INTRODUCTION

Viral warts are common skin infections of the epidermis with human papillomavirus (HPV). They can persist and increase in size and number. Recurrent multiple viral warts are a cause of great concern to the patient and the treating dermatologist, being nonresponsive to conventional treatment. The role of immunity is documented by the appearance and persistence of warts in immunosuppressed individuals. Spontaneous regression of the majority of warts is related to cellular immunity, A fully functional immune system is necessary to clear HPV from the epidermis.

Removal of warts by ablative therapies frequently leads to recurrence and thus persistence. Immunotherapy is a promising modality for the treatment of recurrent and resistant warts which could lead to resolution without any physical changes or scarring and, in addition, would augment the host response against the causative agent, thereby leading to complete resolution and decreased recurrence. Various studies have been done in the past where immunotherapy has been tried with variable success.

A few agents have been tried and studied extensively such as cimetidine, imiquimod, and interferons; others being under evaluation such as Echinacea, green tea catechins, Candida albicans antigens, measles, mumps, rubella (MMR) vaccine, Measles, mumps, rubella (MMR) vaccine, Mycobacterium w vaccine, and HPV vaccine. Intraleosional tuberculin purified protein derivative (PPD) is effective for the warts over injected as well as distinct site and also prevents reoccurrence. We undertook a study to evaluate the safety and efficacy of intraleosional immunotherapy using tuberculin PPD in the treatment of viral warts.

MATERIALS AND METHODS

The study was conducted at a tertiary care hospital and referral center in Central India after obtaining permission from the Institutional Ethics Committee. Intraleosional immunotherapy using tuberculin PPD was studied to know its safety and efficacy. Written informed consent was obtained from all patients. A total of forty-five patients with viral warts were enrolled in the study after the inclusion and exclusion criteria were satisfied. Patients

ABSTRACT

Introduction: Viral warts are caused by human papillomavirus. Although various treatment modalities are available, many of them result in the partial clearance of warts or recurrence. Immunotherapy has been tried in the recent times with variable success rates. We undertook a study to evaluate the safety and efficacy of immunotherapy using tuberculin purified protein derivative (PPD) for the treatment of viral warts. Materials and Methods: A total of 45 patients were included in the study. Each patient was injected with 10 TU of tuberculin PPD (0.1 ml) intraleosionally in the largest wart at 2 weekly interval. A total of maximum six treatment sessions were conducted. Resolution of viral warts was considered as the clinical end point of the study. The clinical assessment was done by photographic measurements at baseline, before each treatment session, and 3 weeks after the completion of treatment.

Results: A total of 62.2% patients (28 out of 45) showed complete clearance at injected and distant warts, eight patients (17.8%) showed partial clearance, and nine patients (20%) showed no improvement. No significant side effects were observed except for localized hair loss around injected viral wart over the scalp.

Conclusion: Tuberculin PPD immunotherapy was found to be a safe and effective treatment modality for the treatment of viral warts.

Key Words: Immunotherapy, tuberculin purified protein derivative, viral wart

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with single or multiple viral warts, age more than 12 years 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, and patients of anogenital warts were excluded.

Each patient was injected 10 TU of tuberculin PPD intrathecally 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 six injections or less in cases of complete clearance of wart. 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, intrathecally PPD therapy was repeated at a scheduled interval.

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, before each treatment session, and 3 weeks after the completion of treatment. The response was evaluated as follows; complete clearing (CC) was defined as total resolution of warts. Partial clearing was defined as decrease in number and/or decrease in apparent size, as assessed by clinician and photographic evaluation. No improvement was defined as there was no decrease in number and no decrease in apparent size. Resolution of distant untreated wart was also assessed. Data were expressed as percentages or proportions of patients who showed treatment responses as mentioned above.

**RESULTS**

In this study of 45 patients, the maximum number of patients were in the age group of 12–20 years (28.9%), i.e., 13 cases with the mean age of patients being 30.6 years, the maximum patients were of multiple warts (82.2%). The study had a maximum number of male patients, i.e., 33 patients (73.3%). It was observed that the most common site of warts was face (31.1%) followed by the neck (26.7%) and upper and lower extremities (22.2%). Lesion over the scalp (4.4%) and periungual (4.4%) region was the least common site for wart. The duration of the disease in maximum patients (55.6%) was ≤6 months with the mean age of duration was 6.8 months.

The study showed that out of 45 patients, 28 (62.2%) showed complete clearance [Figures 1-4], eight patients (17.8%) showed partial clearance, and nine patients showed no improvement.

Out of 25 patients with positive “PseudoKoebners phenomenon,” twenty patients (80%) showed complete clearance while eight patients (40%) with negative PseudoKoebners phenomenon showed complete clearance. All the 45 cases had a history of vaccination with Bacillus Calmette–Guérin. A total of six patients (13.3%) had a history of recalcitrant warts. The maximum number of patients (67%) showing complete clearance had no history of recalcitrant wart. In cases of multiple warts, 59.45% (22/37) patients showed complete clearance [Figures 1-4] while 75% (6/8) of the patients with single wart showed complete clearance.

Patients with warts started responding at the end of 6 weeks. A total of 10 patients showed complete clearance at the sixth visit [Figures 1 and 2] (at the end of 10 weeks of treatment), followed by seven cases which showed complete clearance 3 weeks after the last treatment was completed [Figure 4] (at the end of 13 weeks). Disappearance in the number of warts at both injected and distant site was similar. Response rates at various visits during PPD immunotherapy are shown in Table 1. In the present study, the mean age of responders was 28.9 years, while the mean age of nonresponders was 33.3 years with P value being statistically nonsignificant (P = 0.4831), and mean duration of the resolved lesion in the patients was 6.5 months while the mean duration of nonresponders was 6.7 months with P = 0.9274 as nonsignificant.

In the present study, it was observed that maximum patients showing complete clearance were of filiform wart (84%), palmoplantar wart (80%), and verruca vulgaris (67%). After complete clearance, there was no recurrence. Periungual wart showed no improvement to the treatment which was statistically significant (P = 0.019). The present study showed that complete clearance occurs maximally in patients having warts over the scalp, face, palm and sole, and extremities. No improvement was seen in patients with periungual wart.

**DISCUSSION**

Intralesional immunotherapy can utilize the immune system to mount a delayed-type hypersensitivity response to various antigens and also the wart tissue. It plays a central role in the regression of warts. The exact mechanism of PPD is not known. Injecting PPD into the HPV-infected tissue probably generates strong pro-inflammatory signals and attracts antigen-presenting cells, which also recognize and
process low-profile HPV particles in the infected tissue that further leads to strong adaptive immune response which successfully evades the host immune response. This therapy has been found to be associated with the production of 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.[7,8]

In the present study, the mean age of responders was 28.9 years, while the mean age of nonresponders was 33.3 years ($P = 0.4831$). Thus, there was no significant difference between the age of responder and nonresponders.

However, a study done by Abo Elela et al. reported that the response is better with older age.[9] The mean duration of the resolved lesion in the patients was 6.5 months while the mean duration of nonresolved lesions was 6.7 months ($P = 0.9274$). This demonstrates that the response to the PPD is not affected by the duration of the lesion. This is similar to a study done by Kus et al.;[10] however, Abo Elela et al.[9] reported that the response to PPD injection is affected by the duration of the lesions, the longer the duration, the less the response to PPD.

Our study showed that out of 45 patients, 28 (62.2%) showed complete clearance, eight patients (17.8%) showed partial clearance, and nine patients showed no improvement. In a study done by Abo Elela et al., complete clearance was seen in 94.1% of the cases when intralesional PPD was administered in the wart while success rates in the intradermal group was 96%. A study done by Kus et al.[10] in 18 patients using intralesional tuberculin injection in wart showed CC in 5 (29%) patients, partial response in 10 (59%) patients, and no response in 2 (12%) patients. In the present study, it seems that the cure rate is different from that obtained by Kus et al. due to small number of the patients or short duration of treatment in their study.

In a study done by Lahti and Hannuksele[11] using tuberculin (PPD) topical jelly in the treatment of warts, 8 out of 14 patients (57%) showed complete clearance.

### Table 1: Comparison of complete clearance (response rate) in the patients of multiple wart (22) at injected wart and wart at distant site

| Visit                  | CC at the site of injected wart (%) | CC of distant wart | $P$  |
|------------------------|-------------------------------------|-------------------|------|
| First visit            | 0                                   | 0                 | -    |
| Second visit (2 weeks) | 0                                   | 0                 | -    |
| Third visit (4 weeks)  | 0                                   | 0                 | -    |
| Fourth visit (6 weeks) | 2 (9.1) 2/45                        | 2 (9.1)           | 1.000, NS |
| Fifth visit (8 weeks)  | 3 (13.6) 3/45                       | 3 (13.6)          | 1.000, NS |
| Sixth visit (10 weeks) | 10 (54.5) 10/45                     | 10 (54.5)         | 1.000, NS |
| 3 weeks after last treatment (13 weeks) | 7 (31.8) | 7 (31.8) | 1.000, NS |
| Total                  | 22 (100)                            | 22 (100)          | 1.000, NS |

CC: Complete clearing, NS: Not significant
The disappearance of wart usually occurred in the 3rd and 4th months. In comparison to PPD immunotherapy, the major disadvantage of topical tuberculin jelly is the long duration of treatment as the disappearance of warts occurred after 4 months of treatment.\(^{[11]}\)

In our study, complete clearance of warts at anatomically distant site was observed at the same time of disappearance of the injected wart. This suggests that the immune response is not restricted to the site of the injection. No recurrence was seen after mean follow-up of 4 months in patients of complete clearance. Wananukul et al.\(^{[12]}\) stated similar observation where complete clearance in 93% of the cases with response rates was 87% in distant warts. Shaheen et al. demonstrated that with PPD immunotherapy, rate of clearance of target and distant warts was 60% while with MMR vaccine, it was 80%.\(^{[13]}\) It was also observed that MMR resulted in a significantly higher serum IL-12 than PPD while in PPD immunotherapy, IL-4 was increased.

The proportion of patients showing complete response was 59.45% (22/37) in cases of multiple warts while 75% (6/8) of the patients with single wart showed complete clearance, although the number of patients with single wart was less in our study. This indicates that patients with both single and multiple warts responded significantly well to intralesional PPD immunotherapy.

In the present study, it was observed that maximum number of patients showing CC were of filiform wart (84%), verruca vulgaris (67%), and palmoplantar wart (80%), with no recurrence, whereas periungual wart showed no improvement to the treatment which was significant \(P = 0.019\). This finding in our study is comparable to that noted by Wananukul et al.\(^{[12]}\). A study by Johnson et al.\(^{[4]}\) found that intralesional immunotherapy using mumps and Candida skin test antigen is an effective treatment for cutaneous wart. A total of 29 out of 39 patients (74%) showed complete resolution with 14 of 18 patients with distant wart had the resolution of distant wart too. However, in the present study, better results were obtained by using intralesional tuberculin PPD demonstrated by complete clearance in both injected and distant warts at the same time. Out of 25 patients with positive PseudoKoebners phenomenon, twenty patients (80%) showed complete clearance, suggesting that intralesional PPD works better in the patients having active disease.

Immunotherapy with tuberculin PPD is well tolerated. Side effects noted in our patients were minimal and not very serious. These included alopecia areata at the injection site which was resolved by the administration of intralesional corticosteroid injection. Local reaction in the form of pain at the injected site and abscess at the injection site was also noted in one patient each. Postinflammatory hyperpigmentation after complete clearance was reported in eight patients, which was resolved by the application of topical depigmenting agents. Immediate hypersensitivity reaction occurred in one patient in the form of urticaria, but none of the patients had any systemic side effects.

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.

**CONCLUSIONS**

Intralesional PPD seemed to be an effective, with good cure rate in treatment of single and multiple warts wart but how exactly it works to stimulate immunity against wart is still unclear. It is effective equally at injected and warts at distant site, and also prevent reoccurrence of wart with completely clearance. It is safe, simple to perform, not very painful, inexpensive with minimal side effects.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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