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Original Research Article

Therapeutic Outcomes of Intra-lesional Immunotherapy with Measles, Mumps and Rubella Vaccine in Cutaneous Warts: A Prospective Study

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Abstract

Background: Common warts caused by Human papilloma virus (HPV) are a widely prevalent condition for which various treatment modalities are present but, all have variable results. Also, the recurrence of warts is commonly faced problem by dermatologist. Our aim is to study efficacy and safety of MMR (Mumps, measles, rubella) antigen as immunotherapy in warts.

Methods: There were 100 patients (M: F= 1.5:1) enrolled in our study. The mean age of presentation of disease was 37.90± 7.30. MMR vaccine 0.5 mL was injected intralesionally in the largest wart and repeated at 3-week interval until complete clearance or maximum of three doses. The outcome was evaluated as complete clearance, excellent, good, or unsatisfactory response on visual analog scale at every visit by comparing baseline clinical photograph. After completion of treatment period, the patients were followed up every 4-week interval for 3 months.

Results: Only 86 patients completed the study and 66 (76.7%) of them showed complete clearance of warts and 17 (19.7%) patients showed good to excellent response. Only 3 (3.5%) patients, had the unsatisfactory response. Except for injection site pain, no major adverse effects were noted. There was no recurrence of warts in follow up period noted.

Conclusion: Intralesional MMR vaccine immunotherapy is a safe and effective treatment option for common warts with advantages of clearance of distant warts, low recurrence and no significant adverse effects. However, more randomised controlled trials are needed to establish minimum effective dose and treatment protocol.

Keywords: Intralesional immunotherapy, Measles–mumps– rubella vaccine, Warts

Introduction

The human papillomavirus (HPV) is a small DNA virus that can infect and cause disease at any site in stratified squamous epithelium, either keratinising (skin) or non-keratinising (mucosa). Over 150 types of HPV have been recognised and characterised. The most common warts on

hands and feet are caused by HPV types 1 and 2. [1]

This virus tends to remain latent in the host cells for a long period of time, causing recurrences, and can cause benign and malignant infections. Among the resulting benign infections, cutaneous warts are the most common. [2]

Cutaneous warts can manifest in various forms—namely, common warts (Verruca vulgaris), plane warts (Verucca plana), plantar warts, and anogenital warts (Condyloma acuminata).

Warts are highly contagious. They can spread from one person to another and from one site to another site in same patient. Extragenital cutaneous warts can be asymptomatic or painful (especially when they are present on the plantar surface) and disfiguring. [3]

Although warts resolve spontaneously in 65%–78% of the patients, many seek treatment because they can be unsightly, tender, or painful.[4]

The treatment of warts depends on two main therapeutic options: conventional destruction and immunotherapy. [5] Management is often challenging because of unpredictable clinical outcomes. Selecting the most appropriate treatment is usually difficult. Many factors affect the choice of treatment such as age, compliance, side effects, costs, pain related to treatment, immunity status, wart location, size, form, and response to previous treatments [6].

Destructive procedures include cauterization with salicylic acid, podophyllotoxin, trichloroacetic acid (TCA), formaldehyde, 5-flurouracil, and photodynamic therapy, or surgical methods like cryosurgery, laser ablation, electrocautery, and excision. They are usually painful, often cause scarring and show inconsistent outcome with high frequency of relapse. Treatment with contact sensitizers, imiquimod, intralesional interferons and oral levamisole, cimitidine, or zinc sulfate has been tried with variable success [7-10].

Most recently, various immunotherapeutic agents have gained popularity for the optimal cure of warts [7]. Antigens such as the measles, mumps, and rubella (MMR) vaccine; Bacillus Calmette–Guérin (BCG), and Mycobacterium indicus pranii are injected intralesionally in and variable responses observed.

Immunotherapy using intralesional MMR vaccine has been found useful in treating common warts particularly in children [11-13]. We conducted the current study to evaluate the efficacy of the MMR vaccine injection in the treatment of cutaneous warts.

Material and Method:

The study was conducted between Jan 2021- March 2022 on patients who presented with cutaneous warts in OPD. Inclusion criteria for study Age>18 yrs, Patient diagnosed with warts, Not using anti wart treatment from last 4 weeks, Patient willing to give informed consent. Pregnant and lactating women; children< 18 yr, patient on immunosuppressive drugs, local site infection, allergic skin disorder, or patient who have received any anti wart treatment in last 1 month were excluded from study.

All of the patients who fulfilled the inclusion criteria underwent clinical examination to confirm the diagnosis of wart. In suspicious cases, a biopsy for histopathological confirmation was done. Detailed history and clinical examination was done to note the duration, number of warts, and the sites involved. Demographic details including age and sex were noted. Photographic records were made before starting treatment and at each subsequent visit. Written consent was obtained from all of the patients. No other treatment for warts was allowed for concurrent use.

Freeze-dried MMR vaccine (Tresivac) single use vials marketed by Serum Institute of India Ltd. Mumbai, India, stored at 2°C–8°C was reconstituted with 0.5 mL of provided diluent (distilled water) as per manufacturer's instruction immediately before intralesional use. All enrolled patients received intralesional injection of 0.5 mL of reconstituted MMR vaccine in largest wart with 30G insulin syringe the dose was repeated at every 3-week interval in a similar fashion until complete clearance achieved or for a maximum of three doses. The patients were evaluated clinically at each treatment session for resolution of treated wart and distant warts, reduced size and number of warts by comparing with baseline clinical photographic records.

The clinical improvement was rated as complete clearance, excellent response, good response, or unsatisfactory response by the patient and physician assessment using visual analog scale score at each visit taking baseline clinical photograph as controls.(Table 1) After completion of treatment period, the patients were followed up every 4-week interval for 3 months.

Table 1: Evaluation of clinical improvement using VAS Score.

Grades of clinical improvement	Definition
Grade 1 Poor response (VAS score ≤50%)	No significant change in size and number of warts
Grade 2 Good response (VAS score=50%-74%)	Some reduction in size only including that of distant ones but no decrease in number of warts
Grade 3 Excellent response (VAS score=75%-99%)	Reduction in size and number including distant ones and few residual warts still visible.
Grade 4 Complete clearance (VAS score=100%)	Complete disappearance of warts including distant ones and skin texture at the site is restored to normal

Result:

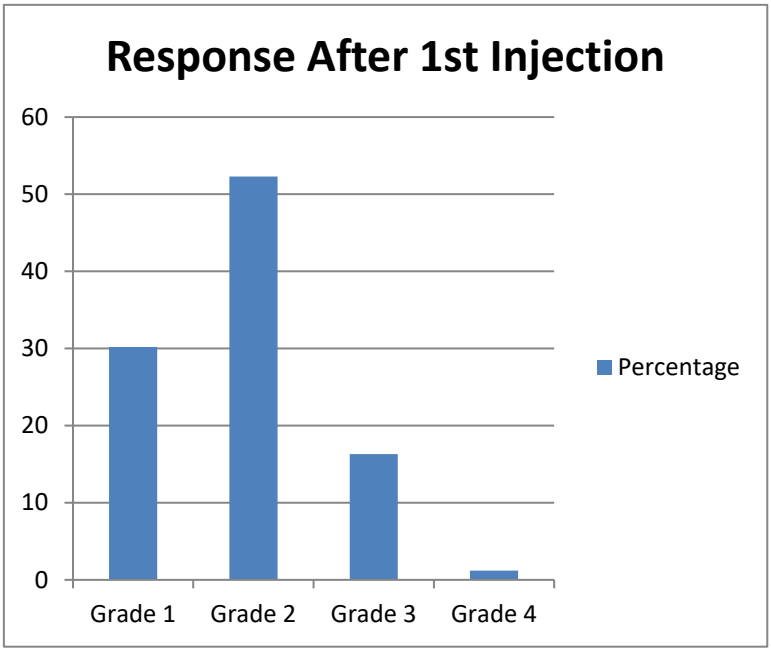
A total of 100 patients were enrolled in study. Fourteen patients in the study did not complete the treatment course citing reasons such as failure to follow up. A total of 86 patients were evaluated, out of which 52 male and 34 were female patients. Male to female ratio M:F=1.5:1.

The mean age of patients was 37.90± 7.30. Mean time for presentation from onset of disease 19.7±12.57. The most common involved site was upper limb (44.2%) followed by head and neck region (26.7%) and lower limb (12.8%). In 16.3% patients warts were present over more than one region.(Table 2).

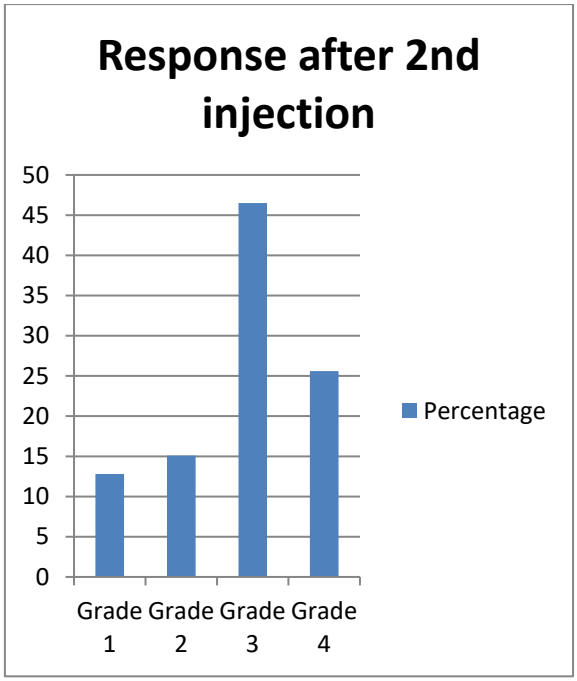
Table 2: Demographic characteristics of the study population

Characteristics	Number of patients(n=86)
Gender	
Male	52(60.5%)
Female	34(39.5%)
M:F	1.53
Age	
Mean Age±SD	37.90± 7.30
<30	19(22.1%)
30-50	53(61.6%)

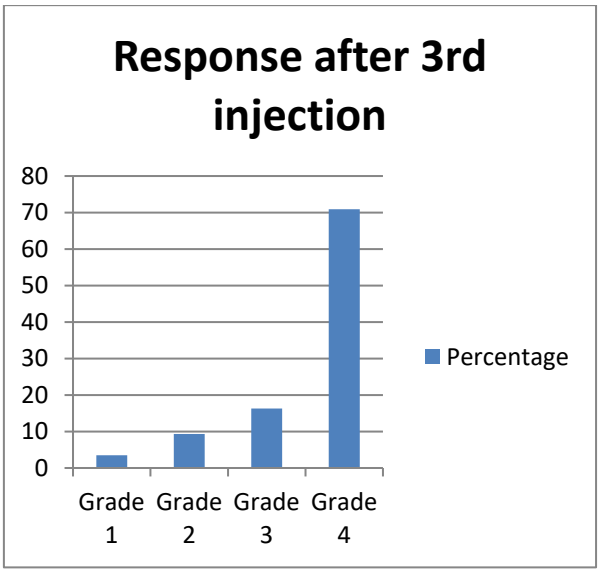
>50	14(16.3%)
Duration in Months	
Mean±SD	19.7±12.57
<12 Months	28(32.5%)
12-60 months	55(63.9%)
>60 months	3(3.6%)
Location of wart	
Upper limb	38(44.2%)
Head and Neck	23(26.7%)
Lower limb	11(12.8%)
Multiple Sites	14(16.3%)



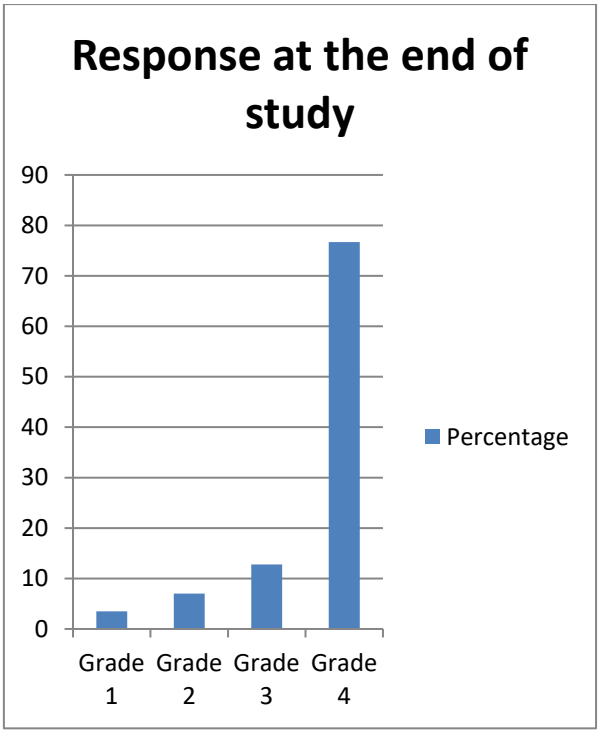
Graph 1: Response at 3 weeks after first dose.



Graph 2: Response at 6 weeks after first dose.



Graph 3: Response at 10 weeks after first dose.



Graph 4: Response at 18 weeks after first dose.

Table 3: Therapeutic response of the intra lesional MMR vaccine

Number of Follow up visits	Therapeutic response	Number of patients (%)
1st Visit(3Weeks)	Grade 1 Grade 2 Grade 3 Grade 4	26(30.2%) 45(52.3%) 14(16.3%) 1(1.2%)
2nd Visit(6 weeks)	Grade 1 Grade 2 Grade 3 Grade 4	11(12.8%) 13(15.1%) 40(46.5%) 22(25.6)
3rd Visit(10 weeks)	Grade 1 Grade 2 Grade 3 Grade 4	3(3.5%) 8(9.3%) 14(16.3%) 61(70.9%)
Final Visit (18 weeks)	Grade 1 Grade 2 Grade 3 Grade 4	3(3.5%) 6(7%) 11(12.8%) 66(76.7%)

At 1st follow up visit 45(52.3%) patients had Grade 2 response and 14(16.3%) patients had grade 3 response. In one patient (1.2%) there was complete resolution of lesion (Grade 4) while 26 (30.2%) patients had grade 1 response. The patient who had grade 4 response in first injection was having a single lesion at periungual region. (Graph 1)

At the end of 6 weeks after 1st dose (3 weeks after 2nd dose) grade 4 response was present in 22(25.6%), grade 3 response in 40 (46.5%) and grade 2 response in 13(15.1%) whereas grade 1 response was seen in 11(12.8%) patients. (Graph 2).

At 3rd follow up visit (10 weeks) 61(70.9%) patients had grade 4 response whereas 66 (76.7%) patients had grade 4 response at the end of study. (Graph 3 & 4) (Table 3)

All patients reported mild-to-moderate injection site pain at the time of intralesional injection. Erythema and edema was noted in 11(12.8%) cases. Other side effects observed were flu-like symptoms (3.5%) and pigmentary changes (1.2%). No systemic adverse effects were noted. (Table 4)

Table 4: Adverse effects

S. No.	Adverse effects	Number of patients(N=86)
1	Pain during injection	86(100%)
2	Edema/erythema	11(12.8%)
3	Flu-like symptoms(Headache and rhinitis)	3(3.5%)
4	Scarring/ Pigmentary changes	1(1.2%)
5	Infection	Nil

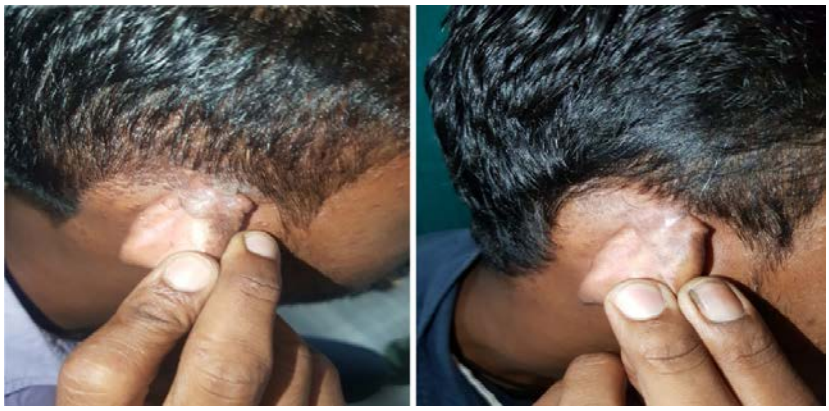


Figure1: Partial response in a verruca plana patient on completion of all three doses

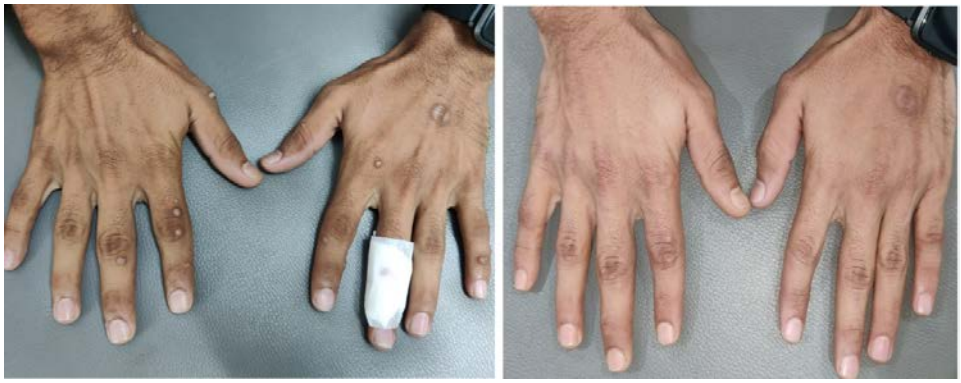


Figure 2: Complete response in a patient having multiple common warts on dorsum of hands after two IL injection of MMR at 3 weeks interval

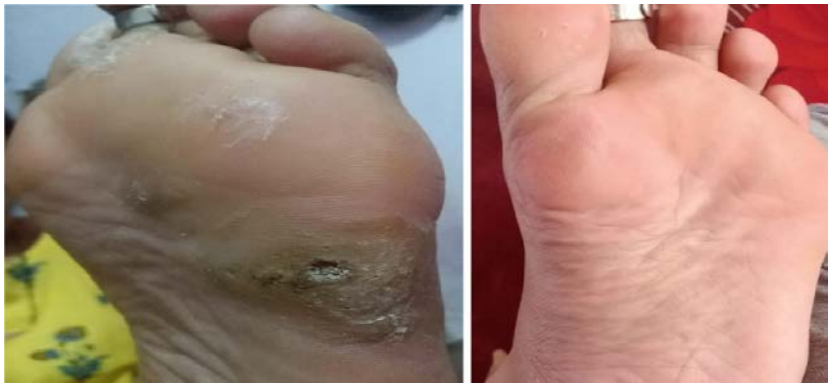


Figure 3: Complete response in case of a plantar wart after two intralesional MMR injection at 3-week interval

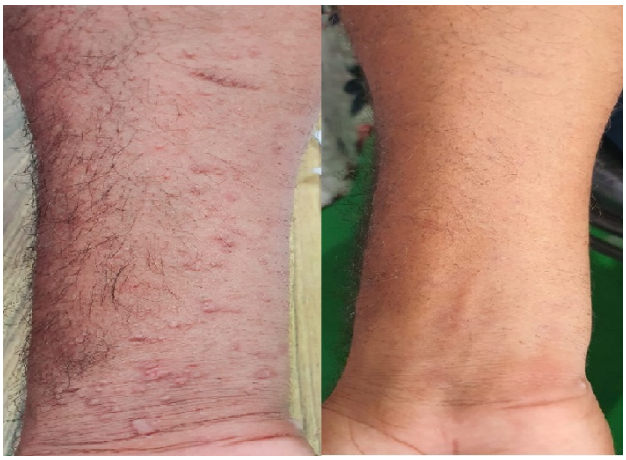


Figure 4: Complete response in a case of verruca plana on ventral aspect of hand after three doses of MMR

Discussion:

Warts affect approximately 10% of total population. They can present at any age but are more prevalent in paediatric age group and immunosuppressed patients [14]. Treatment of common warts is challenging due to their recurrent and relapsing nature [15]. Multiple therapeutic options are available for warts but role of immunotherapy is most widely studied. This is due to an observation of the spontaneous resolution of warts [16]. Evidence shows that cell mediated immunity (Th1 response) leads to infiltration of CD4 T cells in epidermal and dermal part of warts hence, play a critical role in resolution of warts. Here, comes the concept of intralesional immunotherapy using different antigens to stimulate cell-mediated immunity and faster clearance of virus infected cells. Intralesional injection of antigens in warts leads to clearance of virus in same and distant lesion with variable success rate, which is proved in various randomized controlled trials with placebo [13]. In recent times many antigens like trichophytin, Candida, BCG and MMR have been tried as intralesional antigens.

Advantage of immunotherapy over traditional tissue destruction methods of wart removal is reduced scarring and post inflammatory pigmentation. Also warts present inside and near ear canal are difficult to remove via destructive methods.

In our study, 100 patients were enrolled mostly adult male and females with mean age of patients 37.90± 7.30. Mean time for presentation from onset of disease is 19.7±12.57. The most common involved site was upper limb (44.2%) followed by head and neck region (26.7%) and lower limb (12.8%). In 16.3% patients warts were present over more than one region.

In an open-label study, Nofal et al. [17] studied intralesional injection with 0.3 ml of the MMR vaccine for 65 patients with recalcitrant warts, 41 patients (63%) had a complete response, and 2 had a recurrence. In another open label study by Na et al., in which 136 patient were given intralesional MMR 0.1-0.3 ml as per wart size, once in 2 weeks till clearance or for maximum of 6 doses. Complete resolution was seen in 26.5% patients, no response in 48.5% patients and partial response in 51.5% patient.

In both studies, most patients required more than one session. At the end of our study 76.7% patients showed complete clearance with disappearance of distant lesions. Grade 2and 3 (partial clearance) was observed in 19.8% of patients. However, 3.5 % patents did not respond even after third dose. The better response in our study can be explained by the amount of antigen taken 0.5 ml.

Gamil et al.,[18] in an open label study treated 40 patients with intralesional MMR 0.5 ml into largest wart every 3 week till complete clearance or maximum of 3 doses Complete clearance in 87%, partial response in 4.3% and no response in 8.7% . The increased response rate in this study could be due to longer follow (9 month) up than ours (18week).

In our study after first dose only one patient had complete clearance of wart. Immune status, number of warts, underlying condition like diabetes and site of presentation can impact the duration of therapeutic response.

Injection site pain is the only major side effect noted which was well tolerated. Only few patients 3 (3.5%) had flu like symptoms.

Limitation:

Smaller sample size, short follow up and lack of placebo control group are few shortcomings in this study.

MMR effects according to type of wart, site and number of lesions needs to be evaluated in further studies.

Also co-morbidities in patients like HIV, diabetes etc. and their impact on treatment results, duration of clearance of lesions further needs to be assessed.

Conclusion:

Advantage of MMR compared to other conventional destructive methods is less downtime, No scarring and pigmentation, less recurrence rate, resolution of distant warts and less side effects compared to other conventional antigens. Also, it seems like a better treatment option for difficult to treat sites like nail bed and ear canal.

Disadvantage of MMR is it has variable results, slow response and long duration of treatment leads to high dropout rate.

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1. **Conflicts of interest:** The authors declare that they have no conflicts of interest.

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