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Assessment Of Efficacy Of Intralesional Vitamin D3 Injection In The Treatment Of Recalcitrant Warts

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Abstract

Objective: To assess the efficacy of intralesional vitamin D3 injection as a treatment modality for recalcitrant warts in a tertiary care setting in Pakistan.

Methods: This quasi-experimental study was carried out in the Department of Dermatology, CMH Lahore, over six months from March 16 to September 16, 2021. After obtaining approval from the hospital's ethical and research committee, 139 patients aged 18–60 years, presenting with recalcitrant warts fulfilling the inclusion criteria, were recruited. Intralesional vitamin D3 (600,000 IU/mL), 0.5ml was injected into the base of up to four warts per session, with injections repeated every two weeks for a maximum of four sessions. Efficacy was defined as the complete resolution of all warts. Adverse events were monitored, and data were stratified by age, gender, and wart characteristics.

Results: The study population had a mean age of 30.3 ± 6.8 years, with a male predominance (57.6%). The average wart duration was 6.5 ± 1.5 months. Complete resolution was achieved in 89.9% of patients. While no statistically significant differences in efficacy were observed across stratified subgroups ($p > 0.05$), patients with shorter wart durations (3–6 months) demonstrated the highest success rate (98.7%), whereas those with warts lasting longer than 6 months showed the lowest response (79.0%). Adverse effects were minimal and resolved on their own, with 15% of patients experiencing injection site pain and 10% reporting temporary erythema.

Conclusion: Intralesional vitamin D3 injections have demonstrated significant efficacy and a favorable safety profile, positioning it as a promising and novel treatment for recalcitrant warts. However, to strengthen the evidence and better understand its long-term benefits, additional randomized controlled trials are essential.

Keywords: Efficacy, Human papilloma virus, Immunotherapy, Intralesional injection, Vitamin D3, Warts

Introduction

Cutaneous warts are among the most prevalent dermatological conditions, affecting approximately 7–12% of the population globally.[1] They are caused by infection with the human papilloma virus (HPV), a virus that infects the epidermis and causes hyper-proliferation of skin cells. HPV has more than 100 distinct types, each associated with various forms of warts. These include common warts (verruca vulgaris), flat warts (verruca plana), plantar warts (verruca plantaris), and genital warts. While warts can develop anywhere on the body, they are most frequently observed on the hands, feet, and genital regions.[2] They are generally considered benign, although they can be cosmetically undesirable and may cause significant physical discomfort when located on the weight-bearing areas or near sensitive structures like the eyes and nails.

In most cases, warts resolve spontaneously within a couple of years, particularly in children.[3] However, a subset of individuals experiences persistent and refractory warts, known as recalcitrant warts. These are defined as the warts which don't respond to the standard treatments. While these conventional interventions may prove effective for many patients, recalcitrant warts often pose significant therapeutic challenge, with high recurrence rates and a substantial impact on quality of life, particularly for those with widespread or stubborn lesions.[4]

Contributions:
S.M, H.M, T.N, A.S - Conception of study
S.M, H.M, T.N, A.S - Experimentation/Study Conduction
S.M, H.M, T.N, A.S - Analysis/Interpretation/Discussion
S.M, H.M, T.N, A.S - Manuscript Writing
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All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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There are several treatment options available for warts which include topical therapies such as salicylic acid, retinoids; invasive therapies like cryotherapy, electrosurgery, and ablative laser treatments; immune-based therapies using medicines, such as intralesional bleomycin and interferons, or by autoinoculation of warts. However, none of these options have proven universally effective and adequate management of recalcitrant warts has always been a significant challenge in the dermatology clinics.[5] Furthermore, a number of these treatments often come with the risk of side effects such as pain, scarring, or residual tissue damage.[6] Considering such limitations, there has been an increasing interest in exploring novel therapies, which are less invasive, easily available and have minimal side effects, especially those that harness immune-modulating properties.[7] Among these options, intralesional immunotherapy, which involves injecting immunomodulatory agents to stimulate the body's immune response against the HPV virus, has now emerged as a promising therapeutic intervention.[8,9]

Vitamin D3 is traditionally recognised for its role in calcium metabolism and bone health, but it has recently gathered interest for its potential immunomodulatory benefits by enhancing the immune response against viral infections.[10] Hence, it is hypothesised that intralesional vitamin D3 injections may offer a promising, effective and safe treatment option for patients with recalcitrant warts.

This study aims to assess the efficacy of intralesional vitamin D3 in the treatment of recalcitrant warts in a tertiary care setting in Pakistan. Considering the paucity of data from South Asia regarding the use of vitamin D3 for recalcitrant warts, this research work may provide valuable insights into its potential as an effective and safe treatment option, especially in the populations who are underrepresented in global studies.

Materials And Methods

This quasi experimental study was carried out in the Dermatology Department of CMH Lahore, a tertiary care hospital, from March 16 to September 16, 2021. The sample size was calculated based on a reference study by Raghukumar et al., which reported an efficacy rate of 90%.[11] A margin of error of 5% and a 95% confidence level were applied using the WHO sample size formula. Non-probability consecutive sampling was used.

A total of 139 patients aged 18–60 years, presenting with recalcitrant warts (1–3 cm in size, no more than four warts per patient) persisting for more than three months despite failure of at least two prior therapies, were included. Patients with genital warts, pregnancy, immunosuppressive conditions, or a history of hypersensitivity to vitamin D3 were excluded.

The participants received 0.5 mL intralesional vitamin D3 (600,000 IU/mL) injected at the base of up to four warts per session. Injections were administered every two weeks, for a maximum of four sessions or until complete resolution of all treated warts was observed. Efficacy was defined as the complete clinical resolution of all treated warts, evaluated two weeks after the final treatment. Adverse events were monitored throughout the study.

The study adhered to the principles outlined in the Declaration of Helsinki, and was approved by the Institutional Review Board (Reference: IRB-2021-09). Written informed consent was obtained from all the participants. Data were analysed using SPSS v26. Continuous variables were expressed as means ± SD, whereas the categorical variables were expressed as frequencies and percentages. Chi-square and t-tests were used for subgroup analyses, where $p < 0.05$ is considered significant.

Results

A total of 139 patients were included in our study, with a mean age of 30.3 ± 6.8 years, and a male predominance (Figure 1). The ages of the participants ranged from 18 to 60 years, with a mean age of 30.35 ± 6.85 years. The average duration of warts was 6.50 ± 1.53 months, where, the mean number of warts was 2.45 ± 0.86, and the mean size of the lesions was 2.24 ± 0.61 cm (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Participants (n=139)

Parameter	Mean ± SD / %
Age (years)	30.345 ± 6.85
Duration of Warts (months)	6.503 ± 1.53
Number of Warts	2.453 ± 0.86
Size of Warts (cm)	2.244 ± 0.61
Efficacy	89.9% efficacy

The overall efficacy of the treatment was 89.9%, indicating a high efficacy of intralesional Vitamin D3 in management of recalcitrant warts. Stratification of efficacy based on age showed slightly better outcomes in patients aged 41-60 years compared to those aged 18-40 years. Gender-based stratification revealed that females responded a little more favorably than males (Figure 1). However, after applying the statistical tests, the difference remained insignificant between the two stratification groups (p values 0.589 for age, 0.268 for gender).

When analysing the duration of warts, it was observed that patients with warts of 3-6 months' duration had the higher efficacy (98.7%), while those with warts persisting for more than 6 months had the lower response rate (79.0%). Upon scientific analysis, the results were significant with a p value of < 0.001. This trend highlights the importance of early intervention in achieving optimal outcomes.

The number and size of warts have a minor influence, if any, on efficacy. Patients with 1-2 warts showed a slightly better response than those with 3-4 warts; while lesions measuring 1-2 cm had slightly better resolution than those larger than 2 cm. However, these differences were not statistically significant, with p-values for efficacy concerning the number of warts and wart size exceeding 0.05 (0.335 and 0.117, respectively). (Figure 2).

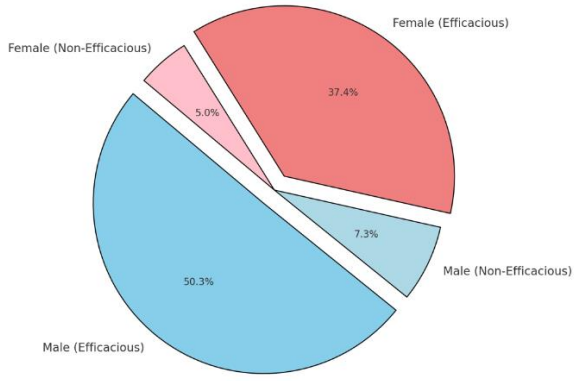

Figure 2: Efficacy of Intralesional Vitamin D3 Injection by Subgroup (n=139)

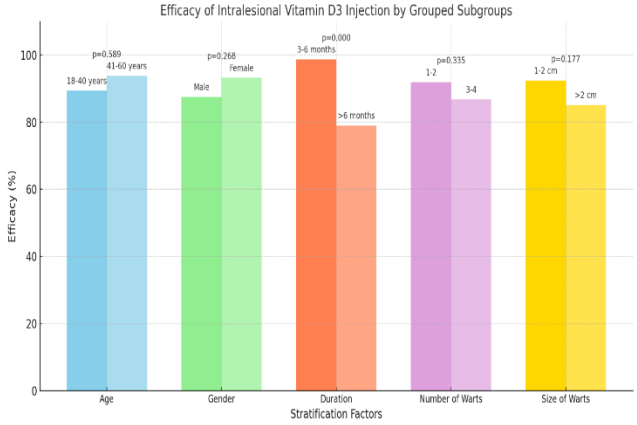

Figure 2: Efficacy of Intralesional Vitamin D3 Injection by Subgroup (n=139)

Discussion

Managing recalcitrant warts is particularly challenging due to their resistance to standard treatment methods and a high likelihood of recurrence. Since none of them is effective in all cases, the quest for novel and efficient therapeutic modalities remains a challenging pursuit. Immunotherapy, yet a novel approach, overcomes the limitations of traditional destructive therapies of warts by enhancing the body's immune response to eliminate the virus-infected tissue. Intralesional immunotherapy with various immunomodulatory agents has recently gained recognition as a promising therapeutic strategy for the difficult-to-treat warts.[11,12] Their effectiveness is attributed to their ability to modulate the immune system, which is crucial for clearing HPV infections. Intralesional vitamin D3 therapy, one such immunomodulatory agent, has demonstrated high success rates, in the research work by Raghukumar et al. and Al-Sabak et al. reporting 90% and 82% efficacy,[13,14] which is comparable with the results of our study (89%).

Exact mode of action of vitamin D3 and its derivatives in the treatment of warts is still unknown. One of the proposed mechanisms of warts clearance is due to their potential to regulate the proliferation and differentiation of epidermis.[15] It also acts by enhancing the immune response by facilitating the stimulation of antigen-presenting cells, which in turn recognise and respond to HPV. Additionally, it boosts the production of antimicrobial peptides by activation of toll-like receptor (TLR) of human macrophages leading to the up-regulation of the expression of Vitamin D receptor and Vitamin D-1-hydroxylase genes, resulting in induction of antimicrobial peptides. These antimicrobial peptides such as defensin B2 and cathelicidin directly target the HPV virions.[15,16] Furthermore, it shifts the immune response toward a Th1-type profile, leading to promotion of cytotoxic T-cell activity and generation of interferon, which is fundamental for clearing viral infections.[10,13] This immunomodulatory property of vitamin D3 aids to overcome HPV's immunoevasive mechanisms, and hence promotes wart resolution.

Several other immunomodulatory agents are also being trialed for the treatment of warts like Candida antigen, Bacille Calmette Guérin (BCG) vaccine and Measles-Mumps-Rubella (MMR) vaccine.[17,18] In comparison with the other agents, Vitamin D3 has several merits. For instance, the Candida antigen is effective in approximately 60-80% of cases but often requires multiple sessions and carries a risk of systemic reactions[17]. Similarly, the BCG vaccine, though freely available and effective, is difficult to administer due to refrigeration requirements[16]. On the other hand, vitamin D3 is easily available, cost-effective, easy to store at room temperature, and most importantly, has a favorable safety profile, which makes it suitable for low-resource settings.[17–19]

Our study found that factors like gender, age, and wart size did not significantly influence outcomes. However, shorter wart duration was associated with higher success rate, supporting the importance of early intervention. Prolonged wart duration may lead to

immune tolerance, reducing the immune system's ability to respond effectively.[20] Early treatment may prevent this tolerance and improve outcomes.

In our study, Intralesional vitamin D3 demonstrated an excellent safety profile, with minor side effects such as mild erythema and injection-site pain. No significant systemic reactions were observed, aligning with previous studies.[13–15] Compared to the invasive treatments like cryotherapy or electrosurgery, which carry risks of discomfort, scarring, and recurrence, vitamin D3 offers a safer and more patient-friendly option.[20]

However, limitations of our study include the absence of a control group and short follow-up periods, leaving long-term efficacy and recurrence rates uncertain. To validate these findings, future randomised controlled trials with larger sample sizes and extended follow-up periods are required. Furthermore, exploring the option of combination therapies, in the hope to have a synergistic effect between vitamin D3 and other conventional treatment modalities, like cryotherapy, electrosurgery, topical agents, etc, could further improve the chances of clearance of warts and minimize recurrence.[21,22]

To summarise, our study provides convincing evidence that intralesional vitamin D3 can be used as an effective and safe treatment for recalcitrant warts. Its ability to modulate the immune response against HPV, easy availability, combined with its ease of administration and an excellent safety profile, makes it a worthwhile addition to the therapeutic modalities available for managing this common and usually distressing condition.

Conclusions

Intralesional vitamin D3 is a novel, effective and safe treatment option for recalcitrant warts. Given its high efficacy, and a favourable safety profile observed in this study, intralesional vitamin D3 could become a reasonable alternative to the conventional wart treatments for recalcitrant warts, particularly in resource-limited settings where the access to more complex therapies is limited. However, further randomised controlled trials with long-term follow-up are needed to validate these findings, and to explore the optimal dosing and treatment protocols.

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