Original Article

Efficacy of intralesional injection of mumps-measles-rubella vaccine in patients with wart

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Abstract

Background: In the previous studies, it has been shown that mumps-measles-rubella (MMR) vaccine resulted in regression of warts via immunomodulatory effect and induction of immune system. Due to the high prevalence of warts in various populations, we evaluated the efficacy of MMR vaccine injection in the treatment of cutaneous warts.

Materials and Methods: This double-blind randomized controlled clinical trial was conducted in Hazrat-e-Rasoul Hospital in Tehran in 2011-2012 on 24 patients with warts who were allocated to two groups including MMR group and normal saline group. MMR vaccine was injected intralesionally in the MMR group, whereas normal saline was injected into the lesions in the second group. These injections were repeated every 2 weeks intervals for maximum 3 injections. All patients were followed up every 15-day interval up to 45 days and then up to 6 months regarding relapses and finally, side effects, probable relapse, and therapeutic outcomes were evaluated and compared.

Results: At the end of follow-up period, therapeutic outcomes in the MMR group included no cure in 2 cases, relative cure in 4 cases, and complete cure in 18 cases. In normal saline group, these rates included no cure in seven cases, relative cure in nine cases, and complete cure in six cases ($P < 0.001$). No significant complication occurred in the two groups.

Conclusion: MMR vaccine may result in desirable therapeutic response. The hypothesis that is considered here is that MMR vaccine, via induction of cellular and humoral immune system, accelerates the destruction of virus and infected host cells.

Key Words: Intralesional injection, mumps-measles-rubella vaccine, wart

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INTRODUCTION

Wart is a mucocutaneous disease that develops as a result of proliferation of infected skin or mucosal cells with human papilloma virus (HPV). There are over 100 types of this virus and some of them have contributed in the pathophysiology of wart.[1,2] Each of its types is different in at least 10% of the sequences encoded

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by major capsid gene (L1). Although these viruses have a tendency to infect some specific body parts, this disease may be manifested in approximately all regions of the skin and mucosa.[3,4]

Although these viruses create no acute signs or symptoms, they induce slow growth of lesions that can remain for a long time.[5] Infections due to these viruses may result in a wide spectrum of clinical manifestations in the skin and mucosa. Primary manifestations of HPV infection include common warts, genital warts, flat warts, and deep palmoplantar warts (myrmecia).[6,7]

Mucocutaneous warts are mostly asymptomatic and usually attract the attention of patients by the cosmetic problems that they cause.[8,9] This disease should be treated because it can influence strongly on the patients' quality of life by causing shame, fear, and anxiety about developing negative attitude in other people and disillusionment due to disease chronicity or relapse.[10]

Due to the above-mentioned reasons, treatment of warts becomes necessary. However, no specific treatment has been effective in achieving a complete cure in all the patients. Consequently, there are various therapeutic approaches for the treatment of wart.[10] Nearly all therapeutic options are effective in some patients.[11] Therefore, a combination of different types of treatments may be used.[12] In addition, different types of warts as well as those in various parts of patients' body may need different treatments.[13] Selective treatment differs according to age, patients' demand, potential adverse effects, and location of the lesions.[14]

In some of the previous studies, it has been shown that mumps-measles-rubella (MMR) vaccine results in regression of warts via immunomodulation and induction of immune system.[15,16] This method can be used in larger populations because of vaccine availability and safety.[16] Due to the high prevalence of warts in various populations, especially in children, as well as the necessity of treatment, we evaluated the efficacy of MMR vaccine injection in the treatment of cutaneous warts. However, for obtaining more definite results, this study needs to be repeated in the Iranian population.

MATERIALS AND METHODS

This double-blind randomized controlled clinical trial was conducted in Hazrat-e-Rasoul Hospital of Tehran University of Medical Sciences in 2011-2012. Our study population included patients with warts who were candidates for treatment. Inclusion criteria were women who were not pregnant or breast feeding, not having received anti-wart treatment within the past 4 weeks, lack of viral infections such as herpes and/or bacterial infections such as impetigo in skin, lack of any infective febrile disease, and completing the treatment course in this study. In this study, all the patients satisfying the inclusion criteria were evaluated until the required sample size was obtained. So, convenient sampling and census were used for selecting samples. Selecting the patients in the two therapeutic case and control groups was performed by simple randomized method.

According to Gamil's investigation[16] in which the cure rate has been reported as 80% in the MMR group and 50% in the placebo group, and based on the relationship of calculation of one ratio in two populations and considering type 1 error as 5% and type 2 error as 20%, the sample size was calculated to be 14 patients in each group. Nevertheless, for compensating probable sample drop-outs, the sample size was increased up to 20 patients in each group.

Full information on the investigation objectives and methods was given to the patients, and consent was taken from the participants or their legal guardian. At first, all patients underwent clinical examination by a dermatologist in the dermatology clinics to confirm the diagnosis of wart. Biopsy and histopathologic examination was done in the suspicious cases. Then, demographic information, clinical history, and present condition of their disease were demonstrated. The information included age, gender, disease duration, number of lesions, and involved sites.

After selecting the patients who satisfied the inclusion criteria, the number of skin lesions was counted and recorded in the questionnaires; and then patients were allocated randomly to MMR and normal saline groups. MMR vaccine 0.5 cc (Merck and Co., Inc. Washington, USA) was injected intralesionally for each single wart in the MMR group, whereas normal saline was injected in the same volume into the lesions in the other group. These injections were repeated every 2 weeks for a maximum of three injections. Neither the patients nor the injectors knew which material had been injected to the patients until the end of the treatment period. Then all patients were followed up for 6 months and in 2-month intervals to evaluate and compare the side effects, probable relapse, and therapeutic outcomes. Lesions with size decrease of less than 50% were defined as no therapeutic response, size decrease between 50 and 99% as relative response, and complete removal of the lesions was considered as complete cure.[9]

Quantitative data were shown as mean ± standard deviation and nominal data as percent and frequency.

Ratios were compared by Chi-square test and means by *t*-test. $P < 0.05$ was considered as significant. SPSS-16 (spss inc, chicago, USA) was the statistical software used.

RESULTS

At the beginning of the study, 30 patients were enrolled in each group. Six patients in the MMR group and eight patients in the normal saline group either did not complete the treatment course or did not refer for consequent follow-up. Finally, 24 patients in the MMR group and 22 patients in the normal saline group were evaluated. MMR group consisted of 13 (54.2%) males and 11 (45.8%) females, whereas there were 12 (54.5%) males and 10 (45.5%) females in the control group. Comparison of these showed no statistical significant difference ($P = 0.944$). Mean of age was 18.9 ± 12 years in the MMR group and 20.1 ± 10 years in the normal saline group, which showed no statistically significant difference ($P = 0.791$). Frequency and therapeutic response rate in the two groups after treatment and according to the time elapsed after treatment are shown in Table 1. Comparison of these rates showed statistically significant difference between the two groups ($P < 0.001$).

Table 2 summarizes the therapeutic response in the two groups at the end of treatment, based on patients' age and sex. This table indicates statistically significant difference in the therapeutic outcomes in both groups of the studied population.

Table 1: Frequency and therapeutic response rate in MMR (*n*=24) and normal saline (*n*=22) groups

Time of evaluation	Therapeutic groups	Therapeutic response	Rates %	*P* value
The first visit (15 days after treatment)	MMR	No response	6 (25)	<0.001*
		Relative response	11 (45.8)	
		Complete response	7 (29.2)	
	Normal saline	No response	14 (63.6)	
		Relative response	6 (27.3)	
		Complete response	2 (9.1)	
The second visit (30 days after treatment)	MMR	No response	3 (12.5)	<0.001*
		Relative response	8 (33.3)	
		Complete response	13 (54.2)	
	Normal saline	No response	11 (50)	
		Relative response	7 (31.8)	
		Complete response	4 (18.2)	
The third visit (45 days after treatment)	MMR	No response	2 (8.3)	<0.001*
		Relative response	4 (16.7)	
		Complete response	18 (75)	
	Normal saline	No response	7 (31.8)	
		Relative response	9 (40.9)	
		Complete response	6 (27.3)	

*Significant difference, MMR: Mumps–measles–rubella

Mean number of primary warts was 4.4 ± 2 and 4.1 ± 2.5 in the MMR and normal saline groups, respectively, which showed no statistically significant difference ($P = 0.869$). Mean number of lesions in each

Table 2: Therapeutic response in two groups based on patients' age and sex

Patient groups	Therapeutic groups	Number of patients	Therapeutic response	Frequency (%)	*P* value
Female	MMR	11	No response	1 (9.1)	<0.001*
			Relative response	1 (9.1)	
			Complete response	9 (81.8)	
	Normal saline	10	No response	3 (30)	
			Relative response	4 (40)	
			Complete response	3 (30)	
Male	MMR	13	No response	1 (7.7)	<0.001*
			Relative response	3 (23.1)	
			Complete response	9 (69.2)	
	Normal saline	12	No response	4 (33.3)	
			Relative response	5 (41.7)	
			Complete response	3 (25)	
Age <20 years	MMR	9	No response	0	<0.001*
			Relative response	1 (11.1)	
			Complete response	8 (89.9)	
	Normal saline	9	No response	3 (33.3)	
			Relative response	4 (44.5)	
			Complete response	2 (22.2)	
Age >20 years	MMR	15	No response	2 (13.3)	<0.001*
			Relative response	3 (20)	
			Complete response	10 (66.7)	
	Normal saline	13	No response	4 (30.8)	
			Relative response	5 (38.4)	
			Complete response	4 (30.8)	
All patients	MMR	24	No response	2 (8.3)	<0.001*
			Relative response	4 (16.7)	
			Complete response	18 (75)	
	Normal saline	22	No response	7 (31.8)	
			Relative response	9 (40.9)	
			Complete response	6 (27.3)	

*Significant difference, MMR: Mumps–measles–rubella

therapeutic group before treatment and in the visits after treatment are shown in Table 3.

Results of this study show that on comparing the two groups, the number of lesions showed no significant difference in the first visit. However, the number of lesions showed significant difference in the second and third visits after treatment ($P < 0.05$).

The findings of this investigation show that there was no relapse in any of the treated cases in both groups. In addition, no important adverse effect was reported in any of the patients in both therapeutic groups. Pain at the time of injection was reported by 100% of patients in both groups; whereas influenza-like syndrome was reported by 30% of the patients in the MMR group and no case in the normal saline group ($P < 0.001$).

DISCUSSION AND CONCLUSION

Various therapeutic options such as cryotherapy, 3-cloroacetic acid, peudophylline, surgery by laser, topical cidofovir, electrocautery, retinoids, and salicylic acid have been recommended for treatment of wart.[17] No specific treatment or therapeutic protocol is completely suitable for all of the patients. Although most of the therapeutic options result in clearing of virus within 1-6 months, in 20-30% of the patients, relapses and new lesions will appear as a result of failure of the cellular immune system to detect and remove the lesions.[5] There are clinical evidences that cellular immune responses play an important role in HPV infection and disease.[18] T cell (CD4, CD8) infiltration, especially, has been found in the warts with spontaneous regression. In addition, prevalence of HPV-related lesions increases in the HPV-infected patients and transplant recipients. Both groups have a compromised cellular immune system.[19] This finding indicates that if immunotherapy modalities are able to induce the immune system for destroying virus and the infected host cells, it could be considered as a therapeutic option for wart. In recent years, immunotherapy has been considered as a novel treating option and some studies have been performed on *Candida* antigens and also on viral antigens that exist in MMR vaccine. Although the mechanism of effectiveness of intralesional injection of MMR vaccine and antigens has not yet been known, it seems that nonspecific inflammatory response to the antigens is the major mechanism of immunotherapy.[20]

Table 3: Mean number of lesions in each therapeutic group before treatment and in the visits after treatment

Time of evaluation	Therapeutic group	Number of patients	Mean of lesions	*P* value
Before treatment	MMR	24	4.4±2	0.869
	Normal saline	22	4.1±2.5	
First visit	MMR	24	2.1±1.5	0.419
	Normal saline	22	4±1.8	
Second visit	MMR	24	1.2±1	0.042*
	Normal saline	22	3.5±2	
Third visit	MMR	24	0.8±0.5	0.021*
	Normal saline	22	3.5±1.5	

*Significant difference, MMR: Mumps–measles–rubella

The results of this study show that the sex ratio and age of the patients were nearly similar and there was no significant difference between the two groups. This finding indicates that underlying factors such as age and sex have not confounded the results of our study. In addition, the number of lesions at the beginning of study and therapeutic intervention had been somewhat similar. In the first post-treatment visit, therapeutic response was seen in 75% of patients in the MMR group, including 30% complete cure and 45% relative cure, whereas only 36% of the control group showed therapeutic response and complete cure had occurred in less than 10% of controls. In the second and third post-treatment visits, the proportion of therapeutic response had increased in the MMR group and reached 87% and 92%, respectively, whereas these rates in the control group were significantly lower. This finding shows that the therapeutic effect of MMR was significantly more than that of normal saline. This effect had been observed early at the initiation of follow-up period, while the therapeutic effect of MMR increased with passing time. This therapeutic effect of MMR was observed in both male and female patients.

In this study, no important adverse effect occurred as a result of MMR injection, and the pain due to injection had been reported with normal saline injection too. On the other hand, influenza-like syndrome was tolerable, and therefore, it is not considered as a contraindication for applying this therapeutic modality.

The results of our study are similar to the previous investigations. In Nofal and Nofal's study, it was reported that the therapeutic response in MMR group (more than 80%) had been significantly higher than in the normal saline group. During the follow-up period in the MMR group, no case of relapse was observed in the recovered lesions; and also, no adverse effect was reported. In this study, investigators concluded that MMR vaccine injection into the wart had significant therapeutic outcomes and low complications.[15] In another study, Gmail *et al*. reported 87% complete cure, 4.3% relative cure, and 8.7% no cure. Authors of this study concluded that MMR vaccine may have desirable therapeutic effect on the treatment of wart.[16] Similarly, it was observed in our study that three injections were accompanied with early and

quicker improvement and rapid removal of the lesions. So, in both studies, it has been observed that about 30% of the patients experienced complete clearance of the lesions within 2 months after treatment. Also, in Johnson *et al*., study, intralesional injection of mumps virus and *Candida* antigens was used in patients with warts and it was demonstrated that the therapeutic response had been significantly higher than in the control group. However, in the mentioned study, relapse after eliminating the lesions occurred in 39% of cases. This finding confirmed that in cutaneous warts, compromising cellular immunity which remains after treatment, has a determinant role in manifesting disease. The mechanism of immune deficiency in patients with wart is not yet known. It seems that compromising cellular immunity has a more important role in this subject.[14]

It has been demonstrated that in these patients, memory T cells are not able to recognize HPV virus antigens.[17] In Horn *et al*., study, the effectiveness of intralesional injection of mumps virus and *Candida* antigens was shown in patients with warts. In this study, that its some parts have been performed as an immunological research, it has been demonstrated that intralesional injection of antigens results in mononuclear cell proliferation and they may result in removing lesions through cytokine production.[22]

The results of this study show that MMR vaccine may result in desirable therapeutic response. The hypothesis that is considered here is that MMR vaccine, by induction of cellular and humoral immune systems, accelerates the destruction of virus and infected host cells. Therefore, this immunotherapy method is recommended for treating patients with wart.

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