J Skin Stem Cell. 2014 May; 1(1): e18875. DOI: 10.17795/jssc18875

Published online 2014 May 15. **Research Article**

Efficacy of Intralesional Bleomycin in the Treatment of Resistant Warts

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Received: November 10, 2013; **Revised:** March 10, 2014; **Accepted:** March 15, 2014

Background: Warts are benign tumors of the skin and mucosa and are caused by human papilloma virus (HPV). They are one of the most common skin diseases found mainly in children and adolescents. Although most of the warts disappear spontaneously or respond to the usual therapeutic measures, resistant forms of the warts impose a problem in dermatology. Intralesional injection of bleomycin has been tried in the treatment of resistant warts with variable results in different studies.
Objectives: This study aimed to assess the efficacy of intralesional injection of bleomycin in resistant warts.
Patients and Methods: In this cross-sectional study, a total of 130 warts in 30 patients were treated with 1 mg/mL intralesional injection of bleomycin. Patients received one to three doses of bleomycin every four weeks, and were followed for six months. Response to the treatment was categorized as complete resolution, partial resolution, and nonresponsive. We employed SPSS version 13 to perform t test and analysis of variance (Anova) as statistical methods for analyzing the data.
Results: Out of 130 warts, 126 (97%) cases showed resolution after bleomycin injections. Ninety-five warts (73%) showed complete resolution and 31 (24%) cases showed incomplete resolution. The cure rate (80%) was better in warts with the size smaller than 20 mm in diameter in comparison with larger lesions (46%). After six months follow-up, 7 patients showed recurrence. Recurrence was seen more among those with greater number of warts.
Conclusions: This form of treatment for resistant warts would be reliable, safe, and acceptable to the patients if it is performed under care and with proper dose and concentration.

*Keywords:*Bleomycin; Injections, Intralesional; Papilloma Virus

1. Background

Warts are the tumor shaped lesions caused by human papilloma virus (HPV); they are polymorphic lesions that infect different areas of the skin and mucous membranes, especially palms, legs, face, trunk, genital mucosa, mouth, larynx, and the cervix (1). The prevalence of common warts is high in children between 12 to 16 years of age. The prevalence usually shows a significant decrease after the age of 20.

The most common indications for the treatment of common warts include pain, functional impairment, cosmetic reasons, and the risk of malignancy (2). Although two-thirds of common warts heal spontaneously within two years, elimination of warts is the most common treatments because of the aforementioned reasons. However, the treatment method should not harm the normal skin or leave a scar. Several therapeutic approaches have been used to treat warts, but resistance to therapy has been observed in these lesions (1-3).

Bleomycin is an anticancer drug that is derived from *Streptococcus verticillus* (4). It inhibits cell cycle at G2 phase and causes destruction of the tumor cells by DNA fragmentation, RNA degradation, and simultaneous free radicals production. Systemic use of this medication poses more toxic effects on lung and skin.

If the total dose reaches 200 to 300 mg, it might lead to skin side effects. Pulmonary complications increases if the therapeutic daily dose exceeds 400 mg. Nevertheless, regarding the low dose of topical form, utilization of the drug does not cause systemic side effects as seen in systemic use; however, local signs such as necrosis, pain, Raynaud's phenomenon, and nail dystrophy may occur in some cases (5).

Although warts are essentially benign in nature, treatment of the resistant cases is necessary in more serious cases. Studies on the treatment of warts are highly variable regarding the methods and materials as well as the

Implication for health policy/practice/research/medical education:
With regard to the different results reported about this treatment, the present study aimed to evaluate the efficacy of this method on resistant warts including its effect on lesion size in different parts of the body.

quality of the study, like limited evidences, especially placebo-controlled studies.

In most studies, intralesional bleomycin injection has not been considered as the first-choice of the treatment in regular warts and utilization of this method has been limited to resistant cases that did not respond to conventional methods (6). Bleomycin application was mostly done by drug injection into the lesion by syringes, but other methods like using dermojet (7), prick method (8, 9), dermatographic method (10), and using pulsed dye laser before bleomycin injection (11) have been also reported in some studies.

The effect of bleomycin injection in resistant warts has been evaluated in several studies. In some studies, this treatment has been rejected (12); however, the usefulness of this method have been reported in other studies. Healing rate has been 14% to 99% in different studies, but the effectiveness of the treatment has been reported mainly in two-thirds of cases (3, 6, 10, 13, 14).

2. Objectives

Regarding the different results available and doubts about the effectiveness of this treatment, the aim of the present study was to evaluate the efficacy of this method on warts resistant to treatment including its effect on lesion size and location in different parts of the body.

3. Patients and Methods

In this retrospective and cross-sectional study, 34 patients with nails, hands, and feet warts –resistant to conventional treatment methods – were assessed. These patients were referred to private dermatology clinics from September 2005 to March 2006. They were considered for treatment in collaboration with dermatology professors of Iran University of Medical Sciences. Of these patients, four withdrew their treatment after the first treatment session and the remaining 30 patients continued for three months and were monitored one month after the last treatment session.

Patients were 15 to 35 years old and consisted of 21 males and 9 females. The total number of warts was 130 and varied from 2 to 21 in each patient (mean 2.6 ± 2.3). All warts were resistant to normal treatment methods, appeared on the skin from eight months to four years prior to the study, and had shown no improvement after trying different treatment methods. Seventy-two warts were located around the nails, while 31 were in palms and soles, and 27 had developed on fingers and toes. Warts size ranged from 4 to 26 mm. There were 39, 63, and 28 warts with the size smaller or equal to 10 mm, between 11 mm and 20 mm, and larger than 20 mm, respectively.

3.1. Injection Method

Each bleomycin vial contained 15 mg of the medication in dry form and each milligram contained 1.5 to 2 units of active bleomycin. Each vial was dissolved with 5 mL of distilled water. Thus, each milliliter contained 3 mg of the drug. Then, we mixed each 1 mL of the solution with 2 mL lidocaine 1%, so that each milliliter contained 1 mg of the drug.

Patients underwent the standard injection protocol recommended by Hayes. Injection was performed with insulin syringe directly into the warts until the color of lesions turned into white. In small warts, injection was done once using 0.1 mL and in the larger warts, the injected drug did not exceed 0.2 to 0.3 mL in various points of the warts. Maximum total dose for each patient per session was less than 2 mg and the interval between injections was approximately four weeks.

After the injections, the patient would experience pain, bruises, and thrombosis. During next two weeks, degeneration or healing of the lesions was expected. In some patients, the pain was so severe that using analgesic would be necessary. The data was analyzed by SPSS version 13 statistical software (SPSS Inc. Chicago, Illinois, USA). The student's t test and analysis of variance (ANOVA) were employed for statistical analysis. In all tests, a P value < 0.05 was considered statistically significant.

4. Results

At the end of the study, 126 out of 130 warts responded to the treatment; 95 cases (73%) showed complete remission, 31 (24%) had partial remission, and in 4 (3%) cases the only reaction to the treatment was pain and swelling at the injection site.

The highest detected cure rate was for the warts around the nails (all 72 warts) followed by hands and feet (25 out of 27). The complete resolution was observed after the first, second, and third injections in 32, 44, and 19 cases, respectively. Partial recovery after three injections was observed in 31 cases.

Pain was reported in 26 (86%) patients, especially during the first and second day after injection. Seven patients had severe pain and needed oral analgesics, while 19 patients experienced moderate pain. Thrombosis started about 36 hours after the injection and continued for the next seven days that led to crust formation and lesion destruction. The degree of thrombosis was associated with the healing success.

Six months after the last injection of the 30 patients, 8 of them had more than 15 warts, 7 (23%) patients experienced recurrence of warts in the same or other parts of the body; therefore, those with fewer warts were associated with complete recovery and lower recurrence rate ($P = 0.04$). No patient developed adverse systemic or local complications as a result of the treatment. The effect of bleomycin injection and its association with the lesion size are shown in Table 1. This effect decreases gradually as the size of the warts increases (up to 20 mm), which is statistically significant ($P = 0.02$).

Table 1. Response to the Treatment in Warts

Wart Size, mm	Complete Cure	Partial Cure	No Cure	Total
≤ 10	31	7	1	39
11-21	51	11	1	63
> 20 (numerous lesions located in a site)	13	13	2	28
Total	95	31	4	130

5. Discussion

In this study, we observed response to treatment in 97% and complete remission in 73% of warts resistant to treatment. This study showed that intralesional bleomycin injection could be advised as an effective treatment for resistant warts. Considering the different number and location of the warts in every patient, like some other similar studies, this study focused on the warts and their response to the treatment.

Regarding the 46% complete cure rate in warts larger than 20 mm versus 80% cure rate in warts smaller than 20 mm in diameter, it seems that the size of the wart before the treatment is an important factor in predicting response to the treatment. On the other hand, we observed higher recurrence rate in patients who had more warts, which should be considered in patients' follow-up visits.

Drug concentration, injection times, frequency and duration of treatment, and follow-up period were similar to the previous studies (12-15). In this study, pain at injection site was the only complication and started in 26 (86%) patients, in the first to second day after injection. Seven patients had severe pain and needed to take oral analgesics, which proves the safety of this treatment method. In this study, no significant difference was detected with regard to the lesion location and response to treatment.

In previous studies conducted in our country (15), this method was introduced as an effective method, especially after two sessions of injection in most patients, and few patients experienced wart relapse after two injections. The study also pointed that necrosis and pain were considered as a complication of this treatment. In more recent studies, like Salk et al. study (13) the cure rate was reported 87% after two injections although 13% of patients needed more than two injection sessions.

Besides, in Price study, the efficacy of this treatment was reported variable regarding the number of injections. In the study performed on 224 lesions, in 211 patients, 6.47%, 8.38%, and 8.9% of patients responded to one, two, and three injections respectively. In this study, less than 2% of patients had chemical cellulitis caused by injection. Sterile abscess hyperpigmentation at injection site were reported in 1% and the 0.5% of the patients respectively ,which introduced this method as a reliable treatment with low complication (16).

Given the above findings, bleomycin injection for treatment of resistant warts is a preferred method in comparison with the other conventional methods such as using salicylic acid 40% in petroleum jelly, salicylic acid-lactic acid in collodion, trichloroacetic acid (TCA) 50%, cryotherapy by liquid nitrogen or carbon dioxide, and topical or oral retinoid acid (1-3).

The limitations of the present study are the lack of control group and short-time follow-up of the patients (not more than six months), which was mainly due to defects in follow-up process and also lack of patients compliance to complete the follow-up period.

Although warts are polymorphic and self-limited lesions, in some cases they may be very resistant and recurrent. Various conventional treatments would not be able to destroy these lesions completely. In such cases, bleomycin can be utilized with precaution (regarding the 97% cure rate resulted in our study) by the experienced physician with providing information pertaining to its probable side effects.

Acknowledgements

There is no acknowledgment.

Authors' Contribution

All authors participated equally in this study.

Financial Disclosure

There was no financial disclosure for the research.

Funding/Support

There was no funding support for the research.

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