Intralesional Injection of Bleomycin versus 5-Fluorouracil in Treatment of Plantar Warts: Clinical and Dermoscopic Study

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ABSTRACT
Background: Plantar warts are skin lesions on the Plantar surface of the foot resulting from infection of keratinocytes by human papilloma virus. Intralesional bleomycin and 5- fluorouracil (5-FU) are therapeutic options utilized to treat various dermatological conditions including planter warts. **Objectives**: This study aimed to compare the efficacy and safety of intralesional injection of bleomycin versus 5-FU in patients with plantar warts. **Methods:** Randomized comparative interventional study included 60 patients complaining of plantar warts, they were divided randomly into 2 equal groups; Bleomycin and 5-FU groups. Clinical examination, photographic and dermoscopic evaluation were done before and after treatment. **Results**: As regard response to treatment, in bleomycin group (63.3%) of patients showed complete clearance clinically and dermoscopically versus (76.7%) in 5-FU group, while warts disappeared clinically, but a dermoscopy revealed vestiges was about (30%) in the bleomycin group versus (16.7%) in 5-FU group without significant difference in response rate or in the patients' satisfaction between the two groups. The most frequent side effect was pain at the injection site without significant difference between bleomycin (66.7%) and 5-FU group (70%). Regarding the follow-up after 3-months, only one case had recurrence in the bleomycin group (3.3%) versus no case in 5-FU group (0%). **Conclusion**: Both Intralesional injection of bleomycin and 5-FU are safe, effective and practical treatment modalities for plantar warts, with higher response rate and lower recurrence in Intralesional 5-flurouracil injection. Dermoscope is recommended in early diagnosis, preventing recurrence and tracking the clinical response to treatment.

Introduction

Plantar warts are a keratinocyte infection with the human papillomavirus (HPV) [1]. These warts have an annual incidence rate of 14% [2]. Transmission happens via direct contact with keratinocytes from an infected person or indirectly via contaminated objects. The virus can also spread to additional skin regions through autoinoculation, facilitated by scratching or skin trauma [3, 4].

Patients with plantar warts often experience pain or a sensation resembling a stone or lump under their foot [5]. Visually, one or more rough, flesh-colored to yellow or grey-brown papules may be the initial sign of a plantar wart. They may thicken into a mosaic wart, which is a conglomeration of several warts that have merged together [6, 7].

The main goals of treatment are to either eradicate the visible wart tissue or cause cytotoxicity by focusing on the diseased cells [8]. Among the techniques are the use of antimitotic agents (podophyllin, bleomycin, retinoids, and 5-fluorouracil), topical virucidal agents (glutaraldehyde and formaldehyde), and destructive agents (keratolytic, photodynamic therapy cryotherapy, cautery, curettage and laser) [9-11]. Intralesional injections employing vaccines and organic antigens (Candida albicans, Measles, Mumps and Rubella (MMR) vaccine, tuberculin antigens like, Bacillus Calmette-Guérin (BCG)and purified protein derivative (PPD)are also utilized [12-14].

Bleomycin, a glycopeptide antibiotic from Streptomyces verticillus, is an antineoplastic agent recognized for its effectiveness against stubborn warts [15]. Its mechanism includes DNA binding that causes single-strand breaks, direct cytotoxicity, virucidal effects, upregulation of tumor necrosis factor-alpha (TNFα), and inducing apoptosis in keratinocytes infected with HPV. Besides warts, intralesional bleomycin is applied in treating various skin conditions like hemangiomas, vascular malformations, and certain skin cancers [16, 17].

5-Fluorouracil (5-FU) is a pyrimidine analog used as an antitumor agent that inhibits DNA synthesis by blocking pyrimidine and thymidine pathways, thereby hindering cell replication and proliferation [18]. This mode of action makes 5-FU suitable for wart treatment, particularly when administered intralesionally to ensure high local drug concentrations with reduced systemic toxicity risks [19]. Intralesional 5-FU is also employed for various dermatological conditions, including genital warts, keratoacanthoma, and skin cancers [20, 21].

To the best of our knowledge, no studies have compared the clinical and dermoscopic effects of intralesional 5 FU and bleomycin in the treatment of verrucae, despite the fact that their efficacy has previously been clinically assessed , the current study set out a dermoscopic confirmation of the efficacy of intralesional bleomycin injection versus 5-flurouracil in treating plantar warts.

Patients and methods

This comparative interventional study was carried out from October 2022 to September 2023 in Dermatology outpatient clinic of Sohag University Hospital after approval from the institutional ethics committee with approval number (Soh-Med-22-06-06).

Patient selection

The study included 60 patients diagnosed clinically and confirmed by dermoscopy as having single or multiple plantar warts, both sexes included, their ages ranged from (18-60) years.

Exclusion criteria

- Patients who have previously experienced sensitivity to either of the two study medications.
- Patients on immune suppressive drugs, Immuno-compromised patients and those with any major medical illness.
- pregnant and lactating females.
- Patients with keloidal tendency.
- Patients received any wart treatment within one month preceding the study.

Treatment protocol:

Following the participants' informed written agreement, at the first visit, history, clinical characteristics, and baseline assessments such as the number, site and size of warts were documented.

Clinical examination was supported by clinical and dermoscopic photos. the patients were divided equally Using computer-based randomization into two groups,

Bleomycin Group (n =30): A bleomycin vial (Bleocin, 15 U vial, Nippon Kayaku Co. Ltd, Japan). 5 ml of distilled water was used to dilute the vial to create a stock solution (3 U /ml) which was stored at 4-8°C for up to 60 days. During the treatment session, 2 ml of 2% lidocaine and 1 ml of the diluted bleomycin solution were drawn into a insulin syringe (100-unit), creating a 1 U /ml bleomycin solution. After alcohol wiping and callus removal with a blade, each wart's base received an intralesional injection of the solution until wart blanching was noticed.

with the injected volume adjusted based on the wart size. A maximum of 2 ml bleomycin solution and 5 warts were injected per session, until full remission, injections were administered every two weeks for a maximum of six sessions.

5-fluorouracil Group (n =30): 5-FU vial (Utoral vial 250 mg/5ml, AL Hikma Pharmaceuticals, Cairo, Egypt) .4 mL of 5-FU (50 mg/mL) was mixed with 1 mL of 2% lignocaine and epinephrine combination making a concentration of (40 mg/ml) 5-FU .For each session, 0.1 ml of the mixture was injected at each wart's base until wart blanching was noticed, 5 verrucae and 2 ml were the maximum to be injected per sessions ,until full remission, injections were administered every two weeks for a maximum of six sessions.

Both groups experienced a black, ecchymosed eschar after two weeks of injection, which was removed, and any remaining warts, were reinjected. Patients were evaluated every session then for 3 months after last treatment for recurrence and new lesion.

Patient assessment and follow-up:

Patients were evaluated clinically & by dermoscopy every session then followed for recurrence and new lesions monthly for three months following therapy.

Clinical evaluation: Treatment efficacy and side effects was evaluated by clinical examination, photographic assessment using a digital camera (honor 9x pro triple camera).

Dermoscopic evaluation:

Hand-held dermoscope was used to examine the warts, (Dermlight 1 -DL1-1401 Rev C, 3 Gen are registered trademark of 3 Gen.Inc 31521 Rancho Viejo Rd. Suite 104 san jaun Capistrano CA 92675. U.S.A). with a (mm) measuring scale, LED illumination and magnification ×10.

A digital camera connected to the dermoscope via an adapter was used to take dermoscopic images. Prior to each examination, the dermoscope was sanitized with 70% ethyl alcohol.

To prevent the vascular structures from being compressed, it was applied to the wart without applying any pressure. The presence of uniform black to red spots and globules, interrupted skin lines, papilliform surfaces, is characteristics of viral warts. [22].

Scoring of treatment response

Based on their clinical and dermoscopic responses to treatment, the patients were divided into four scores [23]:

- Score 3 (full response): all treated warts have completely disappeared, as shown by both dermoscopic and visual inspection.
- Score 2 (clinical clearance & dermoscopic remnant): Despite all treated warts have been disappeared clinically a dermoscopic evidence of residual warts is present
- Score 1 (clinical & dermoscopic decrease): clinically significant reduction in the size and/or warts number (>50%) with dermoscopic evidence of residual warts.
- Score 0 (no response): neither a dermoscopic improvement nor a clinical resolution of warts has been observed.

Statistical Analysis:

IBM-SPSS 24.0 was used to code, validate, and analyze the data. Means, standard deviations, medians, frequencies, percentages, and ranges were examples of descriptive statistics. Frequency distributions between groups were evaluated using chi-square, Fisher's exact, and Monte Carlo tests. The normality of continuous variables was examined using the Shapiro-Wilk test. Mann-Whitney U tests and independent sample t-tests were used to compare group means and medians. A statistically significant p-value was defined as less than 0.05.

Results

The current study involved 60 patients with planter warts divided equally in two groups; Bleomycin and 5-FU groups. The patients were between the ages of 18 and 60. The patients in bleomycin group and in 5-FU group had mean ages of (32.1 ± 9.9) and (32.0 ± 11.45) years, respectively (Table 1).

There was no statistically significant difference in the distribution of instances between the 5 FU and bleomycin groups according to age, sex, duration, number and size of warts ($P > 0.05$). (Table 1).

The mean number of sessions was insignificantly different between the two groups, Bleomycin group (3.07 ± 2.1) and 5-FU group (2.67 ± 1.8) (p=0.665). As regard response to treatment, score 3 was about (63.3%) in the bleomycin group versus (76.7%) in 5-FU group and Score 2 was about (30%) in the bleomycin group versus (16.7%) in 5-FU group without significant difference in response rate or in the patients' satisfaction between two groups. (Table2), (Figure 1-4).

Correlation between response of injected wart (score) and other determinants showed that There was insignificant mild negative correlation between response of injected wart (score) and age of the patients, duration and size of wart (r = -0.23, -0.109 and -0. 25 respectively). (Table3)

The most frequent adverse reaction was discomfort and pain at the injection site, without significant difference between bleomycin (66.7%) and 5-FU group (70%) (p = 0.781). Also, both groups had comparable percentage (50%) vs (56.7%) of hemorrhagic eschar (p = 0.605). During the 3-months follow-up, only one case had recurrence in the bleomycin group vs no case in 5-FU group (Table 4).

Table 1: Baseline clinical and sociodemographic data of the studied groups.

Parameter	**Bleomycin Group (n = 30)**	**5-FU Group (n = 30)**	**P-value***
Age/years			
• **Mean ± SD**	32.07 ± 9.9	32.03 ± 11.4	= 0.992*
• **Median (Range)**	29.5 (18 - 55)	25.5 (18 - 60)	
Sex			
• **Female**	7 (23.3%)	10 (33.3%)	= 0.321**
• **Male**	23 (76.7%)	20 (66.7%)	
Duration of Wart/months			
• **Mean ± SD**	7.43 ± 7.1	8.20 ± 7.8	= 0.599***
• **Median (Range)**	4 (1 - 36)	5 (1 - 36)	
No. of Warts before Treatment			= 0.589**
• **Single**	19 (63.3%)	17 (56.7%)	
• **Multiple**	11 (36.7%)	13 (43.3%)	
Size of Warts/ml			
• **Mean ± SD**	8.70 ± 3.2	8.40±1.9	**0.923*** **
• **Median (Range)**	10 (1 - 20)	10 (2-10)	
Size of Wart			
• **≤ 5 ml**	6 (20%)	5 (16.7%)	=0.73**
• **> 5 ml**	24 (80%)	25 (83.3%)	

*Independent t-test was used to compare difference in mean between groups
**Chi square test was used to compare the difference in frequencies among groups
***Mann Whitney U test was used to compare the difference in Medians among groups

Table 2: Comparison of the number of sessions, clinical & dermoscopic responses and satisfaction of patients in the two groups.

Parameter	Bleomycin Group (n = 30)	5-FU Group (n = 30)	P-value*
No. of Sessions			0.677*
Mean ± SD	**3.07±2.1**	2.67 ± **1.8**	
Median (Range)	**2(1-6)**	2 (1 - 6)	
Response of injected wart			
➢ **Mean ± SD**	2.57 ± 0.6	2.7 ± 0.6	= 0.3*
➢ **Median (Range)**	3 (1 - 3)	3 (1 - 3)	
▪ **Score 1**	2 (6.7%)	2(6.7%)	**0.46****
▪ **Score 2**	9 (30%)	5 (16.7%)	
▪ **Score 3**	19 (63.3%)	23 (76.7%)	
Patient satisfaction	**n=30**	**n=30**	
Unsatisfied	9 (30%)	5 (16.7%)	= 0.477**
Satisfied	7 (23.3%)	8 (26.7%)	
Very satisfied	14 (46.7%)	17 (56.7%)	

*Mann Whitney U test was used to compare the difference in Medians among groups
**Chi-square test was used to compare the difference in frequencies among groups

Table3: Correlation between response of injected wart (score) and other determinants in the studied groups.

	Response of Injected Wart (Score)	
	rho*	**p value**
• **Age**	-0.23	0.077
• **Sex**	0.01	0.93
• **Disease Duration/months**	-0.109	0.405
• **No. of Warts**	0.22	0.07
• **Size of wart**	-0.25	0.053

*Spearman's Rank Correlation **significant at level 0.01
Minimal or mild when rho > 0 to < 0.2 moderate 0.3 to 0.4 good between 0.5 to 0.6
Excellent above and equal 0.7

Table 4: Comparison of recurrence and adverse effects between the two studied groups.

Parameter	Bleomycin Group (n = 30)	5-FU Group (n = 30)	P-value*
Complications			
• **Pain**	20 (66.7%)	21 (70%)	= 0.781*
• **Haemorrhagic Eschar**	15 (50%)	17 (56.7%)	= 0.605*
• **Superficial Ulcer**	5 (16.7%)	5 (16.7%)	= 1.000*
• **Hyperpigmentation**	0(0%)	3 (10%)	= 0.119**
Recurrence			
• **No Recurrence**	29 (96.7%)	30 (100%)	= 0.501**
• **Recurrence**	1 (3.3%)	0 (0%)	

*Chi-square test was used to compare the difference in frequencies among groups
**Fisher's exact test was used to compare the difference in frequencies among groups

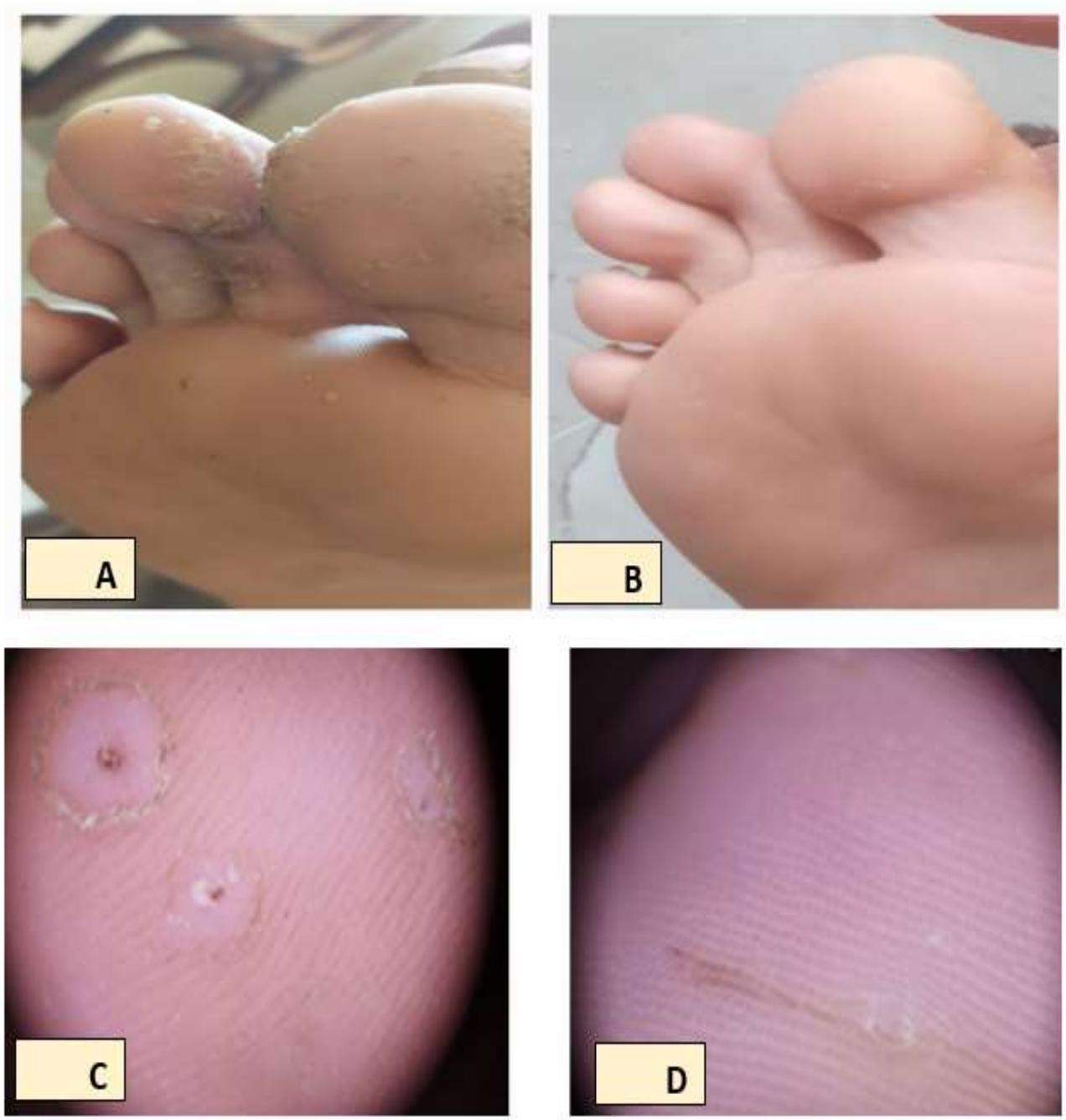

Fig 1: (A): Male patient aged 19 years with multiple plantar warts before treatment. (B): The same patient after 4 sessions of IL bleomycin with excellent response. (C): Dermoscopic picture of the same patient before treatment showing interrupted skin lines, red and black dots. (D): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after 4 sessions of treatment.

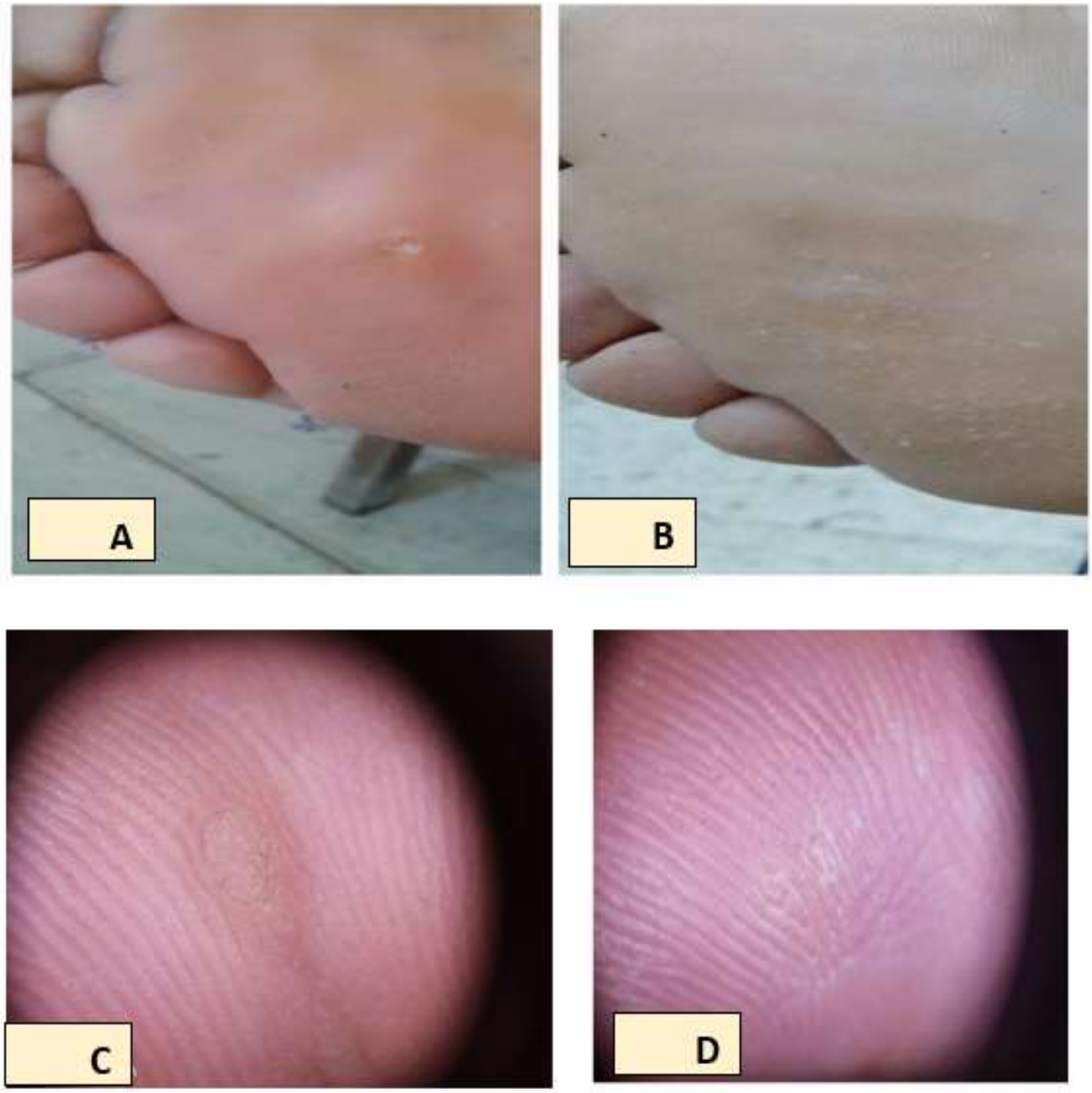

Fig 2: (A): Female patient aged 38 years with single plantar wart before treatment (B): The same patient after 3 sessions of IL bleomycin with excellent response. (C): Dermoscopic picture of the same patient before treatment showing interrupted skin lines and black dots. (D): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after 3 sessions of treatment.

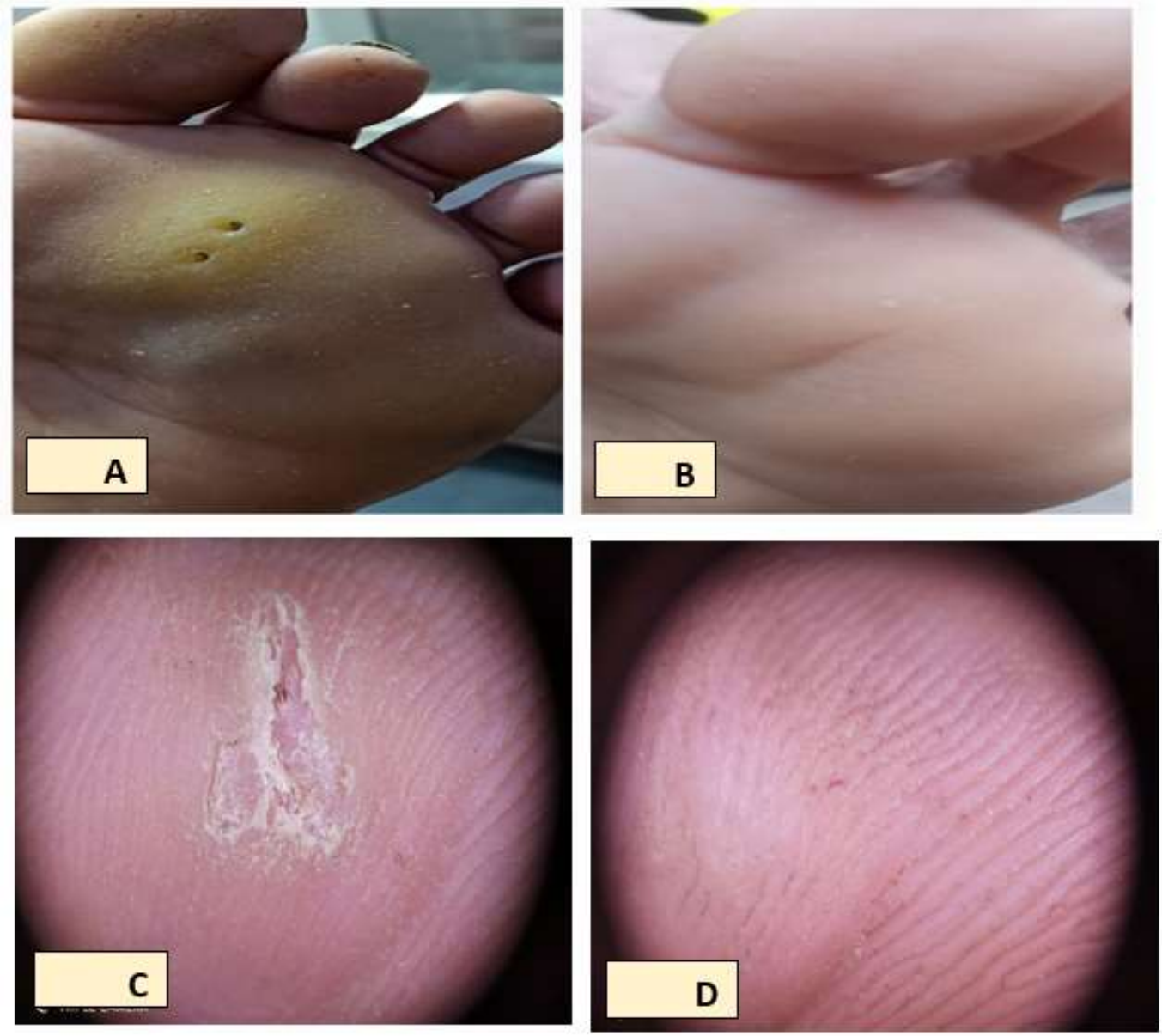

Fig 3: (A): Female patient aged 43 years with multiple plantar warts before treatment. (B): The same patient after 2 sessions of IL5-FU with excellent response. (C): Dermoscopic picture of the same patient before treatment showing interrupted skin lines and black dots. (D): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after 2 sessions of treatment.

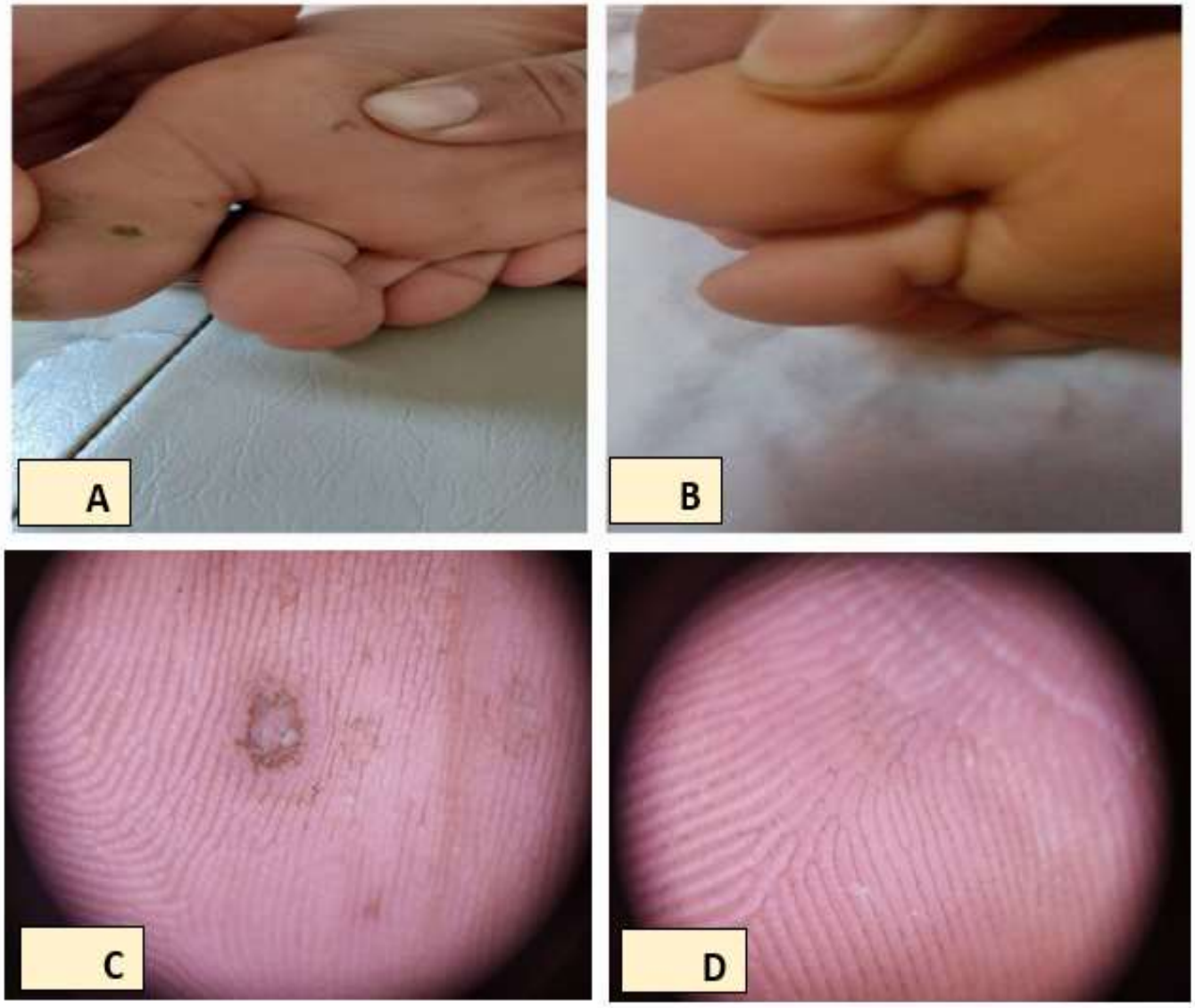

Fig 4: (A): Male patient aged 19 years with multiple plantar warts before treatment. (B): The same patient after 1 session of IL 5FU with excellent response. (C): Dermoscopic picture of one wart before treatment showing interrupted skin lines, red and black dots. (D): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after1 session of treatment.

Discussion

Warts are the most prevalent cutaneous viral infection that significantly lowers a patient's quality of life. Even though many lesions can heal spontaneously, it is also known for being persistent and recurring as well. Even after numerous treatments using different physical modalities, the majority of them remain resistive. [24].

Intralesional injection of immunotherapeutic or anti metabolite agents to treat warts, allows for increased drug concentrations in the lesion, with minimal systemic absorption.

Intralesional injection show less adverse effects when compared with cytodestructive methods, which show scarring in 30%, also 30% of warts reoccur, and 64% experience pain that results in significant morbidity with cytodestructive methods [25].

Bleomycin is a glycopeptide antitumor agent with the antiviral property [16] .5-Fluorouracil (5-FU) is a fluorinated pyrimidine that acts by preventing DNA synthesis through its antineoplastic and antimetabolite effects [17]. Although studies have previously assessed the efficacy of intralesional 5- FU and Bleomycin in the treatment of cutaneous verrucae separately, few studies have compared the two intralesionally administered medications. According to previous researches, no study has used a dermoscopic examination to guarantee total clearance and provide an accurate recurrence rate.

Therefore, the present study was undertaken to evaluate the Clinical efficacy and the dermoscopic assessment of intralesional bleomycin and 5-FU in the treatment of plantar verrucae.

In this trial, 60 patients were recruited and splited into two groups: 30 patients in the bleomycin group and 30 patients in the 5-FU group.

Our findings indicated that both treatments were comparably effective in resolving plantar warts, with no significant difference in efficacy between the two groups. Score 3 (complete clearance clinically and dermoscopically) was about (63.3%) in the bleomycin group versus (76.7%) in 5-FU group and Score 2 (warts disappeared clinically but dermoscopy revealed vestiges) was about (30%) in the bleomycin group versus (16.7%) in 5-FU.

As regard intralesional Bleomycin injection, these results align with other studies, Comparable findings were noted by Sachan et al. in treatment of resistant palmo-plantar warts, who compare intralesional 5-FU injection with intralesional bleomycin injection, in bleomycin group (85.72%) achieved complete improvement [26]. Also, another study by Marhatta et al. found that (80%) full response rate while treating refractory plantar and periungual warts with intralesional bleomycin [27]. Jan Muhammad et al. noted a higher (90%) complete response rate when comparing bleomycin with cryotherapy [28].

Even though the current study's reported cure rate of plantar warts treated with intralesional bleomycin (63.3%) is lower than some earlier studies' [26_27], so our result is more accurate because the treatment's effectiveness was assessed based on both clinical observations and dermoscopic findings. so clinically cured patients without dermoscopic confirmation are anticipated to exhibit a recurrence of their warts shortly.

The difference between dermoscopic evaluation and clinical evaluation alone was supported by Barkat et al., who reported that (88.5%) of patients reported clinical clearance of plantar warts However Only (69.3%) of patients demonstrated dermoscopic complete clearance of their plantar warts (Score 3); the remaining five patients (19.2%) had clinical clearance but dermoscopy indicated remnants of the warts [23].

In this study, insulin syringe was used to inject bleomycin solution into the verruca. In other studies, bleomycin has been delivered to the verrucae using a variety of methods, as in Al-Naggar et al., who compare intralesional bleomycin administered alone with microneedling-assisted bleomycin for plantar warts, they observed a (70 %) in intralesional group versus (83.3%) in microneedling group with no statistically significant while Bleomycin spraying after microneedling was less painful than bleomycin injection. [29]. Additionally, Agius et al. who applied bleomycin (1 mg/ml) to plantar warts using a dermojet for a maximum of five sessions

spaced five weeks apart. When employing dermojet, they obtained an (89.9%) cure rate for warts, but with a (4.4%) recurrence rate. [30].

For intralesional 5-Fluorouracil, similar to our study, Ghonemy et al., who assess treatment of plantar warts with intralesional Injection of 5-Fluorouracil versus microneedling with 5-FU solution, they reported a (76.7%) complete response rate [31], also Rafique et al. noted a (76.8%) of patients showed complete response rate when comparing 5-FU with MMR vaccine in Palmo-plantar Warts treatment [32], while Zohier et al. found an (80%) complete success rate in treatment of Plantar Warts, when comparing 5-FU with methotrexate [33].

However, a lower rate of complete response reported by Sachan et al. in treatment of resistant palmo-plantar warts, when comparing intralesional 5-FU injection with intralesional bleomycin injection as (65.59%) showed complete response rate in the intralesional 5-FU group, which might be due to fewer treatment sessions (maximum 4 sessions) in their study compared to (6 sessions) in other studies [26]. Also, fewer treatment sessions (3 sessions) conducted by Kannambal et al., who reported a (60 %) complete response after intralesional 5-FU injection in planter warts [34].

Isçimen et al. conducted a study using intralesional 5-fluorouracil in treatment of common, plantar, and periungual warts, complete response was reported in (54%) of lesions, this lower rate of complete response may be explained by the short time between sessions as weekly injections given by Isçimen et al doesn't allow the reaction of previous injection to settle down before the next injection [18].

Regarding the number of sessions needed to obtain a complete response, in our study, there was no significant difference in the mean number of sessions between the bleomycin group (3.07±2.1sessions) and (2.67 ± 1.8) in 5-FU group. Specifically, 42.8% of the bleomycin group showed complete response after just one session, whereas 58% of the 5-FU group achieved complete response after two sessions.

Comparable findings were noted by Al-Naggar et al., who found that (44%) of patients showed complete response after the third session of intralesional Bleomycin Injection [29]. Also, Barkat et al. reported a treatment session range of 1–4, with an average of 3.8 sessions in the bleomycin group [23]. Our results in 5-FU group were in agreement with Zohier et al., who observed (35%) complete response in the fourth session of intralesional Injection of 5-FU [33], whereas complete response after just one session was achieved by Sachan et al.in (80.95%) in bleomycin group versus (48.14%) in 5-FU group [26].

The two groups showed no significant difference regarding side effects, also all side effects were mild and transient. Pain at injection site, which disappear gradually in 2 days was the most common side effect, occurred in (66.7%) of bleomycin group and in 5-FU group, (70%) complained of pain, however Co-administration of lidocaine significantly mitigated the pain, Hemorrhagic eschar and hyperpigmentation were more prevalent in the 5-FU group (56.7%) (10%) than in the bleomycin group (50%) (0%) respectively. Mild erythema and edema were observed post-session in both groups.

Similarly, in bleomycin group our results were in line with a study by Al-Naggar et al., in which complications such as pain (100%), erythema (46.7%) was occurred [29]. Also, Sachan et al. showed that Pain was present in all patients (100%) and hyperpigmentation was present in (70%) in bleomycin group while in 5-FU group reported a (72%) incidence of pain at injection site, hyperpigmentation in (66%) of patients [26]. Similarly, Ghonemy et al. found that 100% of the 5-FU group experienced pain, while Pain associated with

hemorrhagic eschar formation affecting (56.7%) [31].

As regard recurrence rate through 3 months of clinically and dermoscopic follow up, in the bleomycin group we had only one case, had recurrence versus no recurrence in the 5-FU group, more or less similar to our study Sachan et al. observed recurrence rate of (1.71%) in bleomycin group versus one plantar wart recurred in 5-FU group [26].

.Ghonemy et al. reported no recurrence in the 5-FU group [31] .,also Sepaskhah et al. found that during the follow-up session, none of the patients who had a full clinical response had a relapseConfirmed by using dermoscopy [35].

On the contrary, in intralesional bleomycin injection, Marhatta et al. had a higher recurrence rate (15.78%) [27]. Additionally, Işçimen et al. using intralesional 5-fluorouracil injection, recurrence was seen in 22% of 118 lesions that responded completely to the 5-FU [18]. Lastly by Rafique et al recurrence of warts was (28.6%) in 5- FU group, possible explanation could be that these studies had not conducted a dermoscopic evaluation to find complete clearance, so remnants of the warts lead to high recurrence rate [32].

Conclusion

Regarding the management of planter warts, both intralesional bleomycin and 5-fulorouracil appear to be practical, safe and effective therapeutic alternative, also it is to use a dermoscope for early diagnosis, treatment response monitoring and recurrence prevention.

Strengths of the Study:

The study directly compares two intralesional treatments, offering clarity on their relative efficacy. The Dermoscopic based assessment enhances diagnostic accuracy, ensuring more precise assessment of treatment outcomes. The random allocation of participants enhances the validity and generalizability of the findings. The study includes a three-month follow-up to evaluate recurrence rates, adding depth to the findings. Both treatment options provide an alternative to more aggressive or systemic therapies, making them relevant for outpatient and community settings.

Limitations of the Study:

A longer follow-up period could provide more insights into the long-term recurrence rates of both treatments. Pain is a subjective parameter, its assessment relies on subjective patient reports, which may vary. The study does not compare the economic impact of both treatments, which could be relevant for decision-making.

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