Evaluation of efficacy and safety of intralesional vitamin D_3 in comparison with intralesional measles, mumps and rubella (MMR) vaccine in the treatment of multiple cutaneous warts

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ABSTRACT

Introduction: Cutaneous warts are caused by human papillomavirus (HPV). Contrary to the painful ablative therapies associated with scarring and recurrence, immunotherapy (cell-mediated, anti-HPV response) adds to the therapeutic armamentarium.

Objective: To compare therapeutic efficacy and safety of intralesional vitamin D_3 versus intralesional measles, mumps and rubella (MMR) vaccine in multiple cutaneous warts.

Material and methods: This prospective, interventional, clinical comparative study was carried out on 96 patients with multiple cutaneous warts. The patients were enrolled after applying inclusion and exclusion criteria and were randomly divided into two groups of 48 patients each. Intralesional vitamin D_3 (group A) and intralesional MMR vaccine (group B) were administered at a maximum of 5 warts per patient for 4 sessions at fortnightly intervals with a follow-up visit at 3 months. The efficacy and safety of vitamin D_3 were compared to MMR vaccine using statistical tests.

Results: A complete clearance of warts (injected and distant) was seen in 58.3% of cases (group A) and 52.1% of cases (group B), with no statistically significant difference. Filiform warts showed a better and faster response with vitamin D_3 compared to MMR vaccine. Both modalities were safe, with no major adverse effects except for a case of post-MMR vaccine orchitis.

Conclusions: Immunotherapy with intralesional vitamin D_3 is as effective and safe as intralesional MMR vaccine in the treatment of cutaneous warts, with gratifying results in both local and distant warts.

Key words: cutaneous warts, intralesional immunotherapy, vitamin D_3, MMR vaccine.

INTRODUCTION

Cutaneous warts (syn: verrucae) are benign epidermal proliferations arising from the skin or mucosa, caused by human papillomavirus (HPV), with a tendency to disseminate in self and others. They have an incidence of 2–20% in school children and 10% in young adults [1]. There exist more than 100 strains of the virus, a few of which are premalignant [1]. Notwithstanding the benign nature of this entity, treatment is sought due to pain and cosmetic

embarrassment [2, 3]. A plethora of conventional treatment modalities exist, which include keratolytics, chemical cauterisation, electrosurgery, cryotherapy, radiofrequency and laser ablation [4]. The limiting side effects of these modalities include pain, scarring and recurrence [5]. Immunotherapy is a novel emerging modality which includes enhancement of antiviral-specific cell-mediated immunity (via T cells and tumour necrosis factor α) against HPV leading to the clearance of local as well as distant warts [6]. The principal agents covered under this umbrella include intralesional vitamin D_3, measles, mumps and rubella (MMR) vaccine, candida antigen, purified protein derivative (PPD), Bacillus Calmette Guerin (BCG) vaccine, Mycobacterium indicus pranii vaccine, zinc and bleomycin. In spite of the aforementioned multitude of options, data regarding the utility of these immunotherapeutic modalities for this indication are scarce. Hence, we undertook this study to elucidate the role of two different approaches of intralesional immunotherapy, in an attempt to address the current challenges in the management of warts.

OBJECTIVE

To compare the therapeutic efficacy and safety of intralesional vitamin D_3 versus intralesional MMR vaccine in the treatment of multiple cutaneous warts.

MATERIAL AND METHODS

This randomised, longitudinal, interventional, clinical comparative study was conducted over a period of 18 months from September 2019 to February 2021 in the Department of Dermatology, Venereology and Leprosy at a tertiary health care centre, after obtaining approval from the Institutional Ethics Committee. 96 patients fulfilling the inclusion and exclusion criteria were enrolled after informed consent was obtained. Males and non-pregnant females (12 to 60 years old) with multiple cutaneous warts (≥ 2) without prior treatment in the past 3 months were included in the study. The patients who were pregnant or lactating, those with hemodynamic instability, sepsis, local infection, bleeding disorders or on anticoagulant therapy, history of cancer, keloidal tendency and immunocompromised patients were excluded.

Patients with clinically diagnosed multiple cutaneous warts were randomly allocated (table of random numbers) to 2 groups of 48 each: group A (intralesional vitamin D_3) and group B (intralesional MMR vaccine). At the commencement of the first session, baseline history and clinical data including age, sex, duration, number and size of warts, location of warts, type of warts and previous treatments were recorded in the data sheet, supported by digital photography. Patients in group A were administered intralesional injections of vitamin D_3 (6 lac IU, 15 mg/ml) with 31 gauge needle after light paring of warts. The biggest warts were treated in each patient (a maximum of 5 warts per session). Patients in group B were treated with intralesional injections of MMR vaccine administered after reconstitution (lyophilized powder with 0.5 ml of distilled water as diluent). Further sessions were administered fortnightly until a maximum of 4 sessions or complete clearance (whichever was earlier). A single post-treatment follow-up visit was ensured after 3 months to document any recurrence. An Excel data sheet was updated at every subsequent session to document the number, size and clearance of local and distant (untreated) warts. Side effects were also documented at every visit.

The outcome was assessed in terms of clearance of warts and graded as complete response: all the warts (both treated and distant) show complete resolution, moderate response: 50 to < 100% reduction in both size and number of lesions, mild response: response between 1% to < 50% and no response: no clearance of warts.

Statistical analysis

The clinical data were recorded in Excel sheet including size,number, duration, morphological type, site of warts, and presence of distant warts. The results were documented and compared statistically with previous sessions. Qualitative data were represented as frequency and percentage. The association between qualitative variables was assessed by χ^2 test. Quantitative data were represented using mean ± SD. Comparative analysis of quantitative data between the two groups was done using unpaired *t*-test for normally distributed data and by Mann-Whitney test for non-normal data. A *p*-value < 0.05 was taken as the level of significance. Results were graphically represented where deemed necessary. SPSS Version 21.0 was used for analysis and Microsoft Excel 2010 for graphical representation.

RESULTS

Demographic and clinical variables of 96 enrolled patients are detailed in table 1 with no statistically significant difference between vitamin D_3 and MMR vaccine treated groups in terms of age, gender, baseline wart number, size, morphological types and mean response time (vitamin D_3: 3.15 sessions, MMR vaccine: 2.98 sessions).

Group A (vitamin D_3): The degree of responses (complete/moderate/mild/no response) in different morphological types of warts has been illustrated in

Table 1. Comparison of demographic and clinical variables in vitamin D_3 and MMR vaccine treated groups

Total patients *N* = 96 Male = 66 (68.75%) Female = 30 (31.25%)	Group A (vitamin D_3) Male = 35 (72.91%) Female = 13 (27.08%)	Group B (MMR vaccine) Male = 31 (64.58%) Female = 17 (35.41%)	*P*-value
Gender ratio	2.69 : 1	1.82 : 1	0.64
Mean age [years]	27.97	29.39	0.119
Mean number of warts at baseline	5.81	4.48	0.23
Median number of warts at baseline	3	4	0.27
Interquartile range	4	3	
Mean size of warts [mm] at baseline	5.40	4.05	0.4
Types of warts, *n* (%):			
Verruca vulgaris	25 (52.08)	20 (41.66)	0.42
Palmoplantar	10 (20.83)	11 (22.91)	
Filiform	6 (12.5)	6 (12.5)	
Verruca plana	4 (8.33)	4 (8.33)	
Periungual	3 (6.25)	7 (14.58)	

N – total number of patients.

Table 2. Treatment response according to the type of wart in vitamin D_3 treated group

Type of response	Verruca vulgaris	Palmoplantar warts	Filiform warts	Verruca plana	Periungual warts	Total (%) *N* = 48
Complete response	13	7	4	3	1	28 (58.3%)
Moderate response	4	1	2	1	1	9 (18.75%)
Mild response	6	1	0	0	1	8 (16.66%)
No response	2	1	0	0	0	3 (6.25%)
	25 (52.08%)	10 (20.83%)	6 (12.5%)	4 (8.33%)	3 (6.25%)	48

N – total number of patients.

Table 3. Treatment response according to the type of wart in the intralesional MMR vaccine group

Type of response	Verruca vulgaris	Palmoplantar warts	Filiform warts	Verruca plana	Periungual warts	Total (%) *N* = 48
Complete response	11	7	1	3	3	25 (52.1%)
Moderate response	4	1	2	1	1	9 (18.75%)
Mild response	3	3	3	0	3	12 (25%)
No response	2	0	0	0	0	2 (4.16%)
Total	20 (41.66%)	11 (22.91%)	6 (12.5%)	4 (8.33%)	7 (14.58%)	48

N – total number of patients.

table 2. Therapeutic failure was observed in 6.25% of patients. A significant negative association was observed between the duration of warts and the response rate ($p < 0.01$), i.e. a poor response rate was observed with a prolonged duration of warts. Mean duration of 6.11 months in patients with complete response versus 10.76 months in those without any therapeutic response.

Intense pain at the injection site (27.7%) and persistent erythematous swelling/induration (8.3%) were the main adverse effects noted in group A patients. Four (14.3%) out of 28 patients with complete clearance had recurrence during the 3-month follow-up period.

Group B (MMR vaccine): The degree of responses in different morphological types of warts has been illustrated in table 3. Therapeutic failure was seen in 4.16% of patients. A significant negative association was observed between the duration of warts and the response rate ($p < 0.01$), i.e. a poor response rate was

observed with a prolonged duration of warts. Mean duration of warts in patients showing complete response was 5.28 months versus 12.12 months in those showing no response.

The most common side effects seen were pain (18.8%) and local swelling (2.1%). There was 1 case each of post MMR orchitis and parotitis. Four out of 25 (16%) patients had recurrence during the 3-month follow-up period.

Comparative analysis between Group A (vitamin D_3) and B (MMR vaccine) revealed that the mean and median number of warts decreased significantly in both groups at each subsequent session ($p < 0.01$). However, the difference between the study groups at the 3 months' post-treatment follow-up visit was statistically non-significant (mean number of warts at follow-up: group A: 1.65, group B: 1.12, $p = 0.42$, median number at follow-up: group A: 0, group B: 1, $p = 0.53$). A similar trend was observed regarding the mean size of warts which decreased significantly in either group at each subsequent session ($p < 0.01$). However, the difference in size was statistically non-significant between the study groups at the end of the follow-up period ($p = 0.65$, mean size at the end of follow-up: group A: 0.95 mm and group B: 0.85 mm). Although there is an apparent percentage difference in complete response rates between the two groups (group A: 58.3%, group B: 52.1%), such difference is statistically non-significant ($p = 0.774$).

In our study, a higher and statistically significant complete response rate was observed in filiform warts treated with vitamin D_3 (66.7%) as compared to MMR vaccine (16.7%) ($p = 0.015$). Statistically comparable complete response rates were observed in other wart types: verruca vulgaris (figs. 1 and 2): vitamin D_3: 52% and MMR vaccine: 55% ($p = 0.89$), verruca plana: vitamin D_3: 75%, MMR vaccine: 75% ($p = 1.0$), periungual warts (fig. 3): vitamin D_3: 33.3% and MMR vaccine: 42.9% ($p = 0.78$), palmoplantar warts (fig. 4): vitamin D_3: 70% and MMR vaccine: 63.6% ($p = 0.58$).

A significantly faster response was seen among cases of filiform warts treated with vitamin D_3 (mean

Figure 1. Intralesional vitamin D_3 – pre-treatment clinical photographs of verruca vulgaris on the bilateral dorsal hands

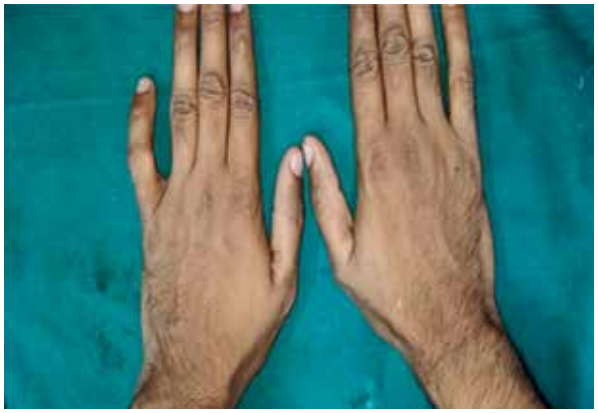

Figure 2. Intralesional vitamin D_3 – verruca vulgaris on the bilateral dorsal hands after 3 treatment sessions showing complete clearance

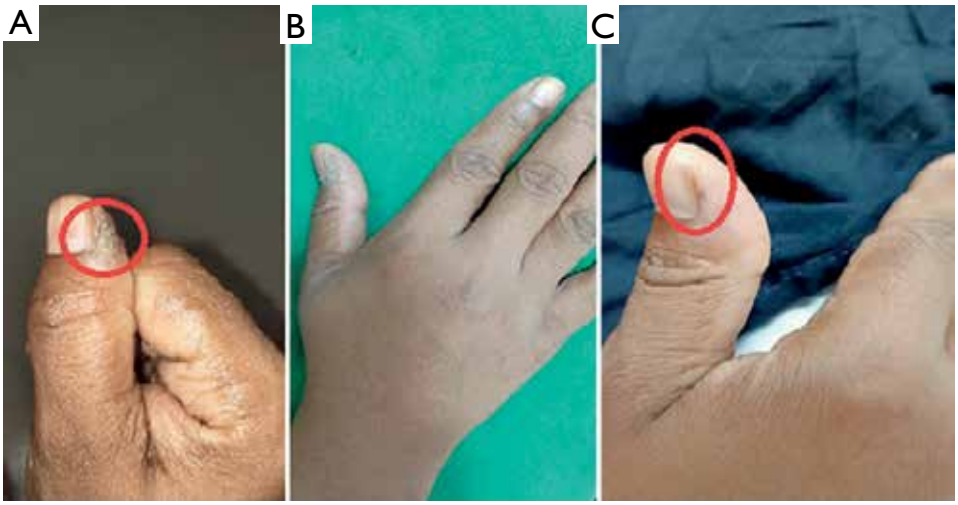

Figure 3. Clinical photographs of periungual warts (red circle) treated with intralesional vitamin D_3 – complete clearance (**A** – pre-treatment, **B** – after 1 session, **C** – after 3 sessions)

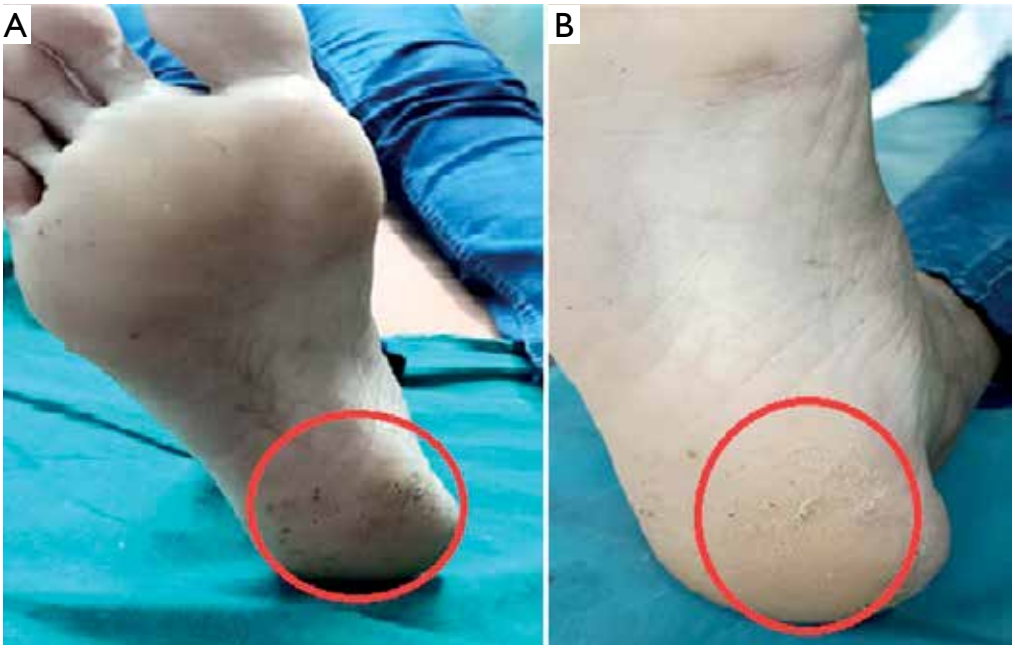

Figure 4. Multiple mosaic plantar warts (on the sole of the foot – red circle) treated with intralesional MMR vaccine (**A** – pre-treatment, **B** – after 3 treatment sessions – complete clearance)

number of sessions 2.5) as compared to MMR vaccine: (3.4 sessions) (p = 0.03). The results were comparable in other types of warts (p > 0.05).

The clearance of distant warts in group A (78.6%) and group B (90.9%) did not show any statistically significant difference (p = 0.61).

DISCUSSION

Local tissue ablation is a commonly employed method in the treatment of warts. However, it is not feasible for multiple lesions and difficult sites because of inaccessibility, pain and undesirable sequelae [2]. In these methods, epidermis and a variable part of dermis are targeted, hence scarring and dyspigmentation are almost inevitable. In immunotherapy, warts regress without any scarring and with minimal recurrence; hence, it is considered useful for palmoplantar, facial and genital lesions. This modality involves targeting the body's cell-mediated immunity to mount a delayed hypersensitivity response against HPV [7]. Injection of the HPV viral antigen results in peripheral blood mononuclear cell proliferation, promoting Th1 cytokine responses, particularly interferon g and interleukin 2, 4 [7], leading to activation of cytotoxic T cells and natural killer cells that help eradicate HPV-infected cells. Stimulation of tumour necrosis factor α and interleukin 1 release downregulates gene transcription of HPV. Immunotherapy is superior to conventional tissue ablative modalities in that it enhances the cell-mediated immune response that clears the virus infected tissue irrespective of whether it is clinically apparent. It is also able to target distant multiple warts, warts at inaccessible sites or sites where ablative therapy is difficult (e.g., subungual or periungual regions).

In our study of 96 patients, the majority of patients (72.9%) were in their third and fourth decades of life with males outnumbering the females in both the groups. The mean number of intralesional injections required for complete clearance was comparable in both the groups.

16.6% of patients from group A (vitamin D_3) and 10.41% from group B (MMR vaccine) did not complete a study. Incomplete response was a major contributor to the loss to follow-up. This may be regarded as a potential limitation of immunotherapy compared to tissue ablative therapies which are single-session modalities (e.g. radiofrequency, laser ablation) giving visible and instantaneous results. Other causes of loss to follow-up were severe adverse reactions (single case of post-MMR vaccine orchitis) or occurrence of id eruptions (1 case in the MMR vaccine group).

In our study, complete clearance was seen in 58.3% of patients in group A (vitamin D_3) and 52.1% of patients in group B (MMR vaccine) whereas failure of treatment was seen in 6.25% of cases treated with vitamin D_3 and 4.16% of cases treated with MMR vaccine. This difference was statistically non-significant. Higher and faster responses were observed in case of filiform warts treated with vitamin D_3 as compared to MMR vaccine. Statistically comparable response rates were observed in other wart types. Regarding

clearance of distant warts, both the modalities were equally efficacious.

Previous studies carried out by Saini *et al.* with intralesional injection of MMR vaccine in cutaneous warts showed a complete response in 46.6% while Nofal *et al.* evaluated 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 [8, 9]. Aktas *et al*. used intralesional vitamin D_3 for plantar warts [10]. Twenty patients were included in the study, and 7.5 mg of vitamin D_3 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. In contrast to our study (comparative between two immunotherapies), the previous studies are either uncontrolled (Saini *et al*.) or placebo-controlled (Nofal *et al*.) trials wherein the results of the former show lower percentage efficacy than that seen in our study (52.1% efficacy with MMR vaccine) while that of the latter show higher efficacy. Aktas *et al.* used intralesional vitamin D_3 in patients with plantar warts (in contrast to our study where the response in various other wart morphologies has been evaluated). Moreover, these authors administered a lower concentration (7.5 mg/ml) of vitamin D_3 than that used in our study (15 mg/ml) with two treatment sessions at monthly intervals, whereas the protocol in our study included four sessions at fortnightly intervals with a post-treatment follow-up at 3 months.

The most common side effects seen in our study in vitamin D_3 and MMR vaccine groups were similar (injection site pain, bleeding and local swelling). Some unusual events were specific to the use of the MMR vaccine such as orchitis (single case) and parotitis (single case). Being a live vaccine such complications are known to occur after subcutaneous dosing (usual route for vaccine administration). However, such an occurrence is rare and hitherto underreported with intralesional route (as in our case). These complications are transient and can be managed by conservative therapy, albeit they warrant immediate attention, counselling and forethought before administering this vaccine.

The studies conducted by Mohta *et al*., Ahmed *et al*., Shaldoum *et al.* and Mittal *et al*. show a similar adverse effect profile with vitamin D_3 and MMR vaccine. as seen in our study [11–14]. Vitamin D_3 has potential advantages over MMR vaccine in terms of its cost-effectiveness and novel mechanism of action in warts (anti-proliferative effects on epidermis and antiviral cathelicidin release).

In our study, recurrence was seen in 14.3% of cases treated with vitamin D_3 as compared to 16% of cases treated with MMR vaccine. Mohta *et al.* observed no recurrence in the MMR vaccine group, whereas 2 cases (6.6%) in the vitamin D_3 group exhibited recurrence in the ensuing 6-month follow-up [11]. Recurrence was observed in 6.7% of cases of vitamin D_3 in the study by Ahmed *et al.* [12]. They encountered no recurrence in the MMR vaccine group. Shaldoum *et al.* observed no recurrence in both groups within the 6-month follow-up period [13].

The strength of our study is that it compares vitamin D_3 (relatively new therapeutic option) with MMR vaccine (time-tested intralesional immunotherapy) rather than a placebo or an uncontrolled study. Further response has been analysed in terms of a large number of parameters like wart morphology and duration. A small number of patients included under each wart type and a relatively short follow-up are the limitations of this study.

CONCLUSIONS

Intralesional vitamin D_3 is as effective as MMR vaccine in multiple cutaneous warts and it is more effective in filiform warts in terms of complete resolution and faster response. Other wart types show comparable responses with either modality. Both modalities are equally effective in clearance of distant warts. Recurrence rates are comparable in both the modalities and seen in 1 in 7 cases. Both the modalities are safe; however, being a live vaccine, few of the rare side effects are specific to use of MMR vaccine like orchitis and mild and transient parotitis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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