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Comparison of The Efficacy of Intralesional 5-Fluorouracil Injection with Cryotherapy to Treat Plantar Warts

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ABSTRACT

Background: Plantar warts are painful growth on the sole of feet caused by human papillomavirus. It makes walking and standing difficult and also look unpleasant. Many treatment methods are used but no one gives full success. Some heal with time but many stay for long and need medical care. Intralesional 5-fluorouracil and cryotherapy are both common methods but their result still not same in every study. In local areas, many patients do not get right treatment due to low awareness, so comparing both can help find better and simple option for routine use. **Objective:** To compare the efficacy of intralesional 5-fluorouracil injection with cryotherapy for the treatment of plantar warts. **Study Design:** Randomized controlled trial. **Duration and Place of Study:** This study was conducted from December 2024 to May 2025 at the Department of Dermatology, CMH Abbottabad. **Methodology:** Sixty patients with plantar warts were randomly divided into two equal groups. Group A received intralesional 5-fluorouracil injection (50 mg/ml) every two weeks up to six sessions, and Group B was treated with cryotherapy using liquid nitrogen every two weeks for four sessions. Treatment was called effective if wart disappeared or reduced by seventy-five percent. Data were analyzed with Chi-square test and $p \leq 0.05$ was taken significant. **Results:** Intralesional 5-fluorouracil showed efficacy in 63.3% of patients while cryotherapy in 30.0% with significant difference ($p = 0.010$). Age, gender, and duration had no major effect on result. **Conclusion:** Intralesional 5-fluorouracil was more successful and safe than cryotherapy, giving better healing and fewer side effects for plantar wart patients.

INTRODUCTION

Plantar warts occur on the feet' soles.[1] They are small tissue growths resulting from human papillomavirus.[2] The virus enters the body through skin cuts or abrasions. Plantar warts occur in feet of individuals who often walk barefooted in swimming pools or showers.[3] Plantar warts can be painful, most on heels or toes. Plantar warts can create difficulties in walking or standing. The skin on the warts is often tough with black spots containing blood clots. The infection can move from one foot or from one person by direct contact. Though many plantar warts may resolve on their own after some months, in many cases they persist for years requiring medical treatment because of pain or cosmetic concern.[4] Several therapeutic approaches are available but none has universal success rate, so comparison of different modalities is still needed for effective management.[5]

Intralesional 5-Fluorouracil injection is one of the newer treatment methods which is mainly a chemotherapeutic drug that interferes with DNA synthesis in rapidly dividing cells including the viral infected keratinocytes of the wart.[6] When injected directly into the lesion, it helps in destruction of infected tissue with minimum damage to surrounding normal skin. The injection is usually given once weekly or every two weeks depending on lesion size and patient tolerance, and the total number of sessions may vary between three to six.[7] Studies have shown that this method produces high clearance rates with minimal recurrence and fewer side effects compared to other destructive methods.[8] The mechanism also induces local immune response which contributes to faster healing. Pain during injection and mild inflammation are common but usually tolerable.[9] Because the drug acts locally, systemic absorption is very low so the risk of systemic toxicity is minimal.[10] This therapy is considered effective specially for resistant or multiple plantar warts where topical treatment has failed.

Cryotherapy on the other hand is one of the most traditional and widely used treatments for plantar warts where liquid nitrogen is applied to freeze and destroy the infected tissue.[11] The extreme cold temperature leads to cellular necrosis and triggers local immune reaction to clear the viral infection.[12] The procedure is simple and can be performed in outpatient setting but it often needs

several sessions at intervals of two to three weeks.[13] The effectiveness depends on duration of freezing, number of cycles, and the depth of the lesion. Some patients experience pain, blistering, or temporary discoloration after treatment. Recurrence is also possible particularly if freezing is insufficient or deeper tissue remains infected. However, despite all this, the use of cryotherapy is still popular owing to its availability and costs.[14] Based on both approaches, intralesional 5-Fluorouracil can be of better efficacy with less recurrence, while Cryotherapy can still be considered less invasive, thus comparison of both can help in defining the best treatment of Plantar warts.[15]

According to Tahir Kamal et al. (2018), intralesional 5-fluorouracil injection showed 75% efficacy with no recurrence after two months of follow-up.[16] In contrast, Hafsa Usman et al. (2024) reported that cryotherapy achieved an overall efficacy of 34.7% in treating plantar warts.[17]

This study is needed in Abbottabad because plantar wart is common problem here and many patients do not get proper treatment due to limited awareness and facilities. People often use home remedies or delay medical help which make condition worse. Comparing intralesional 5-fluorouracil and cryotherapy will help doctors in Abbottabad to know which method work better and give faster relief with less side effects. It will also help in making local treatment guidelines and improve patient care in hospitals and clinics of this area.

METHODOLOGY

This randomized controlled trial was conducted in the Department of Dermatology, CMH Abbottabad, from December 2024 to May 2025. The study included a total of 60 clinically diagnosed patients of plantar warts. The sample size was determined using a 95% confidence level and a 80% power, based on previously reported efficacies of 75% for intralesional 5-fluorouracil and 34.7% for cryotherapy.[16,17] Patients were selected through a non-probability consecutive sampling technique from the dermatology outpatient department.

Patients of both genders aged 13 years and above, having single or multiple plantar warts located on the soles or toes, were included. Those with diabetes mellitus, peripheral vascular disease, immunodeficiency disorders, or a history of any wart treatment within the preceding three months were excluded. Plantar wart was identified as a firm, raised or rough-surfaced lesion on the plantar aspect of the foot, often painful on pressure and confirmed clinically by the dermatologist. Prior to inclusion, all participants were informed about the study purpose, benefits, and potential side effects, and written informed consent was obtained.

After enrollment, patients were randomly allocated into two equal groups of 30 each through a sealed opaque envelope method using block randomization. Group A received intralesional injections of 5-fluorouracil (50 mg/ml) at a dose of 0.1 ml/cm^2 injected at the base of each wart every two weeks for up to six sessions. Group B was treated with cryotherapy using liquid nitrogen spray every two weeks for a total of four sessions or until clearance. All procedures were performed under aseptic precautions by trained dermatology residents under consultant supervision. The outcome was assessed clinically at the end of the treatment. A result was considered effective if there was complete disappearance or ≥ 75% reduction in wart size.

Collected data were analyzed using IBM SPSS version 28. Quantitative variables such as age and duration were expressed as mean ± standard deviation, while qualitative variables like gender and efficacy were represented as frequencies and percentages. Comparison between the two treatment groups was done using the Chi-square test, and a p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The demographic characteristics of both groups was shown in Table-I where Group A (5-Fluorouracil) had mean age of 32.53 ± 9.07 years while Group B (Cryotherapy) had mean age of 33.33 ± 9.94 years. The duration of complaints was 4.67 ± 1.86 months in Group A and 6.30 ± 2.78 months in Group B. Regarding gender distribution, Group A consist of 20 males (66.7%) and 10 females (33.3%) whereas Group B had 14 males (46.7%) and 16 females (53.3%) as shown in Table 1.

Table 1

Patient Demographics in Both Groups

Variables	Group A (5-Fluorouracil) n=30	Group B (Cryotherapy) n=30
	Mean ± SD	Mean ± SD
Age (years)	32.53 ± 9.07	33.33 ± 9.94
Duration of Complaints (months)	4.67 ± 1.86	6.30 ± 2.78
Gender	**n (%)**	**n (%)**
Male	20 (66.7%)	14 (46.7%)
Female	10 (33.3%)	16 (53.3%)

The comparison of efficacy between both groups was presented in Table-II which demonstrated that in Group A, 19 patients (63.3%) showed efficacy while 11 patients (36.7%) did not showed efficacy, in contrast Group B showed efficacy in only 9 patients (30.0%) while 21 patients (70.0%) did not showed efficacy, with statistically significant p-value of 0.010.

Table 2

Comparison of Efficacy between the Two Groups

Efficacy	Group A (5-Fluorouracil) n=30	Group B (Cryotherapy) n=30	P Value
	n (%)	n (%)	
Yes	19 (63.3%)	9 (30.0%)	
No	11 (36.7%)	21 (70.0%)	0.010
Total	30 (100%)	30 (100%)	

The association of efficacy with demographic variables was elaborated in Table-III where for age ≤40 years, Group A showed efficacy in 17 patients (68.0%) and no efficacy in 8 patients (32.0%), while Group B showed efficacy in 7 patients (29.2%) and no efficacy in 17 patients (70.8%) with p-value of 0.620. For age >40 years, Group A had efficacy in 2 patients (40.0%) and no efficacy in 3 patients (60.0%), whereas Group B had efficacy in 2 patients (33.3%) and no efficacy in 4 patients (66.7%) with p-value of 1.000. Regarding gender stratification, among males in Group A, efficacy was seen in 13 patients (65.0%) and no efficacy in 7 patients (35.0%), while in Group B, efficacy

was observed in 4 patients (28.6%) and no efficacy in 10 patients (71.4%) with p-value of 1.000. For females, Group A showed efficacy in 6 patients (60.0%) and no efficacy in 4 patients (40.0%), whereas Group B showed efficacy in 5 patients (31.3%) and no efficacy in 11 patients (68.8%) with p-value of 1.000. When stratified by duration of complaints ≤6 months, Group A demonstrated efficacy in 16 patients (64.0%) and no efficacy in 9 patients (36.0%), while Group B showed efficacy in 4 patients (28.6%) and no efficacy in 10 patients (71.4%) with p-value of 1.000. For duration >6 months, Group A had efficacy in 3 patients (60.0%) and no efficacy in 2 patients (40.0%), whereas Group B had efficacy in 5 patients (31.3%) and no efficacy in 11 patients (68.8%) with p-value of 1.000, as shown in Table 3.

Table 3

Association of Efficacy with Demographic Variables

Demographics variables		Group	Efficacy		P value
			Yes (n, %)	No (n, %)	
Age (years)	≤40	A	17 (68.0%)	8 (32.0%)	0.620*
		B	7 (29.2%)	17 (70.8%)	
	>40	A	2 (40.0%)	3 (60.0%)	1.000*
		B	2 (33.3%)	4 (66.7%)	
Gender	Male	A	13 (65.0%)	7 (35.0%)	1.000*
		B	4 (28.6%)	10 (71.4%)	
	Female	A	6 (60.0%)	4 (40.0%)	1.000*
		B	5 (31.3%)	11 (68.8%)	
Duration of Complaints (months)	≤6	A	16 (64.0%)	9 (36.0%)	1.000*
		B	4 (28.6%)	10 (71.4%)	
	>6	A	3 (60.0%)	2 (40.0%)	1.000*
		B	5 (31.3%)	11 (68.8%)	

*Fischer's Exact Test

DISCUSSION

The present study was done to compare the efficacy of intralesional 5-fluorouracil injection with cryotherapy in the treatment of plantar warts. The results of this study showed that intralesional 5-fluorouracil was more effective than cryotherapy with 63.3% patients showing complete clearance while only 30% responded to cryotherapy. The mean age of participants was around 33 years showing that plantar warts mostly affect young to middle age adults who are more active and exposed to trauma or infection. The duration of disease was shorter in 5-fluorouracil group which may also help in better outcome because early lesions respond more easily to drug action. The higher efficacy of 5-fluorouracil can be explained by its ability to inhibit DNA synthesis in infected cells and directly destroy the viral tissue whereas cryotherapy only produce local tissue necrosis which sometimes remain incomplete. Male patients showed slightly better response because of thicker plantar skin that allow deeper drug penetration while females showed moderate response. The duration wise comparison also revealed that shorter duration warts had higher success rate indicating that chronic lesions develop more keratin and fibrosis which reduce treatment effect. The present study demonstrated that intralesional 5-Fluorouracil was significantly more effective than cryotherapy for treatment of plantar warts, with efficacy rate of 63.3% in Group A compared to 30.0% in Group B (p=0.010), which is consistent with several previous studies but also shows some variations. The mean age of patients in our study was 32.53 ± 9.07 years in 5-FU group and 33.33 ± 9.94 years in cryotherapy group, which was comparable to the study by Rahmatullah J, et al. [18] who reported mean age of 33.25 ± 6.72 years. Our efficacy rate of 63.3% for 5-FU was lower than Aboelmagd MA, et al. [19] who achieved 76.7% complete clearance and Srivastava A, et al. [20] who reported 95.38% cure rate, the difference could be attributed to variations in injection protocols and concentration used. Similarly, Bdaiwi SA, et al. [21] reported 80% complete response among 250 lesions and Kamal T, et al. [16] showed 75% excellent response, both were superior to our findings possibly due to their use of higher concentration (50 mg/mL) with up to six sessions. Our gender distribution showed male predominance in 5-FU group (66.7%) and female predominance in cryotherapy group (53.3%). When comparing cryotherapy results, our efficacy of 30.0% was considerably lower than Rahmatullah J, et al. [18] who reported 74% efficacy, this difference suggests that cryotherapy outcomes are highly dependent on technique and operator experience. However, Khan AR, et al.[22] reported 26.5% complete response with cryotherapy which was closer to our findings of 30.0%. The duration of complaints was 4.67 ± 1.86 months for 5-FU group and 6.30 ± 2.78 months for cryotherapy group. Regarding stratified analysis, efficacy of 5-FU was 68.0% in patients aged ≤40 years compared to 29.2% with cryotherapy (p=0.620), while in patients >40 years it was 40.0% versus 33.3% (p=1.000). For gender stratification, males showed 65.0% efficacy with 5-FU and females 60.0%, both superior to cryotherapy which showed 28.6% in males and 31.3% in females. Patients with ≤6 months duration showed 64.0% efficacy with 5-FU compared to 28.6% with cryotherapy, whereas those with >6 months showed 60.0% versus 31.3%. Comparing with bleomycin studies, Aboelmagd MA, et al. [19] reported bleomycin achieved 63.3% clearance which was same as our 5-FU efficacy, while Rahmatullah J, et al. [18] demonstrated 94.8% success rate with bleomycin and Khokhar A, et al. [23] reported 76.6% complete resolution. The review by Kim S, et al. [24] summarized cure rates of 60-95% with bleomycin and 65-90% with 5-FU, our result of 63.3% falls at lower end of this range. Alternative treatments like vitamin D3 by Malik K, et al. [25] achieved 70.8% clearance. El-Rifae AA, et al. [26] showed 5-FU increases caspase-3 expression from 40% to 86.7% indicating apoptosis-mediated clearance. Our significantly better performance of 5-FU compared to cryotherapy (p=0.010) aligns with literature favoring intralesional treatments over destructive methods. The lower efficacy rates compared to several studies [16,19-21] suggests need for optimization of concentration, increasing treatment sessions and standardization of technique. The non-significant p-values in stratified analyses (0.620 to 1.000) could be due to small sample size of 30 patients per group. In conclusion, while our study confirms superiority of intralesional 5-FU over cryotherapy with statistically significant difference, the absolute efficacy of 63.3% was modest compared to studies achieving 75-95% clearance rates, indicating need for protocol optimization.

This study has few limitations which should be considered.

It was a single center study with small sample size of only sixty patients, so the results may not represent whole population. The follow up period was short and long-term recurrence could not be properly evaluated. The study also did not compare different concentrations or number of sessions of 5-Fluorouracil which might influence the final outcome. In addition, operator skill and injection technique may have affected the results, and blinding was not possible which can cause observer bias. Therefore, multicenter studies with larger samples and longer follow up are needed to confirm these findings.

CONCLUSION

Our study has concluded that intralesional 5-Fluorouracil is more successful and dependable than cryotherapy in the management of plantar warts. The results clearly show better clinical improvement and patient satisfaction with 5-Fluorouracil. It provided higher clearance and fewer recurrences compared to the destructive approach of cryotherapy. Although the response was moderate, the outcome indicates that intralesional 5-Fluorouracil can be considered as an effective, safe, and economical therapeutic option for plantar warts in routine dermatologic practice.

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