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Effect of Intralesional vitamin D in treatment of cutaneous viral warts

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Abstract
Objective: To explore this potential effect of intralesional vitamin D in treatment of cutaneous viral warts.
Methodology: All the patients with cutaneous viral warts coming to the Department of Dermatology, Venereology and Leprology at our tertiary care hospital was included in the study from October 2017 to May 2019. Total 35 patients were included. Clinical response was documented by recording the decrease in number and size of viral warty lesions at each visit i.e. at 2 weekly intervals for 4 sessions and follow up and examination of patient was done 3 months after last injection
Result: Most common type of viral warts were verruca plana (45.7%) followed by filiform viral warts (22.9%) and verruca vulgaris (20%). Almost half of the patients have complete response (51.4%) than 37.1% have partial response and only 11.4% did not have any improvement
Conclusion: Intralesional Vitamin D3 injection is an innovative approach for the treatment of viral warts.

Keywords: Vitamin D3, intralesional injection, cutaneous warts

Introduction

Cutaneous viral warts result from the infection of the epidermis with Human Papilloma Virus (HPV). Human Papilloma Virus is a small 50-55 nm non-enveloped double stranded DNA virus. Different HPV types are responsible for particular clinical varieties. Spontaneous resolution occurs within 2 years in 65%–78% of viral warts; still almost all patients seek treatment of viral warts as they are sometimes painful and cosmetically disfiguring. Poor prognostic indicators include viral warts in adults, long duration, involvement of palms and soles and large numbers; such cases are resistant to therapy and are less likely to remit spontaneously [1].

Numerous therapeutic modalities are available for viral warts with variable success rate. These modalities include topical therapies as salicylic acid, tretinoin, podophyllotoxin, formaldehyde, 5-fluorouracil, trichloroacetic acid and surgical/cytotoxic modalities such as cryotherapy, intralesional bleomycin, laser ablation, electrocautery and surgical excision [2, 3].

Treatment of multiple or refractory lesions is a challenge since destructive modalities can clear only the treated lesions and not the distant lesions. Immunotherapeutic modalities used for viral warts include contact sensitizers, imiquimod, intralesional interferons, and oral drugs such as zinc sulfate, levamisole, and cimetidine [4]. Immunomodulating agents have generated considerable interest as it is well known that cell mediated immunity is involved in the clearance of cutaneous viral warts. Several intralesional antigens have been tried including MMR (measles, mumps, rubella) vaccine, BCG (Bacillus Calmette-Guerin) vaccine, Mycobacterium W vaccine, skin test antigens (mumps, candida, Trichophyton) and PPD (purified protein derivative) [5].

Few studies have been done showing efficacy of topical and intralesional Vitamin D3 derivatives in the treatment of viral warts. The exact mechanism of Vitamin D against viral warts remains elucidated; however it controls epidermal cell proliferation and differentiation and has immune-regulatory activity. The effects of vitamin D3 are mediated via the vitamin D receptor (VDR) which is present in melanocytes, fibroblasts, keratinocytes and immune system cell of the skin [6].

Hence this study was undertaken to explore this potential effect of intralesional vitamin D in treatment of cutaneous viral warts.

Materials and Methods

Sample size

All the patients with cutaneous viral warts coming to the Department of Dermatology, Venereology and Leprology at our tertiary care hospital was included in the study from October 2017 to May 2019. After getting approval from the institutional ethical committee, written informed consent was obtained from all participants before enrolment.

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 or injection lignocaine.
4. Any evidence of immunosuppression including HIV.

5. Patients less than 12 and more than 60 years of age.
6. Patients who have taken Injection PPD/other immunotherapy in last six months.

Method of administration of vitamin D3

Vitamin D3 injection is available in vials containing 6,00,000 IU of cholecalciferol in 1 ml (15 mg). 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) after few minutes, 0.2 ml of Vitamin D3 (15 mg/ml) was slowly injected into the base of each viral wart with a 27 gauge insulin syringe. Post treatment, the patients was advised not to use any topical and oral medication.

Clinical response was documented by recording the decrease in number and size of viral warty lesions at each visit i.e. at 2 weekly intervals for 4 sessions and follow up and examination of patient was done 3 months after last injection. Standard digital photography at each visit to support the data.

Statistical analysis

The data was coded and entered into Microsoft Excel spread sheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations.

Results

Table 1: Age wise distribution of the study

	Frequency	Percent
10-20	8	22.9
20-30	13	37.1
30-40	5	14.3
40-50	7	20.0
>50	2	5.7
Total	35	100.0
mean ± SD	30.45 ± 12.02	

In 20-30 age groups there were highest number of patients found (37.1%) follow by 10-20 year age groups (22.9%) and 40-50 years age groups (20%).

Table 2: Gender wise distribution of the study

	Frequency	Percent
F	9	25.7
M	26	74.3
Total	35	100.0

Males (74.3%) were higher as compared to females (25.7%) Palm (25.7%), face (22.9%), beard (20%), forehead (20%) and scalp (5.7%) were common sire for viral warts in our study. Most common type of viral warts were verruca plana (45.7%) followed by filiform viral warts (22.9%) and verruca vulgaris (20%)

Table 3: Numbers wise distribution of the study

	Frequency	Percent
1-5	8	22.9
5-10	19	54.3
>10	8	22.9
Total	35	100.0

Almost 5-10 number of viral warts (54.3%) were most common involved than others.

Table 4: Response of treatment given among study

	Frequency	Percent
Complete response	18	51.4
Partial response	13	37.1
Not improved	4	11.4
Total	35	100.0

Almost half of the patients have complete response (51.4%) than 37.1% have partial response and only 11.4% did not have any improvement.

Table 5: Response according to follow up

	Complete response	Percent	Partial response	Percent
1st visit	0	0	0	0
2nd visit (2 week)	2	11.11	1	7.69
3rd visit (4 week)	1	5.55	1	7.69
4th visit (6 week)	3	16.6	2	15.38
5th visit (8 week)	5	27.7	3	23.07
3 month after last injection	7	38.8	6	46.15
Total	18	100	13	100

Follow up at 2nd visit showed 11.11% complete response and 7.68% partial response. Follow up at 3rd visit showed 5.55% complete response and 7.68% partial response. Follow up at 4th visit showed 16.6% complete response and 15.38% partial response. Follow up at 5th visit showed 27.7% complete response and 23.07% partial response. Follow up at last injection showed 38.8% complete response and 46.15% partial response.

Discussion

Viral warts are the common viral infection on the skin and mucosa and are prevalent worldwide. Viral warts are caused by HPV (DNA virus), which has more than 150 strains depending on the basis of their DNA. Some viral warts may spontaneously disappear while others persist and spread on other body sites provoking physical and emotional stress to the patient [7]. Viral warts treatment depends on two main therapeutic options, the first line is a conventional destructive and aggressive method which includes treatment with chemical cautery, cryotherapy, electro cautery, surgical excision, laser ablation and second line of treatment includes immunotherapy which is based on activation of immune system to deal with HPV virus and suppress its activity. Such therapy is applied topically, intralesionally or systemic administration [8]. Intralesional immunotherapy utilises the immune system to mount a delayed type of hypersensitivity response to various antigens and also to viral wart tissue. Immunotherapy associated with production of Th1 cytokines that activate cytotoxic and natural killers to eradicate HPV infection. This clears not only local viral wart, but also distant viral warts unlike traditional viral wart therapy [9].

Treatment of multiple viral wartsis difficult and it needs multiple sittings by destructive methods such as cryotherapy and electrocautery. These destructive procedures are usually associated with scarring and pigmentation. In addition, some viral warts are resistant to these treatments and recurrence

rate is also high. Hence, immunotherapy is the novel option available in treating viral warts as it boosts the immune system to HPV virus leading to clearance of both treated and untreated viral warts. Recurrence rate is also low when compared to destructive methods [10, 11, 12, 13].

Various intralesional immunotherapeutic agents are used in treatment of viral warts, for example, purified protein derivative, vitamin D3, MMR vaccine, BCG vaccine, candida, trichophyton antigen etc [14, 15, 16]. The exact mechanism of vitamin D activity against viral warts remains elucidated; however, it controls cell proliferation and differentiation and has immune-regulatory activities. Its effects are mediated via the vitamin D receptor (VDR), which is present in keratinocytes, melanocytes, fibroblasts, and immune system cells of the skin [17].

Few studies have been published showing the efficacy of topical Vitamin D3 derivatives in the treatment of viral warts [18, 9]. However, intralesional Vitamin D3 injection was tried first time by Aktas et al. (2016) [20] for the treatment of plantar viral warts and reported encouraging results.Hence we conducted this study and we evaluated the results.

Age Group

In the present study, maximum subjects were found in the age group of 20-30 years (37.1%) followed by 10-20 years (22.9%) and 40-50 years (20%). M. Naresh. (2019) [21] showed that the mean age of the patients was 31 years (range, 10-60 years) which is similar to the present study. Banoth S. (2019) [22] reported that the maximum number of patients were in the age group of 20-30 years which were 18 (69.2%) followed by <20 years which were 8 cases (30.7%) mean age of the patient was 26.6 yrs±5.5 yrs.

Gender

In our study, males comprised of 74.3% of the study subjects and females consisted of 25.7% of subjects, hence indicating male dominance. Similar male dominance was revealed by M. Naresh. (2019)[21] who found that amongst the 60 patients enrolled 40 were males and 20 were females. Kavya M et al. (2017) [23] included 27 males and 15 females in his study. Males were more commonly affected than females because of a greater likelihood of occupational trauma and environmental exposure.

Type Wise

Verruca plana, filiform wart, verruca vulgaris and palmar wart were reported among 45.7%, 22.9%, 20.0%, 11.4%, 45.7% and 20.0% of the subjects respectively. Raghukumar S et al. (2017) [24] in their showed that 29 (48%) patients had palmoplantar viral warts, 27 (45%) had common viral warts, 2 (3%) had periungual viral warts, 1 (1.7%) had filiform viral warts, and 1 (1.7%) had plane viral warts.

Numbers Wise Distribution

1-5, 5-10 and >10 lesions were revealed among 22.9%, 54.3% and 22.9% of the subjects in the present study. The mean number of warts ranged from 2.00 to 40.00 with a mean of 8.31±3.05 in the present study. Kavya M et al (2017)[23] revealed that the number of warts ranged from 2 to <30. According to Aktaş H et al(2016)[20], most of the patients had 1 to 5 warts while 1 patient had 23 warts.

Improvement and Outcome of Treatment

In our study out of 35 patients 18(51.4%) patients showed complete response, 13 (37.1%) patients showed partial response and 4 (11.4%) patients showed no response. Verma A et al. (2019) [25] showed that out of 36 patients 25 (69.44 %) had complete resolution of their warts, both at the injection and distant sites, 8 (22.22 %) had very good response and 3 (8.33 %) had good response. Naresh NM et al.(2019)[21] revealed that 48 of 60 patients (80%) showed a complete response, 6 patients(10%) showed moderate response and 6 patients (10%) showed a mild or no response

In our study maximum response was seen at last follow up that is 3 months after last injection which was 38.8% followed by 27.7% on 5th visit (8 week) followed by 16.6% on 4th visit and least on 1st and 2nd visit which was 11.11% and 5.55%.

In present study, we used intralesional Vitamin D3 injections in cutaneous viral warts which was a relatively new treatment option for viral warts. Intralesional immunotherapy reportedly causes the resolution of the longstanding benign proliferations. The exact mechanism of immunotherapy has not been completely elucidated but is believed that the injection to the HPV-infected tissue induces a strong nonspecific proinflammatory signal and attracts the antigen-presenting cells. This is associated with the release of different cytokines such as IL-2, IL-8, IL-12, IL-I8, tumor necrosis factor–α, and interferon-γ. Significant peripheral mononuclear cell proliferation promotes a Th1 cytokine response. This successively activates the cytotoxic T cells and natural killer cells to eradicate the HPV-infected cells. Furthermore, the trauma of the injection may cause resolution in previously sensitised individuals .

Intralesional injection is not a new proposition for the treatment of recalcitrant viral warts. Encouraged by the reported beneficial effects of topically applied vitamin D in the treatment of viral warts, we attempted to use an intralesional vitamin D as an immune stimulant in cases of recalcitrant viral warts, and excellent results were achieved at the end of the study period. Unlike other immunotherapeutic options, vitamin D3 injections were not associated with any systemic adverse effects. The local side effects encountered were trivial and easily controlled. Our results show that intralesional vitamin D is a novel addition to the therapeutic armamentarium of extra genital recalcitrant viral warts. It is a simple, effective, well-tolerable, and inexpensive therapeutic method with negligible side effects. However, as our study was an open-label and uncontrolled study, we recommend a control study to further validate our findings.

Conclusion

Intralesional Vitamin D3 injection is an innovative approach for the treatment of viral warts. It is an effective with good cure rate in treatment of viral warts. It is a safe and acceptable modality in treatment of viral warts. It is simple to perform and in-expensive form of treatment with minimal side effects.

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