Intralesional Bleomycin in the Treatment of Common Warts

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Abstract

Background: Warts are one of the most common benign growths in the dermatological outpatient department but are many times tough to treat as they are chronic, resistant, and relapsing to available treatment. A variety of therapeutic modalities have been used with varying degree of success. However, till date, no therapeutic modality had been fully successful. Aim and Objectives: The present study was conducted to evaluate the therapeutic efficacy and safety of intralesional (IL) bleomycin injection in common warts. Materials and Methods: A total of 50 patients of common warts were enrolled in this evaluator blinded randomized placebo-controlled study. Group A consists of patients to be treated with IL bleomycin, and Group B consists of patients to be treated with IL normal saline. A total of 25 patients were enrolled in each group. Patients of both groups were asked to follow-up after 4 weeks for maximum of 4 times, i.e. at 8 weeks, 12 weeks, at the end of 6 months as a final visit, and assessed clinically every time. Results: Out of 87 wart lesions in Group A patients, 81 (93.10%) showed a complete resolution. A progressive clearance of the warts was seen, after the first injection (64%) and second injection (36%), only 6 warty growths (7%) were nonresponders to treatment. However, in Group B, only 4 (5%) showed disappearance within 12 weeks and even after 6 months of follow-up (P < 0.05 by × 2 analysis and risk ratio = 7.67). Conclusion: IL bleomycin injection was significantly safer and effective, with better patient acceptance in treating common warts.

Keywords: Bleomycin, common warts, intralesional, normal saline, outpatient department procedure

Introduction

Common warts are one of the most common viral infections affecting the skin. It is known since the early Greek and Roman times. It is caused by the human papillomavirus (HPV) out of which mainly HPV Type 2 and HPV Types 1, 4, 7, 57 are responsible. Warts present as firm keratotic papules that can appear on any cutaneous surface and mucosa. Common warts are also called as “verrucae vulgaris.”[1-3]

Common warts are treated with different physical modalities such as electrosurgery, cryosurgery, and different physical or chemical assaults with variable results.[4] High rates of recurrence or scarring are reported in all these modalities. Intralesional (IL) bleomycin is suggested to be potential treatment modality in treating warts and has been used since the 1970s in western countries. Bleomycin is a cytotoxic glycopeptide antibiotic isolated from a strain of bacteria Streptomyces verticillus. It has antitumor, antibacterial, and antiviral activities which may be related to its ability to bind with deoxyribonucleic acid (DNA), causing DNA strand scission, and elimination of pyrimidine and purine bases. Bleomycin does not bind directly to HPV.

The probable mechanism of action of bleomycin is by affecting cellular DNA synthesis; and also by controlling keratinocyte turnover thereby affecting viral survival.[5-8] Thus, we conducted this study to assess efficacy and safety of bleomycin for treatment of common warts.

Materials and Methods

We performed a prospective, randomized, evaluator-blinded, placebo-controlled study enrolling 50 patients of common warts attending the outpatient department (OPD) of Dermatology at MIMSR Medical College and YB Chauhan tertiary care hospital in central India. This study was conducted after obtaining ethical committee clearance as well as informed and written consent from all patients.

Study groups included consenting patients with clinically diagnosed viral warts above 12 years of age seen in our OPD.

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Exclusion criteria included patients who were not willing and not consenting for the study, pregnant and lactating women, patients having Raynaud’s phenomenon, pulmonary fibrosis or scleroderma; patients who received prior treatment for warts and children below 12 years of age. Patients were categorized into two groups, Group (A and B). Group A consists of patients to be treated with IL bleomycin, and Group B consists of patients to be treated with IL normal saline. A total of 25 patients were enrolled in each group. Patients of both the groups were asked to follow-up for a maximum of 4 times, i.e. at 4 weeks, 8 weeks, 12 weeks, and at the end of 6 months as the final visit. The treatment was repeated if required at the end of 4 weeks. If warts persisted beyond 12 weeks of starting treatment, it was considered as a failure of treatment.

Cutaneous side effects of treatment modality were noted, and patients were also examined for any systemic side effects. Patients were followed up for 6 months for the assessment of any recurrence of warts. Serial photographic assessment and clinical assessment was made during each visit to look for efficacy and safety profile of the treatment as well as for recurrence. The pain was assessed by oral questionnaires such as no pain, mild pain, moderate pain, and severe pain.

Materials required were bleomycin vial (containing 15 mg of powder of bleomycin), distilled water, Bupivacaine hydrochloride injection (0.5%), and normal saline and insulin syringe. Group A patients were treated with injection bleomycin after sensitivity testing and routine clinical examination. The concentration of bleomycin used was 1 unit/1 ml. Bleomycin is available in a powder form in vial containing 15 units of the drug. We reconstituted it with 5 ml Distilled water to make it 3 units per 1 ml. Further 2 ml of local anesthetic bupivacaine hydrochloride (0.5%) was added, to make the concentration of bleomycin 1 unit in 1 ml. Bupivacaine hydrochloride (0.5%) was added to decrease the pain due to bleomycin injection. Under all aseptic precautions, bleomycin was injected at the base of warts using insulin syringe. The doses were adjusted according to the size of warts. The total dose of bleomycin not exceeding 1 unit/ml per wart and maximum of two injections were given. Group B patients were treated with IL normal saline. Under all aseptic precautions, normal saline was given intralesionally at the base of warts with the help of insulin syringe.

Patients of both groups were asked to follow-up after 4 weeks for a maximum of 4 times (i.e. at 4 weeks, 8 weeks, 12 weeks, and the end of 6 months) for clinical assessment. If warts persisted after 12 weeks of starting treatment, it was considered as a failure of treatment. Data obtained were analyzed with Chi-squared test and Fisher’s exact test.

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. 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.

### Results

A total of 50 patients were included in the study with group A and B having 25 patients of common warts patients who attended OPD of Dermatology at a tertiary care hospital. Age of patients ranged between 12 and 50 years (mean age for group A 25.12 years and group B 25.44 years). The commonest age group of patients having warts was 21‑30 years in both groups. Thirty three were males (64%) and 17 were females (34%). Duration of warts ranged from a minimum of 1 month to a maximum of 2 years, with a mean of 9 months. Most common site of warts in both groups was over hands (44%), followed by legs (22%), foot (10%) and then forearm (8) and forehead (8) [Table 1].

Of the total 25 patients intralesional bleomycin group, with a total number of warty growths of 87, 81 (93.10%) showed a complete resolution. Distribution of study subjects according to number of warts cleared and not cleared at the end of 12 weeks [Figures 1-2] (Chi-square test).
test $\chi^2 = 128.44$, df $= 1$, $P < 0.05$). A progressive clearance of the warts was seen, after the first injection (64%) and second injection (3%). Only 6 warty growths (6%) were nonresponders to treatment [Table 2]. Out of 81, 13 cleared warts showed recurrence during follow-up (16%). We had 79 warts under Group B, only 4 (5%) showed disappearance within 12 weeks and showing a clear difference in results in both groups.

Most common side effect at the end of 4 weeks was hemorrhagic eschar (ecchymosis), which was shown by the entire group A (cases) patients, hyperpigmentation was seen in 22 (88%) of 25 patients, hypopigmentation in 2 (8%) of 25 patients, scarring was seen in 2 (8%) of 25 patients, and none of the patients showed any systemic side effects. The pain was the most common complaint in group B patients during injections.

**DISCUSSION**

The present study was an attempt to assess the efficacy of IL bleomycin injection for the treatment of common warts by comparing with placebo (normal saline). As well as to assess the systemic or local side effects that were encountered during the study and the analysis was performed on 50 patients having 166 warts which were divided into two groups.

IL bleomycin has been favorably used to treat various skin conditions. These include warts, hemangiomas, vascular malformations, telangiectasias, several types of cutaneous malignancies, condyloma acuminate, and the lesions of leishmaniasis cutis. The use of IL bleomycin has not been approved by the US Food and Drug Administration. Bleomycin when used in high doses (>450 units) as in cancer chemotherapy can cause pulmonary fibrosis. For a very low dose (1 mg/mL), no systemic side effects have been observed. Numerous reports have been published on the use of IL bleomycin for the treatment of recalcitrant warts with cure rates ranging from 14% to 99%. The majority of the data suggest that bleomycin is effective in over two-thirds of the reported cases with minimal side effects.

At the end of the study period, the following conclusions were drawn that the overall clearance rate of warts with IL bleomycin was 93.1%. Out of all cleared warts, 64.19% warts were cleared with single IL injection of bleomycin and 35.80% warts after second IL injection of bleomycin. Most of the studies done in literature are in palmo-planter warts or periungual warts, and some studies are done with cryotherapy, electrocautery, etc. In 1980, studies by Buxton et al., a total of 24 patients, with proven resistance to treatment, to study the effectiveness of the IL injection of 0.1% solution of bleomycin sulphate found that 87.5% of patients showed a more favorable response to bleomycin ($P < 0.001$); 76% of the 59 warts treated with bleomycin were cured by one to three injections of up to 0.2 ml of solution. Subsequently 75% of 32 patients with resistant hand warts and 66% of fifteen patients with mosaic plantar warts were cured of all their warts. No patient received more than 4 mg of bleomycin. No toxicity was experienced. Local pain was on the whole well tolerated. This form of treatment for resistant warts is reliable, safe, and acceptable to patients.

In 1983, Shumer and O’Keefe conducted a double-blind placebo-controlled study and treated 151 warts with IL bleomycin and 55 warts with normal saline as placebo. Their study showed a 60% cure rate for plantar warts and a 94% rate for periungual warts. No systemic side effects have been observed. Indian study by Soni et al., showed clearance of 96.10% in 2001. Dhar et al. used IL bleomycin in 39 patients with 87 warts with 94.9% clearance rate and another 68 warts with cryotherapy. Aguis et al. used IL bleomycin in 47 patients with 138 plantar warts that were resistant to cryotherapy. Multiple puncture technique using a bifurcated vaccination needle used by Shelly and Shelly in a study also mentioned a success rate off 92%. Hayes and O’Keefe used more diluated (0.05%) of bleomycin injected in 62 warts of 26 patients where cure rate was 76%. The clearance rate of warts with bleomycin was unrelated with the duration of warts. Mild-to-moderate pain was the main problem experienced by patients during procedure, for which addition of bupivacaine hydrochloride (0.5%) to bleomycin solution helps to relieve pain. Furthermore, analgesics were helpful to relieve persistent pain.

No severe adverse effects were noted. However, hemorrhagic eschar (ecchymosis) was seen in most of the patients with belomycin injection, which regressed with

| Table 1: Distribution of study subjects according to site of warts |
|----------------------|-----------------|---------------------|
| S. no | Site of wart | Groups | Control no. % |
|---|----------------|---------|----------------|
| 1 | Hand | 10 | 40 | 11 |
| 2 | Foot | 02 | 08 | 03 |
| 3 | Forearm | 02 | 08 | 02 |
| 4 | Forehead | 01 | 04 | 01 |
| 5 | Hand and Foot | 02 | 08 | 00 |
| 6 | Hand and leg | 01 | 04 | 02 |
| 7 | Hand and forearm | 01 | 04 | 01 |
| 8 | Leg | 06 | 24 | 05 |
| Total | 25* | 100 | 25* |

| Table 2: No of warts cleared after 1st or 2nd injection and Non responsive warts after IL Bleomycin treatment |
|---------------------|----------------------|
| Warts | Cases (n=25) |
| No. of warts before treatmeant | 87 (100%) |
| Total no.of warts cleared after 1st or 2nd injections | 81 (93.1%) |
| No. of warts cleared after 1st injection out of all cleared warts | 52 (64.19%) |
| No. of additional warts cleared after 2nd injection out of all cleared warts | 29 (35.80%) |
| No. of warts required 2nd injection out of all warts | 35 (40.23%) |
| No. of warts not responsive to treatmeant out of all warts | 6 (6.89%) |
hyperpigmentation, hypopigmentation, or minimal scarring. There was no systemic toxicity noted due to bleomycin during our study period indicating that IL is less absorbed systemically. A total of 13 (16.04%) out of 81 cleared warts showed recurrence during follow-up.

The small sample size is the main limitation of this study. This was because of the placebo-controlled study design as a number of patients consenting for this type of study was less.

**Conclusion**

Bleomycin treatment does not require any special equipment or setup, it has short course of therapy reducing patient time and low recurrence rate. IL Bleomycin is found to be safe and effective treatment for the treatment of viral warts in our study. Treatment has good safety profile as well as a high cure rate of more than 90%. Side effects are few and rare. More randomized and double-blind studies of adequate sample size are required to further establish safety and efficacy of IL bleomycin in the treatment of viral warts.

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**Conflicts of interest**

There are no conflicts of interest.

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