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A Comparative Study of Therapeutic Efficacy of BCG Immunotherapy (50 Cases) and Vitamin D (50 Cases) in Cutaneous Warts (Total 100 Cases)

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ABSTRACT

Background: Human papilloma virus infects the epithelium of skin or mucosal cells to cause warts. Most of the current therapeutic modalities are ablative, act only on targeted lesions, and lack a well-defined treatment endpoint. These procedures have high recurrence rates, side effects and are not effective over distant warts. Intralesional immunotherapy acts on cell mediated immunity to treat local as well as distant lesions.
Aims and objectives: To evaluate the efficacy and safety of intralesional BCG and intralesional VITAMIN D and to compare efficacy and safety of intralesional BCG and intralesional VITAMIN D in the treatment of patients with cutaneous warts.
Materials and Methods: This study included 100 adult patients with single or multiple warts of different size, number and duration with or without distance warts. Each patient was randomly assigned into Group 1 (BCG : 0.1mL of 1mg/mL) and Group 2 (vitamin D3 : 0.2mL of 15mg/mL). One or two warts were injected per session at interval of 21 days for three sessions. Response was assessed. Adverse effects were noted. Cases were further followed up after 3 months without any treatment to assess for any recurrences. In both the groups, standard medical treatment will be also given. Standard digital photographs were taken at each visit to support the data.
Results: The BCG group had the maximum patients with complete response (36 of 50, 72%) followed by VITAMIN D group (24 of 50, 48%). No major adverse drug reactions were reported in any of the group.
Limitations: Small sample size and absence of control group were the main limitations of our study.
Conclusion: Immunotherapy offers a safe, effective and affordable approach in the patients with multiple cutaneous viral warts with lesser side effects and recurrence rate.

KEYWORDS: BCG, Vitamin D, Warts

INTRODUCTION:

Human papilloma virus (HPV) infects and proliferates in both keratinizing and non keratinizing epithelium producing cutaneous, genital, oral and laryngeal warts. Trauma and maceration are the important predisposing factors. According to a population survey in adults, the highest prevalence of cutaneous wart was in socioeconomic class three.[1]

The immune system in healthy individuals is apparently not able to clear warts for months. T lymphocytes are low and Langerhans cell numbers are reduced within warts suggesting a lower local immune response. In cases of recalcitrant or recurrent wart, it is possible that immune

system is not able to target certain HPV proteins, possibly due to poor antigen presentation, poor response, or virus induced local immunosuppression resulting in the development of tolerance.[2]

Currently various destructive and ablative treatment options available like topical therapy which includes salicylic acid, imiquimod, diphencyprone, 5- Fluorouracil, tretinoin, trichloroacetic acid and energy based therapies which includes radiofrequency, electrosurgery, cryotherapy, carbon dioxide laser, photodynamic therapy, but these modalities can not be 100 % effective, failure of treatment and recurrences being common. Most of the therapeutic modalities for warts are ablative in nature with side effects, variable results and recurrence.

The cell-mediated immunity (CMI) has a role in the HPV proliferation through stimulation of cytokines.[2] Mechanism of Intralesional immunotherapy is that the immune system is able to recognize the injected antigens, which may induce a type IV hypersensitivity reaction to the antigen and HPV, making the immune system more pronounced for recognizing and clearing HPV at both the treated and distant warts and preventing recurrences.[3] Other antigens are available to treat wart like measles, mumps and rubella (MMR) vaccine, tuberculin purified protein derivative(PPD), Bacillus of Calmette-Guerin (BCG) vaccine, mycobacterium w(Mw) vaccine, Candida albicans antigen, etc .Other antigen like biologically active compound like vitamin D3.

Through this study, an attempt was made to evaluate the role of intralesional antigen in cutaneous warts and to make a head-to-head comparison of two modalities, namely BCG and vitamin D3.

Our objective was to study and compare the response in terms of efficacy, safety profile, clearance of distance warts and recurrence rate of two modalities of intralesional immunotherapy (BCG and vitamin D) in the treatment of viral warts.

MATERIALS AND METHODS

STUDY DESIGN

The study was carried out in accordance with the Good Clinical Practices and in compliances with the institutional regulations. This prospective, single centre, parallel comparative study of efficacy of intralesional BCG and vitamin D3 was undertaken in outpatient department of Skin V.D and leprosy in a tertiary care hospital over a period of two years. The ethical approval to conduct the study was taken from the Institutional Ethics Committee. The study was carried out in 100 patients. 100 patients who are clinically diagnosed as warts were selected. Patients were randomly allocated in to two groups, each group comprised of 50 patients.

STUDY POPULATIONS

The study population was comprised of 50 patients of Group A and 50 patients of Group B coming to skin OPD fulfilling the inclusion criteria.

INITIAL ASSESSMENT

The diagnosis of warts was made clinically, following which detailed cutaneous examination was done and detailed relevant clinical history of patients regarding onset, duration of symptoms, severity of lesions, past history, history of any medication was taken.

All the patients were explained about the study, nature of the disease, intervention, chances of recurrence and possible side effects. After obtaining written informed consent from all patients, baseline characteristics of warts, including number, size, site, duration of disease and the presence or absence of distant warts, were noted.

MATERIAL:

1) Live attenuated Bacillus Calmette Guerin (BCG), Reconstituted with 1 ml of sodium chloride IP(w/v%)
2) Cholecalciferol injection IP 1ml - 6,00,000IU (VITAMIN D3)

METHOD OF ADMINISTRATION OF BCG (GROUP A)

This study included 50 adult patients with multiple recurrent extragenital warts of different sizes, numbers, and duration, with or without distant warts. BCG Vaccine IP (freeze dried) live attenuated BCG was reconstituted with 1 ml sodium chloride injection IP (0.9%). Lignocaine jelly was applied on selected viral warts or in few cases viral warts were injected with 0.2 ml of lignocaine (20 mg/ml) and after few minutes, intralesional 0.1 ml BCG vaccine given into the largest wart at every 3-week interval, directly without a pre-sensitization skin test for maximum 3 sessions. Follow-up was done at 1.5 month and 3 months to detect any recurrence and clearance of lesions.[4]

METHOD OF ADMINISTRATION OF VITAMIN D3 (GROUP B)

This study included 50 adult patients with multiple recurrent extragenital warts of different sizes, numbers, and duration, with or without distant warts. Vitamin D3 injection is available in vials containing 6,00,000 IU of cholecalciferol in 1 ml (15 mg). Lignocaine jelly was be applied on selected viral warts or in few cases viral warts were injected with 0.2 ml of lignocaine (20 mg/ml) and after few minutes, 0.2 ml of Vitamin D3 (15 mg/ml) was slowly injected into the base of viral wart with a 27gauge insulin syringe at every 3week interval for maximum 3 sessions, follow-up was done on 1.5 month and 3 months to detect any recurrence and clearance of lesions. Post treatment, the patients were advised not to use any topical and oral medication.[2]

INCLUSION CRITERIA

1. Patients willing to participate in the study.
2. Age more than 12 years and less than 60 years.
3. No concurrent systemic therapy of viral warts in the last 4 weeks or topical treatment of viral warts in the last 2 weeks.
4. Recurrence of viral warts after taking treatment.
5. Patients who have taken treatment for more than six months other than immunotherapy

EXCLUSION CRITERIA

1. Patients with keloidal tendency of skin.
2. Pregnant and lactating females.
3. Any prior history of hypersensitivity to vitamin D3, BCG and Injection lignocaine.
4. Any evidence of immunosuppression including HIV.
5. Age less than 12 and more than 60 years.

The response was evaluated as:

1. Complete response-Complete absence of clinically apparent wart
2. Partial response- Decrease in size > 25%.
3. No response-<25%Decrease in size. [5]
4. “Recurrence” in cases of new warts appearing following complete clearance.

STATISTICAL COMPARISON:

We applied chi square test for response of treatment in Group A and Group B. The chi square value come out to be 6.092 and p value come out to be 0.047 ($p<0.05$) suggesting of statistically significant.

RESULTS

The mean age in both treatment groups were comparable and were in the range of 21 to 30 years. Male patients outnumbered female patients in both treatment groups. The highest efficacy was seen in the BCG group, with complete response in 36 patients (72%), partial response in 15 patients (30%) and no response in 18 patients (36%), followed by vitamin D group, with complete response in 24 patients (48%), partial response in 19 patients (38%), and no response in 20 patients (40%). (Chart 1). Response was greater in the injected warts than in distant warts in both groups (Chart 2).

TABLE 1 COMPARISON OF RESPONCE (CHART 1)

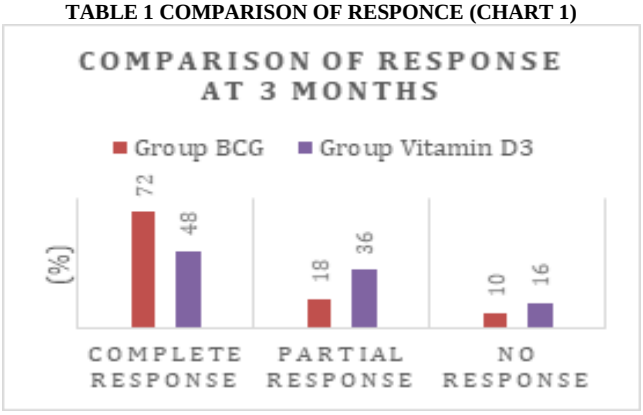
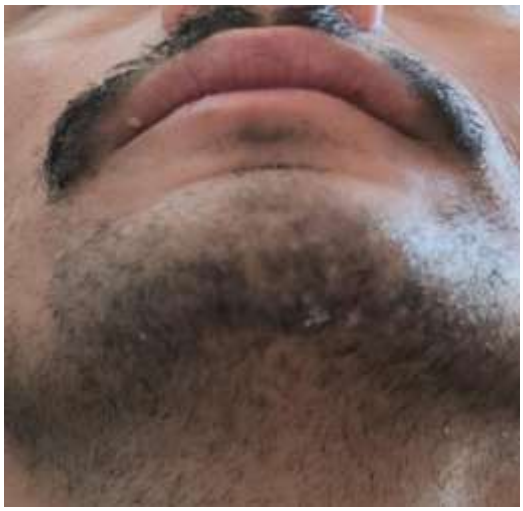


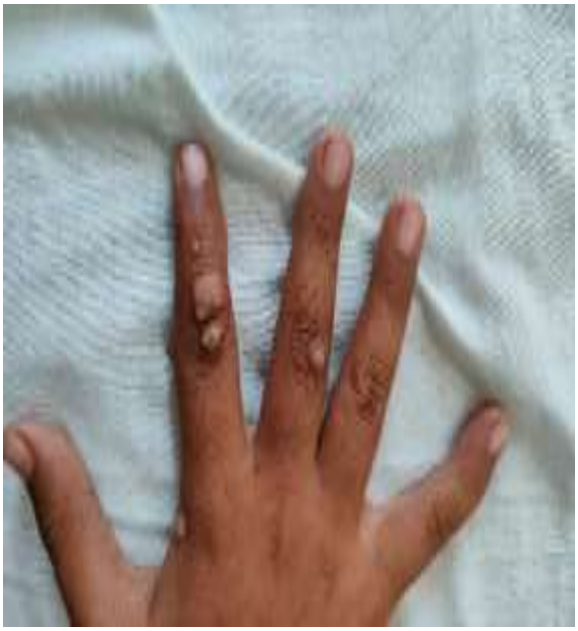
FIGURE 1: RESPONSE OF VITAMIN D

BEFORE TRATMENT

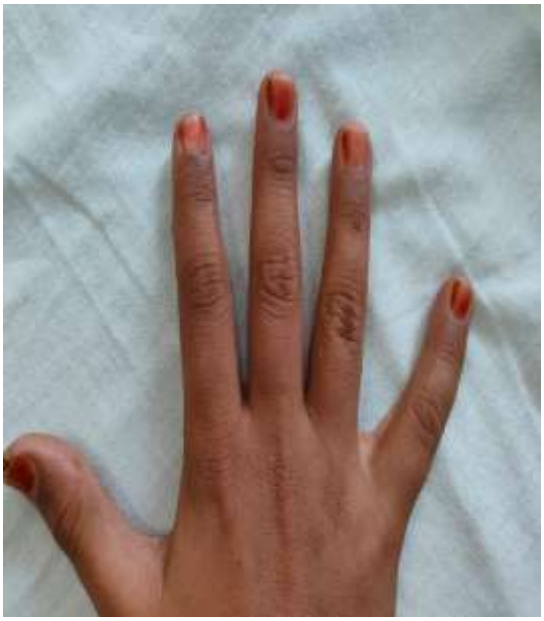


AFTER TREATMENT

FIGURE: 2 RESPONSES OF BCG

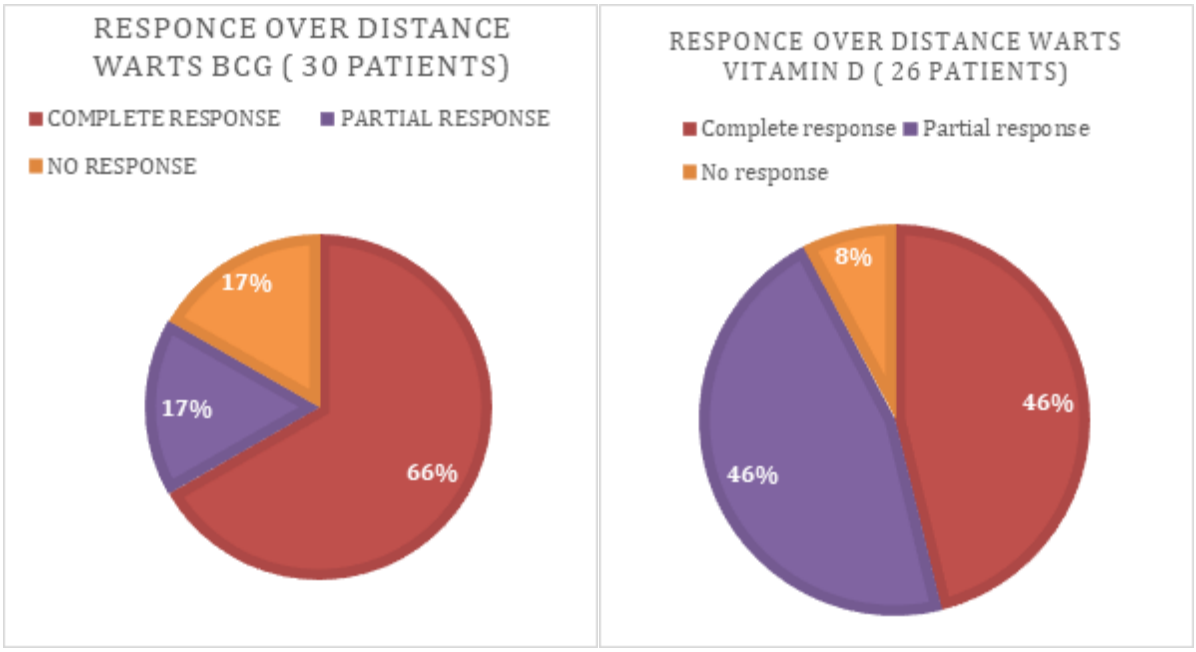


BEFORE TREATMENT



AFTER TREATMENT

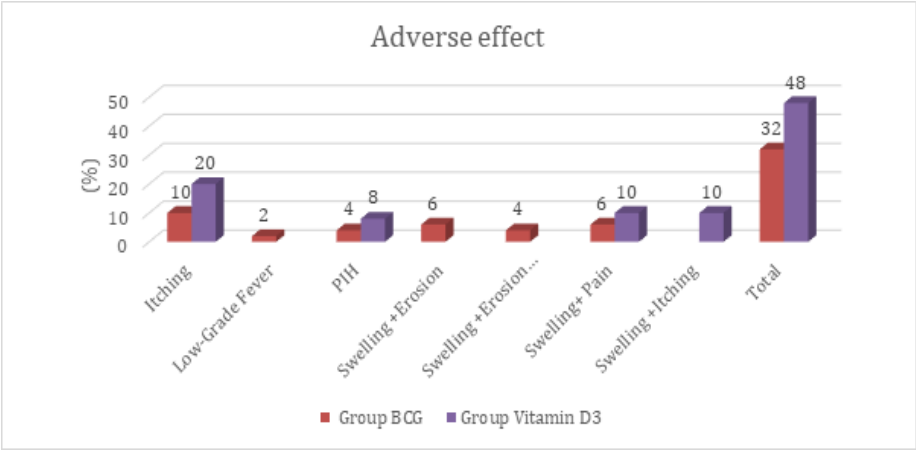
CHART 2: RESPONSE IN DISTANT WARTS



Maximum adverse effects were seen in the vitamin D3 group, followed by BCG group (Chart 3). Itching was most common side effect which was seen both groups, 10% and 20% in BCG and VITAMIN D respectively. Painful swelling with itching was seen in 10% patients treated with vitamin D and swelling with erosion in 6% patients. Post inflammatory seen in 4% patients treated BCG, which may have occurred due to accidental subcutaneous injection and it resolved with in few days with oral analgesics and anti-inflammatory drugs, superficial erosion was managed by topical antibiotics. Post-inflammatory hyper-pigmentation was the most common residual skin change observed at three months follow-up in the both groups, low grade fever was observed in a single patient in the BCG group.

Not a single case of recurrence was seen in both groups at three-month follow up.

CHART: 3 ADVERSE EFFECTS



DISCUSSION

Traditional ablative therapies used in the treatment of warts are not 100% effective, recurrence is a common frustrating domain, apart from recurrence, such treatments are expensive, time consuming, painful and limited to local site of application as they don't act systemically, therefore they are not suitable for multiple warts and distant warts. [6-9]

Mechanism of intralesional immunotherapy is that the immune system is able to recognize the injected antigens, which may induce a type IV hypersensitivity reaction to the antigen. [3]

Intralesional BCG is effective treatment modality for management of warts act via activation and infiltration of CD4 T-lymphocytes and macrophages in site of lesions and increase in Th1 cytokines such as interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferons (IFN-α, β, and γ) have antiviral effects on HPV. Down-regulation of gene transcription and activation of cytotoxic and natural killer cells. [10,11]

Vitamin D act via epidermal cell proliferation and differentiation. Activate toll-like receptors and increases expression of vitamin D receptor and VD 1 hydroxylase gene, leading to production of anti-microbial peptide. [9,12]

Complete Response was seen in 36(72%) and 24(48%) in treatment with BCG and Vitamin D groups respectively. Our results were slightly lower than those observed by Maheshwari et al [13] who had evaluated the effect of BCG vaccine in 30 patients and Vitamin D in 30 patients was reported complete response 76% and 67.8% respectively.

CONCLUSION

As per the present study, the maximum number of patients showing complete response belonged to the BCG group (24 of 50, 72%), followed by the VITAMIN D group (24 of 50, 48%).

Adverse effects were reported by the majority of patients in the vitamin D3 group (24 of 50, 48%), followed by the BCG (16 of 50, 32%). No major adverse drug reactions were reported in any of the groups.

The present study conclude that intralesional BCG scored over the intralesional Vitamin D for the treatment of cutaneous warts, as there was significant response over distant warts with lower side effects and long term better response after intralesional BCG therapy.

Immunotherapy offers a safe, effective and affordable approach in patients with multiple cutaneous viral warts with lesser side effects and recurrence rate.

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: The authors declare no conflict of interest.

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