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" *Intralesional vitamin D_3, zinc sulfate, and topical potassium hydroxide for the treatment of recalcitrant warts: A three-armed randomized controlled study.* *"Recalcitrant warts treatment* "

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ABSTRACT:

Warts are benign epidermal proliferations caused by the human papillomavirus. The current therapies are either destructive, leading to scar formation, or less effective, causing recurrences. Therefore, the study aims to investigate the efficacy and safety of vitamin D_3, zinc sulfate, and potassium hydroxide for the treatment of recalcitrant warts.

MethodsA three-arm randomized controlled clinical trial was carried out in the Dermatology, Andrology, and Sexually Transmitted Diseases Department of Mansoura University Hospitals, Dakahlia, Egypt, from August 2022 to May 2023. Eighty patients were randomly recruited into 4 groups, including Intralesional injections of vitamin D_3 (group 1), zinc sulfate 2% (group 2), potassium hydroxide 10% (group 3), and normal saline (group 4). The dermoscopic examination was used to diagnose and monitor treatment.

ResultsThere was statistically significant therapeutic improvement in groups 1, 2, and 3 compared to the control group (P 0.001). The complete cure was achieved after 6 weeks of therapy in 75%, 70%, and 55% of patients in groups 1, 2, and 3, respectively, with a statistically insignificant correlation with the control group (P >0.05). The best responses involved all types of warts treated with vitamin D_3. Common warts were highly responsive to zinc sulfate (90% of the patients), while plane warts were 100% responsive to potassium hydroxide. Recurrences were observed only in groups 1 (5%, n = 1) and 2 (15%, n = 3).

ConclusionIntraregional administration of vitamin D_3, zinc sulfate 2%, and potassium hydroxide 10% was effective and safe for the treatment of recalcitrant warts.

Keywords: immunotherapy, vitamin D_3, zinc sulfate, KOH, saline, recalcitrant warts

Introduction

Warts develop from the epidermal skin layer as a benign growth induced by human papillomavirus strains (HPV) (Aqil et al., 2019). The most effective preventive measure against genital warts is vaccination. The bivalent vaccine (Cervarix^{TM}) contains HPV-16 and HPV-18. Gardasil TM contains HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58. A significant reduction was noticed regarding the incidence of warts and, consequently, HPV-related skin cancer. However, the other types like common, planter and plane warts are not affected by the vaccines (Lee et al., 2019). On the other hand, different therapeutic approaches are available either topically, systematically, or intralesional. Topical therapeutic modalities include the application of salicylic acid, imiquimod, cryotherapy, and bleomycin injection. Moreover, surgical excision, electrocautery, and laser vaporization are invasive therapeutic approaches that require fewer treatment sessions, yet scarring may occur. For multiple lesions, systematic therapeutic modalities are preferred like systemic acitretin or recombinant human interferon α-2b (Zhu et al., 2022). The utilization of recombinant human interferon α-2b as an adjuvant to ablation therapy was concluded to be beneficial (Westfechtel et al., 2018). The intralesional approach adopted the use of cytostatic treatments (such as 5-fluorouracil [5-FU] and bleomycin), immunomodulators including vaccines such as measles, mumps, and rubella (MMR), Mycobacterium, and Bacillus Calmette-Guerin (BCG) vaccines (Saha et al., 2022; Shaker et al., 2021), as well as organic antigens as a potential intraregional warts therapy, including *Candida albicans* (Eldahshan et al., 2022), *Trichophyton*, and tuberculin antigens (purified protein derivative (PPD)) (Aldahan et al., 2016; Thappa & Chiramel, 2016).The immunomodulator's suggested mode of action is the activation of a T-cell-mediated response with a release of cytokines (Nofal et al., 2013).

Topical vitamin D has been tried as a potential therapeutic cure for warts with promising results (Abdelaal et al., 2021; Singh et al., 2022). Furthermore, intralesional zinc sulfate 2% was concluded to be safe and effective for viral wart therapy compared to either PPD or vitamin D_3 (El Sayed et al., 2020,Awad et al., 2022;). A systematic review study concluded that intraregional zinc sulfate is a simple technique that is also safe and cost-effective (Song et al., 2022). In addition, potassium hydroxide has emerged as a promising therapeutic alternative. A recent study concluded that 75% of the patients treated with potassium hydroxide showed complete clearance of viral warts with no recurrences (Kandil et al., 2016). However, potassium hydroxide was found to be superior to cryotherapy in terms of crust and scar formation (Abdelaal et al., 2021).

Given the promising potential of vitamin D_3, zinc sulfate, and potassium hydroxide, the current study aimed at comparing the safety and efficacy of the three compounds against a placebo through a three-arm randomized controlled trial. The findings of this research would determine the effectiveness and safety of each substance, as well as the appropriate order in which to place them.

Patients and Methods

Study design

This was a three-arm randomized controlled clinical trial carried out in the Dermatology, Andrology, and Sexually Transmitted Diseases (STDs) Department at Mansoura University Hospitals, Dakahlia, Egypt, from August 2019 to May 2021.

Patients

Eighty patients were recruited from the outpatient clinics of the Dermatology and Andrology clinics.

Inclusion criteria:

Adult patients of either sex with recalcitrant warts were selected for the study. The wart is considered

recalcitrant if it is resistant to one or more lines of treatment for at least a 6-month duration.

Exclusion criteria:

The excluded patients were:

1-pregnant and lactating females.

2- patients less than 10 years of age;

3- Patients with any systemic, autoimmune, or immunosuppressive diseases;

4- Patients suffering from hypercalcemia, hypercalciuria, calci lithiasis, or any renal disease;

5- patients who were on Vit D (any type) supplementation;

6- Patients received any wart therapy during the previous 4 weeks;

7- Patients with a prior history of sensitivity to any component of the used medications.

Clinical proceedings:

All patients were subjected to detailed history-taking, detailed dermatological examination, photography by (Sony Cyber-shot DSC-W620) camera and dermoscopic examination at baseline, before every session, and after 2, 4, and 6 months of treatment.

Patients were randomly assigned to one of four equal groups, each with 20 patients: intralesional (IL) Vit D3 (group 1), IL sterile 2% ZnSO4 (group 2), topical 10% potassium hydroxide (group 3), and IL 0.9% normal saline (control group).For IL injections, 0.2 ml of injected substances were slowly injected into the base of one wart (if a single wart) or up to five warts (if multiple warts) per session every 2 weeks (4 sessions). The potassium hydroxide solution was applied every night and left all night long for six weeks.

We used an aqueous solution of cholecalciferol (Devarol, S, 200,000 I.U., 5 mg/2 ml; Ampoule ® Memphis Co., Egypt), purchased from local pharmacies. In the laboratories of the Pharmacognosy Department, Mansoura Faculty of Pharmacy, Dakahlia, Egypt, a sterile solution of 2% zinc sulfate was prepared by dissolving 2 g of zinc sulfate powder in 100 ml of sterile distilled water. The 10% potassium hydroxide solution was prepared by dissolving 10 g potassium hydroxide crystals in 100 ml of sterile distilled water. Both solutions were autoclaved at 95 °C for 20 minutes.

For IL injections, topical anesthesia (prilocaine cream) was used for 30 minutes, then 70% ethanol was applied as an antiseptic. In the potassium hydroxide group, perilesional skin was covered with Vaseline to minimize contact irritation, then the solution was applied once at night with one touch using a toothpick with a cotton-wrapped tip to avoid any spillage around for a maximum of 6 weeks.

Clinical examination and follow-up

Clinical examinations, including type, size, number of warts, and dermoscopic evaluations, were done at baseline, and every treatment visit. Similarly, follow-up was done monthly for 6 months after the last session to detect any recurrence. Two independent observers performed the clinical and dermoscopic examinations.

Dermoscopic examination

The dermoscopic evaluation was done using Dermlite II PRO HR, 3Gen, USA. Polyvinyl chloride food wrap (plastic wrap) was applied to the lesions before placing the Dermoscopy to prevent cross-infections. The parameters included in the dermoscopic evaluation were the presence of a papillomatous surface, background color (red, pink, yellow, and brown), the type of vascular component if any (dots, globules, linear, and loops), and the presence of hemorrhagic spots.

The outcomes

The outcomes were based on clinical, dermoscopic, and digital photographic assessments. The response to therapy was considered the primary outcome and divided into three categories: the first category is the complete response to therapy that was identified by the clearance of all studied warts; the second category is a partial response that was identified by the reduction of the warts size and/or number by more than 50%; and the third category is no improvement identified by the improvement of less than 50% of the studied warts.

Ethics

Approval of the Institutional Review Board (IRB) of Mansoura Faculty of Medicine (Code Number: MS/18.03.71. Before enrolling in the trial, all patients provided written informed consent.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp.). The Mann-Whitney and Kruskal-Wallis tests were used to compare non-parametric data, and the one-way ANOVA test was used to analyze parametric data. Different variables were correlated using Spearman correlation.

Results

Demographic data

This study included 80 patients with either single or multiple recalcitrant warts categorized into 4 equal groups according to the treatment modality used: Group 1 received vitamin D_3, Group 2 received zinc sulfate, Group 3 received potassium hydroxide, and Group 4 (the control group) revived normal saline **(Table 1)**. There were no statistically significant differences in the demographic or clinical criteria of any of the groups. Therefore, any difference in response could be attributed to the applied treatment**.**

Grade of response

The grades of response (complete, partial, and no response) in the studied groups are shown in Fig. 1. Statistically significant therapeutic improvement occurred in groups 1, 2, and 3 compared to the control group ($P<0.001$).

The response started after 2 weeks of therapy in 8 patients (40%) of group 1, 5 patients (25%) of group 2, and 10 patients (50%) of group 3 ($P >0.05$) **(Table 2)**. However, a complete cure occurred after 6 weeks of therapy in 75%, 70%, and 55% of patients in groups 1, 2, and 3, respectively, showing a statistically insignificant correlation with the control group ($P >0.05$).

In Group 1, complete clearance occurred in 15 patients (75%): one patient with plane warts after one session, two patients after two sessions, seven patients after three sessions, and five patients after four sessions. A partial response was reached in 3 patients (15%) after 4 sessions (Fig.2,3). However, in Group 2, complete clearance occurred in 14 patients (70%): one patient with common warts after 2 sessions, 5 patients after 3 sessions, and 8 patients after 4 sessions. A partial response had been reached in 2 patients (10%) after 4 sessions. In contrast to the Vitamin D_3 group, no patient reached complete clearance after one session (Fig.4,5). In Group 3, complete clearance occurred in 11 patients (55%): one patient with plane warts after 2 weeks, 4 patients after 4 weeks, and 6 patients after 6 weeks. A partial response was reached in six patients (15%) after six weeks (Fig.6,7). There was a positive relationship between the therapeutic effect of potassium hydroxide and the duration of therapy, with a statistically significant increase in response rate ($P < 0.01$).

Age and gender

No significant correlations were found between the response and patients' gender or the size or site of warts. However, in the vitamin D_3 and potassium hydroxide groups, better responses were noticed in younger patients. In addition, the responses were inversely correlated to the number and duration of warts **(Table 3)**.

Types of warts

As for the type of wart, the best responses occurred in all types of warts with Vitamin D_3, in common warts (90%) with zinc sulfate, and in in-plane warts (100%) with potassium hydroxide. In Group 3, there were statistically significant differences between the responses in different types of warts, with the best responses among plane warts (100%) vs. 45% and 25% in common and plantar warts, respectively (P = 0.04).

Dermoscopic evaluation

The dermoscopic evaluation of the studied cases vs. the demonstration in **Table 4**

Before treatment Common warts have many tightly packed papillae (papillomatous surfaces) and vascular components as randomly dispersed red spots, linear vessels, or black dots Plantar warts showed **a** yellowish papilliform surface, a yellow grey structureless pattern with interrupted skin lines, black hemorrhagic spots, and irregularly distributed red-dotted or linear vessels. *Plane warts* revealed **a** pale, red-yellow background with regularly distributed red, tiny, dotted vessels.

After treatment, Dermoscopic examination of the examined common and plantar warts revealed that vascular components, black spots, and papillomatous structures completely disappeared (full recovery) in 14 cases in the Vitamin D3 group vs. 14 cases in the zinc sulfate group and 6 cases in the potassium group. In cases with plane warts, complete disappearance of vascular components and colored background (hyperkeratosis) in all cases These changes occurred in cases showing complete cure and declined partly in partially responding cases.

Side effects

As regards side effects, all patients in the vitamin D_3 and zinc sulfate groups showed transient pain during injection. Edema and erythema were reported in 16 patients (80%) in the zinc sulfate group, 10 patients (50%) in the potassium hydroxide group, and 2 patients (10%) in the vitamin D_3 group that were tolerable and subsided without treatment. Depigmentation occurred in 15% (n=3) and 20% (n=4) cases in the zinc sulfate and potassium hydroxide groups, respectively. Re-pigmentation occurred gradually during the follow up period without any intervention.

No recurrence was reported in the potassium hydroxide group, while recurrence was reported in 5% (n=1) of patients who used Vitamin D_3 and 15% (n=3) of patients who used zinc sulfate during the follow-up period (6 months).

Discussion:

Recalcitrant viral warts are a challenge to a dermatologist due to their unsatisfactory response to therapy after six months of robust treatment (Leerunyakul et al., 2022). In addition, the recurrence of warts due to the recrudescence of the virus from adjacent reservoirs adds to the treatment burden (Zampella & Cohen, 2022). Therefore, new modalities of therapy have been investigated to identify the most effective and safe treatment options. Consequently, intralesional injection of substances with immunological properties may influence the outcome of treatment for patients with recalcitrant viral warts (Awad et al.,2022). The three most promising therapeutic modalities include vitamin D3 (Singh et al., 2022), zinc sulfate (Song et al., 2022), and potassium hydroxide (Galal et al., 2020). The first two therapies, vitamin D3 and zinc sulfate are modulated by the

immune system response (Abdelaal et al., 2021; El Sayed et al., 2020). However, potassium sulfate demonstrates its anti-wart effect through the keratolysis of infected cells, leading to wart resolution (Alawady et al., 2022). It was claimed that intraregional potassium sulfate stimulates the immune response through the irritation mechanism (Mohta et al., 2021).

The current study showed that the three therapeutic modalities (Vitamin D3, zinc sulfate, and potassium hydroxide) are comparably effective and safe in the management of recalcitrant viral warts in adults. The therapeutic response appeared after 2 weeks of intraregional injections, and most of cases showed a complete cure after 6 months of therapy. A complete cure was diagnosed by Dermoscopy to ensure complete clearance of the microscope lesions. Neither age, lesion size, nor wart site are correlated to the response of the investigated medications. It was noticed that vitamin D3 was substantially effective against all types of warts, while zinc sulfate and potassium hydroxide were highly effective against common and plane warts, respectively. Transient pain was experienced by almost all patients. Most of the patients experienced edema and erythema, mainly among those who received zinc sulfate. Dyspigmentation appeared mainly among patients treated with zinc sulfate and potassium hydroxide. Recurrence was not noticed with potassium hydroxide. A few cases of recurrence were reported with vitamin D3 and zinc sulfate alone.

To the best of the author's knowledge, this is the first study to compare the three promising therapeutic modalities with each other. In a randomized clinical trial, El-Sayed and colleagues concluded that both IL 2% zinc sulfate and vitamin D3 are effective in the treatment of plantar warts with comparable side effects (El-Sayed et al., 2020). Comparably, this study reported a higher cure rate for common warts in patients receiving IL zinc sulfate (90% vs. 71%). However, the findings of the current study were based on the dermoscopic diagnosis rather than the macroscopic findings.

Vitamin D3 is known for its promising effect against viral warts (Abdel-Azim et al., 2020) due to the immunotherapeutic properties retained by vitamin D3 (Bersanelli et al., 2017). The active form of cholecalciferol, vitamin D3, is substantial for the activation of the immune system and T-cell differentiation (Infantino et al., 2022). Moreover, vitamin D3 has an antiproliferative effect (Spath et al., 2017). These two mechanisms are considered to operate synchronously to combat HPV warts (Singh et al., 2022). Therefore, vitamin D3 was concluded to be comparable to other immunotherapeutic modalities, including MMR and tuberculin PPD vaccines (Shaker et al., 2021). Based on its immunotherapeutic qualities, prospective randomized controlled research indicated that vitamin D3 was comparable to the MMR vaccine in the treatment of resistant viral warts (Mohta et al., 2021). Similarly, the efficacy and safety of vitamin D3 were confirmed in a single-blind, randomized, controlled study on 100 patients, showing no clinically significant difference between vitamin D3 and the MMR vaccine. Furthermore, IL-vitamin D3 was emphasized as the first line of therapy against viral warts due to its greater efficacy and safety findings when compared to bleomycin, 5-fluorouracil, zinc sulfate, tuberculin PPD, and candida antigen (Martin et al., 2022). The current study was in agreement with the literature, as the findings showed that vitamin D3 was effective against all types of warts tested in the study. Vitamin D3 showed a high degree of complete clearance and minimal side effects, with few recurrences (5%).

Moreover, IL zinc sulfate was considered an effective therapeutic modality against warts compared to tuberculin PPD (Awad et al., 2022). In an immunocompetent patient, IL zinc sulfate 2% was highly successful in completely clearing a recalcitrant wart lesion (El Taweel et al., 2019). Similar to and comparable to candida antigen, zinc sulfate exerts its anti-wart effect through its potential immunotherapeutic properties (Youssef et al., 2022). Zinc is an important immune system modulator through the activation of T cells and natural killer cells (El-Khalawany et al., 2015). In comparison to 7% hypertonic saline, IL zinc sulfate 2% cleared 80.92% of numerous verruca vulgaris (common warts) in 2 weeks (Sharquie & Al-Nuaimy, 2002). According to a recent study, IL zinc sulfate 2% completely eradicated 60% of common warts after the first session with low-

tolerated side effects (Mohamed et al., 2016). However, in plantar warts, IL zinc sulfate 2% was placed in third place, after vitamin D3 and candida antigen (Nofal et al., 2022). The current study concurred that IL zinc sulfate 2% was highly effective against common warts (90% of the patients were completely cured). However, the recurrence rate was comparatively higher than that of vitamin D and potassium hydroxide that correlates with the study of (Abd El-Magid et al., 2012) who reported higher recurrence in zinc sulfate vs vitamin D group.

Topical application of potassium hydroxide (5–10%) showed satisfactory improvement results in young and adult patients (Jayaprasad et al., 2016). According to a comprehensive review, 5% potassium hydroxide had a higher clearance rate than cryotherapy with no recurrences and was comparable to intraregional 5-fluorouracil, salicylic acid, and carbon dioxide laser vaporization. (Abalos-Babaran et al., 2019). However, the highest percentage of wart clearance appeared after 12 weeks (Alawady et al., 2022). Although Yaghoobi and colleagues observed a higher proportion of complete clearance (Yaghoobi et al., 2019), a higher potassium hydroxide concentration of 30% was tested to improve the response rate (Alawady et al., 2022). The rate of potassium hydroxide 30% side effects, including abnormal skin pigmentation and scarring, was reported to be higher than potassium hydroxide 5–10%; however, the difference showed no statistical significance (Alawady et al., 2022). In this study, a topical application of potassium hydroxide (10%) was used. Compared to IL normal saline, topical potassium hydroxide (10%) showed complete clearance in 55% of patients within 6 months, with depigmentation in 15% and edema and erythema in 50% of patients. These findings were in accordance with the literature. Contrary to the literature, this study noticed no recurrence with potassium hydroxide applications. Compared to IL vitamin D_3 and zinc sulfate outcomes, potassium hydroxide outcomes showed no statistical difference.

Strengths and limitations

The main strength of this study is the dependence on Dermoscopy for the diagnosis of warts and the detection of clearance of the lesion following the application of therapy. A macroscopic, naked-eye diagnosis based on the disappearance of the lesion may be misleading. Although the diagnosis of warts is mainly based on typical clinical features, clinicians may occasionally be confronted with features that overlap with those of other skin lesions or that make it difficult to accurately diagnose viral warts based on clinical criteria alone. Furthermore, Dermoscopy helps visualize microstructures located in the epidermis and upper dermis; thus, the clearance of a wart lesion is accurately confirmed. The second point of concern is randomization. By randomly assigning the patients to the treatment modalities, selection bias is minimized or nullified. Therefore, the results represent the actual impact of each therapeutic modality on the recalcitrant wart.

On the other hand, the main limitation of the study is the recruitment of a small number of patients in each group. However, the promising results of the study would encourage the future application of these therapeutic modalities, vitamin D_3, zinc sulfate, and potassium hydroxide, on a large scale.

Conclusion

Here we conclude that IL injection of vitamin D and zinc sulfate as well as topical application of potassium hydroxide for viral warts are promising therapeutic modalities for vial warts. The three modalities were found effective and safe for the treatment of warts. The side effects are limited and tolerable. Moreover, the study found that zinc sulfate was highly effective on common warts, while potassium hydroxide was highly effective on plantar warts. Therefore, the subtle difference in efficacy and side effects, as well as the predilection for certain types of warts, may determine the preference for each substance on an individual basis.

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Table 1: Demographic & Clinical Criteria of the Studied Patients.

Items	Group 1 N=20		Group 2 N=20		Group 3 N=20		Group 4 N=20		Test
	N	%	N	%	N	%	N	%	
Age/yrs: Mean±SD (range)	**32.7±13.6** **(13-60)**		**30.9±9.5** **(17-55)**		**26.3±11.7** **(10-50)**		**36.3±11.7** **(19-58)**		***F* = 2.49** ***p* = 0.07**
Type of warts:									
• Common	**11**	**55**	**10**	**50**	**11**	**55**	**9**	**45**	**MC** ***p* = 0.39**
• Plantar	**8**	**40**	**9**	**45**	**4**	**20**	**9**	**45**	
• Plane	**1**	**5**	**1**	**5**	**5**	**25**	**2**	**10**	
No. of warts:									
(Range) Median	**(1-25) 3**		**(1-15) 3**		**(1-20) 1**		**(1-8) 1**		**KW** ***p* = 0.15**
Duration/months:									
Mean±SD (range)	**16.1±8.4** **(6-36)**		**14.4±5.7** **(6-18)**		**14.5±5.1** **(6-33)**		**8.8±2.1** **(6-12)**		**KW** ***p* = 0.29**
Size of warts: **< 1cm** **≥ 1cm**	**6** **14**	**30** **70**	**10** **10**	**50** **50**	**12** **8**	**60** **40**	**12** **8**	**60** **40**	**KW** ***p* = 0.32**
Site of warts:									
Acral (hands or feet):	**18**	**90**	**18**	**90**	**12**	**60**	**17**	**85**	**MC** ***p* = 0.05**
Body:	**1**	**5**	**2**	**10**	**3**	**15**	**2**	**10**	
Head & neck:	**1**	**5**	**0**	**0**	**5**	**25**	**1**	**5**	

F: One Way ANOVA test ***χ^2= Chi-Square test*** ***MC:Monte Carlo***
KW: Kruskal Wallis test ***p > 0.05 = non-significant.***
Group 1 ***(Vit D_3 group) using IL aqueous solution of Cholecalciferol (200,000 IU/2mL),*** **Group 2** ***($ZnSO_4$ group) using IL 2% Zinc Sulfate***

solution, Group 3 *(KOH group) using topical 10% Potassium Hydroxide solution,* Group 4 *(Control group) using IL 0.9% NaCl solution.*

Table 2:Progression of Response during Follow Up Period Among The Three Studied Groups.

Response		Group 1 N=20						Group 2 N=20				Group 3 N=20						Significance
		Common warts		Plantar warts		Plane warts		Common warts		Plantar warts		Common warts		Plantar warts		Plane warts		
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
1st session (2 weeks)	No response	7	35	5	25	0	0	6	30	9	45	6	30	4	20	0	0	P1=0.908 P2=0.187 P3=0.301
	Partial response	4	20	3	15	0	0	4	20	1	5	5	25	0	0	4	20	
	Complete response	0	0	0	0	1	5	0	0	0	0	0	0	0	0	1	5	
2nd session (4 weeks)	No response	4	20	2	10	0	0	3	15	7	35	3	15	3	15	0	0	P1=0.99 P2=0.264 P3=0.887
	Partial response	6	30	5	25	0	0	6	30	3	15	7	35	1	5	1	5	
	Complete response	1	5	1	5	1	5	1	5	0	0	1	5	0	0	4	20	
3rd session (6 weeks)	No response	2	10	1	5	0	0	1	5	5	25	1	5	2	10	0	0	P1=0.832 P2=0.535 P3=1.0
	Partial response	4	20	3	15	0	0	6	30	2	10	5	25	1	5	0	0	
	Complete response	5	25	4	20	1	5	3	15	3	15	5	25	1	5	5	25	
4th session (8 weeks)	No response	1	5	1	5	0	0	1	5	3	15	1	5	2	10	0	0	P1=0.158 P2=0.56 P3=0.269
	Partial response	2	10	1	5	0	0	0	0	2	10	5	25	1	5	0	0	
	Complete response	8	40	6	30	1	5	9	45	5	25	5	25	1	5	5	25	

MC nemar test ***Stewart Maxwell test*** ***P > 0.05 = non-significant.***

P1: Group 1 vs Group 2 ***P2: Group 1 vs Group 3*** ***P3: Group 2 vs Group 3***

Table 3:Correlations between the Response and the Main Demographic & Clinical Criteria of Cured Cases.

item	Group 1 N=15		Group 2 N=14		Group 3 N=11		Group 4 N=2	
	N	%	N	%	N	%	N	%
Age/yrs: < 20	3	20	2	14	4	36	0	0
20-40	9	60	9	64	6	55	1	50
> 40	3	20	3	22	1	9	1	50
Significance	r = -0.15 p = 0.53		r = 0.01 p = 0.95		r = -0.14 p = 0.56		r = 0.09 p = 0.72	
Sex: Male	10	67	8	57	7	64	0	0
Female	5	33	6	43	4	36	2	100
Significance	r = 0.09 p = 0.70		r = 0.11 p = 0.65		r = 0.12 p = 0.63		r = 0.45 p = 0.06	
Type: Common	8	53	9	64	5	45	1	50
Plantar	6	40	5	36	1	10	0	0
Plane	1	7	0	0	5	45	1	50
Significance	MC p = 0.99		MC p = 0.09		MC p = 0.04*		MC p = 0.26	
No. of warts: < 3	7	47	7	50	8	73	1	50
3-8	6	40	7	50	2	18	1	50
> 8	2	13	0	0	1	9	0	0
Significance	r = -0.16 p = 0.50		r = -0.19 p = 0.43		r = -0.31 p = 0.18		r = -0.26 p = 0.27	

Duration/yrs: < 1	9	60	8	57	7	64	2	100
1-2	4	27	6	43	1	9	0	0
> 2	2	13	0	0	3	27	0	0
Significance	r = -0.30 p = 0.21		r = -0.44 p = 0.05*		r = -0.1 p = 0.67		r = -0.07 p = 0.76	
Size of warts:								
< 1cm	4	27	8	57	8	73	2	100
≥ 1cm	11	74	6	43	3	27	0	0
Significance	r = 0.13 p = 0.85		r = 0.25 p = 0.69		r = 0.15 p = 0.69		r = 0.22 p = 0.54	
Site of warts:								
Acral (hands or feet):	13	86	12	86	5	45	1	50
Body:	1	7	2	14	1	10	1	50
Head & neck:	1	7	0	0	5	45	0	0
Significance	MC P = 0.84		MC P = 0.80		MC P = 0.15		MC P = 0.55	

r: Spearman correlation coefficient, MC: Monte Carlo test, p < 0.05 * = significant.

Table 4:Dermoscopic Evaluation of the Studied Cases Before & After Treatment.

Dermoscopic findings:	Group 1 N=20		P value	Group 2 N=20		P value	Group 3 N=20		P value
	Before	After		Before	After		Before	After	
***Common warts*:**	N=11			N=10			N=11		
Papillomatous surface	11 (100%)	3 (27%)	0.001**	10 (100%)	1 (10%)	0.001**	11 (100%)	6 (54.5%)	0.035*
Vascular component	11 (100%)	3 (27%)	0.001**	10 (100%)	1 (10%)	0.001*	11 (100%)	4 (36%)	0.004*
Plantar warts:	N=8			N=10			N=4		
Papilliform surface/ yellowish structureless pattern	8 (100%)	2 (25%)	0.01*	10 (100%)	5 (50%)	0.03*	4 (100%)	3 (75%)	1.0
Interrupted skin lines	8 (100%)	2 (25%)	0.01*	10 (100%)	5 (50%)	0.03*	4 (100%)	3 (75%)	1.0
Vascular component	6 (75%)	1 (12.5%)	0.04*	8 (80%)	3 (30%)	0.07	3 (75%)	2 (50%)	1.0
Plane warts:	N=1			0			N=5		
Red/ Brown/ Pale background	1 (100%)	0	….				5 (100%)	0	….
Vascular component	1 (100%)	0	….				3 (60%)	0	0.67

MC nemar test ***Stewart Maxwell test***

P > 0.05 = non-significant ***P < 0.05 * = significant*** ***P < 0.001** = highly significant.***

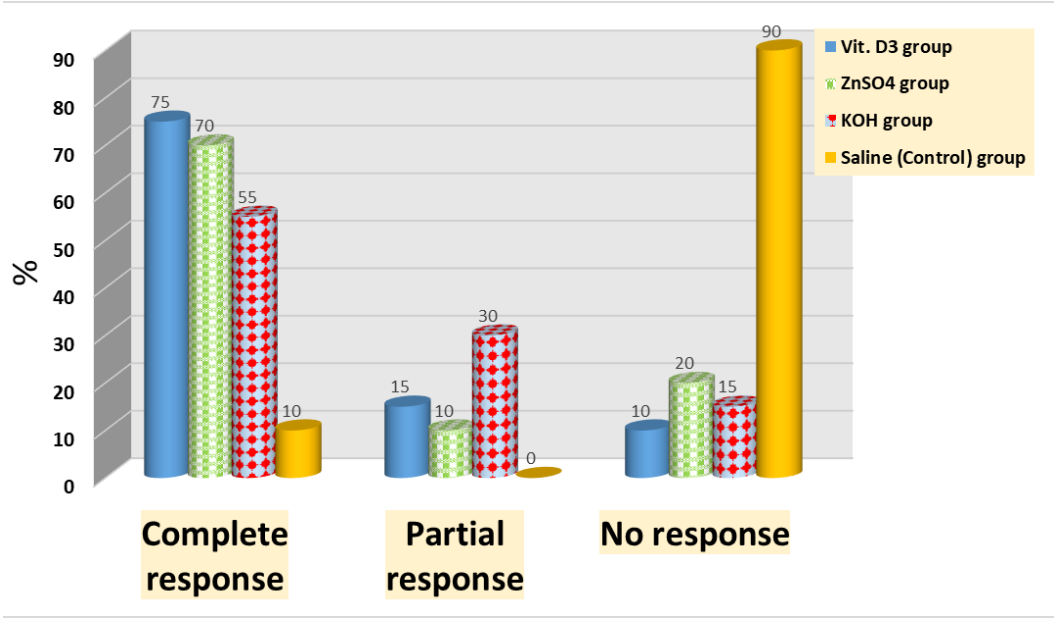

Figure 1:Distribution of Different Grades of Response Among The Studied Groups.

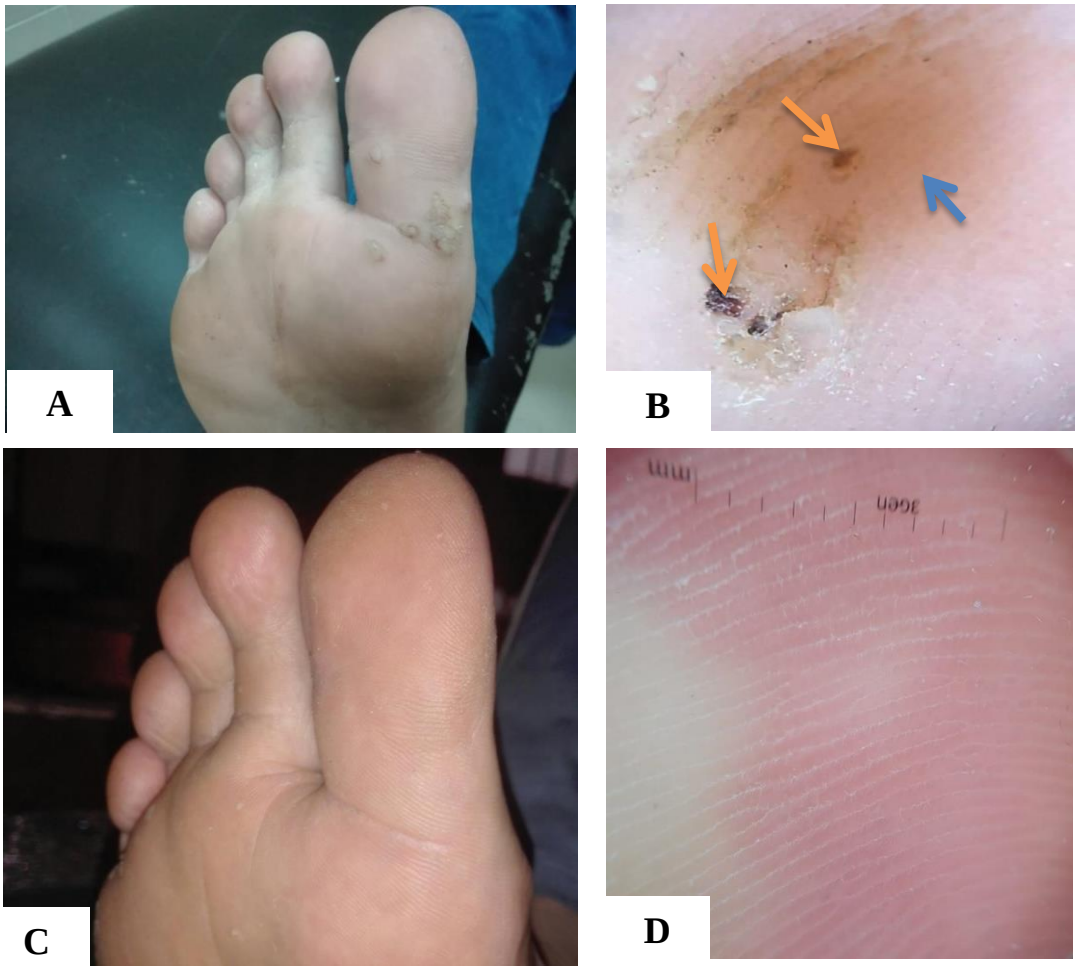

Figure 2:

A.Multiple plantar warts in right foot of 33 years male patient before treatment.
B.Dermoscopy: showing red & black hemorrhagic spots (yellow arrow); interrupted skin lines (blue arrow).
C.Complete resolution after 3 sessions of IL Vit D_3.
D.Dermoscopic photo: showing restoration of normal skin lines.

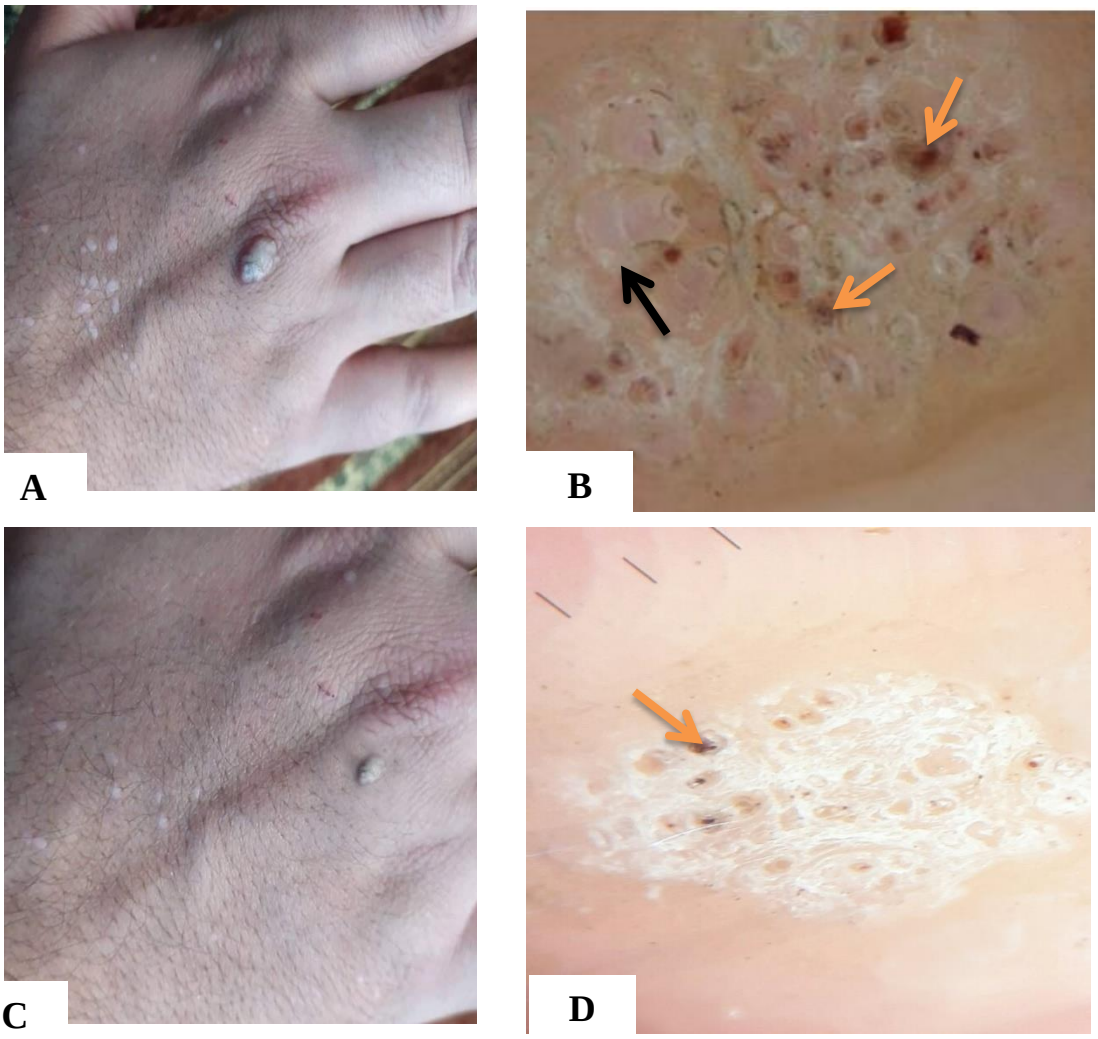

Figure 3:

(A) Common wart and multiple plane warts in right hand of 31 years male patient before treatment.

(B) Dermoscopy: showing papillomatous surface (black arrow); red & black dots (yellow arrow).

(C) Partial response after 4 sessions of IL Vit D_3 (clinical decrease in size of common wart and number of plane warts).

(D) Dermoscopic photo: showing small sized residue with few black dots.

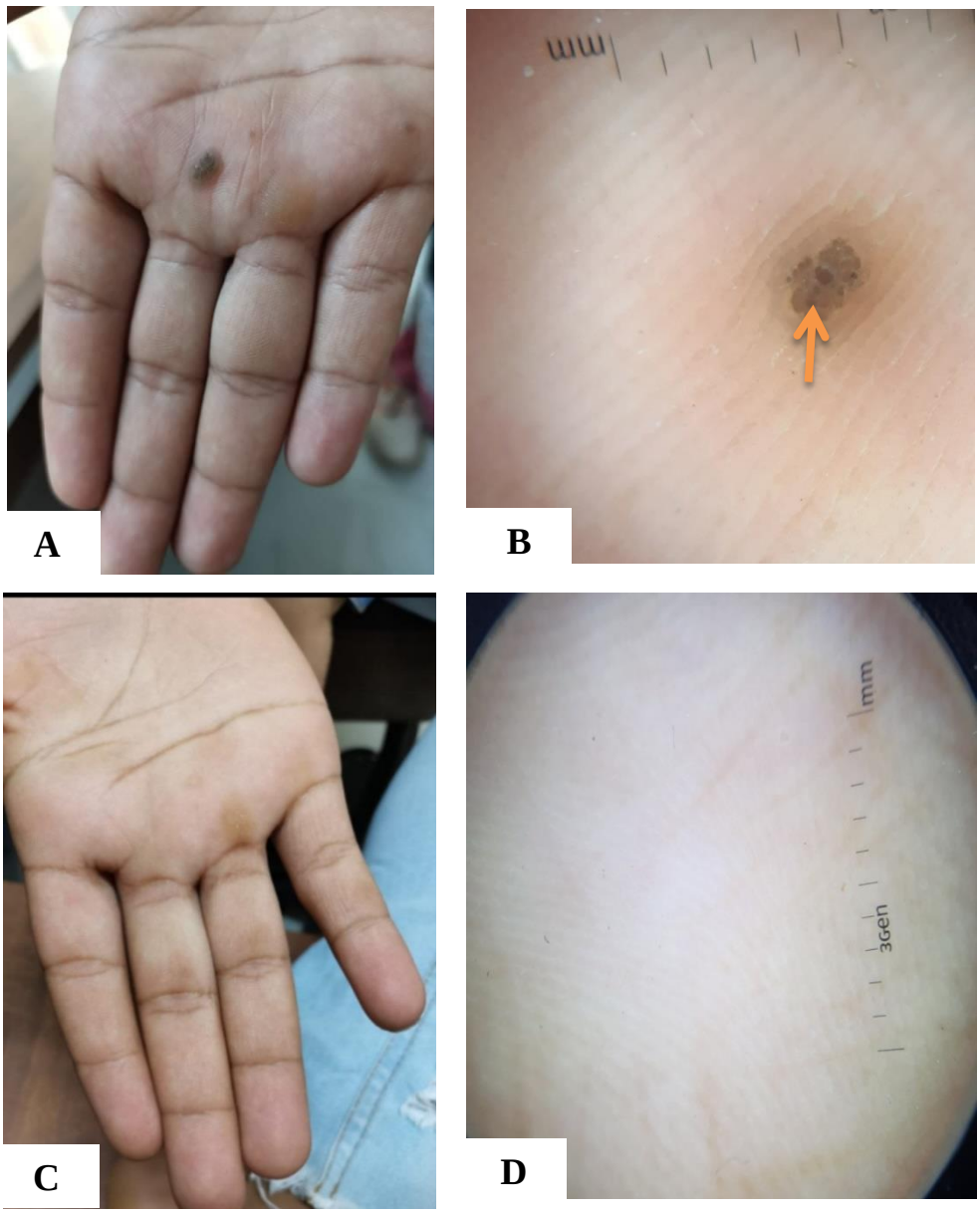

Figure 4:

(A) Multiple common warts in right hand of 33 years female patient before treatment.

(B) Dermoscopy: showing black dots (yellow arrow).

(C) Complete resolution after 4 sessions of IL 2% $ZnSO_4$.

(D) Dermoscopic photo: showing restoration of normal skin lines.

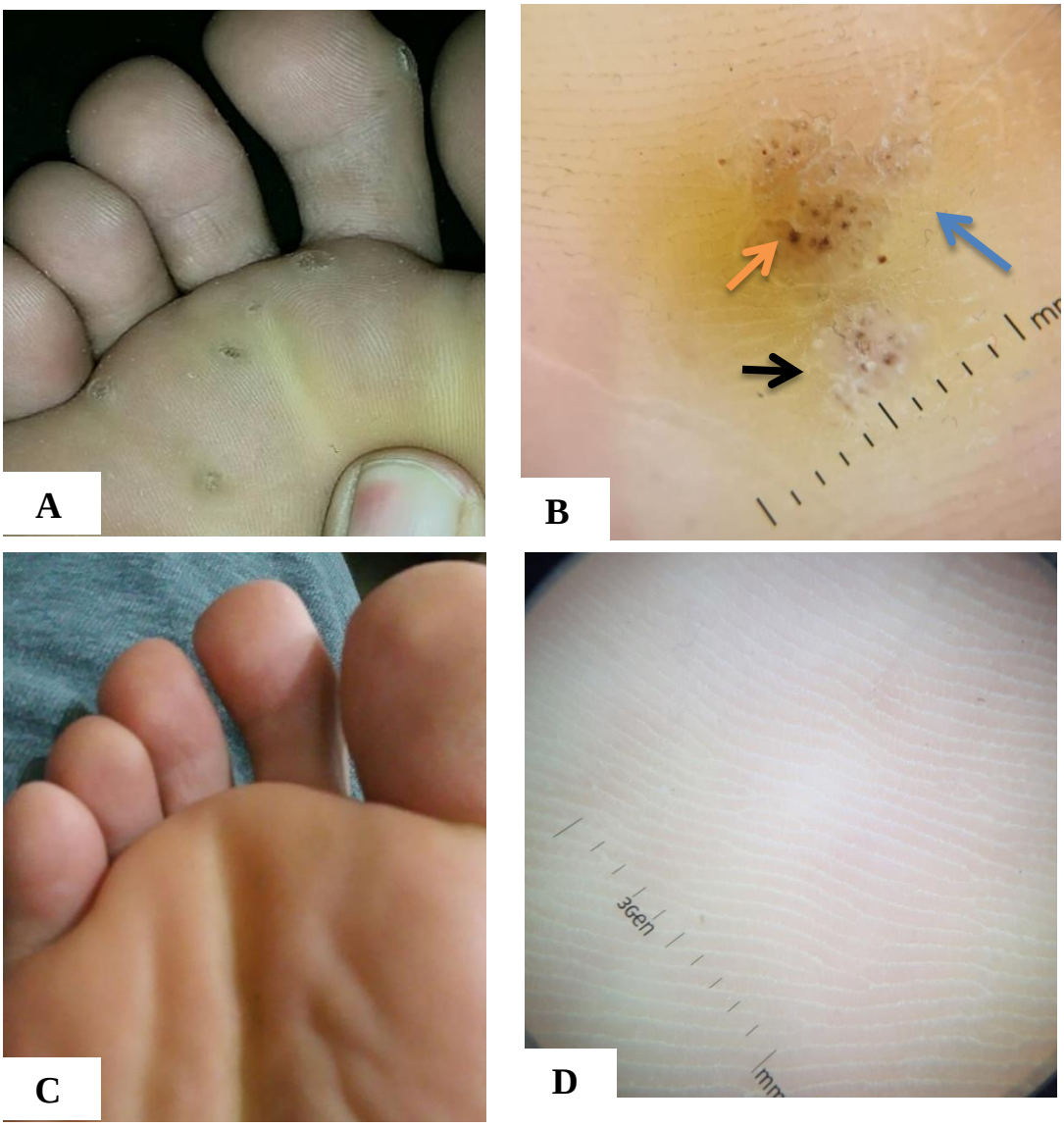

Figure 5:

(A) Multiple plantar warts in right foot of 25 years male patient before treatment.

(B) Dermoscopy: showing papilliform surface (black arrow); red & black dots (yellow arrow); interrupted skin lines (blue arrow).

(C) Complete resolution after 3 sessions of IL 2% $ZnSO_4$.

(D) Dermoscopic photo: showing restoration of normal markings of plantar skin.

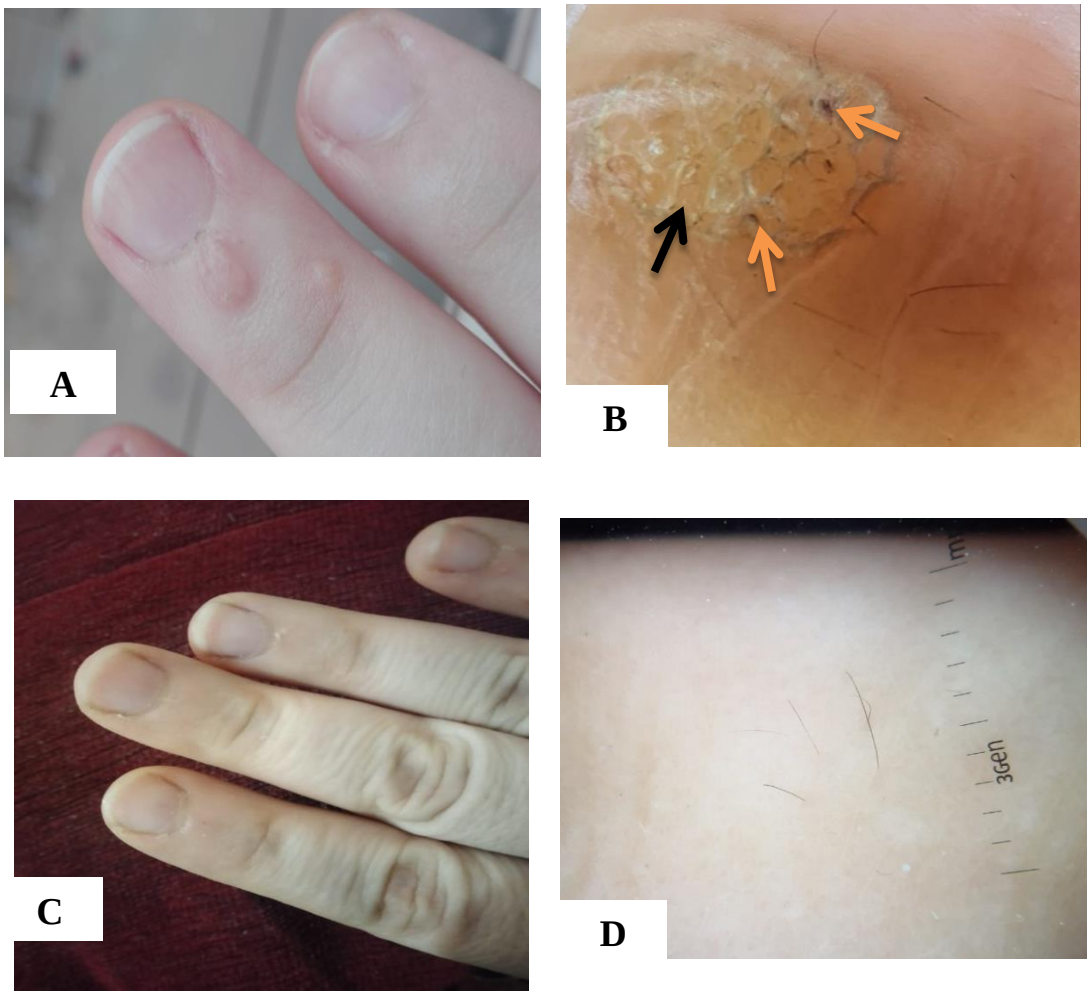

Figure 6:

(A) Multiple common warts in right hand of 40 years female patient before treatment.

(B) Dermoscopy: showing papillomatous surface (black arrow); red & black dots (yellow arrow).

(C) Complete resolution after 6 weeks of application of topical 10% KOH.

(D) Dermoscopic photo: showing disappearance of previous findings.

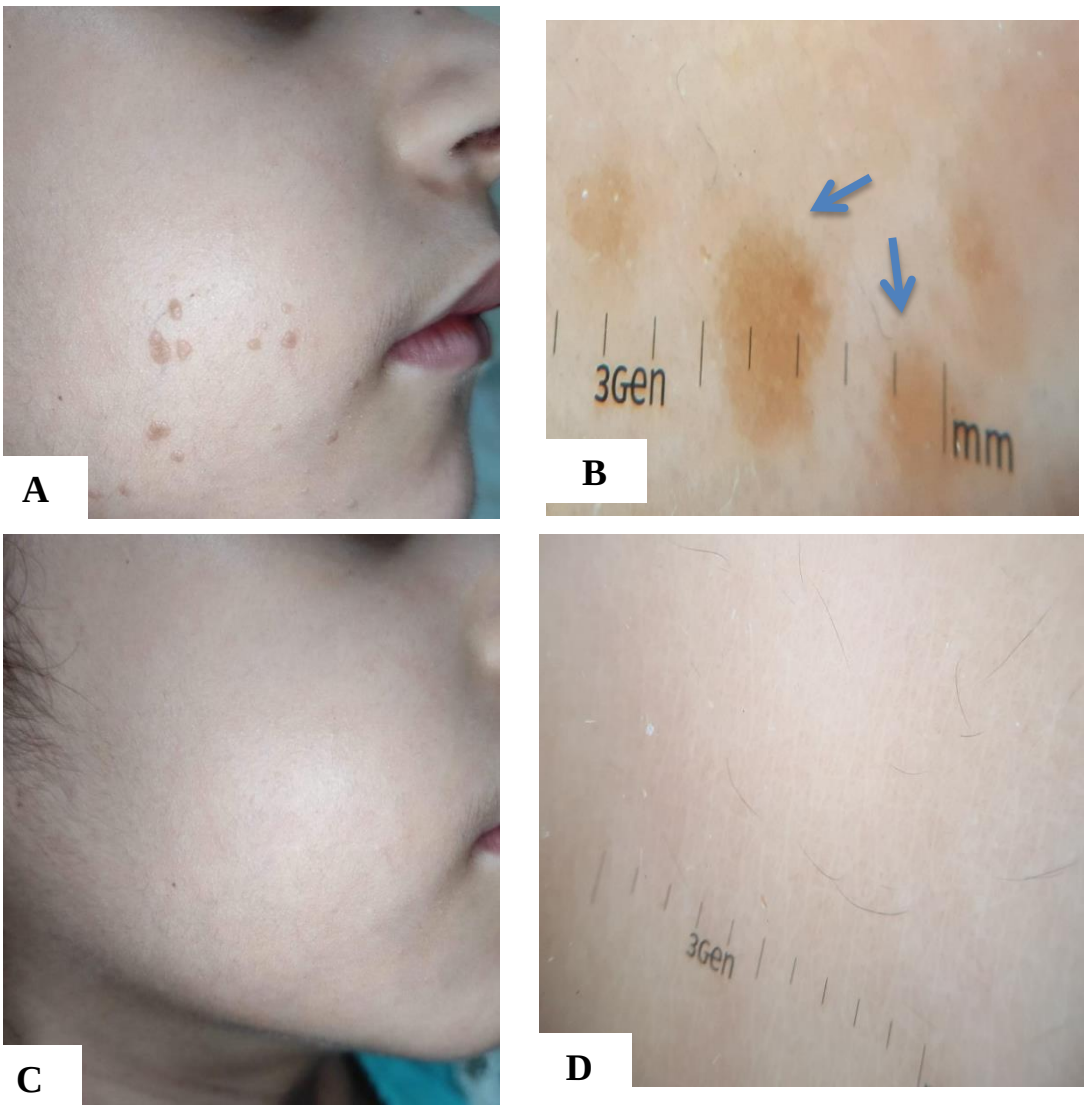

Figure 7:

(A) Multiple plane warts in face of 10 years female patient before treatment.

(B) Dermoscopy: showing brown background (blue arrow).

(C) Complete resolution after 4 weeks of application of topical 10% KOH.

(D) Dermoscopic photo: showing disappearance of previous finding.

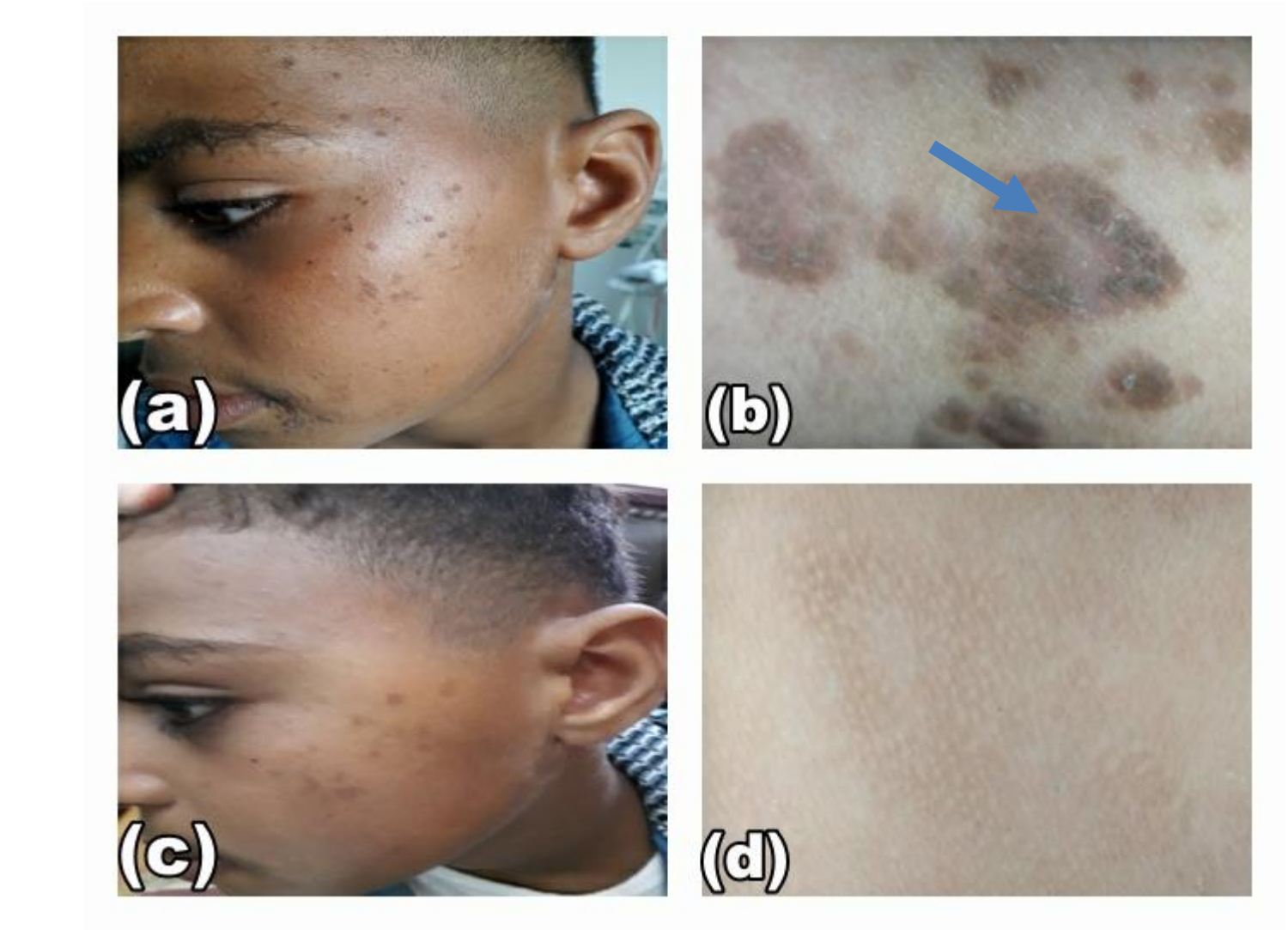

Figure 8:

a. Multiple plane warts in face of 13 years male patient before treatment.
b. Dermoscopy: showing brown background (blue arrow).
c. Complete resolution after 3 sessions of IL vitamin D (there are scars of previous aplative procedures).
d. Dermoscopic photo: showing disappearance of previous finding.