INTRALESIONAL MEASLES, MUMPS AND RUBELLA (MMR) VACCINE-AN EFFECTIVE THERAPEUTIC TOOL IN THE TREATMENT OF WART

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ABSTRACT: BACKGROUND: Warts are common cutaneous viral infection. Various therapeutic modalities have been using in treatment of wart, but none of them are standardised. Immunotherapy is new current approach in the treatment of wart.
AIMS: To know the efficacy and safety profile of Measles Mumps Rubella (MMR) Vaccine in the treatment of wart.
METHODS: MMR vaccine was injected into a largest single wart intralesionally and subsequent injections given every 2 weeks apart for about 3 to 5 times. Every month followup of patients was done to know the clearance of wart.
RESULTS: Complete remission of warts seen in 70.4% of patients, partial remission seen in 22.2% and no response was seen in 7.4% of patients. No serious adverse side effects were seen in the current study.
CONCLUSION: MMR vaccine can be considered as a safe, effective, inexpensive intralesional immunotherapeutic modality in the treatment of wart.

KEYWORDS: Immunotherapy, MMR Vaccine, Wart.

HOW TO CITE THIS ARTICLE: J. Raju, Ashwini V. Swamy, B. L. Nanjunda Swamy, K. R. Raghavendra. "Intralesional Measles, Mumps and Rubella (MMR) Vaccine - An Effective Therapeutic Tool in The Treatment of Wart." Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 50, November 23, 2015; Page: 8548-8551,
DOI: 10.18410/jebmh/2015/1176

INTRODUCTION: Warts are common cutaneous viral infections involving skin and mucous membranes caused by Human Papilloma Virus (HPV) characterised by benign proliferartive hyperkeratotic lesions. HPVs are ubiquitous in nature and non-enveloped ds DNA virus. More than 100 species have been reported till now.[1] Spontaneous resolution occurs in 65% to 70% of warts within 2 years.[2] Although a wide spectrum of therapeutic modalities have been used for the management of warts, none has yielded consistently effective results or succeeded in preventing recurrence of wart.[3] Destructive modalities are designed to remove the visibly infected lesions; however, non-visible infected tissues are not targeted by these approaches.[4,5] The topical therapies are salicylic acid, tretinoin, podophyllotoxin, trichloroacetic acid, formaldehyde, 5-fluorouracil, photodynamic therapy and surgical/cytotoxic modalities such as cryotherapy, laser ablation, intralesional bleomycin, electrocautery, and surgical excision.[6,7,8,9] Each mode of therapy has its own complications and failure rates. After successful clearance of existing lesions some patients still develop new warts in other areas. This leads to think of new therapeutic modalities, which cure and develop immune response towards HPV. Although, the exact mechanisms are unclear, but most literature and evidences suggest that cell mediated immunity (CMI) plays an important role in control of HPV infection.[10] Many authors have tried various methods to stimulate the immunological response such as oral levamisole, cimetidine, zinc sulfate, cidofovir, intralesional interferons, topical dinitrochlorobenzene (DCP), squaric acid dibutyl ester (SADBE), imiquimod, intralesional immunotherapy with mumps, candida and trichophyton antigens, intradermal BCG vaccine, and intralesional Measles Mumps Rubella (MMR) vaccine.[2,4,11] Hence, we conducted the study to know the efficacy and safety of intralesional MMR vaccine in the treatment of wart.

Submission 16-11-2015, Peer Review 17-11-2015,
Acceptance 19-11-2015, Published 23-11-2015.
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DOI: 10.18410/jebmh/2015/1176

METHODS: STUDY DESIGN: We undertook a prospective study of injecting intralesional MMR vaccine into single largest wart in our Outpatient Department of Skin and STD MMC and RI Mysuru from Janaury 2015 to June 2015. The ethical committee clearance was taken before starting the study.

Patients: Patients who had more than five extra genital warts involving more than one body site or difficult to treat sites (periungual, palms and soles), untreated cases from the past 6 months with no signs of spontaneous regression in the past 6 months were administered intralesional MMR vaccine. Informed consent for therapy was taken from all patients. Patients aged <18 years, pregnant and lactating women, recent history of viral infections such as herpes and/or bacterial infections such as impetigo in skin, recent history of any infective febrile disease, suffering from chronic diseases such as diabetes/renal/hepatic illness, and immune compromised patients (human immunodeficiency virus [HIV], other immunodeficiency disorders, patients

taking immunosuppressive drugs, etc.) were excluded. All patients underwent clinical examination by a dermatologist in the dermatology clinic to confirm the diagnosis of wart. Biopsy and histopathological examination was done only in the suspicious cases. Then demographic information, clinical history, and present condition of their disease were noted. The information about age, gender, disease duration, number of lesions, and involved sites also noted. Complete blood profile, FBS, PPBS, RFT, LFT, HIV 1 and 2 and urine routine were done in all patients.

Treatment Protocol of MMR Vaccine: MMR vaccine 0.3 cc (Tresivac ® Serum Institute of India Ltd., Pune) was injected intralesionally after reconstitution with diluent to a single largest wart under aseptic precautions. If the reconstituted vaccine not reused within 8 hours it was discarded. The injections were repeated every 2 weeks for a maximum of five injections. Then all patients were followed up monthly for 6 months to evaluate the side effects, probable relapse and therapeutic outcomes.

Assessment of Response: Clinical response like decrease in size, changes in the surface, decrease in number were noted in both injected and un-injected warts at each visit and a sequential clinical photographic record was maintained. Both local as well as patient-reported side effects were noted. The response was expressed as a percentage improvement from baseline based on physician assessment. Lesions with size decrease of less than 50% were defined as no therapeutic response, size decrease between 50% and 99% as partial response, and complete clearance of the lesions was considered as complete cure or response.[5,12]

Quantitative data were shown as Mean±Standard Deviation and nominal data as percent and frequency. SPSS-16 (SPSS inc, chicago, USA) was the statistical software used.

RESULTS: Total 30 patients with multiple warts who gave informed consent were included in study. Out of which 3 patients were lost for followup. Total 27 patients completed the study. Out of 27 patients, 17(62.9%) were male and 10(37.03%) were female. Most of the patients were adults between 20 to 40 age (63%) with mean age of 30.98±8.13. Duration of wart was less than 1 year in 18 patients (66.6%). Total number of lesion were 5-15 in 16 cases (59.2%), more than 15 in 9 cases (33%). Hand and foot involvement was there in 25 cases (92.6%) and face and neck involvement in only 2(7.4%) cases. Number of injection required were 3 doses in 13 cases, 4 doses in 4 cases and 5 doses in 10 cases. Complete remission was noticed in 19 cases (70.4%) [Figure 1a, 1b], partial remission occurs in 6 cases (22.22%) [Figure 2a, 2b], and no response was seen in 2 cases (7.4%) (Table 1).

	Number of Patients(n)	Total Number of Patients(n)	%
Complete Remission	19	27	70.3
Partial Remission	6	27	22.22
No Response	2	27	7.4

Table 1: Therapeutic Response of Intralesional MMR vaccine

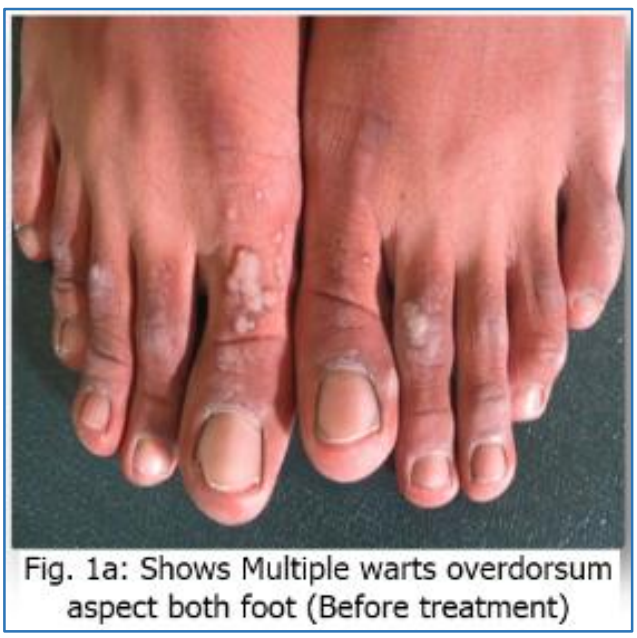

Fig. 1a: Shows Multiple warts overdorsum aspect both foot (Before treatment)

Fig. 1b: shows complete clearance of wart (After treatment)

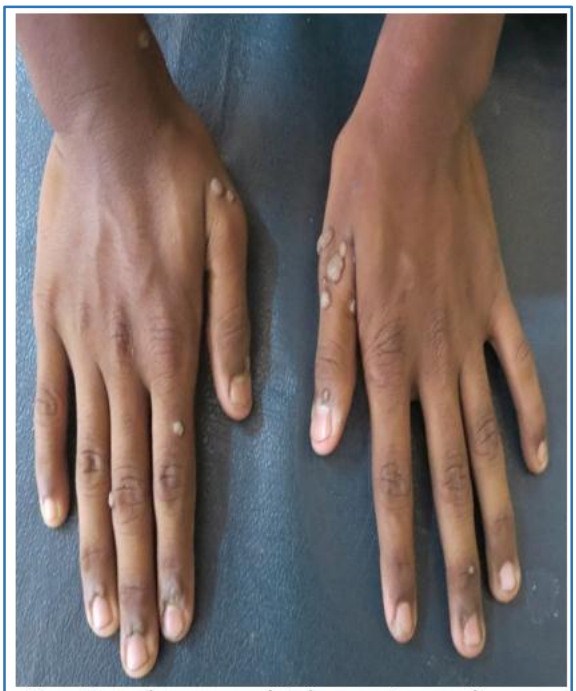

Fig. 2a: shows multiple warts on dorsum aspect of both hands (Before Treatment)

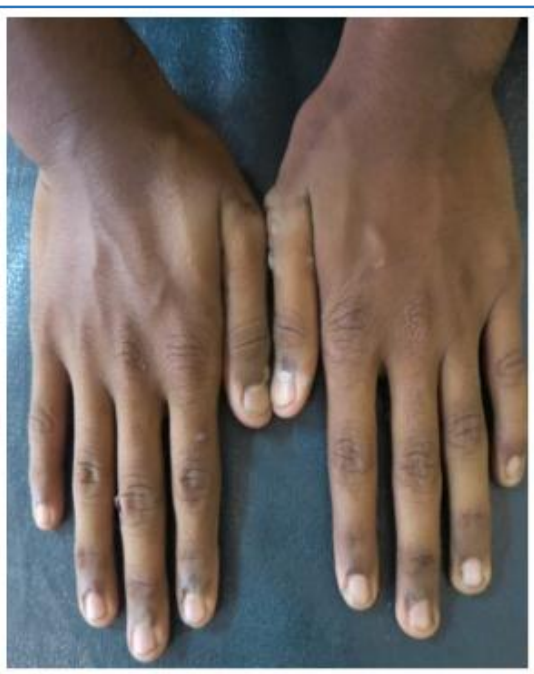

Fig. 2b: shows partial remission i.e 50-99% clearance of wart (After treatment)

DISCUSSION: Various therapeutic options are available for the treatment of wart, but none of them have satisfactory outcome. Side effects like scarring, relapse and recurrence are more in treatment of multiple and difficult site wart. Most of the current therapeutic options result in clearing of wart within 1-6 months, but in 20-30% of the patient's relapse occurs and new lesions may appear as a result of failure of the cellular immune system to detect and remove the lesions completely.[13] The cellular immunity plays important role in the development of wart.[14] T cell (CD4, CD8) infiltration in the wart lesion has been found in spontaneously resolving wart and also prevalence of HPV-related lesions increases in the HIV-infected patients, transplant recipients and other immunosuppressive conditions.[15] Above finding suggests that if therapeutic modalities are able to induce the immune system for clearing the virus and the infected host cells, then it could be considered as a best therapeutic option for the treatment of wart.

Various immunotherapeutic antigens have been used for intralesional immunotherapy include tuberculin.[15] BCG.[16] Candida and trichophyton.[17] and MMR.[18] The mechanism of action of intralesional MMR immunotherapy is still an enigma. Some authors hypothesize that it acts through the induction of strong nonspecific inflammatory response against the HPV-infected cells.[19,20] It has also been suggested that the trauma itself may cause wart clearance in previously sensitized individuals.[15] The cytokines produced by immune system such as interleukin (IL)-2, IL-4, IL-5, IL-8, Interferon (IFN)-γ and Tumor necrosis factor (TNF)-α stimulate a strong immune response against HPV may be another possible mechanism of action.[21] Another author reports that the response to antigen injection was associated with proliferation of peripheral blood mononuclear cells that promotes Th1 cytokines including IFN-γ and IL 2, which further activate cytotoxic T cells and natural killer (NK) cells that eradicate HPV-infected cells.[17]

In our short study, most of the patients belonged to adult age group and males outnumbered the female patients. Hands and feet involvement commonly seen in our study group might be because of more exposure and susceptible for trauma, pricks and inoculation. In our study complete remission seen in 19 patients (70.4%), partial remission seen in 6 patients (22.2%) and no remission seen in 2 patients (7.4%), results were in concordance with Nofal A.[18] et al. which showed 80% clearance rate, Mohammad NS.[22] et al. showed 82% of complete remission, Gamil H.[23] et al. also reported 87% clearance rate in injected warts, Horn TD.[17] et al. reported 74% clearance of wart in their study. In a case controlled study by Zamanian A.[12] et al. reported complete clearance of wart in more than 75% cases, which was statistically significant compared to normal saline control. During our 6 months follow-up period, no recurrence of lesion was seen in complete remission group. During study no serious adverse reaction occurred except pain during injection and flu-like symptoms in only 2 patients which was subsided within 24 hours after taking anti-inflammatory medications. Advantages of MMR vaccine were safe, cost effective, no scarring, needs treatment of largest single wart only and patients are able to resume daily activities immediately.

CONCLUSION: Intralesional immunotherapy of wart by MMR vaccine promises as a good efficacious therapeutic modality as it has advantage of injecting single wart, less side effects and cost effective. Limitations of this study were less number of cases, larger studies and more randomised controlled studies needed to standardise treatment.

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