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Original Article

Efficacy of intralesional bleomycin versus cryotherapy in the treatment of palmoplantar warts

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Abstract

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

Methods The study was conducted for 09 months from March 2020 to December 2020 at outpatient department of dermatology Nishtar Medical University Multan.102 patients were included in the study. Patients randomly allocated into two groups by lottery method. Group A, having 51 patients were given intralesional bleomycin for two sessions at 3 weekly intervals, and group B, also having 51 patients were given cryotherapy also for two sessions at 3 weekly intervals. Patients were followed up at 3 weekly intervals, i.e. at visit for the next session and at the end of 6 weeks. Efficacy was assessed at the end of 6 weeks. Those who cleared their warts after 1st session were not given a 2nd session of treatment.

Results Out of 102 patients, 60 were males (58.82%) and 42 were females (41.18%). Mean patient age was 24.69±8.052 years. Mean patient weight was 49.17±10.475 kg. Mean duration of warts was 57.50±23.131 days. Mean number of warts was 1.84±1.167 and mean size of wart was 4.76±2.016mm. In bleomycin group, 43 patients showed effective response (84.31%). In cryotherapy group, 33 patients showed effective response (64.71%). The efficacy of both groups was compared by applying chi square test and p value was found to be 0.023, which was quite significant (<0.05) showing that there was statistically significant difference between the efficacy of two therapies.

Conclusion Intralesional bleomycin is a superior treatment option as compared to cryotherapy in treatment of palmoplantar warts in terms of increased efficacy, cost effectiveness and better tolerability.

Key words
Palmoplantar warts, bleomycin, Intralesional, cryotherapy.

Introduction

Cutaneous warts are benign skin tumours and are usually self-limited. Infection of epidermal cells with the human papillomavirus (HPV), a DNA virus,[1] results in cell proliferation and a thickened, warty papule on the skin. There are over 100 different types of HPV.[2] Cutaneous warts can present as common warts (verrucae vulgaris), plane warts (predominantly located on the face and on the dorsa of the hands) or on the soles of the feet (plantar warts).[3]

HPV infects the basal keratinocyte of the epidermis through disruptions of the skin or

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mucosal surface. Spread of HPV infection is usually through physical contact. They usually resolve spontaneously as a result of natural immunity within months or years. The rate of resolution depends on several factors, including host immunity, age, HPV type, and site of infection. Immunocompromised patients have higher rates of plantar warts, along with increased severity and duration of the lesions.[4]

Prevalence of common warts varies widely with different age groups.[5] It is highest in children and young adults with a rate of 3-24%.[6]

Various treatment options are available such as electrocautery, cryotherapy, pulsed dye laser, topical chemotherapeutic agents, topical caustics such as salicylic acid, lactic acid, trichloroacetic acid (TCA), topical retinoic acid, oral cimetidine etc.[1,7] None is 100% effective and recurrences are common. Cryotherapy using liquid nitrogen is one of the most common treatment for cutaneous warts with relative safety and variable effectiveness. In one study, cure rate for cryotherapy was 39% [8], in another it was 82%.[9]

Intralesional bleomycin therapy has been used in the treatment of viral warts since 1970. Since then many studies have found bleomycin to be effective in treating warts[10] with cure rates ranging from 14% to 99%.[11,12] Administration of intralesional bleomycin has also been done using a microneedling pen.[13] A bleomycin covered microneedle patch and combination of local electroporation with intralesional bleomycin have also been tried with successful results.[14,15] Bleomycin is cytotoxic agent having an antitumour, antibacterial and antiviral activity. It disrupts DNA synthesis and causes scission of DNA strands by causing oxidative damage to the deoxyribose of thymidylate and other nucleotides. The result is an arrest in cell cycle and cell proliferation. The bleomycin hydrolase enzyme which inactivates bleomycin is normally found in all body tissues but in very small amount in skin. Thus, after injecting intralesionally, a large amount of drug is available at site and so even a small amount of drug is enough for warts.[17] Most serious complications of systemic bleomycin are pulmonary fibrosis and impaired lung functions. Others are fever, rash, dermographism, hyperpigmentation, alopecia and Raynaud's phenomenon. These adverse effects are less with intralesional administration of bleomycin.

Multiple visits are usually required for cryotherapy which increases the cost of procedure and discomfort to the patient as well; whereas in case of bleomycin, on an average 2 visits are usually sufficient.[7] Bleomycin can be stored for 6-8 weeks, which lowers the overall cost of bleomycin. The pain period is also relatively shorter than in cryotherapy group. So this study was conducted to find a more efficacious treatment modality in terms of patient visits, cost and side effects.

Methods

The randomized controlled trial was conducted for a period of 9 months from March 2020 to December 2020 at outpatient department of dermatology Nishtar Medical University Multan. 102 patients were included in the study via non-probability consecutive sampling. Patients of both genders, aged between 15-40 years, with warts less than 05 in number and upto 15 mm in size present on palmoplantar surface were included in this study. Pregnant and lactating women and females with child bearing potential not using any adequate contraception method were excluded from study. Similarly, patients with periungual warts, patients with history of peripheral vascular diseases such as Raynaud's phenomenon, systemic sclerosis, livedo reticularis and chillblains and those who took any medication for warts in last one month were

also excluded from study. Patients were randomly allocated into two groups A and B by lottery method each having 51 patients. In Group A, patients were given intralesional bleomycin for two sessions i.e. at the time of presentation and at next follow up after 3 weeks. In group B, patients were given cryotherapy also for two sessions at 3 weekly intervals. Patients were followed up at 3 weekly intervals, i.e. at week 3 (visit for the next session) and at the end of 6 weeks. Efficacy was assessed at the end of week 03 and week 06. Those who cleared their warts after 1st session were not given a 2nd treatment session.

Bleomycin for injection is available in a vial containing 15mg in powder form. It was diluted first with 5ml distilled water to prepare the stock solution which can be stored for 6-8 weeks at 4°C. One ml of stock solution was diluted with two ml of 2% lidocaine so that final concentration became 1mg/ml. Wart and adjacent skin was cleansed with spirit swab. Superficial paring was also done to remove the callus surrounding the wart. Fresh solution was injected intralesionally till blanching of the lesion. The amount of injection given depended upon the size of the wart. The wart up to 5mm, 10mm or more received 0.2ml, 0.5ml, and 1ml respectively. The total volume injected at one treatment sitting was limited to 2ml and injection into single wart limited to 1ml. After injection, within 48 hours, a haemorrhagic bulla was formed in some patients lying beneath the wart. This was a normal reaction. Incision with a blade was done to release tension.

Cryotherapy was performed by applying liquid nitrogen with a cotton swab for 10-30 seconds until ice ball formation spreading from centre of the lesion to the edge of wart including 1mm of surrounding normal skin. Patients were evaluated for treatment efficacy at the end of 6 weeks. At that time, any local or systemic adverse effects were also noted.

Results

Of the 102 patients, 37 (72.5%) were males in bleomycin group A versus 23 (45.1%) in cryotherapy group B. Females were 14 (27.5%) in group A as compared to 28 (54.9%) in group B.

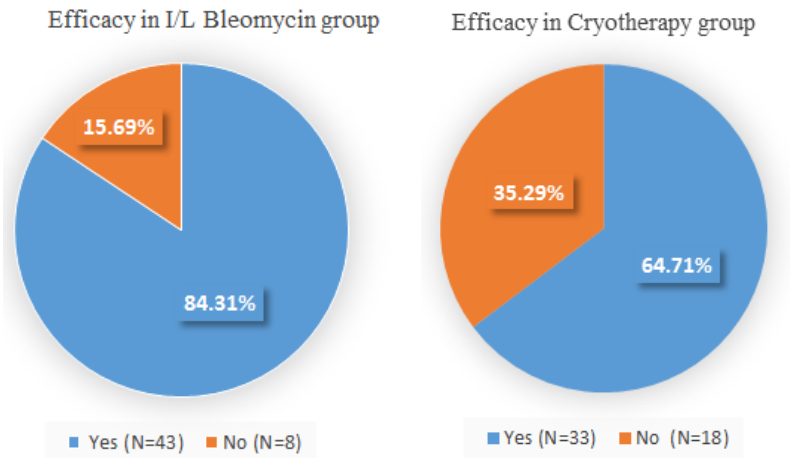
Mean patient age was 24.61±7.76 years in group A and 24.39±7.7 years in group B. Mean patient weight was 49.12±10.14 kg and 49.53±10.23 kg in group A and B respectively. Mean number of warts was 1.90± 1.08 in group A and 1.78±1.25 in group B. Mean duration of warts was 54.12±24.39 days and 60.88±21.51 days in group A and B respectively. Mean size was 4.88±2.33 mm in group A and 4.59±1.83 mm in group B.

Out of 102 patients, intralesional bleomycin was given to 51 patients in group A and cryotherapy was given to remaining 51 patients in group B. Out of total 188 warts treated, 97 warts were given intralesional bleomycin and 91 warts were treated with cryotherapy. 82 out of 97 warts cleared (84.54%) in bleomycin group, while 15 warts did not clear (15.46%). 65 out of 91 warts cleared in cryotherapy group (71.43%) and 26 did not (28.57%) **(Table 1**).

Efficacy of both groups was recorded. Overall 76 patients (74.51%) showed effective response and 26 patients (25.49%) showed ineffective response.

Table 1 Efficacy in both groups with respect to number of warts.

Treatment Group	*No. of warts*		*Total no. of warts treated*
	Cured	*Not cured*	
Intralesional bleomycin	82 (84.54%)	15 (15.46%)	97 (100%)
Cryotherapy	65 (71.43%)	26 (28.57%)	91 (100%)
Total	147	41	188



P Value: 0.023

Figure 1 Efficacy statistics.

Table 2 Stratification of Efficacy with regards to age, weight, gender, no. of warts, disease duration and size of wart.

With respect to		*Group A* (I/L Bleomycin) *Efficacy*	*Group B* (Cryotherapy) *Efficacy*	*P Value*
Age (years)	15-20	16	18	0.583
	21-25	10	07	
	26-30	08	03	
	31-35	03	02	
	36-40	06	03	
Weight(Kg)	30-40	10	13	0.33
	41-50	17	08	
	51-60	10	09	
	61-70	06	03	
Gender	Male	31	12	0.004
	Female	12	21	
No. of warts	01	22	25	0.15
	02	12	07	
	03	08	01	
	04	01	00	
	05	00	00	
Duration (days)	01-30	17	08	0.277
	31-60	15	17	
	61-90	11	08	
Size of warts(mm)	01-05	59	52	0.404
	06-10	22	13	
	>10	01	00	

In bleomycin group, 43 patients were cured showing effective response (84.31%) and 8 patients (15.69%) showed ineffective response. In cryotherapy group, 33 patients were cured (64.71%) and 18 patients showed ineffective response (35.29%) **(Figure 1)**.

The efficacy of both groups was compared by applying chi square test and p value was found to be 0.023, which was significant (<0.05) showing that there was statistically significant difference between the efficacy of two therapies. Stratification was done with regards to age, weight, gender, number of warts, duration and

size of warts and chi square test applied to see the effect of these on outcome **(Table 2)**.

Conclusion

Warts are grey colored, rough surfaced papules or plaques that can be found on any cutaneous surface. Various treatment modalities have been used to treat warts, but none is uniformly effective and different types of treatment may be combined.

Numerous reports have been published on the use of intralesional bleomycin for the treatment of warts, with cure rates ranging from 14% to 99%.[11] However, cryotherapy is a widely accepted mode of treatment in the country. Although both these treatments are painful and very often need to be combined with local anesthetics, bleomycin may be more easily available and accessible in peripheral practices. Bleomycin is cytotoxic antibiotic having an anti-tumor, antibacterial and antiviral activity. Intralesional bleomycin therapy has been used in the treatment of viral warts since 1970s. Since then many studies have found bleomycin to be effective in treating warts.[10]

A study conducted in 2011 by Soni P and colleagues compared therapeutic efficacy of I/L bleomycin (1mg/ml solution) versus placebo. Injections were given fortnightly for maximum up to two injections. The cure rate in bleomycin group was 96.47% (82/85 warts) and 11.11% (8/72 warts) in controls after one or two injections within 12 weeks. The difference in the cure rate between two groups was statistically highly significant (<0.0001). In bleomycin group, a haemorrhagic eschar was formed which gradually healed in 8-12 weeks without atrophy or pigmentation; this phenomenon was not seen in controls. Only moderate pain was observed by most of the patients during injection in both groups.[16]

A study conducted in Karachi in 2019 by Muhammad J and colleagues compared the efficacy of intralesional bleomycin with cryotherapy in planter warts. A total of 160 patients were enrolled in the study. 90% efficacy was seen in intralesional bleomycin group whereas 72.5% efficacy was noted in cryotherapy group. P value was noted to be 0.005 which was highly significant. They concluded that intralesional bleomycin was more effective than cryotherapy in the planter warts.[17]

A RCT study conducted in Bangladesh 2009 by Dhar SB and colleagues compared I/L bleomycin (1mg/ml, 1U/mL or 0.1%) with cryotherapy for cutaneous warts. At the end of treatment, warts were cleared in 94.9% of bleomycin group.

In cryotherapy group, 76.5% of patients showed clearance. Statistically significant difference was observed between the two groups. An average of 1.38 treatment visits were needed in bleomycin group whereas 3.09 treatment visits were needed per case in cryotherapy group patients, which is significantly higher in cryotherapy group. Recurrence, found to be 13% in bleomycin-treated warts and 23% in cryotherapy-treated warts, but differences in this regard were statistically insignificant. Considering the adverse reactions of treatment, pain and dyspigmentation were found. 5% of patients in bleomycin group and 12% in cryotherapy group suffered pain, ranging from few minutes to 3 days. Dyspigmentation developed in 67% of total patients during the study period in the treated area of warts. Among them, a majority were from cryotherapy group.[9] In another study conducted in 2012, Alghamdi *et al*. used low concentration of I/L bleomycin (0.1U/ml) for the treatment of plantar warts. The results revealed complete clearance of warts in 17 of 23 (74%) patients, partial response in 1

(4.3%) patient, and no response in 3 (13%) patients. Recurrence was observed in 2 patients at 3 months of follow-up. Only three patients (13%) had localized moderate pain for 2 to 3 days after the injection. This showed that very low-concentration (0.1 U/mL) bleomycin is also effective and safe treatment modality for plantar warts.[18]

A RCT study in Iran 2007, conducted by Adalatkhah H and colleagues compared therapeutic efficacy between I/L bleomycin (0.5mg/ml) and cryotherapy for common warts. Results revealed a cure rate of 86.4% in bleomycin group patients as compared to 68.2% in cryotherapy group. Wart clearance rate was 87.6% in bleomycin group and 72.3% in cryotherapy group. So it was concluded that I/L bleomycin is more effective than cryotherapy in treating warts on hands and feet.[10]

A higher concentration of I/L bleomycin (1.5U/mL) was used for treating plantar warts by Salk R and Douglas TS, showing a cure rate of 87%.[19]

In my study, concentration of 1mg/ml (0.1% 0r 1U/mL) was used for bleomycin. It was found that patients in bleomycin group showed an effective response rate of 84.31% as compared to 64.71% in cryotherapy group patients. As for number of warts concerned, again bleomycin group showed better response. Out of total 188 warts, 97 warts were given intralesional bleomycin and 91 warts were treated with cryotherapy. 82 out of 97 warts cleared (84.54%) in bleomycin group, while 65 out of 91 warts cleared in cryotherapy group (71.43%). The efficacy of both groups was compared by applying chi square test and p value was found to be 0.023, which was significant (< 0.05) showing that there was statistically significant difference between the efficacy of two therapies. No serious side effects developed during the study and no patient left the treatment. Local side effects included pain and dyspigmentation in both groups. Pain period was relatively shorter in bleomycin group as compared to cryotherapy group, this might be because 2% lidocaine solution was mixed with bleomycin injection. Dyspigmentation in post treatment follow up period was also seen more commonly after cryotherapy. This might be due to more post inflammatory reaction after cryotherapy.

Conclusion

This study concludes that Intralesional bleomycin is significantly more effective than cryotherapy in the treatment of palmoplantar warts with an effective response of 84.31% as compared to 64.71% and p value of 0.023. It can be concluded that intralesional bleomycin is a good alternative with high safety profile and overall low cost of therapy due to low cost of medicine and less number of visits as compared to cryotherapy.

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