



ORIGINAL ARTICLE

Efficacy of Punch Reduction Prior to Cryotherapy in Patients with Viral Warts: A Case-Control Study in a Single Tertiary Center

Ju Yeon Choi, Ji-Hye Park¹, Seung Hwan Oh¹, Jong Hee Lee¹, Joo-Heung Lee¹, Dong-Youn Lee¹, Jun-Mo Yang¹

Department of Dermatology, Kangbuk Samsung Hospital, ¹Department of Dermatology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Cutaneous warts are a common complaint to visit dermatologic clinic and its course is variable, ranging from spontaneous resolution to a chronic condition refractory to treatment. **Objective:** To evaluate the efficacy and safety of punch biopsy for cutaneous warts. **Methods:** Thirty-nine patients who received punch biopsy for warts were reviewed through charts and photos. Among them, 15 were matched with cryotherapy-only controls in terms of size and location of the wart. We compared the number and cost of treatments between the two groups. **Results:** Eleven of the total 39 patients were treated with cryotherapy in addition to punch biopsy and the average number of treatments was 4.1 ± 3.3 (mean \pm standard deviation). In a case-control study, the ratio value of cost was 2.9 ± 3.6 in the experimental group and was 5.9 ± 4.1 in controls ($p < 0.05$). **Conclusion:** Punch biopsies can decrease the number and cost of treatment by reducing the size of warts and inducing local inflammation to accelerate resolution. Therefore, punch reduction should be considered as a viable measure to treat warts. (Ann Dermatol 29(2) 200~205, 2017)

-Keywords-

Biopsy, Cryotherapies, Papillomaviridae, Therapy, Warts

INTRODUCTION

Cutaneous warts are benign papillomas of the skin caused by infection with human papillomavirus (HPV). There are many different clinical manifestations, such as verruca vulgaris, verruca plana, verruca plantaris, and genital warts (condyloma acuminata). Among them, verruca vulgaris and verruca plantaris are the most common^{1,2}. They are a common complaint occurring in up to 5% to 30% of in children and young adults, although they can occur at any age³⁻⁵. Wart resolves spontaneously without treatment in more than one-third of children^{5,6}. However, it takes several months or years to complete clearly and can be much slower in adults. Warts may occasionally be resistant to treatment. Additionally, they tend to spread, increase in size, and can be contagious. Warts located on the soles of the feet and around nails can be painful and cause deformity of the nail structure. There is no single therapy that has proven effective at achieving complete remission⁷. The most common treatments are topical salicylic acid application and liquid nitrogen cryotherapy⁷⁻¹⁰. Alternative therapeutic regimens include pulsed dye laser, topical imiquimod, intralesional injection of bleomycin, systemic retinoids, and immunotherapy using viral and fungal antigens⁷⁻⁹. Despite the claims of these various treatments, a Cochrane review concluded that there was a lack of evidence from randomized controlled trials of these therapies⁸. Individual treatments can be selected based on clinician experience, patient preference, and the size and loca-

Received March 29, 2016, Revised August 2, 2016, Accepted for publication August 8, 2016

Corresponding author: Ji-Hye Park, Department of Dermatology, Samsung Medical Center, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. Tel: 82-2-3410-6578, Fax: 82-2-3410-3869, E-mail: jh1204@samsung.com

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tion of the warts. In the case of an uncertain diagnosis or refractory to treatment, we chose punch biopsy to reduce the wart size and to provide a definitive diagnosis. To investigate the effectiveness of punch biopsy, we compared punch biopsy prior to cryotherapy with sole cryotherapy.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Samsung Medical Center, Sungkyunkwan University School of Medicine in Seoul, Korea (IRB no. SMC 2015-06-116-002). We reviewed the charts and photos of cases that underwent punch biopsy and collected controls of similar size and location according to the medical records. We compared the number and cost of treatments. Thirty-nine patients received punch biopsy to diagnose or treat their warts. Among them, 15 cases were matched with controls of similar wart size and location. "Case group" was used to designate those cases that received punch biopsy as a first procedure, and "control group" indicated those cases treated by cryotherapy alone. One of 3-, 4-, or 5-mm-diameter punch instruments was chosen according to the size and location of the wart. A 4-mm punch biopsy was most often used, while a 3-mm punch

biopsy was used on the face and a 5-mm punch was rarely used except on the palms and soles. We analyzed the total cost and number of treatments between case and control group statistically by Wilcoxon's signed rank test because case and control group were matched data but the data did not follow a normal distribution. And we compared the age distribution between two groups by t-test because the data followed a normal distribution. With regard to age

Table 1. Demographic and clinical characteristics of enrolled patients (n=39)

Characteristic	Punch biopsy treatment
Sex	
Male	24 (61.5)
Female	15 (38.5)
Age (yr)	35.3 ± 20.8/2 ~ 73
Location	
Sole & toe	17 (43.6)
Palm & finger	11 (28.2)
Face, neck and scalp	7 (17.9)
Arms and legs	3 (7.7)
Trunk	1 (2.6)

Values are presented as number (%) or mean ± standard deviation/range.

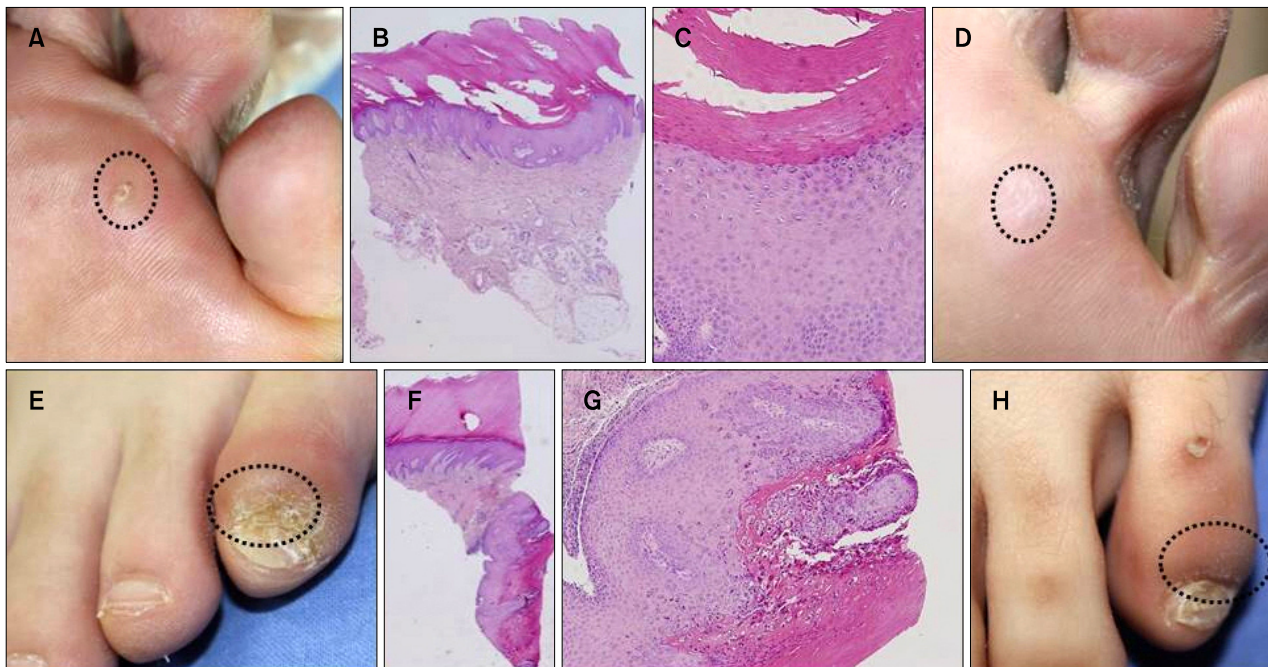


Fig. 1. (A) Clinical image of the sole prior to treatment (51 years/male, dotted circle: viral wart). (B, C) Cup-shaped mass with hyperkeratosis, acanthosis and koilocytes, total excision (H&E; B: ×40, C: ×200). (D) Complete clearance without scar six weeks after punch biopsy (dotted circle: treated area). (E) A wart on the proximal nail fold of fifth toe, prior to treatment (25 years/female, dotted circle: viral wart). (F, G) Partially removed hyperkeratotic mass with koilocytes and eosinophilic keratohyaline granules (H&E; F: ×40, G: ×100). (H) Complete clearance without scar or nail deformity seven weeks after punch biopsy (dotted circle: treated area).

between two groups, we analyzed by Mantel-Haenszel test after matching site as upper extremities and lower extremities (p -values of <0.05 being considered statistically significant, IBM SPSS Statistics ver. 20.0; IBM Co., Armonk, NY, USA).

RESULTS

Thirty-nine patients were collected who received punch biopsy. The mean age of patients is 35.3 ± 20.8 years (range, 2~73 years) and the sex ratio is 1.6 (Table 1). The age distribution of patients that underwent punch biopsy in this study is as follows: 0~9 years, 15.4%; 10~19 years, 10.3%; 20~29 years, 23.1%; 30~39 years, 10.3%; 40~49 years, 10.3%; 50~59 years, 17.9%; and ≥ 60 years, 12.8%. Common wart locations include the feet (43.6%) and hands (28.2%). Other sites include the face, scalp, leg, arm and trunk in descending order. Twenty three cases were suspected of warts clinically, but sixteen were presumed to be corn, seborrheic keratosis, malignancy, epidermal cyst, or pyogenic granuloma. Histopathologically, 17 patients were totally excised and 19 patients were partially excised (Fig. 1, 2). In three cases, it is unclear as whether to excise completely. All patients came to the clinic 2 or 3 weeks after removal of stitches for decisions on additional treatment. There were no adverse effects such as wound dehiscence or infection.

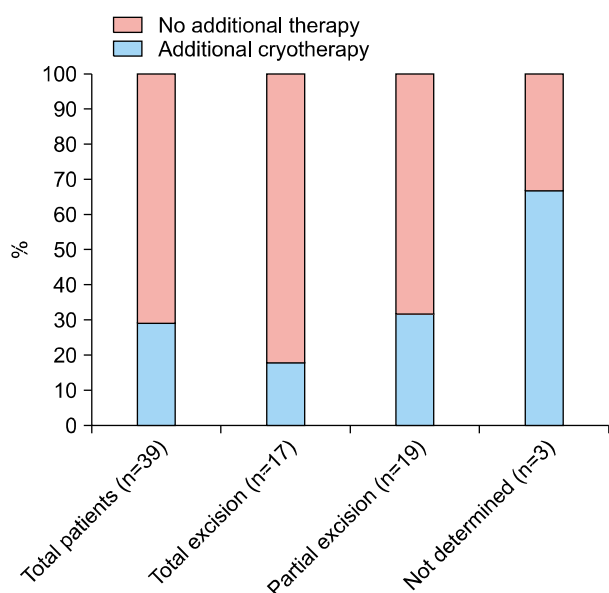


Fig. 2. The percentage of patients who were treated with additional cryotherapy after punch biopsy. Three of 17 patients (17.6%) needed further cryotherapy despite total excision and 6 of 19 patients (31.6%) with specimens that were partially excised needed additional cryotherapy.

Twenty-eight patients (71.8%) had no residual warts (Fig. 2). Eleven patients (28.2%) were treated by cryotherapy after punch biopsy and the average number of cryotherapy treatments is 4.1 ± 3.3 (mean \pm standard deviation). All patients were treated to complete remission and there were no recurrences during the follow-up period (30 ± 16 months).

Among 39 patients, 15 were matched with controls. The case and control groups were similar in size and location of the warts (Fig. 3). The average age of the case group is 27.5 ± 19.6 years (range, 2~66 years) and the sex ratio was 1.1. The average age of the control group was 30.3 ± 17.9 years (range, 9~60 years) and the sex ratio was 2.75. There is no statistically significant difference in age and sex distribution between case and control group (Table 2). The average number of all procedures in the case group is 2.3 ± 3.6 , which also equals the number of visits to clinic. Eleven of the 15 patients in the case group did not need further treatment after punch biopsy. In the control group, the average number of procedures is 5.9 ± 4.1 . The number of treatments in the case group is less than that in the control group ($p < 0.05$). The cost of a punch biopsy is 1.6 times that of a cryotherapy (The cost of cryotherapy is \$22.30, that of a punch biopsy is \$35.68, and the ratio of the former and latter is 1:1.6.). The ratio value of average total cost is 2.9 ± 3.6 in the case group and 5.9 ± 4.1 in the control group ($p < 0.05$; Table 2).

DISCUSSION

Viral warts are one of the most common skin problems. Cutaneous nongenital warts cause various degrees of physical and emotional discomfort. Periungual warts lead to pain, nail dystrophy and paronychia. Plantar warts induce pain with walking. Warts on exposed areas can be cosmetically unseemly. In addition, warts are an infective viral disease and are associated with premalignancy and squamous cell carcinoma of the skin. Although warts often resolve spontaneously, especially in children, many patients come to clinic to be treated for the aforementioned reasons. In particular, warts in adults can be much slower to resolve than warts in children, and are often recalcitrant to treatments. Also, viral warts sometimes need to be distinguished from wart-like lesions such as seborrheic keratosis, epidermodysplasia verruciformis, and verrucous carcinoma. Several studies and guidelines have suggested salicylic acid and cryotherapy as first line management, despite the lack of formal trials^{7,9,11-14}. However, it is not uncommon for patients to complain of the ineffectiveness of salicylic acid, pain of cryotherapy, and scarring after complete remission. In our hospital, warts are usually treated

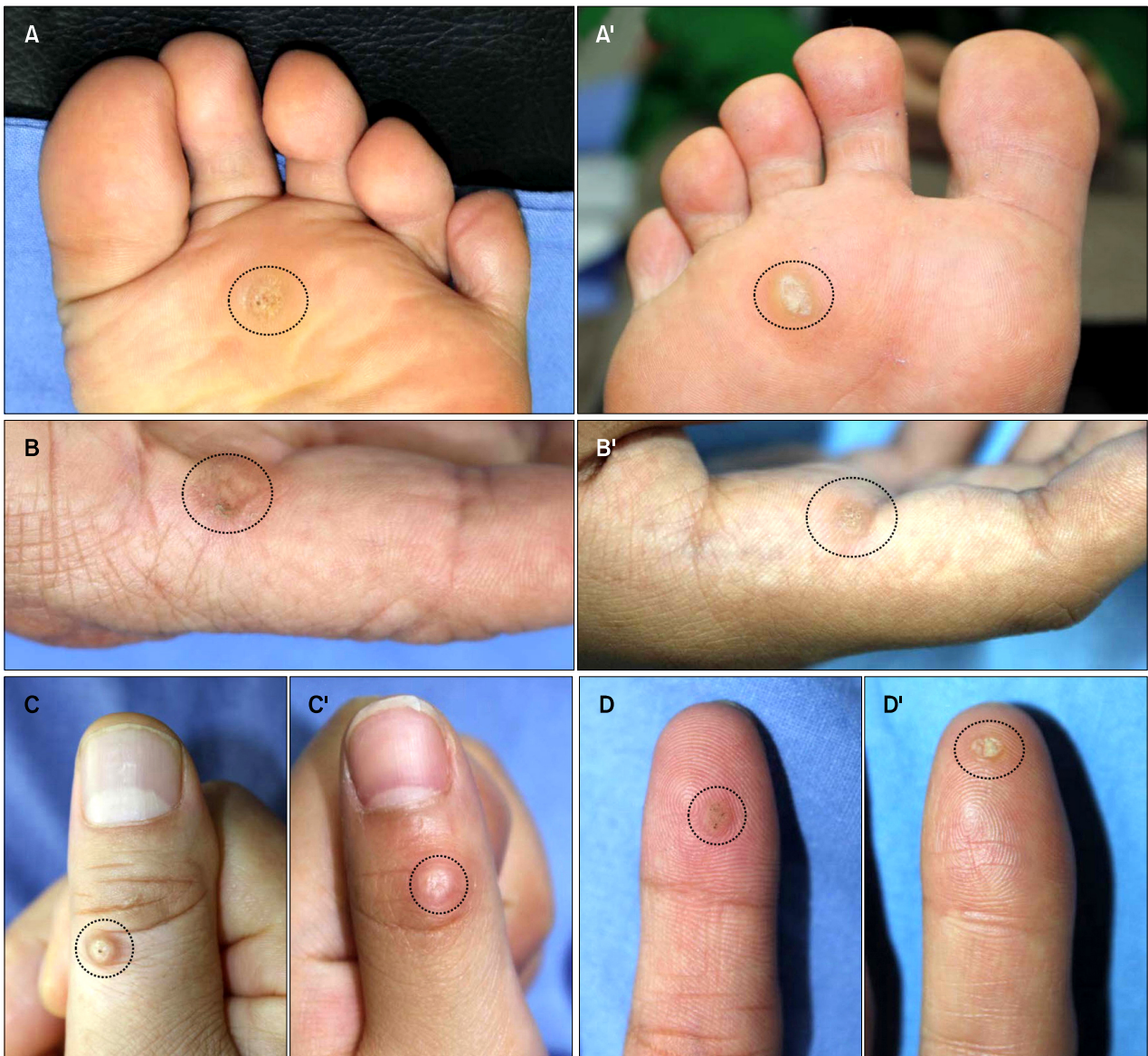


Fig. 3. Clinical image of the matched case (A, B, C, D) and control (A', B', C', D') groups (dotted circles: viral wart).

by cryotherapy, although there are other modalities such as laser treatment, topical salicylic acid, and contact immunotherapy using diphenylcyclopropanone. Punch biopsies were sometimes done as well. Warts on locations other than hands and feet were treated with punch biopsy to diagnose and treat with minimal scarring. Warts on hands and feet were also chosen for punch biopsy for diagnosis or to avoid repeated painful cryotherapy. This data showed a pretty even age distribution unlike previous reports, which showed a peak in children and young adults^{1,3,4}. One of the reasons for this is that adults with long-standing warts often come to a tertiary hospital rather than a primary clinic. Another reason is that patients older than 20 tend to choose punch biopsy because it is hard for

them to go to the clinic for repeated treatments. The other reason for this age distribution difference is that verrucous lesions in old age are often suspicious for diseases other than warts. Although the punch biopsy did not have the goal of total excision, 17 of 39 specimens were totally excised histopathologically. Among these 17 specimens, three cases needed further cryotherapy (17.6%) despite total excision by pathology review. Although wart is excised totally based on pathological result, an invisible virus remained can cause epithelial proliferation. Six of the 19 specimens, that were excised partially, needed additional cryotherapy (31.6%). Two of the three specimens with unclear excision margins were treated with cryotherapy. Although we can assume viral infection to be the cause

Table 2. Demographic data, cost and number of treatments

Variable	Case group (n=15)	Control group (n=15)	p-value
Age (yr)	27.5±19.6/2~66	30.3±17.9/9~60	0.679
Gender			0.259
Male	8 (53.3)	11 (73.3)	
Female	7 (46.7)	4 (26.7)	
Number of treatments*	2.3±3.6	5.9±4.1	0.013
Ratio value of total cost [†]	2.9±3.6	5.9±4.1	0.031
Location			
Foot	10	10	
Hand	4	4	
Knee	1	1	

Values are presented as mean±standard deviation/range, number (%), or number only. *Number of visits, [†]ratio value of a cryotherapy=1 (\$22.30), ratio value of a punch biopsy=1.6 (\$35.68); case and control groups are matched with the size and location of a wart.

from the epidermal and dermal changes observed, viral particles cannot be detected by simple microscopy. Therefore, we cannot ascertain a complete cure based purely on microscopic findings. We should thus monitor the condition of these patients for several weeks after punch biopsy. Among the 19 cases that were partially removed, 13 cases did not need additional treatment. This result leads us to posit that the local inflammatory reaction after punch biopsy helped to eradicate the viral infection. Cell-mediated immunity plays an important role in controlling the progression of natural HPV infection. CD4+ T-cell regulation is particularly important in HPV infections, as evidenced by the higher rates of infection among immunocompromised individuals. Jin et al.¹⁵ reported that there were predominantly CD3 and CD4+ T-cells in the dermis in case of a rapidly regressing wart following punch biopsy¹⁵. Coleman et al.¹⁶ showed that regressing warts contained significantly more CD4+ lymphocytes and macrophages than non-regressing controls. This study supports that CD4+ lymphocytes dominant inflammatory reaction after punch biopsy helps to treat viral warts.

We evaluated the cost-effectiveness of punch biopsy prior to cryotherapy and cryotherapy alone. We compared 15 cases and 15 controls matched in size and location of warts. Most wart locations in this case-control study are on the hands and feet. Palms, soles and periungual sites didn't show hypertrophic scar, nail dystrophy or suture tracks after punch biopsy. The cost of punch biopsy (\$35.68) is 1.6 times of that of cryotherapy (\$22.30). The number of treatments in the case group is statistically less than that in control group ($p=0.008$). The total cost in the case group is less expensive than that in control group ($p=0.019$). We acknowledge that there are some limitations. We designed case-control study to match only the size and location of warts and didn't cover giant warts.

In conclusion, warts can be resolved through an immune reaction to viral antigens and punch biopsy can induce and promote this process. We proved this hypothesis by monitoring patients who received punch biopsy compared with cryotherapy alone. Therefore, partial removal using punch biopsy can be used to manage warts, especially long-standing warts, on soles, palms and periungual sites in adults.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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