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Effectiveness of New 5-Fluorouracil/Salicylic Acid Application Method for Periungual Warts: A Descriptive Study

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Dear Editor:

Topical salicylic acid (SA) has been suggested as first-line therapy for common warts[1]. If SA treatment has failed, liquid nitrogen cryotherapy could be considered as a second-line treatment[2]. However, in the periungual area, aggressive treatment increases the risk of serious side effects such as nail dystrophy regardless of higher efficacy[2,3]. Young and Cohen[4] reported that application of 5-fluorouracil (FU) and SA combined with regular paring down at 1- or 2-week intervals was safe and effective for plantar warts. However, they did not use commercially available 5-FU/SA preparation and the efficacy was not investigated for periungual warts. In this study, we report on the efficacy of a new application technique using commercially available 0.5% 5-FU/10% SA preparation for periungual warts.

We reviewed the medical records of all patients who began 5-FU/SA treatment for periungual warts at the SMG-SNU Boramae Medical Center from April 2012 to January 2018. Patients who were being treated concurrently with other treatments were excluded. Clearance was defined clinically as disappearance of warts with sustained normal skin color and skin lines for at least 4 weeks after the last application. If the lesion was enlarged during treatment or if the lesion size did not decrease significantly within 1 month, it was considered treatment failure. The study protocol was approved by the Institutional Review Board of the SMG-SNU Boramae Medical Center (30-2017-30) and the requirement for informed consent was waived.

The patients received one of two application methods: the new application method and the conventional method. Patients using the new application method were instructed to reapply 5-FU/SA over the film coating once a day, and the whitened film was pared only once a week, unlike the instructions in the drug label. This technique made the film firmer, and consequently, a larger portion of warts could be removed. During the first two to three weeks, the film was removed by a doctor. Later, the patients removed the film themselves with a nail clipper, except when they had difficulty in doing so, in which case the film was removed by the doctor. Alternatively, patients using the conventional method were instructed to apply 5-FU/SA to each wart once or twice daily and remove the existing film coating before reapplying 5-FU/SA according to the drug label. Logistic regression analyses were used to evaluate associations between predictive factors and treatment response. Variables included in the multivariable model were identified by backward selection.

A total of 50 patients with periungual warts were identified and treated with 5-FU/SA (Table 1). Thirty-six (72.0%) were male and median age at the time of presentation was 9.5 years (range, 1～49 years). Lesions were most frequently located on fingers (82.0%) and median number of involved digits was two (range, 1～10). Twenty-three patients (46.0%) had received prior treatments including cryotherapy, bleomycin intralesional injections, and ablative laser therapy. Of all the patients treated, with either conventional or new application treatment, twenty-five patients (50.0%) achieved clearance of periungual warts. Erythema and scaling were the most common adverse events. However, no patient discontinued treatment because of

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Table 1. Demographic and clinical characteristics of patients

Variable	All patients (n=50)	New method (n=34)	Conventional method (n=16)	*p*-value*
Age (yr)	9.5 (1.0~49.0)	10.0 (1.0~31.0)	7.5 (2.0~49.0)	0.715
Sex				
Male	36 (72.0)	23 (67.6)	13 (81.3)	0.501
Female	14 (28.0)	11 (32.4)	3 (18.8)	
Infection site				
Hand	41 (82.0)	28 (82.4)	13 (81.3)	>0.999
Foot	9 (18.0)	6 (17.6)	3 (18.8)	
Number of involved digits	2.0 (1.0~10.0)	2.0 (1.0~10.0)	1 (1.0~6.0)	0.472
Confined to the proximal nail fold				
No	30 (60.0)	24 (70.6)	6 (37.5)	0.034
Yes	20 (40.0)	10 (29.4)	10 (62.5)	
Previous treatment				
No	27 (54.0)	13 (38.2)	14 (87.5)	0.002
Yes	23 (46.0)	21 (61.8)	2 (12.5)	
Duration of therapy (d)	63.0 (7.0~331.0)	59.5 (7.0~161.0)	80.5 (10.0~331.0)	0.632
Clearance	25 (50.0)	21 (61.8)	4 (25.0)	0.032

Values are presented as median (range) or number (%).*Fisher's exact test or Mann–Whitney U-test for discrete and continuous variables, respectively.

Table 2. Univariable and multivariable analysis of treatment response to 5-FU/SA preparation in periungual warts (n=50)

Variable	Univariable analysis				Multivariable analysis*	
	Clearance (n=25)	Persistent (n=25)	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (yr)	10.0 (7.0~18.0)	8.0 (3.0~22.0)	0.987 (0.937~1.040)	0.625	-	-
Sex						
Female	5 (20.0)	9 (36.0)	Reference		-	-
Male	20 (80.0)	16 (64.0)	2.250 (0.628~8.057)	0.213	-	-
Infection site						
Hand	22 (88.0)	19 (76.0)	Reference		-	-
Foot	3 (12.0)	6 (24.0)	0.432 (0.095~1.966)	0.278	-	-
Lesion number	2.0 (1.0~3.0)	1.0 (1.0~3.0)	1.121 (0.874~1.437)	0.368	-	-
Confined to the proximal nail fold						
No	13 (52.0)	17 (68.0)	Reference		Reference	
Yes	12 (48.0)	8 (32.0)	1.962 (0.621~6.193)	0.251	5.398 (1.052~27.713)	0.043
Previous treatment						
No	12 (48.0)	15 (60.0)	Reference		-	-
Yes	13 (52.0)	10 (40.0)	1.625 (0.530~4.984)	0.396	-	-
Duration of therapy (d)	63.0 (33.0~91.0)	67.0 (42.0~97.0)	0.995 (0.984~1.006)	0.340	-	-
Treatment group						
Conventional method	4 (16.0)	12 (48.0)	Reference		Reference	
New method	21 (84.0)	13 (52.0)	4.846 (1.287~18.255)	0.020	11.006 (1.916~63.232)	0.007

Values are presented as median (interquartile range [IQR]) or number (%). 5-FU: 5-fluorouracil, SA: salicylic acid, CI: confidence interval, -: not available. *Variables included in the multivariable model were identified by backward selection.

the adverse events.

As shown in Table 2, the univariable logistic regression analysis revealed that the treatment group was the only variable associated with treatment response. However, in the multivariable logistic regression analysis, we found a significant association of treatment response with both the type of treatment and whether or not the wart was confined to the proximal nail fold (Table 2). Lesions confined to the proximal nail fold were associated with a significantly greater treatment response (odds ratio [OR], 5.398; 95% confidence interval [CI], 1.052～27.713; $p=0.043$). Additionally, a greater treatment response was seen for those with the new application compared with the conventional method group (OR, 11.006; 95% CI, 1.916～63.232; $p=0.007$) (Table 2).

These results suggest that the new 5-FU/SA application method is more effective for periungual warts compared with the conventional method. There are several studies comparing the effect of conventional 5-FU/SA application with the control group such as diathermocoagulation or placebo, showing clearance rates of 46%～85%, which are higher than the clearance rate of our conventional method group[5]. This discrepancy could be partly explained because previous studies examined rates of warts in general, whereas our study examined the efficacy of the drugs specifically in the periungual region.

Patients in the new application group were more likely to be refractory because there was a higher percentage of patients who had previous treatment and failed. Nevertheless, the new application method was associated with a higher clearance rate of periungual warts compared with the conventional method both in univariable and multivariable analyses. These results suggest that the higher success rate of the new method was due to the technique of the application of 5-FU/SA itself rather than the different baseline patient characteristics.

When cryotherapy fails, treatments such as ablative laser can be tried, which require relatively expensive devices and involve high costs. In contrast, our new method is inexpensive (one bottle of 5-FU/SA preparation is approximately $10 in Korea) and easy to apply (no need for additional occlusion or normal skin protection). Most of all, this method is nearly painless even though patients have multiple periungual lesions.

In this study, warts confined to the proximal nail fold were associated with good clinical outcomes. Choi et al.[6] reported that proximal nail fold warts had higher clearance rates with diphenylcyclopropenone immunotherapy than warts on the lateral nail fold or hyponychium. These findings suggested that the eponychium may serve as a barrier protecting the nail bed[6].

Our study had several limitations. Similar to other retrospective chart review studies, there is a possibility that biases were present. Also, we only included patients with periungual warts in our cohort; therefore, our results may not be generalizable to all cutaneous warts.

Despite these limitations, our results suggest that the new application method of 5-FU/SA for periungual warts is an effective alternative. Because of convenience and low cost, the new application method of 5-FU/SA preparation should be considered first before other more painful and expensive treatment modalities.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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