Reprint. Topical 5% 5-Fluorouracil cream in the treatment of plantar warts: a prospective, randomized, and controlled clinical study

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ABSTRACT

Topical 5-Fluorouracil (5-FU) is an antineoplastic antimetabolite, which inhibits DNA and RNA synthesis, thereby preventing cell replication and proliferation. This mechanism of action may allow topical 5-FU to be utilized in the treatment of human papilloma virus (HPV). We conducted a study comparing 5% 5-FU cream under tape occlusion versus tape occlusion alone in 40 patients presenting with plantar warts. Nineteen out of 20 patients (95%) randomized to 5% 5-FU with tape occlusion had complete eradication of all plantar warts within 12 weeks of treatment. The average time to cure occurred at 9 weeks of treatment. Three patients (15%) had a recurrence at the 6 months follow-up; accordingly an 85% sustained cure rate was observed. It is concluded that use of topical 5% 5-fluorouracil cream for plantar warts is safe, efficacious, and accepted by the patient.

INTRODUCTION

There is no uniformly effective treatment for warts, and therapy is often difficult and unrewarding. Plantar warts are particularly challenging to treat and are one of the most difficult types of warts to eradicate with sustained cure. Since antiquity, dozens of treatments for plantar warts have been proposed. The mainstay of topical treatment is over-the-counter (OTC) salicylic acid in patches, solutions, and plasters.[1]

However, less than half of patients have success with OTC therapies.[2] Other modalities include cryotherapy, surgical excision and curettage, laser ablation, immunotherapy, electrodessication, caustics, chemical destruction, psychotherapy, and simple tape occlusion. Many of these treatments may result in scarring. Pain may be just as problematic as scarring, particularly in children and adolescents. Furthermore, mosaic warts and multiple warts may be too complex and extensive to treat with surgical therapies. Therefore, better treatment modalities are necessary.

5-Fluorouracil (5-FU) 5% cream is a topical preparation containing the fluorinated pyrimidine 5-fluorouracil, an anti-neoplastic anti-metabolite, and is approved for the treatment of actinic keratoses and superficial basal cell carcinomas. Growth and replication of the human papilloma virus (HPV) requires an effective supply of DNA and RNA for both the virus particles as well as for the proliferating epidermal cells. It has been suggested that 5-FU's ability to inhibit DNA and RNA synthesis prevents cell proliferation and restricts propagation of the virus.[3] The effects of DNA and RNA deprivation are most pronounced on HPV infected cells, which grow more rapidly and incorporate fluorouracil at an increased rate as compared to healthy tissue. As a result, 5-FU has an affinity for the rapidly proliferating epidermis and virally infected cells, and has limited effects on the healthy surrounding skin.

5-FU 5% cream has been reported to be an effective treatment for HPV. In 1962, Goldman et al first reported the use of topical 5-FU for the treatment of warts.[4] In 1970, Hursthouse[5] treated warts on 18 patients with 5% 5-FU ointment applied daily with a small adhesive pad as a cover. In 12 patients (67%), all lesions disappeared in 2 to 6 weeks. Hursthouse[6] then performed a double-blind, placebo-controlled study in 66 patients with 5% 5-FU and demonstrated an overall cure rate

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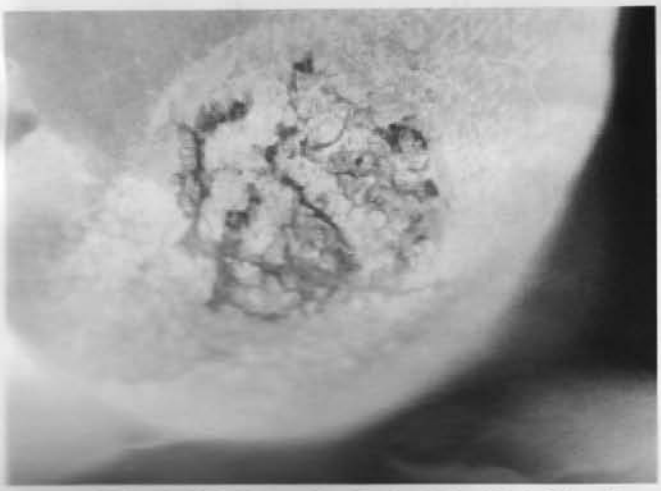


Figure 1. Patient #1: Plantar wart on the heel of subject at baseline visit. This patient was randomized to the 5% 5-Fluorouracil with tape group.

Figure 3. Patient #1: No evidence of wart at 3 months after cessation of treatment.

Figure 2. Patient # 1 at Week 11 of treatment. Note the ulceration that has occurred. This superficial ulceration is mildly painful. There was no evidence of residual wart after debridement and therefore treatment of 5-FU with tape was stopped.

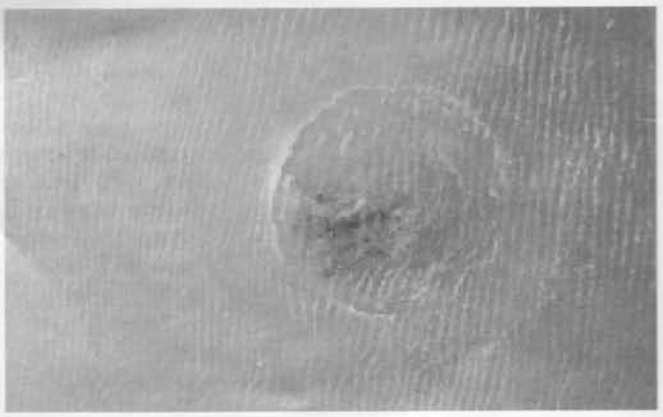


Figure 4. Patient #2: Baseline visit. The hyperkeratotic tissue surrounding the wart was debrided and pinpoint bleeding is noted. This subject was treated with 5-FU and tape occlusion.

of 60% with 5% 5-FU compared to 17% with placebo cream. Although this study showed promising results compared to placebo, the inherent limitations included only 1 month of treatment, once-daily dosing, and no debridement. If indeed patients had a longer treatment course, twice-daily dosing and debridement, higher cure rates may be expected. In 1979, McCarthy et al[7] described the use of 5-FU in the treatment of human pedal verrucae with intradermal introduction of 5-FU solution, demonstrating a 92% cure rate.

MATERIALS AND METHODS

Study Group

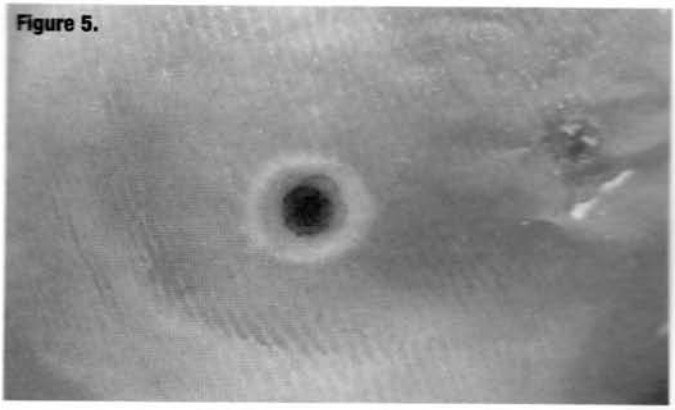
Subjects were drawn from private practice patient populations in 2 podiatric clinics. All patients signed an Informed Consent fully disclosing the risks and benefits of study participation which, along with the study protocol, were approved by an independent institutional review board (IRB) and performed under an Investigational New Drug (IND) application.

Forty consecutive patients with a diagnosis of plantar warts were enrolled into the study. A detailed history and physical was obtained from patients who presented with plantar warts. The diagnosis was established by both clinical examination and a confirmed pathology sample for HPV. A shave biopsy measuring less than 1/4 of the total wart diameter was taken from one representative lesion. All patients were 18 years of age or older with a history of plantar warts for a minimum of 3 months and were otherwise healthy. Women of childbearing potential were willing to practice 2 methods of adequate contraception.

Key exclusion criteria included the following: 1) patients involved in an experimental study of their foot within 3 months of screening; 2) concurrent disease that may interfere with assessment, safety or completion of the study (ie, cancer, HIV/AIDS, pregnancy, diabetes, and peripheral vascular disease); 4) patients with current skin infection overlying the proposed treatment site; 5) patients with a history of allergy to 5-FU or tape; 6) prior treatment of warts topically, surgically, or with laser therapy, cryotherapy, and other methods in the past 3 months; and 7) patients with a known history of dihydropyrimidine dehydrogenase (DPD) deficiency.

Study Design

Patients were randomly assigned into 2 treatment groups: 1) 5% 5-FU cream (Efudex®, Valeant Pharmaceuticals International) under tape occlusion; and 2) tape occlusion alone. The same



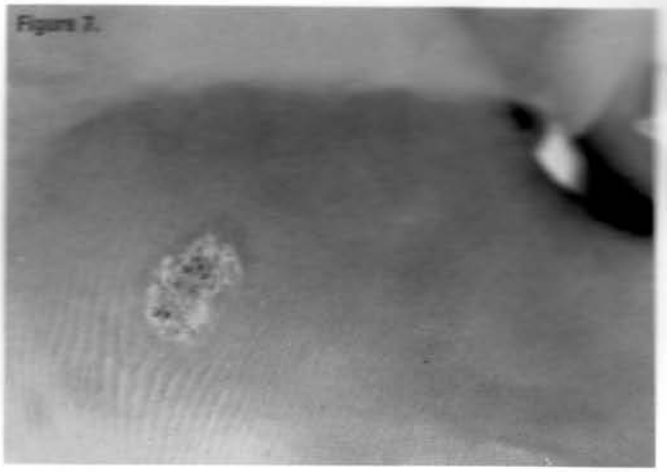


Figure 5. Patient #2: Showing erosion of the wart with complete eradication at Week 8. To the right of the wart, another smaller wart has manifested itself and was also eradicated by the 5-Fluorouracil. The patient was instructed to stop treatment and apply a Band-Aid and OTC antibiotic ointment. This patient had little to no pain with treatment.

Figure 6. Subject #2 at 6 months after cessation of treatment with 5-Fluorouracil. There is no evidence of the warts.

Figure 7. Patient #3 at baseline visit showing a wart between the third and fourth metatarsal heads. This patient was randomized to the 5-FU and tape group. This photo was taken before debridement.

waterproof adhesive tape was used in both groups (Blenderm®, 3M Pharmaceuticals). Assignment of patient number included stratification for total number of lesions present and total size of all lesions (length x width). In patients with a bilateral presentation of plantar warts, the more severely affected foot was defined as the "study foot." All plantar warts on the study foot were treated in each patient.

The treatment course was as follows: patients were screened (Week -2) and started treatment at the baseline (Day 0) visit, after which patients were examined every 2 weeks for up to 12 weeks (Weeks 2, 4, 6, 8, 10, and 12). Patients with clinical evidence of plantar wart(s) at the Week 12 visit were considered study failures and did not continue further with the study. Follow-up for wart recurrence occurred at 2 weeks, 3 months, and 6 months after all lesions were clinically cured.

At each visit, the warts were debrided using a #15 surgical blade with the goal of removing all hyperkeratotic tissue overlying the virus. Attention was given to consistent debridement of lesions between the 2 groups. If bleeding occurred, hemostasis was achieved by applying direct pressure to the lesion before application of 5% 5-FU or tape occlusion.

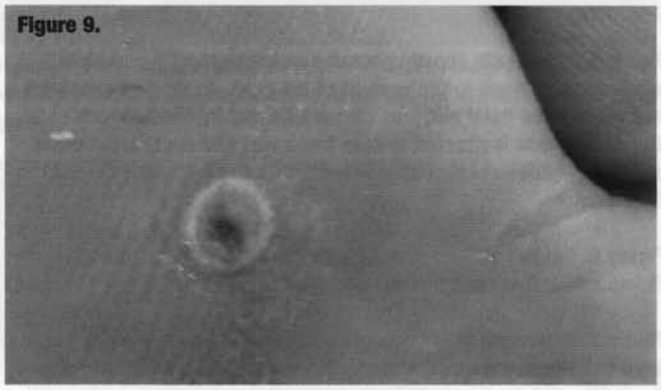
Patients randomized to receive 5% 5-FU cream were instructed to apply the cream twice-daily (morning and evening) onto all warts after daily self-debridement with a pumice stone to remove excess hyperkeratinized tissue. The goal of debridement was to reduce the thickened hyperkeratinized skin to a point where no raised area of skin was palpated. The cream was applied in a thin layer to cover the surface of each wart. Patients were instructed to use a cotton-tip applicator (ie, Q-tip) to rub the medication into the wart for 10 to 15 seconds and then apply a small dollop of additional medication on top of the wart. Next, the occlusive waterproof tape was placed to completely cover each wart. For those patients receiving tape occlusion alone, the tape was similarly applied twice a day (morning and evening) after daily debridement with a pumice stone. The treatment course was identical for both groups, with the only difference being application of 5% 5-FU cream.

All supplies were provided to patients to maintain uniformity between groups. Both groups utilized the same type of tape and pumice stone. Written and verbal instructions were provided regarding both treatment courses and confirmed at each follow-up visit. Total number and size of warts were documented, with photographs taken of the affected area(s) at every visit. Patient self-assessment forms were completed at baseline and then at 3 months and 6 months after therapy completion. Patient assessment of pain on a 5-point categorical scale (none, slight, mild, moderate, severe), patient assessment of overall improvement (complete recovery, much better, somewhat better, no change, somewhat worse, much worse), and a Short-Form 12 Health Survey[9] (SF-12) were also performed at these visits. Blood tests for hepatic function and complete blood count were performed at baseline and end of treatment to assess safety.

EFFICACY AND SAFETY MEASURES

Efficacy and safety were assessed at each visit. Safety was evaluated by the following parameters: 1) adverse events (assessed by overall frequency, severity, seriousness, duration, relationship to study drug, and action taken) and 2) laboratory tests which included hepatic function panel, complete blood count, and pregnancy testing for women of child-bearing potential.

The primary efficacy endpoint was the percentage of patients with sustained complete cure of all warts at the 6-month follow-up visit. The secondary efficacy endpoints included the following:



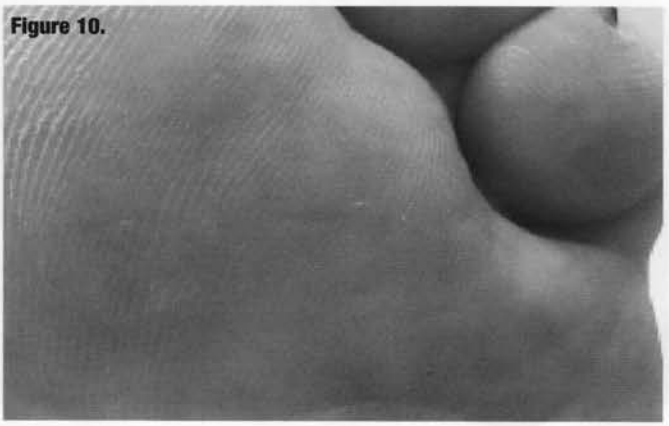


Figure 8. Subject #3 after 2 weeks of treatment with 5-Flourouracil with tape. Note the macerated and hyperkeratotic tissue that has been debrided. The HPV is macerated secondary to the tape occlusion and 5-FU treatment; this is a consistent sign before erosion and ulceration occurs.

Figure 9. Patient #3 at Week 12 and end of treatment. Note the maceration and mild ulceration that has occurred. This signifies end of treatment. The patient is then instructed to apply a Band-Aid and antibiotic ointment.

Figure 10. Patient #3 at 6 months after cure. There is no evidence of wart recurrence.

1) mean decrease in total size and number of lesions at the 6-month follow-up visit; 2) reduction of number of warts over the 12-week treatment course; 3) patient's global assessment of improvement and categorical scale of pain; and 4) SF-12 Health Survey.

STATISTICAL METHODS

Univariate analysis was performed to obtain mean distribution for demographic characteristics. The primary outcome measure was the percentage of patients with sustained complete cure of all warts from baseline to the 6-month follow-up. The analysis for this variable was conducted by comparing the mean differences in complete cure rate at the 6-month post-therapy visit for 5% 5-FU cream under tape occlusion versus tape occlusion alone, using an analysis of variance (ANOVA). Analysis was also performed to obtain ratio of mean square (F-value) and p values using repeated measure ANOVA (between and within subject effects), and related interactions between 5% 5-FU cream with tape occlusion and control group in time.

Secondary efficacy variables that were continuous such as change in total size of lesions and number of lesions were analyzed by using pairwise t-tests to compare means and standard deviations. Categorical variables were analyzed using chi square test for trend and Fisher's exact test. Other categorical data such as EUROQOL (EQ-5D) was presented using frequency, percentage and p values from Fisher's exact tests. The SF-12 Health Survey was scored using algorithms where the mean scores between groups were compared using Student's t-tests. All statistical tests with p values were two-sided and the selected level of significance for all variables was $\mu=0.05$. The SAS statistical software version 8.2 (SAS, Cary, NC, USA) was used to analyze all continuous and categorical data.

RESULTS

Of the 161 potential subjects screened, 40 met the entrance criteria. The 121 patients who did not meet the entrance criteria had other medical conditions (7), calluses (75), porokeratoses (36), or were on anti-coagulant therapy (3). Thirty-eight of the 40 enrolled patients completed the study protocol. The demographic characteristics of the patients in the 5% 5-FU with tape occlusion group and the patients in the tape occlusion alone group are summarized in Table 1. The mean age was comparable between the 2 groups. Other descriptive characteristics were similar between both groups such as height and weight. Notably, there were more females (4:1) among the tape alone group compared to the 5% 5-FU group (1:1), although this difference was not statistically significant ($p=.10$) and would not be expected to effect the outcome of the study.

The average number of warts treated per patient was similar between the 2 groups (2.9 warts in the 5% 5-FU group and 3.5 warts in the tape alone group). The average length of time that participants had warts present was also similar, 4.6 years among the 5-FU with tape group and 5.1 years among the tape alone group. There was no statistical difference when comparing the patient-rated baseline severity of warts between both groups as shown in Table 2. The mean area of treated warts was not statistically different for the tape alone group compared to the 5-FU group. However, the tape alone group had a larger mean area due to one patient who was randomized to this group with a total wart area nearly four-fold higher than the largest total area of any patient in the 5-FU group.

In addition, both groups had a similar history of prior treatments. Ninety-three percent (37/40) of patients had previous therapy on the treated lesions prior to study enrollment. These treatments

Figure 11. Patient #4 at baseline visit. Multiple warts were debrided under the second through fourth metatarsal heads. This patient was randomized to the tape alone group (no 5-FU was utilized).

Figure 12. Patient #4 at Week 12 of treatment with tape alone. Evidence of maceration of the warts is present, but no cure and no erosion of the warts is noticed as with the 5-FU treated subjects.

	5-FU with Tape (n=20)	Tape only (n=20)
Age, years		
Mean (SD)	48 (14.0)	43 (11.7)
Min-Max	22-74	19-62
Sex*		
% Female:Male	1:1	4:1
Height, inches		
Mean (SD)	68 (3.2)	67 (3.3)
Min-Max	62-73	61-74
Weight, pounds		
Mean (SD)	178 (55.1)	169 (43.8)
Min-Max	115-370	116-290
Affected side		
Left	6	9
Right	14	11
Length of time warts present, years		
Mean (SD)	4.6 (3.9)	5.1 (4.0)
Min-Max	0.4-15	0.4-15

** P value = 0.10*

	5-FU with Tape (n=20) No (%)	Tape only (n=20) No (%)
Patient-rated baseline severity of warts*		
Severe	7 (35)	10(50)
Moderate	9(45)	7(35)
Mild	4 (20)	3(15)
History of other treatments*		
Salicylic acid	15	12(60)
Cryotherapy	13(65)	9(45)
Other (Surgical excision, laser excision, or electrocautery)	7(35)	11(55)

** No significant difference between groups*

Table 1. Demographics and Selected Characteristics among the Cases and Controls.

Table 2. Descriptive Variables among the Cases and Controls.

included salicylic acid (68%), cryotherapy (55%), surgical intervention including curettage, laser excision, or electrocautery (38%), duct tape (10%), imiquimod cream (8%), oral cimetidine (3%), cantharidin (3%), and intradermal bleomycin (3%). Sixty percent (24/40) of patients enrolled stated they attempted 2 or more of the above treatment modalities without success, and 23% (9/40) attempted 3 or more. Seventy percent (28/40) of patients had at least one prior visit to a physician for treatment of their plantar warts. There was equal distribution between the 2 groups on these prior treatments.

PRIMARY EFFICACY ASSESSMENT

At the end of the 12-week treatment period, 19/20 patients (95%) achieved complete cure of all warts with 5% 5-FU under tape compared to 2/20 patients (10%) in the tape alone group ($p<.0001$). Both groups had a similar average length of time to cure (9 weeks in the 5-FU group and 11 weeks among the controls as presented in Table 3).

Six months after therapy completion (primary efficacy endpoint), 3/20 patients (15%) in the 5-FU treatment group had a recurrence whereas 1 out of 2 patients (50%) in the control group had a recurrence. Therefore, an 85% sustained cure rate was maintained through the 6-month follow-up period using 5-FU under tape. Correspondingly, only a 6% (1/18 patients) sustained cure rate was seen with the tape alone group through the 6-month follow-up visit. Notably, 94% (17/18 patients) in the tape alone group had a reduction in size of their lesions after 12 weeks of treatment.

SECONDARY OUTCOME MEASUREMENTS

There was a trend toward decreased pain as reported by patients in both groups. In the 5-FU group, the mean pain score decreased from "slight" at baseline to "none" at the 6 months follow-up. Participants in the study were also surveyed regarding assessment of overall improvement. At 6 months follow-up, there were a significantly greater percentage of cases (17/20 or 85 %) with "complete recovery" compared to controls (2/18 or 11 %). Accordingly, the patients' assessment of improvement matched that of the investigators. Among the 3 patients in the 5-FU group who had a recurrence at 6 months follow-up, 2 patients rated their overall condition as "much better" and 1 patient answered "no change."

	5-FU with Tape (n=20)	Tape only (n=20)
Cure (%)*	19(95)	2(11)
Length of time to cure, weeks†		
Mean (SD)	9(2.8)	11(1.4)
Min-Max	4-12	10-12

* *p value* <.0001
† *p value* = N.S.

Table 3 (above). Complete Cure Rates by 12 Weeks.

	Baseline		12 weeks	
	(N)	Mean (SD) Min-Max	Mean (SD) Min-Max	Mean Reduction (Baseline to 12 Weeks)
Wart size*			16-930 mm^2	0-867 mm^2
5-FU /Tape	(20)	68.3(59) mm^2 20-228 mm^2	0.1 mm^2 0-4 mm^2	99%
Tape	(20)	196.8(284) mm^2	116.4 mm^2	41%
Number of warts†			1-11	0-11
5-FU/Tape	(20)	2.9 (2.3) 2-10	0.02 0-1	-2.9 warts
Tape	(20)	3.5 (3.0)	2.7(2.7)	-0.8 warts

*At baseline p= N.S.; 12 weeks p <.0001
†At baseline p = N.S.; 12 weeks p = .015

Table 4 (right). Change in Total Wart Size and Number of Warts by 12 Weeks.

Other variables examined were wart size and total number of warts. Both groups showed a decrease in size and total number of lesions (Table 4). The mean percentage reduction in total size of warts from baseline was significantly greater in the 5-FU group compared to the control group at the end of treatment. However, one patient who was randomized to the tape alone group had a total surface area four-fold higher than the largest area of any patient in the 5-FU with tape group. This explains the discrepancy in overall size of lesions between groups. Although this particular patient did not obtain a cure, a substantial reduction of total size of lesions occurred.

The mean number of warts cured by the 12-week end of treatment time point was significantly greater for the 5-FU group compared to the tape alone group (Table 4). There was an average reduction of 2.9 warts from baseline to end of treatment for the 5-FU group compared to an average reduction of 0.8 warts in the tape alone group ($p<.05$). All the participants in the 5-FU under tape group responded "definitely yes" when they were asked if they were willing to perform the therapy again, which was statistically significant compared to the controls ($p<.0001$). By contrast, 40% of patients in the control group answered either, "probably yes" or "definitely yes," to this question.

Summarizing the patient self-assessment forms, no significant difference between groups was seen in severity of warts at baseline. A total of 16/20 patients in the 5-FU group rated the classification (mild, moderate, or severe) of their warts prior to treatment as "moderate" or "severe" versus 17/20 in the control group. All patients who completed the 6-month follow-up responded "very much" (90%) or "somewhat" (10%) to the question, "Overall, how satisfied were you with the ease and comfort of the procedure?"

Pain at the site of treatment was described by 60% (12/20) of patients in the 5-FU group versus 50% (9/18) of patients in the tape alone group. Pain was primarily described as slight to mild and typically resolved within 1 week after treatment was stopped. Patients also related most of this discomfort during later follow-up visits. It is important to note that all patients who experienced pain related no negative effect in their activities of daily living. No patients stated they missed time from work or changed their activities as a result of discomfort from the treatment.

SAFETY

No serious adverse events were observed during the course of this study. The treatment was well-tolerated in both groups. No allergic reaction to 5-FU was observed; however, one patient in the tape-control group developed a skin irritation with the tape consistent with a mild tape allergy. This consisted of mild erythematous papules throughout the area of tape application. This reaction occurred in the last few weeks of treatment, did not prevent the patient from completing treatment, and resolved within 1 week after treatment stopped. One patient in the 5-FU with tape group presented with pitted keratolysis surrounding the location where tape was applied. This was caused by corynebacterium and actinomyces, which commonly occurs on the plantar surface of the feet. Hyperhidrosis secondary to prolonged tape occlusion was the likely cause. This event was deemed unrelated to the study drug and did not affect the patient's treatment course. This condition resolved within 2 weeks after the patient stopped treatment. The 2 patients who discontinued the study were both in the tape control group. One patient was withdrawn from the study due to poor compliance with the treatment protocol and the second patient was lost to follow-up at 6 weeks of treatment.

No hematologic abnormalities were observed in hepatic function test or complete blood count in any of the 20 patients in the 5-FU with tape group. Excellent compliance was achieved as all 20 patients in the 5-FU with tape group completed all required labs and follow-up visits.

DISCUSSION

The authors have used 5% 5-fluorouracil cream to treat more than 300 patients with solitary, multiple, and mosaic plantar warts. Prior studies have shown end of treatment wart clearance rates with 5% 5-FU ranging from 50% to 67%. However, these studies did not incorporate debridement, twice-daily dosing, and tape occlusion.[5-8,10,11] Incomplete resolution may be the result of limited penetration of 5-FU due to the highly keratinized skin overlying the HPV. The key to topical treatment of plantar warts is aggressive debridement of the hyperkeratotic tissue to allow penetration of medication into the virally infected skin. Most plantar warts resolve with 5% 5-FU under tape occlusion, but the recalcitrant wart may be better treated in conjunction with combination therapy (ie, cryotherapy, cantharidin). With combination therapy, 5% 5-FU may potentially be a potent treatment option for refractory warts as well.

Topical 5% 5-FU cream is well-tolerated by the patient. A mild to moderate ulceration with mild perilesional maceration and erythema will

be observed during the course of treatment. This is considered a positive sign in eradicating the HPV and should be visualized. When this is observed the patient is instructed to continue application for 1 to 2 more weeks and is then instructed to discontinue treatment. Simple local wound care consisting of a Band-Aid and OTC antibiotic ointment is then employed. The mild ulceration will heal generally within a couple of weeks.

For many years, clinicians have known the benefit of tape occlusion in treating warts. Tape occlusion is effective by causing: 1) maceration of tissue with resultant cell death; 2) decreased oxygen locally to the HPV; 3) increased local temperature; and 4) irritation of the HPV. Focht et al[12] described an 85% cure rate of warts in children with duct tape occlusion compared to a 60% cure rate with cryotherapy. Although treatment in our study with tape occlusion in adults was not as impressive as described by Focht in his study with duct tape, a robust response was seen in decreasing the size of lesions. Ninety-four percent (17/18) of patients in the tape alone group had a reduction in overall size of lesions using occlusive tape alone. However, only 2 patients (11%) had complete resolution of all warts at 6 months follow-up compared to 85% of patients in the 5-FU group. The addition of 5% 5-FU under tape occlusion appeared to increase the likelihood of complete cure in this study, as compared to tape occlusion alone.

There are a myriad of treatment modalities for plantar warts. This is due in part to insufficient treatments and few controlled studies describing consistent and predictable results. In our clinical experience, 5-FU has proven to be an advantageous and consistent first line treatment in our armamentarium of plantar wart therapies. This controlled clinical study has helped confirm our results. If used appropriately, with twice-daily dosing, tape occlusion and regular debridement, 5% 5-FU cream can be an effective treatment modality in treating plantar warts. In the present study, we found 5% 5-FU cream under occlusion to be safe and effective in the treatment of plantar warts.

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