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ORIGINAL ARTICLE

Treatment efficacy of 0.9% saline and mepivacaine infiltration with Dermojet® in eliminating plantar warts

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Abstract

Background: Plantar warts are benign, epidermal neoformations, viral, and easily transmitted. Although 30% of these warts disappear spontaneously, the American Association of Dermatology recommends treatment if they cause pain or bleeding.

Objectives: The aim of this study was to determine the efficacy of Dermojet® infiltration using a solution composed of equal parts of 0.9% saline and 2% mepivacaine in the treatment of plantar warts, and to identify the type of necrosis achieved at 7–10 days after the infiltration (M1 sample) and at 15–17 days (M2 sample).

Method: In this analytical prospective observational study, 102 histories were reviewed by the same researcher. The patients were treated with this technique at four private podiatry clinics.

Results: A total of 61.8% of the patients were male. The patients' mean age was 26.6 ± 14.10 years. A total percentage of 78.4% of the patients achieved complete elimination of the lesion by the second evaluation and after a single infiltration. Bivariate analysis revealed a significant inverse relationship between treatment efficacy and a history of previous disease ($p < 0.001$) and the period of evolution of the lesion ($p < 0.001$; 95% CI [0.78–7.91]). Multivariate linear regression analysis revealed an association with the number of evaluation sessions ($p < 0.001$) and with previous illnesses ($p = 0.014$). A total percentage of 82.35% presented partial necrosis in the M1 sample and 76.92% had complete necrosis in the M2 sample.

Conclusions: In 78.4% of the patients considered, the plantar warts treated disappeared after a single infiltration. The variables associated with treatment efficacy were the number of follow-up visits and the existence of associated diseases.

KEYWORDS
Dermojet, infiltration, plantar warts, saline, verrucas

1 | INTRODUCTION

Plantar warts (verrucas) are benign, epidermal neoformations, viral in origin, and easily transmitted.[1] They affect both sexes, with a prevalence of 79% among the general population.[2] According to some authors, they most commonly affect children aged 6–12 years.[3–7]

They are frequently found on the soles of the feet, presenting as endophytic lesions, measuring 1–10 mm, thick and hyperkeratotic, and generally painful. Initially, a small, shiny, well-defined papule appears, which later transforms into a rough hyperkeratotic plaque, sometimes studded with black or brown dots (thrombosed capillaries), and with a loss of continuity of dermatoglyphics (skin patterns).[8]

Although 20%–40% of these warts disappear spontaneously within 3 years,[3] the American Association of Dermatology recommends treatment if they cause pain, bleeding, or disability, or are long lasting or if necessary to prevent contagion in immunosuppressed patients[9] and possible malignancy.[3] However, treatment may be frustrating, for clinicians and patients, due to the persistence and high rate of recurrence of lesions.[10]

In this respect, the use of hypertonic saline solution in concentrations of 18%, 20%, 23.4%, or 25%, as employed to address phlebosclerosis, has been proposed.[11] This treatment produces moderate irritation of the vascular intima with inflammation, edema, and occlusion of the lumen by the replacement of scar tissue.[12] The extravasation of a hypertonic solution invariably produces significant edema with subsequent necrosis of the affected area. Several studies have shown that its infiltration with Dermojet® can be effective, compared to treatment with bleomycin, and has fewer side effects.[13–15]

Dermojet®, designed by Dr. Alfred Krantz, is a needleless injection system that uses compressed air to introduce the medicine through the skin at a pressure of approximately 100 kg/cm. It is composed of a four-element cylinder and a reservoir from which the liquid is expelled under pressure by a piston.[16]

The aim of this study was to determine the efficacy of Dermojet® infiltration using a solution composed of equal parts of 0.9% saline and 2% mepivacaine in the treatment of plantar warts, considering the clinical characteristics of the patient and the lesion. After applying this treatment, the histopathological evolution of the lesion was evaluated in a random sample of patients.

2 | MATERIALS AND METHODS

An analytical prospective observational study, based on a single follow-up group, was conducted on patients diagnosed with plantar warts and treated with the intralesional infiltration of a solution composed of equal parts of 0.9% saline and 2% mepivacaine. This anesthetic was added in order to reduce pain during and after the infiltration. The evolution of each case was followed up for 1 year after the conclusion of treatment. The study population consisted of 102 patients treated with this technique between January and June 2017, at four private podiatry clinics. All case histories were reviewed by the same researcher. Medical records from which any study variable was missing during the 1-year follow-up were excluded from analysis. All these patients gave prior signed informed consent. In the case of minors, this consent was provided by their guardians.

A clinical diagnosis was made of the lesion, deeming a plantar wart to be present on observing a hyperkeratotic lesion with capillary hemorrhages (black dotted lines), a loss of continuity of skin dermatoglyphics and pain when subjected to pressure.

Prior to its application, the following treatment protocol was previously agreed with the podiatrists at the clinics participating in this study:

Treatment session:

1. Preparation of the solution with equal parts of 0.9% saline and 2% mepivacaine, with no vasoconstrictor. The Dermojet® was purged by pressing the trigger several times, to ensure that the pressure was sufficient to ensure penetration of the preparation into the skin tissues (Figure 1).
2. Disinfection of the skin with an antiseptic solution, followed by infiltration with the preparation to a depth of 0.25–1 mm (maximum 3 mm), depending on the size of the lesion. The Dermojet® was placed in contact with the skin and applied 1–4 times until the lesion whitened (Figure 2).

First evaluation:

At 7–10 days after the infiltration, evaluation with a Dermlite DL200 HR dermatoscope, recording the size of the lesion and any presence of dermatoglyphics and papillae. A sample was randomly collected from the lesion, by debriding, for histopathological analysis (M1 sample). Any adverse treatment effects were recorded.

Second evaluation:

At 15–17 days after infiltration, the condition of the lesion was again assessed and another random sample was taken for histopathological analysis (M2 sample). If signs of the wart persisted, home treatment with 16.7% salicylic and lactic acid, applied once daily, was prescribed, as an adjuvant treatment.

Third evaluation:

At 25 days after infiltration, if any signs compatible with the lesion were still apparent, this fact was recorded in the patient's clinical history as treatment failure.

2.1 | Participants and sample

Selection criteria: patients were included in this study according to the following criteria: (a) the presence of at least one plantar wart; (b) patient aged at least 7 years; (c) duration of the lesion to the

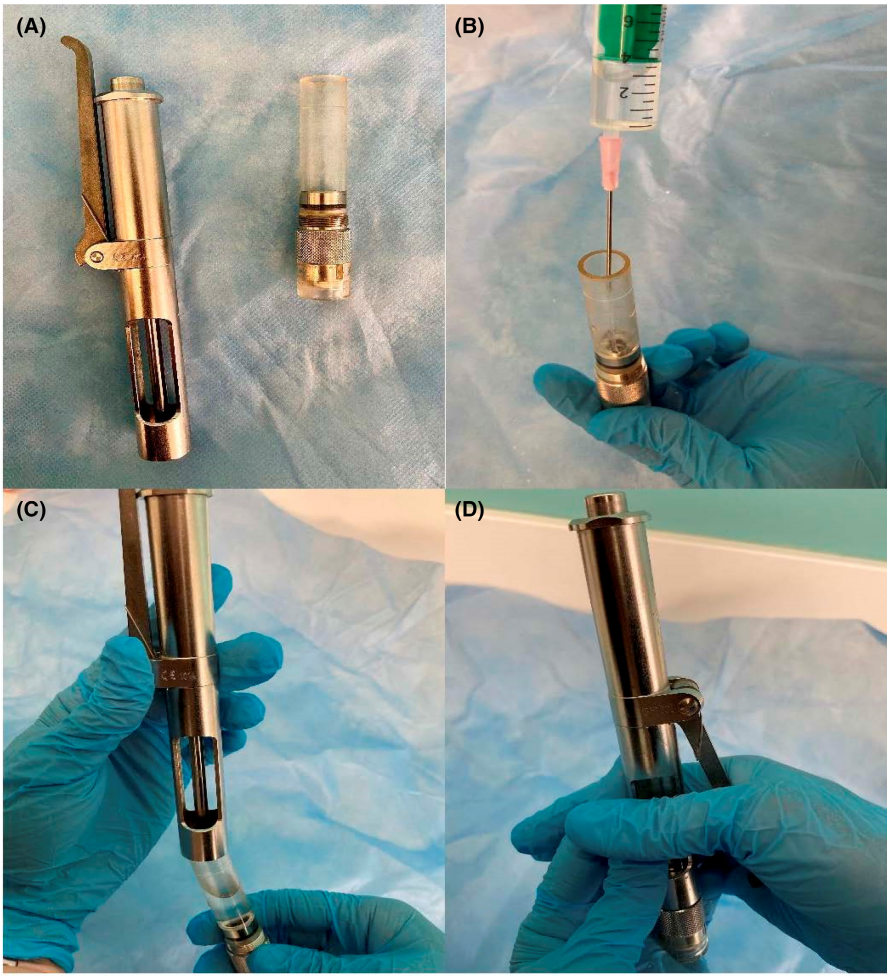

FIGURE 1 Preparation of the material necessary for infiltration with Dermojet®. (A) Dermojet; (B) Preloading the syringe with equal volumes of serum and mepivacaine, inserting the solution into the Dermojet® cylinder; (C) Screwing the barrel onto the syringe, and (D) Loading the syringe, lowering the lever.

present, 1 month–3 years. Any case histories that were incomplete at the time of assessment were excluded from the analysis. Sampling was consecutive by order of arrival at the clinic until the necessary sample size was obtained, subject to the criteria for inclusion.

The necessary sample size was calculated to be 102 subjects, for an estimated success rate of 80%, a confidence level of 95%, an accuracy of 8%, and 15% possible losses to follow up.

2.2 | Data collection

Relevant sociodemographic and clinical variables (age, gender, and previous pathologies) were collected for every participant.

In relation to the injury, the following data were noted: location (forefoot, midfoot, or heel), number of injuries, duration, and previous treatment.

The effectiveness of the infiltration treatment was assessed in terms of the number of evaluation visits made until the lesion healed (absence of clinical signs and symptoms on examination), the need for further intervention to achieve complete healing, and any recurrence observed at 12 months after treatment. The treatment was considered effective when the lesion disappeared after a single infiltration with Dermojet®.

The criteria considered to determine whether the wart had been eliminated were the reappearance of dermatoglyphics plus the absence of stippling and of pain. The patient's condition was followed up for 1 year to detect possible recurrences.

Finally, a random histopathological analysis was performed of 25% of the lesions detected, classifying the results as absence of necrosis, presence of partial necrosis, or presence of total necrosis.

2.3 | Statistical methods

All statistical analyses were conducted using SPSS v.22.0 (SPSS Inc.). Quantitative variables are reported as means and standard deviations. Categorical variables are reported as frequencies, cross-tabulations, and descriptive analysis.

The relationships between the different variables were considered using parametric or nonparametric tests (chi-squared or Cramer's *V*, the independent samples *t*-test or the Mann–Whitney *U*-test, and the Student *t*-test or the Kruskal–Wallis test). Spearman's rho test was used to study the correlations of the qualitative variables. A multivariate linear regression model was applied to evaluate the variables associated with treatment efficacy. A $p < 0.05$ was considered statistically significant and the confidence interval applied was 95%.

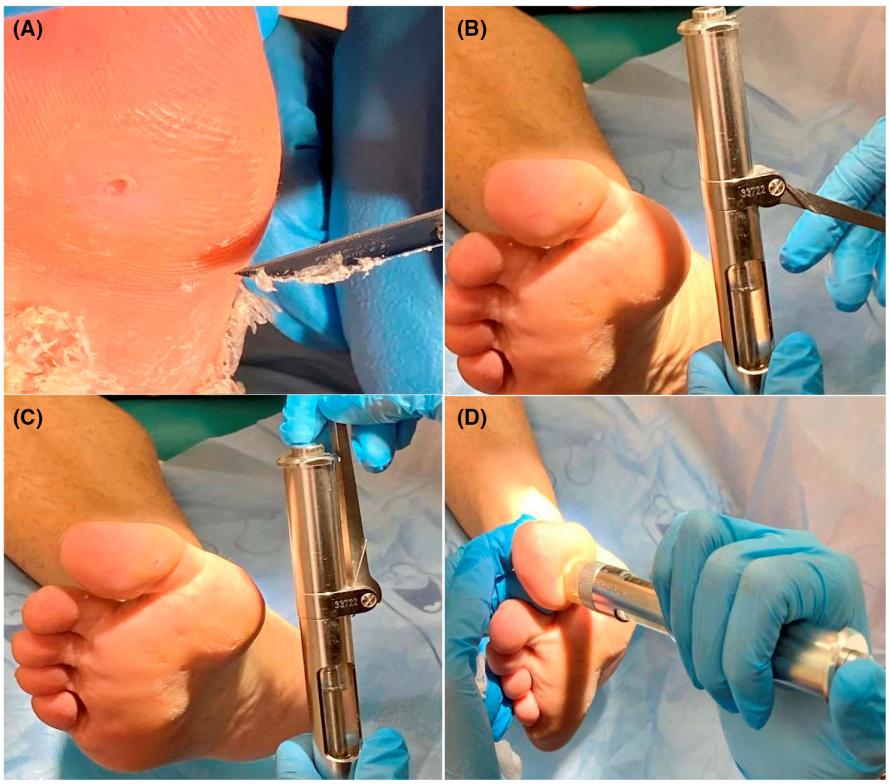

FIGURE 2 Infiltration technique with the Dermojet. (A) Debriding the lesion with a scalpel; (B, C) Loading the Dermojet, activating the lever; and (D) Performing the infiltration, using the thumb to press the trigger that expels the liquid.

3 | RESULTS

Treatment results were analyzed for 102 patients and a total of 233 verrucas. None of the patients were excluded due to incomplete information in their clinical history. The majority (61.8%, $n = 63$) were male. The patients' mean age was 26.6 ± 14.10 (7–64) years. Nine (8.8%) had a previous history of pathologies such as diabetes, immunosuppression, bacterial infection, or depression.

In 8.8% of the patients, the lesion was bilateral, and in 91.2%, it was unilateral. By location, 26.5% ($n = 27$) of lesions were on the heel, 6.8% ($n = 7$) on the midfoot and 66.6% ($n = 68$) on the forefoot (plantar metatarsal area, subdigital area, and toes). The mean period of evolution of the verruca was 6.8 ± 7.5 months (minimum 1 month, maximum 36 months). Eighty-three patients (81.4%) had not received previous treatment for this condition. Nineteen patients (18.6%) required complementary treatment; of these, 11 (10.8%) were treated with salicylic acid, five (4.9%) with cryotherapy, and three (2.9%) with monochloroacetic acid. In no case, complete resolution was obtained, and so infiltration was applied.

Regarding treatment efficacy, 78.4% of the patients ($n = 80$) achieved complete elimination of the lesions (restoration of dermatoglyphics, plus absence of stippling and pain) by the second evaluation and after a single infiltration. Only 21.6% ($n = 22$) required adjuvant treatment with 16.7% salicylic and lactic acid, applied once daily. Nine patients (8.8%) presented a recurrence in the evaluation performed at 1 year after the treatment.

The bivariate analysis revealed a significant inverse relationship between treatment efficacy and a history of previous disease ($p < 0.001$). In 66.7% of patients with such a history, the wart was not eliminated with a single application and required adjuvant treatment. A significant relationship was also observed between treatment efficacy and the period of evolution of the lesion ($p < 0.001$; 95% CI [0.78–7.91]). Thus, when the lesion was resolved with a single infiltration, the mean duration of its evolution was 5.86 ± 5.67 months, compared to the 10.21 ± 10.60 months for the cases in which a single infiltration was ineffective. There were no differences in treatment efficacy according to gender ($p = 0.77$), previous treatment ($p = 0.073$), or the patient's age ($p = 0.713$).

Multivariate linear regression analysis, performed to determine which factors were related to treatment efficacy (Table 1), revealed an association with the number of evaluation sessions ($p < 0.001$) and with previous illnesses ($p = 0.014$). In the latter case, patients who had suffered a prior illness were 11.16 times less likely to achieve a successful treatment. The analysis obtained a Nagelkerke's R^2 value of 0.59.

In the histopathological analysis, a sample was randomly taken from 26 patients. However, in four cases, it was not possible to obtain M2 samples, due to staining problems or because there was insufficient skin for the sample.

Histological microscopy showed that the processed tissues contained layers of preserved (vitalized) squamous cells (Figure 1). Some images showed ghost cells combined with active ones, either polynucleated or mononucleated, with flattened nuclei embedded in the keratin: parakeratin layers (Figure 3A). This finding reflects a process of progressive cell devitalization due to post-infiltration necrosis. Dilution of the nuclei (karyolysis) was also apparent, with empty spaces where there had previously been a cell presence (Figure 3B).

Variables	B	p Value	Exp(B)	95% CI for Exp(B)	
				Lower	Upper
Age	−0.049	0.098	0.952	0.898	1.009
Duration of evolution (months)	−0.078	0.086	0.925	0.845	1.011
Evaluation sessions (*n*)	−2.147	<0.001	0.117	0.038	0.358
Previous treatment	−0.715	0.465	0.489	0.072	3.332
Previous illness	2.413	0.014	11.164	1.624	76.730
Constant	9.456	<0.001	12786.272		

TABLE 1 Multivariate linear regression analysis. Association between the effectiveness of treatment with equal parts of 0.9% saline infiltration and 2% mepivacaine, injected by Dermojet, and the patient's age, duration of evolution of the lesion, number of evaluation sessions, previous illnesses, and previous treatments.

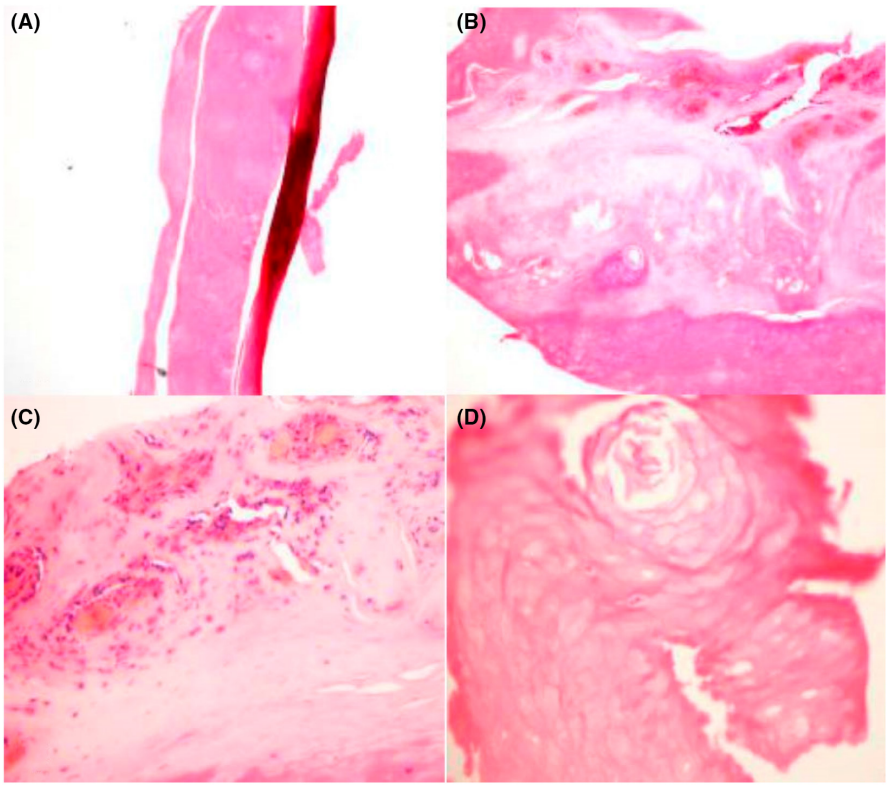

FIGURE 3 Microscopy images of tissue samples. (A) Microscopy image of M1 sample, P25 Hematoxylin–eosin × 10. Presence of abundant necrotic tissue with no vitalized cells in this fragment; (B) Microscopy image of M1 sample, P25. Hematoxylin—eosin × 40. Presence of visible globus corneum, parakeratosis, and inflammatory exudate; (C) Microscopy image of M1 sample, P25. Hematoxylin–eosin × 200. Detailed image of the presence of vitalized cells and parakeratosis. Presence of necrotic tissue with ghost cells; (D) Microscopy image of M2 sample, P2. Hematoxylin–eosin × 400. Absence of vitalized cells, globus corneum, and necrotic tissue.

TABLE 2 Type of necrosis observed in the histopathological analysis, patient-related characteristics, and characteristics of the lesion.

Variables		Partial necrosis M1			Partial necrosis M2			Complete necrosis M2		
		Yes (%)	No (%)	Sig	Yes (%)	No (%)	Sig.	Yes (%)	No (%)	Sig.
Sex	Male	8 (66.7)	4 (33.3)	0.89	4 (33.3)	8 (66.7)	0.79	6 (50)	6 (50)	1.00
	Female	9 (64.3)	5 (35.7)		4 (28.6)	10 (71.4)		7 (50)	7 (50)	
Age (years)	7–12	0 (0)	3 (100)	0.037	3 (100)	0 (0)	0.046	0 (0)	3 (100)	0.087
	13–23	10 (90.9)	1 (9.1)		2 (18.2)	9 (81.8)		7 (63.6	4 (36.5)	
	24–30	4 (80)	1 (20)		0 (0)	5 (100)		4 (80)	1 (20)	
	31–40	1 (50)	1 (50)		1 (50)	1 (50)		0 (0)	2 (100)	
	41–50	2 (50)	2 (50)		2 (50)	2 (50)		1 (25)	3 (75)	
	>51	0 (0)	1 (100)		0 (0)	1 (100)		1 (100)	0 (0)	
Previous treatment	Yes	6 (60)	4 (40)	0.64	4 (40)	6 (60)	0.420	4 (40)	6 (60)	0.420
	No	11 (68.8)	5 (31.3)		4 (25)	12 (75)		9 (56.3)	7 (43.8)	
Duration of the lesion (months)	<3	2 (50)	2 (50)	0.31	1 (25)	3 (75)	0.026	3 (75)	1 (25)	0.314
	4–6	12 (75)	4 (25)		2 (12.5)	14 (87.5)		9 (56.3)	7 (43.8)	
	7–10	2 (100)	0 (0)		2 (100)	0 (0)		0 (0)	2 (100)	
	>12	1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)		1 (33.3)	2 (66.7)	

The M1 samples also contained inflammatory exudate with polynucleated or mononucleated cells with morphologically normal nuclei, which in the microscopic image were more strongly stained, while the keratin areas were homogeneous and presented pyknotic nuclei (Figure 3C). In addition, there were remains of stratified squamous epithelia. In most cases, the sample contained both vitalized cells and necrotic tissue.

In the M2 samples, obtained 2 weeks after infiltration, there was a greater presence of necrotic tissue and a total absence of vitalized cells, indicating that karyolysis had advanced to total necrosis of the tissue, although in some cases, the necrosis was not total and parakeratosis was also observed (Figure 3D).

Seventeen of the M1 samples presented partial necrosis, while nine had no type of necrosis. Among the M2 samples, 13 presented complete necrosis.

Among the verrucas treated, 82.35% presented partial necrosis in the M1 sample and 76.92% had complete necrosis in the M2 sample.

Analysis of the relation between type of necrosis (according to histopathological observation), the characteristics of the lesion, and patient-related variables revealed a significant association between the patient's age and the type of partial necrosis presented, for both sampling periods ($p = 0.037$ for M1; $p = 0.046$ for M2), see Table 2.

4 | DISCUSSION

The first-line treatments for plantar warts are salicylic acid and cryotherapy, with cure rates of 45.61% and 13.6%, respectively.[17] These methods are easy to apply and have minimal adverse effects.[18] However, they may require more treatment time and a greater number of visits, possibly reducing adherence to treatment and increasing the risk of abandonment.

Among invasive treatment options, multi-puncture or infiltration may be performed with bleomycin,[16,19–21] hypersaline solution, or 0.9% saline solution[22] using Dermojet®, a needleless system consisting of a metal syringe fitted with a piston, a spring and a lever, which allows liquid to be introduced into the skin at a pressure of 100 kg/cm, provoking cell damage.

Bleomycin is the generic name of a group of cytotoxic sulfur-glycopeptide antibiotics produced by *Streptomyces verticillus*,[21] which inhibits DNA synthesis and heightens the formation of microthromboses.[23] Although the mean cure rate with this treatment is 83.37%,[24] and it is highly effective in the treatment of resistant plantar warts,[19,25] it can have adverse effects on the patient.[26] In view of these considerations, this study was conducted to determine the effectiveness of an alternative method, namely infiltrations of saline solution applied using Dermojet®.

In studies of infiltrative treatments using a control group, saline (injected in various ways) has been used as a placebo, obtaining better results than the intervention group treated with interferon or photodynamic therapy.[27,28] However, these findings should be interpreted with caution since the relevant characteristics of the patients are not fully described. Nevertheless, this treatment is known to be safe, with no adverse sequels such as scarring.

In our own study, 78.4% of the patients obtained complete healing after a single infiltration of equal parts of 0.9% saline solution and 2% mepivacaine, in a mean posttreatment time of 4 weeks. This effectiveness is similar to or even better than that reported for the two most commonly employed treatments in dermatology consultations.

A related study by Pérez Alfonzo[22] used saline infiltration, achieving an effectiveness of 73%. However, given the few studies that exist in relation to this type of treatment, it is unclear whether this effectiveness is due to the composition of the product or to the pressure exerted by the syringe, which may also provoke cell necrosis and destruction of the virus.

In our case, the treatment with saline infiltration using Dermojet® required four visits to the podiatry clinic (initial reception, application of the treatment, and two progress reviews). The lesion was successfully resolved in 87.3% of cases, with a single application and within an average period of 4 weeks, which surpasses the results obtained by common therapeutic options such as salicylic acid and cryotherapy, for which the average healing time is 6–12 weeks.[13]

Multivariate analysis showed that the presence of chronic disease such as diabetes or immunosuppression, or a history of acute disease such as flu, is an important risk factor, reducing treatment efficacy. Accordingly, many current therapies seek to enhance the ability of the host's immune system to combat papillomavirus.[29]

The participants in this study presented lesions with an evolution ranging from 1 to 36 months. A total of 18.6% had previously been treated (at home or in a podiatry/dermatology clinic). However, there were no significant differences between the two groups regarding the effectiveness of this therapy, although the lesions with a shorter period of evolution tended to present greater treatment efficacy.

In line with a previous study,[30] we observed no differences in treatment results according to the patient's gender or age, or the location of the lesion. Unlike Amer et al.,[31] we were unable to assess the type of wart (myrmecia or mosaic) or its size, because these data were not given in the medical records reviewed. Amer et al. employed different doses of bleomycin according to the size and type of the lesion. Moreover, when the patient had more than six warts, they were not all infiltrated at the same time, perhaps considering the possible adverse effects of bleomycin.

The patients' medical records were reviewed for 12 months posttreatment, and recurrences were detected in only 8.8% of cases, which leads us to consider the treatment highly satisfactory.

There were no reports of post-infiltration pain, infections, complications in the infiltrated area, or scarring.

The histopathological microscopy studies, conducted after the infiltration, revealed tissue necrosis, which was more strongly present in the M2 than in the M1 samples. From this, we conclude that posttreatment necrosis tends to increase with time, although further study with a larger sample is needed to confirm this conjecture.

Histologically, it has been observed that infiltration with Dermojet eliminates the virus, provoking necrosis, probably due to

the intracellular pressure caused by the infiltration, but the inflammatory process caused by the patient's immune response to the infiltration may also contribute to the effectiveness of the treatment.

4.1 | Limitations

One of the main limitations of our study is the lack of a control group, a decision taken due to the complexity and greater cost involved in this type of clinical trial. In view of the results obtained, it would be desirable to compare them "head to head" with those of a conventional treatment approach, and our research group hopes to do so in the near future. Nevertheless, we did compare the treatment efficacy obtained in our study with published results for conventional treatments. Furthermore, ours is the first study of this new and promising technique to be carried out in Spain with a large sample of patients. In addition, a 1-year follow-up was conducted to monitor the patients' condition and detect recurrences, a prolongation that corroborates our conclusions on treatment efficacy.

5 | CONCLUSIONS

In 78.4% of the patients considered, the plantar warts treated disappeared completely, after a single infiltration. Only 21.6% required adjuvant treatment with 16.7% salicylic acid and lactic acid. On the other hand, 8.8% experienced a recurrence within 12 months of treatment. The variables associated with treatment efficacy were the number of follow-up visits and the existence of associated diseases.

AUTHOR CONTRIBUTIONS

ECL, AOR performed the research; AOR designed the research study; SGL, AGS, and SZG collected the data; ECL analyzed the data; ECL and AOR wrote the article. All authors approved the final document.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by the Ethics Committee from University Miguel Hernández (DPS.AOR.01.16).

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