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ORIGINAL ARTICLE

Cidofovir Intralesional Injection for Recalcitrant Common Warts: A Comparison with Sodium Tetradecyl Sulfate Intralesional Injection

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Background: A novel treatment method is required for recalcitrant common warts. **Objective:** This study aimed to compare the complete wart removal rate of cidofovir, a broad-spectrum antiviral agent, intralesional injection and sodium tetradecyl sulfate intralesional injection. **Methods:** This retrospective study included 45 patients with recalcitrant common warts on the hands and/or feet, treated with cidofovir or sodium tetradecyl sulfate intralesional injection. **Results:** The treatment results were evaluated in three groups as follows: (1) failure - recalcitrant common warts remaining despite three or more injections, (2) success - free from warts for more than 6 months after the injection, and (3) recurrence. The cidofovir group (n = 22) showed significantly higher treatment success rates than the sodium tetradecyl sulfate group (n = 23) (90.91% vs. 26.09%, $p < 0.001$). Two immunosuppressed patients in the cidofovir group had recurrent lesions after 2 months of being declared free from warts. Considering adverse effects, two patients in the cidofovir group complained of bulla formation with severe pain requiring narcotic painkillers. **Conclusion:** Although this study has the limitations of a small sample size and retrospective design, patients with recalcitrant common warts showed a dramatic response to the treatment with cidofovir intralesional injection, with minimal complications. **(Ann Dermatol 32(4) 273~279, 2020)**

-Keywords-
Cidofovir, Sodium tetradecyl sulfate, Warts

INTRODUCTION

Warts are an infectious disease caused by human papillomavirus (HPV), which can be naturally cured if the cellular immunity of the infected keratinocytes is strengthened. Spontaneous resolution rates in children were reported as 30% at 3 months, 50% at 1 year, and 90% over 5 years[1]. Despite a high spontaneous resolution rate, a small subset of warts, termed recalcitrant common warts (RCWs), resist most conventional treatments, including cryotherapy, bleomycin injection, topical keratolytic agents, and immunotherapy. In addition, the recent popular use of immunodepressants appears to increase the prevalence of RCWs[2,3]. The main problem for patients with RCWs is a quality of life impairment due to the unsightly appearance of warts, pain, and the concern that warts might be transferred to other people[4]. However, no complete treatment is available for RCWs.

Cidofovir, a broad-spectrum antiviral agent, was recently tried off-label to treat RCWs via intralesional injection (ILI) and showed a higher clearance rate of 98.5%[5]. Currently, it is one of the only methods available for controlling the infectivity of HPV. It acts by incorporating into the growing DNA strand and blocking further viral DNA synthesis, leading to a nonproductive infection and apoptotic cell death[6]. However, ILI should be performed with careful monitoring of skin changes and pain, as the pharmacoki-

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netic features of cidofovir in humans have only been reported following intravenous injection, not ILI[7]. Careful monitoring for nephrotoxicity after ILI may also be necessary, especially in patients that require a large dose of cidofovir or are taking other renal excretion drugs.

Sodium tetradecyl sulfate (STS) is a strong detergent that can reduce viral infectivity. It is also an agent used for sclerotherapy in vascular disease and may effectively eliminate blood vessels around warts. Based on these hypotheses, it was used in the past to treat warts[8].

I have carefully applied these two drugs to long-lasting RCWs that showed no response to other treatments. In this retrospective study, I compared the complete wart removal rates and adverse effects of cidofovir and STS ILI treatments as a possible new therapy for RCWs.

MATERIALS AND METHODS

Patients and methods

I retrospectively reviewed the medical records of 45 patients with RCWs who were treated with STS ILI between May 2014 and February 2015 or cidofovir between November 2017 and March 2019 at Severance Hospital in the Yonsei University Health System, Seoul, Korea. RCW was defined as a histopathologically confirmed wart, which lasted for more than two years and has shown resistance to conventional wart removal methods including cryotherapy and bleomycin ILI.

The patients' medical records were reviewed for age, sex, location and number of warts, photographs taken during visits, number of injections needed to resolve the lesions, complications, and follow-up periods. This study protocol was approved by the institutional review board of Yonsei University Severance Hospital (IRB No. 4-2018-1058) and conformed to the principles of the Declaration of Helsinki. Patient records and information were de-identified before analysis.

We received the patient's consent form about publishing all photographic materials.

Cidofovir intralesional injection

I administered cidofovir (Cidofovir Injection®; Heritage Pharmaceuticals Inc., Eatontown, NJ, USA) to patients who had pathologically confirmed warts and consented to this treatment; patients were hospitalized for the 1st injection and 24 hours of observation. Before the injection, cidofovir (75 mg/ml aqueous solution) was mixed at a ratio of 1:4 with normal saline (1 ml of cidofovir in 4 ml of saline) to make a final solution with a concentration of 15 mg/ml. Several cidofovir (15 mg/ml) ILIs were administered under local anesthesia with 1% lidocaine; the number of injections depended on the number and size of the warts but did not exceed 5 ml (75 mg of cidofovir) per day. This procedure was repeated monthly until the resolution of the lesions, which was assessed by the absence of dermoscopic findings of warts, such as dotted vessels and mosaic patterns[9]. If there were no problems during the follow-up period after the 1st injection, the 2nd injection was administered in an outpatient setting 1 month after the 1st injection. All patients' renal function was evaluated

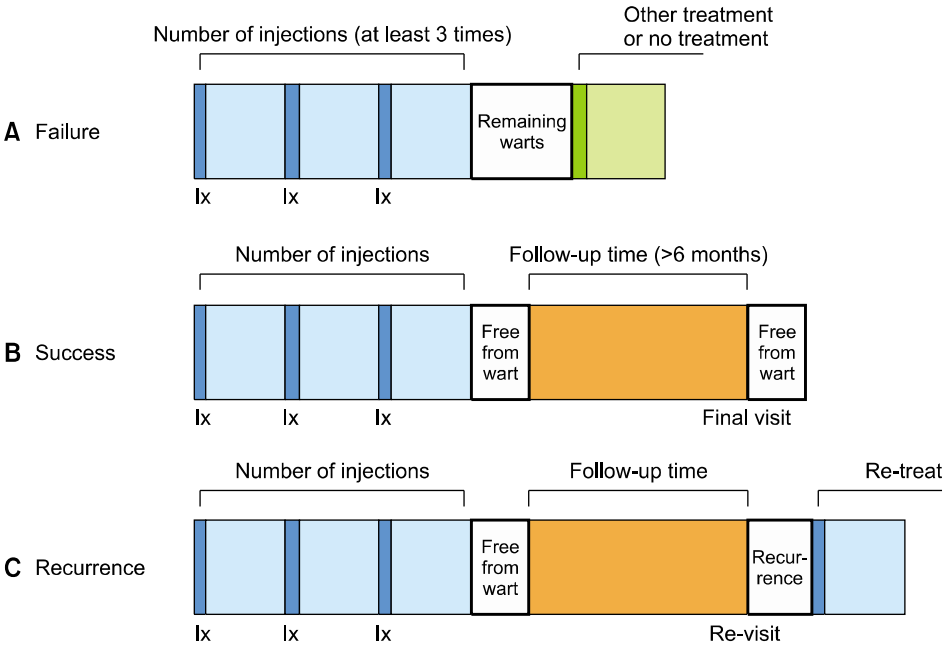

Fig. 1. Three groups for evaluating treatment outcomes. Ix: injection.

Table 1. Patient characteristics

Parameter	STS group	Cidofovir group	*p*-value
Patients	23	22	NA
Sex			
Male	11 (47.8)	15 (68.2)	NA
Female	12 (52.2)	7 (31.8)	
Age	26.43±11.37 (11~56)	30.91±15.27 (12~65)	0.3229
Disease duration (yr)	3.80±1.96 (2~20)	4.86±2.40 (2~10)	0.0820
Number of warts	4.39±4.54 (1~20)	6.14±6.13 (1~20)	0.3464
Site of occurrence			
Hands (finger, palm, periungual area)	6 (26.09)	10 (45.45)	NA
Feet (toe, sole, periungual area)	14 (60.87)	8 (36.36)	NA
Both	3 (13.04)	4 (18.18)	NA

Values are presented as number only, number (%), or mean±standard deviation (range). STS: sodium tetradecyl sulfate, NA: not applicable. Statistical test: non-parametric Mann–Whitney U-test.

Table 2. Treatment outcomes

Outcome	STS group	Cidofovir group	*p*-value
Total	23 (100)	22 (100)	
Tx. failure	16 (69.57)	0 (0)	<0.001*
Tx. success	6 (26.09)	20 (90.91)	
Recurrence after Tx.	1 (4.35)	2 (9.09)	
Adverse events			
Bulla formation with severe pain	-	2	
Skin necrosis	-	-	
Nail deformity	-	-	

Values are presented as number (%). STS: sodium tetradecyl sulfate, Tx.: treatment. Statistical test: chi-square test. *Difference was considered statistically significant at $p<0.05$.

Table 3. Comparison of successful patients

Parameter	STS group	Cidofovir group	*p*-value
Number of patients	6	20	
Number of warts	3.33±2.34 (2~8)	5.40±5.55 (1~20)	0.5796
Number of treatments	1.83±0.41 (1~2)	2.00±0.97 (1~3)	0.7218

Values are presented as number only or mean±standard deviation (range). STS: sodium tetradecyl sulfate. Statistical test: non-parametric Mann-Whitney U-test.

Table 4. Recurrence characteristics of cidofovir intralesional injection

Parameter	Recurrence 1	Recurrence 2
Patient age (yr)	46	16
Sex	Male	Female
Location	Sole, finger, toe	Sole, finger, toe
Initial number of warts	20	7
Co-morbidities	Immunosuppressive medication due to myasthenia gravis	Immunosuppressive medication after liver transplantation
Number of treatments	3	2
Treatment period (day)	92	60
Period of complete loss	2 months	2 months
Treatment after recurrence	Cidofovir intralesional injection	Cidofovir intralesional injection
Adverse events	-	-

both before and 12 hours after the injection.

Sodium tetradecyl sulfate intralesional injection

I diluted 1% sodium tetradecyl sulfate (Trombojet®; Omega Lab., Montreal, QC, Canada) in normal saline to make a 0.5% solution and performed the intralesional injections under local anesthesia; I injected 0.1∼0.2 ml per wart site. The treatment was repeated at 2∼3-week intervals.

Assessment of the outcomes

The clinical effects and sequential changes were evaluated using photographs of the warts to calculate the area of the warts. A free from wart (FFW) status was established if there were no findings of warts by dermoscopic evaluation. The treatment results were evaluated in three groups as follows: (A) failure: RCWs remaining despite three or more injections, (B) success: FFW lasting more than 6 months after the final injection, (C) recurrence: new lesions developed within 6 months of being declared FFW (Fig. 1).

Statistical analysis

Discrete variables were presented using counts and percentages, whereas continuous variables were reported using the mean±standard deviation. I compared patient age, disease duration, number of warts, number of treatments, and treatment periods using the nonparametric Mann–Whitney U-test. Complete wart removal rates in each group were compared using the chi-square test. Statistical analysis was performed using DBSTAT ver. 5.0 (DBSTAT, Chuncheon, Korea; http://dbstat.com/). Differences were considered statistically significant at $p<0.05$.

RESULTS

A total of 45 patients (26 males and 19 females) with RCWs on their hands and/or feet were treated with STS or cidofovir ILI (Table 1). The average age of the patients was 28.62 years and ranged from 11 to 65 years. All patients had a history of warts for more than 2 years, and the average duration of the disease was 4.34 years. The patients had, on average, 5.24 warts that showed resistance to conventional wart removal methods including cryotherapy and bleomycin ILI.

During the investigation, 23 patients were treated with STS (STS group) and 22 patients were treated with cidofovir (cidofovir group) (Supplementary Fig. 1, 2). There were no differences in mean age, disease duration, or number of warts between both groups (Table 1). The complete wart removal rate in the STS group was 26.09% compared to 90.91% in the cidofovir group, which was statistically significant ($p<0.001$) (Table 2). In the STS group, an average of 1.83 injections was required, whereas in the cidofovir group, 2.00 injections were required for treatment success (Table 3). Two patients from the cidofovir group had recurrent lesions after 2 months of being declared FFW, and both patients received immunosuppressive treatment (Table 4).

Regarding adverse effects, two patients in the cidofovir group complained about bulla formations, which were located on the weight-bearing area of the sole, with severe pain requiring narcotic painkillers. After aspiration or partial debridement, the patients' symptoms were relieved (Fig. 2). Biopsy in one patient revealed changes from hyperkeratosis and papillomatosis from before the injections. Furthermore, there was extensive necrosis of the surrounding keratinocytes with edema in the epidermis and in-

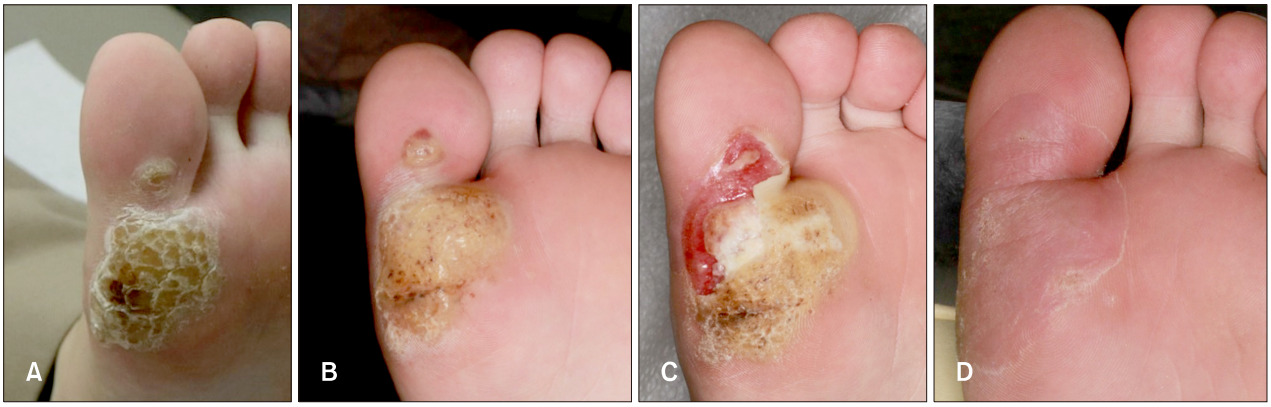

Fig. 2. Sequential changes of the warts on the sole after cidofovir intralesional injection. A 15-year-old boy with warts that resisted treatment for five years. (A) The initial image of warts on the sole. (B) Five days after treatment with peri-lesional inflammation and bulla formation. (C) Two weeks later, I performed partial de-roofing of the bulla. (D) Four weeks after the 1st injection, over 80% of the warts were removed.

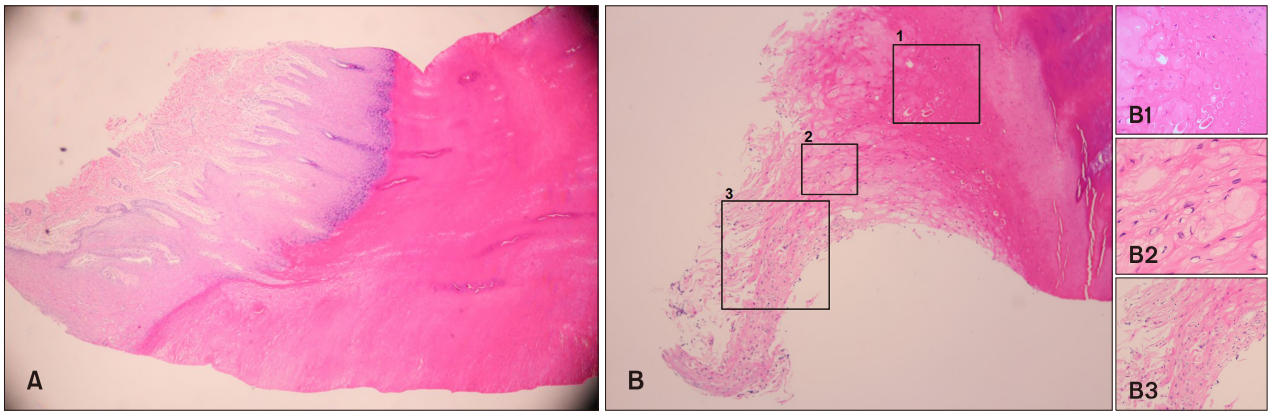

Fig. 3. Histopathologic findings before and after the cidofovir intralesional injections. (A) Hematoxylin and eosin stained section (×40) of biopsy specimen from the wart obtained prior to the treatment showed hyperkeratosis, papillomatosis, and hypergranulosis. (B) Five days after the 1st injection, extensive necrotic keratinocytes with edema in the epidermis and inflammatory cellular infiltration in the dermal and epidermal junction with bulla formation were identified. (B1～3) Enlarged images of black-dashed-box regions in.

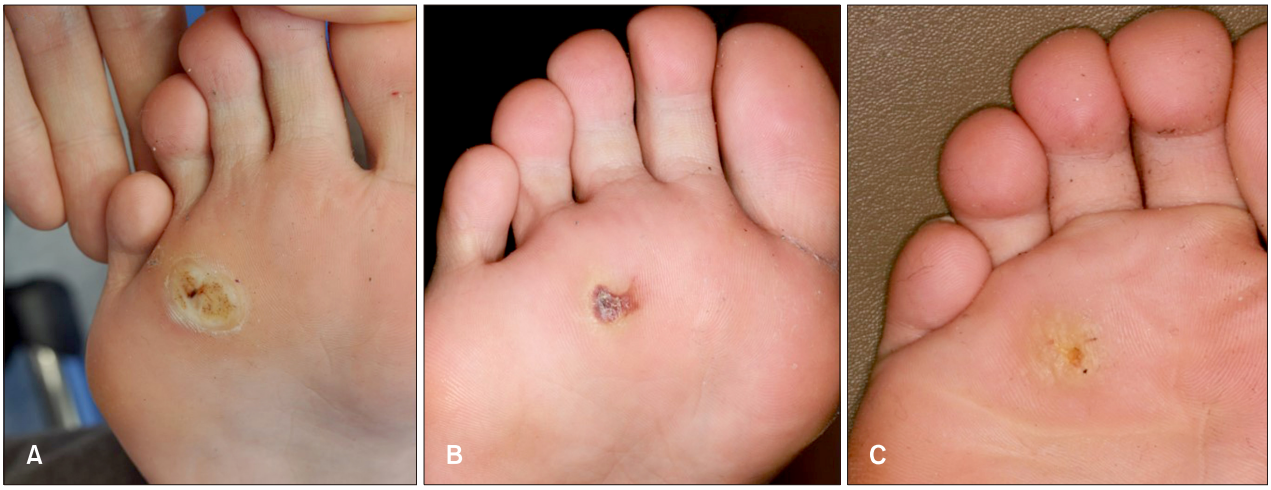

Fig. 4. Sequential changes in the warts on the sole after sodium tetradecyl sulfate intralesional injection. A 15-year-old boy with warts that resisted most treatments for three years. (A) The initial image of warts on the sole. (B) Purpura 1 week after injection. (C) The size of the wart decreased 3 weeks after the 1st injection.

flammatory cellular infiltration in the dermal and epidermal junction, with bulla formation between the dermis and epidermis, after the cidofovir injection (Fig. 3). In addition, hypergranuloses were diminished, and koilocytes disappeared after the injections. Patients treated with STS injections developed purpura at the injection site and had some pain, which was controlled by acetaminophen (Fig. 4). There were no other side effects including abnormal elevation in renal function tests.

DISCUSSION

There are a variety of methods for wart removal, but none are 100% successful. The complete clearance rate (CCR) of cryotherapy, a popular method in South Korea, was reported as only 58%, even if an aggressive and repetitive treatment regimen was used. Repetitive laser treatments with a pulsed dye laser and long-pulsed neodymium-doped yttrium aluminum garnet laser, which targeted the destruction of blood vessels in the papillomatosis of warts, only have CCRs of 49.5% and 56%, respectively[10,11].

For the effective removal of warts with minimal treatment repetition, inflammatory reactions similarly occurring in spontaneous regression such as intensification of cellular immunity in the dermis and spongiosis of the epidermis are necessary[12]. High dose oral cimetidine or zinc sulfate, convenient methods of immunomodulation, were tried and showed about 30%, and 50% CCR, respectively[13,14]; this was a disappointing result compared to the rate of spontaneous regression (30% after 3 months). In addition,

possible side effects of high-dose cimetidine, such as a headache, dizziness, diarrhea, rash, gynecomastia, and those of zinc toxicity, such as nausea, vomiting, pain, cramps, and diarrhea, should be considered.

To intensify cell-mediated immunity, an application of diphenylcyclopropenone was tried[15], but there was variation in CCR from 30% to 88%, explained by the clinicians as being due to the initially optimizing sensitization and controlling side effects[16]. Intralesional injection with tuberculin or measles, mumps and rubella vaccines, which can induce a strong non-specific inflammatory response against HPV infected cells, showed a CCR of 80% and 60%, respectively[17]. The cause of failed immunotherapy may be the immune evasion mechanisms of HPV, such as the inhibition of interferon synthesis and delayed Langerhans cell antigen presentation[18]. Interestingly, puncturing warts with a 25 gauge needle also showed a good response of 64.7% of CCR[19], which highlights the importance of basement membrane disruption and inflammatory cell migration through the spongiosis of the epidermis for effective wart removal.

Quadrivalent HPV vaccination, which may induce humoral and cellular immune responses combined with cross-reactivity with the L1 capsid protein, was tried in several case reports and showed good responses, however, CCR 6 months after the scheduled injection and 2 months after follow-up was 46.7%[20]. In India, autoimplantation methods employing the pared stratum corneum tissue deep into the subcutis of patients' forearm, which may elicit immunity against the same serotypes of HPV, showed a 74.1% CCR within 3 months[21]. However, there were complications of granulomas or cysts at the implantation site in 3 (11.1%) patients.

Recent approaches with cidofovir, a broad-spectrum antiviral agent, could be the essential modality to treating RCWs. In this study, 91% of patients in the cidofovir group were cured using an average of 2.00 monthly injections, while in the STS group, 26% were cured using an average of 1.85 injections at 2～3 week intervals. Six patients who were cured by STS ILI were found to have significantly shorter treatment periods because STS was injected at 2～3 week intervals rather than at 1-month intervals. From the pathologic findings after cidofovir ILI, which showed swollen necrotic keratinocytes in the epidermis and upper dermal inflammation, cidofovir might directly and promptly act on the infected keratinocytes and cause cell death by apoptosis, which is crucial for the treatment of HPV infection.

Recurrences were noted in two immunosuppressed patients in the cidofovir group. Considering the period of subclinical infection, known to be possible from 2～9 months[22], adjuvant topical treatments, such as keratolytic agents and topical cidofovir creams, are expected to help improve treatment success.

Despite several dramatic treatment outcomes, including this study, cidofovir is not commonly recommended for the treatment of RCWs; and importantly, there is still a need to validate its safety when administered via intralesional injection. In my cases, I used diluted cidofovir ILI, so nephrotoxicity did not occur. Recently intralesional cidofovir injection was successfully used for the treatment of recurrent respiratory papillomatosis without nephrotoxicity, and the authors concluded that it does not increase the risk of laryngeal dysplasia[23]. In addition, there was a report highlighting that cidofovir can be considered as a promising broad-spectrum anti-cancer agent[24].

Although this study has the limitations, such as the small sample size and its retrospective design, cidofovir ILI showed a dramatic response compared to STS ILI, with few complications, in the treatment of RCWs. For patients with long-lasting warts that are refractory to conventional treatments, cidofovir ILI is a possible treatment option. However, larger studies will be necessary to determine the safety, appropriate concentration, and the best dosing schedule for cidofovir ILI.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-32-273-s001.pdf.

CONFLICTS OF INTEREST

The author has nothing to disclose.

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