

Intralesional bleomycin in the treatment of cutaneous warts: A randomized clinical trial comparing it with cryotherapy

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ABSTRACT

Background: Though not in regular practice, intralesional (IL) bleomycin has been used for the treatment of warts since the 1970s and on the other hand, till now cryotherapy is quite regularly used to treat warts. **Aim:** Our aim was to assess the evidence for the efficacy of IL bleomycin, in comparison with a control group of similar sample receiving cryotherapy, in the treatment of cutaneous warts. **Methods:** Patients were randomized using computer-generated codes to receive either cryotherapy (double freeze-thaw cycle) or IL bleomycin (0.1% solution with concurrent anesthesia) for a maximum of four treatments 3 weeks apart and a maximum of five warts treated in each visit for both groups. Patients had their warts measured at base-line and with each return visit including a post treatment follow-up that was 8 weeks apart from last treatment taken. **Results:** Of the 73 patients completing the study, 39 (53%) were treated with IL bleomycin and 34 (47%) were treated with cryotherapy. Out of 155 treated warts, 87 (56%) were treated with IL beomycin and 68 (44%) were treated with cryotherapy. The clearance rates in context of number of patients and number of warts were 94.9% and 97% for bleomycin and 76.5% and 82% for cryotherapy respectively ($P < 0.05$ by χ^2 analysis and $RR = 7.67$). **Conclusion:** IL bleomycin injection was significantly more effective than cryotherapy for treatment of cutaneous wart.

Key words: Bleomycin, Cryotherapy, Intralesional, Wart

INTRODUCTION

Warts are scaly, rough, spiny papules or nodules that can be found on any cutaneous surface.^[1] Cutaneous warts are the cutaneous manifestations of human papillomavirus (HPV)^[2] infection. Over 100 HPV types are recognized, with affinity for different sites of the body. The clinical appearance of warts is variable and depends to some extent on the type of HPV involved and the site of infection.^[3-5] Diagnosis of warts is usually based on clinical examination.^[6]

There is no treatment, which is 100% effective for warts and different types of treatment may be combined.^[6] Cryotherapy is widely practiced in treating cutaneous wart in hospitals, clinics, and in some health professional's office set up with relative safety and variable effectiveness.^[7-14] However, intralesional bleomycin is not yet known to be used

in treating cutaneous warts in our country, although it has been used abroad in the treatment of warts since 1970s.^[7,8,15-28] Numerous reports have been published on the use of intralesional bleomycin for the treatment of warts, with cure rates ranging from 14% to 99%.^[15] In Bangladesh, still there is no study that has been conducted with intralesional bleomycin for the treatment of warts. 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 available and easily accessible in peripheral practices. In spite of many available studies on bleomycin and cryotherapy in treating warts, little head-to-head research is carried out to compare the efficacy of these treatments in similar settings.^[29] This study has been designed to use intralesional bleomycin injection comparing with a group receiving cryotherapy in treating cutaneous wart to find out whether there is another

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effective and safe option for the treatment of cutaneous warts. Our primary objective was to assess the evidence for the efficacy of intralesional bleomycin and secondary objectives were to identify side effects, if any, due to study medications while treating cutaneous warts and also to see the relative outcome of the study medications in the context of total time taken and number of visits in treating cutaneous warts, in comparison with a group of similar sample receiving cryotherapy.

METHODS

The clinical trial was carried out between february 2006 and September 2007, at the Department of Dermatology and Venereology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. A total of 80 patients (age range, 5-50 years, otherwise healthy) were enrolled in the study; of these, 73 patients (having 155 treated warts) completed the study and were available for analysis.

Study design

All consecutive patients, both male and female (nonpregnant and nonlactating), having cutaneous warts (with no prior treatment) were primarily selected for the study. Diagnosis was made by its history and clinical features. Primarily selected 80 patients were randomized using computer-generated codes into two groups each of which included 40 patients. One group was arm A that was treated with bleomycin and another was group B that received cryotherapy. In both groups, patients were visited at 3-week intervals, to a maximum of four times and the treatment was repeated if required. Post-treatment follow-up was done 8 weeks after the end of the last treatment given, as a final visit to assess any recurrence of the cleared wart or remaining side effects.

Baseline evaluation was made at the first visit. A graphical wart map was prepared for each patient, and location of warts along with data regarding wart size and type were recorded on it. The location, number, dimensions and clinical type of each wart selected for treatment and the total surface area to be treated was also recorded on standardized data collection sheets. Photograph of each lesion was also taken at every visit to support the recorded data. The efficacy of the study medications was documented by counting the number of warty lesions and their size measuring the surface area at each visit. A wart was considered cleared if it completely resolved, otherwise it was considered as a treatment failure.

A maximum of 5 warts were treated in each patient in a single visit and they were numbered from above downward or proximal to distal on the basis of location. Treatment session was a minimum of 1 and a maximum of 4 occasions, depending on the treatment response at 3-week intervals. Patients were evaluated for the treatment's efficacy and safety in each follow-up visit at 3-week intervals, with or without applying study medication depending on the previous treatment outcome. Treated areas were finally assessed in the post-treatment follow-up after 8 weeks of completion of the final treatment session to quantitate the recurrence rate of the treated warts and to ensure resolution of any adverse events.

At each visit, any possible systemic or local adverse reactions (including pain during and after treatment, pigment changes, Raynaud's phenomenon, scarring, tissue/nail damage, itching and skin rash) and their severity, was noted.

The study was approved by the ethical committee of the Department of Dermatology and Venereology of BSMMU.

Study medications and methods of administration

Bleomycin for injection is available in vials containing 15 mg powder. It was diluted first with supplied 5 ml diluents (distilled water) with the package. Before injecting it was further diluted by adding 2% lidocaine, double the amount taken from the vial, so that the concentration become 1 mg/1 mL (0.1% or 1 unit/mL). This was injected into the base of the wart, using a 100-unit insulin syringe that also provides a concurrent acceptable anesthesia.^[15] Injection was continued until each wart had blanched. In a single visit, less than 2 mL of 0.1% bleomycin solution was given to avoid any systemic side effects in a given patient.

Cryotherapy with a spray gun was performed, using nozzles of suitable sizes appropriate for the patient. The spray gun was held perpendicular to the wart at a distance of 1 to 2 cm. The wart was sprayed until the ice-ball formation had spread from the center to include the edge of the wart and a 1-mm margin. A double freeze-thaw cycle was practiced in our cases.

Data collection and analysis

All data were collected using a structured questionnaire and then checked and edited. Data were analyzed by computer with the help of SPSS win 12 and Epi-info 2006

software packages under the supervision of a statistician. Statistical analyses were done by using appropriate procedures as applicable. Statistical significance was set at 0.05 level and confidence interval at 95%.

RESULTS

One patient from group A and 6 from group B were excluded due to infrequent follow-up. So, ultimately, there were 39 patients (53%) in group A, 34 (47%) in group B and in all there were 73 patients. A total of 155 warts were treated in all 73 patients. In group A, among 39 patients, 87 warts (56%) were treated and in group B among 34 patients, 68 warts (44%) were treated. No statistical significant differences were observed between groups in terms of age, sex, diagnostic subcategory of warts, distribution of number of warts and their surface area during enrollment.

At the end of the treatment, in 94.9% of group A patients, warts were cleared and only 5.1% of patients had a single wart to be cleared. In group B, in 76.5% of patients, warts were cleared and were yet to be cleared in the remaining 23.5% of patients. It seems that palmoplantar warts respond less likely to cryotherapy. Statistically significant difference was observed between the two groups. Table 1 presents clearance of warts in two groups.

Chi-square test and proportion test was done to find out significant difference between the two groups where the calculated value indicates that clearance rates differ significantly at 5% level of significance. Relative risk was estimated at 7.67. So, we can infer that bleomycin was more than 7 times better in resolving the disease state during the treatment period.

An average of 1.38 treatment visits were needed in group A [Figures 1-4], whereas 3.09 treatment visits were needed per case in group B patients [Table 2], which is significantly higher in group B.

There was a strong positive correlation between surface area of the treated warts and amount of bleomycin

needed to treat ($P < 0.05$ by r analysis). On average, 1 mL bleomycin covered 94mm² area of a wart. One important fact in treating warts was 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 reaction of treatment, nothing but pain and dyspigmentation were found noteworthy. In fact, every patient experienced some degree of pain but only 5% of patients in group A and 12% in group B suffered pain, which hampered their routine activities 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 group B (91% of group B patients and 46% of group A patients). These pigmentary changes persisted till post-treatment follow-up, although they tended to gradually decrease.

DISCUSSION

Among numerous reports published, no consistent evidence was found for the efficacy of intralesional bleomycin in systematic review by Gibbs.^[7,8] The majority of the available data suggests that bleomycin is effective in over two-thirds of the reported cases with minimal side effects.^[15] In our study, greater efficacy in clearing warts was shown with intralesional bleomycin vs. cryotherapy. Here, 0.1% concentration of bleomycin was used. Concentrations of bleomycin, such as 0.15% and 0.05% had also been used to treat warts.^[15] In our study, the clearance rates of warts for intralesional bleomycin therapy found were 97%, and in 94.9% of patients, all warts treated with bleomycin were cleared.

Aguis *et al.*,^[30] used intralesional bleomycin in 47 patients with 138 plantar warts that were resistant to cryotherapy. Their cure rate was 89.9%. Bunney *et al.*,^[22] carried out a study on 59 matched pairs of hand warts in 24 patients with intralesional bleomycin, compared with a normal saline placebo injected into the paired warts in the same patient found a cure rate of 76%. In Munn *et al.* study,^[31] bleomycin solution was dropped on to the wart and then “pricked” into

Table 1: Clearance of warts in two groups

Group		Bleomycin	Cryotherapy	Total
All warts cured	No	2 (3)	12 (18)	14 (9)
	Yes	85 (97)	56 (82)	141 (91)
Total		87 (100)	68 (100)	155 (100)

X² (with Yates correction) = 10.363, d = 3.307; Relative risk, RR = 7.67
Figure in paranthesis are in percentage

Table 2: Number of treatment visit in the two groups

Group	No. of patients	Mean	Standard deviation	t	P
A	39	1.38	0.63	-8.036	0.0001
B	34	3.09	1.14		



Figure 1: Warts on dorsum of hand before treatment



Figure 2: Clearance of warts but dyspigmentation seen 8 weeks after treatment with intralesional bleomycin



Figure 3: Wart on thumb before treatment



Figure 4: Clearance of warts on thumb after 8 weeks after treatment with intralesional bleomycin

the wart. The clearance rate here was 92%. Multiple-puncture technique using a bifurcated vaccination needle to introduce bleomycin in warts done by Shelly and Shelly^[32] in a study also mentioned a success rate of 92%. In these studies, during pricking of wart surface, bleeding may occur. Hayes and O'Keefe^[23] used more dilute concentrations (0.05%) of bleomycin injected in 62 warts of 26 patients where cure rate was 76%.

In our study, wart clearance rate by cryotherapy was 82%, and in 76.5% of patients all warts treated with cryotherapy were cleared. In a study by Berth-Jones *et al.*,^[13] the clearance rate was 57% for single-freeze technique, and 62% for the double-freeze technique. In Bourke *et al.* study,^[12] the clearance rate was 66% in the group treated weekly, 47% in the group treated every 2 weeks, and 30% in those treated every 3 weeks. However, the clearance percentage is

related to the number of treatments received, and independent of the interval between treatments. It was seen that, most of the trials of cryotherapy studied different regimens rather than comparing cryotherapy with other treatments or placebo.^[8] Although, there is more controversy about its efficacy, most studies show lower cure rates for cryotherapy when compared with other studies done on bleomycin. An Iranian study^[29] compared the efficacy of bleomycin with cryotherapy on the same patients group. They used 0.05% bleomycin solution and single-freeze cryotherapy on the alternate limbs of the same patient presenting with almost symmetrical and bilateral presentation of warts. In their study, they found that the clearance rate for intralesional bleomycin therapy was 87.6% for warts, and in 86.4% of patients all the warts treated with bleomycin were cleared. They found cryotherapy to have a wart clearance rate of 72.3%, and in 68.2% of patients all the warts treated with cryotherapy were

cleared. Calculating the relative risk they estimated that bleomycin had 1.23 times more efficacious than cryotherapy. In our study, the success rate in both groups found relatively higher. Ninety-seven percent wart clearance rates and 94.9% patient clearance rate for bleomycin compared to 82% wart clearance rate and 76.5% patient clearance rate for cryotherapy. The relative risk found in the study was 7.67, which indicates that bleomycin was more than 7 times more efficacious than cryotherapy in clearing warts. Here, 0.1% bleomycin solution and double-freeze thaw cycle technique was used. The patients selected here had limited number (maximum 5 warts were treated) of warts. All these factors might have contributed to the higher rate of success. In bleomycin-treated patients, there was a significant positive correlation found between the surface area of wart and the amount of bleomycin needed to treat the wart.

Pain was the major bothering factor both in cryotherapy and intralesional bleomycin. Pain period was shorter in bleomycin group compared with the pain and discomfort in cryotherapy group, which might continue for several hours after cryotherapy. Perhaps 2% lidocaine that was mixed to dilute bleomycin solution helps to avoid severe pain during injection, which is usually experienced by a patient when the solution is not mixed with anesthetics. Dyspigmentation observed during post-treatment follow-up in both groups in significant number of cases. Due to greater post inflammatory reaction, dyspigmentation was more marked in cryotherapy-treated patients. Although dyspigmentation was gradually fading out but how long it takes to resolve could not be assessed due to limited time frame of the study. Other side effects were negligible. Difference in recurrence of warts was insignificant in two groups.

There was significantly less number of treatment sessions, with a mean of 1.38 in case of bleomycin treatment than the cryotherapy where the mean is 3.08. So, patients required shorter course of therapy in case of bleomycin therapy saving them time. The study conducted in Singapore^[27] found that to treat warts with 0.1% bleomycin solution, an average of 1.5 treatment sessions were required for each patient.

If group treatment can be arranged, the cost of bleomycin therapy will be significantly minimized. As bleomycin therapy required less equipment than cryotherapy, it would be more suitable for peripheral

practice considering its tolerance and efficacy for warts.

CONCLUSION

Intralesional bleomycin injection was significantly more effective than cryotherapy and was a safe alternative for the treatment of cutaneous warts.

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