Treatment of Common Warts with an Intralesional Mixture of 5-Fluorouracil, Lidocaine, and Epinephrine: A Prospective Placebo-Controlled, Double-Blind Randomized Trial

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BACKGROUND 5-Fluorouracil is an antimetabolite that has been known to be effective for the treatment of common warts.

OBJECTIVE The objective was to evaluate the efficacy of a combination of 5-fluorouracil, lidocaine, and epinephrine (5-FU + LE) for the treatment of common warts.

MATERIALS AND METHODS Of the 40 patients initially enrolled, 34 patients with at least 68 verruca vulgaris (one pair for each subject) completed the study. The selected warts were randomized into two treatment groups, with one wart on each patient receiving intralesional 5-FU + LE (4 mL of 50 mg/mL 5-fluorouracil and 1 mL of a mixture of 20 mg/mL [2%] lidocaine and 0.0125 mg/mL epinephrine) and the other receiving intralesional normal saline placebo using a Mantoux needle. Patients received up to four injections at weekly intervals and were followed at 1 and 6 months after the initial injection.

RESULTS Complete response was observed in 64.7% of the warts treated with 5-FU + LE compared to 35.3% in the warts treated with placebo ($p < .05$). Systemic reaction or treatment-related adverse medical events and recurrence rate did not differ significantly between two groups.

CONCLUSION The results show that intralesional 5-FU + LE is a safe and effective approach for common warts with high success rate.

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Warts are benign epithelial neoplasms affecting the epithelium of the skin and mucous membranes that result from infection with human papillomavirus. Warts are a common dermatologic condition with an estimated incidence of 10% in children and young adults.[1,2] The prevalence of viral warts in the city of Hamedan in western Iran has been recorded at 5.2%.[3]

Many treatments have been described for viral warts. Common therapeutic approaches include liquid nitrogen cryosurgery, topically applied acids, chemical and thermal cautery, virucidal agents, cantharidin application, photodynamic therapy, electrosurgery, intralesional bleomycin, and carbon dioxide laser ablation.[4–10] 5-Fluorouracil (5-FU) is an antimetabolite that has been used topically for the treatment of common warts.[9] We performed this study to evaluate the efficacy of a combination of 5-FU, lidocaine, and epinephrine (5-FU + LE) for the treatment of common warts.

Materials and Methods

We performed a prospective, double-blind, placebo-controlled, randomized trial including 40 patients with common viral warts reporting to a referral dermatology center in the city of Hamedan, Iran. Inclusion criteria consisted of a minimum age of 18 years; having at least two symmetric common warts; acceptable pretreatment laboratory studies (complete blood cell count, serum chemistries, urinalysis, and pregnancy test); no history of hypersensitivity to fluorouracil, lidocaine, or epinephrine; and a mini-

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mum 1-month prior treatment-free period for the warts. Patients who were either pregnant or planning pregnancy in the near future, lactating women, patients with chronic renal failure, or those showing any abnormalities of liver function tests or complete blood count were excluded from the study. Plantar and periungual warts were excluded from this study.

All of the patients were healthy volunteers with clinically diagnosed common cutaneous warts (verruca vulgaris). Prior to treatment, each patient was informed of the nature and risks of the study and signed a consent form approved by the Institutional Review Board and Ethics Committee of Sina Hospital and Hamedan University of Medical Sciences, Hamedan, Iran. The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Patients were barred from receiving any other treatment for the warts throughout the study period. Two similar warts were measured and selected for treatment in each patient.

The selection of a pair of the similar lesions was arbitrary for patients with multiple similar warts. To facilitate repeated assessments of the treated lesions throughout therapy, the lesions were photographed and distances from fixed anatomic points were recorded. The selected warts were randomized into two treatment groups, with one wart on each patient receiving intralesional 5-FU + LE and the other receiving intralesional normal saline. Patients, physicians, and nurses who participated in this study were blinded to the exact nature of the medications being injected throughout the study.

A solution was created containing 4 mL of 50 mg/mL 5-FU and 1 mL of a mixture of 20 mg/mL (2%) lidocaine and 0.0125 mg/mL epinephrine. The solution was injected intradermally into the base of the treatment group warts using a Mantoux needle until the entire lesion seemed to puff up. Normal saline placebo was injected into the placebo group warts on the same patient. The actual delivered volume of solution was adjusted according to the dimension of each lesion (range, 0.05–0.15 cm^3). Patients received up to four injections at weekly intervals and were followed at 1 and 6 months after the final injection.

The degree of pain and any cutaneous reaction during or after injection were recorded. Pain intensity was recorded for each injection using a visual analog scale along a 10 cm horizontal line, with a visual analog scale greater than 3 cm considered moderate to severe pain.[11]

Complete response was defined as the complete absence of clinically apparent wart. Partial response was defined as greater than 50% reduction in wart size, and no response defined as less than 50% reduction in wart size. Complete blood count along with renal and liver function tests were also repeated at the completion of treatment.

Data tabulation and statistical analyses were performed using computer software (SPSS, SPSS Inc., Chicago, IL). To evaluate the differences between both groups, we utilized the chi-square test. A p value below .05 was considered statistically significant.

Results

Of the 40 patients initially enrolled, 34 patients (22 men and 12 women) with at least 68 verruca vulgaris (one pair for each subject) completed the study. The 6 patients who withdrew did so for reasons unrelated to treatment, such as job relocation and scheduling conflicts. The mean age of patients was 19 ± 4.5 years (range, 15–38 years). The follow-up period ranged from 4 to 10 months.

Complete response was observed in 64.7% of the warts treated with 5-FU + LE compared to 35.3% in the warts treated with placebo. These differences were statistically significant ($p < .05$). Partial response was seen in 17.6% of the common warts treated with 5-FU + LE combination and 20.6%

TABLE 1. Number of Lesions Showing Complete Response (CR), Partial Response (PR), and No Response (NR) in Both Treatment Groups

	Verrucae (No./%)	p *Value*
CR		
5FU + LE	22/64.7	<.05
Placebo	12/35.3	
PR		
5FU + LE	6/17.6	NS*
Placebo	7/20.6	
NR		
5FU + LE	6/17.6	<.05
Placebo	15/44.1	
Total (5FU + LE/placebo) = 34/34		

*Not significant.

of the patients treated with placebo. This difference was not statistically significant (Table 1).

Recurrences of lesions were observed in 3 of 22 lesions (13.6%) with complete response receiving 5-FU + LE and 2 of 12 lesions (16.6%) with complete response receiving placebo. The difference between these recurrence rates was not statistically significant.

Most patients found the injections to be painful. Although the incidence of moderate to severe pain was higher in the 5-FU + LE group compared to the placebo group, the differences were not statistically significant (Table 2).

No clinically significant systemic reaction or treatment-related adverse medical events were reported. There were no changes in laboratory values or physical examination findings except for cutaneous reactions. Local cutaneous reactions differed significantly between two groups. They were confined to the treatment site and consisted of erythema and edema ($n = 6$), hyperpigmentation ($n = 6$), hypopigmentation ($n = 1$), ulceration and necrosis ($n = 4$), and scarring ($n = 2$) in the 5-FU + LE–injected verrucae. Only three cases of erythema and edema and one case of hypopigmentation were reported in placebo-treated lesions.

TABLE 2. Pain Assessed by Visual Analog Scale Immediately after Each of Four Intralesional Injections

Number of Intralesional Injections	*VAS > 3 cm,* No. /%*		p *Value*
	5FU + LE (n = 34)	*Placebo (n = 34)*	
1	14 (41.2)	12/35.3	.527
2	12 (35.3)	11/32.4	.665
3	12 (38.2)	10/29.4	.257
4	11 (32.4)	10/29.4	.705

*VAS greater than 3 cm considered as moderate to severe pain.

Discussion

5-Fluorouracil is an antimetabolite that suppresses cell division and produces growth arrest at any stage of the cell cycle.[12] As treatment for ordinary warts, topical fluorouracil appears to be primarily of historical interest, with most of the trials mentioned in reviews in the 1970s and 1980s. Evidence provided by these trials was limited by the heterogeneity of the methods and designs. Overall, this treatment was not considered to be very effective.[13–15]

Intralesional injection of 5-FU + LE has several advantages over topical 5-FU cream or intralesional injection of 5-FU alone. Intralesional injection of 5-FU permits higher drug concentrations throughout the lesion. The addition of lidocaine makes the injection less painful.

This study shows a response rate of approximately 82.3% (64.7% complete response, 17.6% partial response) versus 55.9% in the placebo group. The high placebo response in our study should be considered; injecting saline could be having a therapeutic effect whether this be from immune mechanisms responding to local trauma or central nervous system–mediated effects. In addition, the 5-FU injection on one side of the body could be stimulating memory T-cells, which have a beneficial effect on the placebo side. The usual dose of 5-FU for systemic chemotherapy of solid tumors is 300 to 1,000 mg/m^2 intravenously or continuous infusion.[16] The mean administered dose of 5-FU in our study was 4 mg

(range, 2 to 6 mg), that is, less than 1/150th of the amount of systemic therapy. Therefore, the adverse effects of 5-FU were eliminated.

In a previous report of the efficacy of treating warts with intralesional 5-FU + LE by Iscimen and colleagues,[17] they obtained clearance rates of 88% (70% complete response and 18% partial response) in 76 patients with a total of 315 warts. The adverse effects of the intralesional treatment used in their study were limited to erythema, edema, hyperpigmentation, hypopigmentation, ulceration, necrosis, and scarring. These reactions gradually subsided and none of them caused significant cosmetic sequelae. These adverse effects are indeed similar to those reported by previous studies using topical 5-FU for the treatment of warts.[10,14]

Swinehart and colleagues[18] and Kontochristopoulos and colleagues[19] used intralesional 5-FU for the treatment of condylomata acuminata and keloids. Both of them reported severe pain following the injection of 5-FU alone. In our study, the addition of lidocaine to the solution allowed the pain level to be statistically similar to that seen with the injection of intralesional saline.

Our prospective study directly compares the efficacy of intralesional 5-FU + LE injection with intralesional injections of saline as a placebo. The results show that intralesional 5-FU + LE is a safe and effective approach for common warts with a high success rate. Further studies with larger number of patients and extended follow-up periods and including more refractory types of warts such as plantar and periungual warts would better define the clinical role of intralesional 5-FU + LE for the treatment of warts.

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