Brief Report

Study of BCG Immunotherapy in the Management of Multiple, Extensive Non-Genital Cutaneous Common Warts

Abstract

Background and Aims: Most of the available treatment therapeutic modalities for warts are aimed at destruction of virus. However, despite adequate treatment, the virus may persist in the surrounding tissues leading to recurrence. Owing to side effects such as pain, scarring, and risk of secondary infection, these modalities may not be suitable for multiple lesions, extensive involvement and for the treatment of warts in the paediatric age group. The aim of the study was to evaluate the efficacy and safety of intra lesional BCG vaccine in the management of patients with multiple extensive non-genital common warts. **Methods:** Thirty patients with multiple, extensive non-genital cutaneous common warts, with age ranging from 6 to 60 years who were not on any treatment for warts and did not have any active infections (including HIV) or past history of tuberculosis attending the department of dermatology of our hospital in a 2-year period were included. Mantoux test was performed in all patients and positive responders were taken up for study. BCG vaccine was administered into the largest wart intradermally and the injection was repeated every 3 weeks for a maximum of five injections or till the complete clearance of warts, whichever was earlier . The efficacy was assessed every 3 weeks and a final assessment was done at the end of the 12th week. Patients were followed up for another 6 months. **Observations:** Majority of patients were in the age group of 5-14 years. Males (63.3%) were afflicted more than females. Most patients (63.3%) exhibited partial response at the site of injected wart at the end of one month and 70% patients showed complete clearance at the end of 3 months and 36.6% responded with 3 injections and 26.6% patients required 4 for response followed 23.3% requiring 5 injections. **Conclusion:** Intralesional immunotherapy using by BCG vaccine appears to be is a promising treatment modality for the treatment of warts, particularly the multiple and recalcitrant ones. The advantages include the resolution of both the injected and distant warts with negligible recurrence and with minimal side effects.

Keywords: *BCG vaccine, immunotherapy, multiple warts*

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Introduction

Recalcitrant warts are defined as the warts which reappear after 4-5 sessions of selected treatment options or fail to improve. Treatment of warts especially multiple, subungual and plantar ones is difficult and painful, with a substantial risk of recurrence. Current therapies include destructive modalities and immunotherapy. Destructive techniques encompass most traditional interventions, such as monochloroacetic/ trichloroacetic/bichloroacetic acid, podophyllin, podophyllotoxin, 5-fluorouracil, bleomycin, retinoids, salicylic acid, glutaraldehyde, formaldehyde and cantharidin, as well as physical modalities such as surgical excision, cautery, diathermy, cryotherapy and lasers.[1] In the recent times, topical and systemic immunotherapy owing to its non-destructive action, ease of use, and promising results has found a significant place in the treatment of warts.

Intralesional immunotherapy utilizes the ability of the immune system to mount a delayed type hypersensitivity response to various antigens as well as the wart tissue. It leads to the production of Th1 cytokines which activate cytotoxic and natural killer cells leading to and eradication of the HPV infection. This clears not only the local warts but also distant warts, unlike traditional wart therapies.[2]

Methods

We carried out a prospective study amongst 30 patients of extensive, multiple non-genital common warts who were administered multiple intralesional

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BCG vaccines. We did not design a placebo arm in our study because the cure rate for a placebo arm was 22% in a Cochrane review.[2] Thirty patients with multiple, extensive non-genital cutaneous common warts, with age ranging from 6 to 60 years who were not on any treatment for warts and did not have any active infections (including HIV) or past history of tuberculosis attending the department of dermatology of our hospital from October 2016 to September 2018 were included in the study. Patients below 5 years and above 60 years of age and immunocompromised patients, pregnant and lactating women, and subjects currently using any other treatment modality for warts were excluded from the study. The institutional ethics committee approved the study. Detailed history and demographic data was recorded. Cutaneous examination was carried out to record the site, number, duration of warts. All the routine investigations including serology for human immune deficiency virus (HIV) was done. Under aseptic precautions, 0.1 ml of BCG vaccine was given intralesionally into the largest wart intradermally, using an insulin syringe to produce a raised, blanched bleb. The intralesional injection was repeated once every 3 weeks till complete clearance of the warts or for a maximum of 5 injections without response. The efficacy of the medications was assessed every 3 weeks, till final assessment at the end of the 12th week. Patients were followed up for another 6 months for any recurrence. All adverse events were recorded. The response was evaluated as: complete response, defined as the complete absence of clinically apparent wart; partial response as decrease in size >25 and no response as <25% decrease in size.

Statistical analysis

Data was analysed by Microsoft excel and graph pad prism software. Data was summarized by Mean ± SD for continuous data and percentages for categorical data. The comparison between two variables was done by chi square test for categorical data. All *P* values < 0.05 were considered as statistically significant.

Observations

Out of the 30 patients, majority (36.67%) were in the age group of 5-14 years, followed by 15-24 years (30%), 25-34 years (23.3%) 35-44 years (6.67%) and 45-54 years (3.3%). There were 19 males (63.3%) and 11 females (36.6%) with a male to female ratio of 1.72:1. Majority of them (83.3%) had warts in the range of 2-21 in number [Figures 1a, 2a and 3a] and 6.67% patients each had warts in the range of 22-41 and 42 to 61, respectively. Only one patient (3.33%) had warts in the range of 62-81. 63.3% patients showed partial response, 10% showed complete clearance and 26.7% showed no response to intralesional BCG at the injected wart at the end of one month. 50% patients showed partial response, 43.3% showed no response and 6.7% had complete clearance in distant non-injected wart at the end of 1 month. [Table 1] Moreover, 70% patients showed complete clearance, [Figures 1b, 2b and 3b] 23.3% showed partial response and 6.7% were non-responders to intralesional BCG injected warts at the end of 3 months. 60% patients showed complete clearance, 26.7% showed partial response and 13.3% did not respond at distant non-injected warts at the end of 3 months. [Table 2] There was no statistical difference between the lesional site and distant site response. 82% children with warts in our study showed complete response and maximum complete response was seen in 5-14 year age group. In the present study, majority (36.6%) responded with 3 injections. 26.6% required 4 followed by 23.3% requiring 5 injections. [Table 3] Only 13.3% patients responded with two sittings of intralesional BCG. The average number of injections for response was 3.6. In the present study, clearance of warts was seen in patients with more number of warts, ranging from 22 to 72. Moreover. 52% showed complete clearance, 40% showed partial clearance and 8% showed no response in patients with warts in the range of 2-21. Most common adverse effect encountered was pain (70%), followed by edema (40%) ulceration (36.6%) scarring (33.3%) and flu like symptoms (10%).

Table 1: Response at the end of 1 month of intralesional BCG

Response	Lesional site		Distant site	
	n	%	*n*	%
Complete	3	10	2	6.7
Partial	19	63.3	15	50
No	8	26.7	13	43.3
Total	30	100	30	100

Table 2: Response at the end of 3-months of intralesional BCG

Response	Lesional site		Distant site		*P*
	n	%	*n*	%	
Complete	21	70	18	60	0.618
Partial	7	23.3	8	26.7	
No	2	6.7	4	13.3	
Total	30	100	30	100	

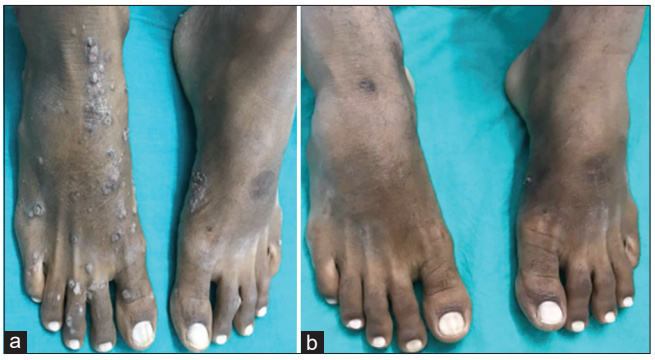

Figure 1: (Original) (a) Multiple warts over dorsum of both feet (b) Complete resolution after 2nd dose of BCG at week 6

Discussion

There is a paucity of studies regarding the efficacy of BCG immunotherapy for the treatment of different types of warts. Bohle *et al*. have utilized topical BCG for condylomata acuminata with complete response in 60% of patients who remained disease free at a median follow-up period of 9.2 months.[3] Similarly, Metawea *et al*. have reported clearance of condylomata acuminata in 80% of their patients after 6 topical BCG applications without recurrence after a 6-month follow-up period.[4] However, our study focussed on extragenital warts that were treated with intralesional BCG vaccine into the largest wart.

In the present study, age range of patients was between 6-51 years, which is in concordance with the study by Sharquie *et al*.[5] However, it is lower than in the study by Jagati *et al*.[6] The male to female ratio in our study was 1.72:1. However, it is higher as compared to the study by Podder *et al*.[7] (1.53:1) Contrarily, female preponderance was reported by Kenawi *et al*.[8] (0.76:1) In the present study, the mean number of warts was 15.4 ± 17.4 with a range between 2-72, which is comparable to the study by Podder *et al*. (13.94 ± 17.02). Our study revealed complete clearance of warts in fewer number of patients at injected (10%) as well as distant sites (6.7%) at the end of 1 month (one dose of BCG). This is in concert with the study by Sharquie *et al*. who claimed complete clearance in 6.4% patients at the end of one month after injecting BCG in the forearm. However, their study did not differentiate between lesional and distant wart response as injection was not given in the largest wart. Our study and that by Sharquie *et al*. elucidate the demand for more number of BCG injections for the clearance of warts.

Table 3: Number of injections of intralesional BCG for resolution of warts

No. of injections	No. of subjects	% of subjects
1	0	0.00
2	4	13.33
3	11	36.67
4	8	26.67
5	7	23.33
Total	30	100.00

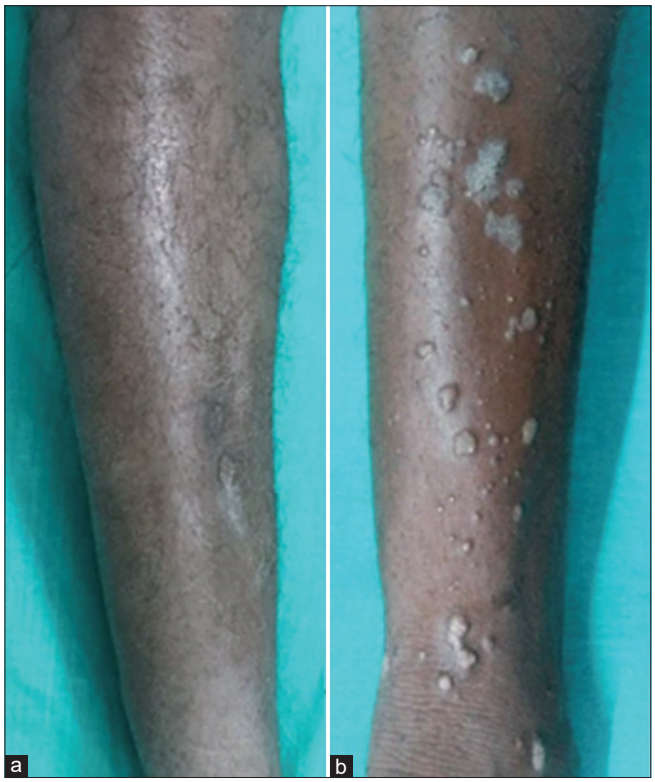

Figure 2: (Original) (a) Multiple warts over shin (b) Complete resolution of warts after 3 doses of BCG

In our study, partial response was seen in 63.3% at the injected wart site and amongst 50% patients at distant sites, at the end of 1 month. This therapeutic response in our study was much higher than that reported by Kus *et al*.[9] (29.4%), Clifton *et al*.[10] (47%), Signore[11] (51%), Horn *et al*.[12] (53%) which used other antigens like tuberculin, mumps, candida and trichophytin respectively. Thus, the BCG immunotherapy validates its supremacy over other antigens. However, further comparative studies using multiple antigens are needed to establish these findings.

The clearance of untreated warts, particularly at distant sites, strongly indicates the acquisition of a widespread CMI against HPV as a response to BCG injection.

Significant response in this study with BCG may be because of use of viable antigen (live vaccine) and antigenic power (vaccines are more antigenic than skin test antigens). From the study, it was also observed that some patients who had response at injected wart did not show response in distant warts. L1-specific T cells which are involved in wart regression might not have been produced adequately in these patients.[13]

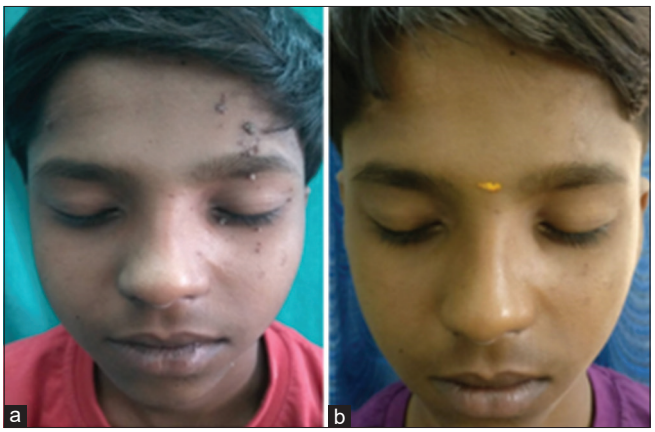

Figure 3: (Original) (a) Multiple warts on face (b) Complete resolution after 3 dosed of BCG

Table 4: Studies involving BCG in the management of common warts

Author	Number of cases	Number of injections	Response	Side effects
Podder *et al*. (2017)[7]	60	3	Complete: 48.5%	Pain Scarring
Jagati *et al*. (2017)[6]	46	1	Complete: 78.26% Partial: 13.04%	Pain Erythema Fever Secondary infection
Sharquie *et al*. (2008)[5]	200	3	Complete: 42.7% Partial: 45%	Itching Tenderness
Kenawi *et al*. (2005)[8]	60	4	Complete: 40% Parial: 40%	Pain Fever, Ulceration, Necrosis, Lymphadenitis
Current report	30	3	Complete: 60% Partial: 26.7%	Pain Eedema, Ulceration Scarring Flu like symptoms

Our study observed complete clearance in 70% patients, partial response in 23.3% and no response in 6.7% at injected warts at the end of 3 months. Similarly, 60% patients showed complete clearance, 26.7% showed partial response and 13.3% patients did not respond at distant non-injected warts at the end of 3 months. This is comparable to study by Jagati *et al*. which showed overall complete response in 78.2% patients, partial response in 13.04% and no response in 8.7%. However, this study did not differentiate between injected and distant wart response. The results of our study (60%) are better compared to the study of Podder *et al*. and Kenawi *et al*. which showed complete response in 48.5% and 40% patients respectively [Table 4].

Three intralesional BCG injections seem to be effective in clearing both injected and distant warts without recurrence in the present study. The 3-week time gap between sessions was to allow severe local inflammatory reaction to subside and to initiate immune stimulation before further stimulating it. This is in concurrence with the findings of Youn *et al*.[14] which states that immune-associated methods show better results than local destructive methods, as these modalities are able to prevent the recurrence of viral warts by maintaining the immune response.

Better response in clearance of warts in patients with large number of warts in our study is noteworthy. This could be explained by the fact that patients who had larger number of warts, continue to follow up for the treatment more than those with fewer warts, who may be reluctant to continue therapy, or may shift to another treatment. Greater number of cross-reacting epitopes are present on the whole bacterial antigen of M. bovis (in Bacillus Calmette–Guerin) and it has been hypothesized that larger warts have larger viral loads and hence greater epitope sharing with the cross-reacting antigen.[7] Interestingly, Choi *et al*. opined that numerous warts and longer treatment periods imply higher therapeutic difficulties.[15]

This study showed that the longer the wart duration better the response to therapy. This may be attributed to the patient's compliance in such cases. On the contrary, Bruggink *et al*. documented lower cure rates among patients whose warts had been present for six or more months than among those whose warts had been present for a shorter duration.[16] Pain, edema, ulceration and scarring, and flu like symptoms noted in our study were also observed in the study by Kenawi *et al*. On the other hand, Sharquie *et al*. have observed no side effects apart from the ordinary mild transient papule or pustule that healed with a mild scar similar to that seen after routine BCG vaccination. This may be explained by the difference in sensitivity to BCG vaccine and mode of injection where they injected BCG intradermally into the arm in contrast to our patient who had been highly sensitive to BCG vaccine and were injected intralesionally into a large wart resulting in a much more severe reaction.

Conclusion

To conclude, intralesional BCG vaccine is effective and safe in the management of extensive warts. It has the advantage of not only being effective in clearing warts at the site of injection, but, also effective in clearing distant warts with no recurrence and negligible side effects. Hence, intralesional BCG should be considered as first line therapy in extensive and multiple warts.

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Conflicts of interest

There are no conflicts of interest.

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