ORIGINAL ARTICLE

Intralesional bleomycin versus cryotherapy for treatment of cutaneous warts: A randomized controlled trial

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Abstract

Objective: To evaluate the effectiveness of intralesional bleomycin in comparison to cryotherapy in the treatment of cutaneous warts.

Method: The randomized controlled trial was conducted at the Department of Dermatology, Jinnah Postgraduate Medical Centre, Karachi, from January to July 2021, and comprised patients of either gender aged 18-60 years who had cutaneous warts for 1-48 weeks. The subjects were divided into group A treated with 0.1% intralesional bleomycin, and group B were treated with cryotherapy through non probability consecutive sampling. Follow-up examination was done at the 2, 4 and 6 weeks. Data was analysed using SPSS 23.

Result: Of the 154 patients, 96(62.3%) were male and 58(37.7%) were females. The overall mean age was 33.253±6.726 years. There were 77(50%) patients in each of the two groups. The therapy after 6 weeks was found to be effective 73(94.8%) group A patients and 57(74%) group B patients (p=0.001).

Conclusion: Intralesional bleomycin was found to be more successful than cryotherapy in the treatment of cutaneous warts.

Clinical Trial Link: https://clinicaltrials.gov RCT No. (NCT05023408)

Keywords: Cryotherapy, Cutaneous, Warts, Intralesional, Bleomycin, Randomised controlled trial. (JPMA 73: 1949; 2023)

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Introduction

The dermatological outpatient department (OPD) sees more cases of warts than any other benign growth, but treating them may be challenging because of the condition's chronicity, recurrence and resistance to current therapies.[1] Wart resistance may reflect a localised or systemic cell medicated immune (CMI) deficiency to human papilloma virus (HPV).[2]

Warts are one of the common dermatological disorders triggered by the HPV. Children and young people are generally affected by warts.

The most common indications for treating warts include cosmetic reasons, functional impairment, risk of malignancy and pain.[3] Electrocautery, cryotherapy, intralesional bleomycin, surgical removal, laser ablation, topical medicines like fluorouracil (5FU)/salicylic acid, and immunotherapy are some of the therapeutic methods available. Other medical possibilities include immunotherapy.

Many therapeutic techniques have been used with constantly changing degree of success. Destructive methods, such as electrocautery or cryotherapy, may be associated with scarring.[4]

Various studies have reported clearance rates fluctuating from 14% to 100% on using intralesional bleomycin for the cure of recalcitrant warts, and that bleomycin is effective with minimal adverse effects in over two-thirds of cases.[5]

Two studies[6,7] compared the success rates of intralesional bleomycin and cryotherapy, and reported that the former showed a 90% success rate and the latter a 72.5% success rate.

Data on the topic is minimal both internationally and locally. The current study was planned to fill the gap by evaluating the effectiveness of intralesional bleomycin in comparison to cryotherapy in the treatment of cutaneous warts in the local population.[8]

Patients and Methods

The randomized controlled trial (RCT) was conducted at the Department of Dermatology, Jinnah Postgraduate Medical Centre, Karachi, from January to July 2021. After approval from the institutional ethics review committee, the RCT was registered with the international RCT registry, clinical trials.gov identifier https://clinicaltrials.gov (NCT05023408). This study adheres to the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting randomized controlled trials.[9] The sample size was calculated using the Power Analysis and Sample Size

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Software-2020 (PASS).[10] The sample comprised patients of either gender aged 18-60 years who had cutaneous warts for 1-48 weeks . Those who had previously been treated for warts using any technique, and patients who had a history of vascular illness, immunocompromised conditions, hypertension, cardiovascular issue, or an allergy to lidocaine were excluded, and so were pregnant and lactating women.

After taking written informed consent from all the subjects, they were sampled using non probability consecutive sampling into group A treated with 0.1% intralesional bleomycin, and group B were treated with cryotherapy.

Demographic and clinical data was collected using a predesigned proforma. Intralesional bleomycin at a concentration of 0.1% was made by diluting 15 mg of powder in 5ml of distilled water. After that, each 1ml was further diluted by adding 2 ml of 2% lignocaine, which was twice the quantity that was taken from the vial. This resulted in a concentration of 1mg per ml, which is 0.1%. Group B patients were treated with liquid nitrogen using a cotton swab wrapped around a wooden stick. The treatment was administered firmly with 01mm of additional healthy skin margin, and continued until the lesion became blanched.

Follow-ups examination was done at weeks 2, 4 and 6. At the end of the 6th week, the effectiveness of the therapy was determined by whether or not it was successful in totally removing the wart. After the completion of 6-week treatment, the patients were followed up after 2 weeks (8 weeks from the baseline) to see any recurrence or adverse effects.

Data was analysed using SPSS 23. Mean and standard deviation were calculated for age, height, body mass index (BMI), body weight, duration and number of cutaneous warts, size of the larger cutaneous warts. Frequencies and percentages were calculated for gender, place of residence (urban/rural), socioeconomic status (SES) (upper class/ middle class/lower class), education level (illiterate/ primary/intermediate/graduate), site of cutaneous warts, and the efficacy of therapy achieved after 6 weeks of therapy (yes/no). Both groups were evaluated and compared for mean values using the student's t-test. For proportions, chi-square test was employed. Effect modifier was controlled through stratification of age, gender, BMI, SES, place of residence, education level, duration of cutaneous warts, site of cutaneous warts, number of cutaneous warts, and the size of larger cutaneous wart to see the effect of these on outcome variable by applying chi-square test. P<0.05 was taken as significant.

Results

Of the 154 patients, 96(62.3%) were male and 58(37.7%) were females. The overall mean age was 33.253+6.726 years. There were 48(62.3%) male and 29(37.7%) female subjects in groups A and B (p>0.05). The mean age in group A was 33.62±7.64 years, while in Group B, it was 33.62±7.64 years (p=0.268).

The mean duration of cutaneous warts in group A was 8.93+6.81 weeks, while in group B it was 10.74±7.00 weeks (p=0.107). The mean size of larger cutaneous warts in group A was 10.11±3.89mm, while in group B it was 11.29±4.29 mm (p=0.08) (Table 1).

Efficacy of therapy after 6 weeks in Group A was achieved in 73(94.8%) patients, while in Group B it was achieved in 57(74%) patients (p=0.001) (Table 2).

Smaller warts showed better results with intralesional bleomycin, while larger sized warts showed good response to cryotherapy (p=0.001). The number of warts also had a significant effect, with patients having lesser number of warts showing complete recovery with intralesional bleomycin, while the response was slow in group B, with fewer patients showing partial clearance (p=0.05). The site of warts was found to be non-significant (p=0.84).

Palmoplantar and periungual warts were less likely to respond to cryotherapy compared to bleomycin.

Those who completely cleared their warts at the 2nd session were not given further sessions. With bleomycin, warts started disappearing after the 2nd session, and there was complete clearance at the end of 4th session compared to group B (Figures 1-2).

At the 8-week follow-up, no adverse effects were noticed except slight dyspigmentation of the treated area.

Table-1: Intergroup comparison of mean duration of warts (weeks) and mean size of larger cut warts (mm).

Variables	Group-A Intralesional bleomycin (n=77)	Group-B Cryotherapy (n=77)	*p*-value
Mean Duration of warts (weeks)	8.93±6.81	10.74±7.00	0.107
Mean size of larger cut warts (mm)	10.11±3.89	11.29±4.49	0.08

Table-2: Intergroup comparison of efficacy of therapy after 6 weeks.

Variables	Group-A Intralesional bleomycin (n=77)	Group-B Cryotherapy (n=77)	*p*-value
Efficacy (%)	73 (94.8%)	57 (74 %)	0.001
95% confidence interval	89.8% - 99.7%	64.2% - 83.8%	

Figure-1: Complete clearance of warts after the 4th session of intralesional bleomycin.

Figure-2: Partial clearance of warts after the 4th session of cryotherapy with some residual hypopigmentation.

Discussion

Warts are one of the common dermatological disorders triggered by HPV. Children and young people are generally affected by warts. Various studies conclude that almost 10% of the young population has suffered from warts.[11] While some warts disappear on their own over time, others continue to develop. They may also spread to other parts of the body, causing the patients to suffer both physically and psychologically as a consequence. Electrocautery, cryotherapy, intralesional bleomycin, surgical removal, laser ablation, topical medicines, like 5FU/salicylic acid, and immunotherapy are some of the therapeutic methods that are available. Other medical possibilities include immunotherapy.[12] The warts may be eliminated with the treatments either by the direct elimination of the warts themselves or through the activation of immunological responses against the virus that has infected the keratinocytes. There are hardly many agents that exhibit inherent antiviral action.[13,14] The clinician should choose the best possible potential cure from the multiple therapeutic alternatives that are available and are appropriate for individual cases. This decision should be made after taking into consideration the patient's age, gender, previous medical history and the properties of the warts.

In the current study, the efficacy of therapy after 6 weeks in group A was achieved in 73(94.8%) patients, while in Group B it was achieved in 57(74%) patients. A study reported 90% efficacy in intralesional bleomycin group and 72.5% in cryotherapy group. In another study,[7] the clearance rates in the context of number of patients and number of warts were 94.9% and 97% for bleomycin and 76.5% and 82% for cryotherapy, respectively. However, till date, no therapeutic modality had been fully successful.[15]

Regarding the 80% cure rate in warts <20mm compared to 46 and for warts >20 mm, it seems that the wart's diameter before intervention is a significant factor in predicting response to the treatment. The recurrence rate was greater in those with more warts. The response rate for palmoplantar warts was 96%, but the response rate for periungual warts was 100%. With intralesional bleomycin, a study found full removal in 95(73%) warts and partial clearance in 31(24%). On the other hand, a significant rate of recurrence was seen in individuals who had a greater number of warts.

In general, the cure rates for intralesional bleomycin (1mg/ml) using alternative procedures, such as dermojet were 77.5%, but in two different investigations, the cure rates for monolet and the bifurcated needle prick approach were 92%.[16,17] This variability may be attributed to insufficient bleomycin infiltration as well as partial coverage of big warts using monolet/bifurcated needle or dermojet procedures. This wastes some of the medicine since it remains on the surface of the wart. The blanching of the lesion is an indication that the bleomycin injectable medication should be given directly into the wart for appropriate administration. An injection that is too superficial might allow the medicine to seep through the warts. Deeper injection does not blanch. It is possible that many punctures in a bigger wart will cause the medicine to seep out, leading to a less effective treatment. To circumvent this problem, one should try to avoid making many punctures in the wart, and should move the needle around within the wart without pulling it out. When treating periungual warts with injections, care should be

taken to prevent causing any damage to the matrix, since this might result in nail abnormalities. However, the current study did not observe this complication in any patient. In order to prevent the medicine from spraying out after the stress of the injection, glasses should be worn by the patients, who should also cover their eyes. However, the dose of intralesional bleomycin may also have an influence on the therapeutic response, as a study noticed.[18] This is something that has to be taken into consideration.

The use of cryotherapy with liquid nitrogen is an effective treatment for warts, especially those located on the periungual and palmoplantar portions of the skin.[19] In a study,[20] the observed rate of recurrence was 24.2% in patients who were treated with cryotherapy, but just 56.7% responded to cryotherapy.

To administer an intralesional injection, no specific puncture needles or technical expertise are required. Additionally, spills result in minimum drug wastage. Although untreated warts have a higher chance of returning, the size of the wart before to treatment and the degree of infiltration of the lesions seem to be crucial factors in determining the success of the therapy. However, future studies could be able to address concerns relating to the treatment protocol and dose of bleomycin for all types of warts, regardless of their, location, duration and treatment history.

The current study has its limitations as it was done at a single centre with a smaller sample size.

Pain was the primary issue that needed to be addressed throughout both the intralesional bleomycin treatment and the cryotherapy procedure. Pain lasted for a shorter period of time in the bleomycin group compared to pain that persisted in the cryotherapy group for anywhere between 6 and 12 hours following treatment. Pain during intralesional injection is something that patients typically go through when the solution is not mixed with a local anaesthetic solution. In a small number of individuals who were given bleomycin, intense discomfort, haemorrhagic eschar development, and localised sclerosis were seen. This was particularly the case when treating periungual warts. These negative effects fully disappeared after a week of treatment. Reducing the amount of solution that is injected and avoiding over-blanching the lesions at the digits will help prevent these complications from occurring. Throughout the course of the follow-up, depigmentation was seen in a considerable proportion of patients in both the groups. Patients who had been treated with cryotherapy had a more severe form of dyspigmentation, which was caused by an elevated post-inflammatory response pattern. While the dyspigmentation was progressively clearing up, it was impossible to determine how much longer it would take to resolve because of the restricted amount of time.

Conclusion

With respect to treatment of palmoplantar warts, intralesional bleomycin was found to be a more successful therapeutic option than cryotherapy. The intralesional injection did not need any specialised pierce needles or technical skills, and there was only a little amount of medicine that was wasted due to spillage. It would indicate that the pre-treatment size of the wart as well as appropriate infiltration of the lesions were critical factors in the therapeutic success.

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