Bleomycin Therapy Using Multipuncture Technique for Resistant Warts

Sir,

The case report titled "Successful Treatment of a Resistant Periungual Wart Case with Bleopuncture Method" by Yalçın *et al*. in the Turkish Journal of Dermatology (Turk J Dermatol 2018; 12: 191–3) recalled an often-ignored bleomycin therapy in the treatment of resistant warts.[1]

Cutaneous warts sometimes fail to respond to routine treatments (cryotherapy, electrosurgery, topical salicylic acid, fluorouracil, potassium hydroxide, and retinoid treatments and combinations). In these cases, bleomycin therapy has been a treatment option which has been in the literature for a long time, but is not preferred too frequently.

Bleomycin is considered as a third-line therapy for resistant warts and has been regarded as level 1 strength of evidence for the treatment of warts.[2] It is obtained from "*Streptomyces verticillus*" and shows an inhibitory effect on the virus and the host cell by inhibiting DNA and protein synthesis. In the treatment of warts, two application methods were noteworthy until recent years. First, intralesional bleomycin (IL Bleo) therapy has been shown to be a very effective treatment method (success rates vary between 14% and 99%), but it is not often preferred because of its rare however scary side effects (pain, chemical cellulitis, postinflammatory hyperpigmentation, Raynaud's phenomenon, tissue necrosis, onychodystrophy, and flagellate hyperpigmentation).[3]

These side effects can be largely preserved by the application of bleomycin utilizing "multipuncture" technique. In our case report and literature review published in 2016, we reviewed the efficacy of bleomycin using "multipuncture" technique in the treatment of warts.[4] According to our literature review, 74%–100% cure rates were obtained for palmoplantar and periungual warts which are resistant to other topical therapies. It was applied in the range of 0.1–3 U/ml in 2–4-week intervals. No significant adverse effects were observed during and after the procedure except for the local pain.[4-9] In our case report, a 56-year-old female with a 3-year history of plantar warts (previously treated with salicylic acid, fluorouracil, and cryotherapy without any success) was treated with multipuncture bleomycin therapy.[4] A concentration of 3 U/mL bleomycin was applied with occlusion after prickling the warts, and it was kept on the warts with a stretch film for 12 h. The procedure was repeated 4 times with 2-week intervals. At the end of 2 months, complete resolution was achieved.[4]

Bleomycin can be found in 15 and 30 mg vials in our country and its cost varies between 30 and 80 TL. The most preferred procedure for multipuncture technique was to prick the wart through the intradermal area with a sterile needle followed by preparing a 1 U/mL bleomycin in saline solution (a vial containing 15 units of bleomycin and 15 mL of normal saline solution is mixed to achieve a concentration of 1 U/mL). One unit is equivalent to the activity of 1 mg of bleomycin. After that, this bleomycin solution dropped to the area or on the gauze and then closed on the area for a few hours with sterile gauze.[1,4-9] A small number of recurrences were observed in 6–18-month follow-up periods in the treated warts[6,8,9] [Table 1].

Furthermore, in recent years, there have been small studies evaluating the efficacy and safety of topical bleomycin therapy applied by coated microneedles or combined with microneedling, electroporation, or ablative laser therapy.[10-15] In some of them, researchers even compared it to IL Bleo, intralesional saline, or cryotherapy.[13-15] First, Konicke and Olasz presented three patients with warts who were cured with microneedling combined with topical application of 1 U/mL bleomycin (MN + Bleo). All patients were cured after an average of four treatments performed in every 2–4 weeks, and no recurrence was seen in 3–5 months' time.[10]

Moreover, in an innovative work, Lee *et al*. created bleomycin-coated microneedles and studied the mechanical properties and drug delivery properties of them. They demonstrated that microneedles delivered bleomycin successfully into the subepidermal skin layer of warts and more than 80% of the bleomycin dissolved into the skin *in vitro* within 15 min. To conclude, they suggested that bleomycin-tip-coated microneedles are an effective, easy, and painless way for wart treatment.[11] Suh *et al*. used a different method and they treated warts with bleomycin application (1 U/mL) after ablative carbon dioxide fractional laser (three passes of laser with single-pulse treatment parameters of 180 mJ pulse energy and 100 spots/cm^2 density in the static mode). Seventeen patients with a total of 38 warts were successfully treated at every 2 weeks with six consecutive sessions of this protocol.[12] Ryu *et al*. conducted a comparative study to evaluate the therapeutic effects of newly developed bleomycin microneedle patch regards to cryotherapy. They recruited 42 patients with more than two wart lesions in each and the lesions were treated by one of the above-mentioned methods randomly. Their study demonstrated 76.2% clearance rate for cryotherapy and 61.9% clearance rate for the bleomycin microneedle patch at week 16. This new therapeutic method was found to be an effective, convenient, and painless treatment modality when compared with cryotherapy.[13] In another study, Al-Naggar *et al*. compared IL Bleo (with a single injection of 1 U/mL bleomycin) and microneedling with topical spraying of bleomycin (MN + Bleo) performed every

Table 1: Multipuncture bleomycin therapy for warts are summarized

Study-case report, years	Method	Number of patients/ warts	Location of warts	Range of application (interval/number)	Concentration of bleomycin (amount used)	Duration of follow-up (months)	Complete clearance (%)	Side effects
Shelley and Shelley, 1991[5]	A bifurcated vaccination needle, 40 times per 5 mm^2, dry dressing for 24 h	66/258	Palms, soles, dorsal aspect of hands and feet, forearms, face, penis, knees, paronychial areas	-/1 once	1 U/ml	6	92	Local pain
Munn *et al.*, 1996[6]	Topical lidocaine for 1 h, monolete needle	62/not given	Palmar, plantar, periungual	4 weeks/4 times	1 U/ml	12	92	Local pain
Sardana *et al.*, 2010[7]	26-gauge hypodermic needle, occlusion for 2 h	1/1	Periungual-subungual	4 weeks/5 times	1U/ml (2 ml)	18	100	Local pain, inflammation, eschar formation
AlGhamdi and Khurram, 2011[8]	Intralesional lidocaine 2% for 1 h, 27-gauge needle, topical antibiotic, applied simple dressing	15/15	Periungual	4 weeks/one or two times	0.1 U/ml (1 ml)	6	86.6	Local pain, mild hyperpigmentation
AlGhamdi and Khurram, 2012[9]	Intralesional lidocaine 2% for 1 h, 27-gauge needle, topical antibiotic, applied simple dressing	23/23	Plantar	4 weeks/one or two times	0.1 U/ml (1 ml)	6	74	Local pain
Temel and Akman-Karakas, 2016[4]	26-gauge needle, occlusion for 12 h	1/3	Plantar	2 weeks/4 times	3 U/ml (1 ml)	18	100	Local pain
Yalçın *et al.*, 2018[1]	Topical lidocaine-prilocaine occlusion for 2 h, multiple pricks with lancet, occlusion for 2 h after bleomycin	1/5	Periungual	-/1	1 U/ml	1	100	None

Concentration of bleomycin: 1 U/ml concentration of bleomycin describes that a vial containing 15 units of bleomycin and 15 mL of normal saline solution is mixed to achieve a concentration of 1 U/mL

2 weeks for a maximum of four sessions. Sixty patients were recruited to the study and divided into two groups equally. They presented 83.3% complete clearance rate of warts in the MN + Bleo group compared to 70% in the IL Bleo group.[14] Gamil *et al*. recently published another comparative study where 54 patients were divided into three groups (18 patients each). The first group was treated by dermapen with topical bleomycin (1 mg/1 mL) for a maximum of four sessions at 2-week intervals. On the other hand, the second group received IL Bleo (1 unit/mL) for a maximum of four sessions at 3-week intervals, and the control group was intralesional saline for a maximum of four sessions. Complete clearance was found to be highest in Group 1 (88.9%) as opposed to 83.3% in Group 2 and 5.6% in the control group.[15]

In the recent case of Yalçın *et al*., a single-session multipuncture method was used to successfully treat periungual warts.[1] As is seen in these case reports and the literature, multipuncture technique is a safe, effective, and well-tolerated treatment. Thus, it should be included in our preferences as its use is easy to apply, it has good results and comfortable for patients, and it keeps the cost low for both the patient and the health system. In the following years, multipuncture bleomycin therapy can take part in the higher step in the treatment algorithm of recalcitrant warts.

However, there is a need for prospective controlled studies to determine the most appropriate frequency and dosage of the method, standardization of the application, and the side effect profile.

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Conflicts of interest

There are no conflicts of interest.

Asli Bilgic, Ayse Akman-Karakas[1]

Dermatology Clinic, Antalya Training and Research Hospital, University of Health Sciences, [1]Department of Dermatology and Venereology, School of Medicine, Akdeniz University, Antalya, Turkey

Address for correspondence: Dr. Asli Bilgic, Dermatology Clinic, Antalya Training and Research Hospital, University of Health Sciences, Antalya, Turkey.
E-mail: aslibilgictemel@gmail.com

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