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Original Article

Comparison of effectiveness and safety of topical 0.1% adapalene gel with cryotherapy in the treatment of plantar warts

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Abstract

Objective To compare the effectiveness and safety of topical adapalene 0.1% gel with cryotherapy in the treatment of plantar warts.

Methods This comparative interventional pre-post study was conducted at outdoor patient department of dermatology, KEMU/ Mayo Hospital Lahore from 1.11.22 to 31.10.23. Total 88 patients (44 in each group) were included in the study. Patients were randomly divided in group A and group B. Group A applied topical adapalene 0.1% gel twice daily under occlusion using plastic wrap. In group B, cryotherapy was performed by doctor, two freeze-thaw cycles, each of 15-20 seconds duration done fortnightly up to 12 weeks, using liquid nitrogen operated cryogun. Patients were assessed monthly till clearance of all warts or completion of therapy and then follow up was done 4 weeks after completion of treatment for 3 months for any recurrences. Effectiveness and safety according to operational definition was noted at 1 month after completion of therapy.

Results Effectiveness of treatment showed no significant difference between both groups at 1st, 2nd and 3rd month. However, at 4th (Group-A: 59.09% vs. Group-B: 27.27%, p-value=0.040) 5th (Group-A: 68.18% vs. Group-B: 43.18%, p-value=0.005) and 6th month (Group-A: 90.91% vs. Group-B: 68.18%, p-value=0.027) effectiveness of treatment groups showed significant difference between groups. As far as side effects are concerned none of the patients experienced any side effects with adapalene gel. However, in cryotherapy group few patients experienced side effects like scarring, cutaneous abscess and cellulitis.

Conclusion It can be concluded from the results of this study that for treating patients with planter warts, topical adapalene gel is safer and more effective than cryotherapy.

Key words
Plantar warts; Effectiveness; Adapalene; Cryotherapy.

Introduction

Viral warts are contagious cutaneous manifestation of infection with Human Papilloma Virus (HPV).[1] They are common presenting complaint in children and adolescents.[2] Girls are affected more frequently than boys.[3] Warts can occur in various forms like common warts, palmoplantar warts and genital warts.[4] Human papilloma virus type 6 and 11 cause anogenital warts.[5] Human papilloma virus type 1, 2, 4, 10, 27 and 57 cause plantar warts.[6] Warts can be painless or painful depending on their location (e.g. soles of foot and near the nails).[3] Palmar and plantar warts may be single or multiple.[7]

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Warts may resolve spontaneously but in some cases may require treatment.[8] There are many treatment options for warts including topical keratolytic agents, cryotherapy, laser, cautery, surgical curettage and alternative therapies.[9] Adapalene is a third generation retinoid commonly used in the treatment of acne. It can modify keratinization and inhibit cell proliferation.[10] It also has anti-inflammatory and immunomodulatory effect and its keratolytic effect leads to destruction of virus-infected cells, thus causing resolution of warts.[11] Cryotherapy is the application of liquid nitrogen gas (temperature-196^{0}C) that is widely used for the treatment of warts.[12] Many studies have been carried out comparing topical treatment with interventional treatment.[13] A study was conducted in department of dermatology, Al-Kindy Teaching Hospital, Baghdad, Iraq for treatment of plane warts with topical adapalene 0.1% gel. This study showed that proportion of patients cured with 0.1% adapalene gel was 30% after 8 weeks of treatment.[14] Gupta *et al*. compared topical adapalene with cryotherapy for the treatment of plantar warts. 50 patients were enrolled in this study. In group A (topical adapalene 0.1% gel), all the warts disappeared in 36.71±19.24 days and in group B (cryotherapy), all warts disappeared in 52.17±30.06 days. Patients treated with topical adapalene showed complete clearance of plantar warts earlier as compared to those treated with cryotherapy.[15]

Topical adapalene therapy for plantar warts in our local community has not been the subject of research. This study was carried out to find a more efficacious, convenient and safe treatment modality for plantar warts after comparing topical adapalene with cryotherapy for the management of plantar warts.

Methods

A comparative interventional pre-post study was carried out at outdoor patient department of dermatology, KEMU/ Mayo Hospital Lahore and study was completed 1 year after the approval of synopsis. Non-probability, consecutive sampling technique was used and patients were randomized in two groups by balloting. A 90% power of test with an anticipated mean value of days was used to determine the sample size of 88 patients (44 patients in each group) at the 5% level of significance. Group A (Topical adapalene twice a day) as 36.71±19.24 days and group B (Cryotherapy done every 2 weekly) as 52.17±30.06 days.[15]

Patients of either gender of ages between 10-60 years with clinical diagnosis of plantar warts were included. Patients on topical therapy in last 1 month or on systemic therapy in last 3 months**,** pregnant women**,** patients with immunocompromised states i.e. diabetes mellitus, HIV, malignancies, immunos-uppressive medicine, known allergies to adapalene**,** extensive lesions (more than 5 warts) and secondary infection were excluded.

All patients gave written informed permission after the approval from institutional ethical board (No.482/RC/KEMU, dated May 23, 2022). Patients were randomized into groups A and B. Group A applied topical adapalene 0.1% gel twice daily under occlusion using plastic wrap. In group B, cryotherapy was performed and two freeze-thaw cycles, each of 15-20 seconds duration were done fortnightly for up to 12 weeks, using liquid nitrogen operated cryogun (made in USA) at -196 0C temperature. Paring of thick regions were performed prior to cryotherapy. Patients had regular evaluations until all warts were removed or completion of therapy whatever was achieved first and then follow up was conducted till 4 weeks after completion of treatment for 3 months for any recurrences.

Patient assessment was done by a grading score

where, Grade 0 (no clearance), Grade 1 (1-24% clearance), Grade 2 (25-49% clearance), Grade 3 (50-74% clearance) and Grade 4 (74-99% clearance) Grade 5 (100% clearance) was noted. Final assessment was carried out by two qualified dermatologists. Complete (100% clearance) removal of plantar warts 12 weeks after use of 0.1% adapalene gel or cryotherapy served as the indicator of effectiveness.

Safety was determined by counting the number of individuals who had adverse effects, such as discomfort, irritability, scarring, erythema, or infection. Mild and significant side effects were divided into categories. For up to three days, the mild side effects included erythema, irritation, eczema, swelling, blisters, and erosions. Scarring, cutaneous abscess, cellulitis, and ulcers were among the worst adverse effects. If a major adverse impact was recorded by more than 30% of patients, the therapy was deemed hazardous. Effectiveness according to operational definition was noted at 1 month after completion of therapy. Serious side effects were recorded at each visit. All the information was recorded on a predesigned proforma. Photographs were taken before and after treatment.

Data was entered and analyzed by using SPSS version 26. Quantitative variables like age, number and duration of plantar warts were presented as mean±SD. Qualitative variables like gender, family history of warts and their site was presented as frequency and percentages. Effectiveness between groups was assessed with chi square test. p-value of $\leq$0.05 was taken as significant.

Results

88 patients were included in this study. Group-A and B patients mean age was 32.36±14.61 and 34.27±14.70 years. Age of patients in both treatment groups ranges between 10-60 years.

In Group-A 25(56.82%) patients were male and 19 (43.18%) were female while in Group-B 23 (52.27%) were male and 21 (47.73%) were female. In Group-A 30(68.2%) patients' duration of disease was <1 year and 14 (31.8%) patient duration of disease was >1 year. While in Group-B 27 (61.4%) patients' duration of disease was <1 year and 17 (38.6%) patients' duration of disease was >1 year. In Group-A 10 (22.7%) patients and in Group-B 9 (20.5%) patients had family history of plantar warts.

In Group-A 33 (75%) patients and 11 (25%) and in Group-B 32 (72.3%) patients and 12 (27.27%) had unilateral and bilateral warts respectively.

Assessment was carried out with the help of physician assessment scale. At 1st and 2nd month no significant difference was seen between groups regarding effectiveness of treatment. However, it was seen that treatment response was higher in topical adapalene after 3 months as compared to cryotherapy **(Table 1)**.

At 3rd month effectiveness of Group-A was higher as compared to Group-B but the difference between groups was not statistically significantly. At this point 15 (34.09%) patients in Group-A and 8 (18.18%) in Group-B had complete clearance. i.e. p-value=0.064. At 4th month effectiveness of treatment was significantly higher for topical adapalene group as that of cryotherapy. i.e. p-value=0.040.

At 5th and 6th month higher effectiveness was seen in topical adapalene group as compared to cryotherapy. At 5th month 68.18% patients in Group-A and 43.18% patients in Group-B had complete clearance (p-value=0.005) while at 6th month 90.91% patients in Group-A and 68.18% patients in Group-B had complete clearance (p-value=0.027) **(Figures-1-3)**.

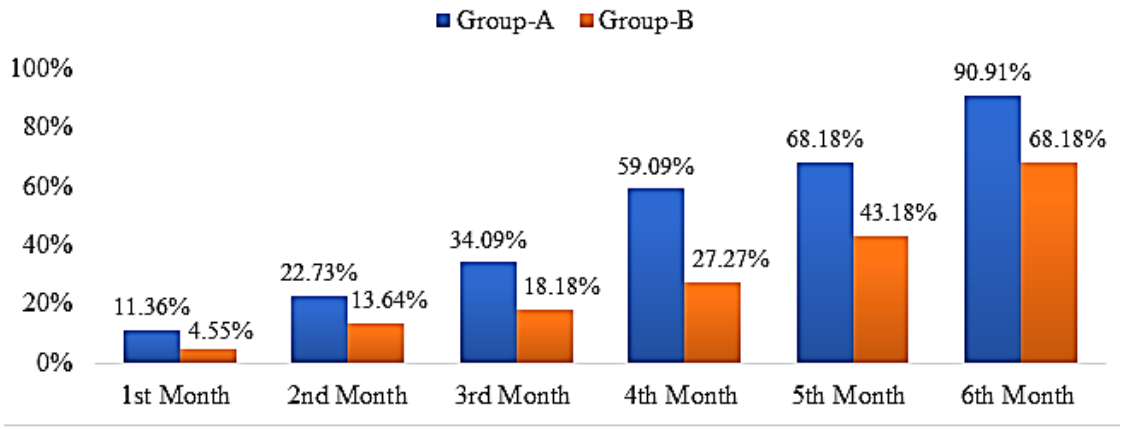

Figure 1 Effectiveness of treatment during follow up interval.

Table 1 Effectiveness of Treatment Groups

	Group-A	*Group-B*	*Total*
Yes	40(90.91%)	30(68.18%)	70
No	4(9.09%)	14(31.82%)	18
Total	44	44	88
p-value		0.0086	

None of the patients in both treatment groups had cellulitis during follow up. However, in Group-B at 4th month, 1 (2.227%) patient and 2 (4.55%) patients at 5th month had cutaneous abscesses. None of the patients experienced scarring in Group-A. However, in Group-B at 2nd month 3 (6.82%) patients, at 3rd month 5 (11.36%) patients and at 4th month 5 (11.36%) patients developed scarring that was superficial that healed later on.

Discussion

Benign growths known as plantar warts arise from the Human Papilloma Virus (HPV) infecting the epidermal cells. Out of all the viral strains, the most commonly seen on the foot are HPV types 1, 2, 4, 10, 27, and 57.[16,17] Various published clinical trials have shown extremely varying cure rates for various therapies.[18] Although eliminating the afflicted epidermal cells is the goal of most of the therapies, sometimes the cellular damage is insufficient to generate the cytokines that would kill the latent virus in nearby cell.[16,19] Therefore, sometimes

Figure 2 A-C: Plantar Warts (Group A).

Figure 3 A-C: Plantar Warts (Group B).

the treatments are ineffective, and refractory warts and recurrences provide a problem for experts from many fields, which has prompted the search for other therapies.[19,20]

In order to cure plantar warts, we examined the safety and effectiveness and safety of topical adapalene 0.1% gel with cryotherapy in this research. Age of patients in this study ranges between 10-60 years with mean age of patients as 33 years.

A recently published study from Karachi reported the mean age of patients presenting with plantar warts as 45 years which is higher as compared to this study.[21] Gupta *et al.* in his study reported the mean age of patients as 27 years (13-55 years) which was slightly lower when compared with the mean age of study. A local study from Abbottabad reported mean age of patients presenting with plantar warts as 32 years (18-45 years) which is in line with the mean age of this study.[22] Mean age of patients reported by Amar *et al*. in his study was less as compared to this study. i.e. 27 years.[23] In this study 54% patients were male and 45% patients were female. Studies have reported male dominance in plantar warts presentation. Arifullah *et al*. in his study reported similar findings as in his study 55% patients were male and 45% were female.[22] Amar *et al*. from Rawalpindi also reported male dominance in his study.[23] Contrary to these findings, Mehboob *et al*. from Karachi reported no significant difference in male and female presentation.[21] In her study population 50% male and 50% female patients were presented with plantar warts. Studies have reported a higher prevalence in older age groups from 8 to 12 years[24,25] and of male sex[26] because men are more likely to engage in outdoor activities that increase the risk of infection, such as being near water channels, feces, and animals.

Adapalene has emerged as a promising treatment modality for treating plantar warts with higher efficacy rates. Studies have reported early resolution of lesion with minimal side effects.[15,22] In this study, it was observed that effectiveness of adapalene was significantly higher as compared to cryotherapy in terms of

complete resolution of lesion during follow up. From 1st month till 6th month (Adapalene: 90% vs. Cryotherapy: 68%, p-value=0.027) effectiveness of adapalene was higher as that of cryotherapy but from 4th month onward significant difference was seen between groups. In local literature not much data is available regarding efficacy of adapalene for treating plantar warts. However few studies have reported its higher efficacy over cryotherapy. Gupta *et al*. in his study reported that adapalene gel 0.1% under occlusion is an effective, safe and easy to use treatment for plantar warts and may help clear lesions faster than cryotherapy.[15] Similar findings were reported by Mahboob *et al*. by reporting shorter time duration for clearance of plantar warts with Adapalene as compared to cryotherapy.[21] Arifullah from Abbottabad reported higher efficacy for adapalene gel as compared to cryotherapy for treating plantar warts patients. i.e. 90% vs. 66%, p-value=0.028.[22]

Contrary to these findings, Amar *et al*. in his study reported no significant difference regarding efficacy of adapalene gel and cryotherapy. As per his observations 72.97% patients in cryotherapy group and 75.68% patients in adapalene gel had complete clearance.[23]

Above mentioned studies by Amar *et al*., Arifullah and Mahboob *et al*. did not report side effects in their studies. This is the limitation of their studies. However, in this study safety of both treatment modalities was assessed in terms of noting the frequency of side effects. None of the patients in adapalene gel group experienced side effects. However, in cryotherapy group few patients experienced side effects like scaring, cutaneous abscess (4.55%) and cellulitis (6.82%). Cryotherapy needs to be carried out under supervision of dermatologist on fortnightly basis. However, adapalene patient can easily apply it at home as directed by the dermatologist, thus making it convenient for the patient to use. Adapalene gel has several benefits, but one disadvantage is that it has to be administered daily under occlusion by a plastic sheet, which some patients may find untidy.

The limitations of over study were small sample size and short follow up and this being a single-center study.

The strengths of over study were that it was inexpensive and comparative.

In futures studies should be done using larger sample size and other modalities such as electro cautery, laser should be evaluated in the treatment of plantar warts.

Conclusion

Based on findings of this study was concluded that topical adapalene gel was more effective and safer than cryotherapy for treating planter warts patients. So, by using adapalene gel, patients can be cured in less time duration with minimal to no side effects as compared to cryotherapy.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

AA: Substantial contribution to study design, acquisition of data, analysis and interpretation of data, manuscript writing, has given final approval of the version to be published.

SS: Substantial contribution to study design and interpretation of data, manuscript writing, has given final approval of the version to be published.

AA,SAAG,WS: Substantial contribution to conception and study design, critical review of the manuscript, has given final approval of the version to be published.

MZ,IH: Substantial contribution to conception, study design and interpretation of data, critical review of the manuscript, has given final approval of the version to be published.

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