

## Original Research Article

# Intralesional bleomycin in palmo-plantar and periungual warts: a therapeutic study

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### ABSTRACT

**Background:** Warts are one of the most common benign growths of skin caused by human papilloma virus. No single treatment has proved to be completely effective and most therapies for palmo-plantar and periungual warts remain unsatisfactory. The present study was conducted to evaluate the therapeutic efficacy and safety of intralesional bleomycin injection in palmo-plantar and periungual warts in patients in region of south east India.

**Methods:** Ninety patients of multiple palmo-plantar and periungual warts were included in the study. They were infiltrated with bleomycin (1 mg/ml) till blanching. The treatment was repeated after paring of eschar at 2 weeks interval in cases with partial or no response. The patients were reviewed at monthly interval for 24 weeks to note cure, adverse effects, recurrence and outcome satisfaction levels.

**Results:** Out of total 305 warts, 103 (34%) were cured after 1st injection and 249 (82%) were cured after 2nd injection. The number of warts requiring more than 2 sittings was 55 (18%). At the end of study, overall cure rate was 94.5% and 10 patients showed recurrence.

**Conclusions:** Intralesional bleomycin injection is an effective and safe treatment option in palmo-plantar and periungual warts.

**Keywords:** Bleomycin, Palmo-plantarwarts, Periungual warts

### INTRODUCTION

Warts are benign, tumor shaped lesions caused by human papilloma virus (HPV).<sup>1</sup> The treatment for warts is commonly sought for cosmetic reasons, pain, functional impairment and fear of spread of infection from autoinoculation. Various treatment options include trichloroacetic acid, 5-fluorouracil, cryosurgery, laser ablation, electrocautery and surgical excision.<sup>2</sup> None of the available modalities have shown 100% efficacy and most therapies for common warts remain unsatisfactory. Warts affecting palms, soles and periungual areas are especially difficult to treat because of procedural pain, relatively thicker glabrous skin of palm and soles and prolonged time required for healing by secondary intention. Bleomycin, an

antibiotic derived from *Streptomyces verticillus* inhibits deoxyribonucleic acid (DNA) and protein synthesis, triggers apoptosis, causes acute tissue necrosis and stimulates an immune response.<sup>3</sup> Many previous studies have shown significant efficacy of bleomycin for both common and palmo-plantar warts.<sup>4-7</sup> Hence, the present study was conducted to know the efficacy of intralesional bleomycin in palmo-plantar warts and periungual warts in patients of south east India.

### METHODS

The present therapeutic study was conducted between November 2017 and October 2018 in the Department of Dermatology, at a suburban medical college hospital after

obtaining institutional ethics committee clearance. Ninety patients with multiple warts over palms, soles and periungual skin were enrolled irrespective of number, duration of warts and previous treatment used. Pregnant and lactating women, children  $\leq 12$  years, patients with apparent skin infection, abnormal hepatorenal functions, Raynaud's phenomenon, peripheral vascular disease or immunosuppression were excluded. In all enrolled patients, general demographic data regarding age, sex and contact information were noted. Detailed history was recorded regarding duration of disease and previous treatment used. Thorough dermatological examination was done in all patients taking note of total number of warts, size and sites effected. Complete hemogram, liver function tests, renal function tests were done.

Bleomycin for injection is available in vials containing 15 mg powder. It was diluted first with 5 ml distilled water to prepare the stock solution which can be stored for 60 days at 4-8°C. Two parts of 2% lignocaine and one part of the bleomycin stock solution was taken in a tuberculin syringe, to attain a final concentration of 1 mg/ml. Each wart and the adjacent skin was cleansed with isopropyl alcohol. Superficial paring was done to remove the callus surrounding the wart; bleeding points were not reached and the fresh solution was injected strictly intralesionally till blanching of the lesion occurred. The amount of the injection given was based on the size of warts: warts up to 5 mm, 10 mm and more than 10 mm received 0.2 ml, 0.5 ml and 1.0 ml respectively. The total volume injected at one treatment sitting was limited to 2 ml and the injection into a single wart was limited to 1 ml. After 2 weeks of bleomycin injection, a black, ecchymosed eschar developed and shed. Residual warts if present were pared and a second injection was given. The clinical improvement was evaluated by comparing clinical photographs and patient satisfaction level on Likert scale (Table 1).

**Table 1: Evaluation of clinical improvement and patient satisfaction level.**

Grades	Definition
<b>Complete clearance</b>	Complete disappearance of warts and skin texture at the site is restored to normal
<b>Partial response</b>	Residual warts still visible
<b>No response</b>	No change in wart size and texture
<b>Reccurence</b>	Recurrence during the study period
<b>Patient satisfaction level</b>	Score on Likert scale
<b>Very much satisfied</b>	5
<b>Somewhat satisfied</b>	4
<b>Undecided</b>	3
<b>Not really satisfied</b>	2
<b>Not at all satisfied</b>	1

After completion of treatment period, the patients were followed up every 4 weeks up to 24 weeks. At each visit, systemic and cutaneous examination was done to note adverse effects such as pain, scarring, blister formation, pigmentary changes and Raynaud's phenomenon. Data obtained from all patients was tabulated. Numerical and graphical techniques were used to summarize the obtained data and perform statistical analysis.

**RESULTS**

In the present study, out of the 90 enrolled patients, 50 were males (64%) and 40 were females (34%) with male: female ratio being 1.8:1. Patients' age ranged from 12 to 50 years, with mean age being recorded as 25.44 years (SD=13.27 years). The commonest age group of patients was between 21-30 years. Duration of warts ranged from a minimum of 1 month to a maximum of 2.9 years, with a mean duration of 9 months (SD=1.23 years). A total number of 305 warts were treated in 90 patients. Details of site of involvement in all the patients are listed in Table 2.

**Table 2: Number of patients and lesions at different sites.**

Total number	Palmar	Plant -ar	Periun -gual	Multiple sites
<b>Patients (90)</b>	40	24	11	15
<b>Lesions (305)</b>	148	40	48	69

The response to treatment with intralesional bleomycin on different location after 12 weeks are described in Table 3. Complete clearance of warts was observed after first bleomycin session in 45 (31%), 16 (33%), 15 (37%) and 27 (39%) lesions in palmar, plantar, periungual and multiple sites respectively (Figure 1). At the end of 4 weeks i.e. after 2<sup>nd</sup> session of intralesional bleomycin, clearance rate of warts achieved were 117 (79%), 40 (83%), 32 (80%) and 60 (86%) in palmar, plantar, periungual and multiple sites respectively (Figure 2 and 3) and they were taken off from further treatment. Number of warts which required more than two sessions were 55(18%) (Figure 4). At the end of study, overall cure rate of 94.5% was achieved. During the follow up period, recurrence was noticed in 10 out of the 90 patients. Warts which were more than 10 mm in size resolved at a slower rate and required two or more treatment sessions as compared to lesions less than 10 mm without any correlation with the site of lesion.

Adverse effects observed in this study were mild in nature and did not lead to discontinuation of treatment. Pain during the procedure and in the initial three days post treatment was the commonest adverse effect which was managed with non-steroidal anti-inflammatory drugs. Alteration in blood counts, abnormal liver and renal function tests were not observed in any of the patients during and after completion of treatment. Administration

of bleomycin for periungual warts did not result in abnormal nail growth and onychodystrophy. All cured patients were very satisfied (overall satisfaction score 5 on Likert scale) with the therapeutic outcome.

**Table 3: Response to intralesional bleomycin at different locations after 12 weeks.**

Site of lesion	No of lesions	Lesions cured after 1st injection	Lesions cured after 2nd injection
Palmar	148	45 (31)	117 (79)
Plantar	48	16 (33)	40 (83)
Periungual	40	15 (37)	32 (80)
Multiple sites	69	27 (39)	60 (86)
<b>Total</b>	<b>305</b>	<b>103 (34)</b>	<b>249 (82)</b>

No. of lesions requiring more than 2 sittings: 55 (18%)

**DISCUSSION**

Warts are one of the most common benign growths seen in the dermatological outpatient department but are difficult to treat as they are chronic and recalcitrant to the available treatment modalities. Warts affecting the palms, soles and periungual region are particularly difficult to treat because of the unique regional anatomical features such as rich nerve, blood supply and thicker skin. Topical treatments including trichloroacetic acid, salicylic acid, 5-flourouracil and procedural treatments such as cryotherapy, electrocautery usually give poor results in patient with extensive palmo-plantar warts.<sup>8-10</sup> The present study was envisaged to determine and confirm the use of intralesional bleomycin for this common therapeutic dilemma.

In the present study, the cure rate observed after one sitting of intralesional bleomycin was 34% and it was 82% after two sittings. The overall cure rate seen in our study was 94.5% after 12 weeks of treatment. Similar observations were reported by Soni et al who reported a cure rate of 96% after two injections.<sup>7,11</sup> The response in periungual warts and palmo-plantar warts was 100% and 96% respectively. Good efficacy of intralesional bleomycin was also reported by Mehta et al and Aziz-Jilali et al in previous Asian studies.<sup>11,12</sup> Previous studies on the use of intralesional bleomycin in warts have shown excellent results particularly in palmo-plantar and periungual warts with cure rate ranging from 14% to 99%.<sup>13,14</sup>

To attain maximum efficacy, the volume of injection for each wart determined according to their size should be followed meticulously. For ideal resolution of warts, formation of haemorrhagic blister at injection site is the desired end point. We observed that size of the lesion is the most important determinant in predicting the number of sittings required and the treatment outcome. Lesions larger than 1cm diameter usually required 2-3 sittings.

Many studies have used different concentrations of bleomycin such as 0.15% and 0.05% to treat warts. One percent concentration of bleomycin used in our study was highly effective in the treatment of palmo-plantar and periungual warts. Stock solution prepared in our study was more concentrated than previous studies. It was diluted with 2% lignocaine which is a local anesthetic and reduced local pain during and after injection. Similar observations were reported by Soni et al and Mehta et al. Hayes and O'Keefe used more diluted (0.05%) bleomycin injected in 62 warts of 26 patients where cure rate was relatively lower (76%).<sup>15</sup> Different methods such as intralesional, sublesional, perilesional and translesional multipuncture techniques for bleomycin delivery have been used with almost equal efficacy.<sup>16-18</sup> Multiple puncture technique using a bifurcated vaccination needle used by Shelly and Shelly in a study also mentioned a success rate of 92% by using translesional multipuncture technique.<sup>19</sup>

Intralesional bleomycin was found to be more efficacious than cryotherapy in a randomized controlled trial conducted by Dhar et al.<sup>20</sup> The clearance rate achieved were 97% and 82% in bleomycin and cryotherapy group respectively. In another study, Anguis et al used intralesional bleomycin in 47 patients with 138 plantar warts that were resistant to cryotherapy with a cure rate of 89.9%.<sup>21</sup> A significantly less number of sessions of treatment were required than cryotherapy. A maximum of 2 ml of intralesional bleomycin can be given in a single sitting. Hence, intralesional bleomycin may be combined with cryotherapy in the same sitting or in sequential sittings in patients with extensive palmo-plantar warts. A study highlighting use of intralesional bleomycin along with cryotherapy in same patients simultaneously was reported by Adalatkah et al.<sup>22</sup> They concluded that the efficacy of bleomycin was superior to cryotherapy (87.6% and 72.3%).

The adverse effects observed in our study were mild self-limiting and didn't lead to discontinuation of treatment in any of the patient. Mild to moderate pain during the procedure and for 2-3 days post procedure was the commonest adverse effect reported. The low concentration of bleomycin used in our study did not lead to systemic toxicity as biochemistry and haemogram profile were normal in all patients. Injection of bleomycin in periungual region also did not result in local adverse effects such as nail growth abnormality or Raynaud's phenomenon. Recurrence rate observed in our study at the end of follow up period of 6 months was 11.1%. Similar observation of very low recurrence rate was reported by Unni et al.<sup>23</sup> Residual effect of bleomycin continued even after the discontinuation of treatment.

**CONCLUSION**

Intralesional bleomycin is an effective and safe treatment option in palmo-plantar warts. It is especially useful in cases of extensive involvement of palms and soles, where there are few therapeutic alternatives. We recommend its

routine use in view of its several advantages such as easy availability, low cost, absence of adverse effects and high patient satisfaction.

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