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ORIGINAL ARTICLE

Efficacy of Topical 1% Adapalene Versus Cryotherapy in Treatment of Plantar Warts

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ABSTRACT

Background: 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 wart. The aim of the current study was To compare the efficacy of topical Adapalene gel 0.1% under occlusion with cryotherapy in the treatment of plantar wart

Methodology: It was Randomized control trial carried out at the Department of Dermatology, Combined Military Hospital, Abbottabad, Pakistan, from Feb 2022 to July 2022. A total of 60 Patients coming to hospital with complaints of plantar warts were randomized into two equal groups of 30 patients. Patients reporting on odd serial number were allocated to group A, treated with application of topical 1% adapalene gel overnight on daily basis under occlusion, while patients reporting on even serial number were allocated to group B, treated with cryotherapy for two freeze thaw cycles, done with liquid nitrogen at -196°C temperature using direct application by a dipstick. The primary outcome was to measure the complete resolution of warts after 8 weeks from start of treatment.

Results: Age range in this study was from 18 to 45 years with mean age of 32.366±8.61 years**,** while duration of disease was from 2 to 12 weeks with mean duration of 6.433±2.90 weeks. After 8 weeks of treatment, 27 patients (90%) in group-A, while 20 patients (66.66%) in group-B achieved complete resolution of warts (p-value 0.028).

Practical implication: In the practical implications of this study, while comparing topical adapalene versus cryotherapy in trials, an important fact is that cryotherapy is done under supervision by the physician on fortnightly basis while adapalene is applied under occlusion by patients themselves daily at home, so, a major advantage of use of adapalene gel is also its simplicity and convenience of use. Another advantage to the patient is in shape of painless application at home compared to the cryotherapy. However, one disadvantage with adapalene gel is that it has to be used under occlusion by plastic sheet on daily basis which may feel messy to some patients

Conclusion: Topical 0.1 % adapalene was more effective than cryotherapy in the treatment of plantar warts.

Keyword: Human papillomavirus, Plantar warts, Adapalene, Cryotherapy.

INTRODUCTION

Plantar Warts which are also called verruca, papilloma or verruca pedis are commonly found skin conditions reported in both adults and children. Warts appear as rough, spiny papules found anywhere on the skin. Human papilloma virus (HPV), which is a DNA virus, is responsible for the infection that causes these warts. The documented types of HPV are more than 100. The subtypes of HPV that typically causes warts on the skins of hands and feet include 1, 2, 4, 27 and 57. The inoculation of a keratinocyte is result of an epidermal abrasion as well as transient impairment of immune system.(1) Estimated annual incidence of plantar warts is 14%.(2) Consultation for warts is approximately 2% by the adults while 6% for the children.

Clinical appearance of warts varies and depends on the HPV type involved and the site of appearance of warts. Although benign, plantar warts can cause discomfort and pain. As reported in some studies, the response to the treatment of plantar warts and natural course may be influenced by the type of HPV involved.(3,4) The plantar warts appear clinically as well-confined lesions along with overlying hyperkeratosis. While debridement done with hyperkeratosis, bleeding is commonly visible along with the pinpointed skin lines interruption. When ambulated directly with pressure, warts are mostly pain full. Nails may also become dystrophic if involved in lesions of warts.(5) Existence of HPV is common on fomites. They also exist on common showers of swimming pools having abrasive surfaces which become high risk places to nurture the virus and cause epidermal erosion. (6) Virus easily lives over longer periods at low temperatures and comes into contact from inert cold objects. The entry of virus is made through small crakes in the skin. Keratinocytes thus become infected leading to hyperplasia of epidermal cells that appears clinically as exophytic lesion. Replication of the basal cell is encouraged by the virus. Granular and prickle cell layers goes through hyperplasia besides the papillae arching up the vasculature upwards into the wart. Eccentric nucleus of the keratinocytes encircled by koilocytosis indicates the cell damage by the virus. (5)

As per reports, 35% of total cutaneous warts are plantar warts. (5) Among these warts 30% are reported to be spontaneously cleared but the remaining ones cause pain, irritation and are also unappealing cosmetically. (6)

The treatments suggested for plantar warts include cryotherapy, salicylic acid, bleomycin, cantharidin, intralesional immunotherapy and laser. Unfortunately, none of these have proven to be vastly effective in all types of patients. (7,8)

Destruction of the affected cells of epidermis through burning it chemically or damaging it by using physical pressure is the idea behind most of above suggested treatments. In this process damage of healthy surrounding tissues causes pain in most of the patients.(8,9) On the other hand this planned cell damage don't destroy the virus in the cells of perilesional tissues resulting in failure of treatment and recurrence of warts.(8) It is reported that 2% of the population again goes for medical consultation after suffering from pain, limitation of their activities, prevention of infection and aesthetics.(2,8,10)

Among the above-mentioned therapies, cryotherapy is the first line therapy selected by most clinicians performed by applying liquid nitrogen directly on the warts.(11) For this purpose liquid nitrogen having a boiling point of -195.6°C is used. Cotton bud or a cryospray is used for application. The protocols of this treatment vary, however, therapy is repeated after every two weeks till the wart is cleared. (12) The therapy is based on producing a localized freezing by applying liquid nitrogen followed by slow thawing that result in destruction of the tissues infected by virus. This method therefore does not directly kills the virus. (13,14) Rapid application is one of the advantage of cryotherapy and it is also proven cost-effective.(12) The commonly found side effects are irritation, pain, scar formation bruising and dyspigmentation. Delayed healing and chances of relapses also accounts for possible disadvantages. (12,15)

Cryotherapies that have newly become available and are over-the-counter are not as cold as liquid nitrogen. These also possess the same types of side effects including pain, hypopigmentation and a "ring wart" (a Koebner response). The cure rate mentioned in literature varies from 39 to 92%, which might be due to difference in using techniques. Aggressive technique of usage may give better outcomes but may also be with increased adverse effects.[16]

In order to avoid these side effects and disadvantages, alternative treatment options are tried in many studies. Adapalene is a good choice among these which is a synthetic naphthoic acid derivative. Being a third generation topical retinoid, it is able to reverse keratinization as well as the affinity for retinoic acid receptors, found in the epidermis. Available as 0.1% aqueous gel, adapalene has anti-inflammatory action, modulates cell differentiation and inhibits cell proliferation.

Few studies with small number of patients have proven efficacy of topical adapalene for treatment of plantar warts in past years. A study on 10 patients, done in 2011, with topical adapalene has shown complete disappearance of the lesions in an average of 39 ± 15.07 days. [11]

Another study by same investigator , done in 50 patients have shown to clear plantar warts earlier than cryotherapy treatment.[13] A study done in Pakistan, published in 2020, has shown that 1% adapalene and cryotherapy were equal in efficacy in treating plantar warts.[17] Hence our study intended to compare the efficacy of topical 1% adapalene versus conventional therapy like cryotherapy in treatment of plantar warts to so that an alternative can be suggested on the basis of more results for patients suffering from this ailment.

METHODOLOGY

This randomized control study was conducted at the Department of Dermatology, Combined Military Hospital, Abbottabad, Pakistan, from Feb 2022 to July 2022. A total of 60 patients coming to hospital with complaints of having 1-3 plantar warts were randomized into two equal groups of 30 patients. Patients enrolled for the study on odd serial number were allocated to group-A, treated with application of topical 1% adapalene gel overnight on daily basis under occlusion with polythene sheet wrap and advised for fortnightly follow up. While patients on enrolled for the study on even serial number were allocated to group-B for cryotherapy treatment for two freeze thaw cycles, done with liquid nitrogen at -196°C temperature using direct application by a dipstick, conducted by paramedics under the supervision of the researcher of the study.

Fortnightly follow up was advised so that procedure can be repeated if needed, assessed through the re appearance of skin texture.

The primary outcome was to measure the proportion of patients with completely cleared warts on physical examination after 8 weeks from start of treatment. The thick skin areas were pared before going through the treatment procedure in both the groups.

Pregnancy, any systematic illness, patients on immunosuppressive therapy, patients presenting with mosaic warts, those who had used any treatment of their plantar warts during last 4 weeks were excluded. Any patient who lost follow up was also excluded.

Data was analyzed using SPSS version 26. The quantitative variables like age and duration of disease were calculated by taking means and standard deviation. The qualitative variables like gender and efficacy were calculated by frequencies and percentages. Efficacy in two groups was compared by chi-square test, where p-value of ≤0.05 was considered significant.

Written consent was obtained from all the patients.

Ethical Approval: Permission for conducting study was taken from ethical committee of Combined Military Hospital, Abbot Abad, Pakistan.

RESULTS

Age range in this study was from 18 to 45 years with mean age of 32.366±8.61 years**,** while duration of disease was from 2 to 12 weeks with mean duration of 6.433±2.90 weeks. Mean age and duration of disease in group-A and group-B are shown in Table-I.

Table-1: Mean±SD of patients according to age and duration of disease in both groups. n=60

Demographics	Group-A Mean±SD (n=30)	Group-B Mean±SD (n=30)
Age (years)	32.2±8.60	32.533±8.77
Duration of Disease (weeks)	6.366±2.95	6.5±2.89

Frequency and percentage of male gender was dominant in both groups as shown in Table- II.

Table-2: Frequency and percentage of patients as per gender in both groups. n=60

Gender	Group-A n=30 n (%)	Group-B n=30 n (%)
Male	17 (56.66%)	16 (53.33%)
Female	13 (43.33%)	14 (46.66%)
Total	30 (100%)	30 (100%)

The residential status of patients as being urban or rural is given in Table-III.

Table-3: Residential status of both groups. n=60

Residential Status	Group-A n=30 n (%)	Group-B n=30 n (%)
Urban	14 (46.66%)	17 (56.66%)
Rural	16 (53.33%)	13 (43.33%)
Total	30 (100%)	30 (100%)

After 8 weeks of initiating the treatment, treatment in group-A was significantly more effective in complete resolution of plantar warts than treatment in group-B as shown in Table-IV.

Table-4: Efficacy of treatment after 8 weeks of treatment in both groups.

	Group-A n=30	Group-B n=30	p-value
Efficacy	n (%)	n (%)	0.028
Yes	27 (90.00%)	20 (66.66%)	
No	3 (10.00%)	10 (33.33%)	
Total	30 (100%)	30 (100%)	

DISCUSSION

Depending upon the anatomical location and patient's sensitivity, plantar warts can be either painful or non-painful. Presence of plantar warts on pressure-bearing areas such as the feet leads to physical morbidity but it's psychological as well. A therapy that is painless, resolves the lesions and leaves no scars in 1 to 3 visits can be taken as ideal.

As in plantar warts, there are interruption of skin lines that is visible with naked eye and enhanced by viewing through dermatoscope, reappearance of these skin lines throughout these lesions help the clinicians to evaluate the resolution of the wart.[16]

The modalities that are available for the treatment of plantar warts include physical destruction like cryotherapy, chemical destruction like salicylic acid and immunomodulator therapy like retinoids.[14] The most conventional among these is the cryotherapy where liquid Nitrogen having a boiling point of -195.6°C is used for this purpose. Kwock et al shared in their results that the results of cryotherapy are comparable with the results obtained with salicylic acid, which can be declared as gold standard modality.[15]

Bruggink et al. shared the results of their study where they found that cryotherapy when compared to salicylic acid is more effective only in common warts but not for plantar warts. [18]

Cryotherapy is mostly painful. It does not work through killing the virus directly rather lead to a cell-mediated response via local inflammation. There are new easily available cryotherapies, which are not as cold as was the liquid nitrogen, but they also have disadvantages in the shape of pain, hypopigmentation, a ring wart, blistering or a circular resurgence of the plantar wart (called Koebner response). Cure rates for cryotherapy is reported from 39% to 92%, the difference is because of using different techniques described in literature.[16]

Keeping in view the above mentioned side effects, better alternative have been studied and used for treating plantar warts, an important one among these are retinoids. Among retinoids, adapalene is the one most commonly employed. With the use of 0.1% topical adapalene under occlusion, Gupta et al, reported that 39 ± 15.07 days was the total time taken for complete clearance of plantar warts. [11]

There is lack of data for direct comparison in efficacy between cryotherapy and adapalene for treating plantar warts as very few studies are carried out for the purpose. Gupta et al, in another study made a comparison between topical adapalene aqueous gel 0.1% under occlusion versus cryotherapy. The reported results were in favor of adapalene as in 24 patients, 286 plantar warts were cleared in 36.71 ± 19.24 days while with cryotherapy 124 warts in 24 patients were cleared in 52.17 ± 30.06 days, the difference was significant with $p<0.05$. It was thus concluded that in the treatment of plantar warts adapalene was more effective than cryotherapy.[13]

A recent study, conducted in Pakistan, published in 2020, compared efficacy of topical 0.1% adapalene versus cryotherapy in 74 patients with plantar warts didn't report significant difference between two groups in complete clearance of warts. There was no significant difference in duration of the plantar warts in both groups. Clearance of warts at 8 weeks was 72.97% and 75.68% in cryotherapy group and 0.1% adapalene group respectively. [17]

The results of our study are also in line with the two studies done by Gupta et al. [11,13] Patients aging between 18 to 45 years were part of the study, designed for comparison of efficacy of 0.1% adapalene versus cryotherapy for treatment of plantar warts. With similar age groups, similar gender ratio, similar residential status and similar duration of disease, treatment of plantar warts with 0.1% adapalene under occlusion was more effective than cryotherapy after 8 week of treatment. Out of 60 patients, each group was allocated 30 patients through randomization, 27 patients (90%) in topical 0.1% adapalene group and 20 patients (66.66%) in cryotherapy group had complete resolution of their warts after 8 weeks of treatment with $p<0.05$. There was good patient compliance and no complaints of like scar formation, irritation, erythema or infections in patients with adapalene.

While comparing topical 0.1% adapalene versus cryotherapy in trials, an important fact is that cryotherapy is done under supervision by the physician on fortnightly basis while adapalene is applied under occlusion by patients themselves daily at home, so, a major advantage of use of 0.1% adapalene gel is also its simplicity and convenience of use. Another advantage to the patient is in shape of painless application at home compared to the cryotherapy. However, one disadvantage with adapalene gel is that it has to be used under occlusion by plastic sheet on daily basis which may feel messy to some patients.

In short, topical 0.1% adapalene gel under occlusion is effective, simple, convenient at home administrated treatment of plantar warts.

It is suggested to conduct further studies with more number of patients to confirm more advantages of using topical 0.1% adapalene gel under occlusion in treatment of plantar warts.

CONCLUSION

This study has concluded that topical 0.1 % adapalene is more effective than cryotherapy in the treatment of plantar warts. It is easy to use with at home administration so offer better patient compliance.

Conflict of Interest: None.

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