Brief Report

A Comparative Study of the Efficacy of Intralesional Measles Mumps Rubella (MMR) Vaccine and Auto Implantation for the Treatment of Periungual and Palmoplantar Warts: A Randomized Controlled Trial

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Abstract

Background: Warts are benign epidermal proliferations, caused by infection of keratinocytes with human papillomavirus (HPV). Auto implantation and intralesional mumps, measles, and rubella (MMR) vaccine are novel methods of immunotherapy for treating periungual and palmoplantar warts. They act by stimulating the patient's immune system; this clears not only the local warts but also distant warts with lesser side effects. **Objective:** We conducted this study to compare the efficacy and safety of both methods in treating periungual and palmoplantar warts. **Materials and Methods:** A total of 160 patients were randomly allocated into two groups of 80 patients. Group A was treated with 0.3 mL of intralesional MMR vaccine at an interval of 3 weeks or for a maximum of three sittings, and Group B was treated with auto implantation. **Results:** At the end of therapy, the result was better in group A (MMR vaccine) as 86% of cases yielded an excellent response as compared to 71% in group B (auto implantation). The recurrence rate was 5% in group A and 4% in group B. There were no serious side effects in both groups with pain during injection (70%) in group A and swelling at the recipient site (8%) in group B being the most common side effect. **Conclusion:** Both MMR and auto implantation had significant response rates. But MMR was faster and better.

Keywords: *Auto implantation, human papillomavirus, measles mumps rubella vaccine, palmoplantar wart, periungual wart*

Introduction

Warts are benign epidermal proliferations, caused by infection of keratinocytes with human papillomavirus (HPV) on the skin and mucosal surface.[1]

Conventional treatments including destructive and surgical modalities are associated with variable efficacy, high recurrence, requiring treatment for each wart along with significant adverse effects such as scarring.

Immunotherapy is an evolving biological therapeutic modality, which uses substances to modify the immune response and help the body to fight an infection, cancer, or autoimmune disease.[2]

Auto implantation is a novel, one-time procedure that treats the warts by stimulating an immune response against HPV. This enhanced immunity helps in clearing both multiple and distant lesions and also reduces the chances of recurrence.

Apart from auto implantation, intralesional immunotherapy is also a promising therapy. It helps in the induction of the immune system. It has been shown that inj. MMR mounts a delayed type of hypersensitivity response against various antigens and wart tissue, which helps in clearing warts.[3]

In recent times, there has been an increase in the popularity of using immunotherapy for the management of warts. Such studies that compare two different modes of immunotherapy are few in the current literature. Therefore, here we conducted a comparative study of efficacy, side effects, and recurrence between MMR vaccine and auto implantation.

Materials and Methods

Trial design and site

The study was a single-center, simple randomized, parallel-group, non-inferiority

How to cite this article: Abusaria R, Yadav C, Jain V, Kachhawa D, Rao P, Lamoria A. A comparative study of the efficacy of intralesional measles mumps rubella (MMR) vaccine and auto implantation for the treatment of periungual and palmoplantar warts: A randomized controlled trial. Indian Dermatol Online J 2024;15:812-6.

Received: 22-May-2023. **Revised:** 17-May-2024. **Accepted:** 03-Jun-2024. **Published:** 16-Aug-2024.

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Access this article online

Website: https://journals.lww.com/idoj

DOI: 10.4103/idoj.idoj_394_23

Quick Response Code:

trial with an allocation ratio of 1:1. The study was conducted at a tertiary center on 160 patients after obtaining due approval from the institutional review board.

Patients were randomly assigned to two groups (A and B) using computer-generated random number tables. Group A patients were treated with intralesional MMR and group B patients by auto implantation.

Sample size calculation

The sample size was calculated using the formula for the sample size for the estimation of proportion with a 95% confidence interval assuming an expected ≥75% efficacy and 10% absolute allowable error. The sample size was calculated to be 75 patients, which was rounded off to 80 on each arm.[4]

Participants

All patients having periungual and palmoplantar warts, >10 years of age, and irrespective of the number of warts and duration were included in the study for 1 year (2020–2021).

Patients who were pregnant, lactating, underwent treatment for wart in the last 3 months, and had a history of MMR vaccine hypersensitivity were excluded from the study.

After obtaining written informed consent from all patients, baseline characteristics of the warts including number, site, size, duration, and the presence or absence of distant warts were evaluated at the start of the study and each follow-up visit.

Intervention

Group A patients were treated with reconstituted MMR vaccine. The MMR vaccine was reconstituted with 0.5 mL distilled water, and 0.2–0.3 mL of this solution was injected intralesionally into the largest wart.

Injections were administered at 3-week intervals until complete clearance was achieved or for a maximum of three treatment sessions.

Before injecting MMR, the total number of warts was calculated and their location was noted. If the lesions were disseminated and involved more than one lymphatic drainage, then the largest wart from each site was taken as a representative lesion and injected. In the case of multiple warts involving the same lymphatic drainage, the largest wart was taken as a representative lesion and injected.

Group B patients were treated with the auto implantation technique.

A well-developed verrucous wart was selected as a donor wart and under local anesthesia and aseptic precautions, a chunk of the wart surface was removed and then transferred to a glass slide. It was then cut into small pieces and introduced subcutaneously into the forearm.

Systemic antibiotics were administered for 5 days. Patients were followed up after 1 week, then every 3 weeks for 2 months, and monthly thereafter for 6 months for clinical assessment of results, recurrence, and any adverse effect(s). The response was evaluated by the decrease in the number of warts along with photographic comparison.

Excellent response was defined as >90% of warts disappeared. Good response was defined as 76–90%, moderate as 51–75%, mild as 25–50%, and poor response as <25% warts disappeared.

Results

A total of 160 patients were selected for the study after applying inclusion and exclusion criteria, out of which 3 patients in the MMR group and 7 patients in the auto implantation group did not complete the treatment course [Figure 1]. Baseline characteristics of the patients in both groups are presented in Table 1.

The therapeutic response rate in the two groups is compared in Table 2 according to the time elapsed and at the end of therapy. In the MMR group, 86% of patients showed excellent response, while in auto implantation, 71% had an excellent response. In the MMR group, the earliest excellent response was observed at 3 weeks, whereas in the auto implantation group, it was noted at 9 weeks. The mean time taken for excellent response in Group A was 8.18 ± 2.69 weeks, whereas it was 11.84 ± 2.03 weeks in Group B. The above result showed that inj. MMR had better and earlier response than auto implantation and it was statistically significant [Figures 2 and 3].

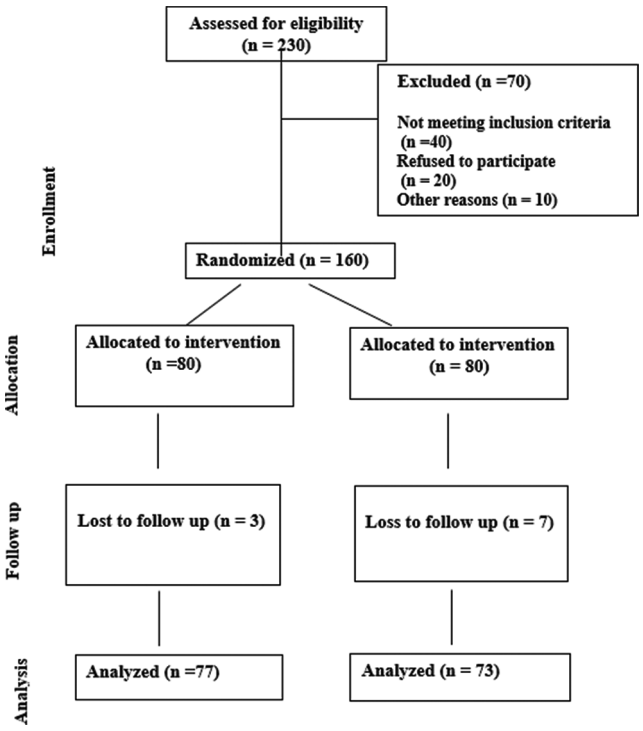

Figure 1: CONSORT diagram showing the flow of participants through each stage of a randomized trial

Table 1: Baseline characteristics of patients

	MMR group (*n*=80)	Auto implantation group (*n*=80)	*P*
Age distribution in years			
10-25	45 (56%)	37 (46%)	0.44
25-40	26 (33%)	33 (41%)	
>40	9 (11%)	10 (13%)	
Range	11-63	10-60	
Mean	28.6±12.56	28.46±12.39	
Gender distribution			
Male	49 (61%)	44 (55%)	0.42
Female	31 (39%)	36 (45%)	
Duration in months			
<6	32 (40%)	27 (33.75%)	0.71
6-12	10 (12.5%)	14 (17.5%)	
12-24	8 (10%)	5 (6.25%)	
>24	30 (37.5%)	34 (42.5%)	
Number			
1-10	44 (55%)	52 (65%)	0.37
11-20	24 (30%)	15 (19%)	
21-30	9 (11%)	11 (14%)	
>30	3 (4%)	2 (2%)	
Mean	9.98±7.35	10.04±7.69	
History of previous therapy	42 (52.5%)	49 (61%)	0.26
Type of wart			
Palmoplantar wart	45 (56.25%)	42 (52.5%)	0.88
Periungal wart	35 (43.75%)	38 (47.5%)	
Occupation			
Student	23 (29%)	19 (24%)	0.81
Agriculturist	13 (16%)	14 (17%0	
Laborer	12 (15%)	10 (12.5%)	
Housewife	7 (9%)	9 (11%)	
Teacher	7 (8.5%)	3 (4%)	
Health professional	5 (6%)	9 (11%)	
Other	7 (8.5%)	10 (12.5%)	
Sportsman	3 (4%)	2 (2%)	
Businessman	3 (4%)	4 (5%)	

Side effects were mild in both groups as shown in Table 3. In Group A, out of 77 patients, the most common side effect was pain (81.4%) during injection, whereas in Group B, painful swelling at the recipient site (5%) was the most common side effect.

Discussion

The role of immune response in the treatment of warts is supported by the fact that spontaneous regression is a well-known phenomenon and these regressing warts show an inflammatory mononuclear cell infiltrate, which is not observed otherwise.[5]

Intralesional immunotherapy includes antigens and vaccines, such as *Candida albicans*, MMR, trichophyton, purified

Table 2: The therapeutic response rate in the two groups according to the time elapsed and at the end of therapy

Response	3 weeks		6wk		9wk		12wk		16wk (*n*=77)		20wk (*n*=77)		24wk (*n*=77)		End of therapy	
Response	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
Excellent	7 (9%)	0	24 (30%)	0	53 (69%)	12 (16%)	66 (86%)	46 (61%)	66 (86%)	53 (70%)	65 (84%)	51 (68%)	62 (81%)	50 (67%)	66 (86%)	53 (71%)
Good	10 (13%)	0	19 (24%)	9 (12%)	11 (14%)	11 (15%)	4 (5%)	8 (11%)	4 (5%)	3 (4%)	5 (7%)	3 (4%)	6 (8%)	2 (3%)	4 (5%)	3 (4%)
Moderate	13 (16%)	0	12 (15%)	11 (14%)	5 (7%)	8 (11%)	1 (1%)	5 (7%)	1 (1%)	5 (7%)	1 (1%)	6 (8%)	1 (1%)	4 (5%)	1 (1%)	5 (7%)
Mild.	11 (14%)	0	9 (12%)	12 (15%)	1 (1%)	19 (25%)	0 (0%)	6 (8%)	2 (3%)	6 (8%)	2 (3%)	6 (8%)	4 (5%)	7 (9%)	0	6 (8%)
Poor	39 (48%)	0	15 (19%)	46 (59%)	7 (9%)	25 (33%)	6 8%)	10 (13%)	4 (5%)	8 (11%)	4 (5%)	9 (12%)	4 (5%)	12 (16%)	6 (8%)	8 (10%)

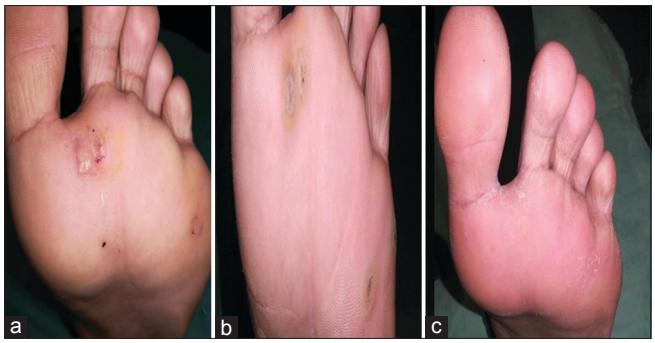

Figure 2: Figures of multiple warts over the foot after intralesional MMR vaccine–(a) before treatment (b) at 3 weeks after the first dose and (c) at 6 weeks after the second dose

Table 3: Side effect of inj. MMR and auto implantation

Side effects	Group A	Group B
Pain during procedure	57 (81.4%)	4 (5%)
Hypo/hyper pigmentation	2 (3%)	4 (5%)
Flu-like symptoms	5 (7%)	0
Infection after procedure	2 (3%)	6 (8%)
Total	66 (82.5%)	14 (18.6%)

protein derivative (PPD), BCG (Bacillus Calmette-Guerin), *Mycobacterium* W. All these agents share a common mechanism of action, that is the induction of cell-mediated immunity by introducing antigens at the wart site. Horn *et al.*[6] reported increased proliferation of peripheral blood mononuclear cells to autologous HPV antigen among responders to mumps, *Candida*, and trichophyton antigen than non-responders. Kim *et al.*[7] further used *Candida* antigen and reported an immune response to HPV 57 L1 peptide among responders, suggesting L1-specific T cell involvement in wart regression. Reports of distant wart resolution suggested a systemic immune response, resulting from intralesional immunotherapy.

In a similar study conducted by Abd El-Magiud *et al.,*[8] comparing inj. MMR with auto implantation showed no statistical difference in the response of manipulated wart among inj. MMR group (72.5%) and auto implantation (60%) group. In contrast, a statistically significant response was found between inj. MMR (20%) and auto implantation (47.5%) among non-manipulated lesions. The author concluded that auto implantation is a suitable approach for patients with multiple warts associated with distant lesions, whereas MMR injection is ideal for a single or fewer number of warts. In contrast, our study concluded that inj. MMR has a better response than auto implantation. This difference can be due to different techniques for administering intralesional inj. MMR. In study by Abd El-Magiud *et al.,*[8] a single wart was injected during each visit, whereas in our study, if lesions were disseminated and involved more than one lymphatic drainage, then the largest wart from each site was taken as a representative lesion and injected with inj. MMR.

The treatment outcome in our study for inj. MMR (excellent response in 86%) was comparable with

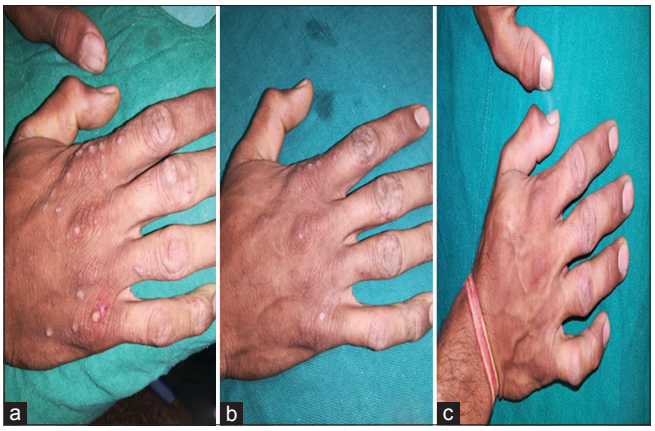

Figure 3: Multiple warts over the hands–(a) before auto implantation, (b) at 6 weeks after auto implantation, and (c) at 9 weeks after auto implantation

a study conducted by Rutnin *et al.*[9] (MMR vs. PPD), in which complete clearance of palmoplantar and periungual warts in inj. MMR was noted in 90% of index lesions and 80.1% of distant lesions, whereas the PPD arm had an 80% improvement in index lesions and 54.6% in distant lesions.

In a study conducted by Rezai *et al.*[10] on resistant palmoplantar warts, the result was 65.2% in the MMR group and 23.85% in the placebo group.

In our study, 5% of patients developed new lesions or recurrent lesions during the follow-up period. This rate of recurrence was similar to that reported in the study by Nofal *et al.*[4] (4.8%).

Among the group A patients (inj. MMR), pain was the most common side effect (81.4%), followed by flu-like symptoms (7%). This was similar to the finding reported by Nofal *et al.,*[4] where tolerable pain during injection was the main side effect observed in 100%, whereas flu-like symptoms were observed in 12.3%.

In the present study, 71% of patients showed an excellent response via auto implantation. This result was comparable with a study conducted by Shivakumar *et al.*,[11] Nischal *et al.,*[3] and Suganthy *et al*,[12] where 80%, 74.1%, and 78% of patients with palmoplantar warts showed resolution of warts within 3 months, respectively. In our study, three patients (4%) developed new lesions during follow-up and had painful swelling (8%) as the commonest side effect. This result was similar to a previous study, where one patient (3.7%) had a relapse, with a new lesion occurring at a different site and 11.1% having similar side effects.[3]

Limitations

The limitation of this study was the absence of a placebo-controlled group and involving only palmoplantar and periungal warts.

Conclusions

In this study, we compared two different ways of

stimulating immunity, that is, either by injecting MMR or by auto implantation. Although both methods have significant response rates, the action of MMR was faster and better compared to auto implantation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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