Al-Rafidain J Med Sci. 2026;10(2):159-163.
DOI: https://doi.org/10.54133/ajms.v10i2.2903

AJMS

Online ISSN (3219-2789)

Research Article

Intralesional 5-Fluorouracil in the Management of Resistant Warts: Outcomes from a Single-Arm Clinical Trial

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Received: 9 March 2026; Revised: 21 April 2026; Accepted: 25 April 2026

Abstract

Background: Treating resistant warts is inconvenient and frustrating both for patients and for treating physicians. One possible therapy option is 5-fluorouracil, an antimetabolite that has shown better results when administered intralesionally rather than topically. ***Objective***: To evaluate the efficacy and safety of intralesional 5-fluorouracil in treating warty lesions not responding to other options of treatment in a sample of Iraqi patients. ***Methods***: A single-arm clinical trial study conducted in Al-Imamain Al-Kadhmain Medical City, Baghdad, Iraq, during a period of 18 months from March 2024 to September 2025. It included 110 patients diagnosed with warts not responding to different treatment options for at least one year. Each patient received an intralesional 5-fluorouracil injection in each session, repeated every two weeks for four sessions or less if the lesions are completely resolved. ***Results***: The differences in mean size and number of warts during visits were significantly decreased (p<0.05) compared to baseline size. The level of pain significantly decreased after six weeks compared to that after two weeks (p=0.001), and no pain was reported after three months. The level of satisfaction of patients significantly increased after three, six, and 12 months compared to that after two weeks (p=0.001). ***Conclusions***: To treat warts that typically don't react to conventional treatments, intralesional 5-FU may represent a promising therapeutic option. It shows promise as a primary treatment for resistant warts.

Keywords: Intralesional 5-FU; HPV; Resistant warts.

5-فلوروراسيل داخل الآفات في علاج الثآليل المقاوم: نتائج تجربة سريرية بذراع واحد

الخلاصة

الخلفية: علاج الثآليل المقاومة أمر غير مريح ومحبط لكل من المرضى والأطباء المعالجين. أحد خيارات العلاج الممكنة هو 5-فلوروروراسيل، وهو مضاد للاستقلاب أظهر نتائج أفضل عند إعطائه داخل الآفة بدلا من الموضعي. **الهدف**: تقييم فعالية وسلامة 5-فلوروراسيل داخل الآفة في علاج الآفات المكشوفة التي لا تستجيب لخيارات علاج أخرى في عينة من المرضى العراقيين. **الطرائق**: دراسة سريرية بذراع واحد أجريت في مدينة الإمامين الكاظمين الطبية، بغداد، العراق، خلال فترة 18 شهرا من مارس 2024 إلى سبتمبر 2025. شملت 110 مرضى تم تشخيصهم بالثآليل ولم يستجيبوا لخيارات العلاج المختلفة لمدة لا تقل عن عام. تلقى كل مريض حقنة 5-فلوروراسيل داخل الآفة في كل جلسة، تتكرر كل أسبوعين لأربع جلسات أو أقل إذا اختفت الآفات تماما. **النتائج**: انخفضت الفروق في متوسط حجم وعدد الثآليل أثناء الزيارات بشكل ملحوظ (p<0.05) مقارنة بحجم الوضع الأساسي. انخفض مستوى الألم بشكل ملحوظ بعد ستة أسابيع مقارنة بعد أسبوعين (p=0.001)، ولم يتم الإبلاغ عن أي ألم بعد ثلاثة أشهر. ارتفع مستوى رضا المرضى بشكل ملحوظ بعد ثلاثة وستة واثني عشر شهرا مقارنة بعد أسبوعين (p=0.001). **الاستنتاجات**: لعلاج الثآليل التي عادة لا تستجيب للعلاجات التقليدية، قد يمثل 5-FU داخل الآفات خيارا علاجيا واعدا. يظهر أنه علاج أساسي للثآليل المقاومة.

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Article citation: Hasan EF, Fadhil N, Khudhair DA. Intralesional 5-Fluorouracil in the Management of Resistant Warts: Outcomes from a Single-Arm Clinical Trial. *Al-Rafidain J Med Sci.* 2026;10(2):159-163. doi: https://doi.org/10.54133/ajms.v10i2.2903

INTRODUCTION

Warts are one of the most common benign lesions. It is probably more common in adults and ranks third among skin problems in children [1]. An estimated 40% of people have HPV infection, and 7% to 12% of people get a wart. The overall population has a 14% yearly incidence of warts [2]. They are typically firm, little, rough growths that are the same color as skin. They often do not produce any other symptoms, except for soreness on the bottoms of the feet. The hands and feet are the main locations; however, other areas may also be affected [3]. The human papillomavirus (HPV) is the causative agent of warts. They can be classified into around 130 different kinds. Squamous epithelium, which is commonly seen in the skin or genitalia, is infected by HPV. However, it's important to note that each kind of HPV can usually only infect a limited number of specific body parts [4]. There was a 12.7% overall HPV prevalence in 2193 samples obtained from women in Iraq who were referred for an HPV DNA test by gynecologists from different areas between 2023 and 2025 [5]. There is no doubt that giving no therapy at all is safe and economical. Considering that 65% of warts may spontaneously regress in two years [6]. Types of HPV, host immunological response, and site of infection are the main factors that affect spontaneous resolution. The length of time required for spontaneous resolution is a common

reason why people seek medical guidance. In fact, some investigations have indicated that spontaneous resolution is only seen in 40% of cases within a 2-year follow-up period [7]. One of the most frequent ways to cure warts is by removing the affected skin layer. Some of these methods include electrocoagulation, cryotherapy, salicylic acid, and retinoic acid used topically, as well as CO_2 laser [8]. Intralesional therapies are a new and promising therapy option for resistant warts, especially those located in difficult-to-treat sites like the periungual and palmoplantar regions, which frequently show resistance to standard therapies [9]. An analog of pyrimidine, 5-fluorouracil (5-FU) has both a pyrimidine and a furan ring. It interferes with DNA and RNA production by blocking thymidylate synthase, and it can incorporate into either DNA or RNA [10,11]. Some studies have shown that 5-FU is both effective and safe in treating warts, and the rationale for this is that it blocks DNA synthesis, which in turn stops cell replication and proliferation [12]. Warts, hypertrophic scars, vascular malformations, and cutaneous cancers are only some of the skin conditions that dermatologists have been utilizing 5-FU off-label [13]. This study aimed to evaluate the efficacy and safety of intralesional 5-FU in treating warty lesions not responding to other options of treatment in a sample of Iraqi patients.

METHODS

Study design and setting

A single-arm clinical trial study was conducted in the Department of Dermatology and Venereology at Al-Imamain Al-Kadhmain Medical City, Baghdad, Iraq, during a period of 18 months from March 2024 to September 2025. The center serves as a major referral facility for dermatological care in central Iraq, providing care to diverse socioeconomic populations.

Patient selection

The study comprised 110 patients aged above 15 years who attended the outpatient clinic of Dermatology and Venereology at Al-Imamain Al-Kadhmain Medical City and were diagnosed with warts not responding to different treatment options such as cryotherapy, electrocautery, topical salicylic acid preparation, or topical podophyllin for at least one year. Diagnosis of warts was made clinically by a dermatologist. Pregnant and lactating women, patients with diabetes mellitus, those who underwent renal transplantation, those who had circulatory problems (peripheral vascular disease), those on steroid treatment, and those who refused to be part of this study were excluded.

Data collection

Demographics (age and gender), clinical variables (number and size of warts), duration of lesions, type of previous treatment, and number of sessions were recorded.

Intervention and follow-up

A specialist dermatologist conducted a clinical evaluation upon admission, diagnosing warts. Each patient received an intralesional injection from a 5-fluorouracil vial (1000 mg/20 ml, 0.3 ml of 5-fluorouracil + 0.7 ml of xylocaine) in each session. The management was repeated every two weeks, and the total sessions were four or less if the warts were completely resolved. Isopropyl alcohol was used to clean each wart and the surrounding skin. To remove the callus that surrounded the wart, superficial paring was performed. A maximum of 1 milliliter (ml) of injection volume was allowed into each wart. The follow-up protocol includes a baseline evaluation that was made at the 1st visit regarding size and number of warts. At each session, after 6 and 12 months, the following parameters were assessed: Size and number of warts. A complete response is defined as 100% resolution of all treated and surrounding warts; a partial response is when there is a 25% to 99% reduction in the size or number of wart lesions, where the warts have regressed but not completely disappeared, while no response is defined as less than a 25% decrease in the size of the lesion [14]. Pain by visual analog scale (VAS) as shown in figure (1). It is a way to quantify intangible, subjective traits. The standard format is a horizontal line 100 mm wide, with a dot ranging from "no pain at all" to "worst imaginable" to indicate the degree of pain experienced by the patient [15,16] (Figure 1). Patients' satisfaction: Assessed by Likert scale for patients' satisfaction score [17] (1 = Not at all satisfied, 2 = Not really satisfied, 3 = Undecided, 4 = Somewhat satisfied, and 5 = Very much satisfied). Additionally, the possible side effects (ulceration, erythema, scarring, pigmentation, and systemic symptoms) were regularly monitored.

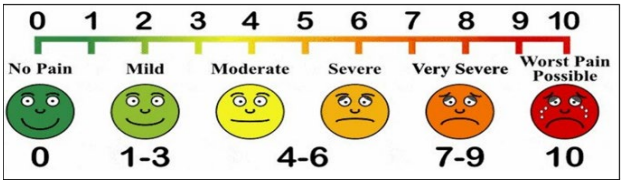

Figure 1: VAS scale for assessment of pain.

Ethical considerations

The Declaration of Helsinki lays forth the ground rules for ethical conduct. Approval was obtained from Al-Nahrain University Ethics Committee. Written informed consent was acquired from all patients. Data were stored securely using coded identifiers in a password-protected environment.

Statistical analysis

We used SPSS 26 (Statistical Package for the Social Sciences) to examine the data. Mean, standard deviation, and range are the data presented. Statistics show as percentages and frequencies for categories. For this reason, we compared the continuous variables using an

independent t-test (two-tailed). The continuous variables were compared before and after treatment using a paired t-test. A *p*-value below 0.05 was considered statistically significant.

RESULTS

The total number of study patients was 110, and the total number of warts was 342. The mean age was 22.83 ± 9.07 years (range: 15–61); 60 (54.5%) were females. Most sites of warts were hands (40%); 81 (73.6%) had warts for less than two years, and 45 (40.9%) of patients had 2 – 5 warts as shown in Table 1.

Table 1: Patients' characteristics (n=110)

Variable	n(%)
Age groups (year)	
< 20	48(43.6)
20 – 39	53(48.2)
≥ 40	9(8.2)
Gender	
Male	50(45.5)
Female	60(54.5)
Site of wart	
Feet	34(30.9)
Hand	44(40)
Both	32(29.1)
Duration of wart (year)	
< 2	81(73.6)
≥ 2	29(26.4)
Number of warts	
One	43(39.1)
2 - 5	45(40.9)
> 5	22(20)

The difference in mean size of warts during visits significantly decreased ($p< 0.05$) after six weeks, three, six, and 12 months compared to baseline size. We noticed that the number of warts decreased after each follow-up visit from 342 lesions to 23 after one year, as shown in Tables 2 and 3, and Figures 2, 3, and 4.

Table 2: Follow up parameters for one year

Time	Follow up parameters			
	Wart Size (cm)	Δ Change (cm)	*p*-value	Wart No.
Before treatment	1.42±0.8		-	342
After two weeks	1.32±0.6	- 0.1±0.03	0.087	331
After six weeks	1.16±0.6	- 0.26±0.06	0.031	237
After three months	0.78±0.3	- 0.64±0.06	0.001	117
After six months	0.44±0.2	- 0.98±0.08	0.001	54
After one year	0.12±0.2	- 1.3±0.12	0.001	23

Values are presented as mean±SD.

Table 3: Vas score of pain during treatment

Time	VAS pain score	*p*-value
After two weeks	5.41±1.4	-
After six weeks	2.18±0.8	0.001
After three months	0	0.001

As shown in Table 3, the level of pain significantly decreased after six weeks compared to that after two weeks ($p= 0.001$) and no pain was reported after three months. The level of satisfaction of patients significantly increased after three, six, and 12 months compared to that after two weeks ($p= 0.001$) as demonstrated in Table 4.

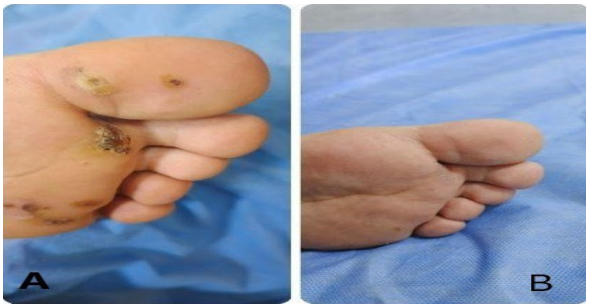

Figure 2: A 27-year-old female presented with resistant plantar warts and treated by four sessions of intralesional 5-FU injections; **A**) Before treatment, and **B**) After four sessions.

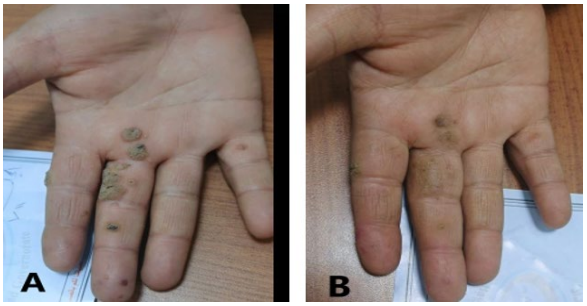

Figure 3: (**A**) Resistant warty lesions are seen over the right middle finger. (**B**) Warts showed response after two sessions of treatment with intralesional 5-FU injections.

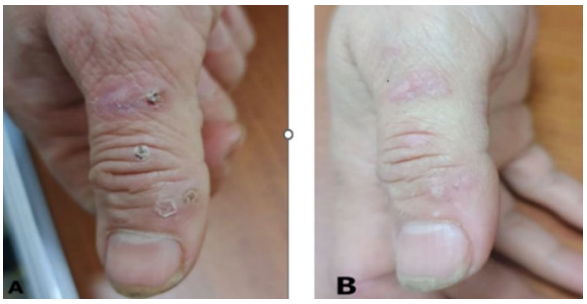

Figure 4: (**A**) Resistant warty lesions are seen over the right thumb. (**B**) Lesions resolved after four sessions of treatment with intralesional 5-FU injections.

Table 4: Patients' satisfaction level after one year

Time	Patients' satisfaction level		
	Satisfaction level (/5)	Δ Change	*p*-value
After two weeks	2.41±0.8	-	-
After six weeks	2.88±1.0	0.47±0.21	0.244
After three months	3.89±1.2	1.48±0.37	0.001
After six months	4.54±1.2	2.13±0.4	0.001
After one year	4.72±0.7	2.31±0.1	0.001

DISCUSSION

The high degree of diversity in the rates of spontaneous regression and responsiveness to standard therapies for warts caused by HPV is driving patients to seek more effective approaches [18]. This study aimed to determine whether 5-FU was safe and effective in treating resistant warts, a prevalent skin condition that can be difficult to treat. According to our research, after a course of intralesional 5-FU injections, wart size and quantity are significantly reduced. Patients also report significantly

less pain and are much more satisfied with the results. Notably, our study introduces an enhanced method for intralesional 5-FU injection, demonstrating its efficacy in treating previously untreatable cases and paving the way for broader clinical application. A study conducted by Sachan *et al*. in 2023 showed similar findings, as intralesional 5-FU showed a complete response in 68% of patients with resistant palmo-plantar warts, although intralesional bleomycin showed a better response, but many more side effects were noted in intralesional bleomycin than in intralesional 5-FU. Moreover, 5-FU is cheaper and more easily procurable than injection bleomycin [19]. Agreement was also reported by the Aboelmagd *et al*. study in 2025, when it found that 76.7% of patients showed a complete response to intralesional 5-FU injections [20]. Immunotherapeutic or anti-metabolite drugs injected intralesionally into warts increase local medication concentrations while reducing systemic absorption [21]. Cytodestructive procedures cause scarring in 30% of cases, wart recurrence in 30% of cases, and pain in 64% of cases, leading to severe morbidity; intralesional injections have fewer side effects [22]. By targeting thymidylate synthetase and disrupting DNA amalgamation in cells that are actively mitotically dynamic, 5-FU acts as a pyrimidine antagonist. It has a topical use in molecular biology. However, 5-FU has not been very successful, even though it is effective despite the challenges of cellular entry. When 5-FU is injected intralesionally, it takes into consideration restorative focuses to reach the injured spot [23]. Most of the research on topical 5-FU as a therapy occurred in the '70s and '80s. The general agreement was that topical 5-FU was not very effective, though, because of variances in study design and technique, which reduced the efficacy of this treatment [12]. Intralesional administration of 5-FU offers distinct advantages over topical application. The typical intralesional dose for wart treatment ranges between 2–6 mg, which is significantly lower than the systemic therapeutic dose (less than 1/150th), thereby minimizing systemic adverse effects. This mode of administration ensures direct drug delivery to the affected tissue, enhancing efficacy while reducing systemic toxicity [24]. Our study found that patients were much more satisfied after this treatment method, which is a strong indication of its therapeutic relevance due to the noticeable decrease in wart burden, the alleviation of pain, and the treatment's overall cosmetic improvement, providing a real and pleasant consequence for people who had been suffering with this chronic illness.

Study Limitations

A comparison control group was not utilized in the study. This was mostly because there were moral and logistical issues with postponing or denying treatment to patients who had tried everything to get rid of their resistant warts. Therefore, although the results are promising, it is important to note that this study did not explicitly compare the treatment's efficacy to that of usual care or a placebo. Additionally, the effectiveness of the treatment in the short to medium term was the primary focus of this study. Important information for evaluating the long-term benefits of intralesional 5-FU, such as recurrence rates and the duration of the therapeutic effects, was not consistently collected over the follow-up period.

Conclusion

To treat warts that are typically not responding to conventional treatments, intralesional 5-FU may represent a promising therapeutic option. It shows promise as a primary treatment for resistant warts. Intralesional 5-FU has the potential to significantly improve clinical outcomes and enhance the quality of life for people affected. To determine its effectiveness and the best ways to administer it, more studies with larger and more representative samples and extended follow-up periods are needed to assess the durability of the treatment response and the potential for recurrence after intralesional 5-FU therapy.

ACKNOWLEDGMENTS

The authors thank the staff of Al-Imamain Al-Kadhimain Medical City for their invaluable contributions to this research, and to the patients for their willingness to share their experiences and data.

Conflict of interests

The authors declared no conflict of interest.

Funding source

The authors did not receive any source of funds.

Data sharing statement

Supplementary data can be shared with the corresponding author based on a reasonable request.

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