

## Original Research Article

# A comparative study between intralesional PPD and vitamin D3 in treatment of viral warts

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### ABSTRACT

**Background:** Viral warts are caused by human papillomavirus. There are innumerable treatment modalities but they may result in partial clearance or recurrence. Some newer and effective treatments include intralesional immunotherapy. We undertook a study to evaluate the safety and efficacy of two such immunotherapy namely tuberculin purified protein derivative (PPD) versus intralesional vitamin D3 for the treatment of viral warts.

**Methods:** A total of 80 patients were included in the study. Group 1 patient were injected with 10 TU of tuberculin PPD (0.1 ml) intralesional while in group 2 patients were injected (0.5 ml) vitamin D3. The clinical assessment was done by photographic measurements at baseline, before each treatment session, and after the completion of treatment.

**Results:** In group 1 A total of 80% (32 patients) showed complete clearance and 20% (8 patients) showed partial response while in group 2 72.5% (29 patients) showed complete clearance while 27.5% (11 patients) showed partial response. No significant side effects were observed except for pain at the site of injection.

**Conclusions:** Intralesional vitamin D and intralesional Tuberculin PPD immunotherapy shows significant results in treatment of viral warts.

**Keywords:** Viral wart, Immunotherapy, Tuberculin purified protein derivative, Vitamin D3

### INTRODUCTION

Viral warts are common skin infections of the epidermis caused by viral infection i.e. human papillomavirus (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.<sup>1-6</sup> Therefore immunotherapy seems to be a promising modality in such cases. The role of immunity is documented by the

appearance and persistence of warts in immunosuppressed individuals.<sup>7</sup>

Immunotherapy agents that have been tried include cimetidine, imiquimod, interferons, *Candida albicans* antigens, measles, mumps, rubella (MMR) vaccine, tuberculin (purified protein derivative) and intralesional vitamin D.<sup>8-12</sup> Intralesional tuberculin purified protein derivative (PPD) is effective for the warts over injected as well as distinct site and also prevents reoccurrence. Similarly vitamin D is an effective and a very recent modality used in treatment. So we undertook a study to evaluate the safety and efficacy of intralesional immunotherapy using tuberculin PPD and intralesional vitamin d in the treatment of viral warts.

**METHODS**

The study was conducted at B.R.D. medical college and Nehru hospital, Gorakhpur between July 2016 to July 2017. After taking a proper clinical history and detailed examination a written informed consent was obtained from all patients. A total of 80 patients with viral warts were enrolled in the study after the inclusion and exclusion criteria were satisfied. Patients with single or multiple viral warts, with no concurrent systemic or topical treatment for warts, and those who have not responded to any treatment were included. Pregnant and lactating women, patients with keloidal tendency of the skin, immunosuppressed individuals, patients with fever or signs of any systemic or local inflammation or infection, patients who have received any other treatment of warts in the past 3 months before enrolment, past history of asthma, allergic skin disorders, meningitis or convulsions were excluded from the study. Statistical tool used to analyse data was unpaired t test.

**Group 1**

Each patient was injected 10 TU of tuberculin PPD intralesionally per dose of 0.1 ml with the help of an insulin syringe in the largest wart at a regular interval of 2 weeks for a maximum of four injections or less in cases of complete clearance of wart.

**Group 2**

About 0.5 ml vitamin D3 solution (600,000 IU, 15 mg/ml) was injected to the base of the wart. A maximum of 4 warts per session were injected at the base of the wart at 2-week intervals until resolution or for a maximum of 4 treatments.

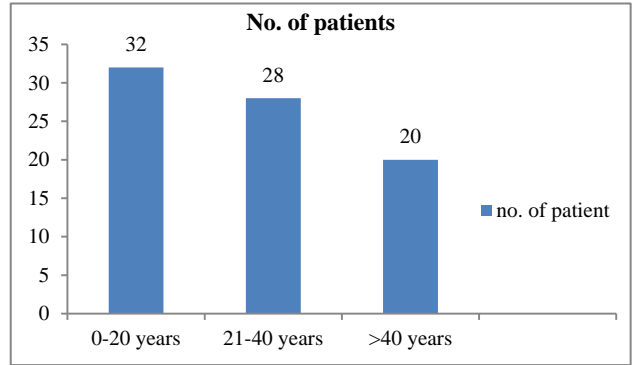
Patients were followed for every 2 weekly for clinical assessment of the result. If there was complete resolution at follow-up visits, treatment was discontinued. However, if there was no improvement or partial clearance, treatment was repeated at a scheduled interval

Patients were followed up for 3 months after the last injection to detect any recurrence. For each patient, age, sex, duration of disease, site of wart, number of wart, presence or absence of distant wart, family history, and past history were noted. The clinical assessment was done by photographic measurements at baseline. Results will be assessed at end of 8 weeks. The results will be assessed as-

- Complete response: responders who show 100% outcome
- Marked response: responders who show 75 to 99% outcome
- Moderate response: partial responders 50 to 75% outcome
- Inadequate response: those who show less than 50% outcome.

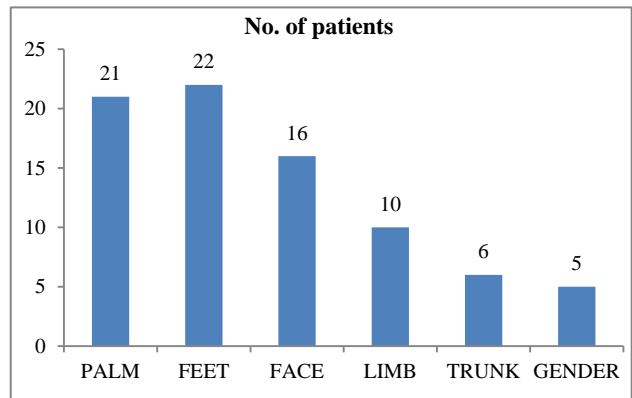
**RESULTS**

In this study the maximum number of patients were in the age group of <20 years which was 32 (40%) followed by 21-40 years which was 28 (35%) as seen in Figure 1. The mean age of patient was 25.98 years.

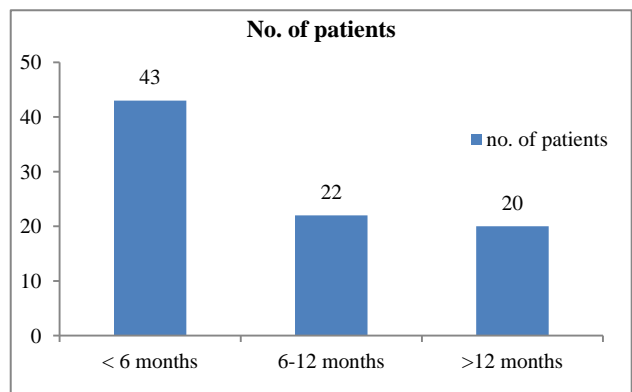


**Figure 1: Showing distribution of patient according to age.**

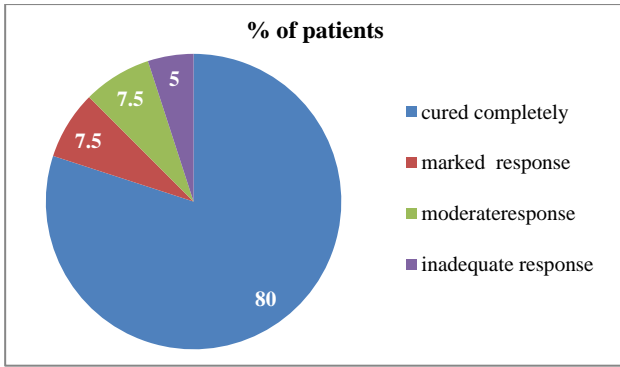
Male outnumbered female in ratio 51:29 that is (1.75:1). Maximum number of patients had multiple warts (80%). Distribution of wart according to site as depicted in Figure 2. Duration of lesion was as per the following Figure 3.



**Figure 2: Distribution of warts according to the site.**

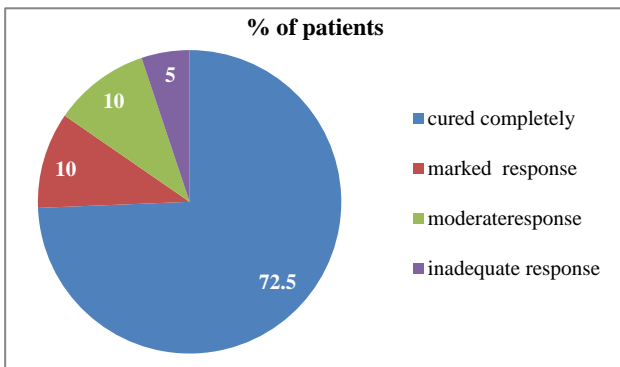


**Figure 3: Duration of illness.**



**Figure 4: Results of group 1 after the completion of intralesional PPD as a treatment modality.**

Mean duration of illness was 6.7 months. The study showed that in group 1 out of 40 patients, 32 (80%) showed complete clearance while 6 patients (15%) showed marked to moderate clearance (Figure 4).



**Figure 5: Results of group 1 after the completion of injection vitamin D3 as treatment modality.**

In group 2 showed that out of 40 patients 29 patients (72.5%) showed complete response 8 patients (20%) showed marked to moderate response (Figure 5).

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, nodule formation, erythema, swelling, itching, dyspigmentation, fever, ulcer, erythema induration or scar formation. 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.

## DISCUSSION

Intralesional immunotherapy is a popular mode of treatment used in viral warts which includes intralesional

injections of tuberculin purified protein derivative (PPD); measles, mumps, and rubella (MMR) vaccine; *Mycobacterium* vaccine; and *Candida albicans* antigen. The host immune system is activated to recognize the virus, leading to wart clearance.<sup>13-18</sup>

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.<sup>19,20</sup>

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.<sup>21-24</sup>

Our study showed that out of 40 patients, 32 (80%) showed complete clearance, six patients (15%) showed partial clearance, and 2 patients (5%) showed no improvement. Similar results were obtained earlier by Elela et al.<sup>25</sup> Complete clearance was seen in 94.1% of the cases when intralesional PPD was administered. Kus et al used intralesional tuberculin injection in 18 patients he showed complete clearance in 5 (29%) patients, partial response in 10 (59%) patients, and no response in 2 (12%) patients.<sup>26</sup>

We also witnessed that there was complete clearance of warts at anatomically distant site at the same time of disappearance of the injected wart. Thus the immune response is not restricted to the site of the injection. Wananukul et al stated similar observation where complete clearance in 93% of the cases with response rates was 87% in distant warts.

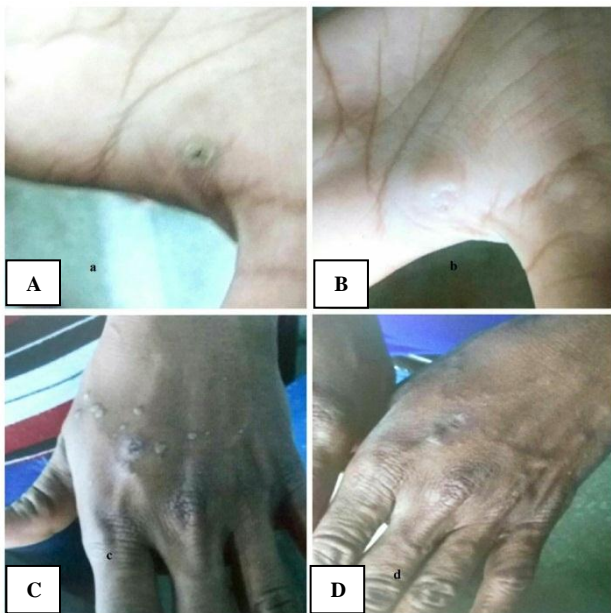
No recurrence was seen after mean follow-up of 4 months in patients of complete clearance.<sup>27</sup>

In the present study, it was observed that maximum number of patients showing. Complete clearances were of filiform wart (80%), verruca vulgaris (72%), and palmoplantar wart (80%), with no recurrence, whereas periungual wart showed no improvement to the treatment which was significant. This finding in our study is also similar to that noted by Wananukul et al.<sup>27</sup>

Immunotherapy with tuberculin PPD is well tolerated. Side effects noted in our patients were minimal and not very serious. Side effects noted were pain at time of injection (75%), nodule formation (25%), hyperpigmentation (30%), swelling fever blister formation, and erythema (10%) with induration (10%).



**Figure 6: (A) Pre and (B) post procedure photographs of genital wart after intralesional PPD; (C) pre and (D) post procedure photographs of plantar wart after intralesional PPD (from left to right).**



**Figure 7: (A) Pre and (B) post procedure photographs of palmar warts after intralesional vitamin D3; (C) pre and (D) post procedure photographs of common warts after intralesional vitamin D3 (from left to right).**

Tuberculin PPD was found to be an effective, well-tolerated mode of treatment with minimal side effects, and it is equally effective over injected and distance sites.

Vitamin D has potential to regulate epidermal cell proliferation and differentiation and modulate cytokine production. It also acts on Toll-like receptor activation which causes human macrophages up-regulation and

expression of VDR and vitamin D<sub>1</sub>-hydroxylase genes, leading to expression and secretion of antimicrobial peptides.<sup>28,29</sup>

Topical form of vitamin D<sub>3</sub> has been used for common as well as anogenital warts showing good results. Topical vitamin D<sub>3</sub> was successfully used by Moscarelli et al in a renal transplant patient to treat recalcitrant wart.<sup>21</sup> Rind et al reported the successful clearance of an anogenital wart in an infant with topical administration of vitamin D.<sup>22</sup> Intralesional vitamin D<sub>3</sub> has been previously used by Raghukumar et al on 64 patients having recalcitrant wart showing that 90% patient have complete clearance while 6.66% has partial response.<sup>28</sup> Similar results were obtained by Aktas et al in plantar warts recalcitrant to various treatment. In his study, intralesional vitamin d<sub>3</sub> was given to 20 patients with viral wart. Out of 20 16 i.e. 80% experienced complete resolution while one patient has partial response and 3 failed to show any response.<sup>29</sup>

While in our study 72.5% (29 patients) showed complete response and 8 patients showed marked to moderate response and 3 patients showed no response.

The most common side effect included pain at site of injection which was managed by injecting local anaesthetic prior to injecting vitamin D<sub>3</sub>.

We obtained good results by both the modalities. Overall intralesional PPD was superior to intralesional Vitamin D<sub>3</sub>.

## CONCLUSION

Intralesional vitamin D<sub>3</sub> injection and intralesional PPD may be a treatment option for warts that are unresponsive to conventional treatments. It is a simple, well-tolerated treatment method that is easy to administer in outpatient clinics.

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