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Intralesional Immunotherapy in Palmo-plantar Warts using Mumps, Measles and Rubella vaccine: A Case-Control Study

C Raghuveer[1], Thameena Mohamed[2]

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Author Affiliation:

[1]Associate Professor, [2]Senior Resident, Department of Skin and STD, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka 583104, India.

Corresponding Author:

Thameena Mohamed, Senior Resident, Department of Skin and STD, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka 583104, India.

E-mail: raghuveermaanas@gmail.com

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Abstract

Background: Palmoplantar warts are always challenging to the treating dermatologist because of their high rates of failures and recurrences. First line treatment modalities available currently are associated with recurrences and second line modalities are associated with scarring. Clinical trials with MMR suggests that this approach could speed up the resolution of recalcitrant warts.

Objective: To evaluate efficacy and safety of intralesional MMR vaccine in treatment of recalcitrant palmoplantar warts by comparing it with intralesional distilled water.

Materials and methods: Seventy clinically diagnosed patients were divided into a study group and a control group. MMR injections (0.5 ml) were administered to the study group patients every 3 weeks to the single largest wart. Distilled water (0.5 ml) was administered to the control group at similar intervals. Follow up of patients in both groups were done every month after completion of treatment for 9 months for result, side effects and recurrence.

Result: Among 64 patients who completed the study, 32 patients received MMR and 32 patients received distilled water. An 81.30% reduction of wart size and number was noted in study group were as only a 18.80% reduction was seen in control group which was statistically highly significant (p value < 0.001).

Keywords: Warts; MMR vaccine; Distilled water.

Introduction

Skin warts are benign tumours caused by infection of keratinocytes with Human Papilloma Virus (HPV), visible as well-defined hyperkeratotic protrusions.[1]

Cutaneous warts are caused by a small group of specific HPV types, with an overall prevalence of 20% in schoolchildren and a decline thereafter with increasing age. Patients living in larger households often report an infected cohabitant, supporting the concept of person-to-person transmission. Majority of warts will regress spontaneously within 1–2 years. Reinfection with the same HPV type appears uncommon after clearance, suggesting that protective type-specific immunity may develop.[2]

There are different types of cutaneous warts such as common, plain, filiform/digitate, anogenital and palmoplantar.[3] Treatment of warts are often difficult despite availability of several modalities, more so of warts affecting periungual area and over soles.[4] The treatment of warts depends on two main therapeutic options: the first is the conventional destruction and aggressive method which includes treatment with chemical cautery, cryotherapy, electrocautery, surgical excision, and laser ablation and the second is immunotherapy, based on the activation of the immune system to deal with the virus and suppress its activity. Such immunotherapy may be applied either topically or through intralesional injection or through systemic administration.[5]

Intralesional immunotherapy utilises the ability of the immune system to mount a delayed type hypersensitivity response to various antigens and also to the wart tissue. This therapy has been found to be associated with the production of Th1 cytokines which activate cytotoxic and natural killer cells to eradicate HPV infection. This clears not only the local warts unlike traditional wart therapies, but also distant untreated warts.[6]

Increasing evidence of cellular immunity playing a vital role in wart clearance supports the use of intralesional MMR vaccine. Open labelled studies have also shown to have a positive result. Lack of enough randomised control studies reporting efficacy of intralesional MMR limits its use to some extent. So, in our study we attempted to prove the efficacy and safety profile of MMR in treatment of palmoplantar warts comparing it with distilled water.

Materials and Methods

Seventy consecutive patients with palmoplantar warts presenting to skin department, VIMS, Ballari were selected. Patients were randomised using block technique. Study design was double blinded and placebo controlled, conducted from January 2016 to December 2016. The study was approved by institutional ethics committee.

Patients with palmoplantar warts with or without warts at distant sites (warts present at sites other than palms and soles) were included in the study. Exclusion criteria were age less than 18 years, prior allergic response to MMR vaccine, acute febrile illness, history of atopy, pregnancy/ lactation and immunosuppression. Written informed consent is taken before starting the study. Patients' details including demographic data and clinical details were taken in a prescribed proforma. Photographs were taken at baseline and before each subsequent injections. Patients were divided using block randomisation technique into a study Group (Group A) and a control group (Group B). MMR vaccine available as single dose vial of freeze dried vaccine with diluent (0.5 ml) is purchased as necessary. This is given at base of largest wart at each visit for a maximum of 3 doses with 30G insulin syringe, each dose 3 weeks apart for patients enrolled in Group A. Group B patients received 0.5 ml of distilled water at same intervals. Patients were followed up every month for a period of 9 months after completion of treatment for results, side effects and recurrences. Data obtained was tabulated and analysed using suitable statistical tools.

The response was evaluated as follows:

1. *Complete:* disappearance of the wart(s) and return of normal skin markings.
2. *Partial:* regression in size by 50% to 99%.
3. *No response:* Zero to 49% decrease in wart size.

Results

Sixty four patients completed the study out of 70 enrolled patients. Thirty two patients were included in group A and the rest 32 in Group B. Table 1 is showing the baseline demographic characters of study as well as control groups. No statistically significant differences were observed with respect to age, gender, number of warts, distant warts, recalcitrant warts and number of previous treatments. Majority of the patients were in 21-30 years age group.

Table 2 is showing the treatment outcomes among study subjects in Group A and B. At 42 days, 20 patients showed partial response and 4 patients showed complete response in study group and 4 patients showed partial response and 2 patients showed complete response in control group. This resolution of warts at 42 days is statistically significant with a p value less than 0.001. Again at 63 days 16 patients showed complete response in study group against 3 patients in control group which is also statistically highly significant ($p < 0.001$). Response of distant warts to MMR injections did not differ much from that of distilled water. Side effects like pain, erythema, edema and flu like symptoms did not show a statistically significant difference between both groups.

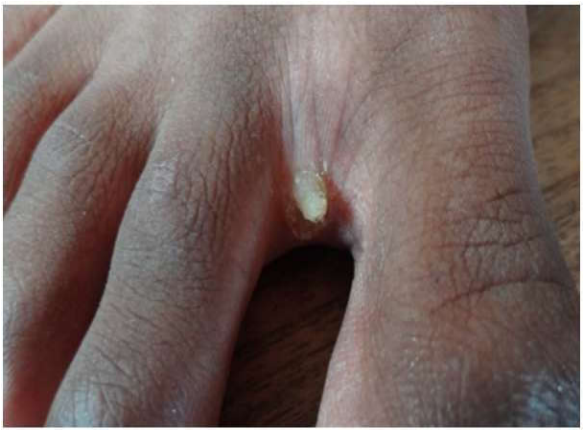

Fig. 1: Plantar wart before MMR injection

Table 1: Clinical Profile of the study subjects among the two treatment Groups

Variable	MMR Group (N = 32) n (%)	NS Group (N = 32) n (%)	*p* value
Age group			
≤ 20 years	7 (21.9)	8 (25.0)	0.424
21–30 years	17 (53.1)	12 (37.5)	
31–40 years	7 (21.9)	8 (25.0)	
> 50 years	1 (3.1)	4 (12.5)	
Mean ± SD	27.31 ± 7.32	28.75 ± 9.44	0.499
Sex			
Female	12 (37.5)	14 (43.8)	0.799
Male	20 (62.5)	18 (56.3)	
Skin leisons			
Single	8 (25.0)	12 (37.5)	0.282
Multiple	24 (75.0)	20 (62.5)	
Distant leisons			
Yes	5 (15.6)	3 (9.4)	0.708*
No	27 (84.4)	29 (90.6)	
Recalcitrant			
Yes	8 (25.0)	2 (6.3)	0.08*
No	24 (75.0)	30 (93.8)	
Previous treatment			
Yes	8 (25.0)	2 (6.3)	0.08*
No	24 (75.0)	30 (93.8)	

*Fisher Exact test

Table 2: Treatment outcome among the study subjects within the two Groups

Variable	MMR Group (N = 32) n (%)	NS Group (N = 32) n (%)	*p* value
Cycles of treatment			
Two cycles	4 (12.5)	2 (6.3)	0.672
Three cycles	28 (87.5)	30 (93.8)	
Response at 21 days	*Cases*	*Controls*	
No response	25 (78.1)	30 (93.8)	0.148
Partial response	7 (21.9)	2 (6.3)	
Response at 42 days			
No response	8 (25.0)	26 (81.3)	<0.001
Partial response	20 (62.5)	4 (12.5)	
Complete response	4 (12.5)	2 (6.3)	
Response at 63 days			
No response	6 (18.8)	26 (81.3)	<0.001
Partial response	10 (31.3)	3 (9.4)	
Complete response	16 (50)	3 (9.4)	
Response of distant wart			
No response	0 (0.0)	2 (6.3)	0.261
Complete response	2 (6.3)	0 (0.0)	
Recurrence			
Yes	3 (9.4)	1 (3.1)	0.223
No	29 (90.6)	29 (90.6)	
Side effects			
No side effects	5 (15.6)	3 (9.4)	0.125
Pain	18 (56.3)	26 (81.3)	
Pain, dizziness	0 (0.0)	1 (3.1)	
Pain, Flu	3 (9.4)	0 (0.0)	
Pain, Erythema	2 (6.3)	0 (0.0)	
Pain, Erythema, Oedema	4 (12.5)	2 (6.3)	

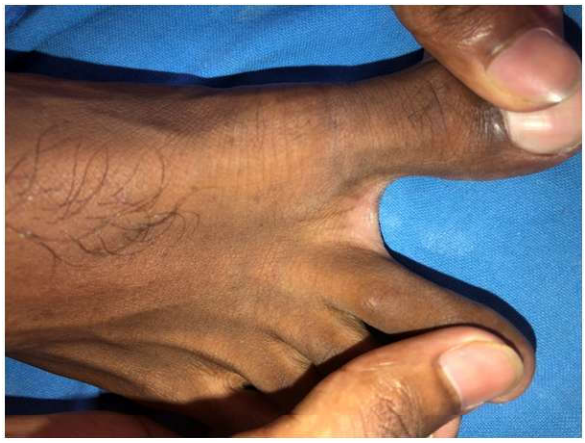

Fig. 2: Plantar wart after single dose of MMR

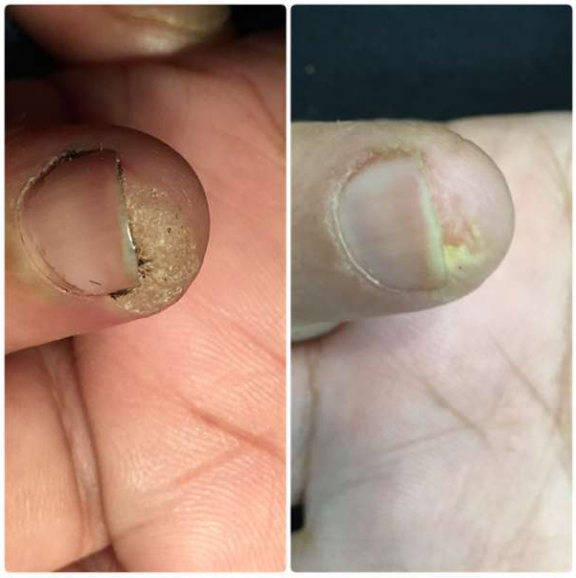

Fig. 3: Periungual wart showing improvement after MMR injection

Discussion

The never ending list of treatment for warts is an evidence to show that no treatment is specific and complete and treatment should be modified accordingly depending on patients' expectations. First line agents are those which can be applied by patients and second line are those modalities which require expertise but is almost always associated with scarring. Those agents which are not studied completely for their efficacy and safety are included in third line therapy. Immunotherapy is one among these third line agents.

Manipulating the immune system to achieve a therapeutic or protective response against diseases caused by HPV is an active field of investigation.[7] It can be achieved by various topical, intralesional, and systemic agents. MMR vaccine accelerates the clearance of virus and viral infected cells by stimulation of cell mediated and humoral immunity. Recently, better results with minimal adverse effects and lower recurrence rates have been reported with this therapy.[8]

In this study including 64 patients, we could obtain a statistically significant difference in the rate of wart resolution as well as in the end result in the group treated with MMR compared to distilled water group. In the study group 12.5% of patients showed complete response after two doses with a total of 75% patients responding to therapy while only 6% patients showed response in the control group. At the third follow up, that is at 63 days, 81.3 patients in the study group showed response to therapy with 50% patients showing complete clearance of the wart with partial return in skin markings. On the contrary in control group 18.8% patients were showing response with 9.4% patients showing complete response.

In an open labelled study on intralesional MMR for cutaneous warts by Saini P et al.[9], a complete clearance of 46.5% was seen with a partial clearance of 20.9%. In a case control study by Dhope A et al.[10] a complete clearance of 65% is noted with a 10% partial response in the study group. Awal G et al.[11] in his case control study showed a 68% complete response and 31.8% partial response to MMR vaccine. A complete response of 81.4% and a partial response of 10% was seen in study by Nofal et al.[12]

The slightly higher responses in these studies may be because these studies were done on common warts and not on palmoplantar warts alone. Palmo-plantar lesions can be harder and inaccessible in some of the patients for intralesional injection. Response of distant warts were also seem to be better with MMR vaccine than distilled water in this study.

In the present study 3 patients (9.4%) showed a recurrence of warts with MMR vaccine during the 9 month follow up period more so with increased duration and number of warts.

In study by Dhope et al.[10] recurrences were noted in 9.1% of patients. Saini et al.[9] showed a recurrence of 5% in the 6 month follow up period in their study.

Side effects associated with MMR vaccine are pain, erythema, edema and flu like symptoms affecting 84.4% of patients in study group. Of which 56.3% of patients had only pain as side effect. This observation is in accordance with other similar studies as well.[13-14]

According to the availability and patients' consent different authors have used different immunotherapeutic agents for intralesional injection for the treatment of warts. These are mainly autologous vaccine[15] candida antigen,[16] trichophytin skin test antigen,[7] tuberculin,[17,18] BCG vaccine,[19] Mycobacterium w vaccine,[20] and IFN-α and IFN-γ injection.[6]

Depending on the antigens the responses varied in different studies. It is difficult to conclude which antigen is efficient and safe. When the side effect profile is compared, intralesional MMR injection is found to be slightly superior than most of the above mentioned antigens.

Limitations of the Study

Increased number of consultations affected compliance of patients which was a major limitation. So was the lesser number of patients in study and control group.

Conclusion

This randomised placebo controlled study further strengthened the efficacy and safety of intralesional immunotherapy in the form of intralesional MMR injection for the treatment of difficult to treat or recalcitrant palmoplantar warts. If return of normal skin markings is taken as the sign of complete cure wen treating warts, intralesional MMR is a promising, safe, simple as well as inexpensive modality with lesser side effects and lower relapse rates compared to other treatment modalities. If enough evidences are available about the safety and efficacy of the MMR immunotherapy, this can be considered as a first line modality for the treatment especially of palmoplantar warts.

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Conflicts of interest: Nil

Permissions: Nil

References

1. Sterling JC. Viral Infections. In: Chalmers R, Barker J, Griffiths C, Bleiker T, Creamer D, editors. Rook's Textbook of Dermatology 9th ed. Oxford: Blackwell Science; 2016.pp.25–46.
2. Kirnbauer R, Lenz P. Human papilloma Viruses. In: Bolognia J L, Jorizzo JL, Schaffer JV, editors. Dermatology 3rd ed. Philadelphia: Elsevier Saunders; 2012.p.1303.
3. Al-Dhubaibi; Comparison of Duct Tape with Adhesive Cyanoacrylate versus Cryotherapy in the Treatment of Palmoplantar Warts. JAMPS, 2016;8(3):1-6, 2016.
4. Kumari P, Yadav D, Vijay A, et al. Falknor's needling method as a potential immunotherapy in palmo-plantar warts. Indian J Dermatol Venereol Leprol. 2019;85:129.
5. Vender R, Bourcier M, Bhatia N, et al. Therapeutic options for external genital warts. J Cutan Med Surg. 2013;17 Suppl 2:61-67.
6. Chandrashekar L. Intralesional immunotherapy for the management of warts. Indian J Dermatol VenereolLeprol. 2011;77:261-3.
7. Horn TD, Johnson SM, Helm RM, et al. Intralesional immunotherapy of warts with mumps,candida and trichophyton skin test antigens. Arch Dermatol. 2005;141:589-594.
8. Zamanian A, Mobasher P, Jazi GA. Efficacy of intralesional injection of mumps-measles-rubella vaccine in patients with wart. Adv Biomed Res. 2014;3:107.
9. Saini P, Mittal A, Gupta LK, et al. Intralesional mumps, measles and rubella vaccine in the treatment of cutaneous warts. Indian J Dermatol VenereolLeprol. 2016;82:343-5.
10. Dhope A, Madke B, Singh AL. Effect of measles, mumps, rubella vaccine in treatment of common warts. Indian J Drugs Dermatol. 2017;3:14-9.
11. Awal G, Kaur S. Therapeutic outcome of intralesional immunotherapy in cutaneous warts using the mumps, measles,and rubella vaccine. J Clin Aesthet Dermatol. 2018;11:15-20.
12. Nofal A, Nofal E. Intralesional immunotherapy of common warts: successful treatment with mumps, measles and rubella vaccine. J Eur Acad Dermatol Venereol. 2010;24:1166-70.
13. Johnson SM, Roberson PK, Horn TD. Intralesional injection of mumps or candida skin test antigens: a novel immunotherapy for warts. Arch Dermatol 2001;137:451-55.
14. Johnson SM, Horn TD. Intralesional immunotherapy for warts using a combination of skin test antigens: a safe and effective therapy. J Drugs Dermatol. 2004;3:263-65.
15. Wiltz OH, Torregrosa M, Wiltz O. Autogenous vaccine: the best therapy for perianal condyloma acuminate? Dis Colon Rectum. 1995;38:838-41.
16. Signore RJ. Candida albicans intralesional injection immunotherapy of warts. Cutis. 2002;70:185-92.
17. Essa BI, Abou-Bakr AA, El-Khalawany MA. Intradermal injection of PPD as a novel approach of immunotherapy in anogenital warts in pregnant women. Dermatol. Ther 2011;24: 137-43.
18. Kus S, Ergun T, Gun D, et al. Intralesional tuberculin

for treatment of refractory warts. J Eur Acad Dermatol Venereol. 2005;19:515-6.

19. Sharquie KE, Al-Rawi JR, Al-Nuaimy AA, et al. Bacilli Calmetti - Guerin immunotherapy of viral warts. Saudi Med J. 2008;29:589-93.

20. Gupta S, Malhotra AK, Verma KK, et al. Intralesional immunotherapy with killed Mycobacterium w vaccine for the treatment of anogenital warts:an open label pilot study. J Eur Acad Dermatol Venereol. 2008;22:1089-93.