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Intralesional Methotrexate Versus Curettage and Application of 100% Trichloroacetic Acid in Planter Warts

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ABSTRACT

Background: Human papillomavirus causes warts, which are benign growths on the skin or in the mucosa. Methotrexate (MTX), trichloroacetic acid (TCA) as well as curettage are just a few of the options for treating common warts. **Objective**: To compare the safety and clinical outcome of MTX application versus curettage and TCA (100%) application in managing planter warts.

Subjects and Methods: At Zagazig University's Department of Dermatology, Venerology, and Andrology, Faculty of Medicine, we did a randomized, controlled clinical trial study from September 2021 to February 2022. Ninety individuals between the ages of 18 and 50 who presented with plantar warts at the time of their initial visit were included in the analysis. Two groups of patients were chosen at random. 45 patients were put into the IL-MTX group (MTX). Group TCA consisted of 45 individuals who were treated with (TCA) 100 % needling. **Results:** Number and size of warts were examined before and after treatment, and both groups showed a statistically significant decrease after treatment compared to before treatment. There was slight advantage of TCA therapy over MTX therapy. Also, assessment of number of sessions required to achieve clinical response revealed statistically significant better response with TCA therapy compared to MTX therapy.

Conclusion: Intralesional MTX is the most economically viable option because it is simple to administer and requires no special equipment. Therefore, it may be used as a primary treatment modality in plantar warts in patients where electrosurgery is limited due to the pain.

Keywords: Methotrexate, Curettage, Trichloroacetic acid, Plantar warts.

INTRODUCTION

Warts, which are produced by the human papillomavirus (HPV), are benign growths that can appear on the skin or in the mucosa. There are more than 170 different kinds of HPV now known. Warts can be caused by any HPV, although some HPV strains have a stronger propensity to infect certain areas of skin. Warts can spread through casual or intimate contact, and an impaired epithelial barrier is a risk factor for contracting them [(1)].

Common warts (verruca vulgaris), flat warts (verruca plana), filiform warts (sometimes called genital warts), plantar warts, and genital warts are the clinically recognized forms of warts (condyloma accuminta) [(2)].

In healthy, immune-competent persons, warts are completely harmless and typically go away on their own within a few months to a few years. However, warts on the face and hands carry a heavy social stigma, and those on the soles of the feet and in the nail beds can be rather painful. As a result, many people seek out medical attention for their warts[(3)].

Cryotherapy, electrocoagulation, topical salicylic acid, topical 5-fluorouracil, and laser surgery are only some of the options for treating warts. None of these treatments is ideal, and they can all be uncomfortable, time-consuming, or costly[(4)].

Tuberculin pure protein derivative (PPD), measles, mumps, and rubella (MMR) vaccination, and Candida albicans antigen have all been used as injectable treatments for warts (candidin). Intralesional immunotherapy refers to a group of treatments that aim to eliminate warts by stimulating the immune system so that it can identify and eliminate the virus[(5)].

In 1971, the FDA in the United States approved methotrexate (MTX) as a medication for treating cancer, inflammation, and immune system dysfunction [(6)].

Inhibiting DNA synthesis in proliferating cells is the pharmacological justification for using MTX. MTX's antiviral effect was observed in the treatment of cells infected with the Zika virus, and this effect was accounted for by the drug's ability to inhibit dihydrofolate reductase[(7)].

Hydrolysis of cellular proteins is triggered by the application of trichloroacetic acid (TCA), which is a topical damaging agent. At concentrations of 70–80%, it is equally effective as cryotherapy in treating common, cervical, genital, and anal warts. The benefit is that it is not poisonous to the body as a whole. However, discomfort, burning, hyperpigmentation, and infrequently scar formation may occur at the site of application [(8)].

This study objective was to compare the safety and clinical outcome of MTX application versus curettage and TCA (100%) application in managing planter warts.

SUBJECTS AND METHODS

Subjects:

During the 6-month period of September 2021 - February 2022, the Department of Dermatology, Venerology, and Andrology of the Zagazig University

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Faculty of Medicine conducted a randomized, controlled, clinical trial study.

At their initial consultation, 90 adults aged 18 to 50 with plantar warts were enrolled in the study. The patients were divided into two groups at random. Using random number generators, we constructed a basic allocation sequence.

Inclusion criteria:

- All consecutive patients more than 18 years old.
- Both sexes
- Participants were screened primarily for the presence of plantar warts.

Exclusion criteria:

- Females who were pregnant or nursing.
- Any issue of blood coagulation in their family.
- Chronic systemic illnesses treated with anticoagulants.
- Existence of immunosuppression or associated administration of an agent known or suspected to have immunosuppressive effects, either on a global or contextual scale
- Participants who had received any kind of systemic or topical wart treatment in the preceding six months were not included.

All patients were categorized into two groups:

- IL-MTX Group: included 45 patients were injected intralesionally with methotrexate (MTX).
- TCA Group: included 45 patients treated with trichloroacetic acid (TCA) 100 % needling.

All patients were subjected to the following:

- Total history included demographic characteristic data (Age, sex, education, occupation).
- Duration of plantar wart disease.
- Previous treatments received for the warts.
- Family history.
- General examination for any associated skin diseases.
- Clinical evaluation of the patient to determine warts size (< or > 1cm), number and distribution.

Techniques:

In this case of plantar warts, the diagnosis was made based on patient history and physical examination. At each checkup, information about the patient's warts (including their location, quantity, size, and kind) was added to a visual "wart map." Before therapy began, during each appointment, after one month, and upon completion, photographs were taken.

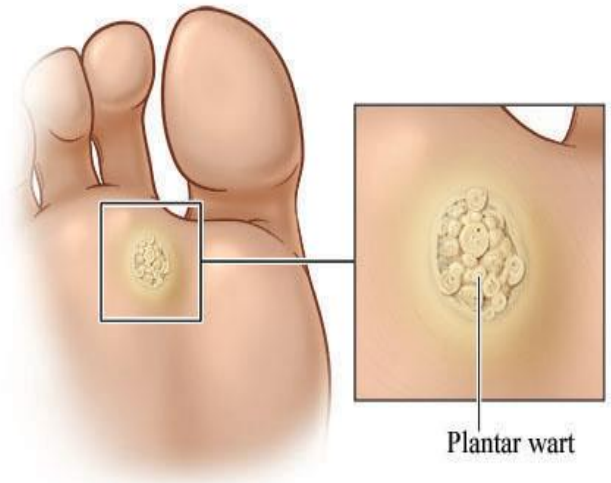

Figure (1): Graphical plantar wart[9].

1- IL-MTX Group:

Technique for Injecting MTX:

For the trial, researchers injected IL-MTX into the skin of the feet of 45 patients aged 18-50 with variously sized plantar warts at their initial visit. An area for injection was sterilised using 75% alcohol. 30 minutes prior to injection, local anesthetic (15 mg pridocaine cream) was given under occlusion to the injection site. Methotrexate (MTX; MYLAN 50 mg/2 ml Vial at a dosage of 0.2 mg/ml per lesion blanch was injected into 45 trial participants. For patients with many lesions, therapy was only injected into the largest ones.

The maximum number of injections was six, and they were given at weekly intervals. Clearance at six injections was considered a treatment success, thus further injections were not given and the patient was monitored for relapse. At each checkup, the number and size of the warty lesions were counted to keep track of the clinical response. If all of the warts, including the ones further away, disappeared after treatment, we judged that stage to be complete. Partial reaction, assuming there were any warts at all, remained the same. If no improvement in the lesions was seen, the treatment was deemed unsuccessful. Adverse events were documented [9].

2- TCA Group:

Method of TCA Application:

Forty-five adults between the ages of 18 and 50 with plantar warts were involved in the trial, and all of them were given a drug with a hundred percent concentration of TCA on their initial visit. Patients underwent six sessions of treatment with 0.5 to 1 cc of 40% TCA applied with a cotton-tipped applicator over the course of six weeks.

The applicator was kept on each lesion for 5–10 seconds throughout each treatment session, with breaks of 30–60 seconds in between. Zinc oxide cream was applied in a circular fashion around the lesion at the end of each session. At the beginning of the trial, the wart's location, size, and number were recorded as baseline

data, and these measurements were repeated weekly until the lesions had completely disappeared.

Photographic documentation was done at the beginning, every follow-up visit and at the end of the sessions. Lesions that were completely removed were followed up on for an additional 3 months to check for recurrence. On first visit application of 100% TCA followed by needling with an insulin syringe on each plantar wart was done. Needling was done to up to the appearance of pinpoint bleeding points. No paring was done at the first visit. This was repeated weekly, and only the necrosed tissue was pared on follow-up without inducing any bleeding points. This procedure was repeated up to 6 visits.

Follow-up:

Treatment efficacy and adverse effects were assessed weekly for the first three months following the final injection to detect recurrence in both groups.

According to **Basavarajappa *et al.*** [10] the evaluation of the response was carried out: (A) Monitoring the size and quantity of warts for improvement over time. If all of the warts, even the ones that were not treated, disappeared entirely, that was called a complete clearance. Only a partial reaction altered, if there are warts at all. If no improvement was seen in any of the lesions, the treatment was declared unsuccessful. (B) Digital photography was performed before first session and every follow up visit after the last session.

Adverse effects:

Adverse effect assessments were performed at each visit, with a focus on local tolerability parameters: (e.g., Erythema, Scaling, Dryness, and Stinging/burning).

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

In order to analyze the data acquired, Statistical Package for the Social Sciences (SPSS), version 20 was used to execute it on a computer. The quantitative data were presented in the form of the mean, standard deviation, and range. The qualitative data were presented as frequency and percentage. The student's t test (T) was used to assess the data while dealing with quantitative independent variables. Pearson Chi-square was used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

Regarding gender and age, there was insignificant difference between both groups. Previous treatments reported in both groups were mainly in MTX group with only one patient in TCA group who reported using collomack, without significant difference between the 2 groups (Table 1).

Table (1): Demographic data of included patients

Variable		MTX group	TCA group	P value
Gender	**Male**	22	21	0.031
	Female	23	24	
Age	**Mean ± SD**	36.6 ± 12.5	38.4 ± 11.5	1.329
Previous therapy	**Collomack**	4	1	0.824
	Duofilm	2	0	
	Salicylic acid	7	0	
	Vaseline	2	0	

There was a statistically significant decrease in the total number of warts in both groups following treatment as compared to pre-treatment. There was slight advantage of TCA therapy over MTX therapy (Table 2).

Table (2): Assessment of warts' number before and after treatment

Variable		MTX group	TCA group
Warts' number before	**Mean ± SD**	7.6 ± 3.57	5.31 ± 2.5
	Range	3-13	2-12
Warts' number after treatment	**Mean ± SD**	5.9± 2.81	3.42 ± 2.89
	Range	2-13	1-10
P value		**0.008**	**0.002**

Comparison of size of warts before and after treatment showed that the size of the warts decreased significantly in both groups after treatment compared to before treatment. As mentioned in warts' number, there was slight advantage of TCA therapy over MTX therapy (table 3).

Table (3): Assessment of warts' size before and after treatment

Variable		MTX group	TCA group
Warts' size before	**< 1 cm^2**	18	24
	≥ 1 cm^2	27	21
Warts' size after treatment	**< 1 cm^2**	27	35
	≥ 1 cm^2	18	10
P value		**0.038**	**0.021**

Assessment of number of sessions required to achieve clinical response revealed statistically significant better response with TCA therapy (31 patients achieved complete clinical remission) compared to MTX therapy (15 patients achieved complete clinical remission) (Table 4).

]Table (4): Number of sessions to achieve clinical response

Variable	MTX group	TCA group
Poor response after 6th session	30	14
Response after 1st session	2	3
Response after 2nd session	2	2
Response after 3rd session	0	3
Response after 4th session	4	7
Response after 5th session	7	12
Response after 6th session	0	4
P value	**0.019**	

There was no statistically significant difference in patient satisfaction between the two groups (Table 5).

Table (5): Assessment of patients' satisfaction

Variable		MTX group	TCA group
Patients' satisfaction	**Satisfied**	14	15
	Not satisfied	31	30
P value		0.822	

Assessment of treatment response after 6 months of treatment revealed statistically significant better response with TCA therapy compared to MTX therapy (Table 6).

Table (6): Assessment of treatment response after 6 months of treatment

Response	MTX group	TCA group
No clearance	24	15
Partial clearance	17	24
Total clearance	4	6
P value	0.159	

Assessment of side effects reported by patients revealed significant association of MTX therapy with side effects (mainly dryness of lesions) compared to TCA therapy (mainly ulceration and burning) (Table 7).

Table (7): Assessment of side effects with each therapy

Variable		MTX group	TCA group
Side effects	**Present**	24	2
	Absent	21	43
Dryness of lesions	**Present**	24	-
	Absent	21	-
Ulceration and burning	**Present**	-	2
	Absent	-	43
P value		**<0.001**	

DISCUSSION

Human papillomavirus infection leads to warts, also known as verrucae, which are benign growths on the skin or mucosa (HPV). About 4.5% of the world's population suffers from plantar warts, making it one of the most prevalent skin conditions. They are frequent cause of pain especially with walking. Therefore, treatment of plantar warts is a must to ease patient's suffering as well as prevent spread, transmission and recurrence [(11)].

In our study, we compared between intralesional methotrexate (MTX) in 45 patients and curettage with applying 100% trichloroacetic acid (TCA) on the affected areas of 45 patients for plantar warts treatment.

Al-Khafaji *et al.* [(12)] selected 42 patients clinically diagnosed as common warts. In total, there were 28.57 percent male participants and 71.43 percent female ones. In the study by **Nischal *et al.*** [(13)], 55% patients were females and 45% were males.

Mean patients age in our study was 36.6 ± 12.5 years in MTX group and 38.4 ± 11.5 years in TCA group. There was a statistically significant age disparity between the two groups. **Al-Khafaji *et al.*** [(12)] found that mean of participants was 22.2 years

Bodar *et al.* [(14)] found that thirty-five (64.8%) patients had <5 warts, 17 (31.5%) patients had 5–10 warts, and only 2 (3.7%) had ≥10 warts. The patients who had <5 warts (n = 35) had complete clearance in a mean duration of 4.3 weeks, the patients who had 5–10 warts (n = 17) had complete clearance in a mean duration of 4.9 weeks, and two patients who had ≥10 warts had complete clearance in a mean duration of 8 weeks. Thus, the mean duration needed for complete clearance of warts increased with increase in number of warts at the baseline.

But we were unable to find a study which compared intralesional methotrexate with TCA for plantar warts which shows that this research paper was the first to compare the two treatments versus each other. **Al-Khafaji *et al.*** [(12)] found that common warts on the hands and feet respond worse to intralesional MTX than they do to electrocautery treatment.

Assessment of side effects reported by patients revealed significant association of MTX therapy with side effects (mainly dryness of lesions) compared to TCA therapy (mainly ulceration and burning), although **Speth *et al.*** [(15)] mentioned many side effects to systemic MTX. But, **Al-Khafaji *et al.*** [(12)] found no adverse complications belonged to MTX.

Bodar *et al.* [(14)] noted side effects including burning sensation on application of TCA which lasted only for the duration of the procedure. Postinflammatory hyperpigmentation after healing was also noted in two patients. No other postprocedural complications were noted.

Both intralesional MTX and curettage and administration of 100% trichloroacetic acid cause significant pain, making analgesia useful for both

treatment groups. MTX appears to be a simple solution for managing pain, and the associated discomfort lasts for just a brief time. There isn't a lot of specialized gear needed for MTX treatment.

CONCLUSION

Although curettage plus 100% TCA is an effective relatively painless procedure for managing plantar warts, however, when it comes to treating plantar warts, it is not as successful as intralesional methotrexate, intralesional MTX is of least cost, easy to control and there aren't any required equipment. Therefore, it may be used as a primary treatment modality in plantar warts in patients where electrosurgery is limited due to the pain.

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