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Intralesional Injection of Mumps, Measles, and Rubella Vaccine, Bleomycin, and Vitamin D3 in Warts Treatment

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Abstract

Objectives: **To compare the therapeutic efficacy of intralesional mumps, measles, and rubella (MMR) vaccination, vitamin D3 (VitD3), and bleomycin injection in patients with warts.**

Background: **With good outcomes, common warts have been treated with immunotherapy using intralesional antigens or vaccinations. It might result in resolution without any outward signs of deterioration or scarring and boost the host's defenses against the agent that caused the problem.**

Methods: **This study involved 84 wart patients in Benha University Hospitals, Egypt. All study participants gave their consent after being informed. MMR, bleomycin, and VitD3 were injected intralesionally to treat warts, whereas normal saline was injected intralesionally in control patients. Patients were followed every session for the size of the mother wart to record the effect of therapy.**

Results: **Comparing the response of mother wart at the last follow-up after MMR, vitD3, or bleomycin injection versus the control group revealed a significantly better response in each modality compared to control groups ($P < 0.001$ for each). However, regarding the response of the mother wart following MMR and vitD3 injection ($P = 0.965$), MMR and bleomycin injection ($P = 0.716$), and vitD3 and bleomycin injection ($P = 0.855$), no significant differences were discovered.**

Conclusion: **MMR, VitD3, or bleomycin injection showed a significantly better response of mother warts or other distant warts than control. When injecting mother warts, intralesional vitD3 provided the best therapeutic response in distant warts, followed by MMR and bleomycin. In comparison, MMR was the most efficient for treating mother warts, followed by vitamin D3 and bleomycin.**

Keywords: Bleomycin, Intralesional, MMR, Vitamin D3, Warts

1. Introduction

Warts are caused by the human papillomavirus (HPV), which is a common viral infection of the skin and mucous membranes. Warts are prevalent worldwide, with an estimated incidence of 7−10% in the European population and 1% in the U.S. population [1], with an estimated prevalence in Egypt (2.92%) [2]. Over 200 types of HPV have been fully recognized and assigned into three genera: Alphapapillomavirus, Betapapillomavirus, and Gammapapillomavirus [3]. Warts' appearance depends on the type of virus and the site of infection. Most common warts are found on the hands and look like rough papules the same color as the skin [4].

With promising results, intralesional immunotherapy using antigens or vaccinations has been tested to treat common warts. In addition to enhancing the host reaction against the causal agent, it could lead to resolution without causing any physical alterations or scarring [5].

Vaccinations for HPV have considerably decreased genital wart and cervical neoplasia

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incidence, but they do not target genotypes peculiar to other cutaneous locations [6]. Mumps, measles, and rubella vaccine (MMR) immunotherapy may utilize the immune system's ability to recognize viral antigens to induce a delayed-type hypersensitivity reaction against HPV, enhancing the immune system's ability to identify and eliminate HPV. As a result, the immune response is triggered, clearing both locally treated lesions and all other lesions on distant body sites [7].

When used topically, VitD3 modulates epidermal cell proliferation and participates in the production of antimicrobial peptides [7]. Bleomycin can treat viral warts because it possesses anticancer, antibacterial, and antiviral properties that may be connected to its capacity to suppress protein and DNA production [8].

The aim of this study was to compare the therapeutic efficacy of intralesional injections of MMR vaccine, VitD3, and bleomycin in patients with warts.

2. Methods

This case–control comparative study comprised 84 participants of both sexes, diagnosed clinically with warts, recruited from the outpatient clinic of the Dermatology and Andrology Department of Benha University Hospital from June 2019 to January 2020. Before beginning the study, approval from the Department of Dermatology, Venereology, and Andrology and the Ethics Committee at the Faculty of Medicine at Benha University was obtained **(MS-21-5-2019)**. All participants in this study gave their written consent after being fully informed.

This study included 64 patients complaining of viral warts (different types and sites were included). Patients were categorized into three groups. We included 20 individuals as a control group suffering from viral warts (different types and sites were included). This control group was age and sex-matched with three patient groups.

The following exclusion criterion was used for all subjects: history of renal diseases, liver diseases, any other dermatological diseases, and those on systemic or topical therapy for more than one month before the start of the study [9].

The following was applied to every individual. History taking included age, sex, duration, course, family history, previous treatments, response to previous treatments, and associated autoimmune or allergic diseases. A general examination was done to exclude systemic diseases. Complete dermatological examination of viral warts to determine the severity of warts.

The individuals were classified into four groups: Group (A) formed of 18 patients injected intralesionally with MMR vaccine into the base of the wart. Eight patients were injected with 0.2 ml in the mother wart only (the largest or that appears first) using a 0.30 mm (30G) x 8 mm insulin syringe (A1), and the other ten patients were injected in all warts with a maximum of 0.5 ml of MMR (A2) in each session. Injections were given every two weeks for up to four times [10]. Group (B) formed of 20 patients injected intralesionally with VitD3 (200,000 IU) solution into the base of the wart. Ten patients were injected only with 0.2 ml in the mother wart only using a 0.30 mm (30 G) x 8 mm insulin syringe (B1), and the other ten patients were injected in all warts with a maximum 2 ml of VitD3 (B2) in each session. Injections were administered every two weeks for no more than four sessions [11].

Group (C) included 26 patients injected intralesionally with bleomycin into the base of the wart. Vials containing 15 mg of bleomycin powder are available for injection. It was initially diluted with 5 ml of distilled water to make the stock solution, which can be kept at 4–8 °C for 60 days. A 0.30 mm (30G) x8mm insulin syringe was loaded with two parts 2% lignocaine and one part bleomycin stock solution, so that the final concentration became 1 mg/ml. Ten patients were injected only with up to 1 ml in the mother wart only (C1), and the other 16 patients were injected in all warts with a maximum of 2 ml of bleomycin (C2) in each session. Every two weeks, injections were given, with a maximum of two sessions [12]. The Control group included 20 patients injected intralesionally with normal saline into the base of warts.

All patients were followed every session for the size of the mother wart and up to 2 months from the last injection. Treatment responses were divided into three, 'no response', 'partial response', and 'complete response'. Of note, 'no response' was defined as absolutely no improvement with injections, 'partial response' as a noticeable improvement but not full clearance, and 'complete response' as total clearance of the wart [11].

2.1. Statistical analysis

Key findings were recorded and analyzed using appropriate statistical tools and the software computer program Statistical Package for the Social Sciences (SPSS) (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Kolmogorov Simonov's test was done to test the normality of data distribution. Descriptive statistics

included median and range for numerical data and frequency and percentage of non-numerical data. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Chi–Square test was used to examine the relationship between two qualitative variables.

Regression analysis: Logistic and ordinal regression analyses were used for prediction of risk factors, using generalized linear models. Odds ratio and 95% confidence interval were calculated. Odds ratios are used to determine whether a particular exposure is a risk factor for a particular outcome, OR = 1 Exposure does not affect the outcome, OR>1 Exposure associated with higher risk of outcome; OR<1 Exposure associated with lower risk of outcome.

All tests were 2-sided, and A *P*-value of 0.05 or less was regarded as statistically significant.

3. Results

The current study included 84 warts patients. Their median age was 22 years, and it ranged from 6 to 62 years. They were 33 children (39.3%) and 51 adults (60.7%). They included 29 males (34.5%) and 55 females (65.5%). All patients had gradual onset and progressive course. The median disease duration was one year, ranging from 0.2 to 56 years. Only 2 cases received previous treatment, with no response to treatment. Past history was positive in 19%, and family history was positive in 11.9% of cases.

The most common type was common warts (29.8%), 14.3% had palmer type, and 34.5% had planter type. Mother wart was on the hand in 50% and foot in 39.3%. The lesion's mean size (the greatest diameter) of the mother wart was 10.9 mm and ranged from 1 to 60 mm. The median number of warts in studied cases was five, ranging from 1 to 30 lesions; 64.3% of patients had less than five warts, 35.7% of subjects had more than five warts, and 40.5% were solitary. Most of the warts were on the hands and feet (visible sites), so patients complained of just cosmetic deformity. The pain was the complaint mainly in the plantar wart type.

There were no observable discrepancies in the studied groups' age or gender ($P > 0.05$ for each).

Comparing the response of mother wart at the last follow-up (Figs. 1–3): Regarding the response obtained after MMR, vitD3 or bleomycin injection compared to the control group revealed significantly better response in each modality compared to control groups ($P < 0.001$ for each). However, no significant variations were found regarding the response of mother warts after MMR and vitD3 injection ($P = 0.965$), MMR and bleomycin injection ($P = 0.716$), vitD3, and bleomycin injection ($P = 0.855$) (Table 1).

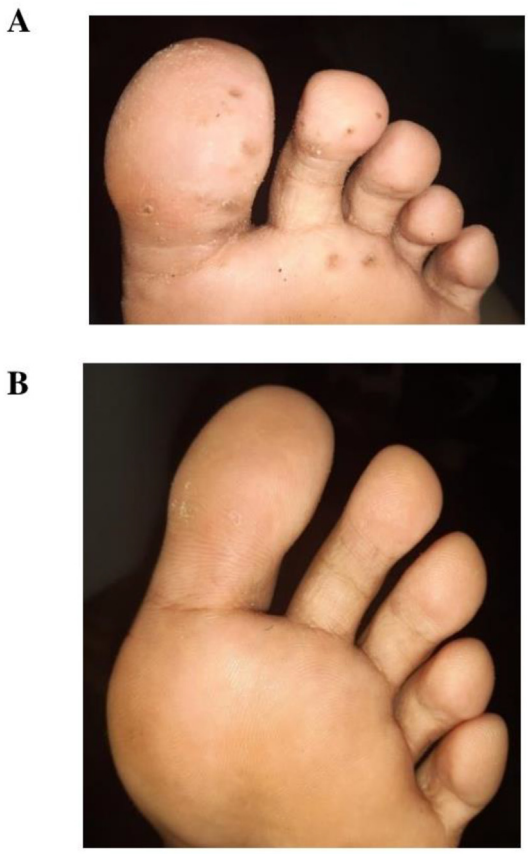

Fig. 1. Planter warts response to intralesional Vitamin D3 (A: before therapy, B: after 3 sessions of intralesional injection of the largest mother lesion). Complete improvement of all wart lesions is noted.

Comparing the response of warts other than mother warts at the last follow-up (Figs. 4–6): Regarding the response obtained after MMR, vitD3 or bleomycin injection compared to the control group revealed significantly better response in each modality compared to control groups ($P < 0.001$ for each). However, no significant differences were found regarding the response of warts other than mother warts after MMR and vitD3 injection ($P = 0.487$) and MMR and bleomycin injection ($P = 0.071$). A significant difference was found regarding the response of warts other than mother warts after vitD3 and bleomycin injection ($P = 0.01$) (Table 2).

Injection with MMR to all had a marginally significantly better response to warts other than mother wart than MMR injection to mother wart ($P = 0.083$). However, it did not reach a significant level. No significant difference was found regarding the response of warts other than mother warts

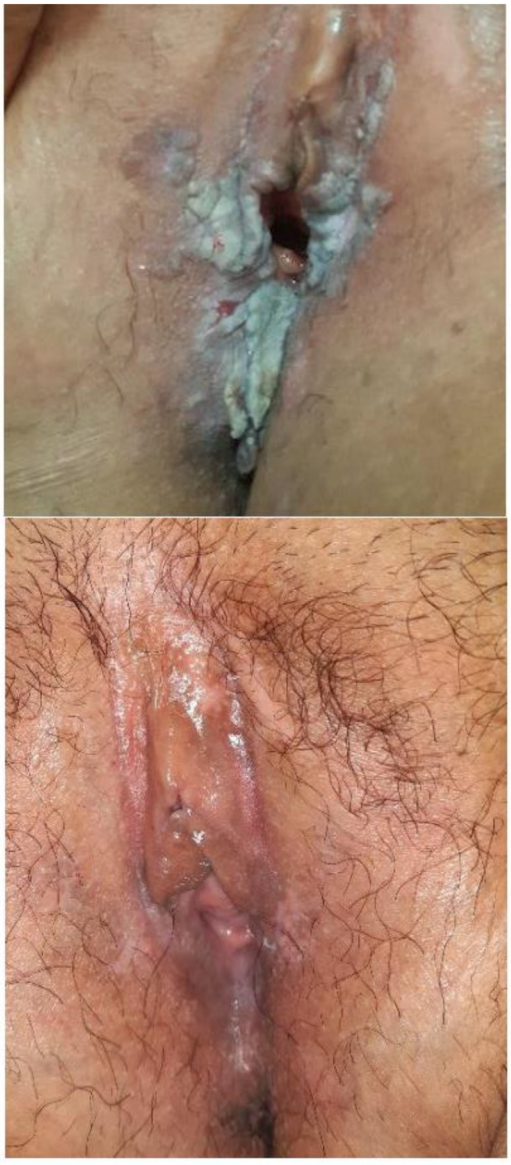

Fig. 2. Anogenital warts response to intralesional MMR vaccine (A: before therapy, B: after one session of intralesional injection of the largest mother lesion). Complete improvement of all wart lesions is noted.

between those injected with vitD3 to all or mother warts ($P = 0.580$). Bleomycin injection to all had a significantly better response to other distant warts when compared to bleomycin injection to mother warts ($P < 0.001$) (Fig. 7).

Response increased gradually through time in all studied cases (n = 64). No significant association was found regarding the response of mother wart to demographic data in all studied case groups. Shorter duration ($P = 0.018$) and smaller size ($P = 0.016$) were significantly associated with a better response. Otherwise, no significant association was found regarding response to type and site of warts in all studied case groups. However, a lower number was significantly associated with a better response ($P = 0.003$). Otherwise, no significant association was found regarding the response of mother warts to features of mother warts in all studied case groups. No significant association was found regarding the

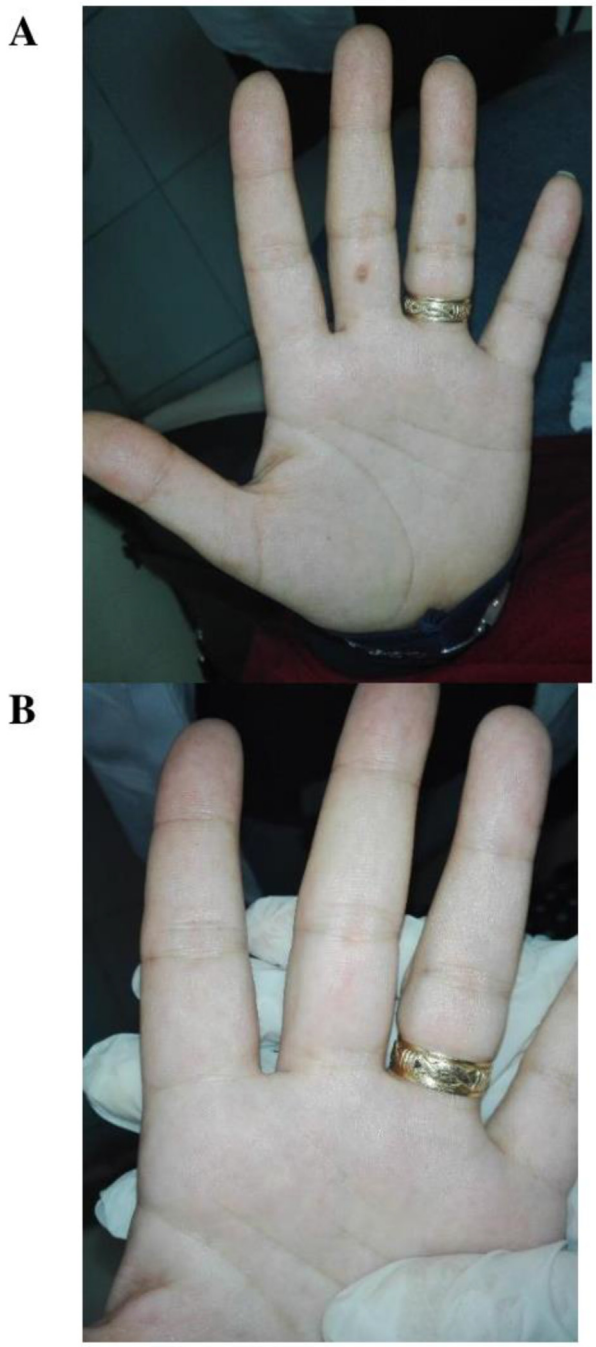

Fig. 3. Palmar warts response to intralesional MMR vaccine (A: before therapy, B: after 4 sessions of intralesional injection of all warts). Complete improvement of the lesions is noted.

Table 1. Comparison of response of mother wart at the last follow-up to various treatment modalities.

	Complete response *N* (%)	Partial response *N* (%)	No response *N* (%)	*P1*	*P2*	*P3*
Control						
N = 20	0 (0%)	0 (0%)	20 (100%)	–	–	–
MMR						
N = 18	14 (77.8%)	3 (16.70%)	1 (5.60%)	<0.001	–	–
VitD3						
N = 20	15 (75%)	4 (20%)	1 (5%)	<0.001	0.965	–
Bleomycin						
N = 26	18 (69.2%)	7 (26.9%)	1 (3.8%)	<0.001	0.716	0.855

*P*1, comparison versus control groups.
*P*2, comparison versus MMR group.
*P*3, comparison versus vitD3 groups.

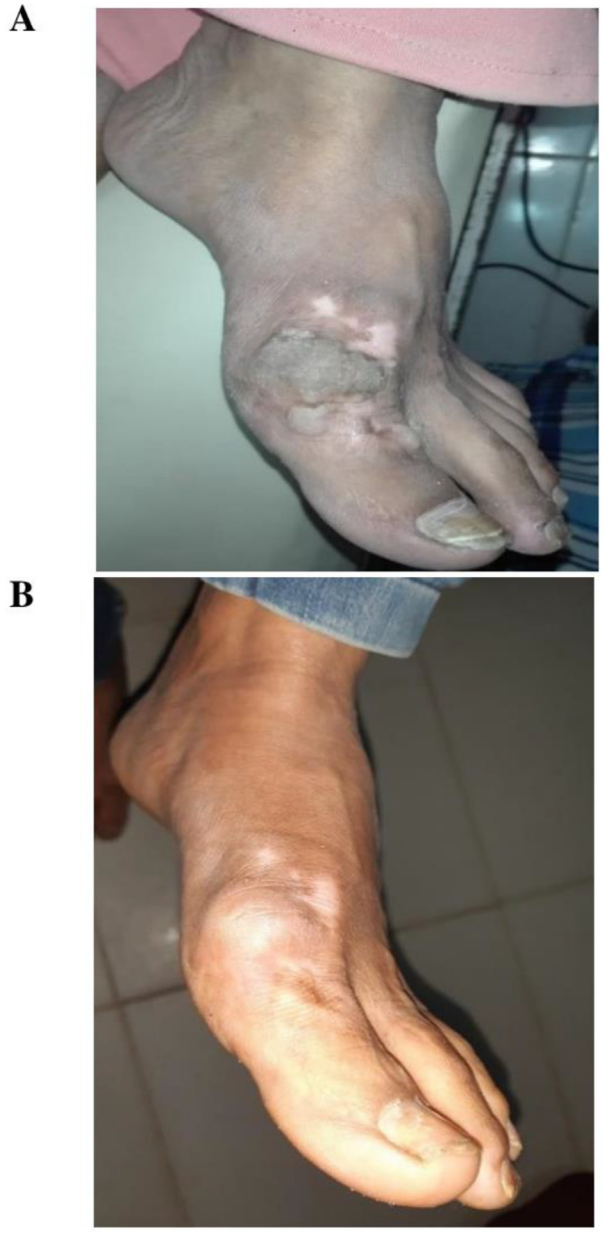

Fig. 4. Common warts response to intralesional Vitamin D3 (A: before therapy, B: after 4 sessions of intralesional injection of all warts). Complete improvement of the lesion injected is noted.

response of mother warts to the history of recurrence in all studied case groups.

A better response to MMR injection was substantially correlated with fewer lesions ($P = 0.041$). Otherwise, no significant association was found

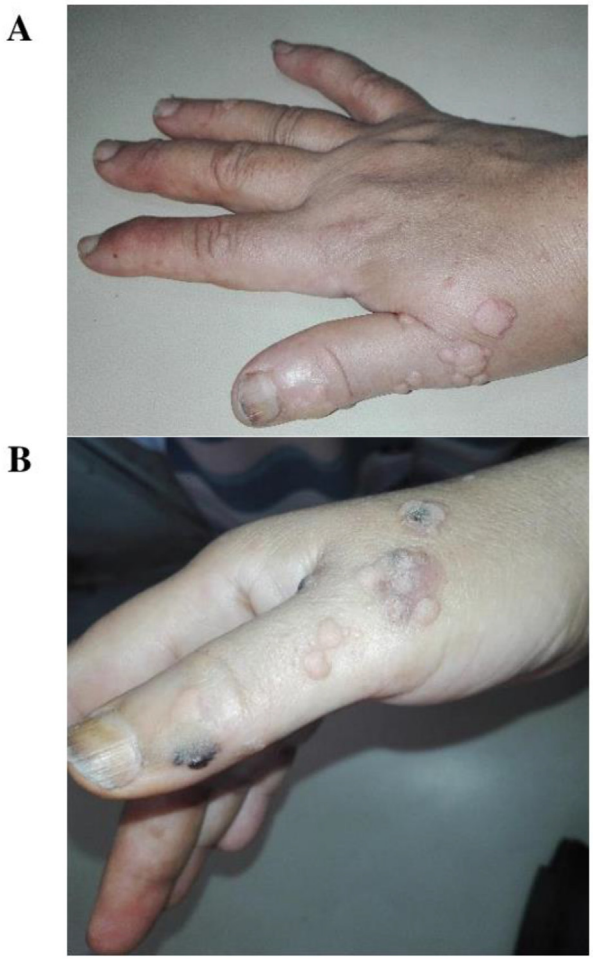

Fig. 5. Common warts response to intralesional bleomycin (A: before therapy, B: after 4 sessions of intralesional injection of the largest mother lesion at the thumb distal phalanx). Partial improvement of the lesion injected is noted, with no significant changes in other distant warts.

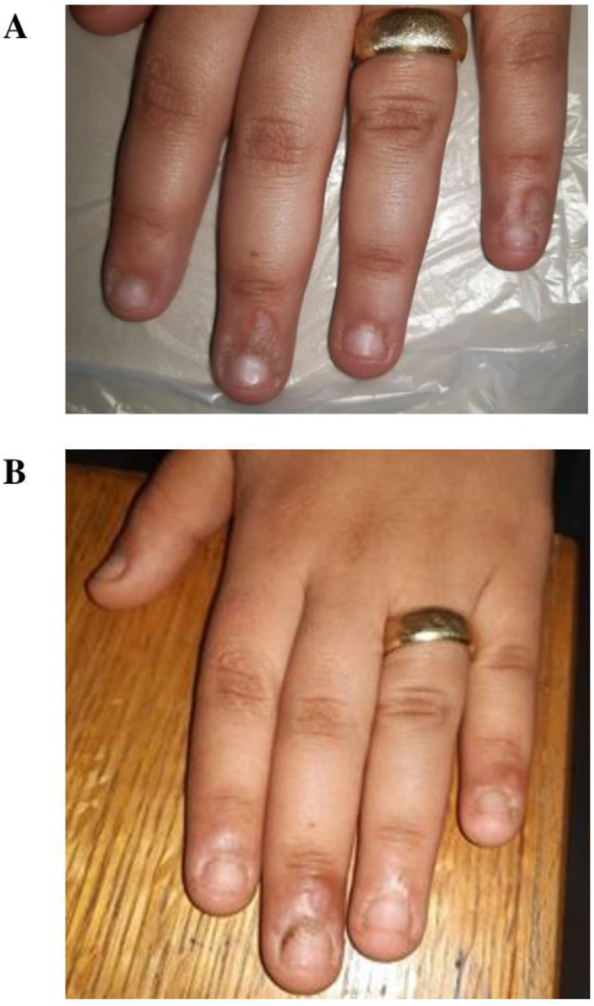

Fig. 6. Periungual warts response to intralesional bleomycin (A: before therapy, B: after one session of intralesional injection of all lesions). Complete improvement of all wart lesions injected is noted.

regarding response to features of mother wart in the MMR group. A better response to vitD3 treatment was considerably associated with a shorter duration ($P = 0.020$). However, no significant correlation has been found between how the mother warts responded and what they looked like in the VitD3 group.

A better reaction to bleomycin injection was positively correlated with a smaller mother wart's baseline size ($P = 0.038$). Otherwise, no significant association was found regarding the response of mother wart to type, location, and duration in the bleomycin group. A lower number ($P = 0.012$) and the absence of callus ($P = 0.041$) were significantly associated with a better response to bleomycin injection. Otherwise, no significant association was found regarding response and wart features in the bleomycin group.

Regression analysis was conducted to predict the worse response of mother warts within all studied cases, using age, gender, recurrence, duration, size, number of primary lesions, MMR, vitD3, and bleomycin injection as covariates. A larger baseline size and a higher number of lesions were associated with worse responses (OR>1). MMR, vitD3, and bleomycin injection were associated with good response (OR<1). The best was MMR, followed by vitD3 and bleomycin (**B** = −1.72, −1.70, −1.65, respectively) (Table 3).

A regression analysis was conducted to predict the poorer response of other distant warts among the participants, using age, gender, recurrence, duration, size, number of primary lesions, MMR, vitD3, and bleomycin injection as covariates. MMR, vitD3, and bleomycin injection were associated with good response (OR<1). The best was vitD3, followed by MMR and bleomycin (**B** = −1.5, −1.28, −1.11, respectively) (Table 4).

4. Discussion

Verrucae, often known as warts, are benign epidermal proliferations of the skin and mucosa produced by HPV [13]. Traditional treatments for warts include cryotherapy, electrocoagulation, salicylic acid, 5-fluorouracil, and laser surgery. None of

Table 2. Comparison of response of warts other than mother wart to various treatment modalities.

	Complete response *N* (%)	Partial response *N* (%)	No response *N* (%)	*P1*	*P2*	*P3*
Control						
N = 20	0 (0%)	0 (0%)	20 (100%)	–	–	–
MMR						
N = 18	8 (44.4%)	7 (38.9%)	3 (16.7%)	<0.001	–	–
VitD3						
N = 20	11 (55%)	8 (40%)	1 (5%)	<0.001	0.487	–
Bleomycin						
N = 26	13 (50%)	3 (11.5%)	10 (38.5%)	<0.001	0.071	0.010

P1, comparison versus control groups.
P2, comparison versus MMR group.
P3, comparison versus vitD3 groups.

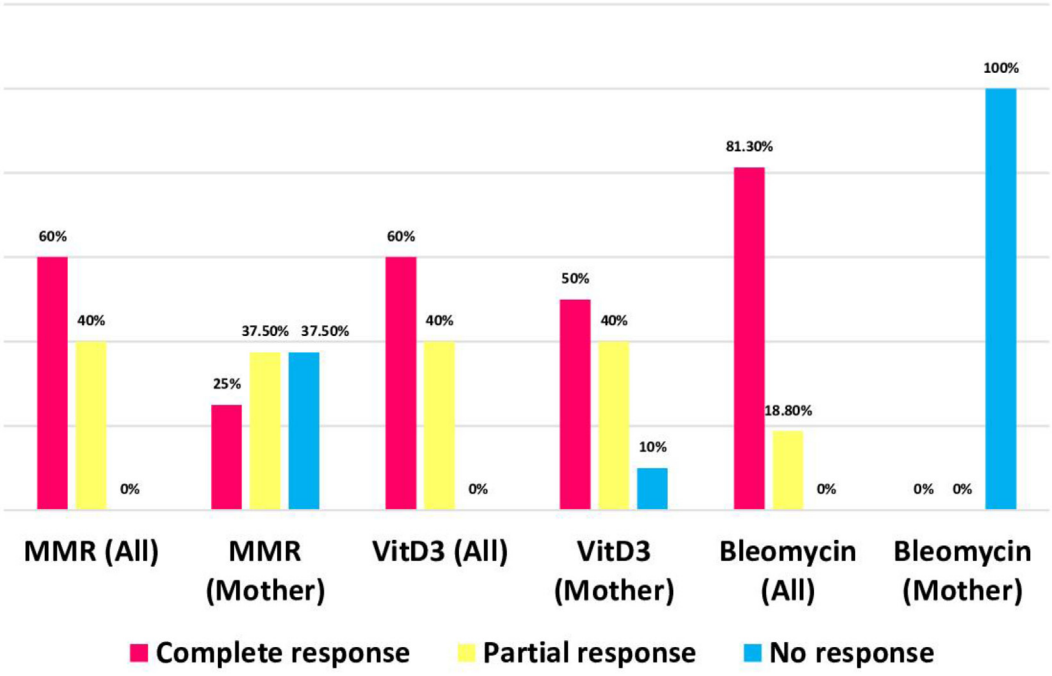

Fig. 7. Response of warts other than mother wart among those injected with MMR, vitD3, bleomycin.

these treatments is considered the gold standard because they can all be uncomfortable, expensive, or time-consuming [14].

Destructive treatments are ineffective for treating numerous recalcitrant warts because they only eliminate the lesions that have been treated. Therefore, immunotherapy is being thoroughly investigated for the treatment of warts to overcome these drawbacks. In addition, it boosts cell-mediated immunity for wart eradication. MMR, tuberculin purified protein derivative (PPD), and Candida antigen have been investigated [15].

Previous studies [16,17] showed the efficacy of topical VitD3 derivatives in treating warts. **Aktas *et al.*** [18] tested intralesional VitD3 injection for plantar warts with positive outcomes.

As a possible result of its capacity to bind to deoxyribonucleic acid (DNA), bleomycin causes the scission and removal of pyrimidine and purine bases, which in turn may be associated with its effectiveness against tumors, bacteria, and viruses [12].

This study compared MMR vaccine, VitD3, and bleomycin intralesional injections in wart patients. The current results were similar to a study [12] that found 157 wart lesions in 50 individuals, 27 men and 23 females, with mean ages of 26.1 years and 29.2 years, respectively. Another study [18] also agreed with the current findings and comprised 20 patients who got injections of VitD3 with an average age of 28.6 years.

In the present study, we found that most warts don't produce any symptoms. However, they can

Table 3. Regression analysis for prediction of worse response of mother wart.

	P	OR	95% CI	
Age	0.920	0.999	0.986	1.012
Sex	0.178	1.462	0.841	2.541
Recurrent	0.195	0.559	0.283	1.105
Duration	0.302	0.979	0.942	1.019
Size	0.008	1.035	1.009	1.062
Number	0.040	1.242	1.095	1.791
MMR	<0.001	0.179	0.131	0.243
VitD3	<0.001	0.183	0.135	0.247
Bleomycin	<0.001	0.191	0.144	0.254

CI, confidence interval; OR, odds ratio.

Table 4. Regression analysis for prediction of worse response of warts other than mother wart.

	P	OR	95% CI	
Age	0.699	0.998	0.985	1.010
Sex	0.340	1.287	0.767	2.157
Recurrent	0.124	1.485	0.259	1.909
Duration	0.110	0.968	0.930	1.007
Size	0.172	1.023	0.998	1.049
Number	0.124	1.039	0.990	1.090
MMR	<0.001	0.279	0.180	0.431
VitD3	<0.001	0.223	0.146	0.341
Bleomycin	<0.001	0.328	0.220	0.488

CI, confidence interval; OR, odds ratio.

result in localized pain and cosmetic deformity. It is possible that the compression and friction caused by plantar warts may result in bleeding, which can be highly uncomfortable. Large plantar warts may even make it difficult for the patient to walk and wear shoes [19].

Similar results on the duration of warts ranging from 1 month to 96 months, with an average of 6 months, were reported by **Kavya** *et al.* [20]. Another study [21] observed that the average disease duration was 6.7 months, with the majority of patients (76%) showing a disease duration of less than one year, which is somewhat different from the current findings regarding disease duration.

However, **Öztekin** *et al.* [22] verified that the average duration of common warts was Twelve (ranging from four to eighteen) years as their study was conducted only on genital warts with relatively longer duration.

Regarding the comparison between responses obtained after MMR, VitD3 or bleomycin injection compared to the control group, the current findings revealed significantly better response in each modality compared to control groups, either for mother wart or all other distant wart injection.

Complete remission was attained in 77.8% of patients for the MMR group, partial remission in 16.7% of cases, and no response in the control patients. These results matched the results of a study [23] which reported that the MMR vaccine significantly impacted how common warts responded to treatment, with about 80% of cases showing a full recovery. Another study [24] also revealed similar results; on the second visit, approximately 87.5 percent of patients who received the MMR vaccine had a relatively complete response, as opposed to 68 percent of control patients who received normal saline injections.

Saini *et al.* [25] observed complete and partial clearance of wart lesions (67.4%) with MMR injection into mother warts, which also aligns with current findings. A significant difference was observed between the two groups in another study [26] in which 72 people received the MMR injection, and 50 people received normal saline injections. There was a complete response in 68% of individuals treated with MMR, whereas only 10% of patients in the control group had a response.

According to the current data, the VitD3 group experienced a full recovery in 75% of patients, a partial recovery in 20% of patients, and no recovery in all control patients. **Wananukul** *et al.* [27] found comparable results in distant location warts, reporting complete clearance in 93% of patients with response rates of 87%.

Aktas *et al.* [18] employed intralesional VitD3 to treat plantar warts, which is consistent with the current finding. At the end of 8 weeks, they reported full clearance in 80% of the patients. According to their results, intralesional VitD3 is as effective as intralesional MMR treatments and is superior to intralesional PPD, bleomycin, and Candida antigen treatments. Also, in line with the current findings, **Kavya** *et al.* [20] noted a complete response in 78.6% of patients after VitD3 injection for wart lesions.

Singh *et al.* [21] discovered the complete elimination of warts at anatomically remote locations concurrent with the clearance of the injected wart by VitD3. So, the immune response is not restricted just to the place where the injection was given.

The findings of the bleomycin group showed complete response in 69.2% of cases, compared to no response in all control patients. The cure rate for palmoplantar warts in another study [28] was reported to be 87% after bleomycin injection, which is lower than the 96% found by **Soni** *et al.* [12].

The current study revealed no significant differences regarding the response of other distant warts after MMR and VitD3 injection, MMR and bleomycin injection. However, the VitD3 injection showed a significantly better response of other distant warts when compared to the bleomycin injection.

No correlation between mother wart response and duration, kind, site, or size in the MMR group was seen in the current investigation. However, a better response to MMR injection was also substantially correlated with fewer lesions.

Compared to the results of **Awal and Kaur** [26], a clinical response based on the type of warts was also detected in the MMR injection group. Palmoplantar warts exhibited the best response, followed by common warts with the subsequent best response. After five injections, complete eradication was observed in 70% of palmoplantar warts and 68% of common warts. The authors highlighted that more patients in their study suffering from plantar warts led to a better response being shown in this particular type [26].

Meanwhile, the current study demonstrated that a smaller baseline size of mother warts was significantly associated with a better response to bleomycin injection. Otherwise, no significant association was found regarding the response of mother wart to type, location and duration in the bleomycin group. The current study also discovered that a better response to bleomycin injection was substantially associated with lower numbers as well as a lack of callus.

The study, on the hand, revealed that a superior response to VitD3 injection was considerably associated with a shorter duration. Otherwise, no significant association was found regarding the response of mother wart to type, site, and size in the VitD3 group.

Larger baseline sizes and more lesions were linked to worse responses regarding mother wart response among all patients investigated. MMR, vitamin D3, and bleomycin injection were additionally associated with good response. MMR showed the best response of mother warts, followed by vitD3 and bleomycin. Vitamin D3 had the best response for all other distant warts, followed by MMR and bleomycin.

The lack of histopathological evidence was one of the limitations of the current study, and it is recommended in the future to perform large-scale comparative studies, including histological examination of the lesions before and after therapy.

4.1. Conclusion

Mother warts and other distant warts responded much better to MMR, VitD3, or bleomycin injection than the control group, with no discernible difference. When injecting mother warts, intralesional vitD3 provided the best therapeutic response in distant warts, followed by MMR and bleomycin. In comparison, MMR was the most efficient for treating mother warts, followed by vitamin D3 and bleomycin.

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Conflicts of interest

The authors have no conflict of interest to declare.

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