Section: Dermatology

Original Research Article

THERAPEUTIC OUTCOME OF INTRALESIONAL VITAMIN D3, INTRALESIONAL BLEOMYCIN AND NEEDLING (BY FALKNOR'S METHOD) IN TREATMENT OF CUTANEOUS WART: A COMPARATIVE STUDY

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Abstract

Background: Cutaneous warts are common viral infection often persistent and difficult to treat. Several treatment modalities are available, failures & recurrences are common with all available treatments. The objective is to study and compare the efficacy of intralesional Vitamin D3, intralesional bleomycin and needling in clearance of cutaneous warts. **Materials and Methods:** The present study was conducted in Hindu Rao Hospital New Delhi, after obtaining approval from the institutional Ethics Committee for a period of 12 months, i.e. from June 2022 to May 2023. **Result:** Mean age of the patients was 28.20 in this group. Out of 30 patients, 21 (70%) patients were males and 9 (30%) were females. Complete, partial and no response was seen in 16 (54%), 9 (30%) and 5 (16%) patients respectively. (Vitamin D3 Group) Mean age of patients was 28.13 in this group. Out of 30 patients, 21 (80%) patients were males, and 6 (20%) patients were females. Complete, partial and no response was seen in 21(70%), 6 (20%) and 3 (10%) patients respectively. (Bleomycin Group) Mean age of the patients was 28.06 in this group. Out of 30 patients, 24 (80%) patients were males and 6 (20%) were females. Complete, partial and no response was seen in 6 (20%), 14 (46.6%) and 10 (33.3%) patients respectively. (Needling Group). **Conclusion:** Our study shows intralesional vit-D3, needling and bleomycin offers a safe and promising approach that can be considered as a first line of therapy in patients having extensive cutaneous viral warts, especially in difficult to treat sites.

INTRODUCTION

The incidence of wart is 2%-20% in children and about 10% in young individuals and tends to decrease with age. The incidence increases in children of the school-going age, peaks in the adolescents and early adulthood, then declines rapidly through the twenties and more gradually thereafter. HPV shows tropism for epithelial cells, mainly infects the basal cell layer through defects in the epithelium. Important predisposing factors are trauma and maceration for cutaneous warts.[1] HPV remain latent in the host cells for a long time, resulting in frequent recurrences. The incubation period varies from few weeks to 2 years. Warts can be of various types–verruca vulgaris, verruca plana, plantar wart, filiform wart and anogenital wart. Warts are contagious and can also cause cosmetic disfigurement. Viral warts are considered to be self-limiting; resolution is seen in some but not always, in many cases they can be a cause of severe distress, physically and psychologically due to persistent warty lesions on skin or mucosa, which is disturbing to the patient.

Several treatment modalities are available, but none is 100% effective, failures and recurrences are common with all available treatments for warts. Treatment varies from topical therapy like tricloroacetic acid, salicylic acid etc. to physical therapy like electrocautery, electrosurgery, cryotherapy, systemic treatments with zinc and levamisole have all been tried with variable results, with scarring and reccurence being common. Immunotherapy has gained attention for the optimal cure of warts.[2] Intralesional immunotherapy,

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significant amount of active drug is available at the site that results in better remission via immunomodulation and induction of immunity to clear wart. The immune system specially the cell mediated immunity (CMI) has a vital role in the HPV proliferation through stimulation of cytokines the most important ones are interferon gamma, IL-2 and IL- 12 that stimulates maturation of cytotoxic killer T-cells which recognizes and destroy cells infected with viruses causing wart. Intralesional immunotherapy is thought to work on the basis that the immune system can recognize the injected antigens which can induce a delayed type of hypersensitivity reaction to the antigen as well as against the wart virus; thus, activating the immune system to recognize and clear HPV, both at the treated as well as distant warts and preventing recurrences.[3]

Another modality is intralesional bleomycin which is a cytotoxic glycopeptide antibiotic. Bleomycin has cytotoxic anti-tumor and anti viral activity that acts by binding with DNA, causing strand scission affecting cellular DNA synthesis and by controlling keratinocyte turnover affecting viral survival.[4,5]

Needling by is another technique that is used in treatment of warts. It is done by creating microinjuries in the wart using needle that activates local immunity to clear wart without use of any chemical.

Recently several studies have been stressing upon the role of immunotherapy and bleomycin to overcome the above-mentioned limitations of physical procedure.[2,3] Through this study an attempt is made to evaluate role of immunotherapy Vit-D3, needling and cytotoxic drug bleomycin (intralesional) in cutaneous warts.

MATERIALS AND METHODS

This Prospective interventional comparative study was conducted among Patient attending to skin Out-patient Department of Dermatology, Venereology and Leprology, Hindu Rao Hospital, Malka ganj, New Delhi.

Study Duration: 12 months (June 2022- May 2023).

Study Population: All cases of cutaneous wart (verruca plana, verruca vulgaris, palmoplantar wart, subungual wart, filiform wart) with 4 or more lesions.

Sample size: Our estimated sample size was based on to study efficacy in terms of clearance of viral warts in three groups. With reference to previous study we defined a relevant clinical difference of 30% in clearance of viral warts between any two groups.

We chose a 60% baseline ratio of clearance of viral warts with any procedure. Thus, sample size Of 32 patients per group provided an 80% power for detecting a significant difference between any two groups at an alpha level of 0.05.

The formula for calculated sample size is given below

$$n = \frac{[z1-\alpha/2.\sqrt{2P(1-P)} + z1-\beta.\sqrt{\{P1(1-P1) + P2(1-P2)\}}]2}{(P1-P2)^2}$$

$$= [1.96*0.612 + 0.842*0.575]^2 / (0.30)^2$$

$$= 2.836/0.09$$

$$= 31.507$$

where Zα/2 is the critical value of the Normal distribution at α/2(e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Zβ is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.842) and p1 and p2 are the expected sample proportions of the two groups.

A total of 98 patients were enrolled in the study, out of which 8 patients did not complete the follow up. 90 patients finally completed the study, 30 in each of the treatment group.

Inclusion Criteria

1. Patients having multiple cutaneous viral warts (4 or more in number) including common warts, plane warts, plantar warts, periungual wart, filiform wart.
2. Age - 18 to 65 years of age.
3. Patients who have not taken any treatment for warts in last 8weeks.
4. Patients who give consent for the study and are willing for follow up.

Exclusion Criteria

1. Patient not willing to participate in the study.
2. Pregnant and lactating women.
3. Oral and Anogenital warts.
4. Age of Patients less than 18years or more than 65 years.
5. Immunosuppressed individuals like Diabetic patients, patient on oral steroid other immunosuppressive agents.
6. Patients with active bacterial and viral infections such as herpes and pyoderma at the site of injection.
7. Previous history of hypersensitivity to the intralesional agent being used.
8. History of raynaud's disease in case of bleomycin injection.

Study Method

The study was conducted in the outpatient departments of dermatology at Hindu Rao hospital. All Patients who were clinically diagnosed with cutaneous wart including verruca vulgaris, verruca plana, periungal, filiform wart, sub ungual, plantar wart were included.

- An informed written consent was taken.
- A personal history of hypersensitivity to local anesthesia, pregnancy, lactation, Diabetes, active bacterial or viral infection at the injection site, along with onset, duration, number, sites was recorded.
- Lab investigations: routine investigations HIV, RBS, CBC was done.

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Patient were divided into 3 groups

Group 1 –(n=30)

Group 1 Patients were intralesional Vitamin D3 group.

The selected wart was injected first with 0.2ml of lignocaine (2%) without adrenaline; after few minutes, 0.2ml of vitamin D3 (6lakh IU/ml) was slowly injected into the base of each wart with a 26 G insulin syringe. Larger warts was taken for injection. Per session, a maximum of two warts were treated. The injections was repeated at 2 weekly intervals, for a maximum of 3 injections. Patients were followed up every 4weeks for 3 months

Group 2 –(n=30)

Group 2 was intralesional bleomycin group.

The selected wart depending on size was injected with 1mg/ml of bleomycin solution intralesionally till blanching occured, 0.2ml of (1mg/ml) for wart upto 5 mm size, 0.5ml for 10mm and1ml for >10mm wart, the total volume injected at one sitting was a maximum of 2ml. The injection was repeated every 2 weeks for maximum of 3 injections. The patients were followed up every 4 weeks for 3 months.

Group 3-(n=30)

Group 3 was be needling-group.

The largest wart was selected in case of multiple warts. First local anesthesia (WITHOUT ADRENALINE) was administered to the area of the lesion chosen for needling, followed by thrusting the needle (26G) in a darting manner so as to penetrate the full depth of the wart and reaching the sub cutaneous tissue till pin point bleeding was seen and continued till there was no resistance from the epidermis. The number of puncture was depended on the size of the lesion. Pressure dressing was done for 24-48 hours. In case of thicker wart, first paring was done followed by needling. Needling was repeated every 2weeks i.e at 0, 2 and 4 weeks. Thereafter, followed up every month for 3 months.

Evaluation of response

Clinical photographs with high-definition cellphone camera with the same view and intensity of light was taken at the baseline visit and then at every follow up visit. At the final visit, responses were noted as "complete response" if all warts (injected as well as remote warts) totally vanished; "partial response" for a decrease in the number or size of warts (but not a complete resolution); or "no response." if there was no effect on the existing lesions. "Recurrence" is used when new warts appeared after complete clearance during or after the follow-up period. Adverse effects (local or constitutional symptoms, if any) was noted. Following a complete response, patients underwent three months of monthly monitoring to look for any persisting skin abnormalities or recurrence. Patients having partial or no response were treated with electrocautery.

Statistical Analysis: Data was entered and analyzed using the SPSS (Statistical package for social science) Version SPSS 17.0. and presented as number and percentage in the form of tables and bar charts. Chi square test was applied for analysis. P value < 0.05 was considered as significant test.

RESULTS

The mean age in all the three treatment groups were comparable and were in the range of 21- 30 years.

Males outnumbered females in all the three treatment groups. Out of 30 patients in each group, 21(70%) males were there in the Vitamin D3 group and 24 (80%) males were there in each Bleomycin and Needling group.

Highest efficacy was seen in bleomycin group with 70% complete clearance, followed by Vitamin D3 group and Needling group with 54% and 20% clearance respectively. [Table 1]

Figure 1: Response of multiple warts to intralesional vitamin D3 injection. (A) Before treatment and (B) following 3 injections

Complete response was seen maximum in verruca vulgaris followed by plantar warts, periungual warts, combination of plantar warts with verruca vulgaris, verruca plana in that order, while no response was seen in verruca vulgaris with filiform wart.

Figure 2: Response of multiple recalcitrant warts to bleomycin injection. (A) Before treatment and (B) eschar formation after 1st injection [c] Complete clearance following 3 injections

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Figure 3: Response of multiple warts to needling .(A) Before treatment and (B) following 3 session of needling complete clearance

Highest number of patients who showed complete clearance in single dose belonged to the Bleomycin group. [Table 2]

Both injected and distant warts showed response in each of the treatment groups with the response in the former being greater than in the latter.

Out of 73 patients belonging to the younger age group (<40 years), 41 (56.16%) patients showed complete response to immunotherapy while in the older age group (>40 years) also, 2 out of 17 patients (11.76%) showed complete response. [Table 3]

Complete response was seen maximum in verruca vulgaris followed periungual wart, combination of verruca vulgaris with filiform or palmoplantar warts, plantar wart, verruca plana in that order. [Table 4]

Complete response was seen maximum in palmoplantar warts, followed by verruca plana and verruca vulgaris. No response was seen in periungual warts and combination group of verruca vulgaris with plantar or filiform wart. [Table 6]

Table 1: Therapeutic Response in each treatment group

Clearance	Treatment Group			Total	p value
	Vitamin D3	Bleomycin	Needling		
Complete	16 (54%)	21 (70%)	6 (20%)	43 (47.7%)	0.0037*
Partial	9 (30%)	6 (20%)	14 (46.6%)	29 (32.2%)	
No	5 (16%)	3 (10%)	10 (33.3%)	18 (20%)	
Total	30 (100%)	30 (100%)	30 (100%)	90 (100%)	

*p value < 0.05 (significant)

Table 2: Number of doses required for complete clearance in each treatment group

	Treatment Group				
No. ofdoses/session	Vitamin D3	Bleomycin	Needling	Total	p value
1	3(18.75%)	4 (19.00%)	0 (0%)	7 (17.5%)	
2	4(25.00%)	3 (14.28%)	0 (0%)	7 (12.5%)	
3	9(56.25%)	14 (66.6%)	6 (100%)	29(42.5)	0.7012*
Total	16 (100%)	21 (100%)	6 (100%)	43(100%)	

*p value > 0.05 (not significant)

Table 3: Response in injected and distant warts in each treatment group

Response	Group			
	Vitamin D3	Bleomycin	Needling	P value
Injected warts	25 (83.00%)	27 (90.00%)	20 (66.60%)	0.0666*
Distant warts	22 (73.33%)	21 (70.00%)	12 (40.00%)	0.01 42**

*p value > 0.05 (not significant) & **p value < 0.05 (significant)

Table 4: Response according to type of wart in Vitamin D3 group

Type of Warts	Complete Response	Partial Response	No Response	Total
Verruca Vulgaris	11 (61.1%)	6(33.3%)	1(5.5%)	18(100.0%)
Verruca Plana	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (100.0%)
Palmoplantar Wart	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (100.0%)
Verruca Vulgaris +Filiform wart	1(50.0%)	0(0.0%)	1(50.0%)	2(100.0%)
Periungual warts	1(50.0%)	0(0.0%)	1(50.0%)	2(100.0%)
Verruca Vulgaris + Plantar Wart	1(50.0%)	1(50.0%)	0 (0.0%)	2(100.0%)
Total	16(53.3.0%)	9(30.0%)	5(16.6%)	30(100.0%)

Table 5: Response according to type of wart in Bleomycin group

Type of Warts	Complete Response	Partial Response	No Response	Total
Verruca vulgaris	12(80%)	2 (13.33%)	1 (6.66%)	15(100%)
Verruca plana	1(50%)	0 (0%)	1 (50%)	2 (100%)
Palmoplantar wart	4(66.6%)	2 (33.3%)	0 (0%)	6 (100%)
Periungual wart	2 (66.6%)	1(33.3%)	0 (0%)	3 (100%)
Verruca vulgaris + plantarwart	2(66.6%)	1(33.3%)	0 (0%)	3(100%)
Verruca Vulgaris + Filiformwart	0 (0%)	0 (0%)	1(100%)	1 (100%)
Total	21 (75%)	6 (15%)	3 (10%)	30 (100%)

Table 6: Response according to type of wart in Needling group

Type of Warts	Complete Response	Partial Response	No Response	Total
Verruca vulgaris	2 (12.5%)	10(62.5%)	4 (25%)	16(100%)

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Verruca plana	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (100%)
Palmoplantar Warts	3 (50%)	1 (16.6%)	2 (33.3%)	6 (100%)
Periungual wart	0 (0%)	0 (0%)	2(100%)	2 (100%)
Verruca vulgaris +Filiform	0 (0%)	0 (0%)	1 (100%)	1(100%)
Verruca vulgaris +plantar	0 (0%)	2(100%)	0 (0%)	2 (100%)
Total	6 (20%)	14 (46%)	10 (33%)	30 (100%)

Table 7: Overall Response according to type of wart (N=90)

Type of warts	Complete Response	Partial Response	No Response	Total(N=90)
Verruca vulgaris	25 (51%)	18 (36.7%)	6 (12.2%)	49 (100%)
Verruca plana	3 (37.5%)	2 (25%)	3 (37.5%)	8 (100%)
Palmoplantar wart	8 (53.3%)	4 (26.6%)	3 (20%)	15 (100%)
Periungual warts	3 (42.8%)	1 (14.2%)	3 (42.8%)	7 (100%)
Verruca Vulgaris + filiformwarts	1 (25%)	0 (0%)	3 (75%)	4 (100%)
Verruca Vulgaris + Plantar wart	3 (42.8%)	4 (57.1%)	0 (0%)	7 (100%)
Total	43 (66.67%)	29(18.33%)	18 (15%)	90 (100%)

8 out of 15 patients (53.3%) of plantar wart showed maximum complete response, followed by verruca vulgaris with 25 out of 49 patient (51%) showed complete response. 3 out of 7 (42.8%) with Periungual warts, verruca vulgaris with plantar wart showed complete response. While 3 out of 8 patients (37.5%) of verruca plana and 1 out of 4 patients (25%) having verruca vulgaris with filiform warts showed complete response.

12 out of 25 (48%) patients with 6 months or less duration and 21 out of 44 (47.7%) patients with 6 months to 1 year duration of warts showed complete response. 7 out of 15 patients (46.6%) with 1 to 2 years duration and 3 out of 5 patient (60%) with more than 2 years duration of warts also responded completely.

DISCUSSION

Singh SK et al,[6] injected 0.5 ml and Raghukumar S et al,[7] injected 0.2 to 0.5 ml while in the present study only 0.2 ml of 15 mg/ml (6lakh unit/ml) vitamin D3 had been injected at the base of the wart, which could be the reason for a greater response in the former two studies.[6,7] 0.2ml of lignocaine was injected prior to injecting vitamin D3 for local anaesthesia.

Kavya M et al,[8] also injected the same dose as the present study (0.2 ml), however the response rate was higher in the former.

Present study shows that complete response was achieved after 1 and 2 doses in 3 (18.75%) patients and 4(25%) patients respectively. After 3 doses 9 (56.25%) patients achieved completed clearance. The response in the untreated distant warts showimg complete and partial clearance were 53% and 20% respectively. Study by Raghukumar et al,[7] also had similar number of doses where on an average 3.66 injections were required for achieving a complete response and all patients showed complete clearance of the distant non-injected warts as well. However, in a study by Madhavi Latha Akula et al,[9] more than 6 sessions were needed for complete clearance of the warts.

Archana Singal et al,[10] injected 3U/ml of bleomycin while other studies including the present study injected 1U/ ml, which could possibly explain the high response rate in the former. In the present study we also found response in verruca other than palmoplantar and periungual type.

In present study, 6 out of 9 (66.6%) patients with palmoplantar and periungual warts showed complete response in the bleomycin group whereas 12 out of 15 (80%) patients of verruca vulgaris had complete response. However, in a study done by Archana Singal et al,[10] palmoplantar and periungual wart showed significantly greater therapeutic response (100%) to intralesional bleomycin. Bremneret al,[11] treated 142 warts in 24 patients with intralesional bleomycin and reported a 63% cure rate which is lower than that in our study. The present study showed efficacy of intralesional bleomycin in 6 patients of palmoplantar and 2 patients of periungual warts that reported complete, partial and no clearance in 66.6%, 33.3% and 0% patients in both groups respectively. Even in the untreated distant warts, the response rates for complete and partial clearance were 43% and 27% respectively.

Present study required more number of doses for complete clearance when compared to the study done by Mahesh unniet al.[12] Possible reason with the same dosage given, but the follow up in present study was for lesser duration (12 weeks) as compared to study by Mahesh Unniet al,[12] where many patient did show clearance after 24weeks. Present study had maximum of 3 doses whereas they had 4 maximum doses. Study by Archana Singal et al,[10] on 250 lesions of wart in 80 patients showed 100% resolution after an average of 2.61 sessions but with a concentration of bleomycin higher than present study. Another study by Soni et al,[13] had higher clearance (96%) than present study after 2 session of bleomycin with 157 lesion in 50 patients.

In the present study, 6 out of 30 cases (100%) required 3 doses/session of needling for complete clearance. Not a single case showed complete response in a single dose. The distant warts also responded to immunotherapy in 12 out of total 30 (40%) cases. In the present study interestingly, individual warts that were subjected to needling showed complete resolution in 20 patients (66.60%).

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Similar finding was also seen in a study by Sukriti Baveja et al,[14] in 35 patients (85.4%).

CONCLUSION

Our study shows intralesional vit-D3, needling and bleomycin offers a safe and promising approach that can be considered as a first line of therapy in patients having extensive cutaneous viral warts, especially in difficult to treat sites. However, large number of studies with bigger sample size are needed to establish more accuracy of outcomes.

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