

# Evaluation of efficacy and safety of intralesional bleomycin in the treatment of common warts: Results of a pilot study

*Karan Inder Singh Mehta, Vikram K. Mahajan, Pushpinder Singh Chauhan, Shailja Chauhan, Vikas Sharma, Ritu Rawat*

Department of Dermatology, Venereology and Leprosy, Dr. R. P. Government Medical College, Kangra, Himachal Pradesh, India

## Abstract

**Background:** This study evaluated the efficacy and safety of intralesional bleomycin in the treatment of common warts in 50 (32 men, 18 women) patients aged between 14 and 80 (mean  $\pm$  SD, 28.5  $\pm$  13.27) years.

**Methods:** The warts were present over dorsal hands, feet, palms, soles and periungual skin for 1 month to 10 years. They were infiltrated with bleomycin (1 mg/ml) till blanching. The total cumulative dose did not exceed 2 mg in one session. The treatment was repeated after paring of eschar at 2 weeks in case there was no or partial response. The patients were reviewed at 4, 12 and 24 weeks for cure, adverse effects or recurrences and outcome satisfaction levels.

**Results:** Complete cure without recurrence occurred in 40 (80%) patients and partial response occurred in 7 (14%) patients at the end of the 24-week study period. Three patients did not complete follow-up. No major systemic or local adverse effects other than injection site pain for 2–3 days were noted. All cured patients were very satisfied (Likert scale 5).

**Conclusion:** Intralesional bleomycin appears to be an effective and safe treatment for common warts including palmo-plantar and periungual warts. It carries the advantage of low dose, no significant adverse effects and high patient satisfaction. Small number of patients, lack of a control group, comparing different bleomycin concentrations and a short follow-up are a few limitations of this study. Better designed studies are warranted for this useful treatment modality.

## Correspondence:

Dr. Vikram K. Mahajan,  
Department of Dermatology,  
Venereology and Leprosy,  
Dr. R. P. Government Medical  
College, Kangra (Tanda) - 176 001,  
Himachal Pradesh, India.  
E-mail: vkm1@rediffmail.com

**Key words:** Bleomycin, human papilloma virus, verrucae, warts

## Introduction

Common warts or verrucae vulgares are hyperkeratotic papillomas caused by human papilloma virus infection. They occur more frequently over hands of children and young adults, but may be located on any cutaneous or mucosal surface. Although spontaneous recovery is possible, it usually takes a long time, even years and remains unpredictable. However, some patients may not show any

tendency toward spontaneous clearance and require active intervention. However, no single treatment has proved to have 100% efficacy and most therapies for common warts remain unsatisfactory. Treatment options include destructive or surgical procedures such as cauterization with salicylic acid, podophyllotoxin, trichloroacetic acid,

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formaldehyde, 5-fluorouracil and photodynamic therapy. Surgical methods such as cryosurgery, laser ablation, electrocautery, and surgical excision are often painful, may cause scarring, have inconsistent results and recurrences are high especially in perirungal warts. Treatment with immune modulators such as contact sensitizers, imiquimod, intralesional interferons and oral levamisole, cimetidine or zinc sulfate has been tried with variable success.<sup>1-4</sup> Immunotherapy using different antigens (autogenous vaccine, *Candida* antigen, mumps antigen, trichophyton skin test antigen, tuberculin, Bacille Calmette Guerin (BCG) vaccine, measles-mumps-rubella (MMR) vaccine, and *Mycobacterium w* vaccine) too has been used with variable outcome.<sup>5,6</sup>

Bleomycin, an antibiotic derived from *Streptomyces verticillus*, selectively affects squamous cells and reticuloendothelial tissue. It inhibits DNA and protein synthesis, triggers apoptosis, causes acute tissue necrosis and stimulates an immune response.<sup>1</sup> Different methods such

as intralesional, sublesional, perilesional and translesional multipuncture techniques for bleomycin delivery have been used with almost equal efficacy.<sup>7-10</sup> In the translesional multipuncture technique, a frequently favored method, bleomycin is dropped over the wart and pricked into by using Monolet™ needle. The exact amount of bleomycin delivered into the lesions may vary as some amount of the drug remains

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

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



**Figure 1a:** A palmar wart



**Figure 1b:** A palmar wart cleared completely after one treatment session of intralesional bleomycin



**Figure 2a:** Multiple plantar warts of variable sizes



**Figure 2b:** The black dry keratotic eschar formed 2 weeks after first bleomycin treatment session and was pared before second treatment session



**Figure 2c:** Complete clearance of warts 2 weeks after second bleomycin treatment session

over wart surface with resulting wastage, and this specialized needle is not widely available. Hence, we evaluated the efficacy and safety of intralesional bleomycin for treating

**Table 2: Baseline characteristics of patients (n=50)**

Baseline characteristics	Number of patients (%)
Gender	
Men	32 (64)
Women	18 (36)
Men:women	1.8:1
Age (years)	
14-20	18 (36)
21-40	25 (50)
>40	7 (14)
Range (mean±SD)	14-80 (28.5±13.27)
Number of warts	
<5	24 (48)
5-10	15 (30)
>10	11 (22)
Range (mean±SD)	1-12 (5.8±3.6)
Duration of warts (range 1 month to 10 years)	
1-6 months	21 (42)
7-18 months	16 (32)
2-3 years	9 (18)
4-10 years	4 (8)
Median±IQR (months)	12±21
Sites of warts	
Plantar	20 (40)
Palmar	17 (34)
Periungual	3 (6)
Multiple sites*	19 (38)
Response to treatment	
First dose	
Complete response	16 (32)
Partial response	34 (68)
Second dose	
Complete response	26
Partial response	5
Lost to follow-up	3
Patient satisfaction score on Likert scale at 24 weeks	
5 (very much satisfied)	42 (84)

\*Included patients having lesions over dorsal hands and feet, palms, soles and periungual skin. SD: standard deviation, IQR: interquartile scale

common warts including palmoplantar and periungual warts which remain difficult to treat because of poor therapeutic response to other modalities.

**Methods**

This open label, uncontrolled, non-randomized study was conducted after approvals from Institutional Scientific Protocol Review Committee and Institutional Ethics Committee (Rgn no ECR/490/Inst/HP/2013) and registration with Clinical trial registry (CTRI No. REF/2017/01/013135). Fifty consecutive patients having common warts over dorsal hands, feet, palms, soles and periungual skin were enrolled irrespective of number and duration of warts or previous treatments. Pregnant and lactating women, children ≤12 years, patients with apparent skin infection, abnormal hepatorenal



**Figure 3a:** Multiple periungual warts over right index finger



**Figure 3b:** Two weeks after first bleomycin treatment

functions, Raynaud's phenomenon, peripheral vascular disease or immunosuppression were excluded.

After informed written consent, clinico-demographic details of participants were recorded and photographic records for warts made at baseline (before the treatment) and at each follow-up visit. The enrolled patients were advised not to use any other wart treatment during the study period. Laboratory investigations included complete hemogram and hepatorenal function tests before and at end of study.

#### Treatment protocol and outcome evaluation

Bleomycin powder for injection (15 mg vial) was dissolved in 5 ml distilled water to prepare the 3 mg/ml stock solution and stored at 4–8°C use up to maximum of 30 days. One part of the bleomycin stock solution and two parts of 2% lignocaine were mixed in an insulin syringe with 30 G needle to obtain a final bleomycin concentration of 1 mg/ml just before intralesional infiltration. Each wart and the adjacent skin were cleansed with methanol and bleomycin (1 mg/ml) injected intralesionally until blanching of the lesion observed.

In case of  $\geq 10$  warts the large lesions were treated in a single session, the amount of bleomycin into a single wart was limited up to 1 ml and total cumulative injected volume did not exceed 2 ml for treated warts at one treatment session. The treated lesions were covered with sterile dressing and patients were prescribed oral diclofenac (50 mg twice daily) for post-injection site erythema, swelling, and pain for 2–3 days. The patients were asked to return immediately in case of any untoward reaction to treatment and after 2 weeks for paring of black, keratotic eschar formed at injection site and to repeat treatment of residual lesions or previously left over lesions. After completion of treatment period, the patients were followed up every 4 weeks up to 24 weeks after last injection for clinical improvement, recurrence, or any adverse effects. The clinical improvement was evaluated by comparing clinical photographic and patient satisfaction level on Likert scale [Table 1]. Systemic or local adverse reactions such as pain during and after treatment, scarring, pigment changes, Reynaud's phenomenon, tissue/nail damage, itching and skin rash, if any, were noted. Results obtained were analyzed statistically.

## Results and Observations

Table 2 depicts baseline characteristics of study patients. The 32 men and 18 women (M: F = 1.8:1) aged between 14 and 80 (mean  $\pm$  SD 28.5  $\pm$  13.27) years had warts for 1 month to 10 years (median  $\pm$  IQR 12  $\pm$  21 months). The number of warts varied between 1 and 12 (mean  $\pm$  SD 5.8  $\pm$  3.6) and were localized over soles (in 20 patients), palms (in 17 patients), periungual skin (in 3 patients) and multiple sites including skin over dorsal hands and feet (in 19 patients). Prior treatment modalities, alone or in combination, with electrocautery (in 9 patients), 40% salicylic acid in corn-plaster (in 7 patients), topical salicylic acid 12% oint, oral levamisole or intralesional MMR (in 1 patient each) had been unsuccessful.

Complete clearance of warts was observed after first bleomycin session in 16 (32%) patients and they were taken off from further treatment [Figure 1]. All 24 patients with partial response after the first dose showed complete clearance of warts after second treatment session [Figures 2–4]. All patients were followed up every 4 weeks for 24 weeks without further treatment. Two of the seven patients with partial response had complete clearance at 12 weeks. Overall, complete clearance was observed in 42 (84%) patients with no recurrence



**Figure 3c:** They cleared after two sessions of intralesional bleomycin without significant alteration of skin or nail texture. Also note complete clearance of other wart over border of middle finger

and partial response occurred in 5 (10%) patients without recurrence at end of 24-week study period [Table 2]. The response was not different in patients who had received other therapies previously, or having multiple warts. Treatment outcome could not be ascertained in three patients who did not follow up due to outstation assignment. It was also observed that lesions sized  $>10$  mm showed slow regression and most required second treatment session as compared to smaller lesions irrespective of their location over palms/soles or periungual skin. The residual effect of bleomycin for treated warts continued even after discontinuation of treatment. All patients experienced mild to moderate injection site pain for initial 2 days post treatment that did not warrant treatment discontinuation. There was no systemic toxicity or alteration of blood counts, hepatorenal function tests repeated at end of study. Scarring and slight hyperpigmentation noted in a few faded gradually. Periungual bleomycin did not affect nail growth, cause onycholysis or onychodystrophy. All cured patients were very satisfied (overall satisfaction score 5 on Likert scale) with the therapeutic outcome.

## Discussion

The treatment for warts is commonly sought for cosmetic reasons, pain, functional impairment and fear of spread from autoinoculation. Their location over hands is often cosmetically disfiguring and cause of social embarrassment affecting the quality of life. Although not USFDA approved, bleomycin has been used to treat common warts with good results particularly those over hands and feet (including



**Figure 4a:** Multiple warts over dorsal hand and a web space

**Table 3: Cure rates for palmo-plantar warts from intralesional bleomycin therapy**

Reference, year of publication	Treatment schedules/methodology	Cure rates (%)	Remarks
Shumer and O’Keefe, 1983 <sup>12</sup>	I/L 1 mg/ml 2 weeks apart and follow up to 12 months	60	Warts of periungual and other skin areas responded better than plantar warts
Bunney <i>et al.</i> , 1984 <sup>11</sup>	0.5 U/ml I/L at 0, 3, 6 weeks and assessed at 12 weeks	76	Included treatment resistant warts
		66	Extended parallel study included treatment resistant warts
Hayes and O’Keefe, 1986 <sup>21</sup>	I/L 1 U/ml at 0, 3, 6 weeks final assessment at 3 months	76	Included periungual and plantar warts
Amer <i>et al.</i> , 1988 <sup>14</sup>	0.1 ml for <5 mm and 0.2 for >5 mm of 1 mg/ml bleomycin warts 2 I/L injections 2 weeks apart for 8 weeks	47.6	Plantar warts
Sollitto <i>et al.</i> , 1989 <sup>15</sup>	Original study could not be retrieved	32.2	Plantar warts
Shelley and Shelley, 1991 <sup>10</sup>	Two I/L injections 1 U/ml 3 weeks apart and followed up to 6 months	92	All types of warts including plantar warts. Response was irrespective of sites
Munn <i>et al.</i> , 1996 <sup>9</sup>	1 U/ml solution dropped on wart surface and pricked multiple times. Repeated monthly till clearance	92	Included palmo-plantar and periungual warts
Sollitto <i>et al.</i> , 1996 <sup>16</sup>	I/L 1 U/ml at 0, 1 week, 1 month and follow up to 6 months	65.4	Mosaic plantar warts
Agius <i>et al.</i> , 2006 <sup>13</sup>	I/L 1 U/ml by dermojet 5 weeks apart for 25 weeks	89.9	Included recalcitrant palmo-plantar warts
Salk and Douglas, 2006 <sup>19</sup>	I/L 1.5 mg/ml 2 weeks apart and follow up to 6 months	87	Plantar warts
Soni <i>et al.</i> , 2011 <sup>18</sup>	Two I/L injections 2 weeks apart in 1 mg/ml strength. Follow up to 1 year	96.5	Included palmo-plantar and periungual warts
AlGhamdi and Khurram, 2012 <sup>20</sup>	Translesional bleomycin 0.1/ml 4 weeks apart till clearance or development of side effects	74	Included planter warts
AlGhamdi and Khurram, 2011 <sup>21</sup>		86.6	Included periungual warts
Kruter <i>et al.</i> , 2015 <sup>17</sup>	I/L 3 U/ml 3 weeks apart. Follow up to 6 months	74	Warts over hands and feet including planter warts

I/L: Intralesional



**Figure 4b:** Two weeks after first bleomycin treatment and paring



**Figure 4c:** Two sessions of intralesional bleomycin led to their complete clearance. The mild textural skin changes were temporary and normalized during follow-up period

palms, soles), and periungual skin with cure rates up to >96% after one to five treatment sessions by using different

techniques [Table 3].<sup>9-22</sup> Soni *et al.*, showed a high efficacy of intralesional bleomycin (1 mg/ml) in the treatment of 85 palmo-plantar and/or periungual warts. They reported complete resolution of more than 96% warts within 12 weeks

after one or two injections.<sup>18</sup> The response in periungual warts was 100% and 96% in palmoplantar warts. Complete remission in 95 (73%) and partial remission in 31 (24%) warts was reported after intralesional bleomycin by Aziz-Jalali et al.<sup>23</sup> However, they also observed high recurrence in patients who had more warts. Overall, complete cure rate of 84% with no recurrences was observed in our study whereas only 10% patients had partial cure at the end of the study period reflecting significant efficacy of this treatment modality. A comparable cure rate of 87% with need for more than two treatment sessions in 13% of patients was reported by Salk and Douglas.<sup>19</sup> In comparison, Bremner reported a cure rate of 63% while treating 142 warts in 24 patients with intralesional bleomycin.<sup>24</sup> Intralesional bleomycin also effectively cleared periungual warts in this study. This has been reported previously wherein a cure rate of 86.6% in 15 patients with periungual warts was observed at 6 months in patients treated with one or two injections of bleomycin sulfate (0.1 U/ml) by translesional multipuncture technique.<sup>21</sup> Apart from the technique of lesional infiltration, the dose of intralesional bleomycin could be an additional factor that may influence therapeutic outcome. However, Hayes and O'Keefe obtained a cure rate of 78% by using a much lower concentration of intralesional bleomycin.<sup>22</sup> However, our observation that lesions sized >10 mm required a second dose for effective clearance reflects that the size of the wart is an important factor in predicting response rather than its location, duration, number, or dose or technique of bleomycin infiltration. This is perhaps due to difficulty in achieving adequate bleomycin infiltration of large warts, whereby they require repeat treatment sessions.

Intralesional bleomycin was also found to be effective in the treatment of plantar warts, with 60% cure rate and for periungual warts with a 94% rate compared to none with placebo in a double blind controlled trial by Shumer and O'Keefe.<sup>12</sup> Intralesional bleomycin was also significantly more effective than cryotherapy in treating warts in a comparative study wherein clearance rate for intralesional bleomycin therapy was 97% and 87.6% for warts versus 82% and 72.3% for cryotherapy in two separate studies.<sup>25,26</sup> A significantly less number of treatment sessions for bleomycin treatment than cryotherapy were needed. Intralesional bleomycin was highly effective in all 19 patients in this study who had been treated earlier unsuccessfully with different modalities reflecting its superiority. This modality appears to be a safe and effective treatment option in warts without causing systemic adverse effects. Common adverse effects observed were injection site erythema, induration and pain in all patients not warranting discontinuation of treatment. Combining the drug with 2% xylocaine ameliorated immediate injection site pain whereas oral diclofenac in recommended doses was enough for symptomatic relief during post-treatment period. Mild textural skin changes in an occasional patient were temporary and reverted to pre-treatment levels.

## Conclusion

It can be inferred from this study that intralesional bleomycin is an effective and safe treatment option in common warts including palmoplantar and periungual warts. It has advantages of low dose, no significant adverse effects and high patient satisfaction. The methodology followed uses much less bleomycin than the usual systemic dose (30 mg twice weekly) and needs no special puncture needles or technique. Pre-treatment wart size is an important factor in predicting therapeutic outcome. Small number of patients, lack of control group as well as comparison of different bleomycin concentrations, and short follow-up remain some of the limitations. Systematic and large controlled studies will perhaps resolve issues related to bleomycin dose or the regimen that might be needed to achieve clinical cure for warts irrespective of location, size, duration or failure of prior therapies.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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