Comparative Study of Therapeutic Efficacy of Intralesional Vitamin D3 versus Intralesional Purified Protein Derivative in the Treatment of Refractory Viral Warts at a Tertiary Referral Centre in Northern Maharashtra

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Abstract: Introduction: Warts are benign epidermal proliferations of skin and mucosa caused by human papilloma virus. There are innumerable treatment modalities but they may result in partial clearance or recurrence. Destructive therapeutic modalities are limited by cost, pain, scarring. Some newer and effective treatments include intralesional immunotherapy. We undertook a study to evaluate the safety and efficacy of two such immunotherapies namely tuberculin purified protein derivative (PPD) versus intralesional vitamin D3 for the treatment of viral warts. Objective: This study aims to evaluate and compare efficacy of intralesional vitamin D3 and purified protein derivative (PPD) in treatment of warts. Materials and Methods: It is a prospective hospital based comparative study among 20 patients with warts. Patients were randomly and equally divided. Group A patients were given intralesional vitamin D3 (0.2ml of 15mg/ml into each wart) and Group B patients were given intralesional PPD (0.2ml of 5TU/ml into each wart). The injections were repeated every 2 weeks until complete clearance. Decrease in size and number of lesions were evaluated and photographic record was maintained. Patients were followed up after 3 months. Unpaired t test was used for statistical analysis. Results: The study found that 7 out of 10 patients (70%) of Group A showed complete response after 4 sessions and 3 patients (30%) showed moderate response. 8 out of 10 patients (80%) of Group B showed complete response, 1 patient (10%) showed moderate response, 1 patient (10%) showed no response. Recurrence was observed in 1 patient after 3 months who received vitamin D3. No serious adverse effects were observed. Conclusion: Both vitamin D3 and PPD showed positive results with PPD having faster and better efficacy in treatment of multiple common warts.

Keywords: Immunotherapy, Warts, Intralesional, Vitamin D3, Tuberculin purified protein derivative

1. Introduction

Viral warts are common skin infections of the epidermis caused by viral infection i.e. human papilloma virus (HPV). Despite having various treatment modalities they are difficult to treat and may recur. Thus there is a need to evaluate various treatment modalities. Warts were earlier treated by destructive modalities namely cryotherapy, electrocoagulation, topical salicylic acid, topical 5-fluorouracil, laser surgery etc. All of these treatments are essentially painful, time consuming, expensive and recurrence is common. (1-4) Therefore immunotherapy seems to be a promising modality in such cases.

The role of immunity is documented by the of warts in Immunotherapies that have been tried include cimetidine, imiquimod, interferons, Candida albicans antigens, measles, mumps, rubella (MMR) vaccine, tuberculin (purified protein derivative) and intralesional vitamin D (5-8). Intralesional tuberculin purified protein derivative (PPD) is effective for the warts over injected as well as distinct site and also prevents recurrence. Similarly vitamin D is an effective and a very recent modality used in treatment.

2. Aims and Objectives

The present study is taken up with an objective to prove and compare the efficacy of intralesional tuberculin purified protein derivative and intralesional vitamin D3 in the treatment of warts.

3. Materials and Methods

The study was conducted between March 2018 to August 2018. Patients with warts, attending the department of Dermatology, venereology & leprosy were enrolled for the study. A proper clinical history with detailed examination and a written informed consent was obtained from all the patients. A total of 20 patients who were aged ≥ 18 years having single or multiple viral warts, with no other concurrent treatment for warts were taken up for the study. Patients with active systemic illness/infection, pregnant and lactating women, patients on immunosuppressive drugs, patients with genital warts and those with keloidal tendency were excluded from the study. Institutional ethics committee clearance had been obtained for the study. 20 patients with warts were taken up for the study and were randomly divided into 2 groups i.e. group A and group B, the patients were explained regarding the objectives as well as the method of study.

Group A: 10 Patients were given intralesional injection of 0.2ml of 15mg/ml (6 lakh IU) vitamin D3 per wart.
Group B: 10 Patients were given intralesional injection of 0.2ml of 5TU/ml purified protein derivative (PPD) per wart.

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Injections were repeated every 2 weeks until complete clearance. Response was evaluated by decrease in size and number of lesions and photographic record was maintained. The response was evaluated as:
1. Complete response – complete absence of clinically apparent wart
2. Partial response – decrease in size > 25%
Patients were followed up for 3 months after the last injection to detect any recurrence. Unpaired t test, chi-square test were used for statistical analysis.

4. Results

In this study the maximum number of patients were in the age group of 20-40 years which was 15 (75%) followed by >40 years which was 5 (25%). The age of patients in group A, who received intralesional vitamin D3 ranged between 18-60 years with mean age ± standard deviation (SD) 25.1±4.41 and that of group B, who received PPD ranged between 20-60 years with mean age ± standard deviation (SD) 26.95±5.49 as shown in Table 1.

| Table 1: Distribution of patients according to age |
|-----------------|-----------------|-----------------|
| Age of Patients | Group A (VIT D3) | Group B (PPD)  |
| Range (years)   | 18-60            | 20-60          |
| Mean Age ± SD   | 25.1 ± 4.41      | 26.95 ± 5.49   |

Male outnumbered female in both the groups with male: female ratio of 2.3:1 and 1.5:1 in group A and B.

| Table 2: Gender distribution in both groups |
|-----------------|-----------------|-----------------|
| Group           | Male | Female | Male : Female |
| A (VIT D3)      | 7    | 3      | 2.3:1         |
| B (PPD)         | 6    | 4      | 1.5:1         |

Amongst group A and B patients majority of the patients had verruca vulgaris followed by plantar warts and peripheral warts. Distribution of patients according to the type of wart is depicted in Fig. 1.

The study showed that in group A who received intralesional vitamin D3 out of 10 patients, 7 (70%) showed complete clearance while 3 patients (30%) showed partial response (shown in Fig. 2).

In group B, patients who received intralesional PPD, out of 20 patients 8 (80%) showed complete response, 1 patient (10%) partial and 1 patient (5%) showed no response. (Figure 3, 4)

Different outcomes are observed with both the drugs when injected into various types of warts. In group B patients complete clearance is seen in 90.9% of patients with verruca vulgaris and that of group A complete clearance was seen in 83.3% in case of plantar warts complete clearance was seen in 83.3% and 42.8% in group B and group A respectively.

Applying unpaired t test to above data the p value is greater than 0.05 thus the difference is not considered as statistically significant.

At the end of follow-up, no recurrences were observed. The patients experienced adverse effects such as pain, erythema, swelling, itching which subsided on its own.

No serious adverse effects observed. No allergic or systemic adverse reactions and no sign or symptoms of hypervitaminosis D were observed. The only patient complaints were of minimal to moderate pain during injection which could be managed by injecting 0.2 ml lignocaine prior to injection and post procedure pain can be managed by NSAIDS.
5. Discussion

Intralesional immunotherapy is a popular mode of treatment used in viral warts. Immunotherapy is defined as a type of biological therapy that uses substances to stimulate or suppress the immune system to help the body to fight cancer, infection and other diseases. It mounts a delayed type hypersensitivity response to various antigens and wart tissue which helps in clearing local as well as distant warts. Various intralesional immunotherapeutic agents are used in treatment of warts, for example, purified protein derivative, vitamin D3, MMR vaccine, BCG vaccine, candida, trichophytin antigen etc. [9-12] The present study clearly demonstrates that warts can be treated successfully with intralesional vitamin D3 and PPD injection.

According to research conducted earlier Injecting PPD into the HPV-infected tissue generates strong pro-inflammatory signals and attracts antigen-presenting cells, which recognize HPV particles in the infected tissue leading to a strong adaptive immune response which helps in clearing the infection. The Th1 cytokines such as interleukin-4 (IL-4), IL-5, IL-8, interferons gamma, and tumor necrosis factor-alpha, which activates cytotoxic and natural killer cells that stimulate a strong immune response against HPV are mainly responsible for this process.13, 14

The proposed mechanism for vitamin D derivatives on warts is proposed to be due its potential to regulate epidermal cell proliferation and differentiation and to modulate cytokine production. Up-regulation of vitamin D receptors in the skin leads to the induction of antimicrobial peptide expression [15-17].

In our study, out of 10 patients who received vitamin D3, majority (60%) had verruca vulgaris, followed by (35%) plantar warts and then (5%) periungual warts. Amongst 10 patients who received PPD, majority (55%) had verruca vulgaris, then plantar warts (30%) and then followed by periungual warts (15%).

In our study, amongst group A patients, 70% of patients showed complete response and 30% of patients showed partial response. These results are comparable to studies done by Kavya M et al (78.5%)[18] and Aktase et al (70%).[19] Also previously a study done by RaghuKumar et
al with intraleisional vitamin D3 on 64 patients having warts showed that 90% of patients had complete clearance and 6.66% of the patients showed partial response.[20]

Amongst group B patients, 80% of patients showed complete response, 10% showed partial response and 10% of the patients showed no response. These results are similar to the results obtained by studies done by Wananukul et al (93%) and Nimbalkar et al (80%).[21,22]

In our study, we observed that efficacies varied among the two drugs in different types of warts. Whengiven to verrucavulgaris patients complete clearance was observed in 90.9% of patients who received PPD and 83.3% of patients achieved complete clearance whereas vitamin D3. In case of plantar warts complete clearance rates were 83.3% and 42.8% and partial response rates were 16.6% and 57.1% with PPD and vitamin D3 respectively. This shows that PPD is more effective in treatment of plantar warts than vitamin D3. When vitamin D3 was injected into periungual warts 100% complete clearance is seen and with PPD the complete and partial responses are 66.6% and 33.3% respectively.

The number of sessions required achieving complete response varied between both the drugs with PPD ranging from 3–4 sessions and vitamin D3 required more than 6 sessions.

No recurrences were observed in patients who received PPD one patient who received vitamin D3 reported relapse at the same site.

Immunotherapy with vitamin D3 and PPD are well tolerated. The side effects observed were minimal and not serious. The common side effects noted were pain at the time of injection, mild swelling and erythema.

Both are cost effective with PPD slightly cheaper than vitamin D3.

Overall, both the modalities proved to be effective in treatment of warts with intraleisional PPD being superior over vitamin D3.

6. Conclusion

Both vitamin D3 and PPD were found to be effective and well tolerated. Amongst the two drugs, Intraleisional PPD is found to be more effective in terms of efficacy, less number of sessions and no relapse. It is safe and simple to perform and has no serious side effects.

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Ethical approval: The study was approved by the institutional ethics committee.

References


