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Original Research Article

Role of intralesional measles, mumps and rubella vaccine in treatment of warts

Noreen Munshi*, Krishnendra Varma

R. D. Gardi Medical College, Ujjain, Madhya Pradesh, India

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***Correspondence:**
Dr. Noreen Munshi,
E-mail: noreenmunshi10@hotmail.com

ABSTRACT

Background: Objective of the research was to study the efficacy and safety of measles, mumps and rubella (MMR) vaccine in the treatment of warts.
Methods: 53 patients with single or multiple warts in all age groups were included in the study. The patients received intralesional MMR vaccine 0.5ml into a single wart or the largest wart in case of multiple lesions at interval of 3 weeks for 3 treatments. All patients were followed up every 2 months up to 6 months regarding relapses. side effects and therapeutic outcomes were evaluated.
Results: Out of 53 patients, 50 completed the study. Complete response was seen in 36 (72%), partial response in 09 (18%) and no response in 05 (10%) patients. 3 out of 36 patients with complete response were having recurrence of warts. Pain at the site of injection and flu like symptoms were the main side effects observed.
Conclusions: Intralesional immunotherapy with MMR vaccine was found to be a simple, effective, and safe treatment for warts. This study proved to be cost effective as patients can be treated with just 03 doses of MMR vaccine given at the interval of three weeks.

Keywords: Measles mumps and rubella, Vaccine, Warts, Human papilloma virus

INTRODUCTION

Warts or verruca are benign growths caused by human papillomavirus infection of keratinocytes. Human papilloma virus (HPV) infections are very common and can cause disease at any site in stratified squamous epithelium (both skin and mucosa). A number of types of verrucae have been identified which include- common warts (verruca vulgaris), plane warts (verruca plana), plantar warts, genital warts, and periungual warts. Although warts may resolve spontaneously in 65-78% of the patients within 2 years, many patients seek treatment because they can be tender, unsightly or painful.[1] Several treatments including surgery, cryotherapy, electrocautery, laser, or topical agents aim to eradicate the lesions; the treatment strategy can vary depending on the disease location, severity, and the patient's immune status.[2] There are many destructive and immunotherapeutic options for warts such as topical salicylic acid, cantharidin, bleomycin, cryotherapy, laser ablation, trichloroacetic acid, formaldehyde, 5-fluorouracil, photodynamic therapy and surgery, contact sensitizers, imiquimod, intralesional interferon, electrocautery, and oral drugs, such as levamisole, cimetidine, and zinc sulfate.[3] Despite the above-mentioned wart treatment modalities, the incidence of recurrence is high and this is where immunotherapy comes into play. Immunotherapy (topical and systemic) now has an important place in the treatment of warts for its ease of use, non-destructive effect and effective results. Immunotherapy is based on activating the immune system

to achieve an HPV-targeted immune response. Immunotherapy can be administered topically, by intralesional injection, or by systemic administration. There are numerous immunotherapeutic agents that have been used for the treatment of warts e.g.: BCG vaccine, measles, mumps and rubella (MMR) vaccine, imiquimod, zinc, and vitamin D. MMR vaccine is a lyophilized (freeze-dried) preparation of live attenuated strains of the measles, mumps and rubella viruses. It accelerates the clearance of virus and viral infected cells by the stimulation of cell mediated and humoral immunity.[4] This method can be used with ease because of the vaccine availability and safety. Even after so many studies and trials, immunotherapy has not yet established itself as a universally accepted treatment for warts. This study is an attempt to ascertain its efficacy in our patients in a tertiary care center.

METHODS

The present study is a prospective observational study undertaken to study the efficacy of intralesional MMR vaccine injection in the treatment of cutaneous warts. This single-blind, randomized, placebo-controlled study was conducted from January 2020 to December 2020. Patients who presented to the outpatient department of dermatology of R.D. Gardi Medical College with cutaneous warts anywhere on the body other than the anogenital area were included. The study was done after obtaining clearance from the ethics committee of the institution. Included patients were of any age with single or multiple warts without using any type of anti-wart treatments for the last one month.

Inclusion criteria

Patients of any age group, willing for the procedure, whose warts have not responded to any other modality of treatment, with recurrent warts, and with any number of warts were included in the study.

Exclusion criteria

Patients with prior hypersensitivity reaction to MMR antigen, pregnancy/lactation, presence of any active infections (e.g., herpes, and tuberculosis), and immunocompromised individuals were excluded.

Methodology

All the patients who fulfilled the inclusion criteria were examined clinically to confirm the diagnosis of wart. Written consent was obtained from all the patients. In suspicious cases, a histopathological confirmation was done.

Detailed history was taken to note the duration, number of warts and the sites involved. Demographic details such as age and sex were noted. Photographic documentation was done.

Procedure

The sample size was 49. Keeping the dropout rate in mind, the sample size was increased to 53 patients. MMR vaccine (TRESIVAC®; Serum Institute of India Pvt. Ltd., Pune, India) is available in a 0.5 ml single-dose vial. Prior sensitivity testing was performed using a dose of 0.1 ml via injecting intradermally into the volar aspect of the left forearm. The injected sites were examined after two weeks for immune response in the form of erythema or nodule formation. In sensitized patients, 0.3 ml of MMR vaccine after reconstitution with distilled water was injected intralesionally into their single largest wart. Injections were given every 3 weeks until a maximum of 3 injections was achieved. Patients were assessed for response and any adverse effects at each visit. Follow-up was performed at every visit and at 2 months and 6 months after the last injection. Wart recurrence was assessed at each visit. Photographic documentation was made before and after the treatment.

Data analysis

All the statistical analysis was done by statistical software statistical package for the social sciences (SPSS) 23.

RESULTS

Table 1 shows the distribution of patients according to age. There were 13 (26.0%) patients were in the age group 11-20 years, 17 (34.0%) patients were in the age group 21-30 years, 10 (20.0%) patients in the age group 31-40 years, 9 (18.0%) patients in the age group 41-50 years and 1 (2.0%) patient was in the age group >50 years. Majority of the patients were in the age group 21-30 years.

Table 1: Distribution of patients according to age.

Age group (years)	Number	Percentage
11-20	13	26.0
21-30	17	34.0
31-40	10	20.0
41-50	9	18.0
>50	1	2.0
Total	50	100.0

Table 2: Distribution of patients according to type of warts.

Type of warts	Number	Percentage
Interdigital	3	6.0
Palmar warts	14	28.0
Plantar warts	16	32.0
Verruca Plana	6	12.0
Verruca vulgaris	11	22.0
Total	50	100.0

Table 2 shows the distribution of patients according to type of warts. 3 (6.0%) patients were having interdigital warts,

14 (28.0%) patients were having palmar warts, 16 (32.0%) patients were having plantar warts, 6 (12.0%) patients were having verruca plana and 11 (22.0%) patients were having verruca vulgaris. Plantar warts were the most common type of wart seen, followed by palmar warts.

Table 3 shows the distribution of patients according to response to treatment. In 5 (10.0%) patients there was no response to the treatment, in 9 (18.0%) patients there was partial response to the treatment, while in 36 (72.0%) patients were having complete response to the treatment.

Table 3: Distribution of patients according to response to treatment.

Response to treatment	Number	Percentage
No response	5	10.0
Partial response	9	18.0
Complete response	36	72.0
Total	50	100.0

Table 4 shows the distribution of patients according to number of sittings. 2 (4.0%) patients required one sitting only, 10 (20.0%) patients required two sittings and 38 (76.0%) patients required three sittings.

Table 4: Distribution of patients according to number of sittings.

Number of sittings	Number of patients	Percentage
One	2	4.0
Two	10	20.0
Three	38	76.0
Total	50	100.0

Table 5 shows the distribution of patients according to clearance of distant warts. In 9 (18.0%) patients there was no clearance of distant warts, in 1 (2.8%) patient there was partial clearance, while in 26 (72.2%) patients there was complete clearance of distant warts. The treatment was quite effective on the distant warts also.

Table 6 shows the distribution of patients according to complete response patients. In 33 (91.7%) patients did not have any recurrence of warts, while in 3 (8.3%) patients were having recurrence of warts.

Table 5: Distribution of patients according to clearance of distant warts.

Clearance of distant warts	Number	Percentage
No	9	25.0
Partial	1	2.8
Yes	26	72.2
Total	36	100.0

Table 6: Distribution of patients according to recurrence of warts in the complete response patients.

Recurrence of warts	Number	Percentage
No	33	91.7
Yes	3	8.3
Total	36	100.0

Table 7 shows the distribution of patients according to adverse events. In 42 (84.0%) patients there was pain during injection, 4 (8.0%) patients reported flu-like symptoms, 2 (4.0%) patients had edema, 2 (4.0%) patients had erythema, 2 (4.0%) patients had itching after injection and 1 (2.0%) patient each had infection, wound formation, scarring after injection and 2 (4.0%) patients had no adverse events.

Table 8 shows the association between type of warts and response to treatment. There was no statistically significant association seen between the type of warts and the response to treatment ($p>0.05$), showing that response to treatment is independent of the type of warts.

Table 7: Distribution of patients according to adverse events.

Adverse events	Number	Percentage
Pain during injection	42	84.0
Flu-like symptoms	4	8.0
Edema	2	4.0
Erythema	2	4.0
Itching after injection	2	4.0
Infection	1	2.0
Wound formation	1	2.0
Scarring after injection	1	2.0
No adverse events	2	4.0

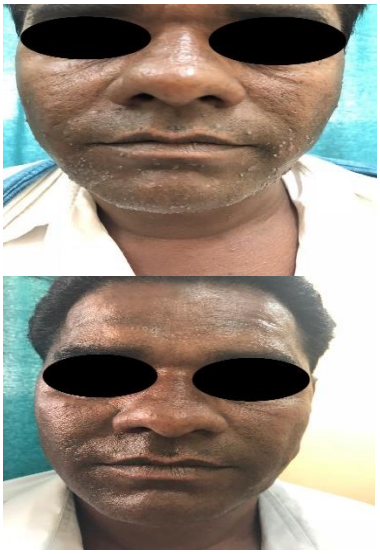

Figure 1: A case of complete clearance of common warts over the face (a) before treatment, and (b) after treatment showing complete clearance.

Table 8: Association of response to treatment in relation to type of warts.

Type of warts	Response to treatment (%)			Total (%)
	No response	Partial response	Complete response	
Interdigital	0 (0.0)	2 (66.7)	1 (33.3)	3 (100.0)
Palmar warts	0 (0.0)	2 (14.3)	12 (85.7)	14 (100.0)
Plantar warts	3 (18.8)	2 (12.5)	11 (68.8)	16 (100.0)
Verruca plana	0 (0.0)	0 (0.0)	6 (100.0)	6 (100.0)
Verruca vulgaris	2 (18.2)	3 (27.3)	6 (54.5)	11 (100.0)
Total	5 (10.0)	9 (18.0)	36 (72.0)	50 (100.0)

Pearson Chi-square value=12.321, df=8, p value=0.137, not significant.

DISCUSSION

Local tissue-destruction is a commonly used method in the treatment of warts. However, it is not practical for multiple lesions such as palmoplantar and facial lesions due to associated risk of scarring or pigmentation. Most current therapeutic options result in resolution of warts within 1–6 months, but 20–30% of the patient usually relapse and new lesions may appear as a result of failure of the cellular immune system to detect and remove the lesions completely. Immunotherapy aims to achieve an HPV-targeted immune response and offers a theoretical advantage in effectively controlling viral proliferation. Hence, various antigens of fungal, mycobacterial and bacterial origin have been used to stimulate cell-mediated immunity. In the present study an attempt has been made to demonstrate the efficacy of intralesional MMR vaccine for the treatment of warts, which is an inexpensive and effective modality to treat the warts.

Out of the total 53 cases recruited, 50 cases completed the study with 3 sittings at an interval of 3 weeks and followed up for 6 months after the final sitting.

In our study the age of the patients ranged from 11 to 54 years with a mean age of 29.3 years. Other studies conducted by Awal et al showed that the minimum age of the patient was 15 years while the maximum was 48 years with a mean age of 28.9 years.[6] Shah et al showed that majority (56%) patients belonged to 18-45 years age group.[7] Zamanian et al carried out study to assess the efficacy of intralesional injection of MMR vaccine in patients with warts which showed mean age was 18.9 years.[5]

There were 8 females and 42 males in our study, showing a male preponderance in the study patients. Males also predominated in other studies conducted by Awal et al, Dhope et al, and Zamanian et al.[5,6,9] This can be attributed to working in outdoors, making males to be more susceptible.

In our study, patients with palmoplantar warts were more in number (32.0%) as palmoplantar warts are comparatively resistant to other treatment modalities. Awal et al conducted a study in which out of 72 patients 23 (31.9%) were having plantar warts which were more in number than any other type of warts.[6] Another study conducted by Shah et al demonstrated that in upper limb particularly the dorsa of hands were the most common site affected in (40%) whereas plantar warts were seen only in 8% patients.[7]

In the present study, out of 50 cases only 5 patients had no improvement, 9 patients had partial improvement while 36 patients had complete improvement accounting to complete response in 72% of cases. Nofal et al in 2010 reported that 81.4% patients showed complete clearance of warts with minimal side effects, partial response in 10%, and no response in 8.6% patients.[8] These findings were slightly better than the results of our study. Similar to Nofal et al's observation, Zamanian et al also observed a slightly higher response (75%) compared to our study. [5,8] Saini et al observed a lower rate of complete clearance (46.5%).[11]

Intralesional injection of MMR vaccine is usually associated with mild side effects such as flu-like symptoms, swelling, erythema, itching and pain at the site of injection. Pain during injection and flu-like symptoms were common side effects reported by patients enrolled in our study. Pain during injection was complained by 84% patients, 8.0% reported flu-like symptoms, 4.0% patients developed edema and erythema, 4.0% complained of pruritus after injection, and 2.0% developed some infection at the site of injection. These findings were comparable with various other studies. In a study by Zamanian et al there were no important adverse effects as a result of MMR injection, except the pain due to injection.[5] Influenza-like syndrome was reported in a few patients but was tolerable. Shah et al observed tolerable pain at the injection site as the main side effect, seen in 36% patients.[7] Flu-like symptoms were reported in 4% patients within 12 hours of injection, which resolved rapidly by NSAIDs. No swelling, redness, or itching at the injection site was observed. In Awal et al's study – 90% of the patients reported pain while receiving the injection.[6] Additionally, 6% patients reported rhinitis and headache (flu-like symptoms), which were relieved using medication. Erythema and edema after injection were observed in only 4% patients.

In this present study, recurrence of warts in the patients with complete response was seen in 3 (8.3%) out of 50

patients were having recurrence of warts. Awal et al also reported a recurrence rate of 2.7%.[6] This was in contrast to the studies done by Nofal et al and Zamanian et al where no relapse was observed.[5,8] In a study by Johnson et al relapse occurred in 2% of the patients who received mumps antiserum.[10] Shah et al have not demonstrated any recurrence in six months follow up after treatment by intralesional MMR vaccine.[7]

Limitations

Lack of control group was a major drawback in this study.

CONCLUSION

There are clinical evidences that cellular immune responses play an important role in HPV infection and disease. In addition, the prevalence of HPV-related lesions increases in transplant recipients and immunocompromised individuals. This finding indicates that if immunotherapy modalities are able to induce the immune system for destroying the virus and infected host cells, they could be considered as a therapeutic option for the treatment of warts. Concomitant use of multiple modalities of immunotherapy or combination of immunotherapy with other destructive modalities such as cryotherapy, radiofrequency ablation etc. has been shown to enhance the treatment response. Although the mechanism of effectiveness of intralesional injection of MMR vaccine is not completely known, the major mechanism of action immunotherapy appears to be non-specific inflammatory response to antigens. From our study, it can be inferred that the intralesional MMR vaccine has therapeutic potential as a safe and effective treatment modality for the treatment of cutaneous warts. Especially multiple warts, as it has advantage of injecting in a single wart and achieving cure even at distant sites. It seems to be efficacious, with good cure rates, an excellent safety profile, good tolerability and cost-effective with fewer side effects and a lower relapse rate as compared to the other treatment modalities. It prevents recurrence of warts with almost complete clearance. With these advantages, we conclude that MMR immunotherapy can potentially be used as a first-line treatment for warts as it is cheap and easily available.

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