Journal of Pakistan Association of Dermatologists. 2024;**34(4)**:953-958.

Original Article

Efficacy of intralesional bleomycin versus cyotherapy in the treatment of palmoplanter warts

Jahangir khan[1], Zarar bin Jamil[2], Ayesha khokhar[2], Huma Gul[3]

[1] Department of Dermatology, Al Adan Hospital, Kuwait.
[2] Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi.
[3] Department of Dermatology, Khyber teaching Hospital, Peshawar.

Abstract

Objective To compare the efficacy of intralesional bleomycin versus cryotherapy in the treatment of palmoplantar warts.

Methods A total of 70 patients having palmoplantar warts presenting to the department of Dermatology, Military Hospital Rawalpindi, from January 2019 onwards were included in the study. Approval from Hospital's Ethical Committee was taken before commencement of the clinical trial. Patients having history of vascular diseases, Rynaurds, Systemic lupus erythematousous, chilblains, pregnant females, immunocompromized and comorbid conditions like diabetes mellitus and hypertension were excluded. Patients were allocated randomly by lottery method in to two groups. Group A patients were given intralesional bleomycin while Group B patients received cryotherapy. The response was then evaluated initially after 2 weeks and then after 2 months. A wart was considered clear if it completely resolves at the final evaluation (60 days after the initial procedure), otherwise, it was considered as treatment failure.

Results The mean age of patients in group A was 31.60±11.52 years and in group B was 33.57±13.76 years. Out of 70 patients, 46 (65.71%) were males and 24 (34.31%) were females with male to female ratio of 1.9:1. Efficacy of Group A (intralesional bleomycin) was seen in 30 (85.71%) patients while in Group B (cryotherapy) it was seen in 19 (54.29%) patients.

Conclusion This study concluded that intralesional bleomycin is better and efficacious than cryotherapy in treating palmoplantar warts.

Key words
Palmoplantar warts; Intralesional bleomycin; Cryotherapy.

Introduction

Warts are one of the most common diseases presenting in dermatological outpatients. They are characterized by rough spiny papules, plaques and large nodular outgrowths.[1] They can affect any mucocutaneous surface. They are caused by human papillomavirus (HPV) infection. Till date, more than 100 HPV types have been discovered.[2] The clinical appearance depends on the type of HPV and the area involved. Humans get infected by direct contact with virus usually through any breakage in the continuity of the skin.[3] Warts are usually classified as common warts, palmar warts, facial warts, plantar warts, flat warts, perianal warts, filiform warts, mosaic warts, periungual warts, oral warts, and genital warts. Commonly they are located on hands, feet, face, knee and around nails and range in size from 1mm to several centimeters.[4]

HPV virus is resistant to heat and drying. It can also survive for a long period of time at a low

Manuscript Received on: January 29, 2024
Revised on: January 31, 2024
Accepted on: July 07, 2024
Address for correspondence
Dr. Jahangir Khan FCPS (Dermatology),
Registrar, Department of Dermatology,
Al Adan Hospital, Kuwait.
Email: kohatian3658@yahoo.com

temperature and therefore, is very contagious. Common warts are the most common type of warts and represent 70% of all cutaneous warts, especially common in school going children. Palmoplantar warts are common in adults. Plantar warts appear as papulonodular outgrowths usually having black dots which represent thrombosed vessels. Palmoplantar warts can be extremely painful when subjected to pressure. Warts are diagnosed clinically and rare if any investigations are required.[5]

Cutaneous warts are treated by numerous methods including cryotherapy, topical salicylic acid, lactic acid, topical imiquimod, duct tape therapy, topical podophyllin, intralesional bleomycin, electrocautery, hypnotherapy, and lasers.[6] Cryotherapy is a safe and effective treatment being used for cutaneous warts although clearance rates don't reach 100%. Intra-lesional bleomycin is an effective alternative according to published literature with cure rates in warts ranging from 14 to 99%.[8]

Despite published literature, the dermatologists are reluctant in using intralesional bleomycin as an alternative to cryotherapy in treating warts, very few head-to-head randomized controlled trials have been conducted to compare the efficacy of these treatments in similar conditions. In one study Intralesional bleomycin was found more effective than cryotherapy with the efficacy of intralesional bleomycin 94.9% vis-a-vis the efficacy of cryotherapy as 76.5%.[9] In other two separate studies, intralesional bleomycin showed the efficacy of 94% and 93.10% for the treatment of warts respectively.[7,12] While in two studies, in which cryotherapy was compared with other treatment modalities in skin warts showed the efficacy of 58.3% and 56.7% respectively.[11,10]

As bleomycin is less painful, easily available and can be administered with ease even in the periphery as compared to cryotherapy, which requires a specialized container for its transport and a specialized cryogun for is administration. So in a resource-poor setting like Pakistan, the use of bleomycin should be encouraged. Hence we aim to conduct a randomized controlled trial to compare the efficacy of intralesional bleomycin versus cryotherapy in treating palmoplantar warts as there are a few published local studies and no such study has been done in the past 5 years in our local setting. This study will provide us with the latest results which will be shared with other healthcare professionals.

Methods

Patients from the Dermatology outpatient department at Pak Emirates Hospital Rawalpindi, fulfilling the inclusion criteria were selected after acceptance of synopsis by the Hospital Ethical Committee, Patients were given the information regarding the context of research and informed written consent was taken. Demographic details like OPD registration number, name, age and gender of each patient were noted. Detailed history and examination of the patients were done and noted. Information was gathered about warts location, size, and its type.

Lottery method was used to allocate the patients into two groups randomly. These were named Group A and Group B, receiving intralesional bleomycin and Cryotherapy, respectively. Vials containing 15mg powdered form of bleomycin are available for injection that are mixed with 5ml distilled water for dilution and can be stored at 4-8^{0}C for around 2 months. A final concentration of 1mg/ml was achieved by adding one portion of diluted bleomycin and two portions of 2% lignocaine when taken in an insulin syringe. Isopropyl alcohol is to be used to clean the warts and the adjoining skin. Scrapping the surface to remove the superficial

thick skin was done while avoiding bleeding points and bleomycin is injected into the wart till blanching of the wart was noticed. The quantity of injection to be delivered varied according to the size of warts: lesions more than 5mm but less than 10mm, equal to or more than 10mm will receive up to 0.5ml and 1 ml each. A maximum of 2 ml volume can be given in one treatment setting, and the injection into a solitary lesion was restricted to 1ml.

Group A patients received intralesional bleomycin 0.1% with a volume sufficient to blanch the lesion and Group B patients were administered liquid nitrogen via cryogun or with a cotton bud and pressed firmly on the warts till the lesion blanches

The researcher examined the patient's response after 2 weeks interval under the supervision of a consultant and the patient was re-treated if required. The wart was labeled as clear if it totally resolved at the final evaluation (60 days after the initial procedure), otherwise, it was considered as treatment failure. Address and telephone numbers of patients were kept in the record to ensure follow up.

All data was documented on a proforma, attached as annexure on which the outcome variable i.e. clearance of warts is mentioned.

The statistical package for social sciences (SPSS) version 20 was used to interpret the research results. Quantitative variables like age and duration of illness were calculated by using the mean and standard deviation while gender and efficacy were determined with the help of frequencies and percentages.

Stratification was used to control the confounding variables like age, gender, and duration of warts. Chi-square test was used to examine the efficacy within groups. P-value of lower than or equivalent to 0.05 was considered as significant.

Results

Participants of the study had ages from 14-60 years with average age of 32.59±12.64 years. Large number of the patients 52 (74.29%) were between 14 to 40 years of age. 31.60±11.52 years was the average age of participant of group A and in group B it was 33.57±13.76 years as shown in **Table 1**.

Out of 70 research subjects, 46 (65.71%) were males and 24 (34.31%) were females and male to female ratio of 1.9:1. Mean duration of disease was 6.47±3.42 weeks, i.e. in group A 6.40±2.26 weeks and in group B 6.54±3.62 weeks as depicted in **Table 1**.

Efficacy of Group A (intralesional bleomycin) was seen in 30 (85.71%) patients while in Group B (cryotherapy) was seen in 19 (54.29%) patients as shown in **Table 2** (p-value=0.004).

Stratification of efficacy with respect to duration of disease is shown in **Table 3**.

Discussion

We have conducted this study to compare the efficacy of intralesional bleomycin versus cryotherapy in the treatment of palmoplantar warts. In our study, a total of 70 patients participated, which were divided by lottery method into group A and group B. Efficacy of

Table 1 Descriptive statistics of Age, duration of disease (in weeks).

Demographics	*Group A (n=35) mean±SD*	*Group B (n=35) mean±SD*
Age (Years)	31.60 ± 11.52	33.57 ± 13.76
Duration of disease (weeks)	6.40 ± 2.26	6.54 ± 3.62

Table 2 Frequency of Efficacy.

Efficacy	*Group A*	*Group B*	*P value*
Yes	30 (85.71%)	19 (54.29%)	0.004
No	05 (14.29%)	16 (45.71%)	

Table 3 Stratification of efficacy with respect to duration of disease.

Duration of disease	*Group A*		*Group B*		*P-Value*
	Efficacy		*Efficacy*		
	Yes	*No*	*Yes*	*No*	
1-6 weeks	21 (60%)	2 (5.71%)	13 (37.14%)	11 (31.42%)	0.004
7-12 weeks	9 (25.71%)	3 (8.5%)	6 (17.14%)	5 (14.2%)	0.304

Group A (intralesional bleomycin) was seen in 30 (85.71%) patients while in Group B (cryotherapy) was seen in 19 (54.29%) patients (p-value=0.004).

Aguis *et al*. concluded in there clinical trial that treatment of plantar warts in 47 patients having a total of 138 warts, that were non responsive to conventional liquid nitrogen application depicted an efficacy of 89.9% with intralesional bleomycin.[13] 76% improvement was noted when bleomycin was injected in the warts on hands as compared to placebo i.e. normal saline as reported by Bunney *et al.* in there experimental research.[14] In an analysis by Munn *et al*. a cure rate of 92% was achieved when topical bleomycin was punctured with a needle into the warts after being applied on to the surface of warts.[15]

Soni *et al.* explored in their work about the effects of injections of bleomycin into the warts around nails and in palm and sole. A success response of 96% was reported in palmoplantar lesions and a 100% clearance was observed in periungual lesions. With only one or two injections an overall efficacy of 96% was attained within 12 weeks.[16] Aziz-Jalali *et al.* published in their work that intralesional bleomycin accomplished complete resolution in 95 (73%) warts whereas a limited response was noticed in 31 (24%) warts. Though they noted a recurrence in a small number of patients specially those having multiple warts.[17] Similar results were seen in a local study where 160 participants were included in an investigative trial, in which injections of bleomycin into the warts were noticed to have 90% effectiveness as compared to cryotherapy that showed 72.5% improvement.[18]

Bremner also contributed by observing a complete remission in 63% lesions in 24 patients having 142 warts that were injected with bleomycin.[19] Injections of belomycin into the plantar and periungual warts were observed to be more effective than liquid nitrogen as described by Shumer and O'Keefe in there double blind placebo controlled clinical trial. They noticed that 60% warts on soles and 94% periungual warts depicted complete remission with intralesional injections.[20]

Ryu *et al.* conducted a comparative study to analyze the therapeutic effects of newly developed bleomycin microneedle patch regards to cryotherapy. They recruited 42 patients with more than two wart lesions in each and the lesions were treated by one of the above-mentioned methods randomly. Their study demonstrated 76.2% clearance rate for cryotherapy and 61.9% clearance rate for the bleomycin microneedle patch at week 16. This new therapeutic method was found to be an effective, convenient, and painless treatment modality when compared with cryotherapy.[21] Gamil *et al*. recently published another comparative study where 54 patients were divided into three groups (18 patients each). The first group was treated by dermapen with topical bleomycin (1 mg/1 mL) for a maximum of four sessions at 2-week intervals. On the other hand, the second group received IL Bleo (1 unit/mL) for a maximum of four sessions at 3-week intervals, and the control group was intralesional saline for a maximum of four sessions.

Complete clearance was found to be highest in Group 1 (88.9%) as opposed to 83.3% in Group 2 and 5.6% in the control group.[22]

Conclusion

This study concluded that intralesional bleomycin is better and efficacious than cryotherapy in treating palmoplantar warts. So, we recommend that intralesional bleomycin should be used as a primary treatment option in these patients in order to reduce the morbidity of our population.

Disclosure Statement: This original article is based on a dissertation. The dissertation has been approved by College of Physicians and Surgeons.

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

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Author's contribution

JK: Contribution to design, data analysis, interpretation, critical review. Has given final approval of the version to be published.

ZBJ: Contribution to data acquisition, analysis, drafting of the work. Has given final approval of the version to be published.

AK: Contribution to result analysis, critical review, drafting of the work. Has given final approval of the version to be published.

HG: Contribution to design, result analysis, critical review. Has given final approval of the version to be published.

References

1. Witchey D, Witchey N, Roth-Kauffman M, Kauffman M. Plantar Warts: Epidemiology, Pathophysiology, and Clinical Management. *J Am Osteopath Assoc*. 2018;**118(2)**:92.
2. Ramachandrareddy D, Prathap R. Human papillomavirus (HPV) causing skin tags. *J Med Dent Sci*.2013;**2(38)**:7357-61.
3. Nofal A, Nofal E. Intralesional immunotherapy of common warts: successful treatment with mumps, measles and rubella vaccine. *J Eur Acad Dermatol Venereol*. 2010;**24(10)**:1166-70.
4. Park I, Introcaso C, Dunne E. Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. *Clin Infect Dis*. 2015;**61(suppl 8)**:S849-S855.
5. de Planell Mas E, Martínez-Garriga B, Zalacain AJ, Vinuesa T, Viñas M. Human papillomaviruses genotyping in plantar warts. *J Med Virol*. 2017;**89(5)**:902-7.
6. Ockenfels HM. Therapeutic management of cutaneous and genital warts. *J Dtsch Dermatol Ges*. 2016;**14(9)**:892-9.
7. Mahajan V, Singh Mehta K, Chauhan P, Chauhan S, Sharma V, Rawat R. Evaluation of efficacy and safety of intralesional bleomycin in the treatment of common warts: Results of a pilot study. *Indian J Dermatol Venereol Leprol*. 2018;**85(4)**:397-404.
8. Dobson JS, Harland CC. Pulsed dye laser and intralesional bleomycin for the treatment of recalcitrant cutaneous warts. *Lasers Surg Med*. 2014;**46(2)**:112-6.
9. SB Dhar, MM Rashid, AZMM Islam, MSI Bhuiyan. Intralesional bleomycin in the treatment of cutaneous warts. *Indian J Dermatol Venereol Leprol*. 2009;**75(3)**:262-7.
10. Izadi Firouzabadi L, Khamesipour A, Gandhi N, Hosseini H, Teymourpour A, Firooz A. Comparison of clinical efficacy and safety of thermotherapy versus cryotherapy in the treatment of skin warts: A randomized controlled trial. *Dermatol Ther*. 2018;**31(1)**. doi: 10.1111/dth.12564. Epub 2017 Oct 30. PMID: 29082602.
11. 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.
12. Unni M, Tapare V. Intralesional bleomycin in the treatment of common warts. *Indian J Drugs Dermatol*. 2017;**3**:73-6.
13. Agius E, Mooney JM, Bezzina AC, Yu RC. Dermojet delivery of bleomycin for the treatment of recalcitrant plantar warts. *J Dermatol Treat*. 2006;**17**:112-6.

14. Bunney MH, Nolan MW, Buxton PK, Going SM, Prescott RS. The treatment of resistant warts with intralesional bleomycin: Acontrolled clinical trial. *Br J Dermatol*. 1984;**11**:197-207.
15. Munn SE, Higgins E, Marshall M, Clement M. A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol*. 1996;**135**:969-71.
16. Soni P, Khandelwal K, Aara N, Ghiya BC, Mehta RD, Bumb RA, *et al*. Efficacy of intralesional bleomycin in palmo-plantar and periungual warts. *J Cutan Aesthet Surg*. 2011;**4**:188-91.
17. Aziz-Jalali M, Ghafarpour G, Rezaei M, Heshmatzadeh Behzadi A, Rohani Nasab M, Nilforoushzadeh M. Efficacy of intralesional bleomycin in the treatment of resistant warts. *J Skin Stem Cell*. 2014;**1**:e18875.
18. Muhammad J, Akhtar N, Ahmad MK, Anwar MI. Comparison of efficacy between intralesional bleomycin and cryotherapy in plantar warts. *J Pak Assoc Dermatol*. 2019;**29(1)**:35-9.
19. Bremner RM. Warts: Treatment with intralesional bleomycin. *Cutis*. 1976;**18**:264-6.
20. Shumer SM, O'Keefe EJ. Bleomycin in the treatment of recalcitrant warts. *J Am Acad Dermatol*. 1983;**9**:91-6.
21. Ryu HR, Jeong HR, Seon-Woo HS, Kim JS, Lee SK, Kim HJ, *et al*. Efficacy of a bleomycin microneedle patch for the treatment of warts. *Drug Deliv Transl Res*. 2018;**8**:273-80.
22. Gamil HD, Nasr MM, Khattab FM, Ibrahim AM. Combined therapy of plantar warts with topical bleomycin and microneedling: A comparative controlled study. *J Dermatolog Treat*. 2019;**17**:1-6.