Comparative study between intralesional Candida antigen and tuberculin PPD in treatment of multiple warts

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Abstract: warts represent a troublesome therapeutic issue for both patients and physicians. Despite the existence of numerous therapeutic modalities, treatment of warts still represents a real challenge and a uniformly effective remedy has not been explored to date. Intralesional Candida Antigen and purified protein derivative (PPD) were not previously compared regarding their efficacy or mechanism of action in treatment of warts. We aimed to compare their efficacy in treatment of multiple warts 60 patients with multiple warts were included (30 treated with Candida antigen and 30 treated with PPD). Injection was done every 3 weeks until clearance or maximum of three treatments. Clinical response of target and distant warts was evaluated. A significantly higher rate of complete response was found in target and distant warts with Candida antigen (66.7%, 56.7 respectively) and with PPD (60%, 50% respectively) and with no significant difference between both treatments. With no serious side effects so treatment of multiple warts by intralesional injection of Candida antigen and PPD. So finally intralesional injection of Candida antigen and PPD is safe and effective, with good cure rates and excellent safety profile in treatment of multiple warts.

[Yasser Fathy Mohamed, Ahmad saeed Al-Adl, Yasser Mamdouh Hasanein. **Comparative study between intralesional Candida antigen and tuberculin PPD in treatment of multiple warts.** *Nat Sci* 2017;15(1):95-98]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 12. doi:10.7537/marsnsj150117.12.

Keywords: Comparative study; intralesional Candida; antigen; tuberculin; treatment; multiple wart

1. Introduction

Warts are benign virus-induced tumors caused by human papilloma virus (HPV) which are epitheliotropic nonenveloped small double-stranded DNA viruses (Sapp and Biankowska-Haba, 2009).

Warts are common in the general population at some point in life. There are more than 100 different genotypes of HPV classified according to their tissue tropism (mucosal or cutaneous) and oncogenic potential. Along with host and environmental factors, HPV genotype influences the type and malignant potential of lesions(Sterling et al., 2001).

The prevalence of cutaneous viral warts in children and adolescents is between 3-5% occurring with similar frequency in adults aged 25-34 years. In 90% of children, warts present by age 11 and clear by 16 years. Other rates of spontaneous clearance have also been reported: 23% at 2 months and 66% by 2 years(Massing et al., 1963).

Host defense against HPV relies on intact and functioning cellular immunity including T cell and natural killer (NK) cell cytotoxicity. Immune mechanisms may explain the spontaneous resolution of warts (Stanley, 2006).

Immunosuppressive therapy of systemic lupus erythematosus is associated with diminished levels of B and natural killer (NK) cells and an enhanced risk for HPV infection (Abud-Mendoza et al., 2013).

If this immunity could be enhanced, wart resolution could be long lasting. The stimulated immune system would destroy all body warts, saving the patients the local treatment for each individual wart (Philips et al., 2000).

Antigens used for intralesional immunotherapy include Tuberculin (PPD), Candida, Trichophyton; and Mumps, Measles, Rubella (MMR) (Horn et al., 2005).

Candida antigen is made from the culture filtrate and cells of two strains of Candida Albicans. It's indicated in origin for use as a recall antigen for detecting delayed-type hypersensitivity by intracutaneous (intradermal) testing, may be useful in evaluating the cellular immune response in patients suspected of having reduced cellular hypersensitivity The inflammatory response associated with the DTH reaction is characterized by an infiltration of lymphocytes and macrophages at the site of antigen deposition. Specific cell types that appear to play a major role in the DTH response include CD4 and CD8 T lymphocytes which leave the recirculating lymphocyte pool in response to exogenous antigen (Paul et al., 1993).

Tuberculin purified protein derivative (PPD) is currently the only available skin test reagent used for the diagnosis of tuberculosis (TB) or for detection of latent TB infection (LTBI). Although tuberculin skin test (TST) has a remarkable sensitivity and has been in use for five decades to identify people infected with Mycobacterium tuberculosis (Farhat et al., 2006).

The sensitization following infection with

mycobacteria occurs primarily in the regional lymph nodes. Small lymphocytes (T lymphocytes) proliferate in response to the antigenic stimulus to give rise to specific sensitized lymphocytes. After 3-8 weeks, these lymphocytes enter the blood stream and circulate for years. Subsequent re stimulation of these sensitized lymphocytes with the same or a similar antigen, such as the intradermal injection of PPD evokes a local reaction mediated by these cells (Menzies, 1999).

Intralesional immunotherapy utilizes the ability of the immune system to mount a delayed type hypersensitivity response to various antigens and also 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 but also distant warts unlike traditional wart therapies (Kim et al., 2010).

Aim of the work

The aim of this work is to compare efficacy of intralesional Candida antigen and Tuberculin PPD in treatments of multiple warts.

Patients and methods

Patients

The study included 60 patients suffering from multiple warts classified as following: 30 patients suffering from planter warts and 30 patients suffering from periungual warts. They were recruited from the outpatient dermatology clinic of Al-Azhar University Hospitals. For each patient Complete history taking, General and dermatological examination, Identify clinical type of warts and site of lesions. and take photos for the lesions at first visit and follow up visits were done.

Inclusion criteria included Patients of different age groups presenting with multiple planter or periungual warts of different sites, sizes and durations with no concurrent use of systemic or topical treatments of warts.

Exclusion criteria included Child less than 6 years, Pregnant or breast feeding females, Patients with known active yeast or tuberculosis infections, Uncontrolled bronchial asthma, Acute febrile illness, Patients who receiving other treatments for warts, Known hypersensitivity to Candida or PPD antigen.

2. Methods

The patients were randomly assigned into one of the two groups: Group 1: Included 30 (thirty) patients classified as 15 patients suffering from planter warts and 15 patients suffering from periungual warts. This group subjected to intralesional injection of Candida antigen, Before treatment patients were tested for existing immunity for Candida antigen by intradermal injection of 0.1 ml Candida antigen in the forearm. The result appear in 48-72 hours by erythema and in duration more than 0.5 cm at the site of injection, Negative patients were excluded from the study, In positive patients we started treatment with itralesional injection of 0.1 ml of Candida antigen and 0.1 lidocaien in the oldest and almost largest wart (Mother Wart), Injection were done every 3 weeks until clearance of lesions or maximum of 3 treatments.

Group 2: Included 30 (thirty) patients classified 15 patients suffering from planter warts and 15 patients suffering from periungual warts. This group subjected to intralesional injection of Tuberculin PPD, Before treatment patients were tested for existing immunity for Tuberculin PPD by intradermal injection of 0.1 ml Tuberculin PPD in the forearm, The result appear in 48-72 hours by induration with or without erythema more than 0.5 cm at the site of injection, Negative patients will be excluded from the study, In positive patients start treatment with itralesional injection of 0.1 ml of Tuberculin PPD in the oldest and almost largest wart (Mother Wart), Injection will be done every 3 weeks until clearance of lesions or maximum of 3 treatments.

The results will be evaluated by clinical response of lesions as Complete resolution: appearance of normal skin, Partial resolution: more than 50% reduction in size, Minimal resolution: less than 50% reduction in size, No response: no reduction in size stable disease, Resolution of distant untreated warts was also assessed.

3. Results

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when parametric distribution and median with inter quartile ranges when non parametric distribution. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent t- test and Mann-Whitney test when non parametric distribution. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p- value was considered significant $P < 0.05$: Non significant $P > 0.05$.

Clinical response

As regard the response of the target wart, each of the Candida antigen and the PPD- treated groups, both showing comparable responce (66.7% and 60

respectively); but as regards partial response it was (13.3 % and 23.03% respectively) and as rgard minimal response, it was (10% and 3.3% respectively) and as regards no response, it was (10% and 13.3% respectively).

In comparing Candida Antigen and PPD-treated groups regarding response of injected warts there was no statistically significant difference in Table (1).

Regarding the response of the distant wart, both the candida antigen- treated group and the PPD-treated groups show complete response (56.7% and 50respectively), partial response (13.3 % and 23.3% respectively), minimal response (3.3% and 0% respectively), and no response (8% and 8% respectively).

On comparing Candida Antigen and PPD-treated groups regarding response of distant warts there was no statistically significant difference In Table (2).

In comparing Candida Antigen and PPD-treated groups regarding side effects there was no statistically significant difference In table (3).

Table (1) Comparison between candida antigen and PPD-treated groups as regard response of injected warts.

Response of injected wart	Candida antigen group		PPD group		Chi-square test	
	No.	%	No.	%	X2	P-value
No response	3	10.0%	4	13.3%	2.066	0.559
Minimal response	3	10.0%	1	3.3%		
Partial response	4	13.3%	7	23.3%		
Complete response	20	66.7%	18	60.0%		

Table (2) Comparison between candida antigen and PPD treated groups as regard response of distant warts.

Response of distant warts	Candida antigen group		PPD group		Chi-square test	
	No.	%	No.	%	X2	P-value
No response	8	26.7%	8	26.7%	1.943	0.584
Minimal response	1	3.3%	0	0.0%		
Partial response	4	13.3%	7	23.3%		
Complete response	17	56.7%	15	50.0%		

Table (3) Comparison between candida antigen and PPD treated groups as regard side effects.

Side effects	Candida antigen group		PPD group		Chi-square test	
	No.	%	No.	%	X2	P-value
No	17	56.7%	20	66.7%	5.465	0.141
Erythema	3	10.0%	0	0.0%		
Pain	8	26.7%	10	33.3%		
Swelling	2	6.7%	0	0.0%		

Conclusion and Recommendations

Conclusion:

Treatment of multiple warts by intra lesional injection Candida antigen and PPD is safe, effective with good cure rates and excellent safety profile, but how exactly they work to stimulate immunity to cause wart clearance is still unclear.

Recommendation

- Further prospective studies on larger population are recommended.
- Correlating the effect of different types of immunotherapy with the different HPV types would be useful in the management of different types of warts.
- Long follow up of the patients is mandatory to assess possible recurrences after both modes of

treatment and to evaluate their long term efficacy.

- Evaluation of TH1 and TH2 cytokines predictors of therapeutic response to intralesional immunotherapy.
- Examination of other possible factors of resistance such as TLRs expression and function, and HLA typing.
- Combination the rap by vitamin D or BCG-PSN may be an alternative solution in the resistant warts.
- Booster dose plan for the responders to decrease the recurrence rate.

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1/2/2017