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Mohamed Zoheir
Dermatology, Venerology and Andrology department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, mohamedgomaazoheir@gmail.com

Abdel Raouf AL Mohsen
Professor of Dermatology, Venerology and Andrology, Faculty of Medicine, Al-Azhar University, Egypt, raoufm6@hotmail.com

Mohamed Amer
Assistant professor of Dermatology, Venereology and Andrology,Faculty of Medicine (for boys), Al-Azhar University, amerrom@yahoo.com

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Dermatology

Efficacy of Intralesional Methotrexate versus 5-Flurouracil in treatment of Plantar Warts

Mohamed Gomaa Tolba Zoheir [1,*] M.B.B.Ch, Abdel-Raouf Mohamed Almohsen [1] MD, Mohamed Abdel-Mawgod Amer, [1] MD

** Corresponding Author:*
Mohamed Gomaa Tolba Zoheir
mohamedgomaazoheir@gmail.com

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[1]*Dermatology &Venereology and Andrology Department, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.*

ABSTRACT

Background: Warts are benign skin lesions that occur as a result of infection with human papillomavirus (HPV). Warts are classified according to their sites and shapes as (i) Common wart; (ii) Plantar wart; (iii) Plane wart and (iv) Genital wart (condyloma accuminatum). The type of wart present on the plantar surface of the foot is called planter wart and there are various types of HPV have been identified to cause planter warts including HPV-1, -2, -3, -4, -27, -29, -57, -60, -63, -65, -66, and -69. It has been already established that radical treatment of warts is often challenging for both the physician and the patient.
Aim of the study: To assess the effectiveness of Intralesional Methotrexate in comparison with 5-Flurouracil in treatment of Plantar Warts.
Patients and Methods: The study was carried out on 40 patients with planter warts. Two groups of patients were obtained. Group A included 20 patients were injected MTX in full concentration into the base of the wart and Group (B) included 20 patients were injected intralesional 5 Fluorouracil in full concentration.
Results: There is a significant difference between the two groups as regard the response (Group B -5-FU group- is more effective) with no statistical significant difference between the 2 groups as regard the type, number, duration of warts or the complications of injection.
Conclusion: MTX is less effective than 5-FU in treating plantar warts.

Keywords: *Planter warts; Methotrexate; 5 Fluorouracil.*

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INTRODUCTION

Warts or verruca are common, benign skin lesions that occur as a result of infection with human papilloma virus. [6]

They are considered to be a popular skin disease that show an incidence of about 33% in children aging between 6 and 12 years and about 3.5% between adults. [9]

The term 'warts' comprises all types of warts and may occasionally refer to wart-like conditions not attributed to HPV infection, as seborrheic keratosis. Warts are classified according to their sites and shapes as (i) Common wart; (ii) Plantar wart; (iii) Plane wart and (iv) Genital wart (condyloma accuminatum). [8]

The variant of wart present on the plantar surface of the foot is called planter wart and there are various types of HPV have been identified to cause planter warts including HPV-1, -2, -3, -4, -27, -29, -57, -60, -63, -65, -66, and -69. [10]

There are multiple treatment modalities for planter warts including cryotherapy, electrocoagulation, topical salicylate, topical 5-fluorouracil, intralesional immunotherapy and laser. Each modality has various degrees of efficacy and side impacts. Almost all the available treatment modalities lack evidence and none of them has a constant efficiency for all patients. [10]

Methotrexate was approved by the US Food and Drug Administration (FDA) in 1971 as an anti-proliferative, anti-inflammatory, and immunomodulating agent. [5]

MTX suppresses DNA synthesis in rapidly proliferating cells so it is used as an anti-proliferative for rapidly growing tumors. [2]

5-Fluorouracil (5-FU) is an antimetabolite that can be used alone or with other chemotherapeutic agents to treat solid tumors. It is one of the pyrimidine analogue type. Due to its structure, 5-FU disrupts nucleoside metabolism and can be integrated into the single and double helix of RNA and DNA, respectively, causing cell cytotoxicity and death. [4]

This study was designed for the comparison between MTX and 5-FU when injected intralesional in plantar warts as regard the safety and the efficacy.

PATIENTS AND METHODS

This study included 40 patients with at least one planter wart. The age of patients was from 18 to 50 years, patients were divided into 2 equal groups: Group (A) included 20 patients (10 males and 10 females), and Group (B) included 20 patients (11 males and 9 females). They Were recruited from out-patient clinic of Dermatology, Venereology and Andrology Department of Al-Azhar University Hospitals from March 2021 to October 2021. Complete medical history, dermatological examination and documented digital photography were done for all patients.

Group A: patients were injected intralesionaly by Methotrexate in full concentration 25mg/ml
into the wart using a 27-guage insulin syringe till blanching. The injections were repeated every 2 weeks till clearance or till completion of 6 sessions.

Group B: patients were injected intralesionaly by 5-Fluorouracil (50mg/ml) in full concentration into the wart using a 27- gauge insulin syringe till the entire lesion begins to puff up.

The maximum dose injected per session was 2ml of 5-FU. The injections were repeated every 2 weeks till clearance or till completion of 6 sessions.

Application of topical anesthesia was done 30 minutes prior to injections.

The clinical assessment:

Evaluation of the response was carried out by:

Clinical evaluation before and after the last session.

Digital photography with camera (Nikon Digital Camera D5300, made in Thailand) at the first visit, prior to each injection and 2 weeks after the last injection.

Clinical response was assessed as follow: complete response; complete clearance of the wart and restoration of the natural skin patterns, partial response; 50% to 99% reduction in the size of wart and no response; 0% to 49% reduction in the size of wart.

Statistical analysis: The study's findings were evaluated using SPSS 25. (IBM, USA). Data were expressed as median, number and percentage. Mann-Whitney U test was used to analyze quantitative variables and Fisher's exact test or the Chi-square test were used to analyze categorical variables. P value < 0.05 was significant.

RESULTS

		Group (A) (20 patients)	Group (B) (20 patients)	P-value
Response (%)	Median	72.5	100	0.01 S
	IQR	45 – 100	100 – 100	
Response	No	5 25%	1 5%	0.015 S
	Partial	8 40%	3 15%	
	Complete	7 35%	16 80%	

Table 1: comparison between the 2 groups regarding the response.

As regard response %, there was a significant difference between the 2 groups (P-value =0.01).
The median response % in group A was 72.5 (45-100) % while it was 100 (100-100) % in group B.
As regard response categories, there was a significant difference between the 2 groups (P-value = 0.015).
Group (A) showed complete resolution in 7 patients (35%), partial resolution in 8 patients (40%) and no response in 5 patients (25%).
Group (B) showed complete resolution in 16 patients (80%), partial resolution in 3 patients (15%) and no response in 1 patient (5%) (Table 1).

		Group (A) (20 patients)	Group (B) (20 patients)	P-value
Sessions	3 sessions	0 0%	6 30%	0.003 S
	4 sessions	2 10%	7 35%	
	5 sessions	4 20%	2 10%	
	6 sessions	14 70%	5 25%	

Table 2: comparison between the 2 groups regarding the number of sessions.

As regard the number of sessions, there was a significant difference between the 2 groups (P-value = 0.003). In group A, there were 2 patients (10%) had 3 sessions, 4 patients (20%) had 5 sessions & 14 patients (70%) had 6 sessions. In group B, there were 6 patients (30%) had 2 sessions, 7 patients (35%) had 4 sessions, 2 patients (10%) had 5 sessions & 5 patients (25%) had 6 sessions (Table 2).

Parameters	Groups	Group (A) (20 patients)		Group (B) (20 patients)		P-value
Sex	Male	8	40%	4	20%	0.752 NS
	Female	12	60%	16	80%	
Age (Years)	Mean	28.5		30.4		0.507 NS
	±SD	8.7		10.2		
Duration (months)	Median	7.5		7.5		0.862 NS
	IQR	6 - 9.75		6 - 10.75		

Table 3: Comparison between the 2 groups regarding sex, age and duration.

As regard sex, age and duration of lesions there was no significant difference between the 2 groups. Group (A) included 10 males (50%) and 10 females (50%) while group (B) included 11 males (55%) and 9 females (45%). The mean age is 28.5 in group (A) and 30.4 in group (B). Duration of the disease median was 7.5 months in group (A) and 7.5 months in group (B) (Table 3).

		Group (A) (20 patients)		Group (B) (20 patients)		Stat. test	P-value
Complications	No	9	45%	10	50%	$X^2 = 0.54$	0.909 NS
	Pain	5	25%	6	30%		
	Mild bruises	3	15%	2	10%		
	Mild bruises & pain	3	15%	2	10%		

Table (4): comparison between the 2 groups regarding complications.

As regard complications, there was no significant difference between the 2 groups (p-value = 0.909). In group A, there was pain in 5 patients (25%), mild bruises in 3 patients (15%) and mild bruises & pain in 3 patients (15%) while there was no complication in 9 patients (45%). In group B, there was pain in 6 patients (30%), mild bruises in 2 patients (10%) and mild bruises & pain in 2 patients (10%) while there was no complication in 10 patients (50%) (table 4).

Fig. 1: female patient, 36 years old, with a single plantar wart showed total resolution after 4 sessions of MTX injection.
(a) Before injections. (b) After injections.

Fig.2: female patient, 59 years old, with a single plantar wart showed total resolution after 3 sessions of 5-FU injection.
(a) Before injections. (b) After injections.

DISCUSSION

Numerous therapeutic modalities have been reported for the treatment of plantar warts. Intralesional MTX in the treatment of planter warts was used by *Abdo*[1] who evaluated the safety and effectiveness of using intralesional injection of methotrexate in a dilution up to 2mg/ml into the wart base. [1]

The study revealed that Intralesional MTX injection in planter wart was safe but with low efficacy. [1]

Intralesional 5-FU was evaluated for treating warts by *Srivastava* [7] and the study revealed that 95.38% of the patients showed complete response indicating that 5-FU is efficient and safe treatment for palmoplantar warts. [7]

A total of 40 patients with plantar warts were included in our study. Patients were divided into 2 groups.

Group (A) included 20 patients were injected intralesional MTX in full concentration (10 males and 10 females) with the mean age (28.5). In Group A (MTX group), there was complete resolution in 7 patients (35%), partial resolution in 8 patients (40%) and no response in 5 patients (25%). As regard the number of sessions, there were 14 patients (70%) completed 6 sessions while 2 patients (10%) showed complete resolution after 4 sessions and 4 patients (20%) showed complete resolution after 5 sessions. This was in agreement with *Abdo*[1] who used methotrexate by intralesional injection for the treatment of planter warts and the study revealed that the efficiency of methotrexate in treating planter warts was low (6.7% showed complete improvement, 26.7% showed partial improvement and 66.7% showed no improvement) the differences in response between the two studies may be due to the difference in methotrexate concentration used (full concentration 25mg/ml in our study and 2mg/ml in the other study).

Group (B) included 20 patients were injected intralesional 5 Fluorouracil in full concentration (11 male and 9 females) with the mean age (30.4). In Group B (5-FU group), there was complete resolution in 16 patients (80%), partial resolution in 3 patients (15%) and no response in 1 patient (5%). As regard the number of sessions, there were 5 patients (25%) completed 6 sessions, 6 patients (30%) showed complete resolution after 3 sessions, 7 patients (35%) showed complete resolution after 4 sessions and 2 patients (10%) showed complete resolution after 5 sessions. This was in agreement with *Srivastava*[7] who used intralesional 5-FU (50 mg/mL) mixed with lidocaine (20 mg/mL) and epinephrine (0.0125 mg/mL) solution in treating palmoplantar warts and the study revealed that 95.38% of the patients showed complete response. Similarly, a study was done by *Ghonemy*[3] who compared intralesional 5-FU versus microneedling alone versus microneedling combined with 5-FU solution in treatment of planter warts in this study intralesional injection of a mixture (1 mL of 5-FU + 0.25 mL of local anesthesia) into the wart base with a complete clearance in 76.7% of patients in this group. [3]

Comparing the results of group A (MTX group) with group B (5-FU group), we can come to a conclusion that MTX has a low efficacy in the treatment of plantar warts in comparison with 5-FU.

CONCLUSION

5-Fluorouracil (5-FU) is more effective than Methotrexate in treating plantar warts with no statistical significant difference between them as regard the type, number, duration of warts or the complications of injection.

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