Intralesional Bleomycin Therapy Using a Lancet in the Treatment of Recalcitrant Warts

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***Background*:** Warts are benign growths caused by human papilloma viruses. Warts can be very difficult to treat, with response being unpredictable and relapse rates high.

***Objective*:** To determine the efficacy of intralesional bleomycin using a lancet in the treatment of recalcitrant warts.

***Methods*:** Thirteen patients who had been unsuccessfully treated with conventional therapy at the dermatology clinic were enrolled onto an open study. Bleomycin, at a concentration of 1 mg/ml in normal saline, was dropped onto the surface of the wart and 'pricked' into the wart with multiple rapid stabs using a Worldlet™ lancet. This was repeated monthly until the wart cleared or the patient withdrew from treatment.

***Results*:** Complete clearance of all warts was achieved. The average number of treatments was three. No patient experienced any side effects such as Raynaud's phenomenon, nail dystrophy, or post-inflammatory hyperpigmentation.

***Conclusion*:** Intralesional bleomycin therapy using a lancet was shown to be effective in the treatment of recalcitrant warts, and caused few adverse effects.

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Key Words: Bleomycin, Warts

INTRODUCTION

Viral warts are very common and affect 7-10% of the population1. Warts are benign growths caused by the human papilloma virus. They can occur on any epithelialized surface of the body. The diagnosis and management of warts is a major burden on time and resources to most dermatology departments[2]. Despite their banal nature, warts can be very difficult to treat, with responses being unpredictable and relapse rates high. Numerous treatment options are available, but no one treatment has emerged as the treatment of choice.

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Intralesional bleomycin therapy has been shown to be effective against warts and various methods of administration have been described[3-5]. We therefore designed this study to determine the efficacy of intralesional bleomycin, using a lancet, in the treatment of recalcitrant warts.

MATERIALS AND METHODS

Patients

Thirteen patients attending the dermatology clinic were enrolled onto an open study (5 females and 8 males). Warts were regarded as resistant, as all previous attempts at treating them had failed. Past treatment has been summarized in Table 1. Eleven patients had solitary warts, and two patients had two warts. Fifteen warts were treated during the study.

Methods

Informed consent was obtained and warts traced

Table 1. Patient Details and Past Treatments

No	Age/Sex	Previous treatments	Sites
1	12/M	Cryo*18, V-beam*3, DNCB*4	Rt. big toe, Rt 3rd finger
2	17/M	Cryo*22, CO_2*4	Lt. 4th finger
3	13/F	Cryo*20, CO_2*2	Lt. thumb
4	15/F	Cryo*20, CO_2*7, V-beam*2, DNCB*3	Lt. 2nd finger
5	29/M	Cryo*10, V-beam*2	Rt. big toe
6	14/F	Cryo*11, DNCB*4	Lt. sole
7	14/M	Cryo*10, CO_2*1	Rt. sole
8	42/M	Cryo*19, CO_2*2	Lt. thumb
9	12/M	Cryo*10	Lt. 2nd finger
10	20/M	Cryo*6	Lt. 3rd finger
11	45/F	Cryo*8	Lt. 5th toe
12	14/M	Cryo*9	Lt. thumb
13	23/F	Cryo*10	Lt. 2nd finger

Cryo: Cryotherapy, V-beam: V-beam laser therapy, CO_2: CO_2 laser therapy, DNCB: Dinitrochlorobenzene application, *Number: The number of treatments

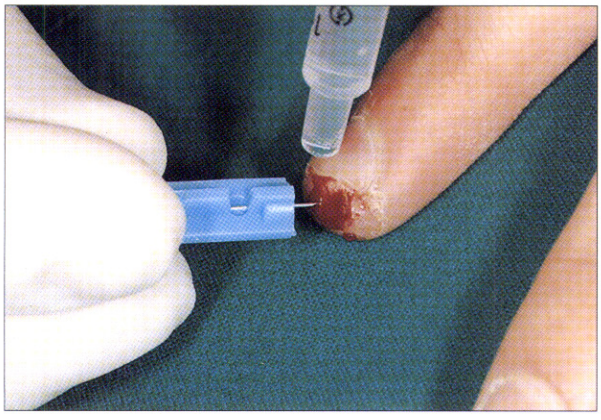

Fig. 1. Injection of bleomycin solution into wart using the 'pricking technique' with a lancet.

and photographed. The area to be treated was anaesthetized with a local anaesthetic injection (Lidocaine HCL 2%). Hyperkeratotic warts were pared down prior to treatment, with care taken to avoid any bleeding. Bleomycin, at a concentration of 1mg/ml in normal saline, was dropped on to the surface of the wart and 'pricked' into the wart with multiple rapid stabs using a Worldlet^{TM} lancet (Fig. 1).

This was repeated monthly until the wart cleared or the patient withdrew from treatment. Any side-effects experienced, were recorded. Photographs were taken at each clinic visit to record responses. Patients were given a supply of further dressings to take home and given instructions on daily care of the treated area. Patients were reviewed after one month following the initial treatment, and repeat treatments were given at monthly intervals until satisfactory clearance was achieved. Clearance was defined when the wart showed no detectable hyperkeratosis or recurrence.

RESULTS

No patients were lost during follow-up. The male/female ratio was 8 males and 5 females, and the mean age was 20.7 years (range 12 to 45 years). Complete clearance was achieved in all warts (Fig. 2). Two warts cleared after a single treatment, four after two treatments, two after three treatments, five after four treatments, and two required five treatments. The average number of treatments was three.

No patient has experienced any recurrence, with a mean follow-up of 13 months (range 4-18 months). Crusting at the treated area lasted an average of 2

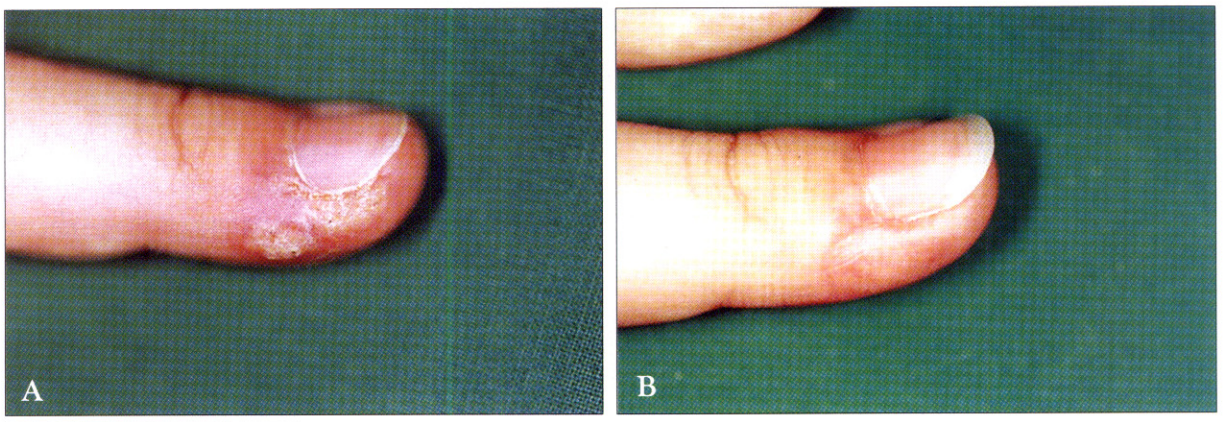

Fig. 2. Periungual wart on the left 3rd finger in patient No. 10 (A). After two treatments with intralesional bleomycin using a lancet (B).

Table 2. Treatment and Follow up Details

Patient number	Number of warts treated	Outcome	Number of treatments per wart	Length of follow-up from last treatment (months)
1	2	Cleared	4(toe), 5(finger)	17
2	1	Cleared	2	14
3	1	Cleared	5	17
4	1	Cleared	4	17
5	2	Cleared	4	13
6	1	Cleared	4	17
7	1	Cleared	3	13
8	1	Cleared	1	12
9	1	Cleared	1	18
10	1	Cleared	2	13
11	1	Cleared	2	4
12	1	Cleared	3	10
13	1	Cleared	2	5

weeks and no patient found simple wound care difficult. No patient experienced side effects such as Raynaud's phenomenon, nail dystrophy, or post-inflammatory hyperpigmentation. Details of long term follow up are presented in Table 2.

DISCUSSION

Warts, or verrucae are benign proliferations of the skin and mucosa that result from infection with papilloma viruses. These viruses do not produce acute signs or symptoms, but induce slow-growing lesions that can remain subclinical for long periods of time[6].

The viral etiology of warts was implied from the observation that inoculation of wart filtrates, from which cellular and bacterial products were removed, could induce papillomas at the site of injection. All warts were considered to be derived from a single virus, because isolates from cutaneous, genital, or laryngeal warts could induce papillomas at other

sites. However, advances in recombinant DNA technology have now identified more than 100 different HPV genotypes[7]. The papilloma viruses comprise a large family of double-stranded DNA viruses found in humans and many other species[8].

Studies of spontaneous regression of warts in children suggest that two-thirds will remit within 2 years, with any remaining verrucae continuing to resolve at this rate[9]. However, new warts may appear while others are regressing. Many treatments for verrucae involve physical destruction of the infected cells. The existence of multiple treatment modalities reflects the fact that none is uniformly effective or directly antiviral[6]. Cryotherapy involves freezing a wart with liquid nitrogen for 10 to 20 seconds every 2 to 3 weeks. Precisely how cryotherapy destroys warts is not well understood, but the prevailing theory is that freezing causes local irritation, leading the host to mount an immune reaction against the virus[10]. Immunotherapies have been attempted in various forms. Induction of allergic contact dermatitis with dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE)[11], or diphenylcyclopropenone (DPC)[12] allows localization of inflammation to warts, on which the allergen is painted; it has been speculated that this treatment stimulates local immunity. DNCB is positive in the Ames bacterial test of mutagenicity, and its use remains controversial. Laser treatment in several different energy formats can be useful for destroying warts that are treatment-resistant or for those that require careful control of width and depth, such as large periungual warts[6]. Continuously our patients failed to have their warts treated successfully by cryotherapy, immunotherapy or laser therapy. Also, warts have a tendency to spontaneously resolve, but we felt this was unlikely in our patients as their warts had proven especially resistant in the past.

Bleomycin is an antibiotic derived from *Streptomyces verticillus*. In low doses, the antineoplastic properties are achieved by inhibition of mitosis. At higher concentrations, bleomycin is cytostatic by blocking DNA uptake of thymidine in the S-phase of the cell cycle[13,14]. It is thought that the bleomycin's efficacy in the treatment of verrucae is due to its effects on cellular DNA, which impede viral survivability by limiting turnover of host cells. But induction of the tumor necrosis factor has also been reported as a possible mechanism[13]. It has been shown that expression and up-regulation of activation antigens (human leukocyte antigen class II) and cell adhesion molecules (intercellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1, and vascular cell adhesion molecule-1) occur after the injection of bleomycin into human skin[13]. Some authors have raised the possibility of using bleomycin as a first-line agent because of the relatively simple procedure and increased patient satisfaction when compared with destructive modalities such as cryotherapy or electrocautery[15].

Direct intralesional bleomycin injection can lead to the injection going too deep and causing excessive pain or leakage into the normal surrounding skin, causing tissue necrosis. There is also the risk of the pressure causing the needle to become separated from the syringe during the procedure, resulting in risk of exposure of bleomycin to the eyes and oral cavity of the patient and physician[16]. In our study, we treated recalcitrant warts by intralesional bleomycin therapy using a lancet. Therefore, we avoided many of these problems.

The results of this study are comparable with the success rates described by other authors. Shelley and Shelley used a similar technique of pricking the bleomycin into the wart, but used a specific bifurcated vaccination needle[5]. In their study, a 92% success rate was achieved after a single treatment, although six of their patients required more than one treatment (range 2-7). This compares with an average of three treatments required in our study (range 1-5).

Because complete clearance was achieved in all warts with an average of 3 treatments, and all treated warts were previously resistant to many therapeutic modalities, we found that intralesional bleomycin therapy using a lancet on the recalcitrant warts was significantly effective. We also expect that intralesional bleomycin therapy using a lancet will be a first-line therapy to periungual warts, which are commonly resistant to conventional therapy.

In conclusion, although many therapies exist for the eradication of warts, the use of intralesional bleomycin using a lancet appears promising as a safe and non-threatening treatment modality especially for recalcitrant warts.

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