

Preliminary Study of Intralesional Bleomycin Injection for the Treatment of Genital Warts

Jin Yong Lee, Chul Woo Kim, Sang Seok Kim

Department of Dermatology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

Dear Editor:

External genital warts, also known as condyloma acuminata, is one of the most common sexually transmitted diseases and is caused by human papillomavirus infection¹. Currently used treatments include imiquimod, podophyllin, interferons, cryotherapy, chemotherapeutic agents, cidofovir, laser vaporization, and surgical removal²⁻⁴. However, none of these modalities are considered to be the gold standard, and all of them vary greatly with respect to cost, adverse effect profiles, dosing schedules, treatment duration, and overall effectiveness. Bleomycin, an antibiotic agent with antineoplastic properties, has been used to treat recalcitrant palmoplantar warts; however, there are few reports in the literature about its effect on genital warts⁵⁻⁷. Therefore, this preliminary prospective study assessed the efficacy and safety of intralesional bleomycin injection for genital warts.

From June 2011 to March 2013, we enrolled 15 patients (14 men, 1 woman) with a total of 164 genital warts. The patients' age ranged from 23~78 years (mean, 43.3 years). Regarding location, 3, 15, 39, 2, and 105 lesions were located on the vulva, scrotum, anus, glans penis, and penile shaft, respectively. The dimensions of these warts (short×long axes) ranged from 2×2 to 22×40 mm. Five patients were previously treated with other modalities (2 with podophyllin, 2 with carbon dioxide laser ablation,

and 1 with 5% imiquimod cream) but experienced recurrence. Genital warts were diagnosed on the basis of clinical examination, and biopsy specimens were evaluated only if the lesions appeared ambiguous. Patients with peripheral vascular disease such as Raynaud's phenomenon were excluded from this study. The study was approved by the institutional review board of Kangdong Sacred Heart Hospital (No. 11-105) and conducted in accordance with the principles outlined in the Declaration of Helsinki. For injections, bleomycin (Bleocin; Nippon Kayaku Co., Ltd., Tokyo, Japan) was diluted with 4 ml normal saline and 6 ml 2% lidocaine to a final concentration of 1.5 mg/ml. This diluted solution was slowly injected into the base of the wart by using a 31-G insulin syringe (BD Ultra-Fine II Needle; Becton Dickinson, Franklin Lakes, NJ, USA) until blanching was observed. At each visit, <2 ml bleomycin was administered to prevent local adverse reactions. Any clinical changes or adverse reactions were recorded every 2 weeks, and injections were repeated if the wart remained. A wart was considered cleared if it was completely resolved; otherwise, the treatment was considered to have failed. The patients were followed up until dermatologists confirmed wart-free status; the total follow-up period ranged from 3~20 months (mean, 12.4 months).

The baseline clinical characteristics and treatment outcomes are described in Table 1. Of the 15 patients, warts were completely resolved in 11 (73.3%) (Fig. 1). Two patients (13.3%) experienced recurrence after complete resolution, and another 2 (13.3%) experienced only partial resolution. The total volume of bleomycin injected ranged from 0.1~1.44 ml, and the mean volume injected per treatment was 0.27 ml. No allergic reactions (e.g., anaphylaxis) or evidence of systemic adverse reactions were reported. Only local adverse reactions including pain, dyspigmentation, crust, and mild scar formation were noted. Five patients (33.3%) experienced moderate to severe

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Corresponding author: Chul Woo Kim, Department of Dermatology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, 150 Seongan-ro, Gangdong-gu, Seoul 134-701, Korea. Tel: 82-2-2224-2285, Fax: 82-2-474-7913, E-mail: kim937121@naver.com

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Table 1. Characteristics and treatment outcomes of patients with genital warts

Patient No.	Sex/age (y)	Location	No. of lesions	Size of the largest lesion (mm ²)	Size group*	Previous treatment	No. of treatment sessions	Outcome	Adverse reactions	Follow-up period (mo)
1	Male/63	Penile shaft	1	6 × 12	Small	None	2	Resolved	Crust	12
2	Male/32	Penile shaft	12	2 × 20	Small	None	2	Resolved, but recurred	Local pain	7
3	Male/43	Penile shaft	2	3 × 3	Small	CO ₂ ablation	6	Resolved	None	18
4	Male/23	Glans penis	2							
4	Male/23	Penile shaft	1	3 × 8	Small	Podophyllin, imiquimod	1	Resolved	None	3
5	Male/45	Penile shaft	11	2 × 2	Small	None	3	Resolved	Crust	18
6	Male/55	Penile shaft	20	3 × 5	Small	None	4	Resolved	Crust	11
7	Male/33	Penile shaft	1	5 × 10	Small	None	5	Resolved	Dyspigmentation, crust	10
8	Female/49	Vulva	3	5 × 25	Large	None	4	Resolved	Local pain, dyspigmentation, crust	12
9	Male/32	Penile shaft	8	2 × 2	Small	Podophyllin, imiquimod, CO ₂ ablation	4	Persisted	None	6
10	Male/78	Penile shaft	14	22 × 40	Large	None	4	Resolved	Local pain, dyspigmentation, crust, scar formation	12
11	Male/25	Penile shaft	6	8 × 25	Large	None	3	Resolved	Crust	20
12	Male/45	Scrotum	3	15 × 20	Large	None	7	Resolved, but recurred	Crust	10
13	Male/59	Penile shaft	5	3 × 3	Small	CO ₂ ablation	2	Persisted	Local pain	10
		Scrotum	12							
		Anus	39							
14	Male/34	Penile shaft	2	5 × 5	Small	Podophyllin, CO ₂ ablation	2	Resolved	Crust, scar formation	19
15	Male/33	Penile shaft	22	5 × 5	Small	None	5	Resolved	Crust	18

*Dimensions of the largest lesion with warts (short × long axes) were estimated by using calipers. Warts were classified as large if they were > 100 mm².

pain after the procedure; however, the pain disappeared within 1 week with or without oral analgesics. Dyspigmentation in the treated region developed in 3 patients (20%) during follow-up. Furthermore, 10 patients (66.7%) experienced crust formation; in particular, 2 patients developed a mild atrophic scar on the lesion site after the crust was removed, whereas the crust resolved spontaneously without scarring in the remaining 8 patients.

Bleomycin is an antitumor, antibacterial, and antiviral agent that was first isolated by Umezawa from the fungus *Streptomyces verticillus* in 1966; it is widely used to treat recalcitrant palmoplantar warts^{6,7}. Several clinical trials have evaluated the efficacy of bleomycin in the treatment of cutaneous warts, with success rates ranging from 16% ~ 94%². However, only a few studies have focused on genital warts. Figueroa and Gennaro⁵ report a 70% treatment success rate of genital warts by using bleomycin with a

few complications such as local soreness, pruritus, and spotting of blood, none of which required further treatment. Similarly, in the present study, bleomycin successfully resolved genital warts in 73.3% of patients, without any significant complications. Complications including pain, dyspigmentation, crust, and scar did not interfere with the ability to administer further treatment. In particular, crust formation may suggest adequate infiltration of bleomycin during the injection, because bleomycin decreases blood flow, thus inducing necrosis and subsequent detachment of the lesion⁸. The most serious complication in such cases is local tissue necrosis, although this was not observed in the present study. Necrosis can occur because bleomycin hydrolase, which inactivates the injected bleomycin solution by hydrolyzing the amide bond in the β -amino-alanine-amide moiety, is present in very small amounts in skin⁹. The most effective strategy for preventing this cuta-

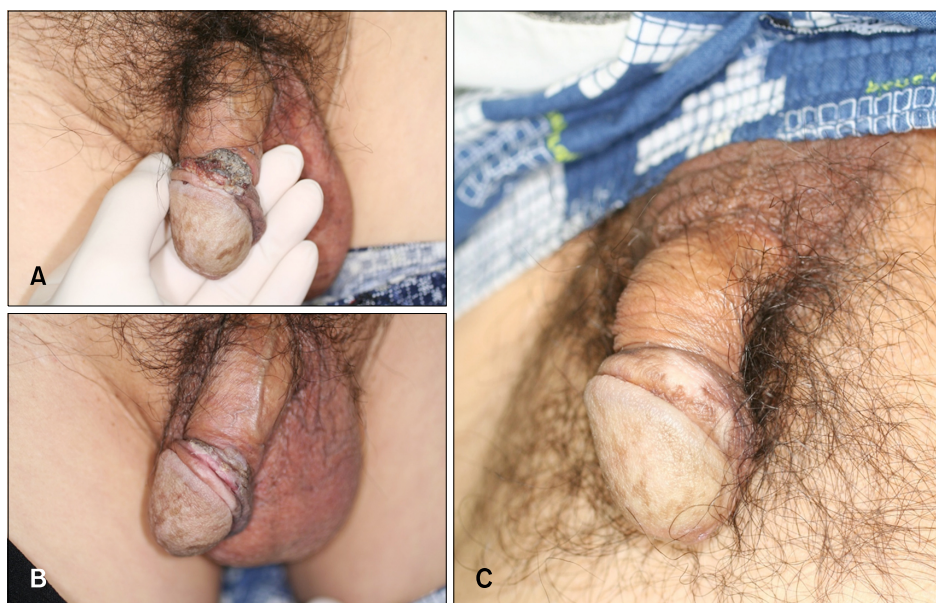


Fig. 1. Clinical findings in patient #10. (A) A crusted, verrucous plaque (average dimensions, 22×40 mm) located on the penile shaft. (B) After the second intralesional bleomycin injection, the genital warts had nearly resolved, although mild erosion had developed. (C) Clearance of genital warts with hypopigmentation at 2 weeks after 4 treatment sessions of intralesional bleomycin injection.

neous toxicity is decreasing the total cumulative dose of bleomycin^{8,9}. In the case of genital warts, the delicate nature of the mucosal skin in the genital area makes it easy to control the amount and distribution of bleomycin, leading to fewer adverse reactions and increasing effectiveness. This study has several limitations such as the small number of patients and lack of precise methods to determine the total number of warts in each patient. The confounding factors in the assessment of the success rate, including the number, location, distribution, and depth of the warts, may be associated with treatment failure and thus require further investigation. Nevertheless, the results of our study suggest intralesional bleomycin injection is a simple treatment with only mild complications that is easy to administer in outpatient settings and may yield a satisfactory success rate for the treatment of genital warts.

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