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EVALUATION OF THE EFFICACY OF A COMBINATION – *MEASLES*, *MUMPS* AND *RUBELLA VACCINE* IN THE TREATMENT OF *PLANTAR WARTS*

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Abstract
Introduction: The treatment of patients with plantar warts continues to be a frustrating matter for both primary care physicians and dermatologists. There are new trends towards the use of immunotherapy in treatment of warts, as the immune system seems to play an important role in the control of warts infection.
Aim: Assessing the efficacy of intralesional injection of MMR vaccine (measles, mumps, rubella) in the treatment of plantar warts.
Patients: One hundred patients complaining of plantar warts were included in this study.
Methods: The patients were divided into two groups:
Group 1: This group included 50 patients subjected to intralesional injection of measles, mumps, rubella vaccine (MMR).
Group 2: This group included 50 patients as a control group and subjected to intralesional injection of 0.3 ml saline.
Only single wart was injected. Injections were done at 3-weeks interval until complete clearance or for a maximum of 3 treatments.
Follow up of patients was done every month for six months for clinical assessment of results and to show any recurrence.
Results: Regarding the response of the target wart, MMR- treated group showed significantly higher rate of complete clearance compared with the control group (82% versus 0% respectively). The rate of partial response was 6% versus 30%, and the rate of no response was 12% versus 70%, respectively. Regarding the response of untreated distant warts, MMR-treated group showed 86.9% complete and 13.1% partial clearance of the warts whereas the control group showed 100% no response. This strongly indicates the development of a widespread HPV-targeted immunity as a response of antigen injection and represents a major advantage of the intra lesional immunotherapy.
Conclusions: We found that treatment of plantar warts by MMR vaccine is effective, with good cure rates and excellent safety profile.

Key words: Immunotherapy; MMR vaccine; plantar warts

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Introduction

Plantar warts are benign epithelial proliferations on the sole of the foot most frequent over pressure points [1,2].
Plantar warts are caused by Human Papilloma Virus (HPV), a small non-enveloped double stranded DNA virus [1].
The treatment of patients with plantar warts continues to be a frustrating matter for both primary care physicians and dermatologists. They are usually treated by a wide variety of methods including cryotherapy, surgical excision, podophyllin, bleomycin and lasers. Each mode of therapy has its own complications and failure rates [3-5].
Previous mentioned methods are not always successful and may be associated with adverse events. Even when existing warts are successfully eradicated, patients may develop new warts in other areas [1,2].

There are new trends towards the use of immunotherapy in treatment of warts, as the immune system seems to play an important role in the control of warts infection. Although the exact mechanisms are unclear but most evidences suggest that cell mediated immunity plays an important role in control of HPV infection as the incidence of warts increases in subjects with cell mediated immune defects e.g (HIV infection patients, malignant diseases. etc….) [6-8].
Various methods have been used to stimulate the immunological response as oral levamisole, cimetidine, zinc sulfate, cidovir, intralesional interferons, topical dinitrochlorobenzene, squaric aciddibutyl ester, imiquimod, intralesional immunotherapy with mumps, candida and trichophyton antigens, intradermal BCG vaccine, and intralesional MMR vaccine [9-11].

The aim of this study was

Assessing the efficacy of intralesional injection of MMR vaccine (measles, mumps, rubella) in the treatment of plantar warts.

Patients

One hundred patients complaining of plantar warts were included in this study (their age ranged from 17 to36 years with a mean of 23.88 ± 4.66 and they were 50% males and 50% females 50% of patients with single wart and 50%of patients with multiple warts and the duration of warts ranged from one to six months).

They were selected from the outpatient dermatology clinic of Alexandria Main University Hospital.

All patients gave informed consent to participate in this work. The study was approved by Ethical Committee of scientific research, Faculty of Medicine, Alexandria University.

They were divided into two groups:

Group 1: This group included 50 patients subjected to intralesional injection of measles, mumps, rubella vaccine (MMR) .

Group 2: This group included 50 patients as a control group and subjected to intralesional injection of 0.3 ml saline.

Inclusion Criteria:

· Patients should have single or multiple plantar warts (from 2 up to 7 warts).
· The age is more than 12 years.
· No concurrent systemic or topical treatment of warts

Exclusion criteria:

· Patients with fever or signs of any inflammation or infection.
· Children < 12 years.
· Pregnancy.
· Lactation.
· Immunosuppression.
· Patients who received any other treatments for their warts in the last month before enrolment.
· Past history of asthma, allergic skin disorders, meningitis or convulsions

Methods

All the patients in the study were subjected to the following:

1. History taking:

- Personal data: name, age, sex, occupation and marital state.
- Present history: pain, disfigurement, interference with function.
- Past history: previous treatments, recurrence and duration of the wart.
- Medical history: systemic diseases as HIV, diabetes, asthma and cutaneous diseases as generalized eczema or urticaria.
- Drug history: corticosteroids or chemotherapeutic drugs.

2. Clinical examination:

For identification of the characteristics of the warts including site, size, number and presence or absence of distant warts before the first treatment session and 3 weeks after the last one.

3. Photography of the lesions:

Before the first treatment session and 3 weeks after the last one.

4. Injection of the target wart with either MMR or saline according to the group assignment.

Group 1:

Patients are subjected to intralesional injection of 0.3ml of measles, mumps, rubella vaccine (MMR) in the target (usually the largest wart). Injections were done at 3-weeks interval until complete clearance or for a maximum of 3 treatments.

There are two available forms of MMR vaccine (Trimovax Merieux):

1. Single dose vial of freeze-dried vaccine. It should be reconstituted with 0.5 ml of diluent (water for injections).
2. Ten dose vial of freeze-dried vaccine. It should be reconstituted with 5 ml of diluent (water for injections).

Its storage: at 2-8oC (36-46oF).

It is preferable to use MMR vaccine immediately after reconstitution. If reconstituted vaccine is not used within 8hours it must be discarded.

MMR vaccine is available at Vacsera company.

Group2:

Patients are subjected to intralesional injection of 0.3 ml saline in the target wart at 3-weeks interval until clearance or for a maximum of 3 treatments.

In both groups, the warts were injected using a built in insulin syringe. Immediate and late side effects were evaluated after each treatment session. Patients were examined before each injection noting the number and surface area of warts.

Follow up of patients was done every month for six months for clinical assessment of results and to any recurrence.

The response was evaluated as follows:

· Complete: disappearance of the wart(s) and appearance of normal skin.
· Partial: 50-99% reduction in size.
· No response: 0-49% reduction in size.

Resolution of distant untreated warts was also assessed.

Statistical analysis of the data

The clinical and laboratory results obtained are statistically analyzed using SPSS/PC* (Statistical package for social science for personal computers).

Results

We found no statistically significant difference in response according to age and sex of patients. The cure rate was better in patients with a shorter duration of the disease and multiple lesions.

Clinical response:

On comparing the treatment responses in the target wart, a significant difference was found between MMR- treated group compared with the control group, showing higher rates of complete response (82% versus 0% respectively), but as regard partial response it was (6% versus 30%) and as regard no response it was (12% versus 70%) (Tabl. I), (Fig. 1).

On comparing different treatment responses in distant wart in both groups, it was found a significantly higher rates in MMR-treated group compared with the control group (complete response: 88.9% versus 0% respectively, partial response: 11.1 % versus 0% respectively, no response: 0% versus100% respectively) by using chi-square test (Tabl. II), (Fig, 2-4).

	Cases (n = 50)		Control (n = 50)		p
	No.	%	No.	%	
Response to treatment					
No response	6	12.0	35	70.0	<0.001*
Partial response	3	6.0	15	30.0	
Complete response	41	82.0	0	0.0	

Table I. Comparison between the MMR- treated group and the control group as regard the response of target wart

p: p value for Monte Carlo test for comparing between the two studied group

***: Statistically significant at p ≤ 0.05**

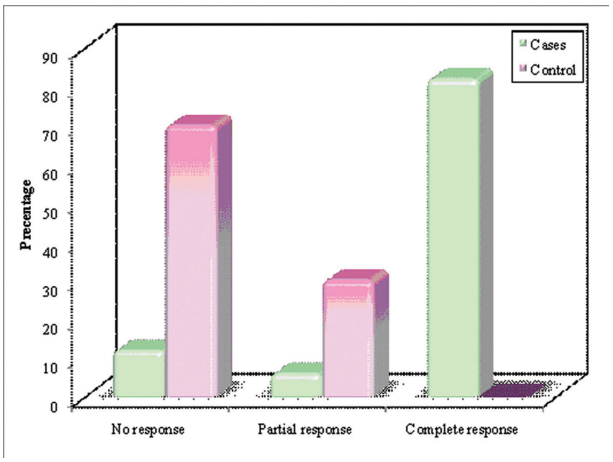

Figure 1. Comparison between the two studied groups according to response to treatment.

	Cases (n = 25)		Control (n = 25)		p
	No.	%	No.	%	
Response to treatment					
No	0	0.0	25	100.0	<0.001*
Partial	3	13.1	0	0.0	
Complete	22	86.9	0	0.0	

Table II. Comparison between the two studied groups according to response to treatment at distant lesions

p: p value for Monte Carlo test for comparing between the two studied group

***: Statistically significant at p ≤ 0.05**

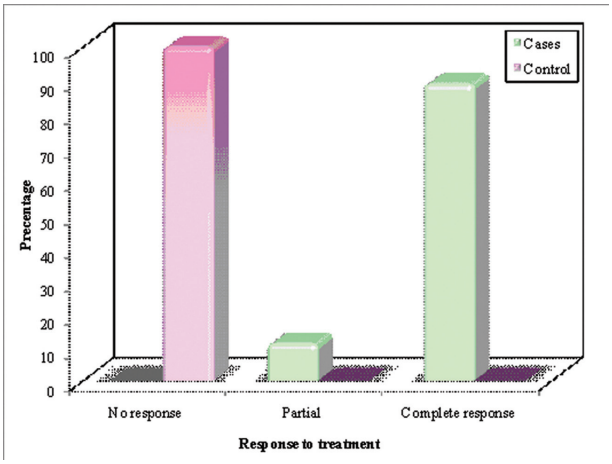

Figure 2. Relation between distant lesions and response to treatment.

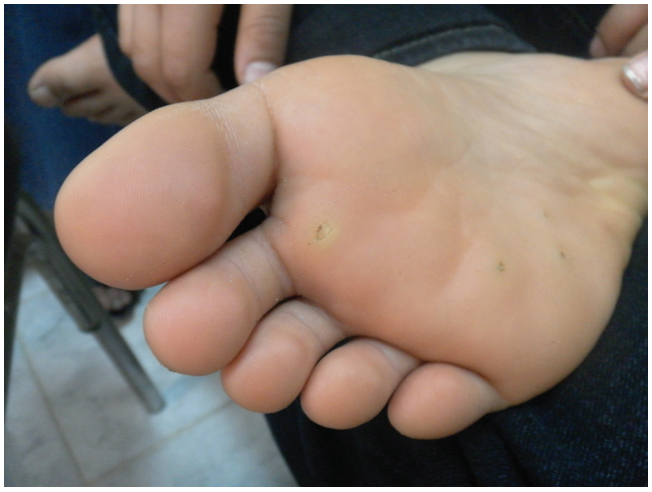

Figure 3. A case of multiple plantar warts before MMR injection.

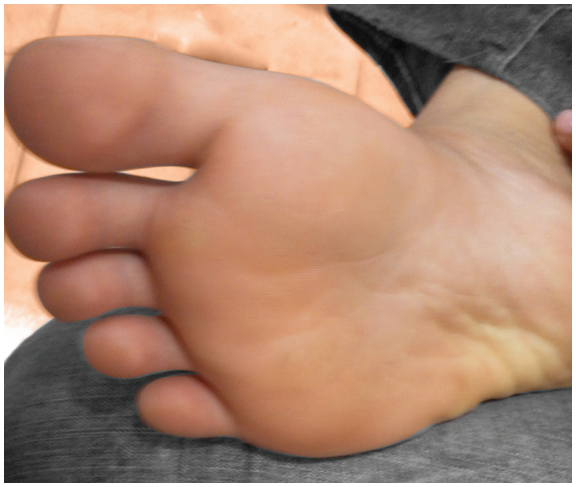

Figure 4. Complete cure of the plantar warts after MMR injection.

Discussion

Plantar warts are common dermatological problem caused by the human papillomavirus (HPV) [1,2].

Papilloma viruses are epitheliotropic non-enveloped small double stranded DNA viruses whose replication is strictly dependent on the terminally differentiating tissue of the epidermis [12].

Immune mechanisms have been suggested to explain the spontaneous resolution of warts. If this immunity could be enhanced, wart resolution could be long lasting. The stimulated immune system would destroy all warts in the body, saving the patients the local treatment for each individual wart [13]. It has been reported that untreated warts resolve after injection of only one wart with intralesional immunotherapy that induces HPV-directed immunity [14]. Antigens used for intralesional immunotherapy include tuberculin [15]; BCG [16]; mumps, candida and trichophyton [17] and MMR [18].

We aimed in this work to evaluate the effectiveness of intralesional injection of MMR vaccine (mumps, measles, rubella) for the treatment of plantar warts.

As regard the response of the target wart, MMR- treated group gave better results compared with the control group, higher rates of complete response (82% versus 0% respectively); but as regards partial response, it was 6% versus 30% respectively and as regards no response, it was 12% versus 70% respectively.

Regarding the response of the distant wart, MMR-treated group showed better results compared with the control group with higher rates of complete response (86.9% versus 0% respectively), partial response (13.1% versus 0% respectively), and no response (0% versus 100% respectively).

The clearance of untreated distant warts strongly indicates the development of a widespread HPV-targeted immunity as a response of antigen injection and represents a major advantage of the intralesional immunotherapy. The total absence of response in the distant warts of the control group confirms the presence of a systemic immune response with MMR treatment.

Our results with MMR-treated group showed a closely similar response rate to those previously reported by Nofal (2010) [18] (his study on the effect of MMR vaccine in the treatment of common warts with complete clearance in 80% of cases and no recurrence was observed during the follow up period), Gamil et al. (2010) [19] (their study on MMR vaccine in treatment of plantar warts with 87% complete clearance in injected warts), Brunk [20] (using candida antigen with 85% clearance) and Gupta et al [21] (using killed *Mycobacterium* W vaccine for the treatment of ano-genital warts with 88.9% clearance), slightly higher than those reported by Phillips et al [13] (using candida antigen injection with72% clearance), Johnson, Roberson, and Horn [22] (using mumps or candida skin test antigens with74% clearance), and Johnson and Horn [14] using combination of skin test antigens with 70.9% clearance), and much higher than those shown by Kus et al [15] (using intralesional tuberculin with 29.4% clearance), Clifton et al [23] (using intralesional mumps or *Candida* antigens with 47% clearance), Signore [24] (using *Candida albican*s intralesional injection immunotherapy of wartswith 51% clearance), and Horn et al [17] (using Intralesional immunotherapy of warts with mumps, candida and trichopyton skin test antigens with 53% clearance).

The relatively higher response in our study as compared to the other related studies which utilize either a single antigen or a combination of antigens may be attributed to the presence of three viral antigens that potentiate each other and could be associated with higher stimulation of the immune system. The differences in the number of the studied patients, the duration and the resistance of warts may also explain this difference.

Although the results of this type of therapy were significantly better than in the control group, a better response might have been obtained if the volume of MMR injected was increased, if more than a wart (not only the target wart) were treated at a time, or if more treatment sessions were used as in Gupta et al. work (2008) [21] showing 88.9% cure 651 ones (>40 years) who showed less immune response.

An important observation in this work was the better cure rate in patients with shorter disease duration. It is quite known that warts typically continue to increase in size and distribution and may become more resistant to treatment over time [23]. So early treatment of warts is mandatory and waiting for spontaneous resolution might sometimes make the condition difficult to treat.

Regarding the number of warts, we found a significant better response in multiple lesions than in single ones.

No serious side effects were reported in patients included in this study. Only reported, tolerable pain during injection was the main side effect.

Flu-like symptoms were reported in two of our patients which resolved within 24 hours, by nonsteroidal anti-inflammatory medications. No swelling, redness, or pruritus at the site of the injection were found.

As regards the benefits to the patients, MMR local injection has significant advantages over other treatments. Most treatment modalities are painful, needing multiple visits (time and money consuming), and are directed to each individual wart. In MMR treatment we have two or three injections, clearance of distant non-injected warts, patients are able to resume normal daily activities and are free of residual scars which was very appreciated by all patients.

The mechanism of action of intralesional immunotherapy is still unclear. It may act through induction of strong nonspecific inflammatory response against the HPV-infected cells [22,23]. It has also been suggested that the trauma itself may cause wart clearance in previously sensitized individuals [15]. Release of cytokines by immune system such as IL-2,IL-4,IL-5,IL-8, IFN-γ and TNF-α stimulate a strong immune response against HPV may be another possible mechanism of action [21]. Horn et al have reported that the response to antigen injection was associated with proliferation of peripheral blood mononuclear cells that promotes Th1 cytokines, including interferon gamma and interleukin 2, which further activate cytotoxic T cells and natural killer cells that eradicate HPV-infected cells [17].

Conclusion

Intralesional immunotherapy by MMR vaccine is a promising modality for the treatment of plantar warts, particularly multiple and recalcitrant warts and those associated with warts at distant locations. It seems to be effective, with good cure rates and excellent safety profile, but how exactly it works to stimulate immunity to cause wart clearance is still unclear.

Recommendation

-Further studies on larger population is recommended.

-Comparing the effect of different types of immunotherapy in the management of plantar warts.

-Comparing the effect of intralesional MMR vaccine in the management of different types of warts.

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