EFFICACY OF TOPICAL ADAPALENE IN TREATMENT OF PLANTAR WARTS

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ABSTRACT

Objective: To compare the efficacy of topical Adapalene gel 0.1% under occlusion with cryotherapy in the treatment of plantar warts.

Study Design: Quasi experimental study.

Place and Duration of the Study: Department of dermatology, Pak Emirates Military Hospital, Rawalpindi, from Jan 2017 to Jun 2017.

Methodology: A total of 96 patients were selected from Dermatology outpatient department, Pak Emirates Military Hospital Rawalpindi. Patients were randomly allocated into two treatment groups: group A and group B by lottery method. Patients in group A were treated with cryotherapy for two freeze thaw cycles using liquid nitrogen at -196°C temperature through direct application by a dipstick with cotton tip while group B were treated with topical adapalene 0.1% gel applied daily under occlusion using plastic wrap polythene sheet. Cryotherapy was repeated on fortnightly follow-up. The primary outcome measured was the proportion of participants whose warts completely cleared at 8 weeks after start of therapy.

Results: Twenty seven patients (72.97%) in group-A and 28 (75.68%) patients in group-B achieved clearance of warts after 8 weeks of therapy. A *p*-value of 0.791 revealed no significant difference in outcome for both treatment groups.

Conclusion: Cryotherapy and topical 0.1% Adapalene under occlusion for the treatment of plantar warts are equally effective.

Keywords: Cryotherapy, Plantar warts, Topical adapalene.

INTRODUCTION

Warts are spiny, rough papules or nodules that can be found anywhere on skin. They are caused by human papilloma virus (HPV) infection. There are over 100 HPV types documented. Approximately 6% of children and 2% of adults consult the doctor for warts. The clinical appearance of warts is diverse and it depends on the type of HPV involved and the site of infection. Plantar warts are benign but they may cause pain and discomfort. They are usually caused by HPV genotype 1, 2 and 4. It has been proposed that HPV type influence the natural course and response to treatment for plantar warts[1,2].

The virus enters the skin through a small breach. It can survive in the environment at low temperatures for prolonged periods and therefore, it can be contracted from inanimate objects. Keratinocytes infection is followed by hyperplasia of the epidermis which clinically appears in the form of an exophytic lesion. Plantar warts represent approximately 35% of cutaneous warts[3].

There are various modalities available for the treatment of warts. Treatment modality should be chosen considering various factors like patient comorbid conditions, age, location of warts, size, number, cost of therapy and adverse reactions associated with the treatment[4].

The pharmacological treatment of warts can be grouped into destructive, virucidal, antimitotic and immunotherapy. Cantharidin (0.7% or 3%) and salicylic acid (15%–60%) are examples of destructive therapy. Topical cidofovir (1%–2%) and intralesional interferon-α (106 IU) are virucidal. Bleomycin, podophyllotoxin (0.5%),

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and 5-fluorouracil (Topical: 5%, Intralesional: 3 mg/mL) have antimitotic effects while candida antigen (0.3 mL) and imiquimod (2.5%, 3.75%, 5%) are modes of immunotherapy. If the patient does not respond to one therapy for three consecutive months, alternate therapy should be ensued. Using quadrivalent HPV vaccine for recalcitrant wart treatment, 58.8% cure has been reported[5,6].

Cryotherapy has been conventionally used in treatment of plantar warts. Liquid nitrogen with a boiling point of -195.6°C is the cryogen of choice. Liquid nitrogen is applied either by cryospray or cotton bud. Cryotherapy induced tissue injury is via ice crystal formation within cells, vascular thrombosis and osmotic difference induced by cooling followed by rapid thawing. Therapy protocols vary among the physicians, however a repeat of therapy after every 2 weeks is recommended till the lesion clears. A clearing rate of upto 69% with a mean of 49% has been reported. However pain, bruising, irritation, scarring, hypopigmentation and hyperpigmentation may be encountered after cryotherapy[7].

To avoid such side effects, many alternative treatment modalities have been tried. Adapalene, a synthetic naphthoic acid derivative, is one amongst them. It is a retinoid and has the ability to alter keratinization and affinity for retinoic acid receptors predominantly found in the epidermis. It has been found to have anti-inflammatory action, inhibits cell proliferation and modulates cell differentiation. It is available as 0.1% and 0.2% aqueous gel. A regional study has shown complete disappearance of the lesions in an average of 39 ± 15.07 days with topical adapalene use[8].

This research was intended to help demonstrate whether topical adapalene is an effective alternative to conventional therapies in treatment of plantar warts.

METHODOLOGY

We carried out this study at Dermatology department of Pak Emirates Military Hospital Rawalpindi, from January to June 2017 after approval from ethical committee of the institute. The sample size was calculated via WHO calculator by using 8 week results of the reference study[9]. A total of 96 patients were recruited by consecutive sampling technique after written informed consent among which 23 patients were lost to follow up, including 11 patients in group A and 12 in group B. Thus, data of 74 patients was finally analyzed. Individuals aged between 15-45 year, of both genders, having 1-3 plantar warts for a maximum duration of twelve months were included in the study. Pregnant ladies, individuals with any systematic illness, on immunosuppressive therapy, those who had used any treatment for plantar warts in the last 4 weeks or presenting with mosaic warts and patients who were unwilling for follow up were excluded from the study.

Patients were randomly allocated into two treatment groups: group A (cryotherapy, n=37) and group B (adapalene 0.1% gel, n=37) by lottery method. Patients in group A were treated with cryotherapy for two freeze thaw cycles using liquid nitrogen at -196°C temperature through direct application by a dipstick with cotton tip while group B were treated with topical adapalene 0.1% gel applied overnight daily under occlusion using plastic wrap polythene sheet. Cryotherapy was repeated on fort-nightly follow-up, when required. Once there was improvement, in the form of return of normal skin texture, they were followed up for clearance without any further cryotherapy. In both the groups, thick areas of skin were pared before doing cryotherapy or applying adapalene gel. The effect of treatment was evaluated fort-nightly. The efficacy measured was the proportion of participants whose warts were cleared at 8 weeks. All data was recorded on a specially designed performa.

Data was analyzed using SPSS version 21. The quantitative variables like age and duration of illness were calculated by taking means and standard deviation. The qualitative variables like gender and the outcome or efficacy were calculated by taking frequency and percentages. Comparison of efficacy in two groups was done

by chi-square test. *p*-value of ≤0.05 was considered as significant.

RESULTS

A total number of 74 patients were selected including 37 patients in each group A and B. Over all mean age of the selected patients was 27.04 ± 9.44 years. Mean age in group-A (n=37) was 27.14 + 9.62 years, whereas it was 26.95 ± 9.39 years for group-B (n=37). Comparison of both groups regarding efficacy in terms of age groups 15-24 years, 25-34 years and 35-45 years revealed *p*-value of 0.36, 0.41 and 0.079 respectively using chi-square test.

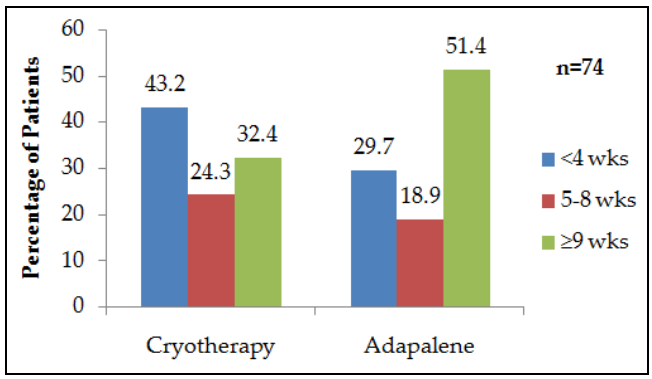

Figure: Frequency of duration of warts in treatment groups.

In group-A, 25 (67.6%) patients were males and 12 (32.4%) were females, whereas in Group-B, 29 (78.4 %) patients were males and 8 (21.6%) were females. Gender stratification in terms of efficacy among study groups showed *p*-value of 0.99 and 0.69 for male and female genders respectively.

16 patients (43.2%) were having disease duration of less than 4 weeks, 9 (24.3%) had duration between 5 to 8 weeks and 12 (32.4%) had duration more than 9 weeks in group-A. In group-B, 11 (29.7%), 7 (18.9%) and 19 (51.4%) had disease duration of less than 4 weeks, 5-8 weeks and more than 9 weeks respectively. Both groups were compared in terms of efficacy for duration of warts in weeks <4, 4-8 and ≥9 revealing *p*-value of 0.683, 0.042 and 0.842 respectively using chi-square test (figure).

In group-A, 7 (18.91%), 18 (48.64%) and 12 (32.43%) patients, while in group-B, 7 (18.91%), 21 (56.75%) and 9 (24.32%) had one, two and three warts respectively. When compared for efficacy between two treatment groups in terms of number of warts, 2 and 3 warts group had *p*-values of 0.52 and 0.44 respectively using chi-square test, while patients with a single wart showed complete clearance at 8 weeks in both treatment groups.

Efficacy in terms of clearance of warts at 8 weeks following therapy (table), was seen in 27 patients (72.97%) of group-A while 28 patients (75.68%) of group-B. Comparison of efficacy in both groups was done using pearson chi square test that showed a *p*-value of 0.791 showing that there was no statistically significant difference between the two study groups.

Table: Comparison of efficacy at 8 weeks following treatment.

Completely Cleared	Group A (n=37)		Group B (n=37)		*p*-value (n=74)
	No. of patients	%	No. of patients	%	
Yes	27	72.97	28	75.68	0.791
No	10	27.03	09	24.32	

DISCUSSION

Warts are spiny, exophytic papules or nodules caused by infection of keratinocytes by human papilloma viruses (HPVs)[1]. There are various modalities available for treatment of warts which include physical destruction (e.g, cryotherapy), chemical destruction (e.g, salicylic acid) and immunomodulator therapy (e.g, retinoids)[10].

Cryotherapy has been conventionally used in treatment of plantar warts. Liquid Nitrogen with a boiling point of -195.6°C is the cryogen of choice. The response to treatment with cryotherapy is comparable to the response achieved with gold standard treatment modality, salicylic acid, as demonstrated by Kwock *et al*[11]. Bruggink

et al demonstrated that cryotherapy is more effective than salicylic acid in treatment of common warts but not plantar warts[18].

Due to adverse effects and availability issues of liquid nitrogen, many alternative agents have been evaluated in treatment of plantar warts. Among them retinoids have shown some promise. Olguin used oral isotretinoin in treatment of recalcitrant facial warts with promising results[19], while Joshipura employed oral acitretin in resistant plantar warts[20]. Among the topical retinoids, adapalene is employed in treatment of warts. Gupta *et al*, observed that total time taken for clearance of plantar warts using 0.1% topical adapalene under occlusion was 39 ± 15.07 days[8]. Gupta *et al*, in another study compared topical adapalene aqueous gel 0.1% under occlusion with cryotherapy and found that use of topical adapalene resulted in complete clearance of 286 plantar warts in 24 patients in 36.71 ± 19.24 days while 124 warts in 24 patients treated with cryotherapy took 52.17 ± 30.06 days (p<0.05), concluding that adapalene is more effective than cryotherapy in the treatment of plantar warts[9].

Little head-to-head research has been carried out to compare the efficacy of topical adapalene and cryotherapy in treating plantar warts. Study conducted in our setup did not show significant difference in cryotherapy (group-A) and topical 0.1% adapalene (group-B) treatment groups. Clearance at 8 weeks was 44% and 80%, in cryotherapy and adapalene groups respectively in the reference study[9], while 72.97% and 75.68% respectively in our study. Mean age in both the groups in our study had no significant difference with most patients falling in 15-34 years age bracket. Gender difference was not marked in both groups. Duration of illness in both groups did not have any significant difference.

The difference of outcome was probably due to the fact that cryotherapy was done on each fortnightly follow-up under supervision by treating physician while adapalene had to be applied under occlusion daily by the patient him/her self at home. Although the technique of application of adapalene under occlusion was adequately explained at first visit and reinforced at follow-ups, correct method of application as well as daily treatment may have been an issue for the patients in adapalene group. On the other hand adherence in cryotherapy group was not a significant problem as patient had to visit once in a fortnight for treatment with no treatment in between. Thus, a major limitation of our study was an unsupervised application and adherence to treatment by the patients in adapalene group.

Whether improving compliance in adapalene group via decreasing the number of applications can change the results significantly has to be established in other studies. It is recommended to carry out further studies employing reduced frequency of applications under supervision in adapalene group. Moreover, increasing the strength of application from 0.1% to 0.2% may also be studied.

CONCLUSION

Cryotherapy and 0.1 % topical adapalene under occlusion are equally effective in the treatment of plantar warts.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare in this study.

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