

# Comparison of efficacy of intralesional methotrexate and Vitamin D3 injections in the treatment of common wart

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**Received:** 6 February 2023      **Accepted:** 28 April 2023

**Citation:** Hussein HI, Qurtas DS, Yaaqub PY (2023) Comparison of efficacy of intralesional methotrexate and Vitamin D3 injections in the treatment of common wart. *History of Medicine* 9(1): 2057–2061. <https://doi.org/10.17720/2409-5834.v9.1.2023.266>

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## Abstract

**Background:** Wart is a common disease caused by infection with human papillomavirus; there are many modalities for treatment, where most of them resolve wart with many side effects as scars and recurrence. **Patients and Methods:** A Hospital based prospective interventional study was conducted from December 2021 to December 2022 among patients with cutaneous warts attending Erbil Dermatology Teaching centre. A detailed history was recorded and thorough physical examination was done. Clinical photographs were taken before and during each visit. Methotrexate and vitamin D3 were injected intralesionally at the base of warts for each group after applying topical anaesthesia. The injections were repeated at 2 weekly intervals until complete clearance or for a maximum of 4 injections. Patients were followed up for a maximum period of 4 months. **Results:** complete clearance of the target injected warts occurred in 40% of patients in cases methotrexate group while it occurred only in 5% of patients in vitamin group ( $P=0.2965$ ) that was no significant difference between two therapeutic treatments. Our result represented adverse events were local reactions in the form of swelling and pain in both groups. **Conclusion:** Comparing the therapeutic effects of intralesional MTX injection with vitamin D3 in the treatment of common warts, there was no statistically significant difference.

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## Keywords

Common Warts, Methotrexate, Vitamin D3, Adverse Effect.

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Warts are common epidermal growths caused by various strains of human papillomavirus (HPV) afflicting all age groups. They have an unsightly appearance and are mostly asymptomatic but sometimes may be painful, as in the case of palmoplantar warts (1). The virus initially targets the basal cells and undergoes a latent phase of slow replication. As the epidermis grows superficially, the virus induces hyperplasia and hyperkeratosis(2) and leading to the maturation of viral particles in the granular cell layer. Meanwhile the viral particles are released with exfoliation of the verruca, causing spread to other regions (3).

Two therapeutic options of warts are commonly used: the first is the destructive method such as chemical cautery, cryotherapy, and electrocautery, and the second is immunotherapy, which is based on the activation of the immune system (4). Immunotherapy could lead to resolution without any physical changes or scarring and in addition would augment the host response against the causative agent (5, 6).

The pharmacological rationale of the use of methotrexate is to inhibit DNA synthesis in actively dividing cells (7, 8). Antiviral effect of methotrexate was observed in the treatment of viruses infected cells

explaining the antiviral effect of it through inhibition of dihydrofolate reductase (9, 10).

Topical and intralesional vitamin D<sub>3</sub> have been tried for treating warts with variable degree of success (11, 12, 13), vitamin D is a group of fat-soluble sterosteroid responsible for enhancing intestinal absorption of calcium, magnesium, and phosphate, and has multiple other biological effects (1). In humans, the important compounds in this group are vitamin D<sub>3</sub> (also known as cholecalciferol) (13) and vitamin D<sub>2</sub> (ergocalciferol) (3, 14). Vitamin D controls cell proliferation and differentiation and has immunoregulatory activities. Its effects are mediated via the vitamin D receptor, which is present in keratinocytes, melanocytes, fibroblasts, and immune system cells of the skin (15, 16). The aim of the study is to measure the effectiveness of international vitamin D<sub>3</sub> in comparison to intralesional methotrexate in management of common wart.

## Patients and Methods

A comparative interventional study is done from December 2021 to December 2022. A total of 60 cases presenting with common warts are recruited from patients attending to the Erbil Dermatology Teaching Center (EDTC) in Erbil city, Kurdistan Region-Iraq. Patients with cutaneous wart aged between 10-60 years included in the study. Twenty two of them were male and 38 patients were females.

Complete medical history, general and dermatological examination, identifying location, number, size and type of warts, taking photos for the lesions at first visit and follow up visits. Patients who are currently on other treatment modality of common wart, those who are allergic to vitamin D<sub>3</sub> or methotrexate, immunocompromised patients, patients with liver disease or renal dysfunction, pregnant and breast-feeding women excluded from study.

**Table 1:** Demographic data of Intralesional methotrexate and Vitamin D3 related to common wart

Variables		All patients with wart		Group A (intralesional MTX) n=30		Group B (intralesional Vitamin D3) n=30		P Value
		No.	%	No.	%	No.	%	
Age	10-20 years	22	36.67	8	26.67	14	46.67	0.1334
	21-30 years	17	28.33	8	26.67	9	30.00	
	> 30 years	21	35.00	14	46.67	7	23.33	
Gender	Male	22	36.67	7	23.33	15	50.00	0.0596
	Female	38	63.33	23	76.67	15	50.00	
Economic status	Poor	16	26.67	7	23.33	9	30.00	0.8256
	Moderate	30	50.00	16	53.33	14	46.67	
	Good	14	23.33	7	23.33	7	23.33	
Address	Inside the city	51	85.00	29	96.67	22	73.33	0.0257
	Outside the city	9	15.00	1	3.33	8	26.67	
occupation	Student	23	38.33	8	26.67	15	50.00	0.1293
	Housewife	10	16.67	4	13.33	6	20.00	
	Employed	23	38.33	15	50.00	8	26.67	
	Not employed	4	6.67	3	10.00	1	3.33	

Regarding physical characteristic of the common wart in both group which was shown in table 2 there

The patients were randomly divided into two groups; group A: consisted of 30 patients, subjected to intralesional injection of methotrexate; 0.1-0.3ml (50mg/5ml) of methotrexate vial was slowly injected in to the base of the oldest and almost largest wart (Mother Wart). This injection is done by using a 30-gauge insulin syringe. In group B, consisted of 30 patients; subjected to intralesional injection of vitamin D<sub>3</sub> (300000IU/1ml), about 0.2-0.5ml was injected applying the same principles of methotrexate injection. A maximum of 5 warts was treated per patient in 1 session.

Follow-up of patients was done every 2 weeks for a period of 2 months to detect any recurrence and to assess the clinical response by recording any decrease in size and number of warts as follows: complete response 100% clearance of warts, moderate response between 50%-100% clearance of warts, mild response less than 50% clearance of wart, and no response when no lesion cured. As well as at each visit, adverse reactions were recorded.

The study's findings were evaluated statistically using graph pad. Data were expressed as median, number and percentage. Chi-square test was used to analyse categorical variables. P value < 0.05 was significant.

## Results

This comparative study contains 60 cases, which were divided to two therapy groups. Clinical data of the patients regarding age, sex, economic status, address and occupation were displayed in table 1. There was no significant difference in age among both study groups (p=0.1334) There was no significant difference in other parameters between both groups.

was no significant difference found between the study groups (p=0.2061).

**Table 2:** Prevalence of wart according to the site and number

Variables		Total No. of patients	Percentage (%)	Intralesional methotrexate	Percentage (%)	Intralesional Vitamin D3	Percentage (%)	P Value
Type of wart present	Common	39	65.00	23	76.67	16	53.33	0.0843
Number of Warts	1-3	33	55.00	18	60.00	15	50.00	0.6172
	4-6	13	21.67	5	16.67	8	26.67	
	>7	14	23.33	7	23.33	7	23.33	
Average size of common warts	1-5 mm	39	65.00	11	36.67	28	93.33	<0.0001
	6-10 mm	8	13.33	6	20.00	2	6.67	
	11-15 mm	4	6.67	4	13.33	0	0.00	
	> 16 mm	9	15.00	9	30.00	0	0.00	
Site of common Warts	Hand	21	35.00	16	53.33	5	16.67	0.02
	Foot	19	31.67	7	23.33	12	40.00	
	trunk	15	25.00	6	20.00	9	30.00	
	extremity	2	3.33	0	0.00	2	6.67	
	head	2	3.33	0	0.00	2	6.67	
Duration of warts	1- 12 Months	42	70.00	23	76.67	19	63.33	0.3714
	13- 24 Months	8	13.33	4	13.33	4	13.33	
	>25 months	10	16.67	3	10.00	7	23.33	
Previous treatment received	No	25	41.67	14	46.67	11	36.67	0.2864
	Tropical	19	31.67	10	33.33	9	30.00	
	Cryotherapy	6	10.00	1	3.33	5	16.67	
	Surgical	5	8.33	3	10.00	2	6.67	
	Home therapy	6	10.00	2	6.67	4	13.33	

Regarding the response of common wart in our study show that the methotrexate receiving group cases who has achieved complete response 12 (40%), 8 (26.67%) moderate response and 5 (16.67%) mild response but 5 (16.67%) has no responses (figure1). Furthermore, regarding those receiving vitamin D<sub>3</sub> intralesional injection, has 5 (16.67%) cases achieve complete response (figure 2), 11 (36.67%) cases moderate response and 12 (40%) mild response. These results indicates no

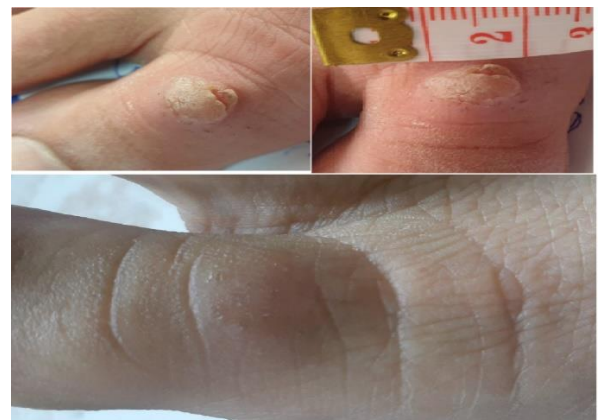
significant difference between groups (p value = 0.2965). Generally, the adverse effects were seen in 21 (21.67%) patients. The adverse effects included pain, swelling and redness. Pain at the site of injection was the most common adverse effect seen in all cases of intralesional methotrexate injection and whereas who received vitamin D<sub>3</sub> intralesionally, only 70% had pain. Figure 1 and 2 showing the improvement of the wart in both groups.

**Table 3:** Clinical response and adverse effects of Intralesional methotrexate and Vitamin D3 for treatment of common wart

Variables		Group A: patients received IL methotrexate (N=30)	Group B: patients received IL Vitamin D3 (N=30)	p Value
Clinical response	no response	5 (16.7%)	2 (6.7%)	0.2965
	mild	5 (16.7%)	12 (40%)	
	moderate	8 (26.7%)	11 (36.7%)	
	complete	12 (40%)	5 (16.7%)	
adverse effect	no adverse effects	0 (0%)	3 (10%)	0.7331
	Pain	30 (100%)	21 (70%)	
	swelling	7 (23.3%)	14 (46.7%)	
	redness	18 (60%)	18 (60%)	



**Figure 1:** Female patient, 36 years old, with a single plantar wart showed total resolution after 4 sessions of MTX injection



**Figure 2:** Male patient, 24 years old, with a single plantar wart showed total resolution after 4 sessions of D<sub>3</sub> injection

## Discussion

Cutaneous warts are common skin lesions caused by human papillomavirus infection. Treatment is aimed at relieving the patient's physical and psychological discomfort and at preventing the spread of infection by autoinoculation. Among the available medical and destructive therapeutic options for cutaneous warts, none is uniformly effective or virucidal. Moreover, in most cases their safety and efficacy has not been assessed (18). A lot of research and medical sources related to the treatment of warts were reviewed (19), and we could not find a study comparable to the current study in comparing the use of methotrexate and vitamin D<sub>3</sub> intralesional in two groups of patients. There was no significant difference were found in demographics and prevalence of wart according to the site and number of the patients in each groups except of residency and size of common warts which are statistically significant difference between both groups. MTX is an anti-proliferative, anti-inflammatory and immunomodulating agent which was approved by the US food and drug administration (FDA) in 1971 (7). MTX is appropriate for rapidly growing tumors since it inhibits DNA synthesis in actively dividing cells. MTX is a folic acid analogue that binds to the dihydrofolate reductase, blocking the formation of tetrahydrofolate and preventing the synthesis of the purine nucleotide thymidine (20). Our study included 60 patients with common warts. 30 patients were injected with MTX in comparison with 30 patients that were injected by vitamin D<sub>3</sub>. In MTX group, 12 patients (40%) showed complete response, 5 (16.67) and 8 (26.67%) patients showed mild and moderate response, respectively. Furthermore, 6 patients (16.67%) showed no response. The result agreed with (21) which showed that, complete clearance of warts was achieved in 2 (10%), 6 (30%), and 7 (35%) patients after 4, 5, and 6 sessions, respectively. Another 8 (40%) patients showed partial improvement after 6 sessions. The response rate did not correlate significantly with the number of warts. As well as, the result disagreed with (10) which revealed that, 2 patients (6.7%) showed complete improvement, 8 patients (26.7%) showed partial improvement and 20 patients (66.7%) showed no improvement.

In second group of present study, we used intralesional vitamin D<sub>3</sub> injections, which is relatively a new treatment option for warts. It is believed that the vitamin D<sub>3</sub> injection into HPV infected tissues induces a strong nonspecific proinflammatory signal and attracts the antigen presenting cells. There is a release of cytokines such as IL-2, IL-8, IL-12, IL-18, tumor necrosis factor,

and interferon gamma. 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 (22). In our study, out of 30 patients with common warts, 5 patients (8.33%) had complete response, 12 (20%) and 11 (18.33%) patients revealed mild and moderate response, respectively. But only 2 cases have no response to vitamin D<sub>3</sub>. The result partially agreed with (14) which revealed that, out of 22 patients 16 patients (72.73%) showed complete response, 5 (22.7%) showed moderate response and 1 patient (4.54%) showed mild response. Furthermore, (23) revealed that, out of 42 patients with multiple warts, 33 (78.57%) patients showed complete response, 6 patients (14.28%) showed moderate response, and three patients (7.14%) showed mild response. (13) which reported complete clearance in 54 (90%) patients, partial response in 4 (6.66%) patients, and no response in 2 (3.33) patients from their study involving 60 patients. (24) Used intralesional vitamin D3 for plantar warts in 20 patients and reported complete clearance in 80% of the patients at the end of 8 weeks.

Regarding efficacy of intralesional methotrexate and vitamin D<sub>3</sub>, there was insignificant difference between both groups ( $P= 0.2965$ ). Furthermore, there was no published study was found to compare the efficacy of MTX with vitamin D<sub>3</sub> on the same patients or the same study group. This research paper was the first to compare the two treatments versus each other. (25) found that common warts on the hands and feet respond worse to intralesional MTX than they do to electrocautery treatment.

Pain is the main problem in both intralesional MTX and vitamin D<sub>3</sub>; analgesia is helpful in both groups. Pain management seems to be easier for MTX and vitamin D<sub>3</sub> and the pain period is the same compared with the pain and discomfort that may continue by other methods which persist for several hours after electrocautery (26). The cost of MTX therapy is less than vitamin D<sub>3</sub> (25, 27). On the other hand, vitamin D<sub>3</sub> is well tolerated with minimal side effects. The common side effects noted were pain and swelling (24).

## Conclusion

In this study, there was larger number of patients (12/30) who received intralesional methotrexate developed a complete clearance of warts, whereas those who received intralesional vitamin D<sub>3</sub> who achieved complete clearance were less (5/30). In spite of aforementioned results, calculation of all categories of the patient responses to both treatment modalities, showed no significant difference

( $p=0.2965$ ). In both groups, patients experienced pain at time of injection, redness and tenderness after the procedures without comparable difference ( $p=0.7331$ ).

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