IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Intralesional bleomycin for treatment of warts: Our experience at a peripheral institute

Prabal Kumar[1]MD, Ayush Sharma[2]• MD

[1]Specialist medical officer, Department of Dermatology, venereology and leprosy, Zonal Hospital, Mandi, Himachal Pradesh, India

[2]Specialist medical officer, Department of Psychiatry, Zonal Hospital, Mandi, Himachal Pradesh, India

Correspondence: Dr Ayush Sharma (E-mail: drayush.sharma90@gmail.com)

Introduction: Warts are benign proliferations of skin and mucosa caused by human papilloma virus (HPV). Over 100 subtypes of HPV are recognized with affinity for different body parts. Warts are generally self-limiting and resolve spontaneously over the period of months to years, hence can be left untreated sometimes. Indications for treatment include pain, functional impairment, cosmetic reasons, and the risk of malignancy[1-4]. There are a large number of treatment options available, including medical modalities (salicylic acid, trichloroacetic acid and photodynamic therapy), surgical and destructive procedures (electrocoutery, laser ablation, cryosurgery, surgical excision), immune-modulators (contact sensitizers, imiquimod, intralesional interferons and oral levamisole, cimetidine or zinc sulfate with variable success[1-6]). There is no treatment proven to be 100% effective. Bleomycin, an antibiotic derived from Streptomyces verticillus, selectively affects squamous cells and reticulo-endothelial tissue. It inhibits DNA and protein synthesis, triggers apoptosis, causes acute tissue necrosis and stimulates an immune response[1]. Intralesional, sublesional, perilesional and translesional multipuncture techniques for bleomycin delivery has been used with variable efficacy[7-10]. Use of intralesional injections of bleomycin has increased widely in recent past and it has proved effective and safe, hence we have conducted this study for evaluation of its use in treatment of warts.

Methods: The study was conducted at Zonal Hospital, Mandi, Himachal Pradesh, India from April 2019 to March 2020. Fifty consecutive patients were enrolled in study having cutaneous warts including common warts, plantar, palmar and periungual warts. Clinical and demographic profile including age, sex, and duration of warts and history of any previous treatment was noted. Investigations including complete haemogram, liver and kidney function tests and serology for HIV were carried out at baseline and end of study. Pregnancy, lactation, age <12 years, immunosuppression due to any disease or drugs were taken as exclusion criteria. Patients requiring more than 2mg of bleomycin injections on a single visit were also excluded. Clinical photographs at each visit were taken.

Methods: The study was conducted at Zonal Hospital Mandi, Himachal Pradesh after obtaining consent from participants.

Procedure: Bleomycin is available in powder form in a vial containing 15 mg of drug. Stock solution was made by adding 5 ml of distilled water. Two parts of lignocaine 2% and one part of bleomycin stock solution was used for injection. Each wart was cleaned with spirit and insulin syringe was used for intralesional injections till complete blanching was achieved. Total dose for injection did not exceed 2 mg at each visit. Patients were prescribed oral diclofenac 50 mg b.i.d for 3 days and oral co-amoxiclav 625 mg t.d.s for 5 days. Patients were followed up at 2 and 4 weeks for paring of eschar and second dose of bleomycin injection. Patients were evaluated at 12 weeks since first injection for clinical outcome. Patients were advised to report immediately in case of any adverse reaction.

Evaluation of clinical improvement: Clinical photographs were taken at baseline; follow up visits and 12 weeks for comparison. Clinical response was graded as: complete clearance, partial clearance and no response.

Results: Out of 50 patients, 42 completed the study comprising 20 males and 22 females, with age between 13 to 61 years. Eight patients did not complete the study. The number of warts varied from 1 to 15, localized over plantar surface in 13 patients, palmar surface in 11 patients, peri-ungual in 5 patients, common warts localized over dorsum of hand and feet in 12 patients and a single patient had mosaic wart located over plantar surface. Twenty-three patients had received treatment for warts in past, including electro-cautery, salicylic acid and lactic acid, oral zinc, corn cap and various homeopathic and indigenous medications. Out of 42 patients, 38 had complete clearance of warts after 12 weeks, 3 had partial clearance and 1 patient did not show any response. It was observed that patients having smaller wart size (<10 mm) showed rapid clearance as compared to patients having larger warts. Number of warts and history of previous treatment did not have any negative impact on final outcome, nor did any systemic disease, as 5 of our patients were diabetic and 3 were hypertensive.

Most common side effect encountered was pain and burning sensation, experienced by every patient at the time of injection. Some patients had pain lasting upto 3 days after receiving injections, however it was managed easily with oral diclofenac 50 mg b.i.d. Hyperpigmentation was seen in 27 patients at the site of injection, which resolved completely in time. Textural changes were seen in 3 patients, which also improved over time. Secondary infection at site of injection was seen in 2 patients, one out of them was diabetic and both were managed with oral antibiotics. A single patient developed mild scarring over dorsum of hand. No nail changes were seen in any of our patients. None of our patients had any hematological or biochemical abnormalities at the end of study and all of cured patients were very satisfied with the final outcome (Likert scale-5)

Table1: Baseline profile of patients

Age		
<20	12	
20-40	21	
>40	9	
Gender		
Male	20	
Female	22	
Site	**n= number of patients**	**n=number of warts**
Plantar	13	40
Palmar	11	31
Periungual	5	11
Common	12	35
Mosaic	1	1
Response to treatment	**Total patients cured n=42(%)**	**Total warts cleared n=118(%)**
Complete clearance	38(90.47)	112(94.91)
Partial clearance	3(7.14)	5(4.23)
No response	1(2.38)	1(0.84)

Table2: clearance of warts at the end of study period

Site	Number	Cleared (%)	Partial (%)	No response (%)
Plantar	40	37(92.5)	3(7.5)	0
Palmar	31	29(93.54)	2(6.45)	0
Peri-ungual	11	10(90.9)	1(9.09)	0
Common warts	35	32(91.4)	2(5.71)	1(2.85)
Mosaic	1	1(100)	0	0

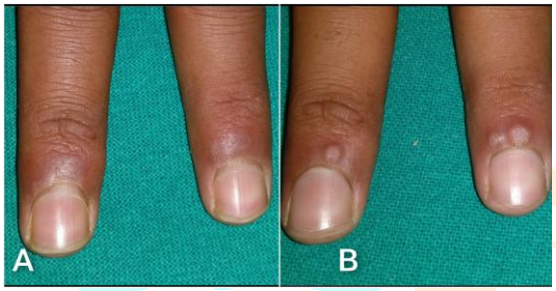

Figure 1: Complete resolution of periungual warts following intralesional bleomycin

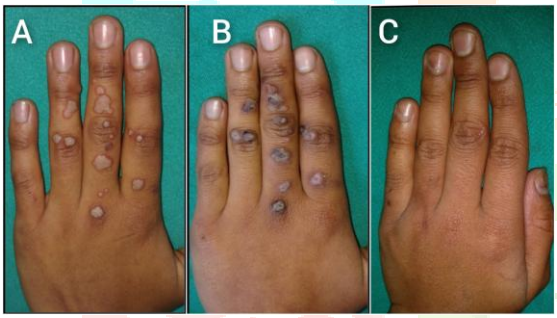

Figure 2: Resolution of warts over dorsum of hand without any skin changes. In second picture(B), eschar following bleomycin injection can be seen.

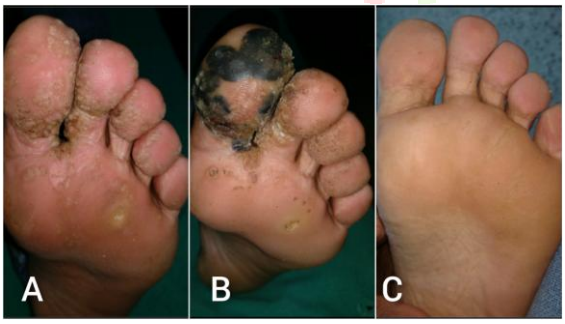

Figure 3: Showing complete clearance of mosaic plantar warts. Eschar following bleomycin injection can be seen. No residual textural or pigmentary changes were seen.

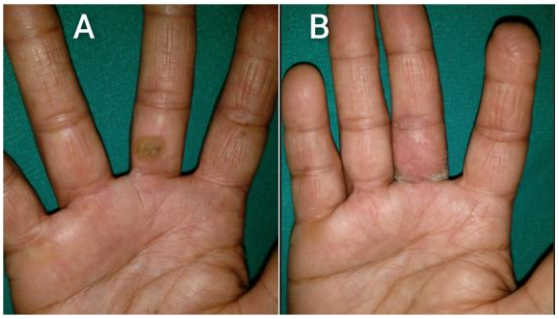

Figure 4: Clearance of palmar wart with minimal textural changes, which disappeared with time.

Discussion: Cutaneous warts are very common infection encountered in dermatology OPD and children aged between 12 to 16 years of age are frequently affected. Most studies do not include children, as warts are mostly self-limiting in children. However, children with treatment resistant warts may be potential reservoirs of transmission of HPV infection.[11] Nevertheless; peri-ungual and plantar warts may be painful and over hand may cause significant cosmetic disfigurement. Most common indications for treatment include pain, cosmetic disfigurement, functional impairment and risk of malignancy. A large number of treatment options are available for warts including medical (Salicylic acid, Podophyllotoxin, Trichloroacetic acid, Formaldehyde, 5-flurouracil, Photodynamic therapy), surgical and destructive methods (Electrocautery, Cryosurgery, Laser ablation, Surgical excision and intralesional bleomycin) and immune-modulators (Topical contact sensitizers, Imiquimod, Intralesional interferons, Intralesional MMR, BCG, PPD and candida antigen, Oral levamisole, Cimetidine, Zinc sulphate). However none has proven to be 100% effective.

Although bleomycin is yet not approved by USFDA for treatment of warts, it has shown excellent results with up to 97% cure rates in some studies (**table 3 and 4**). Concentrations of bleomycin varying between 0.15% and 0.05% have been used for treating warts.[7] Soni et al used intralesional bleomycin (1 mg/ml) to treat 85 palmo-plantar and periungual warts with high efficacy.[15] They observed complete resolution of 82 (96.5%) warts after one or two intralesional injections of bleomycin within 12 weeks.

Table3: Therapeutic outcome following different techniques of bleomycin injection

Technique	**Dosage and schedule**	**Cure - rates (%)**	**Remarks**
Prick with monolet needle[9]	1 mg/mL repeated monthly until clearance of warts	92	Included palmoplantar and periungual warts
Multiple pricks with bifurcate needle[10]	1.0 mg/ml	92	Included periungual and genital warts
Dermojet[12]	1-3 ml bleomycin (1.0 mg/ml)	89.9	Included recalcitrant palmoplantar warts
Pulsed dye laser with bleomycin[13]	Laser 7 mm spot, fluence 10 J/cm2, + Bleomycin 0.5 mg/ml	89	Resistant warts. Immunosupressed patients were also included
Micro-needle patch[14]	Micro needle patch containing 15% bleomycin	61.9	Common warts including plantar warts

Table4: Therapeutic outcome following different intralesional injections of bleomycin

Soni et al[15]	Two injections 2 weeks apart in 1 mg/ml strength and followed up to 1 year	96.5	Included palmoplantar and periungual warts
Sollitto et al[16]	1 mg/ml at 0, 1 week, 1 month and followed up to 6 months	65.4	Mosaic plantar warts
Hayes and O'Keefe[17]	1 mg/ml at 0, 3, 6 weeks final assessment at 3months	76	Included periungual and plantar warts
Amer et al[18]	0.1 ml for <5 mm and 0.2 for >5 mm of 1 mg/ml bleomycin, 2 injections 2 weeks apart for 8 weeks	47.6	Plantar warts
Bunney et al[19]	0.5 mg/ml at 0, 3, 6 weeks and assessed at 12 weeks	76 66	Included treatment resistant warts. In extended parallel study.
Dhar[20]	1 mg/ml 3 weeks apart for maximum 4 injections	97	Efficacy of IL bleomycin and cryotherapy was compared
Shumer and O'Keefe[21]	1 mg/ml 2 weeks apart and followed up to 12 months	60	Warts of periungual and other skin areas responded better than plantar warts
Aziz-Jalali et al[22]	1 mg/ml 4 weeks apart for maximum of 3 doses and followed up for 6 months	73	Included periungual warts

Barkat et al[23]	1mg/ml 2 weeks apart for maximum of 4 injections	69.3	Plantar warts
Unni and Tapare[24]	1 mg/ml 2 injections 2 weeks apart and followed up to six months	93.1	Common warts
Mehta et al[25]	1 mg/ml 2 injections 2 weeks apart and followed up for 6 months	85	Common warts including periungual warts

We found this treatment modality highly effective in treatment of warts, with overall cure rates of 90.47%, partial response was seen in 7.14% patients and a single patient did not show any improvement. Cure rates were of 92.5% for plantar warts, 93.54% for palmar warts, 90.9% for peri-ungual warts, 91.4% for common warts over dorsum of hands and feet. Comparably, Salk and Douglas reported cure rate of 87% with intralesional bleomycin in treatment of plantar warts[28].

In a similar study, cure rates of 85.7% were obtained in peri-ungual warts with one or two treatment sessions of bleomycin sulfate using translesional multipuncture injections[26]. Sollitto et al[16] achieved a cure rate of 67 % in mosaic plantar wart with intralesional bleomycin injection. We had a single patient with similar presentation, who showed complete resolution of wart.

In general, cure rates with intralesional bleomycin (1 mg/ml) by other techniques such as dermojet was 77.5%, while it was 92% with monolet and bifurcated needle prick method in two separate studies[9,10,12]. This variability may be due to inadequate concentration of bleomycin in wart tissue when delivered through bifurcate or monolet needle or dermojet techniques, as some amount of drug remains over the surface of wart with resultant wastage.

The efficacy of intralesional bleomycin in warts has been found superior to placebo, cryotherapy and pulsed dye laser, etc. Shumer and O'Keefe in a placebo controlled double blind study found intralesional belomycin superior in efficacy with cure rates of 60% for plantar warts and 94% for periungual warts[21].

A significantly less number of treatment sessions for bleomycin treatment than cryotherapy were needed in a comparative study wherein clearance rate for warts was 97% and 87.6% for intralesional bleomycin therapy versus 82% and 72.3% for cryotherapy in two separate studies[20,27].

Partial response was seen in 3 patients having 5 warts. It was reported by Bunney et al[19], that some warts may resolve even after discontinuation of therapy due to persistence of drug in tissues, however we were not able to trace our patients for confirmation of this theory.

Adverse effects observed included pain in all patients, not warranting discontinuation of therapy. Bleomycin was diluted with 2% lignocaine for ameliorating immediate injection pain and better patient compliance. Patients were also given oral diclofenac 50 mg twice daily for 3 days. Hyperpigmentation was observed in

27 patients, which was temporary and improved over time. Mild textural changes were seen in 3 patients, which normalize over time. Secondary bacterial infection at injection site was seen in 2 patients including one diabetic patient, which was seen 7 and 10 days after second injection of bleomycin. Both were given oral co-amoxiclav 625 mg three times a day for 5 days and infection was settled.

Conclusion: Intralesional bleomycin appears an effective and safe treatment for warts even at health institute with limited resources, as no specialized equipment is needed unlike cryotherapy or pulsed dye laser. Bleomycin can be easily delivered through insulin needle without need of specialized needles like bifurcate or monolet needle. Moreover the injections were not associated with any systemic adverse effect or hematological or biochemical abnormalities. Also, only two visits are required in most of patients, an advantage helpful in the times of current pandemic.

Limitations: Small study sample, lack of control group, short term follow up and use of only one bleomycin concentration are the main limitations of study.

Funding: No funding sources

Conflict of interest: None declared

References:

1.Lipke MM. An armamentarium of wart treatments. Clin Med Res. 2006;4:273-93

2.Rivera A, Tyring SK. Therapy of cutaneous human papillomavirus infections. Dermatol Ther. 2004;17:441-8.

3.Lichon V, Khachemoune A. Plantar warts: a focus on treatment modalities. Dermatol Nurs. 2007;19:372-5.

4.Dasher DA, Burkhart CN, Morrell DS. Immunotherapy for childhood warts. Pediatr Ann. 2009;38:373-9.

5.Maronn M, Salm C, Lyon V, Galbraith S. One- year experience with candida antigen immunotherapy for warts and molluscum. Pediatr Dermatol 2008;25:189- 92.

6.Brunk D. Injection of Candida antigen works on warts. Skin Allergy News 1999;30:5.

7.Lewis TG, Nydorf ED. Intralesional bleomycin for warts: A review. J Drugs Dermatol 2006;5:499- 504.

8.Sterling JC, Handfield- Jones S, Hudson PM; British Association of Dermatologists. Guidelines for the management of cutaneous warts. Br J Dermatol 2001;144:4- 11.

9.Munn SE, Higgins E, Marshall M, Clement M. A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. Br J Dermatol 1996;135:969- 71.

10.Shelley WB, Shelley ED. Intralesional bleomycin sulfate therapy for warts. A novel bifurcated needle puncture technique. Arch Dermatol 1991;127:234- 6.

11.Bacelieri R, Johnson SM. Cutaneous wart: an evidence based approach to therapy. Am Fam Physician 2005;72:647-52.

12.Agius E, Mooney JM, Bezzina AC, Yu RC. Dermojet delivery of bleomycin for the treatment of recalcitrant plantar warts. J Dermatol Treat 2006;17:112-6.

13.Pollock B, Sheehan-Dare R. Pulsed dye laser and intralesional bleomycin for treatment of resistant viol hand warts. Laser Surg Med. 2002;30:135-40.

14.Ryu HR, Jeong HR, Seon-Woo H-S, Kim JS, Lee SK, Kim HJ, et al. Efficacy of a bleomycin microneedle patch for the treatment of warts. Drug Deliv Transl Res. 2017;8:273-80.

15.Soni P, Khandelwal K, Aara N, Ghiya BC, Mehta RD, Bumb RA. Efficacy of intralesional bleomycin in palmo-plantar and periungual warts. J Cutan Aesthet Surg. 2011;4:188-91.

16.Sollitto RJ, Napoli RC, Gazivoda PL, Hart TJ. Bleomycin sulfate in the treatment of mosaic plantar verrucae. A follow-up study. J Foot Ankl Surg. 1996;35:169-72.

17.Hayes ME, O'Keefe EJ. Reduced dose of bleomycin in the treatment of recalcitrant warts. J Am Acad Dermatol. 1986;15:1003-6.

18.Amer M, Diab N, Ramadan A, Galal A, Salem H. Therapeutic evaluation for intralesional injection of bleomycin sulfate in 14 resistant warts. J Am Acad Dermatol. 1988;18:1313-6.

19.Bunney MH, Nolan MW, Buxton PK, Going SM, Prescott RJ. The treatment of resistant warts with intralesional bleomycin: A controlled clinical trial. Br J Dermatol. 1984;110:197-207.

20.Dhar SB, Rashid MM, Islam A, Bhuiyan M. Intralesional bleomycin in the treatment of cutaneous warts: A randomized clinical trial comparing it with cryotherapy. Indian J Dermatol Venereol Leprol. 2009;75:262-7.

21.Shumer SM, O'Keefe EJ. Bleomycin in the treatment of recalcitrant warts. J Am Acad Dermatol. 1983;9:91-96.

22.Aziz-Jalali M, Ghafarpour G, Rezaei M, Heshmatzadeh Behzadi A, Rohani Nasab M, Nilforoushzadeh M. Efficacy of Intralesional bleomycin in the treatment of resistant warts. J Skin Stem Cell. 2014;1:e18875.

23.Barkat MT, Abdel‐Aziz RT, Mohamed MS. Evaluation of intralesional injection of bleomycin in the treatment of plantar warts: clinical and dermoscopic evaluation. Int J Dermatol. 2018;57:1533-7.

24.Unni M, Tapare V. Intralesional bleomycin in the treatment of common warts. Indian J Drugs Dermatol. 2017;3:73-6.

25.Mehta KIS, Mahajan VK, Chauhan PS, Chauhan S, Sharma V, Rawat R. Evaluation of efficacy and safety of intralesional bleomycin in the treatment of common warts: Results of a pilot study. Indian J Dermatol Venereol Leprol 2018.

26.Al Ghamdi KM, Khurram H. Successful treatment of periungual warts with diluted bleomycin using translesional multipuncture technique: a pilot prospective study. Dermatol Surg. 2011;37:486-92.

27.Adalatkhah H, Khalilollahi H, Amini N, Sadeghi-Bazargani H. Compared therapeutic efficacy between intralesional bleomycin and cryotherapy for common wart: A randomized clinical trial. Dermatol Online J. 2007;13:4.

28.Salk R, Douglas TS. Intralesional bleomycin sulfate injection for the treatment of verruca plantaris. J Am Podiatr Med Assoc. 2006;96:220-5.