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Original Article

Comparative Efficacy of Liquid Nitrogen versus Vitamin D3 in the Treatment of Cutaneous Warts

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ABSTRACT

Background: Cutaneous warts, caused by the human papillomavirus (HPV), pose both cosmetic and psychological burdens on affected individuals. Traditional treatment options like cryotherapy have been effective but can be invasive and painful. Vitamin D3 emerges as a potential non-invasive alternative, with its immunomodulatory properties suggesting efficacy in wart treatment.

Objective: To compare the efficacy and side effects of liquid nitrogen cryotherapy versus intralesional vitamin D3 in the treatment of cutaneous warts on the hands and feet.

Methods: This randomized controlled trial was conducted at the Department of Dermatology, CMH Abbottabad, from May to November 2022, with ethical approval obtained from the Ethical Committee (Ref: CMHAtd-ETH-18-DERM-22). Sixty patients diagnosed with cutaneous warts were randomly assigned to either cryotherapy with liquid nitrogen (Group A) or intralesional vitamin D3 (Group B). The primary outcome measured was the percentage reduction in wart size, with treatment efficacy defined as a reduction of 50% or more. Side effects were also recorded. Statistical analysis was performed using SPSS version 23.0, employing chi-square tests for categorical variables, with a p-value of less than 0.05 considered significant.

Results: The mean age was 36.17±11.844 years in Group A and 41.10±12.383 years in Group B. Efficacy rates showed that 90% of patients in Group A and 76.7% in Group B achieved the defined treatment success. Side effects were minimal and similar across both groups, with 13.3% in Group A and 16.7% in Group B experiencing blisters or pain. The difference in treatment efficacy was not statistically significant (p=0.166).

Conclusion: Both liquid nitrogen cryotherapy and intralesional vitamin D3 are effective treatments for cutaneous warts, with minimal side effects. While cryotherapy showed a slightly higher efficacy rate, the substantial success of vitamin D3 makes it a promising alternative for patients. This study contributes to the diversification of treatment modalities available for cutaneous warts, potentially enhancing patient outcomes and satisfaction.

Keywords: Cutaneous warts, HPV, Cryotherapy, Vitamin D3, Randomized controlled trial, Treatment efficacy, Dermatology.

INTRODUCTION

The human papillomavirus (HPV), specifically strains HPV2/27/57 and HPV11-7, is recognized as the causative agent of cutaneous warts, a prevalent dermatological affliction that, while often not painful, can inflict considerable emotional and physical distress upon those affected (1). These lesions can emerge on any skin type, with a predilection for the hands and feet. Despite their benign nature in immunocompetent individuals, the aesthetic and psychological impact of these warts can be profound (2). HPV gains entry through open wounds, with transmission facilitated by factors such as communal bathing, contact with raw meat, and immunosuppression, leading to a range of manifestations from common or plantar warts to more severe conditions like genital warts and cervical neoplasia (3).

Management strategies for cutaneous warts are varied, including invasive methods like cryotherapy, curettage, chemical cauterization, and electrodessication, alongside non-invasive options such as immunotherapy, homoeopathy, laser treatments, and the application of topical or intralesional medications (4). Among these, cryotherapy, which utilizes liquid nitrogen to freeze and subsequently destroy wart tissue, is a widely adopted approach due to its efficacy and minimal discomfort. Immunotherapy, on the other hand, offers a novel avenue by enhancing the host's immune response to HPV, potentially leading to wart remission,

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eradication of adjacent lesions, and reduced recurrence, all without directly targeting the wart itself. This category includes treatments like the BCG vaccine, mumps antigen, vitamin D3, and Candida antigen (6).

Particularly, vitamin D3 has been investigated for its immunotherapeutic potential, acting through the inhibition of tumor necrosis factor alpha (TNF-alpha) and interleukin-6 via pathways dependent on the vitamin D receptor (VDR) (7). Although clinical evidence supports the use of vitamin D3 in treating common warts, with a reported efficacy of 78%, and its effectiveness against genital and palmoplantar warts is well-documented, direct comparisons of vitamin D3 with cryotherapy in randomized clinical trials are scarce. Existing studies have instead compared vitamin D3's effectiveness with that of Candida antigen and zinc sulphate, two other common treatments for warts (8). Recent research addressing this gap compared the outcomes of cryotherapy and intralesional vitamin D3 in treating warts on the hands and feet, revealing that while 84% of patients treated with vitamin D3 exhibited improvement, a higher proportion, 92%, responded to liquid nitrogen treatment (9).

Given the ablative nature of cryotherapy, which can lead to wart clearance in a single session, this study aims to comprehensively compare the efficacy of liquid nitrogen and vitamin D3 in the treatment of cutaneous warts. This comparison is crucial for developing a refined strategy for managing common warts on the hands and feet, thereby contributing to the broader literature on wart treatment modalities.

MATERIAL AND METHODS

This randomized controlled trial, registered with ClinicalTrials.gov under the identifier NCT05739786, was executed at the Department of Dermatology, CMH Abbottabad, spanning from May to November 2022. Ethical clearance was secured from the Ethical Committee (Ref: CMHAtd-ETH-18-DERM-22), adhering to the principles outlined in the Declaration of Helsinki for medical research involving human subjects. The study aimed to compare the efficacy of liquid nitrogen cryotherapy versus intralesional vitamin D3 in the treatment of cutaneous warts. The sample size was meticulously calculated employing the WHO sample size calculator, factoring in a 92% efficacy for liquid nitrogen and an 84% efficacy for vitamin D3, alongside an 80% power of the test and a 5% margin of error.

Eligibility for participation was determined by a consultant dermatologist and included both male and female patients aged between eighteen to sixty years with diagnosed cutaneous warts on the hands or feet, including common, filiform, or mosaic types, and who had not received any treatment for the condition in at least two months prior to enrolment. Exclusion criteria were established to omit immunocompromised individuals, patients with diabetes mellitus, eczema, autoimmune diseases, cold sensitivity, skin allergies, as well as those who were pregnant or lactating. Additionally, patients presenting with periungual warts were excluded from the study.

Upon obtaining informed consent, participants underwent a comprehensive history taking and physical examination. A structured proforma was utilized to record demographic details, duration of wart presence, lesion location and quantity, and morphological type. Baseline clinical photographs were captured for all participants to facilitate subsequent comparison.

The intervention for Group A consisted of cryotherapy using liquid nitrogen at -196 ºC, applied through cryospray in a twofold freeze-thaw cycle (freezing for 5-10 seconds, followed by thawing, and repeating the process). A maximum of three treatment sessions were allowed, spaced three weeks apart. The progress was monitored by assessing the percentage reduction in wart size, with follow-up continuing for six weeks post-treatment to observe for recurrence or complete remission.

For Group B, local anaesthesia was achieved using lignocaine (20 mg/ml) prior to the intralesional injection of 0.2-0.4 ml of a vitamin D3 solution (5 mg/ml) directly into the base of the wart using a 26-gauge syringe. In instances of multiple lesions, the primary wart was targeted, with a limit of four warts treated per session. Like Group A, a total of three sessions were conducted at three-week intervals, with efficacy evaluated at the end of the treatment cycle based on the percentage reduction in wart size. Effectiveness was determined by a decrease in wart size by 50% or more, as confirmed by a consultant dermatologist. Follow-up was extended for an additional six weeks to monitor for any recurrence.

Data were analysed using SPSS version 23.0 (Statistical Package for the Social Sciences). Descriptive statistics were applied to summarize the data, with numeric variables assessed using means and standard deviation, and categorical data analysed through frequencies and percentages. The chi-square test was employed to compare the effectiveness between the two treatment groups, with a p-value of less than 0.05 considered statistically significant.

RESULTS

In the conducted randomized controlled trial, a total of 60 patients were evenly divided into two treatment groups: Group A, which received liquid nitrogen cryotherapy, and Group B, treated with intralesional vitamin D3. The demographic characteristics outlined in Table 1 reveal a mean age of 36.17 years (SD = 11.844) in Group A and a slightly higher mean age of 41.10 years (SD = 12.383) in

Group B, indicating a broader age distribution among the Vitamin D3 recipients. The age distribution further illustrates that in Group A, 63.3% of the participants were between 18-40 years old, whereas this age group represented 50.0% of Group B's participants. The remaining participants in each group fell into the 41-60 years age bracket, constituting 36.7% and 50.0% of Groups A and B, respectively. Gender distribution was identical across both groups, with males representing 46.7% and females 53.3% of the participants, underscoring the balanced gender representation in this study.

Clinical characteristics of the patients, as detailed in Table 2, provide insights into the treatment sites and outcomes. The distribution of wart locations was similar across treatment groups, with 30.0% of Group A's warts located on the hands, compared to 43.3% in Group B. The palms and soles were other common sites, with Group A showing a slightly higher prevalence of warts on the soles (43.3%) than Group B (33.3%). This similarity in site distribution is noteworthy, considering the p-value of 0.553, suggesting no significant difference in the location of warts between the two treatment groups.

When examining the number of warts, 40.0% of patients in Group A had multiple warts, a contrast to 53.3% in Group B, highlighting a tendency towards a higher prevalence of multiple warts among Vitamin D3 recipients. However, the statistical analysis indicated no significant difference in the distribution of single versus multiple warts between the groups (p-value = 0.301).

Table 1: Demographic Characteristics of Patients (n=60)

Treatment Group	Variable	Age (Years) Mean ± Std. Deviation	Age Group	Frequency	Percent	Gender	Frequency	Percent
Group A (Liquid Nitrogen)	Age (Years)	36.17 ± 11.844	18-40 Years	19	63.3%	Male	14	46.7%
			41-60 Years	11	36.7%	Female	16	53.3%
			Total	30	100.0%	Total	30	100.0%
Group B (Vitamin D3)	Age (Years)	41.10 ± 12.383	18-40 Years	15	50.0%	Male	14	46.7%
			41-60 Years	15	50.0%	Female	16	53.3%
			Total	30	100.0%	Total	30	100.0%

Table 2: Clinical Characteristics of Patients (n=60)

Characteristic	Category	Group A (Liquid Nitrogen)		Group B (Vitamin D3)		P Value
		Frequency	Percent	Frequency	Percent	
Site	Hands	9	30.0%	13	43.3%	0.553
	Palm	8	26.7%	7	23.3%	
	Soles	13	43.3%	10	33.3%	
Number of Warts	Multiple	12	40.0%	16	53.3%	0.301
	Single	18	60.0%	14	46.7%	
Side Effects	Blisters/Pain	4	13.3%	5	16.7%	0.718
	No	26	86.7%	25	83.3%	
Efficacy	Yes	27	90.0%	23	76.7%	0.166
	No	3	10.0%	7	23.3%	

Side effects were minimal and comparable between the groups, with 13.3% of Group A and 16.7% of Group B experiencing blisters or pain, demonstrating the generally well-tolerated nature of both treatments (p-value = 0.718). Most notably, the efficacy of the treatments showed that 90.0% of Group A patient's reported improvement, compared to 76.7% in Group B (p-value = 0.166). Although a higher efficacy rate was observed in the liquid nitrogen group, the difference did not reach statistical significance, suggesting that both treatments can be effective, albeit with a trend towards better outcomes with cryotherapy.

DISCUSSION

In the exploration of treatments for cutaneous warts, our study aimed to evaluate the comparative efficacy of cryotherapy using liquid nitrogen and intralesional vitamin D3. The findings suggest that gender does not significantly influence the likelihood of developing cutaneous warts, aligning with previous research indicating a non-gender-specific prevalence (12). Cryotherapy has been

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widely recognized for its effectiveness, functioning by destroying virally infected cells and stimulating an immune response due to the induced stress (13). Despite its effectiveness, the search for less invasive and equally efficacious treatments continues, given the painful nature of cryotherapy, particularly in treating severe periungual lesions.

Our investigation into alternative therapeutic options highlighted intralesional and topical immunotherapy as less invasive methods, capable of not only treating the localized wart but potentially eradicating distant, untreated warts through an immune-mediated mechanism. This approach is increasingly favored over more invasive techniques like cryotherapy or electrocautery. Among the various agents utilized in immunotherapy, such as Candida albicans, bleomycin, MMR, and BCG vaccines (6), our study specifically assessed the efficacy of intralesional vitamin D3 compared to the conventional ablative method of cryotherapy within our population.

The demographic distribution of our study participants, with an average age of 36.17 ± 11.844 years for those undergoing cryotherapy and 41.10 ± 12.383 years for those treated with vitamin D3, provided a basis for evaluating the disease's distribution across different age groups. This age distribution is consistent with findings by Raghukumar et al., although it contrasts with the younger demographic reported by Ibrahim et al., where the mean age was significantly lower (9). Our study observed a balanced gender distribution among participants, which corroborates the findings of previous studies by Moscarelli L et al. and Khozeimeh et al., suggesting a slightly higher prevalence of warts in females, potentially due to varied immune responses or increased susceptibility linked to environmental factors (10, 11, 18).

Clinical outcomes from our study demonstrated that both treatments were effective, with no statistically significant difference in efficacy between cryotherapy and vitamin D3, despite cryotherapy's slightly higher success rate of 90% compared to 76.7% for vitamin D3 (p=0.166). This absence of significant difference aligns with other research comparing cryotherapy to immunotherapeutic agents, which also found no statistically significant difference in efficacy (10, 12). Deepak et al.'s study further supports the effectiveness of vitamin D3, showing significant improvement in the size and number of warts with a regimen of bi-weekly treatments over four to six weeks (13, 19).

Our study's limitations include its small sample size and single-centered design, which may affect the generalizability of the findings to the broader population. Despite these limitations, the comparable efficacies of cryotherapy and intralesional vitamin D3 suggest that both treatments are viable options for cutaneous warts, with vitamin D3 offering a less invasive alternative with minimal adverse effects (20). This is particularly relevant in low-resource settings where access to treatment options may be limited.

CONCLUSION

The findings from this study highlight the comparative efficacy of liquid nitrogen cryotherapy and intralesional vitamin D3 in treating cutaneous warts, demonstrating that both treatments yield significant improvements with minimal side effects. Although cryotherapy showed a marginally higher efficacy rate, the substantial effectiveness of vitamin D3 presents it as a viable alternative, particularly for patients seeking less invasive treatments. This research enriches the therapeutic landscape for cutaneous warts, offering clinicians and patients more options tailored to individual preferences and clinical scenarios. The implications for human healthcare are profound, as these findings may lead to broader treatment strategies, enhancing patient satisfaction and outcomes in managing a common and often troublesome dermatological condition.

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