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TOPICAL 5 FLUOROURACIL AND MICRONEEDLING IN THE TREATMENT OF PLANTER WARTS: RANDOMIZED COMPARATIVE TRIAL

By

Ali Mohamed Ali Zeyada, Shaker Mahmoud El-Sayed Ezz El-Din and Sameh Fawzy Fahmy Mohamed

Department of Dermatology, Venereology and Andrology, Faculty of Medicine - Al-Azhar University

Corresponding Author: Ali Mohamed Ali Zeyada,

Mobile: +201208551238, **E-mail:** mohamedzeyada85@gmail.com

ABSTRACT

Background: Warts are benign proliferations of skin and mucosa that result from infection with human papilloma virus (HPV) which are double stranded deoxyribonucleic acid (DNA) viruses that replicate inside the nucleus. Infection with HPV may be clinical, subclinical, or latent.

Objective: To compare the efficacy and safety of intralesional 5-FU solution and 5-FU solution using micro needling technique in the treatment of planter warts.

Patients and methods: Our study was carried out on 60 patients complaining of planter warts divided into two equal groups: A and B from June 2020 to Janurary 2021, Group A: with planter warts received intralesional 5-FU solution every two weeks, and Group B:with planter warts received 5-FU solution using a micro needling pen type device every two weeks, for maximum period of six sessions or complete absence of the lesion. Patients were selected from out-patient clinic of Dermatology, Venereology and Andrology Department of Al-Azhar University Hospitals.

Results: The present study showed complete cure rates of 21 patients (70%) in group A and 25 patients (83.3%) in group B. Partial cure rates occurred in4 patients (13.3%) in group A, and2 patients (6.7%) in group B after 12 weeks of treatment. No response occurred in 5 patients (16.7%) in group A, and 3 patients (10%) in group B. Most of partial and nonresponsive patients had lesions of mosaic type infection.

Conclusion: Derma pen use in the treatment of planter warts by 5- fluorouracil solution 50 mg/ml was superior to intralesional injection of the same medication.

Keywords: Derma pen, 5-Flurouracil, Micro needling, plantar warts.

INTRODUCTION

Plantar warts are hyperkeratotic papules caused by human papilloma virus infection. They are often affecting the pressure areas of the plantar surface of the foot *(Abeck et al., 2019)*.

Although most warts are asymptomatic, the plantar type is often associated with pain on walking causing physical and psychological stress *(Ghadgepatil et al., 2016)*.

Treatment of plantar warts poses challenge. No single treatment is effective

in most of patients, often painful and associated with high recurrence. 5-Fluorouracil (FU) is an antitumor agent blocks DNA synthesis by inhibition of pyrimidine and thymidine. Therefore, it inhibits cellular proliferation and replication. This action helped 5-FU to be used in the treatment of warts *(Kannambal et al., 2019).*

Microneedling is a fine needle that penetrates the skin to induce micro-injuries leading to production of collagen fibers and release of growth factors. It has been used as an adjuvant therapy helping a drug delivery and also used in treatment of various dermatologic diseases *(Ita, 2017).*

The aim of this work was to compare the efficacy and safety of intralesional 5-FU solution and 5-FU solution using micro needling technique in the treatment of planter warts.

PATIENTS AND METHODS

This study was carried out on a total of 60 patients with planter warts from June 2020 to Janurary 2021. The patients were diagnosed by typical clinical findings. The patients were able to read and give consents.

Exclusion criteria:

Patients aged less than 18 years or more than 65 year old, patients who received any local or systemic treatments for their warts for at least one month before the study, pregnant or lactating females and patients diagnosed with acute or chronic diseases. Patients were selected from out-patient clinic of Dermatology, Venereology and Andrology Department of Al-Azhar University Hospitals.

All patients were subjected to complete medical history, dermatological examination and documented digital photography.

The patients were divided into two equal groups: Group A received intralesional 5-FU solution. 5-FU injected intralesionally with 0.1 ml/cm2 (50mg/ml) using insulin syringes (0.25mm× 6mm), at the base of each wart, after cleansing the area with isopropyl alcohol. Injections were repeated every two weeks, maximum for six sessions or complete cure of the lesion. Group B received 5-FU solution using a micro needling pen type device with a 1-cm tip diameter at a 2-3mm depth according to the expected depth of the lesion for 2-3 minutes every two weeks, maximum for six sessions or complete cure of the lesion.

Response to treatment:

i. **Complete response:** 100% clearance of warts.
ii. **Partial resolution:** 25%-99% improvement.
iii. **No response:** <25% improvement.

Follow-up of patients was done monthly for 2 months to detect any recurrence. The side effects of treatment were recorded such as pain and scarring.

Statistical analysis: All data were collected, tabulated and statistically analyzed using IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Quantitative data were expressed as the mean ± SD (range), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). The following tests were

done: Shapiro Wilk test was used for continuous data to be checked for normality, Mann Whitney U test was used to compare between two groups of non-normally distributed variables, and Chi-square (X2) test or Fisher's exact test of significance was used in order to compare percentage of categorical variables. All tests were two sided. Probability (P-value) <0.05 was considered significant.

RESULTS

Regarding demographic data, there was no statistically significant difference between both groups regarding age, sex, duration of lesions, previous treatments and type of previous treatment **(Table 1)**.

Table (1): Comparison between studied groups as regard demographic data

Groups / Variables	GroupA (n=30)	Group B (n=30)	P
Age (years):			0.42
Mean ± SD	34.67±12.24	36.13±9.92	
Minimum –maximum	19-56	20-57	
Sex	**No (%)**	**No (%)**	0.196
Male	17(56.7)	12(40)	
Female	13(43.3)	18(60)	
Duration of lesion (months):			0.245
Mean ± SD	13.53±6.07	12.37±7.54	
Range	3-26	2-36	
Previous treatment			0.99
Yes	5(16.7)	4(13.3)	
No	25(83.3)	26(86.7)	
Type of treatment			0.247
Surgery	2(6.7)	0	
Cryotherapy	3(10)	2(6.7)	
Electrocautery	0	1(3.3)	
Medical treatment	0	1(3.3)	

Regarding number of sessions required for treatment of planter warts for both groups, there was statistically significant difference between both groups regarding patients required six sessions FP(0.029)**(Table 2)**.

Table (2): Comparison between studied groups as regard response

Groups / Parameters	GroupA (n=30)		Group B (n=30)		P
Number of current treatment sessions	No	%	No	%	
One session	0	0	1	3.3	0.99
Two sessions	2	6.7	7	23.3	0.145
Three sessions	7	23.3	11	36.7	0.398
Four sessions	4	13.3	3	10.0	0.99
Five sessions	2	6.7	2	6.7	-
Six sessions	15	50.0	6	20.0	0.029

Regarding therapeutic response in both groups: Group A revealed that 21 patients (70%) showed complete response, 4 patients (13.3%) showed partial response and 5 patients (16.7%) showed no response. Group B, 25patients (83.3%) showed complete response, 2 patient (6.7%) showed partial response and 3 patients (10%) showed no response. There was astatistically insignificant difference in the therapeutic response between both groups **(Table 3)**.

Table (3): Therapeutic response among the studied patients

Groups / Response for treatment	GroupA (n=30)		Group B (n=30)		P
	no	%	no	%	
Complete	21	70.0	25	83.3	
Partial	4	13.3	2	6.7	0.46
No response	5	16.7	3	10.0	

Regarding the side effects recorded during this study, Pain was noted in all patients received treatment in both groups. Scar formation was observed in seven patients in group A with significant difference between both groups P=0.01. No recurrence was observed among both groups till two months **(Table 4)**.

Table (4): Comparison between studied groups as regard side effects

Groups / Adverse effects	GroupA (n=30)		Group B (n=30)		FP
Pain	30	100.0	30	100.0	-
Scar	7	23.3	0	0.0	0.01
Recurrent	0	0.0	0	0.0	-

Regarding patient satisfaction in Group A, 15 patients (50%) were highly satisfied, 7 patients (23.3%) were satisfied, and 8 patients (26.7%) were unsatisfied In Group B, 20 patients (66.7%) were highly satisfied, 6 patients (20%) were satisfied and 4 patients (13.3%) were unsatisfied. There was no significant difference between both groups **(Table 5)**.

Table (5): Patient satisfaction of the two studied groups after therapy

Groups / Satisfaction level	GroupA (n=30)		Group B (n=30)		p
	No	%	No	%	
Highly satisfied	15	50.0	20	66.7	
Satisfied	7	23.3	6	20.0	0.35
Unsatisfied	8	26.7	4	13.3	

Before After

Figure (1): A 46 years old female patient with planter wart on the big toe of the left foot treated by 5-fluorouracil solution using amicroneedling pen type device showing complete clearance after three sessions.

Before After

Figure (2): A 20 years old female patient with planter wart on the right foot treated by intralesional injection of 5-fluorouracil solution showing complete clearance after three sessions.

DISCUSSION

Treatment of warts is frequently frustrating as there is no perfect treatment, i.e. there is no one treatment that is fast, painless, highly effective, and associated with a low risk of recurrence. Many treatment options, therefore, exist and the choice of one or another will depend on the number of warts, their location, their size, the age of the patient, and the experience of the dermatologist *(Gerlero and Hernández-Martín, 2016)*.

5-Fluorouracil (5-FU) is an antimetabolite that suppresses cell division and causes cell cycle arrest *(Kamal et al., 2018)*.

Microneedling is a simple, safe, effective, and minimally invasive therapeutic technique which is used for the treatment of skin wrinkles and atrophic scars. It produces controlled skin injuries. These micro injuries set up a wound healing cascade, in which platelets release chemotactic and growth factors causing invasion of other platelets, neutrophils, monocytes/macrophages, and new collagen production *(De Vita and Goldust, 2018)*. It also creates a pathway for immune cells to access the lesion, and increases blood flow to the lesion, all of which may lead to an immune-mediated destruction of the wart *(Mclaughlin et al., 2019)*.

In this study, there was a statistically insignificant difference in the therapeutic response between both groups. Complete clearance was detected in 70% of patients in group A, and 83.3% of patients in group B, with no recurrence during the 2 months follow up.

Comparing the results of treatments between patients of the two groups in our study, although there was no statistically significant difference in the response to treatment by either procedure, there was 83.3% complete cure among 30 patients in case of micro needling compared to 70 % complete cure using intralesional injection.

There was difference of 13.3% of the number of patients between the two

groups. Although statistically non-significant, but numerically was quite a number of importance between treated patients, (25 patients and 21 patients, respectively).Most of the cases which showed partial or no response were of the mosaic type infection. This statistical undifference may be related to the total number of patients (30) and it might have been changed if the number of patients was higher.

This observation was accepted also as regards the groups of partial response which was 13.3% of the intralesional injection group compared to only 6.7% of the second group. No response was 16.7% in the first group compared to only 10% in the second group.

Microneedling is still superior than intralesional injection in the number of patients showed either complete, partial or no response to treatments. We think that the only limitation of this study was the number of patients which should have been more than (30) in each group as to be doubled or tripled. This could be available observation in future studies comparing of evaluating treatment modalities of this type.

The results of the present study in group A (treated by intralesional injection of 5-FU solution 50mg/ml) showed complete clearance in 70 % of patients. This result was lower to that reported by *Srivastava et al. (2016)* which 95.35 % complete clearance (using 5-FU+lidocaiene epinephrine for the treatment of palmoplantar warts). *Kamal et al. (2018)* reported 75 % complete clearance (using injection of 5-fluorouracil solution at the base of palmoplantar and genital warts).

Ghonemy et al. (2020) reported 75% complete clearance (using intralesional injection of 5-fluorouracil solution 50mg/ml in planter warts).

Our results was higher than that reported by *Kenawi et al., (2012)* as 62.5% complete clearance rate (using intralesional 5-FU+ lidocaiene epinephrine in palmoplantar, genital and periungual warts). This difference may be due to fewer number of cases, multiplicity of the types of warts and insufficient statistics.

The results of our study in group B (treated by 5-FU using a microneedling pen type device) showed complete clearance in 83.3 % of patients. Our results were higher than those reported by *Ghonemy et al., (2020)* where 80% complete clearance (Using microneedling followed by spraying of 5-fluorouracil solution).

After 2 months of follow-up period after the last session, none of the patients had recurrence in our study which were coincident with those of *Kamal et al. (2018), Mclaughlin et al. (2018), Kumari et al., (2019)* and *Ghonemy et al. (2020)* who also reported no recurrences in their patients during their follow up period.

Srivastava et al., (2016) found that recurrences of lesions were observed in two lesions during one year of follow-up .

Regarding side effects, pain was reported as a constant local side effect, and this was as reported by *Srivastava et al (2016)* and *Kamal et al. (2018).*

CONCLUSION

Treatment of warts (especially planter warts) responded better to the procedure

of use of derma pen which proved superior than the intralesional injection in conducting the medication to the deeper layers of the tissues., Most of the cases which showed partial or no response were of the mosaic type infection.

Conflicts of interest: No conflicts of interest were encountered.

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5-فلورويوراسيل الموضعى واستخدام تقنية الابر المجهرية مع 5-فلورويوراسيل فى علاج الثآليل الغراسة (تجربة مقارنة عشوائية)

على محمد على زيادة، شاكر محمود السيد عز الدين، سامح فوزى فهمى محمد

قسم الأمراض الجلدية و التناسلية وأمراض الذكورة، كلية الطب، جامعة الأزهر

E-mail: mohamedzeyada85@gmail.com

خلفية البحث: الثآليل هي تكاثر حميد للجلد والأغشية المخاطية ناتج عن الإصابة بفيروس الورم الحليمي البشري (HPV) وهي فيروسات حمض الديوكسي ريبونوكلييك المزدوج تتكاثر داخل النواة. قد تكون الإصابة بفيروس الورم الحليمي البشري سريرية أو تحت إكلينيكية أو كامنة.

الهدف من البحث: مقارنة فعالية وسلامة محلول 5-فلورويوراسيل داخل الآفة ومحلول 5-فلورويوراسيل باستخدام تقنية الابر المجهرية في علاج الثآليل الغراسة.

المرضي وطرق البحث: أجريت دراستنا على 60 مريضًا يشكون من الثآليل الغراسة مقسمين إلى مجموعتين متساويتين من يونيو 2020 إلى يناير 2021: المجموعة (أ) يعانون من ثآليل غراسة محلول 5-فلورويوراسيل حقنا داخل الافة كل أسبوعين والمجموعة (ب) يعانون من ثآليل غراسة محلول 5-فلورويوراسيل باستخدام الابر المجهرية بجهاز الديرما بن كل أسبوعين لمدة أقصاها ست جلسات أو الغياب التام للآفة. وقد تم اختيار المرضى من العيادة الخارجية للأمراض الجلدية والتناسلية وأمراض الذكورة في مستشفيات جامعة الأزهر.

نتـــائج البحـــث: أظهـــرت الدراســـة الحاليـــة معـــدلات شـــفاء كاملـــة لـــ 21 مريضـــــاً (70٪) فـــــي المجموعـــــة (أ) و 25 مريضـــــاً (83.3٪) فـــــي المجموعـــــة (ب). وحـــــدثت معـــــدلات الشـــــفاء الجزئـــــي فـــــي 4 مرضـــــى (13.3٪) فـــــي المجموعـــــة (أ) و 2 مرضـــــى (6.7٪) فـــــي المجموعـــــة (ب) بعـــد 12 أســـبوعًا مـــن العـــلاج. ولـــم تحـــدث إســـتجابة فـــي 5 مرضـــى (16.7٪) فـــــي المجموعـــــة (أ) و 3 مرضـــــى (10٪) فـــــي المجموعـــــة (ب). ومعظـــــم المرضـــــى المســـــتجيبون جزئيـــــا وغيـــــر المســـــتجيبين لـــــديهم آفـــــات عـــــدوى مـــــن نوع الفسيفساء.

الاســـتنتاج: إســـتخدام ديرمـــا بـــن فـــي عـــلاج الثآليـــل الغراســـة باســـتخدام محلـــول 5-فلورويوراســـيل 50 مجـــم / مـــل أفضـــل مـــن الحقـــن داخـــل الآفـــة لنفس الدواء.

الكلمـــات الدالـــة: ديرمـــا بـــن 5- فلورويوراســـيل الابرالمجهريـــة الثآليـــل الغراسة.