Original Article

# Comparative Study of Efficacy of Intralesional Purified Protein Derivative (PPD) Versus Intralesional Measles, Mumps, and Rubella (MMR) Vaccine in Management of Multiple Viral Warts

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## Abstract

**Background:** Multiple viral warts represent a frustrating challenge for both patients and physicians. Management is difficult, primarily due to recalcitrance to standard therapy and high recurrence rates. Recently, intralesional antigen immunotherapy has shown promising efficacy in the treatment of warts. **Objective:** The aim of our study was to compare efficacy and safety of intralesional PPD versus measles, mumps, and rubella (MMR) vaccine in the management of multiple warts. **Materials and Methods:** One hundred and five patients having multiple warts were randomly divided into group A (PPD), group B (MMR) and group C (normal saline), with 35 patients in each group. In each group, the largest wart was injected intralesionally with 0.1 mL of vaccine at 2 weeks interval until complete clearance or for a maximum of 8 weeks. **Results:** Out of 105 patients enrolled in the study, 27, 25, and 21 patients completed the study in group A, group B, and group C, respectively. Rest were lost to follow up due to various reasons such as pain and long treatment duration. Complete clearance was seen in 14 patients (51.85%) in group A, 14 patients (56%) in group B, and 0 patients in group C. Partial clearance was seen in four patients (14.81%) in group A, four patients (16%) in group B, and three (14.28%) patients in group C. Nine patients (33.33%) in group A, seven patients (28%) in group B and 18 (85.71%) patients in group C did not respond to immunotherapy. **Conclusions:** Intralesional immunotherapy by both vaccines is a promising, effective, and safe treatment modality with MMR having slight edge.

**Keywords:** Immunotherapy, MMR, PPD, vaccine, viral warts

## Introduction

Verrucae are cutaneous papillomas caused by human papilloma virus (HPV), a double stranded DNA non-enveloped virus of the Papovaviridae family. Till date, more than 200 subtypes of HPV have been classified in literature.[1] Types of warts include common warts (verrucae vulgaris), genital warts (condyloma accuminata), flat warts (plane wart), and palmoplantar warts.

Treatment modalities of warts include cytodestructive methods such as topical application of podophyllin, salicylic acid, trichloroacetic acid, imiquimod, cryotherapy, electrocautery, carbon dioxide laser, and surgical excision. Adverse effects of these methods include severe pain, scarring, and dyspigmentation. Most of these methods are ineffective in prevention of recurrence of warts.

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Recently, intralesional immunotherapy has been used in the treatment of different types of warts.[2] Various antigens such as *Trichophyton*, *Candida*, *Mycobacterium welchii*, Bacillus Calmette-Guerin (BCG), purified protein derivative (PPD), measles, mumps, and rubella (MMR) have been used with varying results.

Considering the paucity of studies on immunotherapy, especially head-to-head comparison studies of different modes of immunotherapy in the treatment of warts, we

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conducted a study to compare the efficacy of intralesional PPD and MMR vaccine in the treatment of multiple viral warts and their long-term safety.

### Aims and objectives

The objective was to determine the efficacy and safety of intralesional PPD in comparison with intralesional MMR vaccine and a control (normal saline) in the management of multiple viral warts.

### Inclusion criteria

Clinically diagnosed cases of warts (>1 in number) of all ages and both genders who consented for the study were included.

### Exclusion criteria

The exclusion criteria are as follows:

1. Known history of hypersensitivity to PPD/MMR vaccine
2. Pregnancy and lactation
3. Immunocompromised status
4. Local site infection/ulceration.

## Materials and Methods

This was a single blind, randomized, controlled trial conducted over a period of 1 year at a tertiary healthcare center. After obtaining institutional Ethics Committee approval, trial was registered in the Clinical Trial Registry-India (CTRI registration number: CTRI/2018/02/012019).

A total of 105 patients fulfilling the inclusion criteria were included in the study. They were randomized using a computer-generated random number table and equally divided into three groups: group A included 35 patients who received intralesional PPD vaccine, group B included 35 patients who received intralesional MMR vaccine, and group C included 35 patients who received intralesional normal saline. They were advised not to use any other treatment modality during the study period of 8 weeks.

Demographic and clinical data of all patients were recorded, including duration of warts, past history, treatment history, type of warts, and site and number of warts before the first injection. Photographs were taken before each injection for documentation of regression in size and number of warts, appearance of new lesions, and side effects.

Group A received 0.1 mL intralesional PPD vaccine (Akray Pharma, Gujarat, India), group B received 0.1 mL intralesional reconstituted MMR vaccine (Tresivac, Serum Institute of India, Pune, India), and group C received 0.1 mL intralesional normal saline as a control group, in the mother wart (largest wart) with the help of an insulin syringe. In all the groups, intralesional injections were given at an interval of 2 weeks till complete clearance of all warts (both treated and distant site) or for a maximum of four treatment sessions. The patients were followed up monthly for the next 6 months after completion of treatment for clinical assessment of any long-term side effects and recurrence.

Response was evaluated as follows: (1) complete clearance which indicated 100% resolution of all warts (both treated and distant site) and normalization of dermatoglyphics in case of palmoplantar warts, (2) partial clearance which meant 50–99% resolution, and (3) no response which meant less than 50% resolution of warts.

### Statistical analysis

Data were entered into the Microsoft Excel sheet and was analyzed using SPSS software (Version 23.0. Armonk, NY, USA). Data were expressed as mean and standard deviation for quantitative variables and as number and percentage for qualitative variables. ANOVA and $\chi^2$ test were used for comparison. *P*-value less than 0.05 was considered significant.

## Observations and Results

Out of the 105 patients enrolled, 73 patients completed the study. The baseline clinical characteristics of all the groups are presented in Table 1. Eight patients in group A, 10 patients in group B and 14 patients in group C dropped out of the study. Reasons for dropout included lack of improvement, side effects such as pain, swelling, and flu-like symptoms.

Therapeutic response and its statistical comparison in three groups are presented in Tables 2 and 3, respectively. Comparing the therapeutic response of group A (PPD) with control group C (normal saline) and group B (MMR) with control group C, *P*-value was significant (<0.001) but it was not significant on comparing group A with group B ($P = 0.917$). Clinical response of various types of warts to group A, B and C immunotherapy at the end of 8 weeks is depicted in Tables 4–6, respectively [Figures 1–5]. The mean numbers of treatment sessions for complete clearance of lesions in PPD-treated group were 3.85 sessions and in MMR-treated group were 3.71 sessions. None of the patients in group C had complete clearance.

The most common side effect reported was pain during injection (100% patients). One patient developed scarring and one patient developed swelling at the injection site in group A (PPD) [Figure 6]. Three patients in group B (MMR) developed flu-like symptoms within 2 days of the injection. Recurrence was observed in one patient in group A (PPD) and no recurrence was noted in group B (MMR) in the follow-up period of 6 months.

## Discussion

Treatment of cutaneous warts includes various topical/local and systemic therapies. These treatment

**Table 1: Baseline characteristic of the patients in treatment groups**

| | Group A (PPD) ($n=27$) | Group B (MMR) ($n=25$) | Control group (normal saline) ($n=21$) |
|---|---|---|---|
| Age distribution (years) | | | |
| Range | 4–41 | 4–51 | 6–51 |
| Mean | 21.62 | 23.24 | 23.61 |
| Gender distribution | | | |
| Male | 16 | 18 | 15 |
| Female | 11 | 7 | 6 |
| Duration of warts (months) | | | |
| Range | 0.5–24 | 2–96 | 2–18 |
| Mean | 5.5 | 13.44 | 6.47 |
| Numbers of warts | | | |
| Range | 2–50 | 2–50 | 2–50 |
| Mean | 12.25 | 10.56 | 8.19 |
| Type of warts | | | |
| Palmoplantar | 8 | 10 | 9 |
| Common | 9 | 10 | 8 |
| Plane | 6 | 1 | 2 |
| Periungual | 2 | 2 | 1 |
| Genital | 2 | 2 | 1 |
| Treatment history | | | |
| Yes | 11 | 14 | 8 |
| No | 16 | 11 | 13 |

**Table 2: Therapeutic response in all the three treatment groups**

| Response to therapy | PPD group | MMR group | NS group |
|---|---|---|---|
| Complete clearance | 14 (51.85%) | 14 (56%) | 0 (0%) |
| Partial clearance | 4 (14.81%) | 4 (16%) | 3 (14.28%) |
| No response | 9 (33.33%) | 7 (28%) | 18 (85.71%) |

**Table 3: Statistical comparison of response between groups**

| Comparison between groups | $\chi^2$ | *P*-value | Significance level |
|---|---|---|---|
| PPD * NS | 16.65 | < 0.001 | Highly significant |
| MMR * NS | 18.77 | < 0.001 | Highly significant |
| PPD * MMR | 0.173 | 0.917 | Non-significant |

**Table 4: Therapeutic response in various types of warts at the end of 8 weeks of intralesional PPD therapy**

| Response | Palmoplantar | Common | Plane | Genital | Periungual | Total |
|---|---|---|---|---|---|---|
| Complete clearance | 6 (75%) | 5 (55.55%) | 1 (16.66%) | 0 (0%) | 2 (100%) | 14 |
| Partial clearance | 0 (0) | 2 (22.22%) | 2 (33.33%) | 0 (0%) | 0 (0%) | 4 |
| No clearance | 2 (25%) | 2 (22.22%) | 3 (50%) | 2 (100%) | 0 (0%) | 9 |
| Total | 8 | 9 | 6 | 2 | 2 | 27 |

**Table 5: Therapeutic response in various types of warts at the end of 8 weeks of intralesional MMR therapy**

| Response | Palmoplantar | Common | Plane | Genital | Periungual | Total |
|---|---|---|---|---|---|---|
| Complete clearance | 7 (70%) | 5 (50%) | 0 (0%) | 1 (50%) | 1 (50%) | 14 |
| Partial clearance | 2 (20) | 1 (10%) | 1 (100%) | 0 (0%) | 0 (0%) | 4 |
| No clearance | 1 (10%) | 4 (40%) | 0 (0%) | 1 (50%) | 1 (50%) | 7 |
| Total | 10 | 10 | 1 | 2 | 2 | 25 |

modalities are often associated with side effects such as scarring, hyperpigmentation, and high recurrence rate.[3] Intralesional immunotherapy with various antigens such as mumps, *Candida*, *Trichophyton*, MMR vaccine, and PPD vaccine has shown promising therapeutic results for warts with better safety, lesser side effects, and a

**Table 6: Therapeutic response in various types of warts at the end of 8 weeks of intralesional normal saline therapy**

| Response | Palmoplantar | Common | Plane | Genital | Periungual | Total |
|---|---|---|---|---|---|---|
| Complete clearance | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 |
| Partial clearance | 3 (33.33%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 3 |
| No clearance | 6 (66.66%) | 8 (100%) | 2 (100%) | 1 (100%) | 1 (100%) | 18 |
| Total | 9 | 8 | 2 | 1 | 1 | 21 |

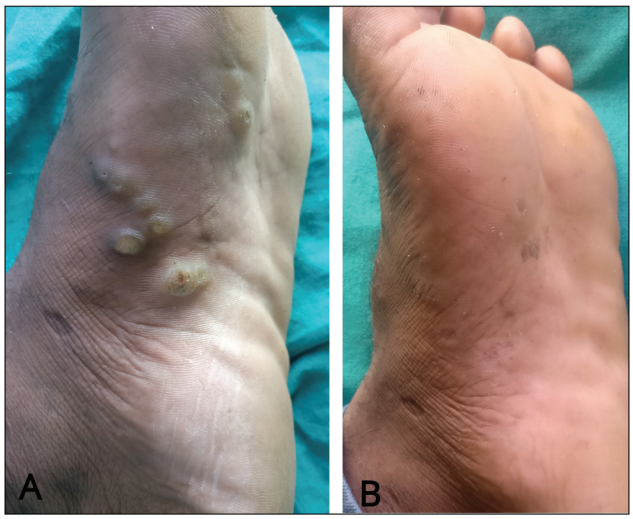


**Figure 1:** A and B show the baseline and complete clearance of plantar warts with three sessions of PPD vaccine

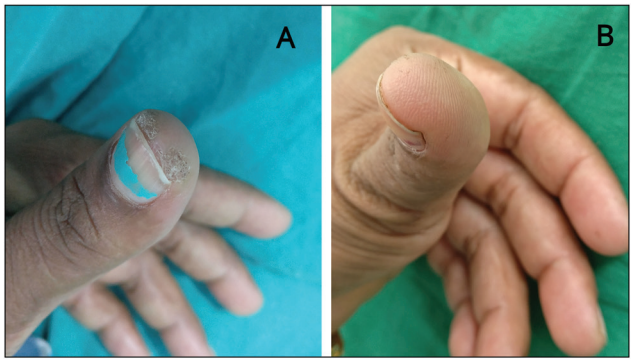


**Figure 2:** A and B show the baseline and complete clearance of subungual warts with four sessions of PPD vaccine

lower recurrence rate. It also has an added advantage of clearance of both treated and distant site lesions.[4,5]

The exact mechanism of intralesional immunotherapy is still unknown. Intralesional immunotherapy enhances the ability of the immune system to identify certain antigens such as bacteria, fungi, and virus that induce delayed type of hypersensitivity (DTH).[5] DTH leads to increase proliferation of macrophages and releases Th1 cytokines such as IL-2, IL-4, IL-5, IL-8, TNF-α, and INF γ. The Th1 cytokines activate cytotoxic T cells and natural killer cells and destroy the HPV.[6]

Our study showed highly significant therapeutic response with MMR and PPD, respectively, in comparison with the control group. On comparison of MMR and PPD, the therapeutic response was slightly better with MMR; however, the difference was not statistically significant. Combination of three antigens in MMR vaccine produces better immunostimulant effect than PPD vaccine alone, which is responsible for slight better response with MMR vaccine.

The therapeutic response seen in our study was slightly higher than that in studies by Kus *et al.*, Clifton *et al.*, Essa *et al.*, King *et al.*, and Signore *et al.* and lower than that in studies by Nimbalkar *et al.*, Saoji *et al.*, Nofal *et al.*, Gupta *et al.*, and Gamil *et al.* [Table 7].[2,4,6-12] The difference in study population, duration, types of warts, and number of treatment sessions may also be responsible for this variation in therapeutic response among various studies. Percentage of complete clearance observed in our study is lower than that reported in a similar comparative study by Shaheen *et al.*[13] The higher therapeutic response in Shaheen *et al.* was explained by the fact that only those patients who demonstrated positive intradermal tests to the specific antigen were recruited in the study.

The average number of treatment sessions required for complete clearance of both treated and distant lesions in the PPD-treated group was 3.85 and in the MMR-treated group was 3.71, which is less than that reported by Johnson *et al.* (4.7 sessions), Na *et al.* (5.38 sessions), and Horn *et al.* (5.8 sessions).[14-16]

The most common side effect noted was pain (100% patients) during injection which resolved within 1–2 h without any intervention. Scarring and swelling were noted in one patient (2.85%) each in PPD-treated group. Three patients (8.5%) in the MMR-treated group developed flu-like symptoms within 2 days of the injection in contrast to 6% patients in a study by Awal *et al.* and 13.6% patients in a study by Johnson.[17,18] No serious side effects such as infection, wounding, redness, severe pruritus, and alopecia at the injection site were observed in our study in contrast to previous studies.[4,14,16,19,20]

Limitations of our study are as follows: (1) This was a single-blind study with a relatively small sample size. (2) Pre-treatment intradermal test (Mantoux test) was not done in our study, which could have helped to include patients with expected better response to immunotherapy. (3) All types of viral warts were included in the study. The number of cases of each type of viral wart was relatively small. Hence, it was not possible to study the comparative efficacy of MMR and PPD in

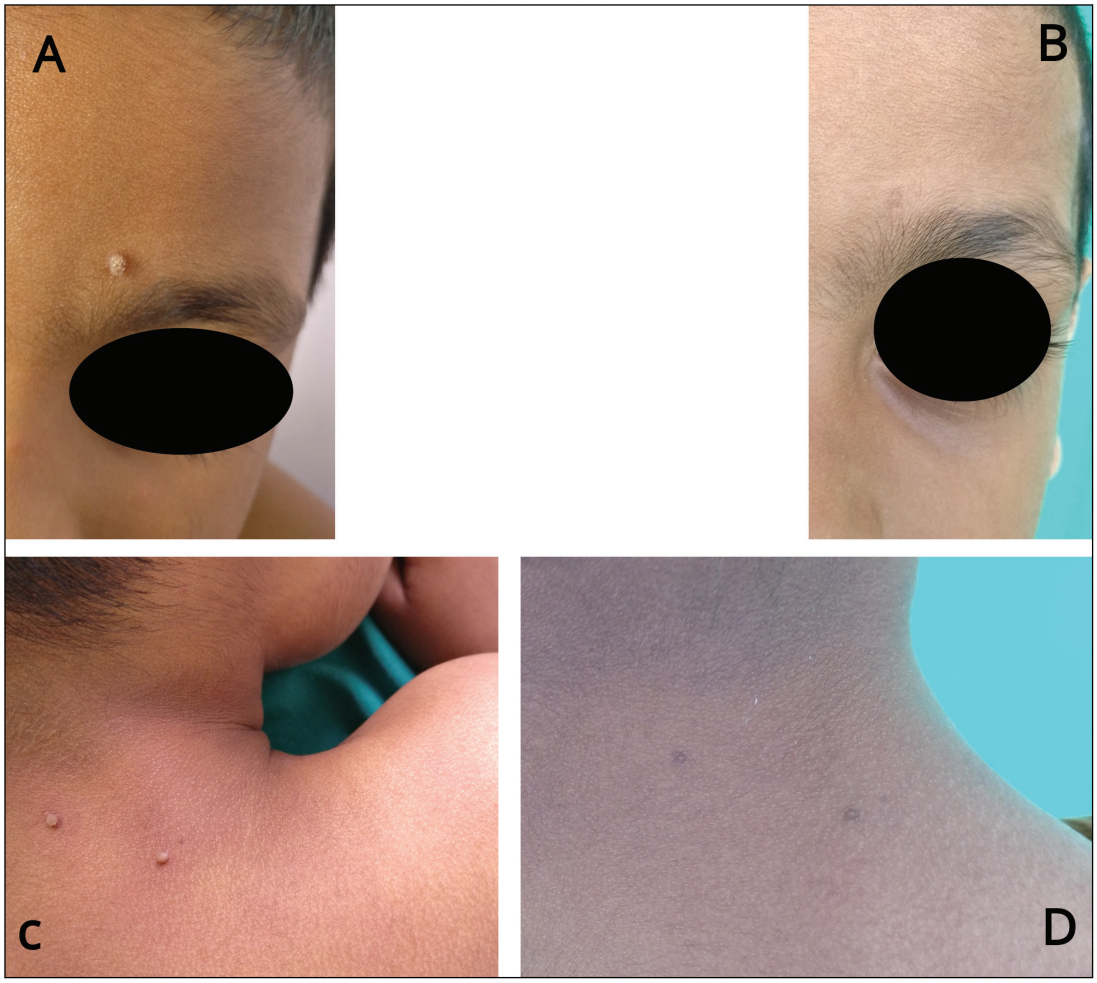


**Figure 3:** A–D show the baseline and complete clearance of filiform wart and common warts with four sessions of PPD vaccine

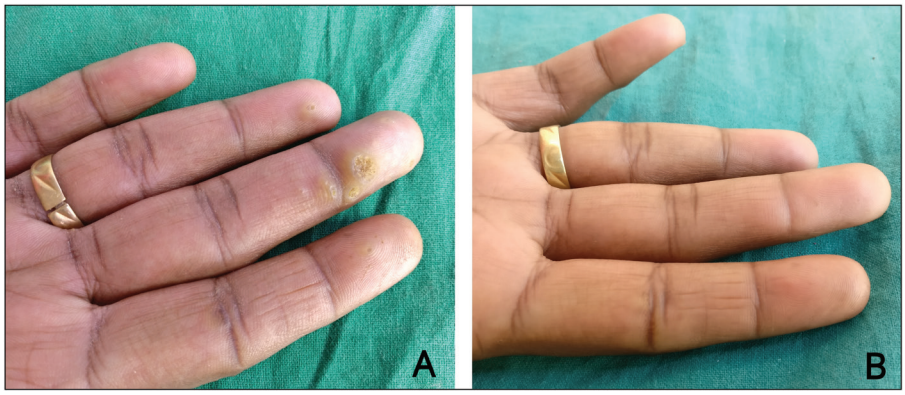


**Figure 4:** A and B show the baseline and complete clearance of palmar warts with four sessions of MMR vaccine

each individual variant. (4) The maximum number of injections given was four. Better therapeutic response could possibly have been obtained by increasing the number of treatment sessions as reported by Gupta *et al.*, showing 88.9% cure rate with 10 injections of killed *M. welchii* vaccine.[6] Larger comparative studies would be required to determine whether more number of injections would result in a better therapeutic response.

## Conclusion

Intralesional immunotherapy using either PPD vaccine or MMR vaccine shows comparable efficacy and safety in the treatment of warts. Immunotherapy is a highly effective, low-cost treatment option with good tolerability. It showed good complete clearance at both treated and distant site lesions. Because of less side effects and low recurrence rate when compared with traditional treatment

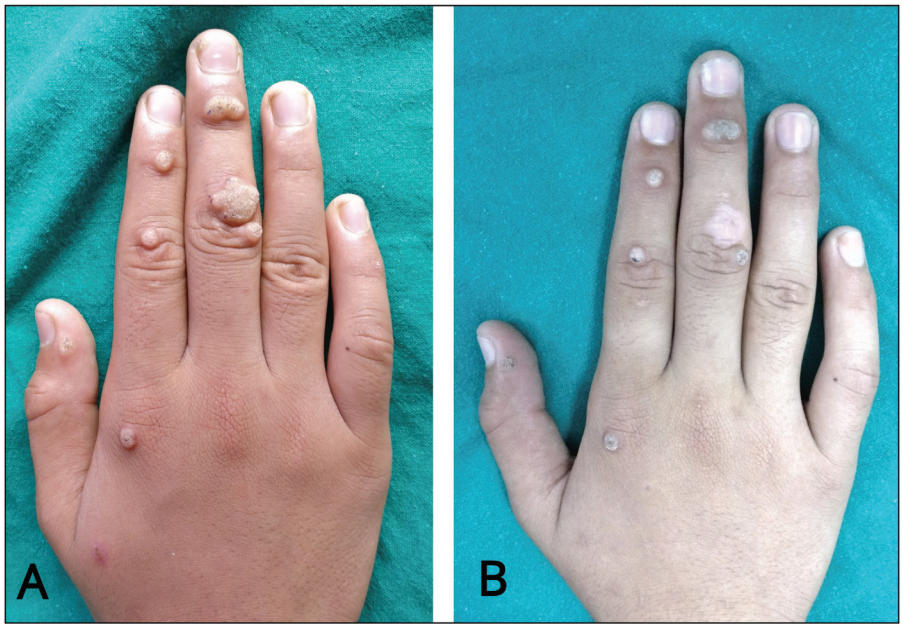


**Figure 5:** A and B show the baseline and partial clearance of common warts with four sessions of MMR vaccine

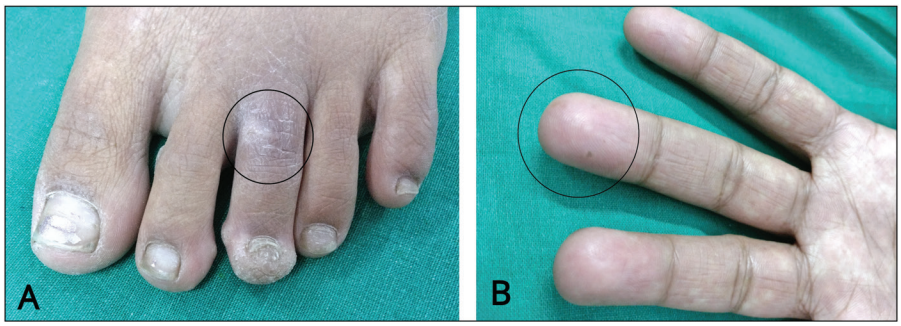


**Figure 6:** A and B show scarring and swelling at injection site respectively in patient treated with PPD vaccine

**Table 7: Comparison with previous studies**

| No. | Study | Cases | Antigen/vaccine | Maximum number of sessions | Complete clearance (%) |
|---|---|---|---|---|---|
| 1. | Kus *et al*.[7] | 13 | PPD vaccine | 3 | 29.4 |
| 2. | Clifton *et al*.[8] | 47 | Mumps or *Candida* antigen | 3 | 47 |
| 3. | Eassa *et al*.[9] | 40 | PPD vaccine | 12 | 47 |
| 4. | King *et al*.[10] | 10 | Mumps, *Candida*, *Trichophyton*, or combination | 2–13 | 50 |
| 5. | Signore[3] | 87 | *Candida albicans* | 4 | 51 |
| 6. | **Present study** | **73** | **PPD and MMR vaccine** | **4** | **52, PPD; 56, MMR** |
| 7. | Nimbalkar *et al*.[4] | 45 | PPD vaccine | 6 | 62.2 |
| 8. | Saoji *et al*.[11] | 55 | PPD vaccine | 4 | 76 |
| 9. | Nofal and Nofal[10] | 70 | MMR vaccine | 5 | 81.4 |
| 10. | Gupta *et al*.[6] | 40 | *M. welchii* antigen | 10 | 83 |
| 11. | Gamil *et al*.[12] | 23 | MMR vaccine | 3 | 87 |
| 12. | Shaheen *et al*.[13] | 30 | PPD vs. MMR vs. normal saline | | 60%-PPD vs. 40%-MMR vs. 0%-NS |

modalities, intralesional immunotherapy with PPD or MMR can be recommended as a first-line treatment option for multiple warts and recalcitrant warts.

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## 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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Nil.

## Conflicts of interest

There are no conflicts of interest.

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