effective in patients without palmoplantar warts, with a complete response in 22% of patients with palmoplantar warts and 19.5% of patients without palmoplantar warts. Partial response rates were 51.2% for patients with palmoplantar warts and 75.6% for patients without palmoplantar warts.¹⁶ Additionally, efficacy varied between patients with and without periungual warts, with most patients with periungual warts experiencing a partial response (91.3%) compared to 52.5% of patients without periungual warts. Only 4.3% of patients with periungual warts had a complete response, while 27.1% of patients without periungual warts achieved a complete response.¹⁶

During the logistic regression model analysis, we observed an association between the event at 12 weeks and the number of applications ($p < 0.01$), indicating that cured patients received a lower mean number of applications than those of uncured patients. To account for potential confounding variables, we considered previous plantar warts, the number of warts at the start of the study, the time of evolution, and the previous treatment. No significant associations were found between cure at 12 weeks and the variables of sex, age, location, biotype, recalcitrant/nonrecalcitrant wart, or type of previous treatment (Table 4).

The mean number of applications was significantly lower in the cryotherapy group (3.6 ± 1.8) than in the nitric–zinc complex group (4.8 ± 1.8) ($p < 0.05$). However, we found no association between the number of applications and treatment in cured patients, nor did we find any difference in the time to cure between the two treatment groups. In the study by Pontini et al.,¹² which focused on AGW, the mean number of sessions required for complete resolution with zinc–nitric complex was 1.83 ± 0.83 , and for cryotherapy, it was 1.88 ± 0.91 , with no statistically significant differences.

Regarding the study by Giacaman et al.¹⁵ on palmoplantar and periungual warts, the mean time for healing was approximately 6.50 ± 3.30 sessions. Our study found no significant association between patient satisfaction with treatment and the treatment group over the 12-week period. Giacaman et al.¹⁵ reported that treatment satisfaction with the zinc–nitric complex was excellent in 25% of patients and moderate in 75% of patients among 12 children with periungual and palmoplantar warts.

This study has several limitations. First, there was no blinding of the investigators or the patients, which could potentially introduce bias in the results of the different treatments. Second, the maximum number of treatment applications was limited to six in both groups. This restriction may lead one to consider that higher numbers of applications could yield higher cure rates. However, we observed that

the number of applications, in general, was lower in the patients who were cured (3.28 ± 1.63), suggesting that the treatment might be effective within the first three to four applications.

Additionally, the study did not extend observation beyond 12 weeks after randomization for each patient, preventing the evaluation of possible recurrences. In studies involving AGW, Ciccarese et al.¹³ observed recurrences in 29% of patients at 3 months and 5% at 6 months after treatment with zinc–nitric complex. In contrast, Pontini et al.¹² observed fewer recurrences in the zinc–nitric complex treatment group (18.4–25%) compared to the cryotherapy group (38.1–40.6%) in their clinical trial on AGW.

In conclusion, both cryotherapy and the zinc nitric complex demonstrate similar efficacy in treating plantar warts. Consequently, the zinc nitric complex could be considered a viable first-choice treatment option for plantar warts, given its higher cure rates than other commonly used treatments, such as salicylic acid.

Although the statistical analysis showed no superiority of cryotherapy over zinc–nitric complex, cryotherapy had slightly better results in terms of cure rate, patient satisfaction, and number of treatment applications. Therefore, the authors believe that zinc–nitric complex is a good treatment option for patients who are contraindicated for cryotherapy.

It would be advisable for future clinical trials to implement blinding of treatments for both investigators and, if feasible, patients. Additionally, conducting a follow-up of 6 months to 1 year in cured patients would be beneficial to assess the recurrence rate of plantar warts accurately.

AUTHOR CONTRIBUTIONS

Sara García-Oreja, Francisco Javier Álvaro-Afonso, 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. Sara García-Oreja and Francisco Javier Álvaro-AfonsoA obtained the data. Sara García-Oreja, Marta García-Madrid, and Mateo López-Moral statistically analyzed the data. All authors interpreted the data, drafted the manuscript, and critically revised the manuscript.

ACKNOWLEDGMENTS

Predoctoral contract co-funded by the Complutense University and Banco Santander.

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* (protocol number 19/471-R_X_Tesis). All patients voluntarily signed

consent statements for the use of their images and publication of their case details.

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How to cite this article: García-Oreja S, Álvaro-Afonso FJ, García-Madrid M, López-Moral M, García-Álvarez Y, Lázaro-Martínez JL. Cryotherapy versus topical nitric-zinc complex solution for the treatment of plantar warts: a randomized controlled trial. *J Med Virol*. 2023;96:e29212. doi:10.1002/jmv.29212