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Research Article

An Open Randomized Comparative Study of Various Intralesional Immunotherapeutic Agents in Cutaneous Warts

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Abstract:

INTRODUCTION: Warts or verruca are benign epidermal proliferation of the skin and mucosa, caused by human papilloma virus (HPV). The treatment depends on two main therapeutic options: the first is the conventional destructive method which is painful and associated with scarring and frequent recurrences. Second modality is immunotherapy, which is based on the manipulation of the immune system to achieve a HPV targeted immune reaction.

MATERIAL AND METHOD: A total of 120 patients attending the Dermatology OPD of our institute, diagnosed as viral warts were enrolled in the study. All patients were assigned individual identification number and were divided randomly into four groups (A, B, C& D) using a table of random numbers. Group A was Injected BCG Vaccine intralesional, Group B was injected MMR Vaccine intralesional, Group C was injected Inj. Vitamin D3 intralesional and Group D was injected Tuberculin purified protein derivative intralesionally, and the result were analyzed.

RESULT: Complete clearance and reduction in numbers of warts on injected and distant are, 76% with BCG vaccine, 45% with MMR vaccine, 55.5% with Inj. Vitamin D3 and 67.8% with Inj. PPD.

DISCUSSION: Local tissue destruction is a commonly employed method in the treatment of warts. However, it is not practical for multiple lesions, palmo-plantar and facial lesions because of associated pain, scarring and pigmentation. In Immunotherapy, warts regressed without any scarring and with minimal recurrence.

CONCLUSION: All the four modality of immunotherapy, which was given intralesional, show positive response and well tolerated therapeutic options for verruca with variable results.

Keywords: Wart, BCG, MMR, Vitamin D3, PPD, Immunotherapy

INTRODUCTION:

Warts or verruca are benign epidermal proliferation of the skin and mucosa, caused by human papilloma virus (HPV). It is prevalent worldwide, which has more than 100 strains; some of them are known to be premalignant.[1] Children and adolescents are mostly affected, although it can appear at any age. The prognosis of wart is unpredictable. In some patients they may spontaneously disappear within two years (65-78%), whereas others show persistence and progression with spreading to other body sites, leading to cosmetic disfigurement and sometimes painful, especially on the soles.[2],[3]

The treatment of warts depends on two main therapeutic options: the first is the conventional destructive method, which includes keratolytics, chemical cautery, cryotherapy, electro cauterization, and laser ablation.[4],[5] All these modalities of treatment can be painful and may be associated with scarring and frequent recurrences.[6],[7] Second modality of treatment is immunotherapy, which is based on the manipulation of the immune system to achieve a HPV targeted immune reaction. Various immunotherapeutic approaches have been attempted which leads to release of different cytokines and tumor necrosis factor (TNF-α) that stimulate a strong immune response against HPV. [8]

There are many factors that should be considered before the treatment of the patients, such as age, sex, area of involvement, previous treatment history, and the clinical characteristics of the warts. Patients with multiple warts or warts resistant to treatment are usually prone to have defective cell-mediated immune response.

We undertook a study to evaluate the safety and efficacy of

Bacillus Calmette - Guerin vaccine (BCG), Measles Mumps & Rubella vaccine (MMR), Vitamin D3 injection and Tuberculin Purified Protein derivative (PPD) injection as intralesional immunotherapeutic agents.

MATERIALS AND METHODS:

This randomized, single-blind, longitudinal, clinical comparative study was undertaken during the period of December 2016 to January 2017 in the Department of Dermatology, venereology & Leprosy at Index Medical College & Hospital Research Centre, Indore (M.P.) after obtaining permission from Institutional Ethical Committee. A total of one hundred fifty three patients attending the Dermatology OPD of our institute, with the clinical diagnosis of viral warts, were enrolled in the study. Among them only 120 patients fulfill the inclusion and exclusion criteria were taken in the study. The patients were clearly explained the nature of the study and a written consent was taken for their participation in the study. Patients with single or multiple viral warts, age more than 12 years, not taking any concurrent treatment for warts, and not responded to any previous treatment were included. Pregnant and lactating women, patients with keloidal tendency, immunosuppressed individuals, any systemic or local inflammation or infection, patients who have received treatment of warts in the past two months before enrollment, allergic skin disorders and patient with past history of meningitis or convulsions were excluded.

Cutaneous warts were diagnosed by history and clinical features. Baseline evaluation was made at the first visit, and the demographic data were recorded in a structured questionnaire designed for this study. A graphical wart map was prepared for each patient; location, number, size and type of wart were recorded on it at each visit. Photographs were taken at each visit to support the recorded data. Clinical response was documented by recording the decrease in number and size of warty lesions at each visit i.e., at 2 weekly intervals for 4 sessions and 6 months after the last injection. Complete clearance was considered if all the warts both treated and distant warts resolved completely. Moderate response if there were 50 to <100% reductions in both size and number of lesions, mild response was considered if response was between 1% and <50%.

Larger warts were considered for the injection. A maximum of five warts were treated at each session with the help of 30 gauze insulin syringes.

All patients were assigned individual identification number and were divided randomly into four groups (A, B, C& D) using a table of random numbers.

Group A (30 patients) received BCG Vaccine 0.1 ml intralesional at 2 weeks interval, to a total of four sessions.

Group B (30 patients) received Measles mumps and rubella vaccine 0.5ml/dose intralesional at 2 weeks interval, to a total of four sessions.

Group C (30 patients) received intralesional Injection Vitamin D3 (cholecalciferol 6,00,000 IU) in 1 ml (15 mg) at 2 week interval , to a total of four sessions.

Group D (30 patients) received intralesional injection of Purified protein derivative (PPD) 5 TU per 0.1ml, (maximum 25TU or 0.5ml) at 2 weeks interval, to a total of four sessions. Post treatment, the patients were advised not to use any topical and oral medications.

Statistical analysis:

Continuous variables like age and duration of wart were compared between the groups by the independent samples *t* test and within each group by a paired *t* test. Categorical data were compared between the groups by Chi square test or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS: The demographic and clinical data of patients are shown in Table 1.

Table 1: Demographic and clinical data

Total patient (n= 120) Male= 73 Female=47	Group A (n=30)	Group B (n=30)	Group C (n=30)	Group D (n=30)
Gender ratio (M/F)	1.5:1	1:1	2.3:1	1.7:1
Mean age in years	32.7	24.7	28.3	34.8
Mean duration of disease in months	5.1	6.9	4.8	5.7
Mean no. of warts	7.2	10.8	5.1	6.8
Types of warts Verruca vulgaris Palmo-plantar warts Fili form warts Genital warts	 06 (24%) 17 (68%) 02(8%) 00	 16(55.5%) 10(34.5%) 01(3.45%) 02(6.9%)	 18(66.6%) 04(14.8%) 01(3.7%) 04(14.8%)	 13(46.4 %) 10(35.8 %) 04(14.2 %) 01(3.6%)

IN GROUP A, Study included 18 males and 12 females (total 30 patients)**.** Five patients left from the group. Age of the patients ranged from 12 to 60 year, with a mean of 32.7 years. The duration of warts ranged from 1 month to 48 months with a mean of 5.1 months. The number of warts ranged from 2 to 30 with a mean of 7.2. Seventeen patients had palmo-plantar warts, two patients had filiform wart over face and six patients

had verruca vulgaris.

The mean number of intralesional injections required for complete clearance which was seen in 19 patients was 3.

Complete clearance was seen in 14(82.3%) out of 17 patients with palmo-plantar warts and 4 (66.6%) of 6 patients with verruca vulgaris and 1 (50%) of 2 patients with Filiform warts. Representative patient showing complete response are depicted in [Figure 1].

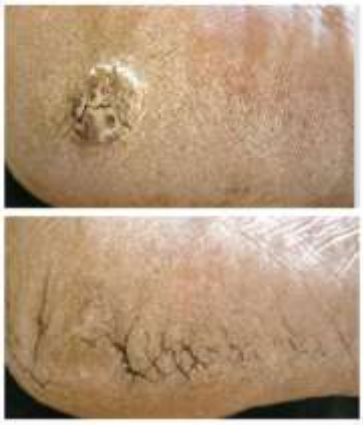


Figure 1: Pre and Post photograph of BCG vaccine. A small scar is noted at the site of injection

3(17.6%) in palmo-plantar, 1(16.6%) in verruca vulgaris group showed moderate response. One each in verruca vulgaris and filiform subtypes of warts showed improvement which ranged from 1 to ≤ 50%. The response rate of various types of warts is shown in Table 2.

Table 2: Treatment response according to type of wart in group A (BCG Vaccine)

	Palmo-plantar wart (n=17)	Verruca Vulgaris (n=6)	Filiform wart (n=2)	Genital wart (n=00)	Total (%) (n=25)
Complete response	14	4	1	0	19 (76%)
Moderate response	03	1	0	0	04(16%)
Mild response	00	1	1	0	02(8%)
Total (%)	17 (68%)	6(24%)	2 (8%)	0	25

Intense pain and swelling at the site of injection was the most common adverse effect seen in each patient. In some patients oral analgesics for a period of 3 days was prescribed for pain. A flu-like illness that rapidly subsided within 3 days was also observed with each injection. Superficial ulcer was also noted in 11 patients. All were prescribed topical antibiotic, among them 7 were healed with superficial scar and 4 sustained with non healing ulcer for more than 4 weeks even after 10 days of oral antibiotic. In such patients BCGitis diagnosis was made and prescribed Anti Tubercular therapy (ATT), after completing the therapy lesion healed completely with superficial scar. No recurrence was observed in patient during 6 month follow up period.

IN GROUP B, study included 15 males and 15 females (total 30 patients). One patient left from the group. Age of the patients ranged from 12 to 60 year, with a mean of 24.7 years. The duration of warts ranged from 1 month to 48 months with a mean of 6-9 months. The number of warts ranged from 2 to 30 with a mean of 10.8. Ten patients had palmo-plantar warts, 1 patient had filiform wart, 16 patients had verruca vulgaris and 2 patients had genital wart.

The mean number of intralesional injections required for complete clearance which was seen in 13 patients was 4.

Complete clearance was seen in 5(50%) out of 10 patients with palmo-plantar warts and 7 (43.76%) of 16 patients with verruca vulgaris, 1 (50%) of 2 patients with genital warts. Representative patients are depicted in [Figure 2].

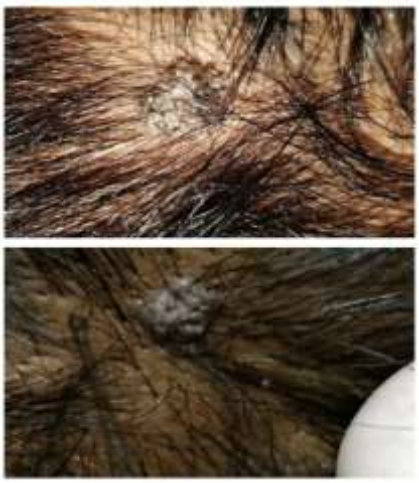


Figure 2: Pre and Post photograph of MMR vaccine. Incomplete clearance after two injections.

3 patients (33.3%) in palmo-plantar, 6(37.5%) in verruca

vulgaris, 1 in filiform wart group showed moderate response. 2 patients (20%) in palmo-plantar wart, 3 (18.75%) patients in verruca vulgaris and 1(50%) in genital warts showed mild improvement. The response rate of various types of warts is shown in Table 3.

Table 3: Treatment response according to type of wart in group B (MMR Vaccine)

	Palmo-plantar wart (n=10)	Verruca Vulgaris (n=16)	Filiform wart (n=1)	Genital wart (n=2)	Total (%) (n=29)
Complete response	5	7	0	1	13(45%)
Moderate response	3	6	1	0	10(34.4%)
Mild response	2	3	0	1	6 (20.6%)
Total (%)	10 (33.3%)	16(55.5%)	1(3.3%)	2(6.6%)	29

Pain at injection site (63%), erythema (5%) and post inflammatory hyper pigmentation (6%) were the main adverse effects noted in the treated patients. 5(16.6%) patients had recurrence of their wart during the 6 month follow up period.

IN GROUP C, study included 21 males and 9 females (total 30 patients). Three patients left from the group. Age of the patients ranged from 12 to 60 year, with a mean of 28.3 years. The duration of warts ranged from 1 month to 48 months with a mean of 4.8 months. The number of warts ranged from 2 to 30 with a mean of 5.1. Four patients had palmo-plantar warts, 1 patient had filiform wart, 18 patients had verruca vulgaris and 4 patients had genital wart.

The mean number of intralesional injections required for complete clearance which was seen in 15 patients was 4.

Complete clearance was seen in 15 patients (55.55%) in which 11(61%) are of verruca vulgaris, 1(25%) are of palmo plantar wart and 3(75%) are of genital wart. Representative patients are depicted in [Figure 3a & b].

Figure 3(a): Pre n Post photograph of Vitamin D3 injection. Post photograph is after 2 injections.

Figure 3(b): Pre and Post (after 15 days) photograph of Vitamin D3 injection. Persistent erythema and edema is appreciated even after 15 days.

1 patients (25%) in palmo-plantar, 6(33.3%) in verruca vulgaris and 1(25%) in genital wart group showed moderate response. 2 patients (50%) in palmo-plantar wart, 1 (3.7%) patients in verruca vulgaris and 1(100%) in filiform warts showed mild improvement. The response rate of various types of warts is shown in Table 4.

Table 4: Treatment response according to type of wart in group C (Vitamin D3)

	Palmo-plantar wart (n=4)	Verruca Vulgaris (n=18)	Filiform wart (n=1)	Genital wart (n=4)	Total (%) (n=27)
Complete response	1	11	0	3	15(55.5%)
Moderate response	1	6	0	1	8(29.6%)
Mild response	2	1	1	0	4(14.8%)
Total (%)	4 (14.8%)	18(66.6%)	1(3.7%)	4(14.8%)	27

Intense pain at injection site (100%), persistent erythematous swelling/induration particularly on the face(82.5%) which resolved without any treatment in 1 month [Figure 3b] were the main adverse effects noted in the treated patients. 4(13.3%) patients had recurrence of their wart during the 6 month follow up period.

IN GROUP D, study included 19 males and 11 females (total 30 patients). Two patients left from the group. Age of the patients ranged from 12 to 60 year, with a mean of 34.8 years. The duration of warts ranged from 1 month to 48 months with a mean of 5.7 months. The number of warts ranged from 2 to 30 with a mean of 6.8. Ten patients had palmo-plantar warts, 4 patients had filiform wart, 13 patients had verruca vulgaris and 1 patient had genital wart.

The mean number of intralesional injections required for complete clearance which was seen in 19 patients was 4.

Complete clearance was seen in 19 patients (67.8%) in which 9(69.2%) are of verruca vulgaris, 8(80%) are of palmo plantar wart and 2(50%) are of filiform wart. Representative patients are depicted in [Figure 4].

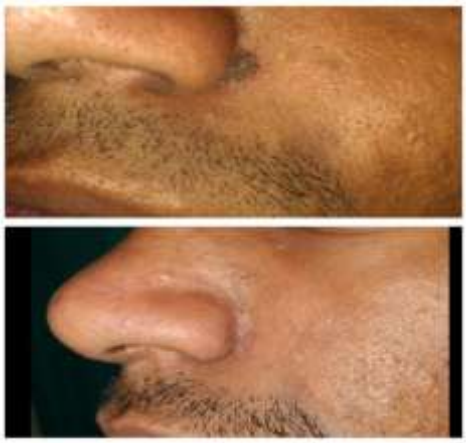


Figure 4: Pre and Post photograph of Inj. Tuberculin Purified protein derivative. Complete clearance is seen after 4 injections.

one patients (10%) in palmo-plantar, 3(23%) in verruca vulgaris and 1(25%) in filiform wart group showed moderate response. 1 patients (10%) in palmo-plantar wart, 1 (7.7%) patients in verruca vulgaris and 1(25%) in filiform warts and 1(100%) in genital wart group showed mild improvement. The response rate of various types of warts is shown in Table 5.

Table 5: Treatment response according to type of wart in group D (PPD)

	Palmo-plantar wart (n=10)	Verruca Vulgaris (n=13)	Filiform wart (n=4)	Genital wart (n=1)	Total (%) (n=28)
Complete response	8	9	2	0	19(67.8%)
Moderate response	1	3	1	0	5(17.8%)
Mild response	1	1	1	1	4(14.4%)
Total (%)	10 (35.8%)	13 (46.4%)	4(14.3%)	1(3.5%)	28

Pain and abscess at injection site (20.8%) and eczematous response (12.4%) were the main adverse effects noted in the treated patients. 2 (6.6%) patients had recurrence of their wart during the 6 month follow up period.

DISCUSSION:

Local tissue destruction is a commonly employed method in the treatment of warts. However, it is not practical for multiple lesions, palmo-plantar and facial lesions because of associated pain, scarring and pigmentation.[2] In these methods epidermis and variable part of dermis are involved, hence scarring is almost inevitable with the use of these modalities.[9] In Immunotherapy, warts regressed without any scarring and with minimal recurrence, hence it is considered useful for palmo-plantar, facial and genital lesions.[10],[11] Immunotherapy for warts employs the ability of the immune system to recognize certain viral antigens that induce a delayed type hypersensitivity reaction which increases the ability of the immune system to recognize and clear the human papilloma virus.[12],[13],[14] Injection of the viral antigen results in peripheral blood mononuclear cell proliferation, promoting Th1 cytokine responses, particularly interferon gamma and interleukin 2,4. This results in activation of cytotoxic T cells and natural killer cells that help to eradicate human papilloma virus infected cells. It is also proposed that antigen immunotherapy can stimulate tumor

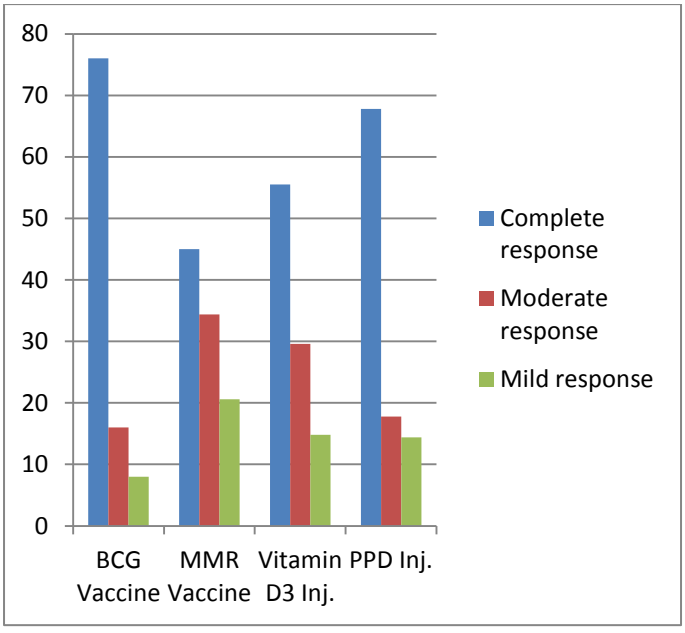
necrosis factor α and interleukin 1 release, down regulating gene transcription of human papilloma virus.[15] Immunotherapy addresses the limitations of ablative therapy in that it enhances the cell mediated immune response that clears the virus infected tissue irrespective of whether it is visible or not. It is also able to target distant warts situated away from the site of the injection and therefore help in treating multiple warts, warts on inaccessible sites or sites where ablative therapy is difficult (e.g., subungual or periungual regions).

In our study, one hundred and twenty patients were randomized into four groups. Thirteen patients were lost to follow up. Among them, five patients in the BCG group left with complaint of scarring (2 patients) and flu like symptoms (3 patients) and did not come for subsequent follow ups. In the Vitamin D3 group, three patients said that pain was the reason for his absence from follow ups. 1 patient in MMR group and 2 patients in PPD group did not came for follow up with some unspecific complaints.

In our study, male patients are more in number in each group. All patients were mostly in their late twenties or thirties. All four groups were comparable with respect to age, sex, residence and income. The mean duration of illness was 5.1 months in the BCG group, 6.9 months in the MMR group, 4.8 months in Vitamin D3 group and 5.7 months in the PPD group, with no significant difference between them. All four groups were also comparable in terms of the mean size of lesions at baseline (P = 0.142) and the type of warts seen (P = 0.119)

All four intralesionally injectable form of immunotherapy appeared effective in our study with variable results. Complete clearance and reduction in numbers of warts on injected and distant are, 76% with BCG vaccine, 45% with MMR vaccine, 55.5% with Inj. Vitamin D3 and 67.8% with Inj. PPD.[Table 6]

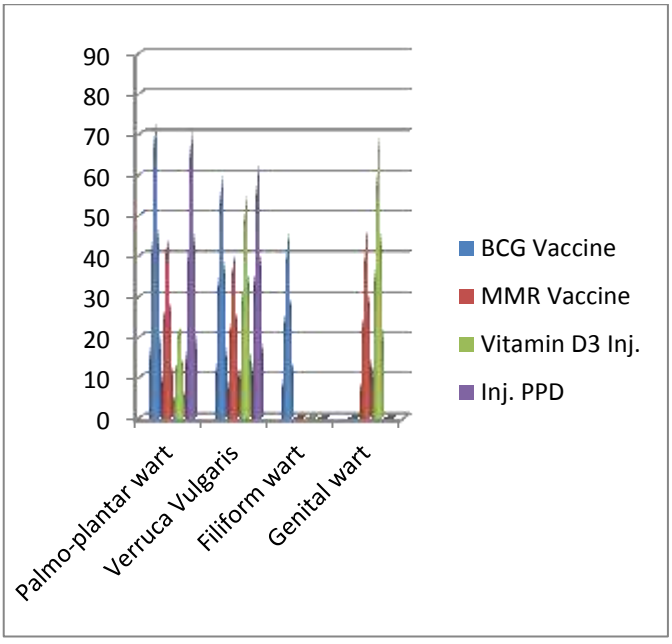
Table 6: Bar chart representing immunotherapeutic response in various groups.



Podder et al in a double blind, randomized controlled trial with BCG in cutaneous warts found same result as we obtained in our study.[16] Saini *et al* evaluated inj. MMR in cutaneous wart with complete response in 46.6% [17] while Nofa *et al.* evaluated mumps, measles and rubella (MMR) vaccine in a randomized placebo-controlled trial and noted a complete response in 81.4% of patients in the vaccine group compared to 27.5% in the placebo group.[18] Aktas *et al.* used intralesional Vitamin D3 for plantar warts. Twenty patients were included in the study, and 7.5 mg of Vitamin D3 injection was given at monthly intervals for a maximum of 2 sessions. They reported complete clearance in 80% of patients at the end of 8 weeks.[19] Essa et all injected PPD in cutaneous warts showed complete clearance of warts in 47% cases[20] while Saoji et all showed complete clearance of warts in 76% patients only after 4 sessions.[21]

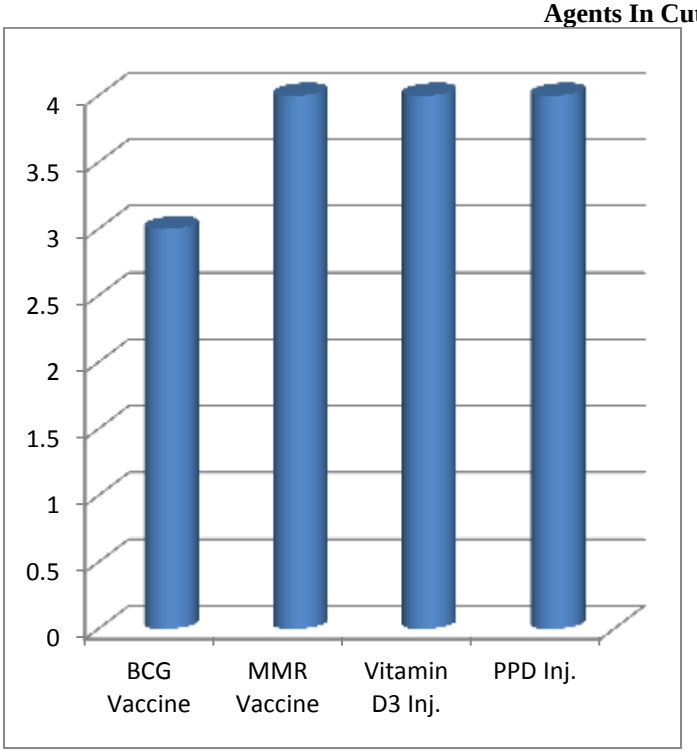
In our study, palmo-plantar wart responded best for BCG Vaccine (82.4%) followed by Inj. PPD (80%), MMR Vaccine (50%) and Inj. Vitamin D3 (25%). Verruca vulgaris responded best for Inj. PPD (69.2%) followed by 66.7% with BCG Vaccine , 61% with Inj. Vitamin D3 and 43.8% with MMR Vaccine. Filiform wart responded well with both Inj. PPD (50%) and BCG Vaccine (50%) while showing mild to moderate response with other therapies. Genital wart responded very well to Inj. Vitamin D3 (75%) and 50%with MMR Vaccine.[Table 7]

Table 7: Bar Chart representing various immunotherapeutic responses according to wart type



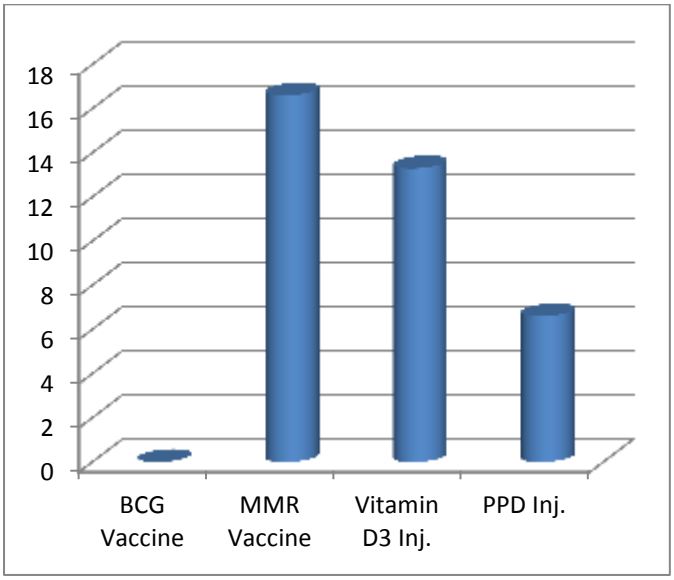
The mean number of intralesional injections required for complete clearance was 3 in BCG while it was 4 with rest of the groups.[Table 8]

Table 8:Bar graph showing number of injection for complete clearance in various immunotherapeutic groups.



Adverse effects were observed more frequently in the BCG group. More patients complained of pain during injection, though it was not statistically significant (*P* = 0.796). Superficial ulcer with scar formation and Flu like symptoms was also found to be higher in the BCG group and was statistically significant (*P* = 0.118). Erythema, edema and persistent swelling at the site of injection was also present in all groups which was not statistically significant (P=0.646). None of the patients experienced any serious adverse event during the period of treatment and after 6 month of follow up period. Recurrences with various agents are given in [Table 9]

Table 9:Bar graph showing recurrence rate with various immunotherapeutic agents after 6 month of follow ups.



The Dermatology quality of life index was comparable (*P* = 0.687) in all the treatment arms at baseline. The index had improved significantly from baseline at the end of the study, but an intergroup comparison showed no significant difference between all treatment groups (*P* = 0.478).

CONCLUSION:

All the four modality of immunotherapy, which was given intralesional, show positive response and well tolerated therapeutic options for verruca. BCG was found to be more effective than all other modalities, though it has the limitations of causing more pain, ulcer with scarring and flu like symptoms. PPD is a relatively better option than BCG, since it has low side effect profile with 67.8% efficacy rate for complete clearance of wart. Vitamin D3 and MMR vaccine are also efficacious but efficacy for complete clearance is low, 55.5% and 45% respectively. Recurrence rate is also higher with these two groups. Since the injections are given at a site away from the lesions being treated, this modality is suited for multiple lesions and for lesions in inaccessible and difficult to treat sites, such as the subungual or periungual regions.

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