ORIGINAL ARTICLE

COMPARISON OF TOPICAL 0.1% ADAPALENE GEL VERSUS CRYOTHERAPY IN PATIENTS WITH PLANTAR WARTS

Maria Mahboob[1], Najia Ahmed[1], Atiya Rahman[2], Kiran Naz1, Furquana Niaz[3], Omer Farooq[1]

[1]Department of Dermatology, PNS Shifa, Karachi, [2]Combined Military Hospital, Lahore, [3]Karachi Institute of Medical Sciences, Karachi-Pakistan

Background: Plantar wart is a common viral infection of the plantar surface of the foot. Multiple treatment modalities are available but there is no definitive management option. The aim of this study is to compare topical adapalene gel 0.1% with cryotherapy in patients presenting with plantar warts in terms of time taken for complete clearance of the lesions. **Methods:** The study was conducted at the Department of Dermatology, PNS Shifa Hospital, Karachi from 28th April to 28th October 2020. Eighty-four patients with plantar warts who fulfilled the inclusion and exclusion criteria were included in the study. Approval from the institutional ethical review committee was sought and written informed consent was taken from all the patients. Patients were divided into two groups, A (Adapalene 0.1% gel) and B (Cryotherapy) of 42 patients each. Adapalene gel was applied twice daily under occlusion at home and cryotherapy was done at the clinic after every two weeks. Patients were followed weekly from the onset of treatment and days taken for complete clearance of plantar warts were noted. Both the groups were compared for the outcome, i.e., time taken for complete clearance of lesions. **Results:** The mean time for complete clearance of plantar warts in group A was 35.619±3.154 days and in group B, it was 50.404±3.178 days. **Conclusion:** Adapalene gel 0.1% used for the treatment of plantar warts helped in complete clearance of lesions faster than cryotherapy.

Keywords: Adapalene; Cryotherapy; Warts

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INTRODUCTION

Plantar wart is a common viral infection of the plantar surface of the foot caused by the human papillomavirus (HPV).[1] More than 180 subtypes of the human papillomavirus have been reported, resulting in diseases ranging from benign warts to cancers.[2] Types of HPV most frequently detected on the foot are 1, 2, 4, 10, 27, and 57.[3] Plantar warts may regress spontaneously. Annually, 2% of the general population seeks medical care for warts due to pain and limitation of physical activities.[3]

Multiple treatments for management of the viral warts are available including cryotherapy, salicylic acid, intralesional immunotherapy and laser. All of these options have been shown to have highly variable cure rates.[4,5] Although, there are many treatment modalities available at present, there is no definitive management option.[6]

Adapalene belongs to third generation of the retinoids and is among the first line treatment for acne vulgaris. It exerts its effects after binding to the retinoic acid nuclear receptors.[7] It has comedolytic, anti-inflammatory, antiproliferative, and immunomodulatory effects. It has a better safety profile as compared to other retinoids. Besides its utility in the treatment of acne vulgaris, recently, it has been found to be effective in the treatment of several dermatological diseases and photoaging.[7] Adapalene is available in aqueous gel form in concentration of 0.1% and 0.3%.[8]

Cryotherapy is one of the standard treatments for the management of viral warts. It is usually offered as the first line treatment for the management of warts. Most frequently used cryogen is liquid nitrogen (N_2) at a temperature of -196 °C, for cryotherapy of cutaneous lesions.[9] Freezing can be done either by using a cotton tip applicator or by the cryo-spray gun.[10]

Gupta *et al*[11] conducted a study to evaluate the treatment by topical adapalene 0.1% gel versus cryotherapy treatment in patients presenting with plantar warts and found time for clearance of the wart in each group to be 36.71±19.24 days versus 52.17±30.06 days respectively.

Cryotherapy must be done in the hospital setting. It is a painful procedure and requires multiple visits. It is also not freely available and require special storage conditions. However, topical 0.1% Adapalene gel can be safely applied at home and is not painful. Our study compares the time taken for complete clearance of plantar warts in cryotherapy treatment group and 0.1% Adapalene gel group. Our local data is scarce in

this regard. Topical adapalene, if found effective, would lead to better patient compliance and overall reduction in the cost of treatment.

MATERIAL AND METHODS

The study was conducted at the Department of Dermatology, PNS Shifa Hospital, Karachi from April to October 2020. It was a randomized controlled trial. Approval was sought from the hospital research ethics committee before conducting the study (Certificate no. ERC/2020/Derma/01). We calculated a sample size of 84 patients, using World Health Organization sample size calculator with Alpha=5%, Power of the test 1-beta=80, and mean days taken to the complete clearance of the plantar warts after topical adapalene 0.1% gel =36.71±19.24 days versus cryotherapy =52.17±30.06 days treatment.[11]

After informed written consent, 84 patients who fulfilled the inclusion and exclusion criteria were enrolled through non-probability consecutive sampling technique and randomized into two groups A and B of 42 patients each by lottery method. Their demographic details, along with complete clinical history and detailed physical examination was recorded including the diagnosis, number and duration of plantar warts.

All patients in group A were treated with topical adapalene gel 0.1% applied twice daily under occlusion using plastic wrap and patients in group B were treated with cryotherapy using cryogun. Liquid nitrogen was applied till a narrow rim of whiteness appeared around the lesions. Two cycles of cryotherapy were done in one session and were repeated after every two weeks. Patients were followed weekly from the onset of treatment and days taken for complete clearance of plantar wart were noted. The findings were entered in the proforma. Inclusion criteria for the study was patients who presented with plantar warts defined by having a well-circumscribed and a rounded lesion with a rough surface, having a tiny black petechiae in the center visible at the time of presentation or after scraping, present on the plantar surface of the foot with diagnosis confirmed by consultant dermatologist, belonging to any gender with age group 12–65 years. Patients who were immunocompromised, who had received other treatment for plantar warts in last 04 weeks, those with known hypersensitivity to topical retinoids, with history of malignancy, Hepatitis B, C or HIV infection, suffering from Epidermodysplasia verruciformis, who received oral retinoids in past 04 weeks and pregnant patients assessed by history were excluded.

Data entry and analysis was done by using SPSS Version 23. Mean and standard deviations were calculated for the quantitative variables like age, number, duration of plantar warts and days taken for complete clearance. For the qualitative variables like gender, frequencies and percentages were calculated. Unpaired t-test was used to compare the mean days taken for the clearance of the plantar warts in both groups. Stratification of age and gender was done to control the effect modifiers. Post stratification independent t-test was applied taking *p*-value of ≤0.05 as statistically significant.

RESULTS

All 84 patients completed the study. In Group A, there were 42 patients of which 21 were male while 21 were female, with mean age of 44.523±8.130 years, and in group B, there were 42 patients of which 22 were male while 20 were female, with mean age 45.952±8.281 years. The overall mean age came out to be 45.238±9.8.188.

There was significant difference of mean time for complete clearance of plantar warts between the group A and group B with *p*-value of 0.001 (as shown in table-2).

In our study, no significant difference of mean time to complete clearance of plantar warts was noted with respect to age, gender, duration of plantar warts and number of plantar warts between the two groups.

Table-1: Mean age, duration and number of warts

Variables	Group A (mean±SD)	Group B (mean±SD)	Overall (mean ± SD)
Age (years)	44.523±8.130	45.952±8.281	45.238±8.188
Duration of warts (days)	21.95±5.96	21.23±4.98	21.59±5.47
Number of warts	2.952±1.681	5.309±2.464	4.130±2.408

Table-2: Comparison of mean time for complete clearance of plantar warts between two groups

	Group A	Group B	Overall time to complete clearance of plantar warts	*p*-value
Mean time to complete clearance of plantar warts (days)	35.619±3.154	50.404±3.178	49.252±3.150	0.001

Table-3: Stratification of mean time to complete clearance of plantar warts between two groups with respect to age, gender, duration and number of warts

Age groups (years)	Groups	mean time to complete clearance of plantar warts (days)	*p*-value
12-44	A B	35.846±3.891 49.615±3.176	0.759
45-65	A B	35.519±2.836 50.758±3.169	0.287
Gender groups			
Male	A	35.666±3.038 49.954±3.139	0.923
Female	B	35.571±3.340 50.900±3.226	0.342
Duration of plantar warts groups (days)			
10-20	A B	36.00±3.20 50.411±2.52	0.566
21-29	A B	35.40±3.16 50.40±3.60	0.991
Number of plantar warts			
1-5	A B	35.435±3.093 49.875±3.261	0.178
6-10	A B	38.000±3.605 51.111±3.007	0.216

DISCUSSION

Viral warts have potential to spread, making satisfactory and in time treatment necessary.[12] There are several conventional treatments available but with variable response.[13]

In our study, the mean time to complete clearance of plantar warts in Group A was 35.619±3.154 days while in Group B, it was 50.404±3.178 days which is comparable to the study done by Gupta *et al*.[11] He took 50 patients in his study with plantar warts and divided them into two groups: one group was given treatment with cryotherapy fortnightly while the second group was treated with 0.1% adapalene gel under occlusion twice daily. In the adapalene gel group, mean time to complete clearance was 36.71±19.24 days while in cryotherapy group, mean time to complete clearance was 52.17±30.06 days. Their sample size was comparatively small and it was a single center study.

Gupta R[14] conducted a study which was a single arm study where plantar warts were treated with topical adapalene and number of days required for complete clearance of plantar warts were noted. They took 10 patients in their study and the mean time for complete clearance of warts came out to be 39±15.07 days. Their results were comparable to our study, but their sample size was quite small, and they didn't take any control group.

A study conducted by Gupta M[15] looked at the efficacy of adapalene 0.1% gel in the treatment of warts in the paediatric population. They took 50 patients in the age group of 3–18 years having different types of warts. They were given once a day application of the gel. They were followed up every month for three months to assess the response. Out of 50 patients, only 5 (11.36%) patients had plantar warts. After three months of therapy, complete clearance of lesions was observed in 26 (59.09%) of the patients. Compared to our study, they looked at the paediatric population. Their sample size was small, and it was a single arm study.

Amar *et al*[16], in a different study, compared the efficacy of topical adapalene 0.1% gel under occlusion with cryotherapy treatment in the management of plantar warts. They took a total of 96 patients and divided them into two groups: one group was treated with cryotherapy and the second one was treated with adapalene gel. They measured the proportion of the participants whose warts completely cleared at 8 weeks after the start of therapy. Clearance of warts after 8 weeks of therapy was achieved in 27 (72.97%) of the patients in the cryotherapy group and 28 (75.68%) of the patients in the adapalene group. A *p*-value of 0.791 revealed no significant difference in outcome between the two groups.[16] They found treatment with 0.1% adapalene gel to be as effective as cryotherapy in the management of plantar warts, hence, providing evidence for using adapalene as an effective treatment option for managing plantar warts. The difference from our study was that they looked at the efficacy of the adapalene by measuring the proportion of the participants whose warts cleared at 8 weeks after the start of the therapy rather than the time required for complete clearance of warts.

Olguin *et al*.[17] used oral isotretinoin in the treatment of recalcitrant facial warts with promising results. He took a total of 31 patients with recalcitrant facial flat warts and divided them into two groups. First group received oral Isotretinoin 30mg/day and the second group was given a placebo for the duration of 12 weeks. Each patient in the isotretinoin

group at the end of 12 weeks, showed complete clearance of all flat warts, while none of the patients in the placebo group showed any improvement. These results again showed that retinoids can be used as an effective treatment as shown by our study. They took a smaller sample size as compared to ours. They did not compare the treatment in question with the standard treatment rather with placebo.

Choi *et al.*[18] have described a case of extensive and recalcitrant viral warts in a 25-year-old man. His lesions were refractory to various conventional therapies including cryosurgery, topical application of 100% trichloroacetic acid and intralesional injection of bleomycin. Surgical excision and electrocauterization caused temporary remission. He was started on oral acitretin at 1mg/kg/day. After one month, there was a considerable regression of the warts and after two months, lesions showed almost complete clearance. Joshua[19] described a case of recalcitrant plantar warts who was given oral acitretin 25 mg once daily. When he was reviewed after one month, his warts were significantly reduced. Complete clearance of warts was seen after four months of therapy. Like our study, these case reports have also shown benefit of retinoids in the management of plantar warts.

Cryotherapy has been conventionally used in the treatment of plantar warts. A study conducted by Kwock *et al.*[20] showed that the response to the treatment with the cryotherapy is comparable to the response achieved by the salicylic acid. However, the above-mentioned study demonstrated that the combined therapy by salicylic acid and cryotherapy had a higher cure rate than either salicylic acid or cryotherapy treatment alone. The results showed a cure rate of 23% in the placebo trials, 52% in the salicylic acid alone trials, 49% in the cryotherapy alone trials and 58% in the combined cryotherapy and salicylic acid trials.[20] Due to the adverse effects and the availability issues pertaining to liquid nitrogen, many alternative agents have been evaluated in comparison with the cryotherapy for the treatment of the plantar warts, as in our study.

Little head-to-head research has been carried out to compare the effectiveness of topical adapalene gel versus cryotherapy treatment in patients with plantar warts. Our study has demonstrated that topical adapalene under occlusion seems to be effective, simple and convenient to apply and a safe modality of therapy for the treatment of plantar warts and helps clear warts sooner when compared to cryotherapy.

The limitations of our study are that it was a single center study and had a smaller sample size. Another limitation is the lack of follow up to assess for recurrence after discontinuing the therapy. The patient is required to use plastic occlusion two times a day while using topical adapalene, which can be messy and may not be liked by some patients. Our results need confirmation by further studies with larger sample sizes involving multiple centers as our study is among the first of its kind.

CONCLUSION

Adapalene gel 0.1% used for the treatment of plantar warts helped in complete clearance of lesions faster than cryotherapy. Therefore, it may be recommended as a safe and effective treatment option for plantar warts.

Conflict of interest: This article has no conflict of interest to be declared by any author.

AUTHORS' CONTRIBUTION

MM, NA: Literature search, conceptualization of study design, data collection, data interpretation, write-up. AR: Data analysis and interpretation. KNK: Data collection, data analysis and interpretation. FN: Data analysis and data interpretation. OF: Proof reading.

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Address for Correspondence:
Maria Mahboob, PNS Shifa hospital, Karachi-Pakistan
Cell: +92 333 550 9090
Email: maria-mahboob@hotmail.com