Comparative study of intralesional BCG and PPD in the treatment of multiple cutaneous warts

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Abstract

Introduction: Multiple cutaneous warts are often asymptomatic, cosmetically disfiguring and difficult to treat with conventional modalities, hence immunotherapeutic modalities can be used in such cases. There are no comparitive studies with immunotherapeutic modalities for the treatment of multiple and extensive warts. This study aims to compare the efficacy and safety of intralesional BCG and PPD in the treatment of multiple cutaneous warts.

Materials and Methods: It is a double blinded randomized clinical trial involving thirty patients having more than ten cutaneous warts with a positive mantoux reaction. The patients were randomly allocated into two treatment groups, group A – PPD and group B - BCG. Intralesional injections were given at two weekly intervals till complete clearance of all the warts or for a maximum of four sessions in both the groups. Response in injected warts and distant warts was assessed at each visit and sequential clinical photographic records were maintained.

Results: Thirty patients with positive mantoux reaction were enrolled for the trial, 17 patients in group A (PPD) and 13 patients in group B (BCG). Complete resolution of lesions was noted in 35.3% in PPD group and 30.8% in BCG group and partial resolution was noted in 47.0% and 38.4 % in PPD and BCG group respectively.

Conclusion: Intralesional PPD showed marginally better results than intralesional BCG in the treatment of multiple cutaneous warts. Majority of the patients treated with BCG had tender nodule at injection site.

Keywords: Immunotherapy, Multiple warts, Intralesional BCG, Intralesional PPD.

Introduction

Warts are benign proliferations of the skin and mucosa that are caused by infection with human papillomaviruses.[1] Acquisition of HPV depends on several factors, including the location of lesions, the quantity of viral load, the degree and nature of the contact, and the HPV-specific immunologic status of the exposed individual.[2] The role of immunity and genetic susceptibility to HPV infection are not clearly understood.[3]

The standard modalities in treatment of warts include destructive therapies such as salicylic acid, silver nitrate, trichloroacetic acid, phenol, canthiridin, cryotherapy, surgical interventions and lasers; antiproliferative agents such as bleomycin, podophyllotoxin, podophyllin, 5-fluorouracil, retinoids and vitamin D analogues; antiviral agents such as cidofovir.[4] Because of the difficult nature of these procedures and a high risk of recurrence, immunotherapy is becoming more popular lately, especially in recalcitrant, recurrent and extensive warts as well as in difficult to treat areas like periungual and palmoplantar sites.[5]

Immunotherapy is defined as a type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.[5] The immunotherapeutic agents may be applied topically, injected intralesionally or administered through systemic route.[5] Common immunotherapeutic modalities used for the treatment of warts include imiquimod, intralesional interferon, contact sensitizers and oral drugs such as levamisole, cimetidine, and zinc sulfate. Intralesional antigens such as MMR (measles, mumps and rubella) vaccine, skin test antigens (Mumps, Candida, and Trichophyton), BCG (bacillus Calmette-Guerin) vaccine and PPD (purified protein derivative) have been reported as successful treatment modalities in various forms of warts.[6]

Purified protein derivative or tuberculin is a sterile protein extract from culture of mycobacterium tuberculosis. It is used in skin testing to detect exposure to the bacillus. It stimulates the cell-mediated immunity non-specifically by activating NK cells, Th1 cells and cytokine production. An increase in IL-12 as a part of the enhanced cell-mediated immunity contributes to its mechanism of action as an immunotherapeutic agent.[7]

Bacillus-Calmette-Guérin (BCG) vaccine is well known for its prophylactic effects against tuberculosis. It has also been used in the treatment of malignant melanoma, alopecia areata, recurrent oral aphthous ulcers and transitional cell carcinoma of the bladder. Its mode of action in verrucae can be explained by its activation of macrophages, T and B lymphocytes, and natural killer cells that promote the clearance of warts.[8]

The aim of this work is to compare the efficacy of intralesional PPD and intralesional BCG vaccine in the treatment of multiple cutaneous warts.

Materials and Methods

Patient Selection: Seventy six patients with clinically diagnosed multiple verrucae were screened and evaluated in detail from the out – patient department of Dermatology, Venereology and Leprosy in a Hospital in Karnataka. Patients having more than ten warts with common, palmo-plantar and/or peri-ungual presentations and with positive mantoux reaction were included in the study. Immunosuppressed patients, patients with past history of TB and/or active TB, pregnant or lactating women, and children less than 15 years of age were excluded.

The study was approved by the Institutional Ethical Committee. A written informed consent was taken from all patients prior to the injections.

Treatment Protocol: Seventy six patients with multiple verrucae of common, periungual and/or palmo-plantar presentations were screened. These patients were evaluated in detail with clinical examination and investigations to rule out any immunosuppresion or active infection. All patients fulfilling the inclusion criteria were subjected to a mantoux test and thirty patients who showed positive mantoux reaction with erythema and induration of ≥ 10 mm, were further enrolled for the study. The thirty patients were alloted into two groups by computer generated randomization list: group A -PPD group and group B - BCG group. Single largest wart was selected in each case and 0.1 ml of the antigen, PPD or BCG depending on the group allocated, was injected into the wart with help of an insulin syringe. This was repeated once every two weeks on the same wart or another wart depending on the regression of the wart. The injections were given till complete resolution of all warts or for a maximum of four injections (0, 2, 4, 6 weeks), whichever was earlier. Both the patient and the investigator assessing the response were blinded to the antigen selected. Follow-up was done once in a month for a period of six months after release from treatment for recurrences and complications.

Assessment of Response: Assessment of response was done by one of the investigator who was unaware of which group the patient was allocated. The number of warts, distribution of warts and evidence of local side effects were noted at week 0, 2, 4, 6 and 8. A sequential clinical photographic record was maintained. The response was evaluated as follows:

i. Complete resolution: Complete clearance of all warts, evidenced clinically by total disappearance of the hyperkeratosis and thickening of the skin.
ii. Partial significant resolution: More than or equal to 50% reduction in number of warts.
iii. Partial insignificant resolution: Less than 50% reduction in number of warts.
iv. No response: No reduction in number of warts.

Analysis of Data: 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 22 version was the statistical software used.

Results

Thirty patients with positive mantoux reaction were divided into two groups, 17 patients in group A-PPD and 13 patients in group B-BCG by computer generated random allocation. Age of the patients ranged from 15 to 36 years, with a mean of 25.3 ± 9 years in PPD group and 26 ± 10 years in the BCG group, showing no statistically significant difference ($p = 0.941$). The PPD group consisted of 11 (66.7%) males and 6 (33.3%) females, whereas there were 8 (61.5%) males in and 5 (38.5%) females in BCG group. The comparison of these showed no statistical difference ($p = 0.751$).

The patients were followed up for assessment of response at 2, 4, 6 and 8 weeks as described in table 1. At the end of 8 weeks, PPD group showed complete resolution in 35.3%, marginally higher than the 30.8 % in BCG group. Fig. 1, 2, 3. However, this difference was statistically insignificant. ($p>0.05$).

Multiple sites involvement and different clinical types were noted in twenty – four of the thirty patients. The therapeutic response based on type of wart was statistically significant in periungual warts ($p<0.05$). Table 2, Fig. 4.

Local side effects like painful induration and blistering at injection site was seen in 9 (69.2%) of patients in BCG group and its severity warranted discontinuation of further injections in two patients (15.4%). This was accompanied by systemic side-effects like fever, myalgia and flu – like symptoms in 4 (30.7%) patients in BCG group. Pain and swelling was present in only one patient (5.8%) belonging to PPD group. Table 3, Fig. 5.

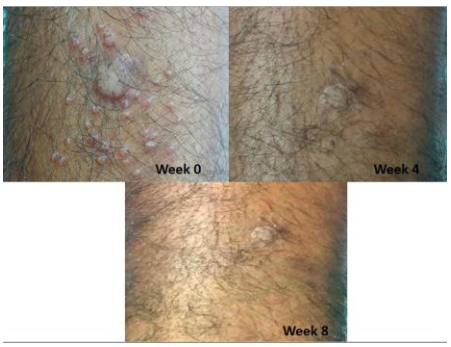

Fig. 1: Warts treated with intralesional PPD at week 0, week 4 and showing response at 8th week.

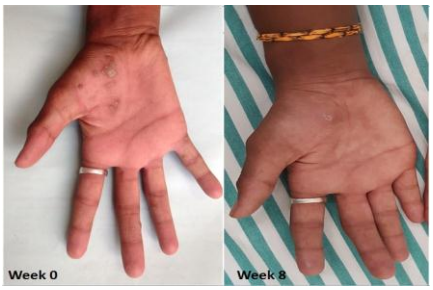

Fig. 2: Palmar warts treated with intalesional BCG at week 0 and showing response at 8th week.

Fig. 4: Periungual wart treated with intralesional PPD at week 0, week 4 and complete resolution seen at 8th week.

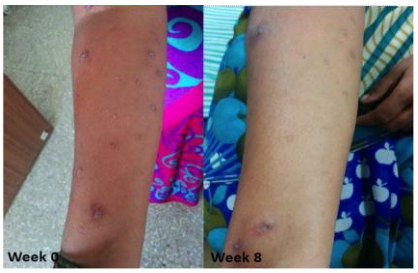

Fig. 3: Common warts on right forearm treated with intralesional BCG at week 0 and response at 8th week showing just residual hyperpigmentation

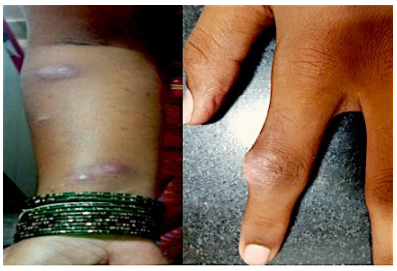

Fig. 5: Tender nodules developed at injection site with intralesional BCG injections

Table 1: Frequency and therapeutic response rate in PPD (n=17) and BCG (n=13) groups

Time of Evaluation	Therapeutic Group	Therapeutic Response	Frequency (%)	P Value
Week 2	PPD (n = 17)	Complete resolution	0 (0%)	0.3
		Partial significant response	3 (17.6%)	
		Partial insignificant response	5 (29.4%)	
		No response	9 (52.9%)	
	BCG (n = 13)	Complete resolution	0 (0%)	
		Partial significant response	0 (0%)	
		Partial insignificant response	5 (38.5%)	
		No response	8 (61.5%)	
Week 4	PPD (n = 17)	Complete resolution	1 (5.9%)	0.9
		Partial significant response	2 (11.8%)	
		Partial insignificant response	7 (41.2%)	
		No response	7 (41.2%))	
	BCG (n = 13)	Complete resolution	0 (0%)	
		Partial significant response	2 (15.4%)	
		Partial insignificant response	4 (30.8%)	
		No response	7 (53.8%)	
Week 6	PPD (n = 17)	Complete resolution	4 (23.5%)	0.9
		Partial significant response	5 (29.4%)	
		Partial insignificant response	5 (29.4%)	
		No response	3 (17.6%)	
	BCG (n = 13)	Complete resolution	2 (15.4%)	
		Partial significant response	4 (30.8%	
		Partial insignificant response	2 (15.4%)	
		No response	4 (30.8%)	
Week 8	PPD (n = 17)	Complete resolution	6 (35.3%)	0.8
		Partial significant response	5 (29.4%)	
		Partial insignificant response	3 (17.65%)	

		No response	3 (17.65%)	
	BCG (n = 13)	Complete resolution	4 (30.8%)	
		Partial significant response	3 (23.0%)	
		Partial insignificant response	2 (15.4%)	
		No response	4 (30.8%)	

P >0.05 (non-significant), <0.05 (significant), <0.01 (highly significant), <0.001(very highly significant)

Table 2: Comparison between response in PPD group and BCG group with regard to type of wart

Type of wart		Response										P value
		PPD					BCG					
		C	PS	PI	NR	Total	C	PS	PI	NR	Total	
Common	No	6	3	1	0	10	5	2	1	2	10	0.3
	%	60.0	30.0	10.0	0	100	50.0	20.0	10.0	20.0	100	
Plantar	No	0	1	1	1	3	0	0	0	1	1	0.1
	%	0	33.3	33.3	33.3	100	0	0	0	100	100	
Palmar	No	4	2	1	2	9	5	2	2	3	12	0.2
	%	44.4	22.2	11.1	22.2	100	41.6	16.7	16.7	25.0	100	
Periungual	No	5	1	0	0	6	0	0	0	4	2	0.03
	%	83.3	16.7	0	0	100	0	0	0	100	100	
Total	No	15	7	3	3	28	10	4	3	8	25	
	%	53.6	25.0	10.7	10.7	100	40.0	16.0	12.0	32.0	100	

C: Complete resolution; PS : Partial significant; PI: Partial insignificant; NR: No response

P >0.05 (non-significant), <0.05 (significant), <0.01 (highly significant), <0.001(very highly significant)

Table 3: Side effects noted in PPD (n=17) and BCG (n=13) groups

Group	Patients Without Any Side Effects	Patients With Side Effects				Total	P value
		Painful nodule		Blisters			
		With fever and flu like symptoms	Without fever and flu like symptoms	With fever and flu like symptoms	Without fever and flu like symptoms		
PPD	16 (94.1%)	0	1 (5.9%)	0	0	17 (100%)	< 0.05
BCG	4 (30.8%)	4 (30.8%)	4 (30.8%)	0	1 (7.6%)	13 (100%)	

Discussion

Local tissue destruction like cryotherapy and electrocautery are the conventional methods in the treatment of warts. However, these methods are not practical for multiple lesions. In recent times, immunotherapy has gained popularity for the treatment of multiple warts and difficult to treat areas.[9] An antigen is injected to the wart to surmount a cell-mediated immunity that not only acts against the antigen but also HPV, resulting in clearance of warts. Also, the recurrence following immunotherapy is minimal when compared to conventional therapies.[10]

Considering the high prevalence of tuberculosis infection in our country, it is easy to induce a positive cell mediated immune response with PPD and BCG, which was the reason for selecting these antigens for immunostimulation in our study. We considered all patients with positive mantoux test in the present study because it is suggestive of an immune response to not only PPD but also BCG as they share multiple common antigens.[11]

The sex ratio and age of the patients were almost similar in both the groups in the present study with no significant statistical difference between the two groups. Hence, it indicates that underlying factors such as age and sex have not confounded the results of this study.

The PPD group showed complete resolution in 35.3% of the patients at the end of 8 weeks when 5 TU PPD (0.1ml) was injected into single largest wart once in two weeks for four sessions. A similar study showed 80%complete clearance in multiple verrucae vulgaris (> 10 warts) and 67% complete resolution in multiple verrucae plana (> 10 warts).[12] The difference of higher resolution in their study can be attributed due to higher quantity of PPD being used as well antigen being injected in each wart. Another study on intralesional tuberculin in 17 patients with warts showed complete clearance in 5 (29%) patients, partial response in 10

(59%) patients, and no response in 2 (12%) patients, similar to our study.[13]

A study comparing the efficacy of intralesional PPD into wart and intradermal PPD for the clearance of warts noted 94.1% and 96% response rate respectively.[14] Another study evaluated the effectiveness of tuberculin (PPD) topical jelly in the treatment of warts and found 57% clearance with three to four months of treatment.[15] In comparison to PPD injections where response is seen within two months, topical tuberculin jelly has the disadvantage of requiring longer duration of treatment for the disappearance of warts.

In the present study, complete clearance of warts at the injection site as well as anatomically distant sites was observed suggesting the immune response was not restricted to the site of the injection. A study with PPD immunotherapy showed 60% clearance of target and distant warts with significant increase in circulating IL-4.[16]

The response varied in the different clinical types of warts with maximum response in periungual warts that showed complete resolution in 66.7% of the cases, followed by common warts and palmar warts that showed complete clearance in 60% and 44.4% of the cases respectively. Only partial resolution was noted with plantar warts. This in in contrast to another study that showed complete clearance in 84% of filiform warts, 67% of common warts and 80% of palmoplantar warts, and no improvement in periungual warts.[17]

Immunotherapy with tuberculin PPD in this study was well tolerated. Pain and swelling was noted in one patient at the injection site following the first injection. This subsided within two weeks with use of analgesics and further injections showed no such swelling. Few other studies with PPD have reported local side effects like abscess formation, alopecia areata, immediate hypersensitivity reaction and post inflammatory hyperpigmentation.[17] The target and distant warts resolved without any scarring and hyperpigmentation in our study.

In the present study, BCG group had complete resolution in 30.8% of the patients, partial response in 38.4% and no response in 30.8% of the patients after 4 sessions of intralesional BCG. A case controlled study on BCG immunotherapy for warts on 200 patients showed 39.7% complete cure after the third session.[8] Similarly, complete clearance of warts in28.6% of patients was noted in another study.[18] A clinical trial comparing the efficacy of intralesional BCG and intralesional 5- fluorouracil in multiple warts showed that 5-FU gave statistically better results.[24] This may be attributed to the small number of patients having more than 10 warts considered in this study, nine patients in5-FU group and four patients in BCG group.

In the BCG group of present study, complete clearance was noted in 50% of the cases of common warts and 41.6% of palmar warts. No response was seen in both plantar and periungual warts. This was in contrast to another study that showed maximum number of patients with complete resolution had palmar warts (55.5%) followed by plantar warts (50%), common warts (35%) and periungual warts (33.3%).[24] Isolated cases of periungual and plantar warts with excellent response to BCG have been reported.[25, 26]

Clearance of more than 50% of genital warts within 6 weeks when treated with topical BCG has been reported in a fewstudies.[19-21] A similar study to evaluate the efficacy of topical BCG vaccine in common and plane warts in children noted a complete response in 65% patients with common warts and 45% with plane warts.[21] The mechanism of action of this type of immunotherapy depends on the activation of CD4 lymphocytes and an increase in cytokines such as interleukinIL-1, IL-2, and TNF-αwhich have been shown to have antiviral effects on HPV through the down regulation of its gene transcription.[23]

In the BCG group, local side effects like painful nodules and blisters developed at the site of injection in 61.5 % and 7.7% of the cases respectively. The patients were given oral analgesics till the pain subsided, which was usually within one week. The nodules gradually regressed over 4 to 6 weeks with hyperpigmentation. In two cases the pain was severe and warranted discontinuation of further injections. Four of the nine patients also had accompanying systemic complaints like fever and flu – like symptoms were seen in the first two days following injections in 4 (30.8%) of the cases. This was managed with oral paracetamol and subsided within two days of initiating treatment. Another similar study with BCG immunotherapy showed painful nodules in 53.3%, ulceration in 26.7%, necrosis in 16.7% and lymphadenitis in 6.7%.[24]

Follow up for a period of six months after release from treatment showed no recurrences in both the groups, however a similar study showed recurrence in 1.8% of the cases treated with PPD immunotherapy at 6 months after treatment.[12]

Despite a small sample size in the present study both intralesional PPD and BCG groups showed good response in the treatment of multiple warts, however PPD was marginally better.

Conclusion

Most reports on the use of intralesional immunotherapy for warts are open label studies and there is a dearth of randomized controlled trials investigating their role. Immunotherapy is an economical therapeutic option for extensive warts and hence can be of special value in developing countries. Large, well-designed, randomized placebo-controlled clinical trials should be undertaken before PPD and BCG can be definitively recommended for treatment of multiple cutaneous warts in clinical practice.

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