ORIGINAL ARTICLE

EFFICACY OF INTRALESIONAL ACYCLOVIR VERSUS CRYOTHERAPY FOR TREATMENT OF PLANTAR WARTS

Faisal Ahmad, Natasha Shahid Janjua, Muneeza Rizwan
Dermatology Centre, PAF Hospital, Islamabad-Pakistan

Background: Warts, benign proliferation of skin and mucosa caused by human papilloma virus (HPV), are treated by different modalities among which cryotherapy remains the most common. The objective of this study was to assess comparative efficacy of Intralesional acyclovir versus cryotherapy for plantar warts. **Methods:** This quasi-experimental study was conducted on eighty-four patients of plantar warts (1–10 in number) enrolled after obtaining ethical approval and written informed consent. Patients were divided into group A and B. Group A patients received intralesional Acyclovir in a dose of 0.1ml (70 mg/ml) at the base of each wart while Group B patients had cryotherapy for two freeze and thaw cycles with each cycle of 10 seconds duration. Lesion size and clinical photographs were recorded at baseline and at follow-up visits scheduled every 2 weeks (maximum 5 sessions) and followed for further 4 months. Response was considered as complete (100% resolution), partial (resolution 50-99%) or no response (resolution <50%). **Results:** A total of 84 patients with 42 (79% Males and 21% females) in group A and 42 (55% males and 45% females) in group B, having mean age 27.79±4.36 and 26.74±6.03 years, mean wart size 0.43±0.09 and 0.49±0.09 cm and mean number of warts 1.61±1.06 and 1.67±1.12 in each group respectively. 83% achieved complete response, 10% lost to follow-up and 7% refused treatment in Group A whereas 48% achieved complete and partial responses respectively and 4% had no response in Group B (p<0.001). **Conclusion:** Acyclovir is an effective treatment modality of cutaneous warts with better results in males presenting with single plantar wart.

Keywords: Viral Warts; Acyclovir; Cryotherapy; HPV

Citation: Ahmad F, Janjua NS, Rizwan M. Efficacy of intralesional acyclovir versus cryotherapy for treatment of plantar warts. J Ayub Med Coll Abbottabad 2025;37(3):352–5.

DOI: 10.55519/JAMC-03-14628

INTRODUCTION

Human papilloma virus (HPV), a DNA virus, cause benign growth of skin and mucosa termed as warts.[1] At present, more than 170 HPV types have been observed. Warts caused by HPV may be present at any part of body but certain HPV types usually infect skin at specific anatomical locations like palmoplantar warts are usually caused by serotypes 1, 2, and 4. Warts can be caused by contact either direct or indirect, and predisposing factors include disruption to the normal epithelial barrier.[2]

Various techniques exist for the management of warts, almost all of which have an effective role in some patients; hence, a combination of these can be used as well.[3] Cryotherapy is being used conventionally for eradication of warts. Liquid Nitrogen, having a freezing point of -195.6 °C, is the cryogen of choice. Various methods of applications, in which cryotherapy is used, include an open spray technique or through direct application of a dipstick or cooled probe.[4] Cryotherapy is usually performed in the outpatient department setting due to its various advantages which include efficacy, safety, economical, good aesthetic results, relative ease of use and lack of the need for local anesthesia.[5] Its mechanism is to cool the affected tissue and causing tissue damage by ice crystals' formation within cells, vascular thrombosis and stasis, imbalance of electrolytes and toxins release.[6,7] Rapid freezing leads to detachment of the epidermis from the dermis. Though many advantages of cryotherapy has been listed, various adverse events like blister formation, bleed, edema, pain, vasovagal syncope, hypo/hyper pigmentation, ulceration etc. do occur.[8] Intralesional therapy with different agents has also been used in the eradication of warts with different results.[9] Fatima SM *et al*. demonstrated complete resolution of warts in 30% of patients who completed six sessions of cryotherapy.[10] Recently, intralesional acyclovir was used as a treatment modality for cutaneous warts and showed 52.6% clearance after five sessions of therapy.[11] Another prospective comparative study conducted showed 60% of complete recovery of viral warts with intralesional acyclovir.[12]

Acyclovir treatment modality is quite readily available, although cryotherapy remains a gold standard treatment for plantar warts. However, cryotherapy in our population is occasionally available

as compared with acyclovir. Cryotherapy requires especial equipment and methods to implement. As no study has been conducted on intralesional acyclovir as a therapeutic modality of treatment for cutaneous warts in our population. This study is being conducted to assess the comparative efficacy of these two treatment modalities and to apply the effective method for treatment of plantar warts in our population.

MATERIAL AND METHODS

This quasi-experimental study was conducted at the Department of Dermatology, Pakistan Air Force Hospital, Islamabad, Pakistan, with prior approval from the "Institutional Ethical Committee" of the concerned institution. A sample size of 84 (42 patients in each group) was calculated using WHO sample size calculator keeping anticipated population proportion P1 as 30%[10] and P2 as 60%[12], power of test 80%, level of significance 5%. Adopting non-probability consecutive sampling, 84 patients were enrolled. The inclusion criteria were patients of either gender between 14-60 years presenting with 1-10 plantar warts. The exclusion criteria were immunosuppression, received treatment for plantar warts in the past one month, on antiviral therapy for other indications, mosaic plantar warts and pregnancy and lactation. Informed as well as written consents were obtained from all study participants or their parents/caregivers.

Baseline demographics data like age, gender, residence, profession, education, socio economic status, size of warts and number warts were recorded. Patients were allocated to either of the two groups, i.e., group-A and group-Patients in Group A were given intralesional acyclovir (70mg/ml) at a dose of 0.1 ml with an insulin syringe at base of each wart while patients in Group B were treated with cryotherapy using liquid nitrogen (-196 ºC) for two freeze and thaw cycles. Each cycle was for 10 seconds. These treatments were repeated every two weeks for a maximum period of five sessions.

Baseline clinical photographs were taken and after five sessions. Size of each wart was measured using measuring tape in maximum diameter length and size of the greatest wart (maximum size of 1 cm). Post treatment completion, these patients were followed-up every month for total four months noting resolution and recurrence of warts. The treatment was considered effective only if there was complete resolution of wart with no recurrence after 5 sessions. Complete response (100% resolution of warts), partial response (50-99% resolution) or no response (less than 50% resolution) was recorded on *Proforma*.

All data on proforma was uploaded and analyzed using statistical software (SPSS) Version 27. For quantitative variables like age, size of warts and number of warts, mean ± standard deviation or median and for qualitative variables like gender and efficacy, Frequency and percentage were calculated. Efficacy was compared in both groups and applying chi square test, a *p*-value of ≤0.05 was considered as significant. Efficacy was stratified with effect modifiers such as age and gender. By applying post stratification chi square test and independent t tests, *p*-value of ≤0.05 was considered as significant.

RESULTS

The study enrolled 84 patients with 42 patients in each group. The mean age, mean wart size and mean number of warts in each group are given in Table-1. Treatment response in Group A is highly significant, Figures 1 and 2. Considering adverse events, pain was observed slightly greater in Group A as compared to Group B but results were insignificant. Similarly, Blister formation and local erythema were each documented in Group A only. Non-compliance to treatment was noted exclusively in Group A, where patients were lost to follow-up or declined further treatment after the initial session. Table-1 shows results of study.

Table-1: Baseline demographics, clinical response and adverse events of Intralesional acyclovir and cryotherapy in warts.

	Acyclovir (N=42)		Cryotherapy (N=42)		*p*-value
Age (years)					0.365
Range	20-39		16-40		
Mean±SD	27.79±4.36		26.74±6.03		
Wart Size (cm)					0.009
Range	0.3-0.7		0.3-0.7		
Mean±SD	0.43±0.09		0.49±0.09		
Number of Warts					0.842
Range	1-6		1-5		
Mean±SD	1.61±1.06		1.67±1.12		
Number of Sessions					<0.001
Range	1-5		1-5		
Mean±SD	2.47±1.18		4.60±0.86		
	N	**%**	**N**	**%**	***p*-value**
Gender					<0.001
Male	33	79	23	55	
Female	9	21	19	45	
Response					
Complete Response	35	83	20	48	<0.001
Partial Response	0	0	20	48	
No Response	0	0	2	4	
Lost to follow-up	4	10	0	0	
Refused Treatment	3	7	0	0	
Adverse Events					
Pain	21	50	16	38	0.267
Blister Formation	1	2	0	0	0.488
Local Erythema	1	2	0	0	0.488

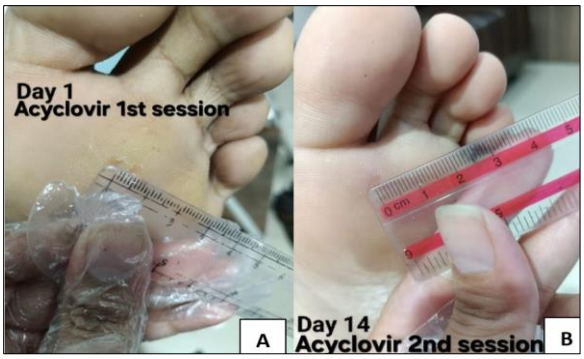

Figure-1: (A) Wart on plantar aspect of patient, pre-treatment with Acyclovir (Group A). (B) Almost complete clearance of wart after 14 days of initiation of I/L Acyclovir (Group A).

Figure-2: (A) Wart on plantar aspect of left foot, pre-treatment with Cryotherapy (Group B). (B) Wart showing no response to treatment after 5 sessions of treatment with Cryotherapy (Group B).

DISCUSSION

Our study showed 83% complete response in acyclovir arm while study done by Elsayed *et al*. showed complete response to acyclovir in 52.6% patients while 36.8% had partial response and 10.5% had no response.[11] Similarly, study done by Elyamany *et al*. showed complete response in acyclovir group in 40% cases.[13] Gharib *et al* showed complete resolution of warts to acyclovir in 37.5% cases.[14] Aziz *et al*. showed complete resolution of recalcitrant warts in 66.7% cases in acyclovir group.[15]

This difference in results is due to key methodological distinctions like our study specifically excluded mosaic and recalcitrant warts and maintained a standardized 5-session protocol for treatment administered every two weeks. The higher male predominance (79%) in our acyclovir group may also contribute, as some studies suggest gender-based differences in immune response to HPV. For cryotherapy, our observed 48% complete clearance aligns closely with García-Oreja *et al*.'s systematic review that reported a 45.61% cure rate.[16] This cure rate highlights cryotherapy's limitations, especially for plantar warts where hyperkeratosis may prevent effective response. The significant proportion of partial responders (48%) and non-responders (4%) in our cryotherapy group further shows its unpredictable efficacy. Network meta-analyses also support these findings, ranking cryotherapy as poor modality of treatment due to its recurrence rates compared to immunotherapies like MMR vaccine.[17]

The efficacy of Acyclovir to treat Human Papilloma Virus (HPV), a DNA virus, remains an intriguing phenomenon. While traditionally targeting herpesvirus thymidine kinase, studies suggest acyclovir triphosphate may competitively inhibit HPV DNA polymerase terminating viral DNA chain elongation.[12,18] Additionally, intralesional injection causes localized inflammation stimulating cell-mediated immunity against HPV antigens.[19] This dual antiviral-immunomodulatory action could explain its ulterior performance over purely destructive cryotherapy, which lacks systemic immune effects and often fails to eradicate subclinical infection. The therapeutic advantages observed in our study are multifactorial such as direct intralesional injection ensures high drug concentrations within infected tissues, minimizing systemic exposure, absence of recurrences during 4-month follow-up period suggests eradication of latent virus which contrasts with cryotherapy's recognized recurrence rates up to 30%[16,17] and unlike cryotherapy-associated scarring and dyspigmentation, acyclovir-treated sites showed excellent aesthetic results with restored skin markings.

While acyclovir demonstrated pain in 50%, blistering and local erythema in 2% each in our study, the injection process itself induced temporary pain and burning in 90-100% of patients across studies[12,19] resolving within hours and were considered bearable by most patients. Notably, severe adverse events (e.g., anaphylaxis, systemic toxicity) were absent in our study and literature reports.[19] Cryotherapy in our study was associated with pain in 38% of patients, however, it caused blistering in 28% and hypopigmentation in 15% of patients in large series.[16] Similarly, Acyclovir's safety profile is particularly effective for periungual warts where cryotherapy has risk of damage to nail matrix. A recent retrospective study confirmed no permanent nail deformities with intralesional acyclovir in periungual locations.[18]

Limitations and Research Implications:

Several methodological limitations like freeze duration and technique can introduce potential performance bias despite standardized protocols, hence affecting efficacy of cryotherapy. The 4-month follow-up period necessitates assessment of long-term recurrence beyond 6 months. Similarly, exclusion of immunocompromised patients, children and recalcitrant warts limits generalizability of acyclovir to complex cases and quasi-experimental design lacked participant/provider blinding due to markedly different administration techniques. Similarly, 10% lost to follow-up and further 7% declined treatment after first

session of intralesional acyclovir in our study. Due to above mentioned limitations, future research should focus on larger multi-center RCTs comparing acyclovir to both cryotherapy and immunotherapies (e.g., MMR, PPD) with extended follow-up, combining acyclovir with physical modalities (e.g., micro needling, which ranked highest in recent meta-analysis)[17] or immunotherapies, finding out acyclovir's exact antiviral action against HPV using molecular techniques and assessment of safety and efficacy in children who frequently develop plantar warts.

CONCLUSION

This study provides significant evidence supporting intralesional acyclovir as first-line therapy for non-recalcitrant plantar warts, particularly in resource-limited settings where cryotherapy equipment is unavailable due to its high cost. Its superior efficacy and minimal requirements (standard syringe vs. liquid nitrogen tanks) makes it a favorable option for primary care dermatology. Intralesional acyclovir (70mg/mL) administered every second week for up to five sessions shows statistically and clinically superior efficacy to conventional cryotherapy for plantar warts, with an 83% complete response rate and excellent tolerability. These findings implicate reconsideration of current clinical guidelines that considers cryotherapy as the gold standard therapy. As wart management evolves toward targeted therapies, intralesional acyclovir shows a promising, accessible, and mechanism-driven approach worthy of broader clinical adoption in developing countries particularly.

AUTHORS' CONTRIBUTION

FA, NSJ, MR: Concept, design, data collection, analysis, interpretation, literature search, write-up, proof reading, final approval, and agreement to be accountable for all aspects of work. All the authors contributed equally.

REFERENCES

1. Gupta AK, Wang T, Cooper EA, Conenello RM, Bristow IR. The treatment of plantar warts using microwave: a review of 85 consecutive cases in the United States. J Cosmet Dermatol 2023;22(10):2729–36.
2. Abdo HM, Elrewiny EM, Elkholy MS, Ibrahim SM. Efficacy of intralesional methotrexate in the treatment of plantar warts. Dermatol Ther 2020;33(2):e13228.
3. Khozeimeh F, Jabbari Azad F, Mahboubi Oskouei Y, Jafari M, Tehranian S, Alizadehsani R, *et al*. Intralesional immunotherapy compared to cryotherapy in the treatment of warts. Int J Dermatol 2017;56(4):474–8.
4. García-Oreja S, Álvaro-Afonso FJ, García-Álvarez Y, García-Morales E, Sanz-Corbalán I, Lázaro-Martínez JL. Topical treatment for plantar warts: a systematic review. Dermatol Ther 2021;34(1):e14621.
5. Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. Br J Dermatol 2011;165(2):233–46.
6. Nofal A, El-Arab RE, Nasr M, Alakad R. Intralesional measles, mumps, and rubella vaccine versus intralesional Candida antigen in the treatment of common and plantar warts. J Cutan Med Surg 2021;25(4):377–83.
7. Awad SM, Gomaa AS, Hassan HA, Tawfik YM. Efficacy of cryotherapy combined with intralesional purified protein derivative (PPD) versus intralesional PPD monotherapy in the treatment of multiple common warts. J Cutan Med Surg 2023;27(2):117–25.
8. Muse ME, Stiff KM, Glines KR, Cline A, Feldman SR. A review of intralesional wart therapy. Dermatol Online J 2020;26(3):13030.
9. Kaimal S, Gopinath H, Premalatha V. Intralesional immunotherapy with purified protein derivative (PPD) for cryotherapy-resistant warts. Int J Dermatol 2020;59(6):726–9.
10. Fatima SM, Ejaz A, Anwar A. Comparison of efficacy of intralesional purified protein derivative (PPD) with cryotherapy in the treatment of cutaneous warts. Pak Armed Forces Med J 2019;69(5):965–70.
11. Elsayed A, Nassar A, Marei A, Hoseiny HA, Alakad R. Intralesional acyclovir: a potential therapeutic option for cutaneous warts. J Cutan Med Surg 2022;26(1):25–30.
12. Reddy EM, Rajashekar TS, Kumar KS. A comparative study of intralesional acyclovir vs immunotherapy for treatment of viral warts. Cureus 2023;15(5):e38781.
13. Elyamany MI, Obaid ZM, Fouda I. Efficacy of intralesional acyclovir versus quadrivalent human papillomavirus vaccine for treatment of recalcitrant cutaneous warts: a clinical trial. Arch Dermatol Res 2025;317(1):1–9.
14. Gharib K, Taha A, Elradi M. Intralesional acyclovir versus intralesional hepatitis-B vaccine in treatment of resistant plantar warts: a randomized controlled trial. Arch Dermatol Res 2024;316(6):325–30.
15. Aziz GABA, Pessar DAEH, Semeda LMR, Ali MSA. Comparative study between intralesional acyclovir versus intralesional 5-fluorouracil in treatment of recalcitrant warts. Arch Dermatol Res 2025;317(1):1–19.
16. García-Oreja S, Álvaro-Afonso FJ, Tardáguila-García A, López-Moral M, García-Madrid M, Lázaro-Martínez JL. Efficacy of cryotherapy for plantar warts: a systematic review and meta-analysis. Dermatol Ther 2022;35(6):e15480.
17. Alrashidi A, Shaheen E, Abualola A, Alharkan AA, Aljuaid A, Alshareef KM, *et al*. The efficacy of cryotherapy compared to other modalities for the management of palmoplantar warts: a systematic review and network meta-analysis. Dermatol Rep 2024;17(2):e10121.
18. Min KH, Yoo EH, Koo HY, Yun SY, Choi JY, Yu DS, *et al*. Exploring the efficacy and safety of intralesional acyclovir for treating periungual and palmoplantar warts. Korean J Dermatol 2024;62(3):129–35.
19. El-Hamd MA, Nada E, Hassan RM, Aboelmagd MA. Clinical and dermoscopic study of intralesional injection of acyclovir versus Candida antigen in treatment of plantar warts. Indian J Dermatol 2025;70(4):171–6.

Submitted: July 7, 2025	*Revised: August 27, 2025*	*Accepted: August 30, 2025*

Address for Correspondence:

Muneeza Rizwan, Dermatology Centre, PAF Hospital, Islamabad-Pakistan
Cell: +92 323 535 9680
Email: muneezar@yahoo.co.uk