

The efficacy of intralesional bleomycin in the treatment of recalcitrant warts: an open therapeutic trial in Iraq

Ahmed Yahya Abbas^{1*}; Mustafa Hazim Ahmed² and Hiba Hikmat Maqdasi³

Dermatologist and veneriologist, CABD, Marjan medical city, Babil, Iraq.¹
Dermatologist and veneriologist, CABMS, Al-Kindy teaching hospital, Baghdad, Iraq.²
Dermatologist and veneriologist, FICMS, Al-Kindy teaching hospital, Baghdad, Iraq.³
Corresponding Auother* ahmed_yahya87@yahoo.com mobil : 0096407704593693

Declarations:

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Conflict of interest:

The authors assert that there is no conflict of interest.

Contributions:

- 1) Ahmed Yahya Abbas collected data, drafted and wrote the manuscript, interpreted and discussed the results. Also oversaw the final version of the paper and agreed to be (corresponding author).
- 2) Mustafa Hazem Ahmed designed the study and participated in data collection.
- 3) Heba Hikmat Al-Maquadisi critically reviewed the manuscript to evaluate the content.

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Ethics approval and consent to participate:

After relying on the protocol prepared by the Ethics Committee of Al-Kindi Teaching Hospital, Iraqi Ministry of Health. Research approval obtained. In addition Approval was taken from Dermatology Scientific Committee of Arab board. Confidentiality was assured with informed consent from all the patients.

Abstract

Background:

Aesthetically, warts effect on face and hands duo to great discomfort to the patient. The common treatment methods cause pigmentary changes and scarring. Moreover, recurrence of infection. Because bleomycin is considered an anti-tumor agent, this project is considered a pioneering study in Iraq to evaluate the efficacy of bleomycin intralesional in treating intractable warts.

A total of 23 patients with (104) rebellious warts were treated with intralesional bleomycin. The response to treatment was followed after 2 weeks, 1 month and 3 months. The follow-up method was calculated by a special recording system (no response = 0), (response = 1) and (complete recovery = 2).

Results:

Results showed at 2 weeks follow up (13.1%) of the palmoplantar, (19.4%) of the periungual and (25%) of the other sites warts improved to score 1. After 1 month the score 1 response for palmoplantar, periungual and other sites warts were (39.2%), (41.9%) and (25%) respectively, while the score 2 response for palmoplantar, periungual and other sites warts were (30.4%), (32.3%) and (75%) respectively. After three month, reaction in periungual and other sites warts is 100%, whereas in palmoplantar warts were 94.2% with a total response rate of 96.1 % according to the scoring system.

Conclusion:

Our findings suggest that Bleomycin is significantly effective in the medication for insurgent warts. It's safe and free of side effects apart from minimal local pain with no recurrence rate of warts after bleomycin treatment.

Keywords: Bleomycin, Warts, Palmoplantar, Periungual, Recalcitrant warts.

Introduction:

The human papilloma virus (HPV) belongs to the family of Papovavirida genera and is widespread in many countries of the world^{1,2}. One of the most common effects caused by this virus is the skin warts in many locations which are often polymorphic, warts is benign tumors are resulting from infection of the keratinocytes³. Cutaneous warts happen at diverse age but are exceptional in infancy stage and school age⁴.

According to age, the extent raise over the school years to reach a crest in puberty, then recede out of the second decade of life, and more gradually thereafter⁵. For infection to manifest, it should secure direct or indirect contact due to virus particle needs to pass into contact with a stem cell in the basal epidermal layer^{6,7}. Consequently, trauma such as slight abrasions causes the entry of the virus within body due to the impairment of the epithelial barrier function of the skin⁸. In some cases, warts may diffusion exceedingly like in peoples who gnaw their nails or/and periungual skin, during shaving, sexual contact and in a genitor- urinary medicine clinic by check-up tools⁹. On the other hand, Individuals with decline immunity are especially receptive to HPV infection like renal diseases and organs transplant patients which immunosuppressive therapy, these patients have contagion possess highly resistant to treatment^{10,11}.

The presence of warts on face and hands often causes pain; weaken function in addition to psychological harm to patient. Moreover, many of the methods that are being used nowadays in Iraq do not give sufficient effectiveness to remove warts permanently, and these methods usually cause scarring and change in skin color. bleomycin is considered an anti-tumor agent, it appears to be a favorable treatment for warts as it has unique healing properties that contribute to eliminating it, including its ability to adhere to squamous cells and to break off DNA strands . This study is designed to evaluate the efficacy of intralesion bleomycin in treating intractable warts.

Patient and Methods:

Study design and setting:

This is an open therapeutic trial conducted in dermatology department in Al-kindy Hospital in Iraq over the duration from 1st of June 2018 to 1st of December 2018. For adult patients (more than 15 years) with a common warts for more than six months. A total of 23 patients (5 man and 18 woman, mean age was 24.2 -24.4 years respectively) with multiple recalcitrant common warts 104 lesions at different locations as illustrated in table (1).

Table (1): Distribution of warts among patients

Pattern of warts	No. (%)
Palmoplantar	69 (66.3%)
Periungual	31(29.8%)
Other sites	4 (3.9%)
Total	104(100%)

Bleomycin is obtainable in vials 15U from a Celon labs company. In the present experiment the vial was diluted as a first step with 5 ml (2% lidocaine) for increase the pain relief effect, to make the stock solution.

The storage time for this solution was approximately 2 month at 4-8 °C, then we taken 2 parts of 2% lidocaine and 1part of a previously prepared bleomycin stored solution in an insulin syringe (1 ml G30), so that the last concentration 1U/ml 12. Each verruca and near skin were disinfected with "isopropyl alcohol" and then anesthetized inside the lesion with 2% lidocaine solution. In order to remove the thick layer covering the wart a superficial peeling was performed. The new solution was injected harshly into the lesion until bleached, the bleeding place were not reach. The injection administered rely on the wart's size: up to 5 mm, 10 mm and more received 0.1 ml, 0.2 ml and 0.3 ml, respectively. The overall volume of bleomycin injected was 2 ml, while injection of a single wart was 1 ml.

Assessment and follow up:

- 1- Patients were instructed to use oral analgesics (NSAIDs) and topical antibiotics (fusidic acid) for two weeks.
- 2- The patients were assessed clinically to see the response of each wart after bleomycin therapy and scoring system done as follows: no response=0, improved (reduce thickness or size) =1 and Cured (disappearance of lesion) =2. The patients were followed up after two weeks, one month and three months of the treatment period.

Statistical Analysis:

The data were analyzed by Statistical bundle for Social Sciences (SPSS). Pearson's Chi-square test was used to determine the reaction of warts to bleomycin. P-value <0.05 were deeming significant.

Results:

After 2 weeks of treatment showed improvement in only 16 (15.4%) of the warts, but after one month the total response (score1+ score2) was 75 (72.2%). While the final evaluation after 12 weeks showed that the total response (score1+ score2) was 100 (96.1%), P-value was

0.0001. In the final treatment period, only 4 lesions were resistant to bleomycin according to the scoring system as shown in Table (2).

Table (2): Response rate of warts during the treatment according to the scoring system

Follow up time	Score 0*	Score 1**	Score 2***	Percentage of total Score 1+2****
Baseline	104	0	0	0%
2 weeks	88(84.6%)	16(15.4%)	0	(16)15.4%
1 month	29(27.8%)	41(39.4%)	34(32.8%))57(72.2%
3 month	4(3.8%)	13(12.5%)	87(83.7%))000(96.1%

* No response, ** response, *** complete recovery, **** P-value = 0.0001

In addition, the table (3) shows the results of the follow-up of three lesion types (Palmoplantar warts, periungual warts and other sites warts). At 2 weeks follow up time only 9 lesions (13.1%) of the palmoplantar warts, 6 lesions (19.4%) of the periungual warts and 1 lesion (25%) of the other sites wart improved to score 1 as illustrated in fig.1.

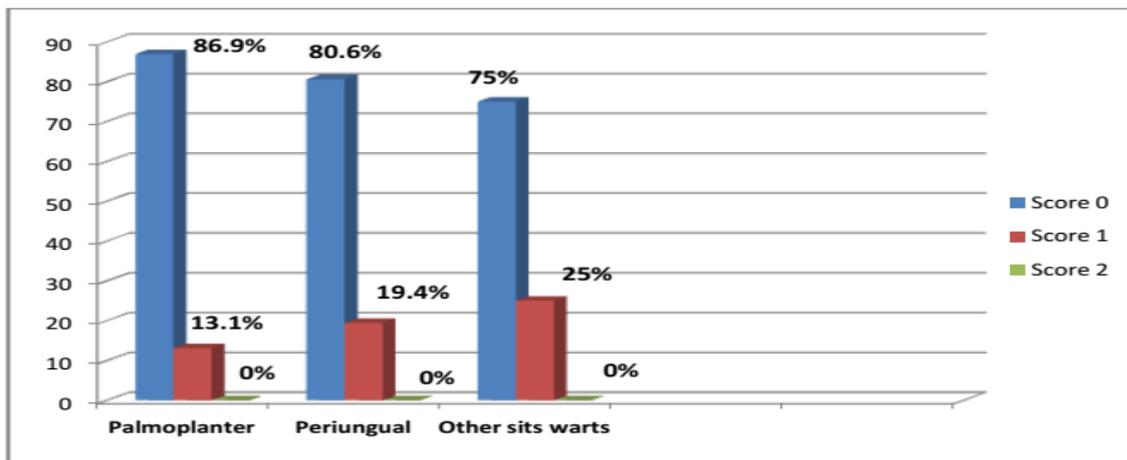


FIG. 1: Response rate of palmoplantar, periungual and other sites warts after two weeks follow up

After 1 month the score 1 response rate of the palmoplantar, periungual and other sites warts were (39.2%), (41.9%) and (25%) respectively, while the score 2 response rate of the palmoplantar, periungual and other sites warts were (30.4%), (32.3%) and (75%) respectively as shown in fig. 2.

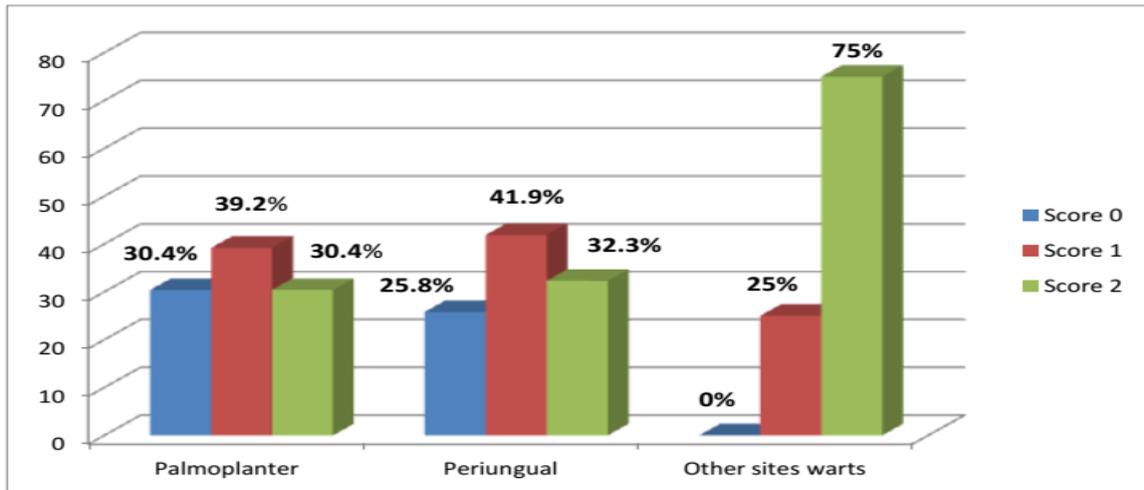


FIG. 2: Response rate of palmoplantar, periungual and other sites warts after one month follow up

After 3 months of follow up that both periungual warts and other sites of showed 100 % response rate (score 1 + score 2), followed by palmoplantar warts which showed 94.2% response rate as indicated in fig.3. Moreover, results in table (3) mention that P-value was 0.0002, 0.0001, and 0.0001 in Palmoplantar, preiungual, and other sites warts, respectively.

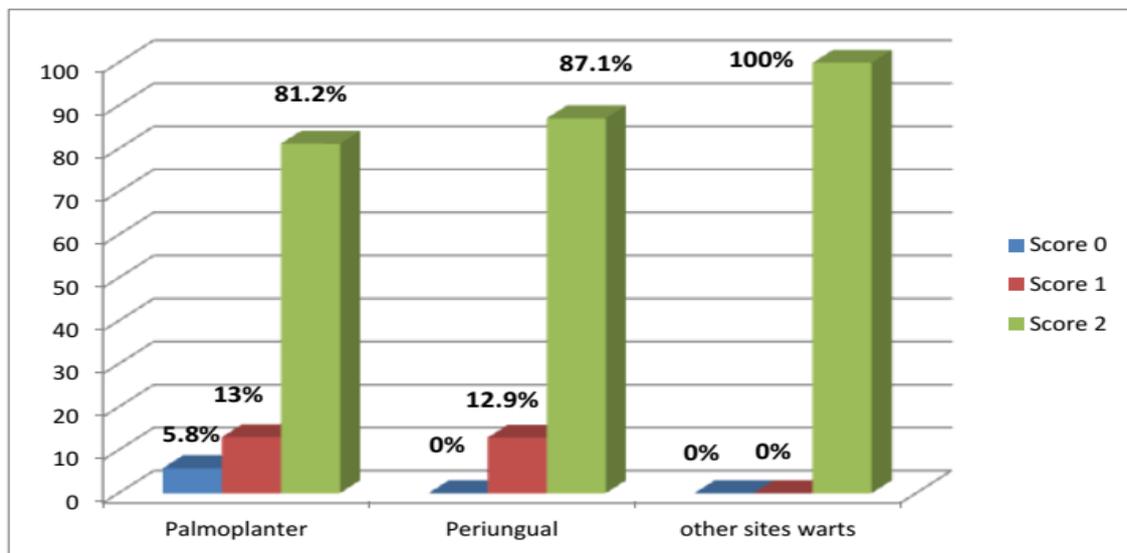


FIG. 3: Response rate of palmoplantar, periungual and other sites warts after three months follow up

Table (3): The response rate of palmoplantar,periungual, and other sites of warts with treatment by bleomycin 1U/ml.

Follow up time	Palmoplantar †			Periungual Warts ††			Other Sites Warts †††		
	Score 0	Score 1	Score 2	Score 0	Score 1	Score 2	Score 0	Score 1	Score 2
Baseline	69	0	0	31	0	0	4	0	0
2 weeks	60 (86.9%)	9 (13.1%)	0	25 (80.6%)	6 (19.4%)	0	3 (75%)	1 (25%)	0
1 month	21 (30.4%)	27 (39.2%)	21 (30.4%)	8 (25.8%)	13 (41.9%)	10 (32.3%)	0	1 (25%)	3 (75%)
3 month	4 (5.8%)	9 (13%)	56 (81.2%)	0	4 (12.9%)	27 (87.1%)	0	0	4 (100%)

† P-Value = 0.0002 / after 3 month follow up: Score 1+ Score 2 = 65 (94.2%);

†† P-Value = 0.0001 / after 3 month follow up: Score 1+ Score 2 = 31 (100%);

††† P-value = 0.0001/ after 3 month follow up: Score 1+ Score 2 = 4 (100%).

During the first week after injection with bleomycin, blackish discoloration, ecchymosed and escarps developed. Later on, the eschar was pared and the overlying skin was sloughed leaving an exposed area which was examined closely for residual wart. There were no signs of pigmentary changes or scar formation at bleomycin injection sites. Few patients by periungual warts suffering significant local pain and tumefaction that took 5 -7 days. No nail atrophy or other effect occurred after intralesional within the nail throughout the course of treatment. None of the patients experienced any systemic side effects. All the patients did not show any recurrence of warts during the 3 months follow up as shown in the fig.4, 5, and 6.



FIG. 4: Palmoplantar warts. (a): Palmoplantar warts before treatment with bleomycin. (b): Palmoplantar warts after 3 month of treatment with bleomycin.



FIG. 5: Periungual warts. (a): Periungual warts before treatment with bleomycin. (b): Periungual warts after 3 months of treatment with bleomycin.

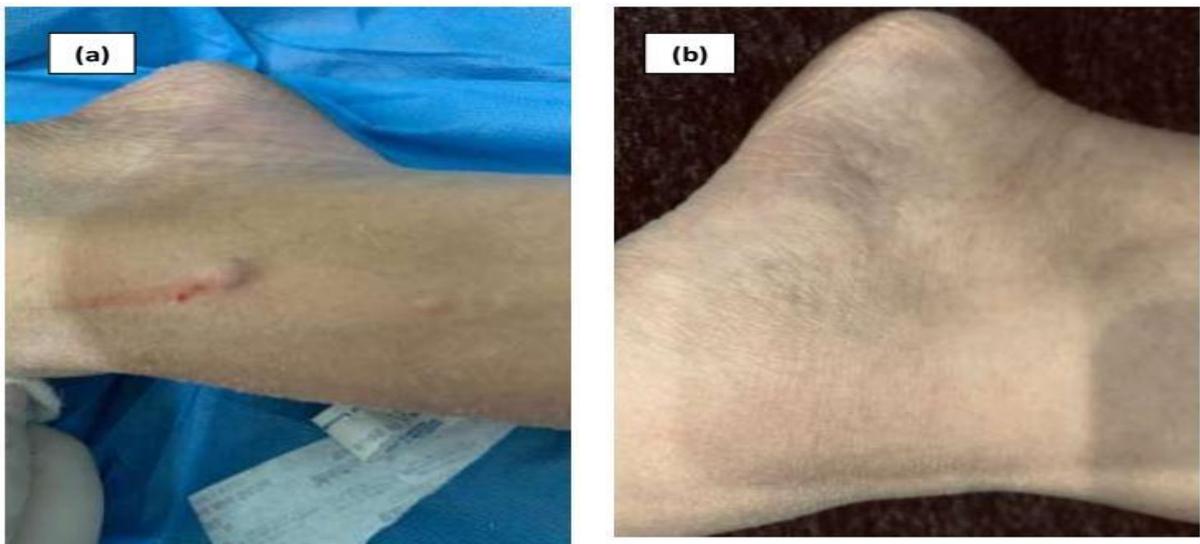


FIG.6: Other sites warts. (a): Other sites warts before treatment with bleomycin. (b): Other sites warts after 3 months of treatment with bleomycin.

Discussion:

Until now, widespread warts are cure in Iraq via diverse physical methods such as electro-method, cryosurgery, and varied types of lasers. These methods have not been 100% effective because of a failure to remove the Warts no matter how often number of therapy

sessions¹³. Which cause major effect on patient by shyness, terror of passive estimate by commune and defeat due to by firmness and/or try again¹⁴. Some recent studies have reported that bleomycin is very effective in treating warts and its response was greater than other methods, in addition to lower rates of side effects, especially in the periungual and the palmoplantar¹⁵. Bleomycin is a metallo-glycopeptide antibiotic it is classified as an antitumor, antibacterial and antiviral. In order for it to be effective it needs a transition metal ion which frequently such as Fe²⁺. A Fe²⁺/bleomycin complex has capability to bind with deoxyribonucleic acid (DNA) and mediate single and double strand DNA cleavage then strand separation and disposal of pyrimidine and purine bases. This practicability is thought to be the main determinant for the cytotoxicity of bleomycin^{16,17}. We used this method for the first time in Iraq, and the final results were shown after 12 weeks of using bleomycin at a concentration (1U / ml) shows response in (periungual and other sites warts) was 100%, while in (palmoplantar warts) was 94.2% with a total response rate of 96.1 % according to the scoring system.

The dosage of bleomycin may be an important agent in effectiveness therapeutic result. Hayes and O'Keefe they arrived in their studies that a cure rate of 73.3%, 87.5% and 90% by intralesional bleomycin in concentration of 0.25 mg/ml, 0.5 mg/ml and 1 mg/ml respectively¹⁸. The injection of plantar warts was characterized by blackening and the appearance of blisters, although exfoliation and follow-up played a prominent role in revealing remaining warts at the base of the treatment site. Bleomycin is not specific; it causes local necrosis at the injection site, so it has been ensured that bleomycin is injected only inside the lesion. The cure rate of warts with intralesional bleomycin was unrelated with the duration of warts. Mild-to-moderate local pain was the main problem experienced by patients during procedure, for which addition of lidocaine 2% to bleomycin solution helps to relieve pain. Furthermore, analgesics were helpful to relieve persistent pain after treatment.

The efficacy of intralesional bleomycin in warts has been found superior to placebo, cryotherapy and pulsed dye laser, etc. Compared with known treatments, bleomycin was treated with only one injection and fewer sessions. Therefore, many patients expressed their gratitude for the final results, especially for those who found a quick and complete solution to the warts they had been suffering from for years.

Conclusion:

Our findings suggest that Bleomycin is significantly effective in the handling for insurgent verruca. It's safe and free of side effects apart from minimal local pain with no recurrence rate of warts after bleomycin treatment.

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