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A Comparative Study on the Efficacy and Safety Profile of Intralesional MMR Vaccine And Autoimplantation in The Treatment of Periungual Warts

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Abstract

Background: Warts are benign epidermal tumors of mucocutaneous surface caused by Human Papilloma Virus. They poses a therapeutic challenge to the treating dermatologist, particularly periungual warts. The treatment modalities for periungual warts are associated with scarring, disfigurement and deformities. Hence immunotherapy has evolved as an effective, safe and inexpensive treatment modality.

Objectives: To evaluate the efficacy and safety profile of MMR vaccine in the treatment of periungual warts and to compare it with autoimplantation.

Methods: In this randomised controlled study on 40 patients with periungual warts, one group (n = 20) were treated with intralesional MMR vaccine and the second group (n = 20) with autoimplantation. Three treatment sessions were carried out in both groups at an interval of two weeks in MMR group and one month in autoimplantation group. Results were assessed by dermatologist's objective assessment and patient's subjective score.

Results: Out of 20 recruited patients in MMR group, 18 (90%) showed complete cure and two (10%) had partial clearance. In the autoimplantation group, 11 (55%) had complete cure, two had partial clearance and seven (35%) had no response. There was statistically significant difference in the response between the two groups during 2nd and 3rd follow up (p value – 0.006 and 0.015) respectively The mean number of treatment sessions required for complete cure showed no statistically significant difference.

Conclusion: Intralesional MMR vaccine was found to be more effective compared to autoimplantation as far as the duration of treatment, cost, procedural time and feasibility issues are concerned.

Keywords: Warts, Nails, Vaccination

Introduction

Warts are benign epidermal tumors caused by human papilloma virus (HPV) which often cause discomfort and embarrassment to the patient [1]. They are usually asymptomatic, but may become tender when fissured or growing beneath the nail plate [1].

Periungual warts are the warts around the nail caused usually due to HPV-1, 2 and 4. The treatment of periungual warts has always been challenging as they are highly recurrent and very often responds poorly to conventional treatment modalities. Treatment of warts by conventional destructive modalities are painful, uncomfortable, time consuming, requiring multiple sessions, expensive with high recurrence rate and cause dyspigmentation or scarring, so none of them has been qualified to be called as gold standard [2,3].

Immunotherapy is a novel approach based on the recognition of virus by immune system [4]. It is necessary to search for a safe, inexpensive, effective and simple immunotheurapeutic agent for the management of warts [5]. Immunotherapy has been carried out using various antigens like mumps, candida and trichophytin [6-8].

Various studies have shown that intralesional mumps, measles, rubella (MMR) vaccine results in regression of warts via immunomodulation and induction of immune system [9].

Homologous autoimplantation is a simple technique wherein the injection of homologous wart tissue from untreated warts leads to resolution of warts [10]. The immune response thus stimulated results in clearance of warts all over the body. It seems to be an inexpensive and effective treatment modality [11].

The aim of this study was to evaluate the efficacy and safety profile of intralesional MMR vaccine for the treatment of difficult to treat periungual warts and to compare its efficacy with that of autoimplantation.

Material and Methods

This was a randomized, unblinded parallel group, active controlled trial conducted on 40 patients with periungual warts attending our outpatient dermatology department. Institutional ethical committee clearance was obtained prior to the start of the study. Patients of more than 12 years of age, with at least one periungual or subungual wart with or without distant warts were included in the study. Patients who were immunocompromised, pregnant, lactating, with acute febrile illness, bleeding disorders, keloidal tendency and with prior allergic response to injected antigen (MMR vaccine) were excluded from the study.

The minimum sample size calculated for the study was 20 per group by considering α error probability of 0.05, power of the study as 80%, with a common standard deviation of 1.12 and 1 as the minimum difference between the groups based on our pilot study. Forty patients satisfying inclusion and exclusion criteria were recruited irrespective of sex, duration and response of disease to previous therapies and assigned to either group 1 or group 2 by simple randomisation technique. Patients in group 1 were treated with intralesional MMR vaccine and group 2 patients were treated with auto implantation. The number of warts and the diameters of the major axis of the largest warts were recorded before treatment and at each follow up visit. Clinical photographs were taken at each visit and compared with baseline.

Group 1 patients were treated with MMR vaccine reconstituted with 0.5 ml of distilled water and was used immediately after reconstitution. The MMR vaccine was injected intralesionally using an insulin syringe held parallel with the skin surface with the bevel facing upwards, with a maximum of 0.1 ml injected into the same single wart or the largest in case of multiple warts, at two week interval until complete resolution was obtained, or for a maximum of 3 sessions. Any adverse effects were noted and treated accordingly.

Group 2 patients were treated by autoimplantation method. A well developed wart of substantial volume (3-4 mm) was chosen as the donor and anesthetized by 2% lignocaine infiltration. It was then shaved using a number 15 scalpel blade. The tissue thus obtained was placed on a sterile surgical gauze and minced into tiny bits. With prior infiltration of local anesthesia using a 20 gauge needle, a small nick was made on the skin at the site of engraftment using an 18G needle in accordance with resting skin tension lines (RSTL). The needle was then introduced subcutaneously and a dermal pocket extending up to the subcutis 3-5mm was created with to and fro motions of the needle over the volar aspect of the left forearm, 5 cm below the antecubital crease. The minced bits of the donor wart was introduced into this pocket to a depth using the Adsons forceps. Margins of the wound was approximated by pressure. Both donor and recipient sites were dressed with sterile medicated gauze. The procedure was repeated once in a month for a maximum of 3 treatment sessions. At each visit a different wart was chosen to obtain tissue for inoculation and a new dermal pocket was made because the old pocket heals in 5-7 days.

Response in both injected and uninjected warts were noted at each visit and a sequential photographic record were maintained. Response to treatment was evaluated by the decrease in size and

Table 1 : Baseline characteristics of the patients in two groups.

Characteristics	MMR group (n = 20)	Autoimplantation group (n =20)	p value
Age (in years)			
Range	13 – 58 years	12 – 35 years	0.135
Mean	26.3 ± 13.89	20.95 ± 7.24	
Sex			
Male	12 (60%)	9 (45%)	0.342
Female	8 (40%)	11 (55%)	
Male:female	1.5	0.8	
Duration of warts			
< 6months	7	3	
6– 12months	8	9	
12- 24months	3	4	
>24months	2	4	
Mean duration of warts	13.10 ± 10.12	17.7 ± 11.2	0.055
Mean number of warts	5.75± 4.7	9.2± 6.203	0.450
Size of warts (mm) (mean ± SD)	1.4835 ± .35	1.3825 ± 1.21	0.721
Distant warts, n (%)	2 (28.4%)	5 (71.6%)	0.181
Previous treatment,n (%)	8(40%)	6 (30%)	0.401

number of warts and disappearance of distant warts with photographic comparison. The response was considered complete if there was disappearance of wart(s) with return of normal skin markings, partial if the wart has regressed in size by 50-99% and no response if the reduction in size and number was 0-49%. The subjective assessment was done by the patient with grades 0, 1, 2, 3, 4 which corresponds to exacerbation, no change, slight improvement, marked improvement and complete cure respectively. Analysis was done by Statistical Package for Social Sciences (SPSS) version 20 and microsoft excel 2007 using descriptive statistics, paired t test, unpaired t test, chi-square test. A p value of <0.05 was considered as statistically significant.

Results

All the 40 patients completed the study. There were no significant difference in the baseline characteristics of the patients in both groups as presented in Table 1. The mean reduction in the number of warts at 1st, 2nd and 3rd follow up is given in Table 2. With the p values of 0.004, 0.008 and 0.014 at 1st, 2nd and 3rd follow up respectively, a statistically significant difference exists between the two groups.

The mean reduction in the size of warts at 1st, 2nd and 3rd follow up is given in Table 3. At the p values of 0008, 0.027 and 0.022 at 1st, 2nd and 3rd follow up respectively, there was statistically significant difference in size of warts between the two groups.

The mean number of treatment sessions required for the complete resolution of warts was 2.88

±.323 in MMR group and 2.545 ± .5222 in autoimplantation group. There is no statistically significant difference between two groups in the number of treatment sessions for the complete resolution of warts.

The objective response (doctor's assessment) to the treatment during each follow up is given in Table 4 with a statistically significant difference between two groups during 2nd and 3rd follow up with p values 0.006 and 0.015 respectively. The subjective response (patient assessment) of the patients to the treatment during each follow up is presented in Table 5. There is a statistically significant difference between two groups in their response to treatment during 2nd and 3rd follow up with p values 0.050 and 0.012 respectively.

All the patients in MMR group experienced pain during intralesional injection, whereas in autoimplantation group none had any adverse effects either during or after the procedure.

Table 2: Mean reduction in number of warts during each follow up.

Mean ± S.D	MMR group	Autoimplantation group	p value
Pretreatment	5.750 ± 4.700	9.200± 6.203	0.055
1st follow up	3.300 ± 3.798	8.100± 5.981	0.004
2nd follow up	1.850 ± 3.578	6.400± 6.369	0.008
3rd follow up	0.100±0.307	3.200±5.386	0.014

Table 3: Mean reduction in the size of warts during each follow up

Mean ± S.D	MMR group	Autoimplantation group	p value
Pretreatment	0.4835 ±.350	1.382 ± 1.22	0.003
1st follow up	.3800 ± .316	1.1630 ± 1.218	0.008
2nd follow up	.1755 ± .2157	.7675 ± 1.126	0.027
3rd follow up	0.0225 ± .0690	.4260 ± 1.118	0.022

Discussion

Warts are one of the common viral infections caused by HPV. Although there is spontaneous resolution of warts over few weeks to several years, many people seek treatment as they are unsightly and can be tender or painful [15]. The conventional treatment modalities destroys only the wart-containing tissue but do not stimulate the immune system against the virus. Hence, for the effective treatment of warts, there should be immune stimulation which can lead to long-term immunity against HPV. Previous studies have found that periungual warts are difficult to treat/cure because of the involvement of the nail and/or nail bed leading to the possibility of deforming or damaging the nail apparatus including nail bed and matrix [16].

The results of our study based on the objective and subjective response of the patient demonstrated a statistically significant difference in the therapeutic response of periungual warts to intralesional MMR vaccine and autoimplantation with 90% (18 out of 20) and 55% (11 out of 20) complete response respectively at the end of the study. (p value = 0.015 and 0.012). This higher response in MMR group compared to autoimplantation might be due to the boosted immune response due to adjuvant effect of different antigens on each other in MMR vaccine.

There have been various studies done in the past about the effects of MMR vaccine on warts other than priungual warts [9,12,21,22,29]. In a study by Gamil et al. [9] on 40 patients with multiple plantar warts, 23 patients completed the study, out of which complete response was seen in 20 patients (87%), partial response in one patient (4.3%), and no response in two patients (8.7%) in three sittings.

Nofal and Nofal [12] conducted a study on 135 patients with 85 patients in intralesional MMR group and 50 in saline group. They reported complete response in 57 (81.4%), partial response in

Table 4: Objective response (doctor's assessment)

	No response	Partial cure	Complete cure	p value
1st follow up				
Group 1	17 (85%)	3 (15%)		
Group 2	17 (85%)	3 (15%)	–	1
2nd follow up				
Group 1	4 (20 %)	14 (70%)	2 (10%)	
Group 2	11 (55%)	4 (20%)	5 (25%)	0.006
3rd follow up				
Group 1	0	2 (10%)	18 (90%)	
Group 2	7 (35 %)	2 (10%)	11 (55%)	0.015

Table 5: Subjective response (patient assessment)

	Grade 1	Grade 2	Garde 3	Grade 4	p value
1st follow up					
Group 1	16 (80%)	3 (15%)	1 (5%)		
Group 2	14(70%)	3 (15%)	3 (15%)	–	0.507
2nd follow up					
Group 1	4 (20%)	3(15%)	11 (55%)	2 (10%)	
Group 2	9 (45%)	3 (15%)	3 (15%)	5 (25%)	0.050
3rd follow up					
Group 1	0 (0%)	0 (0%)	2 (10%)	18 (90%)	
Group 2	7(35%)	2 (10%)	0 (0%)	11 (55%)	0.012

seven (10%) and no response in 6 patients (8.6%) of the MMR group as compared with complete response in 11 (27.5%), partial response in 6 (15%) and no response in 23 (57.5%) in the saline group. There was a statistically significant difference between the therapeutic response to MMR and saline.

Nofal et al [21] in his study on treatment of warts using intralesional MMR vaccine, among the 65 patients who completed the study, there was complete response in 41 patients (63%), partial response in 15 patients (23%), and no response in nine patients (14%).

Na et al [22] in a study on 136 patients of cutaneous warts showed complete resolution of lesions only in 5.6% patients, with 51% patients showing more than half reduction in the size of wart.[57] Pain at the site of injection was the only adverse effect noted.

In a study by Shaheen et al [29], comparing MMR vaccine with intralesional PPD and saline in 10 patients each, the rate of lesional and distal resolution were 60% each with PPD and 80% and 40%with MMR and 0% with saline. The variable therapeutic outcome in different studies might be due to difference in the vaccines used. The relatively less response in the study by Nofal et al [18] might be due to the higher mean age group of 38.9 years, which was significantly higher than the mean age of our patients. The difference in responses might be related to differences in the population selected, number of patients studied, number of warts (multiple vs. single or multiple), and duration of their presence. The partial response after three treatment sessions in our study might have been due to different HPV types, diverse wart types, variable duration of warts and different vaccines which might induce slightly different immunogenicity.

To the best of our knowledge, there have been no studies done exclusively regarding immunotherapy on periungual warts. It is possible that MMR vaccine when used intralesionally accelerates the clearance of virus and virus infected cells by stimulation of cell mediated immunity and humoral immunity or perhaps the non specific inflammatory response to the antigens is the major mechanism of immunotherapy [17-19,22].

The efficacy of autoimplantation in our study was 55 % as compared to 44 % in a study on anogenital warts by Usman et al [23] where autoimplantation was performed only once instead of thrice as done by us. But Shivakumar et al [24] and Lal et al [27] had a higher clearance rate of 73.3% and 62.5% respectively. Partial clearance was not observed in studies done by Usman et al. or Shivakumar et al, but in our study partial clearance was seen in 10%. In a study by Nischal et al [26] a complete clearance rate of 74.1% was seen, where they used a novel modification of autoimplantation wherein the pared wart tissue was implanted deep into subcutaneous tissue by stab incision by a blade. Srivastava and Bajaj [25] found a response rate of 89% (66 % with complete resolution and 22 % with partial improvement) where autowart injection of wart tissue suspension into the gluteal region was used.

A similar study by M.I EIGhareeb [25] , comparing the efficacy of intralesional MMR vaccine and autoimplantation on common warts, where 40 patients each were treated by autoimplantation and intralesional MMR vaccine respectively, every 2 weeks for maximum 4 treatments. Autoimplantation group showed 60% and MMR vaccine group showed 72.5 % clearance of donor wart completely which was not significant. But there was a significant difference in response among non manipulated warts in both groups where complete clearance was seen in 47.5% in autoimplantation group and 20 % in MMR group. They concluded that autoimplantation was suitable for patients with multiple warts associated with distant lesions while MMR injection was ideal for single or fewer number of warts.

Homologous autoimplantation is an easy, minimally invasive technique, which works by activating a delayed hypersensitivity response to the wart tissue antigens, aiding the clearance of both local and distant warts associated with the production of Th1 cytokines [12].

Earlier studies with intralesional MMR vaccine have reported side effects like pain during injection, flu like symptoms, edema, erythema and itching at the site of injection caused by intralesional MMR vaccine. But in our study using intralesional MMR vaccine, pain during injection was the only side effect observed in all the patients which was well tolerated. In the autoimplantation group of our study no side effects, either local or systemic were noted either during or after treatment. But in a study by Nischal et al [26], reaction in the form of erythematous tender nodules was observed at the site of engraftment in three patients out of 27

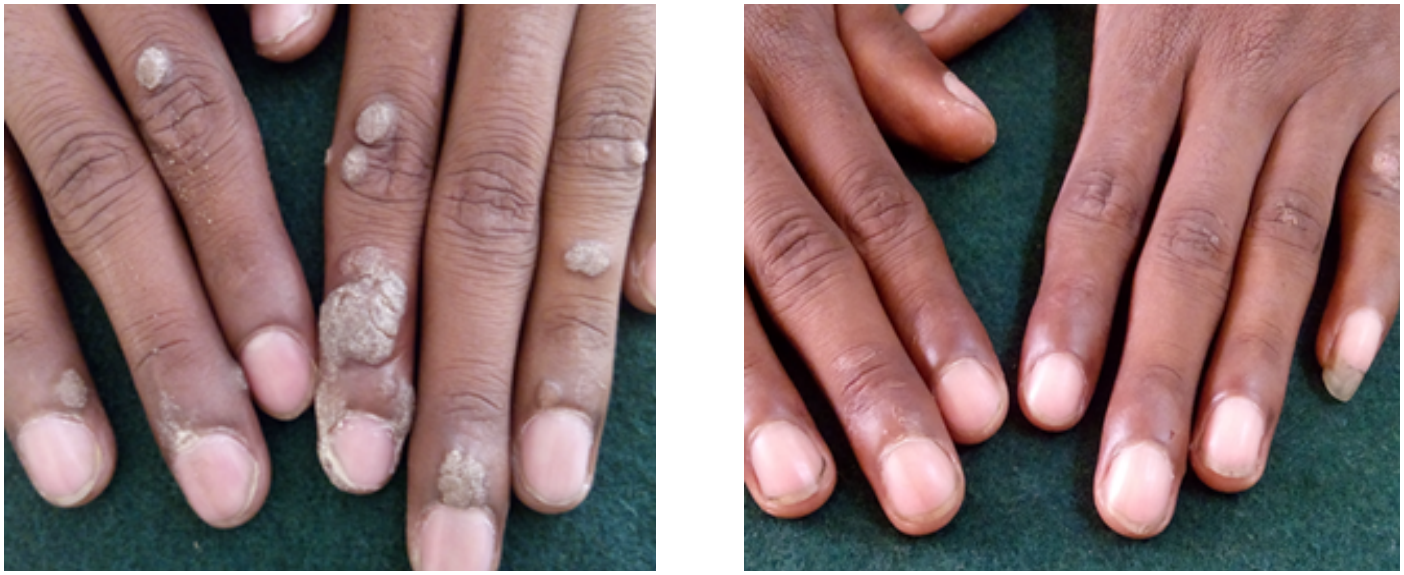

Figure 1 : Before and after treatment in autoimplantation group

patients who completed the study, with a purulent discharge from one nodules which subsided with systemic antibiotics and healed with post-inflammatory hyperpigmentation. Shivakumar et al [24] also noticed reactions at the injection site in few patients but have not disclosed the exact number.

None of the patients in our study reported with any recurrence of warts after the treatment period during 6 weeks of follow up. This may be attributed to the acquisition of a long-term HPV-directed immunity [6,8] by its ability to induce CMI, which enables the body to recognize HPV, stimulate the production of memory T cells against the virus and intensifies the effector response mechanism. Our results are in accordance with other studies in this regard [8,16,20].

In our study there was complete clearance of both treated and untreated warts, both near the injected wart and at distant anatomic sites, in patients with multiple lesions, which was similar to that seen in previous studies [12,21,22,29]. This finding may be explained by the higher viral load expected to be increased with more number of warts to stimulate the immune system.

In our study, the mean age of patients in autoimplantation group was lower than MMR group, but this was not statistically significant. In comparison to other studies that have reported a better response in the younger age groups [14,15], our study did not find any relation between the response rate and age group. Signore [14] reported a better response in younger patients and those with lesser number of warts. This could be due to better immune response of young patients to the virus which affect the treatment response. Similar to few previous studies, our study also found a significant relation between the pretreatment number of warts and treatment response (lesser the number of warts, higher the response) [14]. The difference in the mean number of warts between the two groups prior to treatment in our study were not statistically significant. Brugginket et al [3] reported that warts having a duration of less than 6 months had a significantly higher rate of spontaneous resolution than warts of longer duration. In our study, the mean duration of warts was higher in autoimplantation group. In line with this, we found a significant negative correlation between disease duration and clinical response between the two groups. The highest clearance rates were observed in younger individuals with a short duration of infection.

Though there were more number of treatment sessions in MMR group, with a mean of 2.88 compared to 2.54 in autoimplantation group, this was not statistically significant. The mean number of

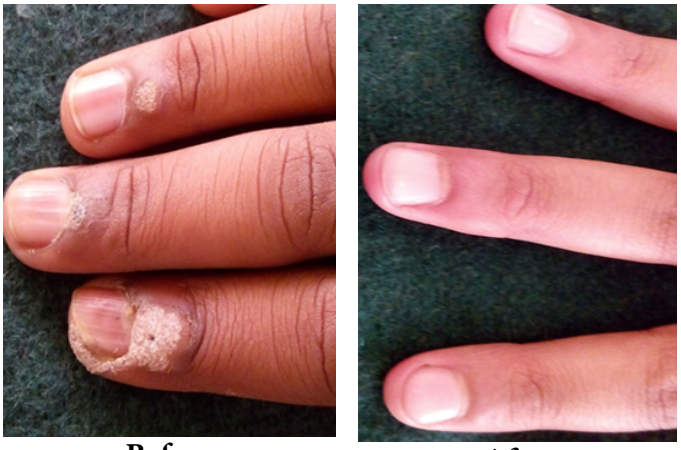

Figure 2 : Before and after treatment in MMR group

treatment sessions to achieve complete cure have varied between 2.3 to 5.9 in different studies[5] which was in concordance with our study. It is likely that if the total number of treatment sessions were more, the efficacy in our study would have been higher with partial cures perhaps turning to complete cure. This variability in the therapeutic response may be related to the demographic characteristics of the patients, amount of antigen used, size and number of warts or a combination of these variables.

However in our study the follow up period could not be extended beyond 2 weeks in MMR group and 1 month in autoinoculation group after treatment period, so recurrence could not be assessed. Besides this, a small sample size, lack of control group which would have helped to assess the chances of spontaneous resolutions are the other limiting factors in our study.

Conclusion

Intralesional MMR vaccine is a very effective, safe and cheap modality in the treatment of periungual warts, hence better accepted by the patients. Absence of scarring and pigmentary changes are the added advantages. We suggest its use as a first-line therapy for multiple warts, particularly those associated with periungual warts. However we recommend further studies in this regard adapting larger sample size and higher number of treatment sessions and assessing the reccurrences after longer follow up periods.

Conflicts of Interest

There are no conflicts of interest.

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