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COMPARATIVE STUDY OF 5% IMIQUIMOD CREAM AND 5% 5-FLUOROURACIL CREAM IN VIRAL WARTS

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Abstract

Background: Aim of the study was to ascertain efficacy of 5% imiquimod cream and 5-FU 5% cream in treatment of all kinds of viral warts. **Material and methods:** A double blind, randomised, controlled trial was conducted in skin OPD of tertiary hospital, during Jul 2007 to Jun 2009. The effectiveness was measured by two variables; complete wart clearance or a ≥50% reduction in total wart sizes within a maximum treatment period of 16 weeks. P value less than 0.05 was considered significant. **Results and analysis:** 192 cases [Imiquimod (n=95) and 5-FU (n=97)] completed the study. Maximum total clearance of warts was in anogenital warts (44.4%) in imiquimod group while it was palmar warts (17.6 %) in 5-FU group. At the end of 16 weeks both the groups shown improvement from baseline, however the difference in efficacy was not statistically significant in any individual type of wart (p>0.05). Adverse effects were seen in 18 patients (18.9 %) and 27 patients (27.8%) in Imiquimod and 5-FU group respectively. This difference was statistically significant. **Conclusion:** There is no significant statistical difference in the efficacy of the two drugs in treatment of different types of viral warts but imiquimod had significantly lesser adverse effects.

Key Words- Viral warts, imiquimod 5% cream, 5-Fluorouracil 5% cream

Introduction

Warts (verrucae) are common dermatoses caused by different types of Human Papilloma Virus. These virus induced skin lesions are pleomorphic and can affect variety of sites, principally skin of extremities and genital area. They present clinically as common warts or verrucae vulgaris, plane warts, plantar warts, palmar filiform or digitate and anogenital warts1[2].

At present, different modalities of treatment are available like excision, laser ablation, electrosurgery, cryotherapy, caustic agents like trichloroacetic acid, podophyllin resins and intralesional interferons[3]. Several other modalities of treatment like intralesional bleomycin, candida antigen and other anecdotal therapies exist[1]. Most of these procedures are painful and require number of visits to the dermatologist and hence frequently, patients default on treatment. Invasive procedures are also associated with complications like scarring, post operative infection, pain and restriction in the activities of the patients.

Topical 5% Imiquimod cream is a relatively new modality of treatment of warts. Imiquimod is a potent stimulator of innate and adaptive arms of immune system through induction of synthesis and release of different kinds of cytokines like interferon- α, tumour necrosis factor-α and interleukins-(1, 6, 8, 10, 12)[4-6]. Presently, Sexually Transmitted Diseases CDC guidelines, approves imiquimod for genital warts while FDA have given approval for use in genital warts, actinic keratosis and basal cellcarcinoma[7]. There are multiple reports of its use in it other conditions like Bowen's disease (in situ squamous cell carcinoma), common warts, plane warts, molluscum contagiosum and herpes simplex with variable outcome[5,6].

Topical 5-fluorouracil (5-FU) has been used in clinical practice since the 1960s. It is a structural analogue of thymine that blocks DNA synthesis by inhibiting thymidylate synthetase[8]. 5-FU 5 percent cream has been approved by the U.S. Food and Drug Administration (FDA) since 1970 for the treatment of actinic keratoses at any location. 5-FU 5% cream is also approved by the FDA for the treatment of superficial basal cell carcinomas[9]. Verrucae vulgaris, verrucae plana, plantar warts, and condylomata acuminatae, keloids and hypertrophic scars, actinic cheilitis, mucosal leukoplakia, radiodermatitis, Bowen disease, Bowenoid papulosis, psoriasis and keratoacanthoma, infantile digital fibromatosis and erythroplasia of Queyrat have been treated with varying response rates with topical and intralesional 5-FU10,11. There is no published comparative study of topical 5% Imiquimod cream and 5-fluorouracil 5% cream in viral warts from India. In view of the above, it was proposed to undertake this study to ascertain comparative efficacy of 5% imiquimod cream and 5-fluorouracil 5% cream in treatment of all kinds of viral warts; to study the adverse effects and make recommendations based on the above study.

Material and Methods

Study design and patient sample

A double blind, randomised, controlled trial was conducted in a tertiary hospital at Pune, during the period Jul 2007 to Jun 2009. Blinding was done by removing the contents of each medicine and putting in small (5g) similar looking plastic jars marked Gp

A and Gp B. The patients and investigator was not aware of the coding till the end of the study, when code was broken. An independent dermatologist not involved in the project did the coding and another dermatologist evaluated the results. Patients were distributed randomly by following simple random table depending upon their wart types. For analytical purpose the patients were divided into two groups Gp A and Gp B depending upon the types of cream they applied in this case imiquimod (Gp A) and 5-Fu (Gp B) cream respectively. Clinically distinct viral warts like verruca vulgaris or verruca plana, palmar warts, plantar warts, genital warts were grouped into distinct groups and studied and compared separately with similar group. The basic aim of the study was to see the effects of imiquimod 5 % cream and 5% 5-fluorouracil cream in all kinds of viral warts. Any adverse effects to creams were entered into proforma..

Institutional Ethical Committee approval was taken. All patients were informed of the study objectives and requirements and written consents were taken. The expected number of visits was three: at study inclusion (baseline visit), after four weeks (visit 2) and at the end of treatment (visit 3 - when complete wart clearance was achieved or up to a maximum of 16 weeks).

The diagnosis of warts was based on clinical examination. The patients were instructed to apply these creams by finger tip on the lesions thrice a week for a period of 12 hours. In case lesions were too small, patients were advised to use cotton tip bud for application of cream. Patient was advised to wash hands with soap water before and after application of drugs. Cream was to be washed in the morning with soap water. For cases of palmar and plantar warts both the cream were applied under occlusion.

The patients were followed up fortnightly for clinical evaluation and to record any adverse effects. Pre and post treatment photographs were recorded. Age, sex, HIV status in genital warts, history of any prior treatment, was noted in proforma.

Exclusion criteria: Patients who had already taken treatment within 01 month prior to study, patients with two or less than two warts, subungual warts, filiform warts, HIV patients on antiretroviral drugs, pregnant and lactating women were excluded from the study.

Study variables

The effectiveness of imiquimod and 5-FU was measured by two variables; complete wart clearance or a 50% or greater reduction in total wart area within a maximum treatment period of 16 weeks. Treatment failure was measured as a reduction of less than 50% of the total wart area. The site and number of lesions was recorded in a clinical photograph. The recorded photograph were also compared.

Data on treatment tolerability were collected by recording the presence of local cutaneous reactions (erythema, oedema, vesicles, erosions, ulcerations, excoriation/flaking, scabs). Any patient-reported symptoms were also recorded and classified by the physician on a severity scale ranging from 1 to 3 (l=mild, 2=moderate, 3=severe).

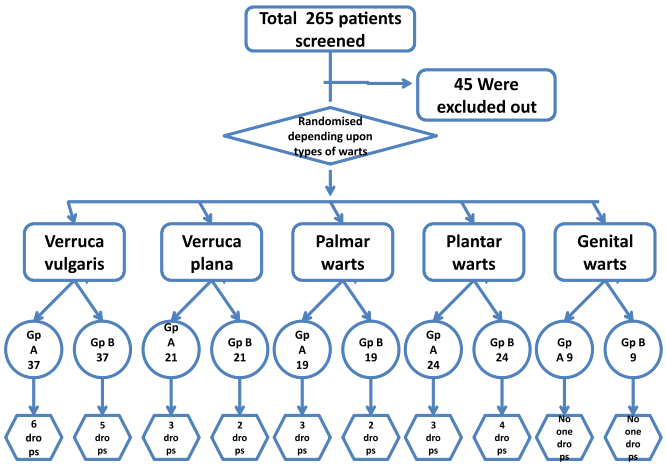
Statistical analysis

A comparative analysis of the effectiveness of imiquimod and 5-FU was done using Epi info 2009. Independent t test, Chi Square test and Fisher Exact test were carried out; P value less than 0.05 were considered statistically significant.

Results and analysis

Total 265 patients with different types of warts were screened, out of that 45 were excluded as they did not fit in to inclusion criteria. Remaining patients were randomised into two groups Gp A and Gp B depending upon their types of warts. This has been depicted in figure 1. Table1 gives the profile of the patients as per their clinical variants. Finally, 192 cases (Gp A 95 and Gp B 97) completed the study from different types of warts from both the groups. Only one patient was HIV positive who was not on any antiretroviral drug.

Figure 1: Flow chart depicting the distribution of patients,



exclusion and drop out in the different types of warts. (Total 265 patients screened for warts. 45 patients were excluded from study as they were not fitting into inclusion criteria)

Table 1: Profile of the patients as per their clinical variants

	Imiquimod 5% cream (Gp A)				5-Flurouracil 5% cream (Gp B)			
Clinical types	**Total no/(%) (n=110)**	**Male/female (total no - 78/37)**	**Average (mean age ± SD)**	**Average duration (weeks± SD)**	**Total no/(%) (n=110)**	**Male/female (n=80/35)**	**Average (mean age ± SD)**	**Average duration (mean weeks± SD)**
Verruca vulgaris	37	25/12	28.32±7.9	6.4±2.1	37	27/10	27.86±7.4	6.6±2.01
Verruca plana	21	13/8	26.04±7.01	5.7±1.6	21	12/9	25.33±6.4	5.66±1.6
Palmar warts	19	11/8	29.21±8.06	6.42±2.4	19	12/7	27.55±7.3	6.6±3
Plantar warts	24	17/7	29.70±7.8	6.5±2.8	24	18/6	28.04±7.3	6.2±2.7
Genital warts	09	8/1	30.6±7.2	3.4±1.4	09	8/1	29.44±7.1	4.4±2.06

Table 2. Percentage reduction in the wart sizes at different visits of follow up in both the study groups in different types of warts. (SD= standard deviation)

	Vulgaris			**Plana**			**Palmar**			**Plantar**			**Genital**		
	Percentage reduction in warts size from baseline± **SD**			Percentage reduction in warts size from baseline± **SD**			Percentage reduction in warts size from baseline± **SD**			Percentage reduction in warts size from baseline± **SD**			Percentage reduction in warts size from baseline± **SD**		
Visits	Gp A (n=31)	Gp B (n=32)	P value	Gp A (n=18)	Gp B (n=19)	P value	Gp A (n=16)	Gp B (n=17)	P value	Gp A (n=21)	Gp B (n=20)	P value	Gp A (n=09)	Gp B (n=09)	P value
Visit at 04 weeks	21.28± 10.61	20.16± 10.65	0.985	32.47± 12.76	32± 10.36	0.388	29.58± 8.27	33.31± 9.35	0.639	33.34± 8.1	29.35± 7.58	0.775	47.16± 18.88	33.8± 14.4	0.46
Visit at 08 weeks	42.69± 15.1	41.21± 14.38	0.787	50.97± 22.36	47.1± 18.28	0.404	47.37± 16.13	50.28± 16.41	0.951	47.31± 14.48	45.12± 13.79	0.841	70.58± 29.49	50.06± 20.78	0.341
Visit at 16 weeks	57.82± 21.63	55.18± 20.29	0.724	61.72± 23.55	57.22± 20.93	0.623	61.9± 21.38	65.41± 23.24	0.741	61.39± 20.77	58.1± 21.05	0.950	77.28± 24.75	63.17± 22.38	0.782

Comparison of imiquimod 5% cream with 5-fluorouracil 5% cream

The efficacy of imiquimod 5% cream and 5-FU is quite variable in different types of warts. Percentage reduction in warts sizes at three different visits in the two groups is shown in table no2. Comparative efficacy of both the drugs at the end of 16 weeks is depicted in table no 3.

	Vulgaris		Plana		Plamar		Plantar		Genital	
Wart clearance	Gp A (n=31)	Gp B (n=32)	Gp A (n=18)	Gp B (n=19)	Gp A (n=16)	Gp B (n=17)	Gp A (n=21)	Gp B (n=20)	Gp A (n=09)	Gp B (n=09)
Complete clearance (n&%)	4 (12.9)	3 (9.3)	3 (16.6)	2 (10.5)	2 (12.5)	3 (17.6)	2 (9.5)	2 (10)	4 (44.4)	1 (11.1)
Equal or more than 50% clearance (n&%)	9 (29.03)	9 (28.1)	5 (27.7)	5 (26.3)	5 (31.2)	5 (29.4)	7 (33.3)	5 (25)	2 (22.2)	3 (33.3)
Less than 50% clearance (n&%)	18 (58.06)	20 (62.5)	10 (55.5)	12 (63.1)	9 (56.2)	8 (47.05)	12 (57.1)	13 (65)	3 (33.3)	5 (55.5)

Table 3: Response of topical Imiquimod 5% cream (Gp A) and 5-Fluorouracil cream (Gp B) in different types of viral warts at the end of 16 weeks. (p value > 0.05)

Average duration in complete clearance of warts in imiquimod group in verruca vulgaris, verruca plana, palmar, plantar warts and genital warts were 10, 7.33, 11.5, 10 and 7 weeks respectively. While average duration in 5-FU group in these warts were 10, 7.5, 10, 11.5 and 8 weeks respectively. Imiquimod is more efficacious in comparison to 5-FU in verruca vulgaris, verruca plana, plantar and genital warts. 5-FU is more effective in the management palmar warts. This is illustrated in figure2.

However, there was no intergroup significant statistical differences in the complete wart clearance or more than 50% warts clearance (p>0.05) in any type of wart. Figure 3 shows before and after result of imiquimod 5% cream in plantar warts

Itching, redness, erosions, oedema were noticed in both the groups while hyperpigmentation (n=2 in verruca plana) and photosensitivity (n=1; verruca plana) were additionally seen in 5-FU group. The maximum adverse effects was seen in anogenital wart; imiquimod (n=2; 22.2%) and 5-FU (n=3; 33.3%). Overall, it was found that 18 patients (18.9 %) developed adverse effects to imiquimod and 27 patients (27.8%)

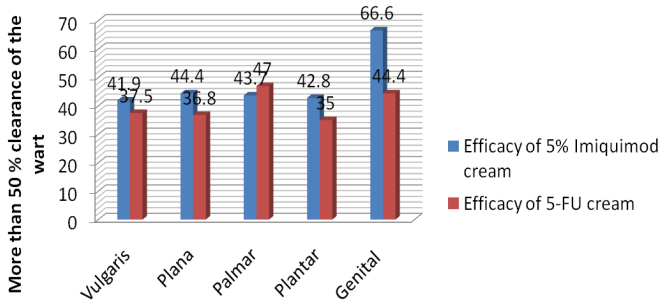


Figure 2: Graph depicting the efficacy of 5% imiquimod and 5-fluorouracil at the end of 16 weeks.

developed adverse effects to 5-FU cream. Although number of the patients with adverse effects were large but most of them had very mild reaction which did not require dropping from the study. They become alright after 3-4 days gap of therapy. The differences in adverse effects between the groups were significant (p<0.05).

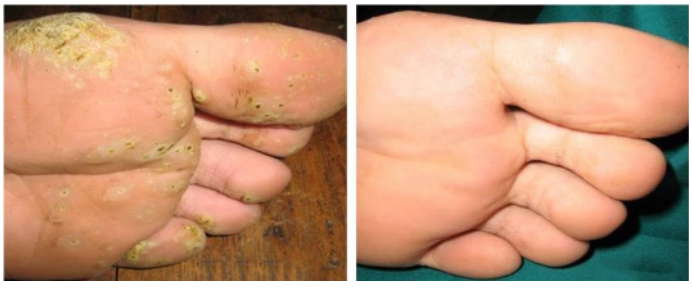


Figure 3: Before and after result of imiquimod 5% cream in a case of plantar warts.

DISCUSSION

This doubled-blind, randomized study has revealed that efficacies of imiquimod and 5-FU in different clinical subtypes of viral warts are quite variable.

Anogenital warts

In the present study, 44.4% patients of anogenital warts achieved complete clearance of lesions over an average treatment duration

of 7 wks in imiquimod groups while it was 11.1% in 5-FU group over a period of 8 wks. This finding about imiquimod is in consonance with other placebo-controlled studies which show complete clearance of anogenital warts in 35-53% patients12-19. Similar to the result found in this study, an uncontrolled observational study evaluating the effectiveness and satisfaction with imiquimod showed a 61% complete wart clearance rate after 16 weeks by Vilata et al[20]. In a study by Beutner et al[13], complete clearance rate was 35%. Treatment duration with imiquimod was eight weeks as opposed to the 16 weeks in this study, which could explain the difference in results. A study by Edwards et al[14] and another study by Beutner et al[15], which include the same treatment duration as this study, found a greater efficacy rate of 50% and 52%, respectively.

Our results regarding 5-FU is less encouraging in comparison to other studies. This may be because of lesser patient numbers and thrice weekly application of drug. In study by Chattopadhyay et al[21] in condylomata acuminata; twenty cases (80%) showed disappearance of all warts, 3 (12%) cases showed moderate response and 2 (8%) cases failed to respond with fluorouracil cream. In a study by Dogra et al[22] efficacy of 5-FU was 100% as both the cases showed complete clearance of warts after 03 wks when applied twice daily. However, in this study, number of patients having anogenital warts was only two.

Our study did not reveal any difference in clinical response on the basis of gender. Some other studies corroborate this finding[23,24]. Some studies published to date reflect a higher efficacy rate in women than in men[15-19].

The incidence of adverse events was slightly higher than that reported in previous studies conducted in a RCT context [16,18].

Verruca vulgaris

For verruca vulgaris, our study revealed complete wart clearance in imiquimod group to be 12.9% and in 5-FU group 9.3% after 16 weeks of therapy and more than 50% clearance in 29 % and 28.1% of patients respectively. The result of imiquimod is similar to study by Hengge et al. Hengge et al[25] treated common warts with imiquimod 5% cream as monotherapy applied overnight for 5 days weekly. Thirty percent of patients had a total clearance of warts and twenty-six percent had equal to or greater than 50% reduction in wart size. In a study by Chattopadhayay[26], in verruca vulgaris group; six (30%) showed 'Good' response while 10 (50%) showed only 'Moderate' response and 4 (20%) cases showed 'Poor' response with 5% 5 fluorouracil cream. In a single-centre, double-blind, randomized, placebo-controlled trial study conducted by Luk NM et al[27], topical 5-fluorouracil has no additional benefit in treating common warts with cryotherapy. An open label pilot study of 5% 5-Fluorouracil cream for treatment of verruca vulgaris in children by Gladsjo JA et al[28] revealed that 88% of treated warts improved after 6 weeks of treatment, and 41% of subjects had complete resolution of at least one wart. The results of 5-FU in verruca vulgaris are much more encouraging than our present studies. This may be because of lesser frequency of 5-FU application in our study to ensure blinding.

In comparison to other modalities of therapy, adverse effects of imiquimod and 5-FU are almost negligible in cases of verruca vulgaris.

Verruca plana

In imiquimod group, complete clearance of lesions was noted in 16.6% and more than 50% reduction in warts size was noted in 27.7 % of patients while in 5-FU group, it was 10.5 and 26.3% respectively. Mild itching, burning sensation were noted in both groups, however, patients of 5-FU group noticed hyperpigmentation (10.5%) and photosensitivity (5.2%) in addition.

Many case reports have suggested therapeutic role of imiquimod in the management of verruca plana[29,30.] Schwab and Elston[29] reported a case of 21-year-old woman with a 2-year history of multiple facial flat warts that were resistant to retinoic acid, adapalene gel, 5-fluorouracil, cryosurgery, and oral cimetidine. Imiquimod 5% cream applied 3 nights per week completely cleared the flat warts in 3 weeks. Complete clearing of facial flat warts in an HIV positive man has been reported [7] with imiquimod 5% cream applied 3 times per week. Flat warts on the fingers and dorsum of the hands in a 42-year-old man cleared with imiquimod applied three times a week for 6 weeks[30]. It is very safe to use imiquimod 5% in verrucae plana as there are no significant adverse effects with therapy. In a study of Dogra et al[22], 4 patients (80%) shown more than 50% reduction in wart size however no patient showed complete clearance of warts. Verrucae plana which are quite extensive where destructive modalities have their own limitations, 5-FU and imiquimod offer a good alternative.

Palmar warts and plantar warts

This study proves that 5-FU is superior to imiquimod in treating palmar warts. In the study by Dogra A et al [22], 5-FU had shown much better efficacy than this study. However, this study had only 07 patients. Sparling et al[31] obtained even better results with imiquimod 5% cream by adding cryotherapy and occlusion. A 17-year-old girl with a plantar wart on each foot (left foot, 2.0 x 4.8 cm) was treated with a nightly application of 5% imiquimod cream under occlusion with complete clearance at 6 weeks. Because of the heavy keratinization of common and palmar warts, imiquimod probably does not penetrate enough to activate an immune response to the human papilloma virus. The addition of keratolytics like tazarotene gel or 40% urea gel applied on alternating nights with imiquimod under occlusion (or applied in the evening and imiquimod at bedtime under occlusion) appears to increase the effectiveness of the latter[7].

In a study conducted by Salk RS et al[32] 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. Better results in this study as compared to ours can be because of twice daily application of 5-FU.

In the overall analysis, it was seen that both drugs are effective in the treatment of various types of warts. However, there was no statistically significant difference between the two drugs in any type of wart or overall. Since there is no other study comparing these two drugs in warts, we are unable to compare our study with other studies in this respect. It is also suggested after comparing with other studies that daily application of imiquimod and 5-FU will show better results. In respect of adverse effects, it was found that there was a statistically significant difference between the two medications in favour of

imiquimod as compared to 5-fluorouracil. Again, comparative adverse effect profile of these two drugs and their significance is not available in the literature. Less number of the patients in each clinical variant was the limitations of the study. A larger sample of each entity will give correct assessment of the efficacy of the drugs.

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