

INTRALESIONAL BLEOMYCIN IN TREATMENT OF PLANTAR WARTS

Ayesha Khokhar, Salman Arif, Farrukh Hussain

Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To assess the efficacy of intralesional bleomycin in treating plantar warts.

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: Combined Military Hospital Lahore, from Jan 2015 to Sep 2015.

Material and Methods: The study was conducted in Dermatology outpatient department, Combined Military Hospital Lahore, from Jan 2015 to Sep 2015. Total of 60 plantar warts in 20 patients were treated with 1 mg/ml intralesional injection of bleomycin. Patients received a total of four doses of bleomycin every three weeks, and were followed for next three months. We categorized the response to treatment as complete or partial resolution, and nonresponsive.

Results: Out of 60 warts 46 warts (76.66%) showed complete resolution and 8 (13.33%) warts showed partial resolution ($p < 0.001$). The cure rate was better in warts smaller than 20 mm in diameter in comparison with larger lesions. After six months follow-up, 3 (15%) of the completely resolved warts showed recurrence. Recurrence was more among those with greater number of warts.

Conclusion: Intralesional bleomycin injections were found to be a reliable, safe and acceptable mode of treatment for plantar warts.

Keywords: Bleomycin, Intralesional, Plantar warts.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Warts are rough papules of varying textures and sizes that can be found on any keratinized cutaneous and non-keratinized epithelial surface¹. These are caused by human papillomavirus (HPV)². There are several types of this virus with affinity for different sites of the body. Overall incidence of warts is approximately 150 per 100,000³. Depending on the type of HPV and the site of infection, different clinical variants of warts are seen⁴. Plantar warts, also known as verruca plantaris⁵ were caused by HPV-1, 2 & 4 occurring on the sole or toes of the foot. Diagnosis is usually based on clinical examination⁴. Although most warts disappear spontaneously within three years⁶ but treatment is generally recommended to lessen pain, decrease duration, and reduce transmission. Several therapeutic approaches have been used to treat warts, but some evidence of resistance to therapy has been

observed in many cases^{7,8}. None of the treatments is completely curative for warts and different types of treatments may be combined⁶.

Bleomycin is a cytotoxic drug which binds with deoxy-ribonucleic acid, causing strand scission preventing cell replication⁹. Although intralesional bleomycin is not generally used in treating cutaneous warts in our country, however it has been used abroad since 1970s for the same^{10,11}. There are several reports published on the use of intralesional bleomycin for the treatment of warts, with cure rates ranging between 14% and 99%¹¹.

This study was designed primarily to assess the evidence for the efficacy of intralesional bleomycin in treating plantar warts and also to see the outcome in terms of duration of treatment in each case and identify side effects, if any, due to this drug.

MATERIAL AND METHODS

This descriptive cross-sectional study was conducted at Dermatology outpatient department, Combined Military Hospital, Lahore from

Correspondence: Dr Ayesha Khokhar, Consultant Dermatologist, PEMH Rawalpindi Pakistan

Email: ayesha.dermatologist@gmail.com

Received: 17 Mar 2017; revised received: 05 Oct 2017; accepted: 21 Feb 2018

Jan 2015 to Sep 2015. Clinically diagnosed plantar warts of more than 2 weeks duration of the patients of either gender and age ≥ 18 years, without any history of previous treatment, were included in the study. Warts of pregnant women and of patients with history of any systemic illness were excluded from this study. By using WHO sample size determination calculator 60 warts of 20 patients were included in the study through non-probability purposive sampling, after informed written consent and permission

stored at 4-8 degree Celsius for 2 months. Two percent lignocaine and this bleomycin solution were taken in an insulin syringe in a ratio of 2:1, making the resulting concentration of 1mg/ml. Each plantar wart and the adjacent skin was cleansed with alcohol swab. According to need, some warts were scrapped superficially to remove callus surrounding the wart. Injection bleomycin 1mg/ml was given intralesionally with blanching of the lesion as end point. Depending on the size of each wart, an adequate

Table-I: Description of type of warts (n=60).

Types of warts	Frequency (%)
Common warts	57 (95)
Mosaic warts	1 (1.66)
Flat warts	2 (3.33)

Table-II: Cross Tabulation of relation of wart size to response to treatment.

Wart size	Response			p-value
	No	Yes	Total	
≤ 20 mm	1	53	54	<0.001
> 20mm	5	1	6	
Total	6	54	60	

Fisher exact value is less than 0.05 ($6e^{-06}$)

Table-III: Cross-tabulation of relation of number of warts and recurrence.

No of warts	Warts Recurrence			p-value
	No	Yes	Total	
1-2	30	0	30	0.037
3-7	13	3	16	
Total	43	3	46	

from Hospital Ethical Committee.

Warts were diagnosed through clinical examination. Disease history and physical examination were recorded on a specially prepared proforma. Disease history included age of onset and duration of warts while physical examination included the clinical type, size (diameter in mm) and number of plantar warts. Complete resolution was considered as disappearance of clinical wart and/or post inflammatory pigmentation at treated sites, partial response was a 90% reduction in original size of the wart, whereas <90% reduction was taken as a non-responding wart.

Bleomycin vials contain 15 mg powdered drug. It was first diluted with 5ml distilled water to make a solution of 3mg/ml which could be

amount of injection was given, limiting the total volume injected per wart to 1ml and per sitting to 2ml maximum dose. Patients were reviewed after 1 week of injection. An ecchymosed eschar developed at the treatment site, which was scraped off. Injections were repeated every three weeks up to three months according to clinical response. Patients were followed up weekly for first three weeks, every three weeks up to three months and then monthly upto six months.

The data was analyzed using SPSS version 20. Descriptive statistics were used to describe the results i.e. mean and standard deviation for quantitative variables while frequency along with percentages for qualitative variables. Fisher's exact test was applied to study the association of

response to treatment with different variables. A p -value<0.05 was considered to be significant.

RESULTS

Sixty plantar warts of various types (table-I) of twenty patients were included in the study. Average age of patients was 30.84 years (SD= 8.97) and majority of patients i.e. 18 (90%) were males. Average age at onset of plantar warts was 27.3 years (SD=3.15). Average duration of plantar warts was 3.7 weeks (SD = 1.5). Total 60 warts were studied, varied from 1 to 7 in each patient with average no. of warts 2.9 (SD=2.1). Warts size ranged from 4 to 26 mm. Majority of warts i.e. 48 (80%) had size between 11 to 20 mm.

Out of 60 warts, 46 (76.7%) warts showed complete resolution and 8 (13.3%) warts showed partial resolution and 6 warts did not heal at all (fig-1). Frequency of complete resolution was significantly higher than no response. Response to the treatment was significantly associated with the size of the warts ($p=0.001$) as the effect of treatment decreased gradually as the size of the warts increased (fig-2, table-II). Most of the patients (55%) experienced some pain during injection which was although of short duration but 7 (35%) needed oral analgesic tab Mefenemic acid 250mg three times a day for three to five days, for pain relief.

At six months follow-up, 3 (15%)warts showed recurrence. Recurrence was seen among those with greater number of warts (3-7). Therefore, those with fewer warts (1-2) were associated with complete recovery and no recurrence ($p<0.037$) (table-III). During six months of follow up, it was observed that the treated warts regressed in size. No scarring but some post inflammatory hyper pigmentation was observed at treated sites. No patients developed any signs of systemic toxicity of the drug.

DISCUSSION

Although literature claims warts, a self-limiting disease but in actual practice it is seen that they are quite difficult to treat and may even be resistant to repeated treatments with various physical modalities. Although there is no specific

antiviral treatment for HPV, a few drugs may have some role in interfering its life cycle. The most common approach is to destroy the HPV infected epithelium. Different studies have shown variable results with ectrocautery, cryotherapy and CO2 LASER¹⁴.

Bleomycin is a cytotoxic drug used as systemic chemotherapeutic agent in Hodgkin’s lymphoma and testicular cancer, but it has been

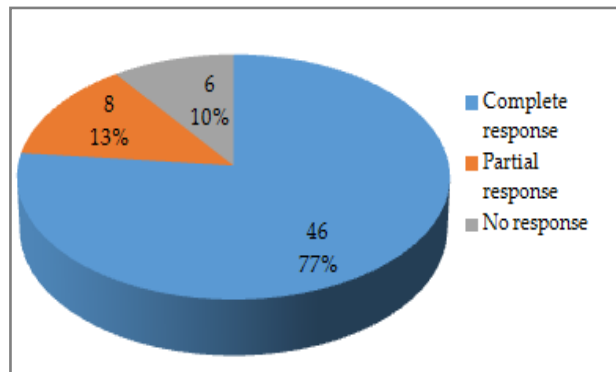


Figure-1: Description of response to treatment (n=60).

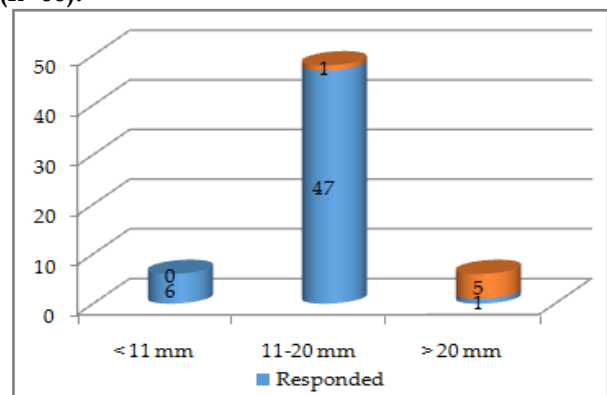


Figure-2: Response to treatment in association with the size of warts.

used as a therapy for warts for many years. It causes DNA strand scission, thus preventing cell replication. Bleomycin is primarily excreted from the body through kidneys. It can also be inactivated in vivo by hydrolase enzymes, whose levels vary in different tissues. Skin has very minimal amounts of this enzyme, because of which injection is given in a much diluted form in order to prevent any chance of systemic toxicity.

In one study on 50 patients, half were treated with intralesional bleomycin while the rest were

given intralesional saline injections. Ninety Six percent of warts treated with bleomycin cleared, while only 11% of warts treated with saline showed clearance at 3 months¹⁵. Another study, which compared the response of wart treatment with bleomycin with saline as control, reported clearance of 58% of bleomycin treated warts compared with 11% of the control cases¹⁶. A few previous studies on treatment of plantar and peri-ungual warts with intralesional bleomycin injections have shown excellent results^{16,17}. No systemic side effects have been observed using it at a dilution of 1mg/ml¹⁸.

In our study, we observed the efficacy of bleomycin in treating plantar warts which are in general considered difficult to treat with other modalities. We have shown a 77% cure rate in our study, which is comparable to the results in a similar study by Salk and Douglas¹⁹. A double-blind placebo-control study was conducted by Shumer and O'Keefe in 1983, in which 151 warts were treated with intralesional bleomycin whereas 55 warts were treated with intralesional saline. Their study showed a cure rate of 60% for plantar and 94% for peri-ungual warts in the bleomycin treated group⁹. Our study has shown a higher cure rate of plantar warts than that in the above mentioned study. Seventy two percent of plantar warts treated with bleomycin, in a study by Olson, were cured compared to 27% of similarly treated warts with placebo²⁰. Since Olson in his study used Dermojet instead of intralesional injections, some scattering of the solution resulting in comparatively lesser dose being delivered, could explain the lower cure rates¹⁹. Bremner reported a cure rate of 63% when he treated 142 warts in 24 patients with intralesional bleomycin²¹. In a study by Shelly and Shelly in which intralesional bleomycin was used to treat warts, reported a cure rate of 92% which is comparable to our results²². In a few of these studies side effects to intralesional bleomycin observed were, dyspigmentation, scarring, nail damage and rarely Raynaud's phenomenon . Bleomycin has been used in

concentrations of 0.05% and 0.15% to treat warts²⁴.

In our study, pain at injection site was the only complication we observed and started in 17 (85%) patients, in the first to second day after injection. Seven patients (35%) had severe pain and needed to take oral analgesics, which proves the safety of this treatment method. The solution prepared in our study was diluted with 2% lignocaine which reduced localized pain during and after injection. The limitations of the present study are the lack of control group and limited follow-up period which was mainly due to patient compliance issues after achieving cure.

Bleomycin therapy requires less equipment, has less storage and transport issues compared to those for liquid nitrogen used for cryotherapy. Besides this injection can also be used in areas where liquid nitrogen is not available. We recommend bleomycin as a more suitable treatment for peripheral practice considering its efficacy and better side effect profile in treating warts.

The results of our study also highlighted the importance of pretreatment wart size as an important factor in predicting response to treatment. We also observed higher recurrence rate in patients who had more warts, which should be considered in patients' follow up visits.

CONCLUSION

Intralesional bleomycin injections were found to be a reliable, safe and acceptable mode of treatment for plantar warts.

Author's Contribution

All authors meet the four mandatory authorship criteria according to ICMJE guidelines.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Lowy DR, Androphy EJ. Warts. In: Freedberg IM, Eisen AZ, Wolf K, Austen KF, Goldsmith LA, Katz SI. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York, McGraw-Hill 2003; 4: 2119-30.

2. Dall'Oglio F, D'Amico V, Nasca MR, Micali G. Treatment of cutaneous warts: An evidence-based review. *Am J Clin Dermatol* 2012; 13(2): 73-96.
3. Health protection agency. A complex picture. HIV and other sexually transmitted infections in the United Kingdom: 2006. Available from: <http://www.hpa.org.uk>.
4. James WD, Berger TG, Elston DM. Viral Diseases. In: James WD, Berger TG, Elston DM. *Andrews' diseases of skin: Clinical dermatology*. 10th ed. Philadelphia, Saunders Elsevier. 2006; 403-15.
5. Dolezel M, Drahansky M, Urbanek J, Brezinova E, Kim T. Influence of Skin Diseases on Fingerprint Quality and Recognition: New Trends and Developments in Biometrics. *Dr. Jucheng Yang Ed.* 2012; 10: 5772-80.
6. Nasser N. Treatment of common warts with the immune stimulant Propionium bacterium parvum. *An Bras Dermatol* 2012; 87(4): 585-9.
7. Mulhem, Elie, Pinelis, Susanna. Treatment of non-genital cutaneous warts. *Am Fam Physician* 2011; 84(3): 288-93.
8. Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. *Br J Dermatol* 2011; 165: 233-46.
9. Shumer SM, O'Keefe EJ. Bleomycin in the treatment of recalcitrant warts. *J Am Acad Dermatol* 1983; 9(1): 91-6.
10. Dobson JS, Harland CC. Pulsed dye laser and intralesional bleomycin for the treatment of recalcitrant cutaneous warts. *Lasers Surg Med* 2014; 46(2): 112-6.
11. 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(3): 262-7.
12. 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(3): 188-91.
13. Asghariazar R, Ghadim HH, Babaeinezhad S, Nobahari S. The Comparison Study of 5 Fluorouracil vs. Cryotherapy in the treatment of the backhand resistant common wart. *Our Dermatol Online* 2014; 5: 258-60.
14. El-Refaei, Asmaa M, EL-Rahman A, Sherine H. Citric acid 50% solution versus tretinoin 0.05% lotion in the treatment of plain Warts. *J Egyptian Women's Dermatol Society* 2015; 12: 113-9.
15. Goldberg DJ, Beckford AN, Mourin A. *Verruca vulgaris*: Novel treatment with a 1064 nm Nd:YAG laser. *J cosmet laser ther* 2015; 17(2): 116-9.
16. Mohamad NS, Badran F, Yakout E. Evaluation of the efficacy of a combination measles, mumps and rubella vaccine in the treatment of plantar warts. *Our Dermatol Online* 2013; 4(4): 463-7.
17. Aguis E, Mooney JM, Bezzina AC, Yu RC. Dermojet delivery of bleomycin for the treatment of recalcitrant plantar warts. *J Dermatolog Treat* 2006; 17(2): 112-6.
18. 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(3): 188-91.
19. Salk R, Douglas TS. Intra lesional bleomycin sulfate injection for the treatment of verruca plantaris. *J Am Podiatr Med Assoc* 2006; 96(3): 220-5.
20. Olson RL. Plantar warts yield to DNA inhibitor. *JAMA* 1977; 237: 940-94.
21. Bremner RM. Warts: Treatment with intralesional bleomycin. *Cutis* 1976; 18: 264-6.
22. Shelley WB, Shelley ED. Intralesional bleomycin sulfate therapy for warts: A novel bifurcated needle puncture technique. *Arch Dermatol* 1991; 127(2): 234-6.
23. Yang F, Qin X, Cheng Z, Xie S. Intralesional pingyangmycin treatment for resistant plantar warts. *Dermatol* 2010; 220(2): 110-3.
24. Martinez C, Miguel F. Results of a combination of Bleomycin and Triamcinoloneacetone in the treatment of Keloids and Hypertrophic scars. *An Bras Dermatol* 2013; 88: 387-94.