

INTRALESIONAL BCG: AN ANSWER TO RECALCITRANT WARTS

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Abstract

Background: To study efficacy and safety profile of intralesional Bacille Calmette Guerin (BCG) in periungual, palmo-plantar and recalcitrant warts.

Materials and Methods: 20 patients with periungual, palmo-plantar, extensive warts and recalcitrant warts from any area except mucosal and genital warts were taken into the study. Each patient was investigated to rule out any infective foci in the body, was asked for the history of Bacille Calmette-Guerin(BCG) vaccination at birth and confirmed by examining BCG scar on left deltoid region. Stipulated dose of antigen is injected into the selected lesions. This was repeated every 2 weeks till 3 cycles of treatment.

Result: Marked response was seen in all 20 cases by the end of 2 months. Earliest response was seen in a case of extensive warts by the end of 12th day following first intralesional injection.

Conclusion: Intralesional immunotherapy using Bacille Calmette-Guerin (BCG) for, periungual, palmo-plantar, extensive and recalcitrant warts is efficacious, less invasive, safe, economic and can be done in any set up with the supply of basic vaccines.

INTRODUCTION

Verrucae or warts are skin lesions affecting the skin and other epithelial tissues caused by Human Papilloma virus. Although warts can appear at any age, they are more common in children and adolescents. The prognosis of warts cannot be predicted, in some patients they may spontaneously resolve, whereas others show persistence and progression with spreading to other body sites, leading to physical and emotional distress to the patients.^[1]

Management of verrucae, particularly over the periungual and palmo-plantar areas, or in cases which are extensive or recalcitrant to most of the destructive procedures are often frustrating and painful to the patient and the physician as well. Immunotherapy for warts has been performed with diphenylcyclopropanone (DCP), squaric acid dibutyl ester (SADBE), imiquimod, tuberculin jelly, and autologous vaccines. Autologous vaccine therapy is limited by the oncogenic potential of the virus. Therefore, a safe, inexpensive, effective and simple immunotherapeutic agent is needed for the management of warts.^[2]

Intralesional immunotherapy utilizes the ability of the immune system to mount a delayed type hypersensitivity response to various antigens and also the wart tissue. A schematic representation of

the pathogenesis by which immunotherapy works is given in [Table 1]. 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. List of immunotherapies available are given in table.^[2]This clears not only the local warts but also distant warts unlike traditional wart therapies.

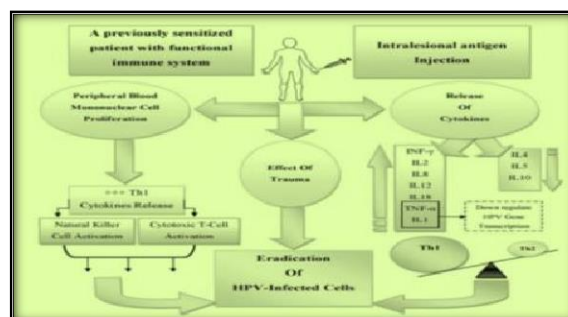


Figure 1: Immunopathogenesis [3]

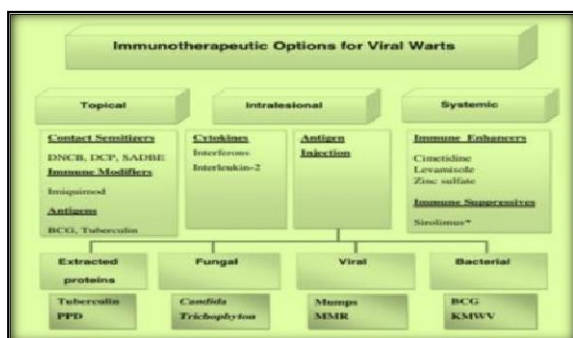


Figure 2: Immunotherapeutics^[3]

MATERIALS AND METHODS

This was a study conducted in 20 selected patients. Inclusion criteria includes multiple warts (>5), recalcitrant warts, periungual warts, palmo-plantar warts, patients willing for procedure after having explained the consequences, patients age between 12-40yrs and irrespective of sex. Exclusion criteria including Pregnant ladies and lactating mothers, Children under 12 years, Immunosuppressed individuals, Patients having any chronic systemic illness, Patients with hypersensitivity to antigens. Written informed consent was taken from the patients / guardian for their participation in the study. Name, age, sex, address, contact number and occupation were noted. Selected patients were thoroughly examined and the number of lesions, site, size, duration of the warts, any previous treatment was recorded. Pre and post procedure photographs were taken at every sitting once in two weeks. A baseline investigation of complete blood count, chest X-ray and HIV testing was done in all patients.

After taking all aseptic precautions, intralesional Bacille Calmette-Guerin (BCG) was injected. In our study we used local anesthesia 2% lignocaine only for periungual warts in the form of ring block. Volume to be injected was decided based on the intradermal antigen test reaction [Table – 3][4]. Antigen injected intradermally on the volar aspect of the forearm and the delayed hypersensitivity response is assessed as erythema and induration 48-72 hours later. Responders (with erythema and induration of 5 mm in diameter) are taken up for the study [3]. This procedure was repeated every 2 weeks till clearance of warts maximum upto 3 treatments without results. Patients and their attenders were thoroughly educated about post procedure precautions, Flu like symptoms which patients usually develop the next day of the

treatment commonly during evening hours, we prescribed analgesics when needed, for 2-3days. Patients were also advised regarding hygiene, healthy diet to keep any infective foci away. All the patients were followed up for a mean duration of 11 months (SD- 2.93).

RESULTS

Out of 20 patients, there were 11 males and 09 females in the age group of twelve to forty-five years and a mean age of 22.57 years (11.106). The number of warts in the patients ranged from 1-15 in number, with the site of involvement of warts in the upper limb being the palm, volar surface of finger, periungual area of the fingernail, subungual area of the fingernails and dorsum of the finger and in the lower limb, the plantar surface of the toes, soles, dorsum of the feet and periungual region of the toes and legs. Out of the 20 patients, 18 (90%) patients had complete resolution of the warts, both at the injected as well as the distant sites [Figures 1 and 2]. In two (10%) patients the warts didn't show complete resolution though a significant degree of response was seen. The mean time to complete clearance of the warts was (41.65) days (SD- 13.33), with the warts on the upper limb clearing in (30.71) days and those on the lower limb clearing in a mean time of (25.98) days (p 0.215). The mean dose of:- Bacilli Calmette Guerin (BCG) that was required for complete clearance of the warts was given much importance since we calculated the dose based on the test patch size [Table- 3.][4]. Systemic side effects experienced by the patient were flu like symptoms for minimum of 2days and maximum of 4 days in all 20 patients, the symptoms were evening rise of temperature in 18 (90%) patients, myalgia in 13 patients (65%), headache in ten (50%) patients and vomiting in two (10%) patients. The local side effects at the site of injection were redness, swelling and induration in 8 (40%) patients. The swelling usually developed within 5 days time of taking the injection and was associated with pain. In most of the patients the swelling subsided within 10 days. Among these 8 patients 5 of them also complained of painful swelling in the ipsilateral dorsum of fingers where intralesional injections were given, they also showed the features of ulceration at the site of injection which subsequently resolved by oral analgesics and antibiotics.

Table 3: ^[4]

SIZE OF TEST REACTION (mm)	VOLUME OF THE ANTIGEN (ml)
1	5-20
2	21-40
3	>40



DISCUSSION

In our study complete clearance of both the treated and untreated distant warts was seen in 18 (90 %) patients. Mean time for clearance of warts was 32.38 days. Warts on the legs subsided much earlier than those on the hands. The BCG vaccine which we used for our study was taken from our own vaccine unit after the days vaccination [left over],

therefore its literally a free of cost treatment. The mean dose required for the clearance of single wart lesion or set of warts was not evaluated since we decided the dose using the test patch size assessing the degree of response of an individual to the antigen.

In a study conducted by Garg et al,^[5] they showed that the mean (SD) dose of Mycobacterium W Vaccine required for complete resolution of the warts was 0.186 (0.101) ml and for this dosing they didn't perform any intradermal test dose to assess the immune response. Based on the below reasons they substantiated that test dose isn't mandatory,

1. Latent infection with Mycobacterium tuberculosis in India, which has antigenic similarity with Bacille Calmette Guerin (BCG). Thus, there are high chances of a good immunological response to MWV injection without prior sensitization.
2. Cases where sensitization would have been required, an intralesional injection at the wart site could have done the same, without any scarring and local complication at the site not having the wart.
3. It also reduced the total dose of vaccine given to each patient, which never exceeded 0.1 ml at any session in our study.
4. We also gave repeat injections at an interval of four weeks to reduce the chances and severity of local side-effects of the vaccine injection.
5. We also injected the vaccine intralesionally into a single wart each time, and hence, multiple painful pricks were not required during each session.

In a study by Meena et al,^[6] using MWV for the treatment of multiple warts, a sensitization dose of 0.1 ml was given in each deltoid region at the baseline. After two weeks, subsequent injections were given at an interval of one week intralesionally into three to five lesions at a time. Complete clearance of the warts at the site of injection was seen in 33 (83%) patients with 23 (70%) of the 33 patients showing resolution of the distant untreated warts. The mean (SD) time to complete clearance was 9.7 (2.6) weeks. Recurrence was seen in three patients during a follow-up period of 4.48 (1.32) months. The side effects reported were tender erythematous papules healing with a scar at the deltoid region in all patients, erythema at the site of the warts in 25 (70%) patients, swelling in six (16%), and superficial ulceration in one patient. Two patients had low-grade fever and two patients had tenderness and swelling of the submandibular lymph node.

In this study, the method of administration of antigen (intralesional, radially) showed a higher rate of clearance of the warts, both at the injected as well as the untreated distant sites. The recurrence rate in our study was slightly less as compared to the study by Meena et al, though the follow up was not even. In another study by Gupta et al,^[7] in which killed Bacille Calmette Guerin (BCG) was used for the

treatment of anogenital warts, a sensitization dose of 0.1 ml was given in each deltoid and intralesional injections were given in ≤ 3 warts at a time, which were repeated at weekly intervals. There was complete clearance of the warts in eight out of the nine patients (88.9%) who were treated. All the patients showed an immunological reaction at the site of sensitization in the deltoids. Adverse effects were seen in four patients. No recurrence was seen after a mean follow-up of 5.1 months.

In a study by Singh et al,^[8] retrospective analysis was done to evaluate the efficacy and safety of MWV in the treatment of extensive extragenital cutaneous warts in 44 patients. The patients were sensitized with 0.1 ml of MWV injected vaccine injected intradermally over each deltoid region. In the sensitized individuals, ≤ 0.1 ml of the vaccine was injected intralesionally in two to four warts after two weeks. The injections were repeated at intervals of two weeks. Complete clearance of the warts was seen in 24 (54.5%) patients, with a mean of 3.4 ± 1.1 injections. Resolution of the warts at distant sites was seen in 38 (86.3%) patients. Adverse effects were present in 36 (81.8%) patients, with the presence of nodule formation at the site of sensitization. In two patients the nodule progressed to form an ulcer, which healed leaving an atrophic scar. In the remaining 34 patients it subsided spontaneously in two to three weeks, without any residual changes. Nodule formation was present in 19 (43.1%) patients at the site of the injected wart and three such nodules healed with atrophic scars.

In a double-blind randomized clinical trial, which was conducted by Kumar et al,^[9] the efficacy and safety of intralesional MWV was compared with that of imiquimod 5% cream, in the treatment of anogenital warts, along with changes in the HPV-6 and HPV-11 viral loads. Fifty nine percent ($n = 26$) of the patients in the imiquimod group and 67% ($n = 30$) of those in the MWV group had complete resolution ($p = 0.52$). There was a significant decline in the mean viral loads of HPV-6 ($p = 0.003$) and HPV-11 ($p = 0.03$) after treatment in the MWV group, but only in the viral load of HPV-6 ($p = 0.01$) in the imiquimod group. The study concluded that both imiquimod 5%, and the Mycobacterium W vaccine were equally effective in achieving clinical and virological clearance for HPV-6, whereas, only

Mycobacterium W vaccine resulted in a significant decline in the HPV-11 viral load.

CONCLUSION

The immunotherapy using intralesional Bacille Calmette Guerin (BCG) has proved to be efficacious in the treatment of warts that are recalcitrant to most of the modalities of treatment like electrosurgery, cryotherapy and wart at sites like periungual, palmar-plantar where destructive methods are painful and the recurrence rate is high. The advantage of this antigen is its wide availability in all primary to tertiary centres in India, cost effective, dramatic response, less recurrence, less number of treatment cycles and less downtime in regression of both lesions at site of injections and distant untreated lesions. The only drawback of this was the systemic side effects and in few patients the local side effects, both are easily treatable.

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