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Original Article

Intralesional Bacille Calmette Guerin as a therapeutic modality in the treatment of warts

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Abstract

Objective To evaluate the effectiveness of intralesional Bacille Calmette Guerin (BCG) immunotherapy in the treatment of warts in immunocompetent patients.

Methods In our study, the sample size included 30 patients with multiple, recalcitrant, and recurrent warts. After taking informed consent, the patients were injected intralesionally with 0.1 ml BCG vaccine into the oldest wart at an interval of 3 weeks for a maximum of three sessions. Patients were evaluated every three weeks for a response, side effects and were followed up to 6 months for recurrences. For assessment of response, the grading scale was used.

Results In our study, out of 30 patients, a good response was seen in 80%, while a partial response in 6.7%, and poor response in 13.3% of patients, and no recurrence was seen in 80% of patients in a follow-up of 6 months. In our study, 90% of patients had pain, 70% flu-like symptoms, 6.7% abscess, 6.7% ulceration, and 10% no adverse effects.

Conclusion Intralesional BCG immunotherapy is a promising, simple, safe, and cost-effective modality for multiple, recalcitrant, and recurrent warts.

Key words
Warts, BCG, immunotherapy.

Introduction

Warts are a common benign proliferation of the skin and mucosa caused by Human Papilloma Virus (HPV) infection. Over 150 HPV types have been recognized and characterized,[1] giving rise to various types like common warts, filiform warts, palmoplantar warts, plane warts, mucosal warts, and even the rare inherited disorder like epidermodysplasia verruciformis.

The mode of transmission of HPV is commonly by contact, which may be either direct or indirect. Basal keratinocytes get infected by inoculation of HPV through a breach in the continuity of mucosa or skin. Individuals whose cell-mediated immunity is impaired are more predisposed.[2]

Although there are many treatment modalities for warts, the treatment of multiple, recalcitrant and recurrent warts remains challenging, which has led to many studies and research in this field in recent times. The various conventional treatment modalities available are salicylic acid, podophyllin, bleomycin, 5-fluorouracil, interferons, imiquimod, cauterization, cryosurgery, laser therapy, and surgical excision.

Immunotherapy is a modality that is being used

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in recent times for the treatment of warts. It stimulates the immunity by mounting delayed-type hypersensitivity reaction to various antigens and also to the wart tissue, thereby treating even distant warts. It stimulates Th1 cytokines, which activate natural killer cells, macrophages, and B and T-lymphocytes, leading to resolution of warts.[3] And thus, it was found to be advantageous over conventional modalities of treatment.

Use of various intralesional antigens injections such as MMR, *Candida* antigen, mumps, *Trichophyton* antigens, tuberculin PPD, BCG, and Mw vaccine is increasingly investigated to treat multiple warts of various types, against HPV for their immunostimulant effect, especially for inducing clearance of lesions distant to the site of application.[3-8]

Methods

The present study was done in the Department of Dermatology, Venereology and Leprosy, VL outpatient department of Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation over two years from November 2017 to October 2019 after obtaining approval from the Institutional Ethics Committee. It was a prospective open-labelled study comprising 30 patients.

Patients who had multiple (>5), recalcitrant, recurrent warts, and between age groups 10 to 60 years were included in the study.

Pregnant females, lactating mothers, immunosuppressed individuals, patients having any chronic systemic illness, genital warts, and warts over the face were excluded from our study. After obtaining written informed consent, all the patients who were enrolled in the study were explained about BCG injection procedure, the therapy duration, possible outcomes of the treatment, associated possible complications, and expected time to get optimum results.

A complete history of the patient regarding the duration of warts, any treatments taken in the past, and clinical characteristics of warts like the number, site, and type were noted. Clinical photographs of the patient were taken before the procedure.

The target wart (oldest) was cleaned with betadine solution and then was injected intralesionally using a built-in needle insulin syringe with 0.1ml of BCG vaccine.

Intradermal BCG vaccine was given at an interval of 3 weeks for a maximum of three sessions. Patients were closely evaluated clinically and photographically for every three weeks for the response to therapy and side effects.

The response to intralesional therapy was assessed as follows:

Poor response: Those who showed less than 25 % improvement.

Partial response: Responders who showed 25 to 75% improvement.

Good response: Responders who showed greater than 75% improvement.

Patients were followed at the 1st, 3rd, and 6th months after completion of treatment sessions for response and recurrences.

Results

In our study, age group of patients ranged from 10 to 60 years, with most patients under the 11-30 years age group, i.e., 23 patients (76.7%), and the mean age of patients was 23.9 years. Out of 30 patients, 27 (90%) were males, and 3(10%) were females.

Table 1 Response to treatment.

Response	*Treatment outcome*		
	Poor response (< 25%)	*Partial response (25 -75%)*	*Good response (> 75%)*
2nd sitting	20 (66.7%)	10 (33.3%)	0 (0%)
3rd sitting	5 (16.7%)	13 (43.3%)	12 (40%)
After 1 month	4 (13.3%)	2 (6.7%)	24 (80%)
After 3 months	4 (13.3%)	2 (6.7%)	24 (80%)
After 6 months	4 (13.3%)	2 (6.7%)	24 (80%)

In the present study, among 30 patients majority of them, 53.3% (16) had common warts (verruca vulgaris) over the forearms and legs, followed by 20% (6) palmar warts, 13.3% (4) plantar warts, 10% (3) periungual warts, and 3.3% (1) filiform warts.

In our study majority of patients had many warts ranging from 5-15 (83.3%), followed by 16-30 (10%) and >31(6.7%).

According to the duration of disease (in months) in our study, the patients were divided into six groups, ranging from up to 6 months to 36 months, and the majority of patients had a duration of less than six months (33.3%). The mean disease duration in patients was 13.3 months, and the median duration was 11.5 months.

After the first dose, 66.7% had a poor response, and 33.3% showed a partial response, and there was no complete resolution of lesions. After 2nd dose, 12 patients (40%) showed a good response with the healing of more than 75% of lesions **(Table 1)**. After all the three doses of BCG injection, a good response was seen in 80 % of patients, while a partial response was seen in 2 (6.7%) patients, and poor response in 4 (13.3%) patients and no recurrence was seen in 80% of patients at a follow up of 6 months **(Figure 1-4)**.

In our study 90% of patients had pain, 70% flu-like symptoms, 6.7% abscess **(Figure 5)**, 6.7% ulceration **(Figure 5)**, and 10% no adverse effects.

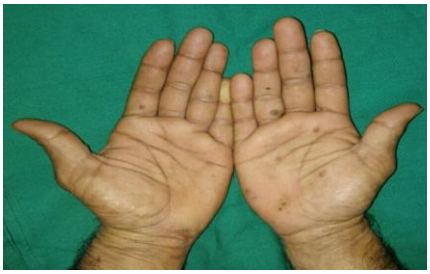

Figure 1 Patient with palmar warts.

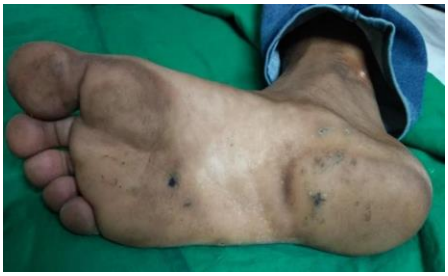

Figure 3 Patient with plantar warts.

Figure 5 Abscess and ulceration after 1st BCG injection.

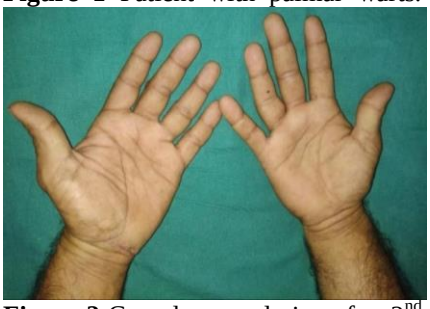

Figure 2 Complete resolution after 2nd session.

Figure 4 Complete resolution after three sessions.

Discussion

Patients and clinicians experience the frustration of treating cutaneous viral warts caused by the infection with the Human Papilloma Virus (HPV). Although a wide range of therapies are available, the treatment of warts remains challenging for a group of patients. Still, there is no single therapeutic option completely successful in treating warts and preventing recurrences.

In immunocompetent patients, due to the prominence of cell-mediated immunity as evidenced by infiltration with CD4 T lymphocytes, macrophages, and increased Th1 cytokines (likeIL-2, TNF-α, and IFN-α, β, and γ) in warts, most of them specially extra genital, were seen to resolve spontaneously.

As immunity seems to play a vital role in the control and clearance of warts, various immunotherapeutic modalities have been used, including oral zinc sulfate, levamisole, cimetidine, etretinate, and topical/ injectable preparations such as contact sensitizers (e.g.-SADBE, DNCB, DPCP), imiquimod, and IFN-α. But to support their use, limited data is available.[9]

Different types of immunotherapeutic agents have been used for intralesional injection. These include autogenous vaccine,[10] Candida antigen,[4,11] mumps antigen,[5] trichophytin skin test antigen,[12] tuberculin,[13,14] BCG vaccine,[7] MMR vaccine,[4] Mycobacterium *w* vaccine,[15] gamma injection, and interferon-alpha. This therapy utilizes the fact that there is a good prevalence of immunity to these antigens in the general population. Most children well-tolerated the dose of the antigen.

BCG (Bacille-Calmette-Guerin) is a live attenuated vaccine derived from Mycobacterium bovis. It is well known for its prophylactic effect against tuberculosis; accidentally, leprosy incidence was also tremendously decreased.[16] BCG also had been used in the treatment of transitional cell carcinoma of the bladder,[17] malignant melanoma,[18] in alopecia areata,[19] and recurrent oral aphthosis.[20]

BCG vaccine stimulates the delayed type of hypersensitivity reaction and increases the recruitment of various immune cells like natural killer cells, macrophages, lymphocytes resulting in the resolution of viral warts.

The first published study on intralesional BCG was reported in 1977 by D'Alessandria,[21] and Lipke [22] reported that viable BCG treatment is based on immune response stimulation.

Chandrashekar L.[23] reported that BCG has the advantage of injecting a single wart that clears the local wart and distant warts.

In the study conducted by Jaisinghani *et al*.[24] the mean age of presentation of warts in patients was 25.5 years, and all were men. In contrast, Ashish Jagati *et al*.[25] observed 23.70±8.43 years of mean age with a male to female ratio 1.5:1, and Indrashis Podder *et al*.[26] observed 28±10.74 years mean age with a male to female ratio 20:13, and in our study, mean age was 23.9 male to female ratio was 9:1.

In the present study of 30 patients, 27 (90%) were males, and this finding concurs with the male preponderance in a wart, as seen in other studies.[26]

In the present study, among 30 patients majority (53.3%) had verruca vulgaris. They were in accordance with studies conducted by Indrashis Podder *et al.*[26] and Mohammed Z. Kenawi *et al*.[27]

According to the number of warts, most of them were in the range of 5-15 (83.3%), which were in accordance with the other studies.[24]

The mean disease duration in patients was 13.3 months, and the median duration was 11.5 months, and Jaisinghani *et al*.[24] reported a median duration of 7.8±4.06 (range: 1-15 months) and as per Podder *et al.*[26] mean duration was 11±13.64 months.

Among 30 patients, 24 (80%) had an excellent response with complete resolution after completion of 3 sessions, and no recurrence were seen during six months of follow-up in our study.

Bohle *et al*.[28] reported that topical application of BCG led to the clearance of lesions within six weeks in six out of 10 (60%) patients at a median follow-up of 9.2 months, and according to the study done by Metawea B *et al*., topical application of BCG in condylomata acuminata showed an 80% response after six applications, without recurrence after a follow-up period of 6 months.[29]

Studies have shown good encouraging results with intralesional BCG immunotherapy in medically resistant condylomata acuminata of the penis,[30] in case reports of the periungual wart,[31] and recalcitrant warts of 5-year duration over the foot.[32] Three patients (10%) in our study had periungual warts, which resolved after three sessions of BCG injection.

Sharquie *et al*.[7] who used the BCG vaccine to treat warts, found that the response was distributed among different types of warts with 63.3% for common warts, 23.3% for plane warts, and 13.3% for a plantar wart.

Four patients, 13.3%, showed poor response (less than 25% improvement) in our study even at six months follow-up, and all these cases were verruca vulgaris. Out of 4 patients, 2 developed ulceration, so treatment was stopped. In the other 2, even though the entire treatment sessions were given, no response was seen.

In a study conducted by Mohammed Z. Kenawi *et al.*[27] 39.3% showed complete clearance after the third session of intralesional BCG. And in a study conducted by Ashish Jagati *et al*. the excellent therapeutic response was seen in 78.26% of patients, and partial response was seen in 13.04% of patients.[25]

Indrashis Podder *et al*. found BCG more efficacious than PPD in their study,[26] whereas Rao AG *et al*. observed complete response in 60% and partial response in 26.7% of patients.[33]

Jaisinghani *et al*. study showed a complete response in 73.53% of patients, with partial response in 23.53% of patients, and no response in one patient. Our study results were in accordance with other studies,[24,25] with 80% of cases showing complete remarkable improvement, thereby proving intralesional BCG to be a useful therapeutic modality in treating multiple and recurrent warts.

In our study, pain (90%), along with flu-like symptoms (70%), were common side effects observed in most of the patients. Abscess formation and ulceration were seen only in 6.7% each. Serious adverse effects like BCGitis were not observed. There were no side effects in 10% of patients. Pain and flu-like symptoms, which subsided with NSAIDS, were seen in most of our patients.

In a study conducted by Ashish Jagati *et al.* pain at the injection site (100%), erythema (78.26%), fever (76.08%), and secondary infection (2.17%) were the main adverse events noted.[25]

Daulatabad *et al*. [34] in a case series of 7 patients, reported BCGitis in 1 and lymphadenopathy in 3 patients treated with isoniazid and rifampicin. In endemic areas, it highlighted the danger of BCG.[15] Conventionally, BCGitis is characterized by local erythema accompanied by ipsilateral regional lymph node enlargement. These are usually seen in children with underlying immunodeficiency, like severe combined immunodeficiency. In our study, none showed BCGitis.

Podder *et al*. observed pain in most patients during injection, abscess at the injection site in one patient, and two scars in one patient.[26] Two patients (6.7%) in our study showed abscess formation, and another two patients developed ulceration, which followed the 1st session of intralesional BCG. These patients were treated with antibiotics, after which ulceration and abscess subsided, and further treatment was stopped in patients who developed ulceration.

Patients with abscess were willing for further injection after the abscess subsided, so it was continued. There was an improvement of warts in these patients without any further abscess formation.

Jaisinghani *et al*. observed mild and insignificant side effects like tolerable immediate pain during injection and flu-like symptoms in all patients. Other local reactions such as itching in 13 (38.2%), erythema in 3 (8.8%), and edema in 2 (5.9%) were seen in patients at the site of injection. Other delayed side effects seen at the site of injection were ulceration (5.9%), nodule/granuloma formation (11.8%), scarring (14.7%), hypopigmentation (5.9%), and BCGitis (2.9%).[24]

Overall, our study's side effects were mild, like pain and flu-like symptoms, ulceration, and abscess formation, but serious adverse effects like BCGitis were not seen.

Conclusion

Thus intralesional BCG immunotherapy is a promising, safe, simple, easy to do, and cost-effective modality for multiple, recalcitrant, and recurrent warts as it has high tolerability, good efficacy, sustained effect with low recurrence rates, and helps in resolution of multiple warts at distant sites.

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